Exploring daily practice performance of dupilumab in atopic dermatitis

Moving towards personalized treatment

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Thesis

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Exploring daily practice performance of dupilumab in atopic dermatitis

Moving towards personalized treatment

De prestatie van dupilumab bij de behandeling van constitutioneel eczeem in de dagelijkse praktijk

Op weg naar gepersonaliseerde behandeling

(met een samenvatting in het Nederlands)

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General introduction

General introduction and thesis outline

This general introduction will provide a brief overview of atopic dermatitis (AD), AD pathogenesis, and the treatment options for AD in daily practice with a focus on dupilumab treatment. This will be followed by an outline of the thesis.

Atopic dermatitis

AD is one of the most common chronic inflammatory skin diseases, with a prevalence currently estimated at 10% in adults and 25-30% in children in developed countries.[1,2] The etiology of AD is multifactorial, involving an interaction between genetic, immunological, and environmental factors. AD most often develops during childhood, although it can manifest at any point in life, and is characterized by chronic pruritus. It is defined as recurrent eczematous lesions with erythematous (red) patches with exudation, blistering and crusting in the early stages, followed by scaling, fissuring (cracking) and lichenification (thickening) of the skin in the chronic phase.[3] Furthermore, AD patients are known to have an increased risk of skin infections, other atopic diseases (e.g. allergic asthma, allergic rhinitis, allergic conjunctivitis, and food allergy) and report more psychological difficulties and interpersonal issues.[4, 5] As a consequence, AD causes a great burden and has a substantial impact on both the quality of life and work productivity.[6]

Type 2 immunity and AD pathogenesis

Type 2 immunity

AD is a disease of typically altered Type 2 (T2) immune response, just as other atopic diseases (e.g. allergic asthma and food allergy).[7] T2 immunity is a particular response of the immune system that is specialized in the protection against extracellular organisms (e.g. parasitic agents) in which T helper 2 (Th2) cells play an important role.[8] However, when this response is activated excessively and chronically, it can be damaging rather than protective. Th2 cells and group 2 innate lymphoid cells produce T2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13. These interleukins promote class switching of B cells to Immunoglobulin E (IgE) production, and play a role in the activation and migration of effector cells such as eosinophils, basophils, and mast cells leading to T2 inflammation and associated allergic diseases, like AD.[9]

AD pathogenesis

AD is characterized by a disrupted skin barrier function, skin inflammation, and chronic pruritus (see Figure 1).[10, 11] The two main factors contributing to the pathogenesis of AD are epithelial barrier disruption and immune dysregulation,[12, 13] with a primary role played by T2-driven inflammation. AD is characterized by an overexpression of T2-related cytokines, such as IL-4, IL-5, IL-13, IL-31, and thymus and activation regulated chemokine (TARC)/CCL17 in both skin and blood.[12, 14] The T2 cytokines in AD skin specifically affect the epidermis by suppressing keratinocyte differentiation, antimicrobial peptide production and downregulation of the filaggrin (FLG) protein, which leads to a decrease of skin barrier function.[15, 16] The defective barrier allows the penetration of allergens and microbes[16, 17] and subsequently activates inflammatory dendritic epidermal cells which initiates T2 cell-mediated responses.[18]The role of immune and inflammatory cells in AD is depicted in Figure 1.

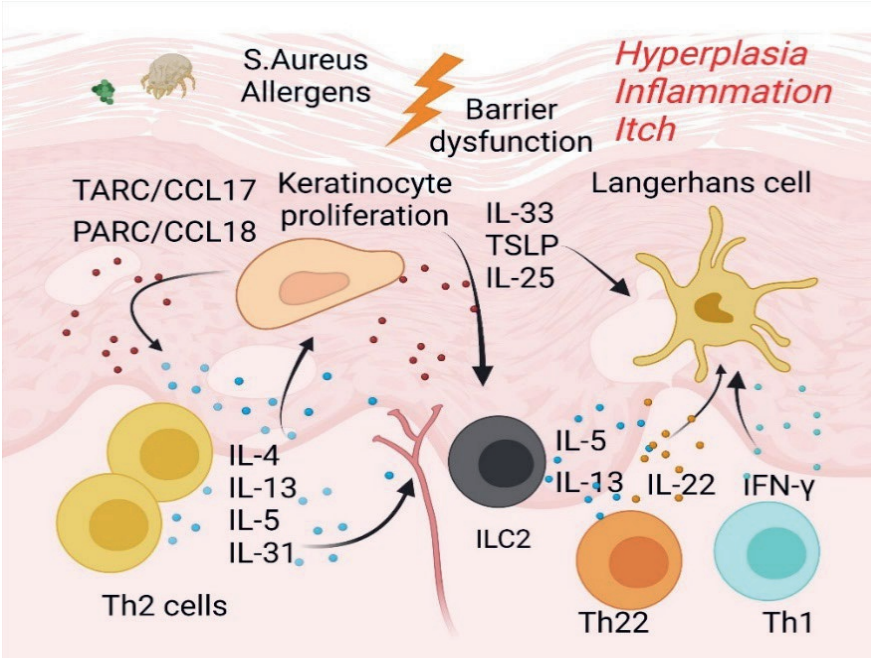

Figure 1. Pathogenesis of atopic dermatitis.

The T2 cytokines (e.g. IL-4, IL-5, IL-13, IL-31, and thymus and activation regulated chemokine (TARC)/CCL17) in AD skin specifically affect the epidermis by suppressing keratinocyte differentiation, antimicrobial peptide production and downregulation of the filaggrin (FLG) protein, which leads to a decrease of skin barrier function. The defective barrier allows the penetration of allergens and microbes and subsequently activates inflammatory dendritic epidermal cells which initiates T2 cell-mediated responses. Figure adapted from 'Immune monitoring and treatment in immune-mediated inflammatory diseases' by van Wijk et al. 2022, Nature communications. Jun 7;13(1):3245.[19]

New era of treatment options for AD

The mainstay of AD treatment are topical agents such as emollients, topical corticosteroids and/or calcineurin inhibitors. However, in patients with moderate-to-severe AD who cannot be controlled by sufficient topical therapy, systemic immunosuppressive or immunomodulatory treatment is indicated.[4, 20] Patients with moderate-to-severe AD were traditionally treated with broad-acting systemic immunosuppressive therapies such as azathioprine, cyclosporine A, methotrexate, and/or mycophenolate mofetil.[6, 20] Many of these systemic drugs are used off-label for AD and are associated with high rates of discontinuation due to ineffectiveness and/or side effects.[21-23] In the past decade knowledge of the immunological pathogenesis of AD has expanded, leading to the development of new advanced targeted therapies, which are nowadays registered for the treatment of moderate-to-severe AD (Figure 2).[24, 25]

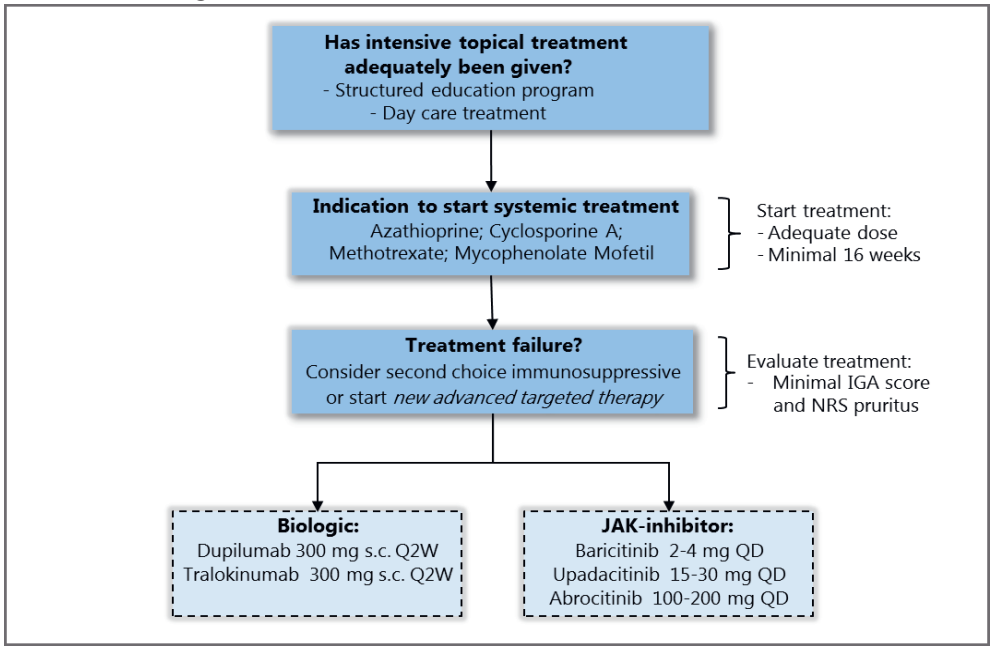

Figure 2. Treatment algorithm for moderate-to-severe atopic dermatitis.

New advanced targeted therapies: biologics and small molecule antagonists

Due to the central role of T2 inflammation in AD, the first biological treatment that has become available for moderate-to-severe AD, dupilumab, targets the T2-related cytokines IL-4 and IL-13[26-29] by binding to the IL-4 receptor α (IL-4Rα).[3, 30-33] Dupilumab has been approved in the EU for the treatment of moderate-to-severe AD in adult patients since September 2017. In the Netherlands, AD patients are eligible to receive dupilumab after insufficient response to topical therapy and failure

of at least one of the conventional systemic immunosuppressive therapies. Dupilumab has shown clinically relevant improvement in signs and symptoms of AD and an acceptable safety profile in both clinical trials and few short-term daily practice studies.[26, 34, 35] However, long-term daily practice data about effectiveness and safety of dupilumab are scarce. Since 2020 other new advanced targeted therapies for the treatment of AD (e.g. Janus kinase (JAK)-inhibitors and biologics) (see Figure 2) became available and more targeted treatments are in the pipeline.[36, 37] Therefore it will be a challenge to provide the right drug to the right patient. Adding knowledge on the performance of these new advanced targeted treatments in daily practice will benefit and optimize the treatment of patients with AD.

Daily practice use of new advanced targeted therapy in AD

Nowadays, large multicenter randomized placebo controlled trials are required before a new drug is registered. Despite the high quality of these clinical trials, results are not always generalizable to daily practice.[38] Prospective observational cohort studies (like daily practice registries) play an important role in gathering long-term safety and effectiveness data for new advanced targeted therapies for AD in daily practice.[39] The strength of these registries is that they reflect regular health care under routine conditions, as opposed to Randomized Controlled Trails (RCTs), and there is no selection of patients (e.g. no exclusion of patients with older age or comorbidities). Registry data are ideal for identifying common characteristics, effectiveness and safety of new advanced targeted therapies for AD in daily practice.

The BioDay registry

The BioDay registry contains observational, longitudinal, prospective data on AD patients (and associated comorbidities) treated with new advanced targeted therapies in daily practice in a multicenter setting. The BioDay registry is coordinated by the department of dermatology of the University Medical Center Utrecht and University Medical center Groningen in the Netherlands. The registry has expanded over the years and currently includes data from 4 university and 10 non-university hospitals in the Netherlands. The first patient in the BioDay registry was recorded in October 2017 and until 2022 more than 1200 patients have been included. The registry contains daily practice data on effectiveness and safety of new advanced systemic therapies for AD, including both patient-reported outcomes (PRO's) as well as clinical parameters. Collected data include, among others: demographics, treatment history, medical history, disease severity scores at initiation of and during

treatment, safety data, serum drug levels, serum biomarkers levels, and patient reported outcomes. Outcome measures are in line with the core outcomes for eczema recommended by the global Harmonising Outcome Measures for Eczema (HOME) initiative.[40] This thesis is based on data of AD patients treated with dupilumab collected in the BioDay registry.

Drug survival

An elegant way to evaluate therapeutic success of a drug in a daily practice setting is by assessment of drug survival. Drug survival analysis gives a reflection of daily practice by analyzing the expected duration of time until the occurrence of an event of interest (e.g. discontinuation of the drug) (see Figure 3). Drug survival is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences.[41] Drug survival and associated predictors are dependent on a combination of factors such as drug effectiveness, the occurrence of severe or disturbing side-effects, patient factors and the availability of other treatment options. It is a valuable parameter for chronic diseases requiring long-term treatment, with prolonged drug survival reflecting therapeutic success in a daily practice setting.[21-23, 42] A short drug survival mostly indicates (premature) therapeutic failure resulting from ineffectiveness, side effects or other negative events. Moreover, clinical characteristics might be predictive for drug survival and predictors for drug survival can guide us to more patient-centered therapy.

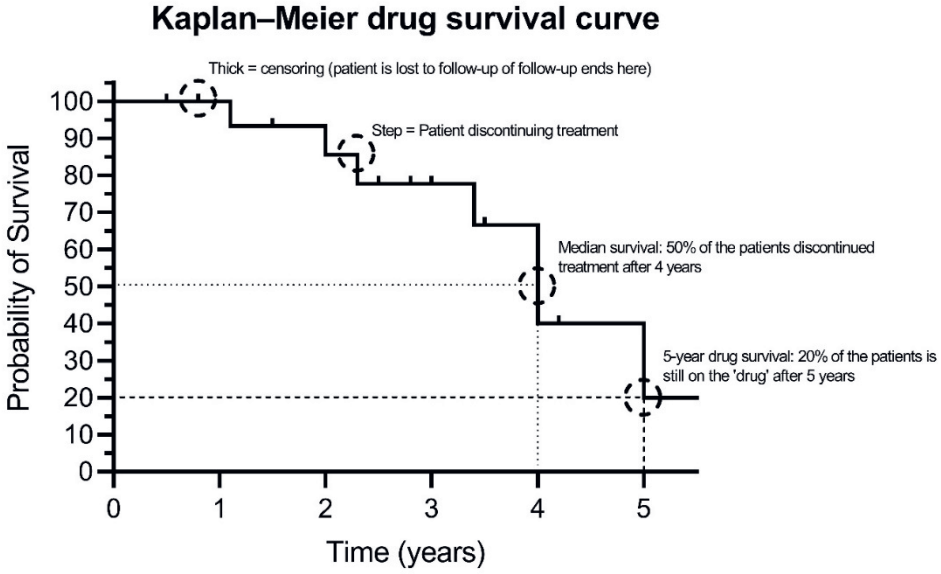

Figure 3. Kaplan–Meier drug survival curve with features explaining a drug survival curve.

Moving towards personalized AD treatment

Predicting response to dupilumab treatment

In patients with chronic inflammatory diseases like AD, lifelong treatment is mostly required, and achievement of long-term disease control in these patients is desirable. However, due to the heterogeneity of AD and clinical differences between patients, treatment responses and the development of side effects vary widely across individuals. Results from phase 3 dupilumab trials demonstrated that 40% of subjects reached the endpoint of clear or almost clear disease at week 52, resulting in 60% of patients still experiencing some symptoms while using dupilumab.[27, 30] This demonstrates that uncertainty in long-term effectiveness remains for these AD patients in daily practice. Little is known about factors that may influence the treatment response to dupilumab and if certain clinical characteristics might be predictive for long-term effectiveness. Previous studies of predictive clinical characteristics are rather limited and mainly focused on the early response up to 16 weeks.[43, 44] In this current era of new upcoming systemic treatment options for patients with moderate-to-severe AD, more knowledge about predicting long-term effectiveness of dupilumab treatment is essential for sufficient clinical decision making and would lead to more patient-centered treatment.

Patient-centered dupilumab dosing regimen

The registered dose of dupilumab for adult patients is a loading dose of 600 mg subcutaneously, followed by 300 mg every other week (Q2W). Most of the current evidence on different dosing regimens in daily practice includes biologic tapering in rheumatologic diseases, inflammatory bowel disease, and psoriasis. The European recommendations for rheumatoid arthritis (RA) already described tapering strategies for biologic treatments in RA patients with persistent remission.[45] In a tapering study with biologics in psoriasis, tight dose reduction did not lead to persistent flares or safety issues.[46] Continuing standard dosage of the biologic dupilumab in patients with persistent controlled AD might lead to overtreatment and an increase in side effects (e.g. injection side reactions, conjunctivitis). Besides, biologic treatment comes with more costs, having a considerable economic impact on the national health care expenditures. Lowering the overall exposure to dupilumab, where possible, could result in a lower risk of side effects and substantial health care savings. Gaining experience with tapering of dupilumab while maintaining clinical effectiveness enables individual dosing, both benefiting the patient and lowering budget impact.

The effect of dupilumab on atopic comorbidities

Allergic asthma

AD is closely related to, and commonly co-occurs with other atopic diseases, such as allergic asthma and food allergy.[47, 48] Asthma symptoms are non-specific, and include wheezing, shortness of breath, chest tightness, and cough.[49] The pathogenesis of allergic asthma is comparable to AD and is characterized by an excessive airway inflammatory Th2-cellular response to (environmental) triggers, such as allergens and irritantia, resulting in airway obstruction, eosinophilia (≥ 300 eosinophilic cells/μL) and increased production of IgE.[50, 51] Eosinophilic asthma, high type 2 inflammation is present in around 50% of adults with asthma.[52] Dupilumab is also available as add-on maintenance treatment for the treatment of severe asthma with type 2 inflammation, characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide and inadequately controlled with high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.[53-55] Several RCTs regarding dupilumab treatment for allergic asthma reported improved clinical outcomes for forced expiratory volume in 1 second (FEV1), 5-item Asthma Control Questionnaire (ACQ-5), asthma exacerbations rate and prednisolone use.[56-58] Furthermore, studies reported sustained reduction of T2 inflammatory biomarkers in asthma patients by using dupilumab.[54] Since the majority of AD patients has comorbid asthma[59], it is clinically relevant to investigate the effect of dupilumab on asthma in patients treated with dupilumab for AD in daily practice. Additionally, in our patients dupilumab treatment is primarily indicated for AD, most of these patients do not fulfill the criteria to start dupilumab treatment due to mild asthma or the absence of blood eosinophilia. It is of interest to investigate the effect of dupilumab in this specific asthma population.

Food allergy

A total of 17.4% to 42.9% of adults with severe AD reported having a food allergy, with a stepwise increase in the 1-year prevalence of food allergy by more severe AD.[60] AD has shown to be a major risk factor for food sensitization and the development of IgE-mediated food allergy as a result of cutaneous sensitization through an increased permeability of the skin for food allergens.[61-63] In daily practice, the diagnosis of food allergy is mainly based on clinical history, supported by the detection of food specific sensitization in vivo by skin prick test (SPT) or in vitro by serum specific IgE (sIgE) levels. The gold standard for diagnosis of food allergy is an oral food challenge. At present, no curative therapy is available once a food allergy

is established. Rial MJ et al. presented a case report showing a diminished food allergic reaction to corn and nuts in a patient using dupilumab for moderate-to-severe AD.[64] This was the first case providing evidence of the effect of dupilumab on diminishing a food allergic reaction possibly by inhibiting the IL-4/IL-13 signaling pathway. Furthermore, research has shown that a decrease in sIgE may represent a higher tolerance for food allergens, as data indicated a correlation between a reduction in sIgE levels and the expression of high affinity IgE receptors on inflammatory cells.[65] As a result, decreasing sIgE levels, by inhibiting the IL-4/IL-13 signaling pathway using dupilumab, could be a surrogate marker for a diminished food allergic reaction.

Outline of this thesis

For patients with moderate-to-severe AD the introduction of the first biological treatment, dupilumab, has vastly improved treatment outcomes and quality of life.[16, 43] To optimize AD treatment, data on the long-term effectiveness and safety of dupilumab in a daily practice setting is required. Furthermore, given the recent developments and pipeline for future advanced targeted therapies for AD,[36, 37] it will be increasingly important to provide the right drug to the right patient. In this thesis, we aim to provide more insight into daily practice performance of dupilumab for AD and its comorbidities, with the goal to move towards personalized therapy.

In **Chapter 2** and **3** we evaluated the effectiveness, disease control, patients' treatment satisfaction and safety of dupilumab in daily practice. In **Chapter 4** and **5** we assessed the performance of dupilumab in daily practice by using drug survival analysis (compared to conventional systemic immunosuppressive therapy) combined with associated predictors. To move towards personalized therapy, we discussed the utility of measuring serum dupilumab levels in clinical practice and its relation to response and side effects in **Chapter 6**. In **Chapter 7**, patient characteristics were evaluated for predicting long-term treatment response to dupilumab. Considering individual dosing of dupilumab, in **Chapter 8** and **9**, we investigated the safety and effectiveness of our patient-centered dupilumab dosing regimen in patients with controlled AD. Lastly, in **Chapter 10** and **11** we analysed the effect of dupilumab on the atopic comorbidities food allergy and asthma in AD patients. In **Chapter 12**, the main results of this thesis are summarized and discussed, followed by clinical recommendations and suggestions for future research.

References

1. Ariens, L.F.M., et al., *Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy.* Ther Adv Chronic Dis, 2018. **9**(9): p. 159-170.
2. Deckers, I.A., et al., *Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies.* PLoS One, 2012. **7**(7): p. e39803.
3. Weidinger, S., et al., *Atopic dermatitis.* Nat Rev Dis Primers, 2018. **4**(1): p. 1.
4. Bruin-Weller, M., et al., *Disease burden and treatment history among adults with atopic dermatitis receiving systemic therapy: baseline characteristics of participants on the EUROSTAD prospective observational study.* J Dermatolog Treat, 2021. **32**(2): p. 164-173.
5. Dalgard, F.J., et al., *The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries.* J Invest Dermatol, 2015. **135**(4): p. 984-991.
6. Ariens, L.F.M., et al., *Economic Burden of Adult Patients with Moderate to Severe Atopic Dermatitis Indicated for Systemic Treatment.* Acta Derm Venereol, 2019. **99**(9): p. 762-768.
7. Nakayama, T., et al., *Th2 Cells in Health and Disease.* Annu Rev Immunol, 2017. **35**: p. 53-84.
8. Gieseck, R.L., 3rd, M.S. Wilson, and T.A. Wynn, *Type 2 immunity in tissue repair and fibrosis.* Nat Rev Immunol, 2018. **18**(1): p. 62-76.
9. Gandhi, N.A., et al., *Targeting key proximal drivers of type 2 inflammation in disease.* Nat Rev Drug Discov, 2016. **15**(1): p. 35-50.
10. Furue, M., et al., *Pathogenesis of Atopic Dermatitis: Current Paradigm.* Iran J Immunol, 2019. **16**(2): p. 97-107.
11. Yang, G., et al., *Skin Barrier Abnormalities and Immune Dysfunction in Atopic Dermatitis.* Int J Mol Sci, 2020. **21**(8).
12. Czarnowicki, T., J.G. Krueger, and E. Guttman-Yassky, *Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications.* J Allergy Clin Immunol Pract, 2014. **2**(4): p. 371-9; quiz 380-1.
13. Fujii, M., *Current Understanding of Pathophysiological Mechanisms of Atopic Dermatitis: Interactions among Skin Barrier Dysfunction, Immune Abnormalities and Pruritus.* Biol Pharm Bull, 2020. **43**(1): p. 12-19.
14. Bakker, D.S., et al., *Early and Long-Term Effects of Dupilumab Treatment on Circulating T-Cell Functions in Patients with Moderate-to-Severe Atopic Dermatitis.* J Invest Dermatol, 2021. **141**(8): p. 1943-1953 e13.
15. Leung, D.Y., *New insights into atopic dermatitis: role of skin barrier and immune dysregulation.* Allergol Int, 2013. **62**(2): p. 151-61.
16. Malajian, D. and E. Guttman-Yassky, *New pathogenic and therapeutic paradigms in atopic dermatitis.* Cytokine, 2015. **73**(2): p. 311-8.
17. Sugita, K. and C.A. Akdis, *Recent developments and advances in atopic dermatitis and food allergy.* Allergol Int, 2020. **69**(2): p. 204-214.
18. Darlenski, R., et al., *Association between barrier impairment and skin microbiota in atopic dermatitis from a global perspective: Unmet needs and open questions.* J Allergy Clin Immunol, 2021. **148**(6): p. 1387-1393.
19. van Wijk, F., et al., *Immune monitoring and treatment in immune-mediated inflammatory diseases.* Nat Commun, 2022. **13**(1): p. 3245.
20. Simpson, E.L., et al., *When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council.* J Am Acad Dermatol, 2017. **77**(4): p. 623-633.
21. Politiek, K., et al., *Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis.* Br J Dermatol, 2016. **174**(1): p. 201-3.
22. van der Schaft, J., et al., *Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis.* Br J Dermatol, 2015. **172**(6): p. 1621-1627.

23. van der Schaft, J., et al., *Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis.* Br J Dermatol, 2016. **175**(1): p. 199-202.
24. Moyle, M., et al., *Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches.* Exp Dermatol, 2019. **28**(7): p. 756-768.
25. Gooderham, M., et al., *Review of Systemic Treatment Options for Adult Atopic Dermatitis.* J Cutan Med Surg, 2017. **21**(1): p. 31-39.
26. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
27. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. **389**(10086): p. 2287-2303.
28. Thaci, D., et al., *Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.* Lancet, 2016. **387**(10013): p. 40-52.
29. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE).* Br J Dermatol, 2018. **178**(5): p. 1083-1101.
30. Rodrigues, M.A., M. Nogueira, and T. Torres, *Dupilumab for atopic dermatitis: evidence to date.* G Ital Dermatol Venereol, 2019. **154**(6): p. 696-713.
31. Seegraber, M., et al., *Dupilumab for treatment of atopic dermatitis.* Expert Rev Clin Pharmacol, 2018. **11**(5): p. 467-474.
32. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.
33. Gooderham, M.J., et al., *Dupilumab: A review of its use in the treatment of atopic dermatitis.* J Am Acad Dermatol, 2018. **78**(3 Suppl 1): p. S28-S36.
34. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2020. **75**(1): p. 116-126.
35. de Wijs, L.E.M., et al., *Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data.* Br J Dermatol, 2020. **182**(2): p. 418-426.
36. Gutermuth, J., et al., *Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7).* Br J Dermatol, 2022. **186**(3): p. 440-452.
37. Nogueira, M. and T. Torres, *Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis: Focus on Abrocitinib, Baricitinib, and Upadacitinib.* Dermatol Pract Concept, 2021. **11**(4): p. e2021145.
38. Bothwell, L.E., et al., *Assessing the Gold Standard--Lessons from the History of RCTs.* N Engl J Med, 2016. **374**(22): p. 2175-81.
39. Schneeweiss, S. and J. Avorn, *A review of uses of health care utilization databases for epidemiologic research on therapeutics.* J Clin Epidemiol, 2005. **58**(4): p. 323-37.
40. Leshem, Y.A., et al., *Measuring atopic eczema symptoms in clinical practice: The first consensus statement from the Harmonising Outcome Measures for Eczema in clinical practice initiative.* J Am Acad Dermatol, 2020. **82**(5): p. 1181-1186.
41. van den Reek, J., et al., *Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls.* J Invest Dermatol, 2015. **135**(7): p. 1-5.
42. Dal Bello, G., et al., *Drug survival of dupilumab compared to cyclosporin in moderate-to-severe atopic dermatitis patients.* Dermatol Ther, 2020. **33**(6): p. e13979.
43. Ferrucci, S., et al., *Clinical Response and Quality of Life in Patients with Severe Atopic Dermatitis Treated with Dupilumab: A Single-Center Real-Life Experience.* J Clin Med, 2020. **9**(3).

44. Olesen, C.M., et al., *Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre.* J Eur Acad Dermatol Venereol, 2019. **33**(8): p. 1562-1568.
45. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.* Ann Rheum Dis, 2020. **79**(6): p. 685-699.
46. Atalay, S., et al., *Comparison of Tightly Controlled Dose Reduction of Biologics With Usual Care for Patients With Psoriasis: A Randomized Clinical Trial.* JAMA Dermatol, 2020.
47. Ravnborg, N., et al., *Prevalence of asthma in patients with atopic dermatitis: A systematic review and meta-analysis.* J Am Acad Dermatol, 2021. **84**(2): p. 471-478.
48. Silverberg, J.I., *Comorbidities and the impact of atopic dermatitis.* Ann Allergy Asthma Immunol, 2019. **123**(2): p. 144-151.
49. Papi, A., et al., *Asthma.* Lancet, 2018. **391**(10122): p. 783-800.
50. Padem, N. and C. Saltoun, *Classification of asthma.* Allergy Asthma Proc, 2019. **40**(6): p. 385-388.
51. Kaur, R. and G. Chupp, *Phenotypes and endotypes of adult asthma: Moving toward precision medicine.* J Allergy Clin Immunol, 2019. **144**(1): p. 1-12.
52. Kulkarni, N.S., et al., *Eosinophil protein in airway macrophages: a novel biomarker of eosinophilic inflammation in patients with asthma.* J Allergy Clin Immunol, 2010. **126**(1): p. 61-9 e3.
53. Chung, K.F., et al., *International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.* Eur Respir J, 2014. **43**(2): p. 343-73.
54. Agache, I., et al., *Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma.* Allergy, 2020. **75**(5): p. 1058-1068.
55. *Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals.* **Version 3.**
56. Castro, M., et al., *Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma.* N Engl J Med, 2018. **378**(26): p. 2486-2496.
57. Rabe, K.F., et al., *Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma.* N Engl J Med, 2018. **378**(26): p. 2475-2485.
58. Wenzel, S., et al., *Dupilumab in persistent asthma with elevated eosinophil levels.* N Engl J Med, 2013. **368**(26): p. 2455-66.
59. Langan, S.M., A.D. Irvine, and S. Weidinger, *Atopic dermatitis.* Lancet, 2020. **396**(10247): p. 345-360.
60. Silverberg, J.I., et al., *Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults.* Ann Allergy Asthma Immunol, 2018. **121**(5): p. 604-612 e3.
61. Rockmann, H., et al., *Food allergen sensitization pattern in adults in relation to severity of atopic dermatitis.* Clin Transl Allergy, 2014. **4**(1): p. 9.
62. Worth, A. and A. Sheikh, *Food allergy and atopic eczema.* Curr Opin Allergy Clin Immunol, 2010. **10**(3): p. 226-30.
63. Hill, D.J., et al., *Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study.* Clin Exp Allergy, 2008. **38**(1): p. 161-8.
64. Rial, M.J., B. Barroso, and J. Sastre, *Dupilumab for treatment of food allergy.* J Allergy Clin Immunol Pract, 2019. **7**(2): p. 673-674.
65. Saini, S.S., et al., *The relationship between serum IgE and surface levels of FcepsilonR on human leukocytes in various diseases: correlation of expression with FcepsilonRI on basophils but not on monocytes or eosinophils.* J Allergy Clin Immunol, 2000. **106**(3): p. 514-20.

2

Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-weeks results from the Dutch BioDay registry

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Abstract

Background: Real-life data on long-term effectiveness and safety of dupilumab in atopic dermatitis patients is limited.

Objective: To study 52-weeks effectiveness and safety of dupilumab in a prospective multi-center cohort of adult patients with treatment-refractory atopic dermatitis.

Methods: Patients treated with dupilumab participating in the Dutch BioDay-registry were included. Clinical effectiveness and safety were evaluated.

Results: 210 atopic dermatitis patients were included. Mean percent change in EASI after 16 weeks was -70.0% (SD 33.2) and further decreased to -76.6% (SD 30.6) by week 52. EASI-75 was achieved by 59.9% at week 16 and 70.3% at week 52. The most reported side effect was conjunctivitis (34%). Limited patients (17 (8.1%)) discontinued dupilumab treatment.

Limitations: Due to the lack of a control-group and observational design, factors of bias may have been induced.

Conclusion: Treatment with dupilumab resulted in a rapid improvement in clinical outcome measures, and effectiveness further improved during the 52-week follow-up period.

Introduction

Dupilumab, a fully monoclonal-antibody that targets the shared receptor component for IL-4 and IL-13, is the first biologic approved for the treatment of patients with moderate-to-severe atopic dermatitis (AD). In phase-3 clinical trials including patients with moderate-to-severe AD, dupilumab ± concomitant topical corticosteroids (TCS) significantly improved disease-severity and health-related quality of life until 16-and 52 weeks.[1-4] The most recent phase-3 open-label extension study showed that dupilumab treatment was effective and well-tolerated up to 76 weeks.[5]

Data derived from daily-practice provides important information, in addition to data from clinical trials, since there may be considerable differences in patient population and treatment conditions. Results from dupilumab treatment in daily practice shows clinically relevant improvement of physician-reported outcome-measures and patient-reported outcome measures after 3-6 months, which is in line with data from clinical trials.[6-8] The proportion of patients developing conjunctivitis during dupilumab treatment was higher in daily practice (34-38%) compared to previous phase-3 clinical trials (9-28%).[1-3, 6-8] However, real-life data on the long-term effectiveness and safety of dupilumab treatment is limited and prospective large cohort studies are scarce.[9, 10] In this prospective real-life registry study, 52-weeks effectiveness and safety of dupilumab was studied in a multi-center cohort of adult patients with treatment-refractory AD.

Methods

Study design

This prospective multicenter observational longitudinal cohort study consecutively included all adult patients who (a) started dupilumab for treatment-refractory AD, according to the criteria established by the Dutch Society of Dermatology and Venereology (NVDV) (treatment ≥4 months with ≥1 conventional systemic therapy in an adequate dose), from October 2017 to September 2018 and (b) participated in the Dutch BioDay-registry.[8] At baseline, all patients received a loading dose of dupilumab 600mg subcutaneously, followed by dupilumab 300mg every other week. Interval adjustment was allowed in case of severe side effects or insufficient response. If possible, systemic immunosuppressive treatment was discontinued before starting

dupilumab treatment. The BioDay-registry was considered as non-interventional by the local Medical Ethics Committee and collection of data was performed according to the Helsinki Declaration. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT03549416.

Patients and outcome measures

Patient characteristics were extracted from the BioDay-registry. All patients were assessed at baseline until 52 weeks of treatment. Disease severity was assessed at baseline, after 4, 16, 28, 40, and 52 weeks (maximal visit window 4 weeks) of treatment, by the Eczema Area and Severity Index (EASI: 0-72) and serum thymus and activation-regulated chemokine (TARC) levels.[11, 12] Patient-reported outcomes, including the Patient-Oriented Eczema Measure (POEM: 0-28), weekly average Numeric Rating Scale (NRS: 0-10) pruritus, Dermatology Life Quality Index (DLQI: 0-30), and generic five-dimension five-level EuroQoL scale (EQ-5D-5L: 0-5 for each dimension) were collected.[13-16] To study longitudinal improvement and course of individual patients, the proportion of patients achieving absolute cut-off scores indicating controlled disease (EASI≤7 and NRS≤4) (week 16, 28, 40 and 52) and relative changes over time (EASI-50, EASI-75, NRS≥4 points improvement from baseline) at 0/4, ≥1/4, ≥2/4, ≥3/4, and 4/4 follow-up visits were analyzed. Patients with baseline EASI<7 and NRS<4 were excluded from these analysis.

Safety

Patients were asked about side effects and medication use during every visit. Ocular side effects and ocular medication use were assessed by standardized questionnaires during every visit, and included severity of redness/itching/tearing/pain/photophobia/burning sensation/blepharitis of the eyes. In case of conjunctivitis with insufficient response to artificial tears and/or topical tacrolimus skin ointment on the eye-lids, patients were referred to an ophthalmologist for standardized examination and ophthalmological follow up. Laboratory parameters were monitored.

Statistical analysis

Clinical outcome measures were compared using the Wilcoxon signed-rank test. Missing data in patients who discontinued treatment during follow-up were imputed by last observation carried forward (LOCF) method. Statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc.) and Prism (version 7.4; GraphPad).

Results

Population

210 patients with moderate-to-severe AD were included (mean (SD) age 43.2 years (15.5); 61.4% male). The majority of patients had been previously treated with oral immunosuppressive drugs (n=208 (99.0%)) (Table 1). Two patients did not use prior oral immunosuppressive drugs because of contra-indications. Treatment with oral immunosuppressive drugs (excluding systemic corticosteroids) was discontinued in almost all patients before start of dupilumab treatment (99.5%). One patient was concomitantly treated with methotrexate (indication rheumatoid arthritis).

Table 1. Baseline characteristics

	Total (n=210)
Age (years), mean (SD)	43.2 (15.5)
Men, n (%)	129 (61.4)
Atopic diseases, n (%)	
Allergic rhinitis	145 (69.0)
Missing	4 (1.9)
Allergic asthma	124 (59.0)
Missing	4 (1.9)
Food allergy	101 (48.1)
Missing	4 (1.9)
Allergic conjunctivitis	125 (59.5)
Missing	5 (2.4)
EASI score, median (IQR)	19.0 (12.6-27.7)
IGA score, median (IQR)	3 (3.0-4.0)
Weekly average pruritus NRS, median (IQR)	7 (6.0-8.0)
POEM score, median (IQR)	20 (16.0-23.5)
DLQI score, median (IQR)	12 (8.0-18.0)
Previous use of oral immunosuppressive drugs[a], n (%)	208 (99.0)
History of ≤ 1 oral immunosuppressive drug, n (%)	100 (47.6)
History of ≥ 2 oral immusuppressive drugs, n (%)	110 (52.4)
Previous use of cyclosporine, n (%)	201 (95.7)
Previous use of methotrexate, n (%)	70 (33.3)
Previous use of azathioprine, n (%)	59 (28.0)
Previous use of mycophenolate mofetil/enteric-coated sodium, n (%)	48 (22.9)
Use of oral corticosteroids at start of dupilumab, n (%)	53 (25.2)

[a]Treatment with oral immunosuppressive drugs for ≥4 months.

Effectiveness of dupilumab treatment

Mean EASI significantly improved from baseline (19.0(IQR 12.6-27.7)) to week 16 (3.6(IQR 1.8-7.2), p<0.001) and week 52 (2.7(IQR 1.4-5.4), p<0.001). Mean percent change in EASI from baseline to week 16 was -70.0% (SD 33.2) and further improved to -76.6% (SD 30.6) in week 52 (Table 2). The proportion of patients achieving the EASI-50, EASI-75, and EASI-90 was 84.2% (n=170), 58.9% (n=119) and 21.9% (n=46) respectively at week 16 and 90.1% (n=182), 70.3% (n=142) and 34.7% (n=70) respectively at week 52 (Figure 1). Median serum TARC levels significantly decreased from baseline (2231.0 pg/ml (IQR 810.0-4747.0)) to week 16 (439.0 (IQR 241.5-766.0)) (p=<0.001) and week 52 (360.0 (IQR 226.0-559.5)) (p=<0.001).

Weekly average NRS pruritus significantly decreased from baseline (median 7.0 (IQR 6.0-8.0)) to week 16 (3.0 (IQR 1.3-4.0)) (p=<0.001) and week 52 (2.0 (IQR 1.0-5.0)) (p=<0.001). A ≥4 point reduction in weekly average pruritus NRS was achieved by 60.2% (109/185 patients (patients with NRS<4 at baseline were excluded) at week 16 and 62.1% (110/185 patients) at week 52. DLQI score significantly decreased from baseline (median 12.0 (IQR 8.0-18.0)) to week 16 (median 3.0 (IQR 1.0-6.0) (p<0.001)) and to week 52 (median 3.0 (IQR 2.0-5.0)). POEM score significantly decreased from baseline (median 20.0 (IQR 16.0-23.5)) to week 16 (median 7.0 (IQR 3.0-11.0)) (p<0.001) and to week 52 (median 6.0 (IQR 3.0-11.0)) (p<0.001). The proportion of patients reporting "no problems" on the EQ-5D-5L pain/discomfort and anxiety/depression subscale increased from baseline (16.1% and 49.4%) to week 52 (59.8% and 72.0%).

At baseline, 53 patients (25.2%) were treated with systemic corticosteroids. Use of concomitant systemic corticosteroids was successfully tapered and discontinued in the majority of patients (Table 2). At week 52, eight patients (3.8%) were still using systemic corticosteroids; two patients due to inadequately controlled AD, three patients because of a tertiary adrenal insufficiency and three patients for the indication asthma.

Table 2. Effectiveness outcomes during dupilumab treatment in 210 patients

	Baseline	Week 4	week 16	week 28	week 40	week 52
EASI score, median (IQR)	19 (12.6-27.7)	7.5 (4.8-12.4)***	3.6 (1.8-7.2)***	3.4 (1.6-6.4)***	2.7 (1.2-6.2)***	2.7 (1.4-5.4)***
Missing	4 (1.9)	2 (1.0)	5 (2.4)	5 (2.4)	11 (5.2)	3 (1.4)
ΔEASI %, mean (SD)	-	-48.9 (37.4)	-70.0 (33.2)	-72.5 (33.0)	-75.0 (33.4)	-76.6 (30.6)
EASI-50, n (%)	-	125 (61.3)	170 (84.2)	175 (87.1)	173 (89.2)	182 (90.1)
Missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-75, n (%)	-	42 (20.6)	119 (58.9)	131 (65.2)	132 (68.0)	142 (70.3)
Missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-90, n (%)	-	6 (2.9)	46 (21.9)	61 (30.3)	72 (37.1)	70 (34.7)
Missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
Controlled AD (EASI≤7), n(%)	15 (7.3)	92 (44.2)	151 (73.3)	157 (76.6)	161 (81.3)	167 (81.1)
Missing	4 (1.9)	2 (1.0)	4 (1.9)	5 (2.4)	12 (5.7)	4 (1.9)
Serum TARC levels, median (IQR)	2231.0 (810.0-4747.0)	652.0 (374.5-1164.5)***	439.0 (241.5-766.0)***	389.0 (256.5-681.5)***	410.0 (252.5-559.0)***	360.0 (226.0-559.5)***
NRS pruritus, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)***	3.0 (1.3-4.0)***	3.0 (1.0-4.0)***	3.0 (1.0-5.0)***	2.0 (1.0-5.0)***
Missing	8 (3.8)	7 (3.3)	6 (2.9)	7 (3.3)	16 (7.6)	9 (4.3)
NRS pruritus[a], ≥ 4 points, n (%)	-	75 (41.2)	109 (60.2)	109 (60.9)	107 (61.8)	110 (62.1)
Missing		3 (1.6)	4 (2.2)	6 (3.2)	12 (6.5)	8 (4.3)
NRS ≤4, n (%)	31 (15.3)	118 (58.1)	146 (71.6)	154 (76.2)	142 (74.3)	148 (75.5)
Missing	8 (3.8)	7 (3.3)	6 (2.9)	8 (3.8)	19 (9)	14 (6.7)

[a]n=185

Table 2 (continued). Effectiveness outcomes during dupilumab treatment in 210 patients

	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52
DLQI score, median (IQR)	12.0 (8.0-18.0)	-	3.0 (1.0-6.0)***	-	-	3.0 (2.0-5.0)***
Missing	10 (4.8)	-	8 (3.8)	-	-	24 (11.4)
DLQI, ≥ 4-point, n(%)[b]			155 (84.7)			145 (86.8)
Missing			3 (1.6)			19 (10.2)
DLQI≤5, n (%)	28 (14.0)		152 (75.2)			189 (97.4)
Missing	10 (4.8)		8 (3.8)			16 (7.6)
POEM score, median (IQR)	20.0(16.0-23.5)	7.0 (4.0-11.0)***	7.0 (3.0-11.0)***	6.0 (2.8-11.0)***	6.0 (2.8-11.0)***	6.0 (3.0-11.0)***
Missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	24 (11.4)	18 (8.6)
POEM, ≥ 4-point, n (%)[c]	-	173 (93.5)	166 (87.4)	163 (85.8)	156 (87.2)	161 (87.5)
Missing		15 (7.5)	10 (5.0)	10 (5.0)	21 (10.5)	16 (8.0)
ΔPOEM item itch, mean (± SD)	-	-1.5 (1.4)	-1.8 (1.5)	-1.9 (1.5)	-1.9 (1.5)	-1.9 (1.5)
ΔPOEM item sleep, mean (±SD)	-	-1.5 (1.5)	-1.8 (1.6)	-1.8 (1.6)	-1.8 (1.5)	-1.9 (1.6)
POEM≤7, n (%)	7 (3.5)	108 (56.5)	99 (50.0)	110 (55.6)	99 (53.5)	111 (57.5)
Missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	25 (11.9)	17 (8.1)
EQ-5D item pain/discomfort: 'no problem', n(%)	32 (16.1)	-	-	-	-	113 (59.8)
Missing	11 (5.2)	-	-	-	-	21 (10.0)
EQ-5D anxiety/depression: 'no problem', n (%)	86 (49.4)	-	-	-	-	136 (72.0)
Missing	10 (4.8)					21 (10.0)
Concomitant use of systemic prednisone, n (%)	53 (25.2)	24 (11.4)	11 (5.2)	12 (5.7)	11 (5.2)	8 (3.8)

[b](n=186), [c](n=200). Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. *, **, *** = p< 0.05,p < 0.01, p< 0.001 to baseline. Missing data in patients who discontinued dupilumab treatment during follow-up were imputed by last observation carried forward (LOCF) method.

Longitudinal effectiveness of dupilumab treatment

EASI≤7 was achieved at all (4/4) follow up visits by 100/190 (52.6%), at ≥3/4 visits by 146/190 (76.8%), at ≥2/4 visits by 164 (86.3%), at ≥1/4 by 173/190 (86.3%) and at 0/4 visits by 17/190 (8.9%) of patients (Figure 1). NRS≤4 was achieved at 4/4 visits by 77/170 (45.3%), at ≥3/4 visits by 112/170 (65.9%), at ≥2/4 visits by 136/170 (80.0%), at ≥1/4 visits by 146/170 (85.9%) and at 0/4 visits by 24/170 (14.1%) patients.

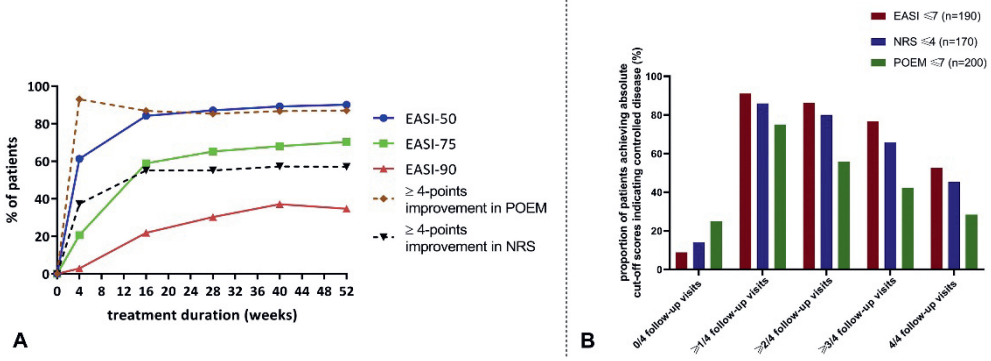


Figure 1. Clinician-reported outcomes, patient-reported outcomes and longitudinal treatment effect of dupilumab

A: Relative changes over time in clinician-reported outcomes and patient-reported outcomes during dupilumab treatment (n=210). B: Longitudinal treatment effect was evaluated by the proportion of patients achieving absolute cut-off scores indicating controlled disease.

Patients with baseline EASI<7, NRS<4 and POEM<7 were excluded from these analysis. EASI, Eczema Area and Severity Index; SD, standard deviation; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; EASI-90, ≥90% improvement in EASI score; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure.

Side effects

The most common observed side effect was conjunctivitis in 34.1% (n=72) (Table 3). Fourteen patients (6.6%) were diagnosed with mild conjunctivitis defined as signs and symptoms that could be controlled with artificial tears, antihistamine eye drops, or topical treatment with anti-inflammatory ointment on the eyelids. Patients were diagnosed with moderate-to-severe conjunctivitis if treatment with ocular anti-inflammatory therapy was prescribed by an ophthalmologist (n=58 (27.5%)). Conjunctivitis during dupilumab treatment was associated with significantly higher EASI scores (p=0.004) and serum TARC levels (p=0.045) at baseline; there were no other predictive factors (Supplementary Table 1).

Other reported side effects included headache (n=20, 9.4%), muscle or joint pain (n=16, 7.6%), fatigue (n=10, 4.7%), gastro-intestinal complaints (n=10, 4.7%), injection-site reaction (n=7, 3.3%), hair loss (n=6, 2.8%), and red face (n=6, 2.8%). The proportion of patients with blood eosinophilia (≥0.45 × 10 × 9/L) increased from baseline (n=67, 33.0%) to week 16 (n=108, 54.5%) and then decreased (n=72, 40.2%) at week 52. No other clinically significant changes in laboratory parameters were observed during dupilumab treatment.

Table 3. Side effects during dupilumab treatment in 210 patients

Number of patients with	**n (%)**
Headache	20 (9.4)
Muscle or joint pain	16 (7.6)
Fatigue	10 (4.7)
Gastro-intestinal complaints	10 (4.7)
Injection-site reaction	7 (3.3)
Hair loss	6 (2.8)
Facial redness	6 (2.8)
Herpes Simplex	3 (1.4)
Herpes Zoster	1 (0.5)
Nasopharyngitis	1 (0.5)
Skin infection	1 (0.5)
Conjunctivitis	72 (34.1)
Mild conjunctivitis	14 (6.6)
Moderate-severe conjunctivitis (treated with anti-inflammatory eyedrops/ointment)	58 (27.5)
Eosinophilia (≥0.45×10x9/L)	
Baseline	67 (33.0)
4 weeks	96 (47.5)
16 weeks	108 (54.5)
28 weeks	89 (46.4)
40 weeks	82 (45.3)
52 weeks	72 (40.2)

Dupilumab dose adjustment

Dupilumab interval was prolonged in 12 patients (7.0%) because of side effects (300mg/3 weeks: n=8 (3.8%); 300mg/4 weeks: n=4 (1.9%)). In 10/12 patients dupilumab interval was prolonged because of persistent conjunctivitis despite treatment with ocular anti-inflammatory therapy. In 2 patients (1.2%), dupilumab interval was prolonged because of severe muscle or joint pain. Dupilumab interval was shortened in 2 patients (300mg/week) due to ineffectiveness.

Discontinuation of dupilumab treatment

Seventeen patients (8.1%) discontinued dupilumab treatment during follow-up (Supplementary Table 2). Eight (3.8%) due to side effects of which 5 (2.4%) were due conjunctivitis during dupilumab treatment. Other side effects resulting in discontinuation of dupilumab included joint and muscle complaints (0.5%), enlargement of lymphoid cells (0.5%), and flare of rosacea (0.5%). Nine patients (4.3%) discontinued dupilumab treatment because of ineffectiveness.

Discussion

In this prospective observational 52-week study, data on long-term effectiveness and safety during dupilumab treatment in patients with moderate-to-severe AD in a real-life setting are presented. Clinical outcome measures rapidly improved in the first 16 weeks of treatment with dupilumab and further improved until week 52. Overall, dupilumab was well tolerated with only 3.8% of patients discontinuing treatment due to side effects. However, 34% of the patients were diagnosed with new onset or worsening of conjunctivitis during dupilumab treatment.

Physician- and patient-reported outcomes at week 16 are consistent with those reported in previous phase-3 clinical trials and daily practice studies.[1-3, 6-8, 17] Concerning long-term outcome, the effectiveness in our daily practice study is comparable with clinical outcomes of the 52-week randomized, double-blinded, placebo-controlled, phase-3 study (LIBERTY AD CHRONOS).[1] In contrast to CHRONOS, nearly all clinical outcome measures, further improved after 16 weeks in the current study. Patients included in CHRONOS had a higher median (IQR) baseline EASI score (29.6 (22.2–40.8)) compared to the patients included in this study (19.0 (12.6-27.7)) which can be explained by the wash-out period of oral immunosuppressive drugs and TCS before the start of dupilumab in CHRONOS. In our study, follow-up visits were performed by specialized physicians and nurses paying specific and particular attention to adequate use of TCS and compliance. This might explain the slightly better performance of this daily practice cohort compared to CHRONOS.

A recently published retrospective study including 52 patients treated with dupilumab in daily practice evaluated the long-term (52-weeks) efficacy, safety and reasons for discontinuation.[9] At week 52, 54% (n=28) achieved the primary outcome of IGA 0/1 (clear-almost clear); 46% of patients were defined as 'non-responders', although dupilumab treatment was continued in these patients because of

significant improvement in quality of life, pruritus and sleep. Bosma et al. published an prospective cohort study including 221 patients treated with dupilumab in daily practice.[10] Linear mixed models were used, as not all patients reached the long-term endpoints. The models showed similar results in clinical outcome measures compared to our study. After starting dupilumab treatment, 46.6% of the patients continued treatment with conventional systemic therapy, which makes the interpretation of the effectiveness of dupilumab difficult in this bridging phase. In our study we preferred discontinuation of systemic immunosuppressive drugs to evaluate effectiveness of dupilumab in the first weeks of treatment. To avoid exacerbations despite intensive treatment with topical steroids, short courses systemic steroids were used in some patients before starting dupilumab treatment. As the number of patients using this recuse medication was rather small and the treatment period in most patients was short, this might not have large impact on our results.

This study found low discontinuation rates of dupilumab treatment after 52 weeks (8.1%), mostly due to side effects (3.8%) and ineffectiveness (4.3%). This percentage of discontinuation is slightly lower compared to the retrospective daily practice study of Jo et al. (12%) and comparable with the discontinuation rate in the study of Bosma et al. (6.1%).[9, 10] In CHRONOS, discontinuation due to adverse events was reported in 2% of patients treated with dupilumab every-other-week + TCS (n=110) at week 52.[1] Long-term effectiveness and safety data of conventional systemic immunosuppressive drugs in AD show high discontinuation rates- up to 50% - in daily practice after 1 year due to side effects and ineffectiveness.[18-20] The low discontinuation rate of dupilumab in the current study, despite the relatively high rate of conjunctivitis, might be explained by the intensive and protocolled ophthalmological care and the lack of alternative treatment options, as most patients had already failed multiple oral immunosuppressive treatments.

In this study cohort, 34% of the patients were diagnosed with conjunctivitis. Literature on patients treated with dupilumab in daily practice shows incidences of conjunctivitis up to 38% which is higher compared to clinical trials.[6-8, 21] Higher conjunctivitis rates during daily practice treatment with dupilumab can be explained by an increased awareness, but can also be related to the differences in AD severity at baseline. The patient population treated with dupilumab shortly after market access represents a rather severe AD population. In this study, conjunctivitis during dupilumab treatment was associated with significantly higher EASI baseline scores

and serum TARC levels, which is in accordance with the clinical trials data. In contrast to trial data, conjunctivitis was not associated with history of conjunctivitis in this study. Despite the fact that moderate-to-severe conjunctivitis, indicated for ocular anti-inflammatory treatment, was observed in 58 (27.5%) patients, dupilumab was discontinued in only 5 (2.4%) patients. The other patients were able to continue dupilumab treatment, but remained dependent on ocular anti-inflammatory treatment. The pathogenesis of dupilumab related conjunctivitis is still unknown. Notably, in asthma and nasal polyp patients, dupilumab treatment was not associated with higher conjunctivitis rates compared to placebo treated patients.[22] It is therefore likely that AD-specific factors contribute to the higher prevalence of conjunctivitis in AD during dupilumab treatment. As ocular comorbidities are highly prevalent in patients with AD compared to the general population, it is possible that pre-existing ocular comorbidities predispose to higher conjunctivitis rates in AD patients during dupilumab.[23] Previously, we described a remarkable scarcity of conjunctival goblet cells and an extensive cellular infiltrate, mainly existing of CD4+ T-cells in the conjunctival stroma, in 6 patients with conjunctivitis during dupilumab.[24]

Comparable with clinical trials, we observed a asymptomatic and transient eosinophilia during dupilumab treatment, which was independent of concomitant treatment with systemic corticosteroids.[1-3, 25-27] The increase of eosinophil levels in the peripheral blood is consistent with the hypothesis that blockage of IL-4 and IL-13 inhibits the production of eotaxins and migration of eosinophils into tissue, but does not inhibit the production and migration from the bone marrow. This mechanism results in a transient increase in circulating eosinophils. Recently, we demonstrated that serum concentrations of eotaxin-1 and eotaxin-3 chemokines significantly decreased during dupilumab treatment.[8] In addition, previous studies in patients with chronic rhinosinusitis patients showed that dupilumab decreased eotaxin-2 and eotaxin-3 levels locally in nasal polyp tissue, nasal secretion, and serum.[25, 28]

Several limitations result from the daily practice setting of this study. Due to the lack of a control group and observational design, factors of bias may have been induced. Additionally, due to the lack of an ophthalmological examination before starting dupilumab treatment, pre-existing specific signs and symptoms of conjunctivitis could not be determined.

In conclusion, this observational 52-week daily-practice study showed long-term effectiveness in a large cohort of treatment-refractory AD patients. Treatment with dupilumab resulted in a rapid improvement of all clinical outcome measures in the first 16 weeks of treatment, and clinical effectiveness was sustained or even improved during the total 52-week follow-up period. A limited number of patients (17 (8.1%)) discontinued dupilumab treatment, with only 8 patients (3.8%) discontinuing dupilumab treatment due to side effects, and 9 (4.3%) due to ineffectiveness. In this study, conjunctivitis was the most common side effect, but this rarely resulted in discontinuation of dupilumab treatment. Future daily practice data derived from the BioDay registry will provide further important information on the long-term effectiveness and safety of dupilumab treatment.

References

1. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. **389**(10086): p. 2287-2303.
2. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ).* British Journal of Dermatology: p. n/a-n/a.
3. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
4. Simpson, E.L., et al., *Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatol, 2019.
5. Deleuran, M., et al., *Dupilumab shows long-term safety and efficacy in moderate-to-severe atopic dermatitis patients enrolled in a phase 3 open-label extension study.* J Am Acad Dermatol, 2019.
6. Faiz, S., et al., *Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort.* J Am Acad Dermatol, 2019.
7. de Wijs, L.E.M., et al., *Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data.* Br J Dermatol, 2019.
8. Ariens, L.F., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2019.
9. Jo, C.E., et al., *Evaluation of long-term efficacy, safety, and reasons for discontinuation of dupilumab for moderate-to-severe atopic dermatitis in clinical practice: A retrospective cohort study.* J Am Acad Dermatol, 2020.
10. Bosma, A.L., et al., *Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry.* J Am Acad Dermatol, 2020.
11. Hanifin, J.M., et al., *The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group.* Exp Dermatol, 2001. **10**(1): p. 11-8.
12. Imai, T., et al., *Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine.* Int Immunol, 1999. **11**(1): p. 81-8.
13. Yosipovitch, G., et al., *Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis.* Br J Dermatol, 2019. **181**(4): p. 761-769.
14. Charman, C.R., A.J. Venn, and H.C. Williams, *The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective.* Arch Dermatol, 2004. **140**(12): p. 1513-9.
15. Finlay, A.Y. and G.K. Khan, *Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use.* Clin Exp Dermatol, 1994. **19**(3): p. 210-6.
16. Vilsboll, A.W., et al., *Mapping Dermatology Life Quality Index (DLQI) scores to EQ-5D utility scores using data of patients with atopic dermatitis from the National Health and Wellness Study.* Qual Life Res, 2020.

17. de Wijs, L.E.M., et al., *Acute arthritis and arthralgia as an adverse drug reaction to dupilumab.* Clin Exp Dermatol, 2019.
18. van der Schaft, J., et al., *Drug survival for azathioprine and enteric-coated mycophenolate sodium in a long-term daily practice cohort of adult patients with atopic dermatitis.* Br J Dermatol, 2016. **175**(1): p. 199-202.
19. van der Schaft, J., et al., *Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis.* Br J Dermatol, 2015. **172**(6): p. 1621-7.
20. Politiek, K., et al., *Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis.* Br J Dermatol, 2016. **174**(1): p. 201-3.
21. Olesen, C.M., et al., *Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre.* J Eur Acad Dermatol Venereol, 2019. **33**(8): p. 1562-1568.
22. Akinlade, B., et al., *Conjunctivitis in dupilumab clinical trials.* Br J Dermatol, 2019. **181**(3): p. 459-473.
23. Govind, K., et al., *Atopic dermatitis is associated with increased prevalence of multiple ocular comorbidities.* J Allergy Clin Immunol Pract, 2019. **7**(1): p. 298-299.
24. Bakker, D.S., et al., *Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis.* Br J Dermatol, 2019. **180**(5): p. 1248-1249.
25. Bachert, C., et al., *Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial.* JAMA, 2016. **315**(5): p. 469-79.
26. Busse, W.W., et al., *Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma.* Adv Ther, 2018.
27. Castro, M., et al., *Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma.* N Engl J Med, 2018. **378**(26): p. 2486-2496.
28. Jonstam, K., et al., *Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis.* Allergy, 2018.

Supplement

Supplementary Table 1. Baseline characteristics in patients with and without conjunctivitis at week 52

	Conjunctivitis at week 52		P-value
	Yes (n=72)	No (n=138)	
Age (years), mean (SD)	42.2 (14.3)	43.2 (16.2)	0.998
Men, n (%)	45 (62.5)	84 (60.9)	0.818
Atopic disease, n (%)			
Allergic rhinitis	51 (70.8)	94 (68.1)	0.876
Asthma	46 (63.9)	78 (56.5)	0.573
Food allergy	41 (56.9)	60 (43.5)	0.177
Conjunctivitis	47 (65.3)	78 (56.5)	0.413
Baseline EASI score, median (IQR)	23.4 (14.4-31.9)	17.7 (11.5-26.9)	0.004
Blood eosinophilia (≥0.45×10x9/L) at screening, n (%)	19 (26.3)	48 (34.8)	0.221
Serum TARC level (pg/ml) at baseline, median (IQR)	2890 (1406-6007)	2022 (748-4709)	0.045

Supplementary Table 2. Reasons for discontinuation of dupilumab treatment

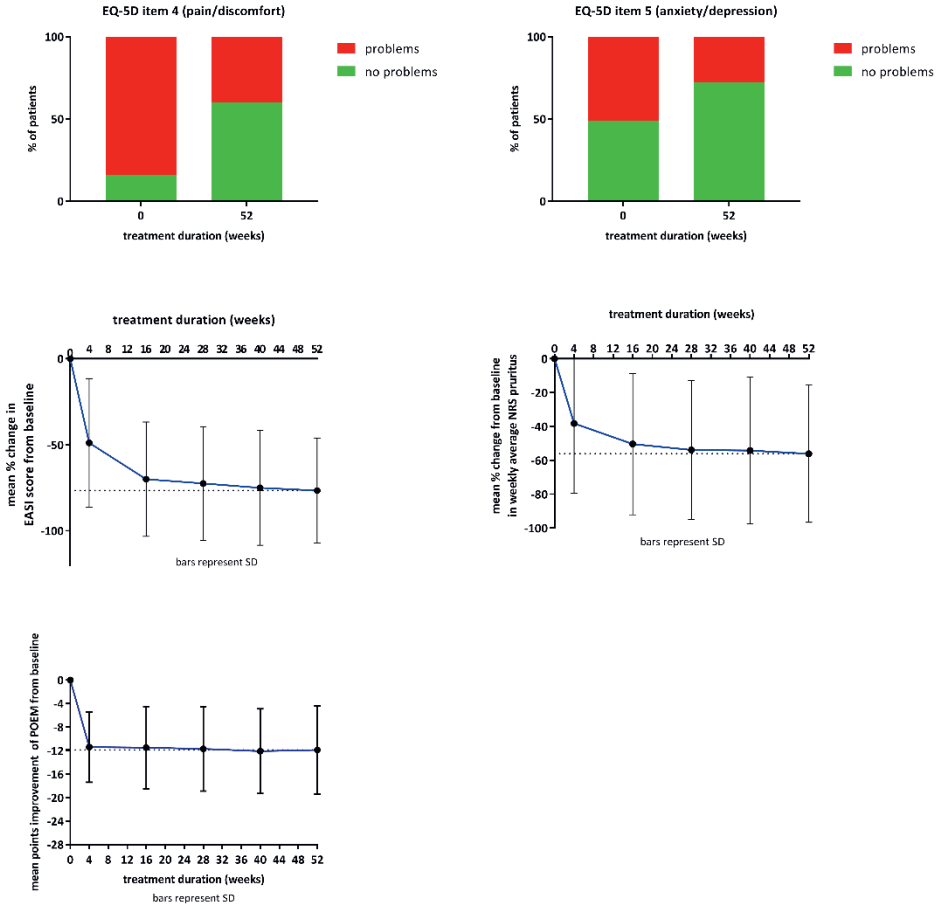
Discontinuation of dupilumab treatment[a], n (%)	17 (8.1)
Side effects, n (%)	8 (3.8)
Conjunctivitis	5 (2.4)
Joint and muscle complaints	1 (0.5)
Enlargement of lymphoid cells[b]	1 (0.5)
Rosacea flare	1 (0.5)
Ineffectiveness, n (%)	9 (4.3)

[a]Multiple reasons for discontinuation per patient; [b]Abnormalities in total blood count were present before starting dupilumab treatment. Dupilumab treatment was discontinued due to persistent enlargement of lymphoid cells and the suspicion of cutaneous t-cell lymphoma. Additional diagnostic tests showed a monoclonal t-cell population but no indication of cutaneous t cell lymphoma.

Supplementary Table 3. Effectiveness outcomes during dupilumab treatment in 138 patients without concomitant use of systemic corticosteroids

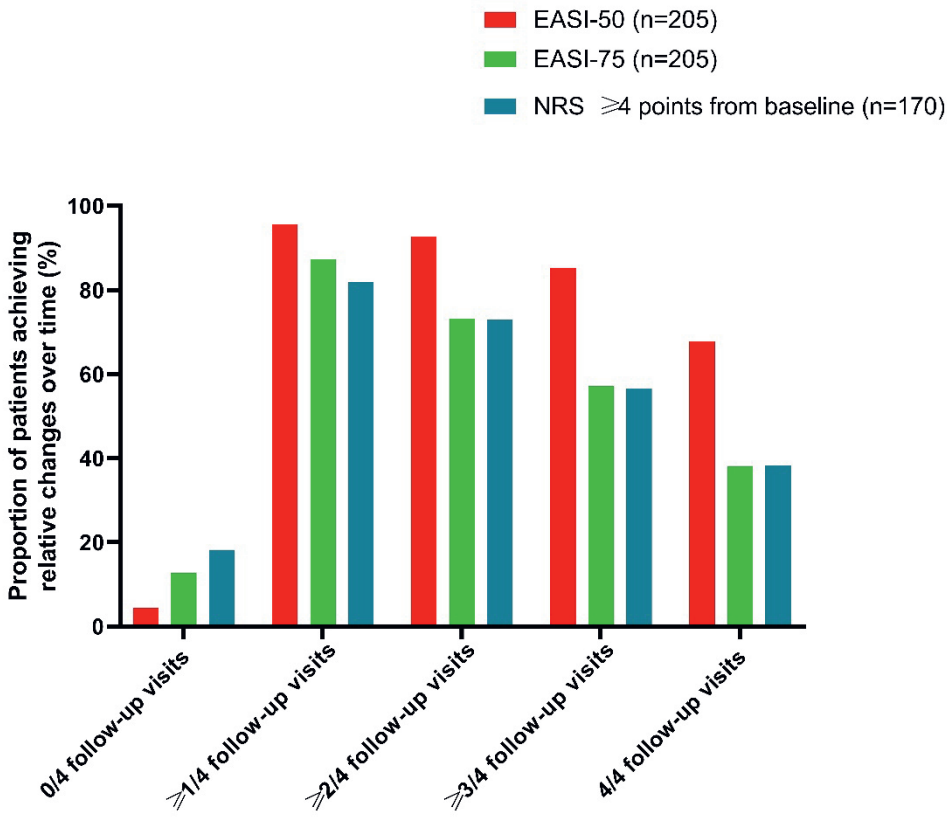
	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52
EASI score, median (IQR)	19.5 (14.17.3)	7.5 (4.8-2.3)*	3.5 (1.6-6.8)*	3.2 (1.6-6.2)*	2.4 (0.9-5.4)*	2.4 (1.4-5.4)*
ΔEASI %, mean (SD)	-	-51.2 (37.2)	-73.2 (29.4)	-76.7 (28.3)	-79.1 (29.8)	-79.1 (27.7)
EASI-50, n (%)	-	97 (64.7)	130 (88.4)	133 (91.1)	133 (93.0)	141 (94.0)
EASI-75, n (%)	-	34 (22.7)	92 (62.6)	103 (70.5)	108 (75.5)	108 (72.0)
EASI-90, n (%)	-	5 (3.3)	36 (24.5)	51 (34.9)	61 (42.7)	58 (38.7)
NRS pruritus, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)*	3.0 (2.0-4.0)*	3.0 (1.0-4.0)*	3.0 (1.0-4.0)*	2.0 (1.0-5.0)*
DLQI score, median (IQR)	11.0 (8.0-17.0)	-	3.0 (1.0-5.5)*	-	-	3.0 (2.0-5.0)*
POEM score, median (IQR),	20.0 (16.0-24.0)	7.0 (4.0-12.0)*	8.0 (3.0-12.0)*	6.0 (3.0-11.0)*	6.0 (3.0-11.0)*	6.0 (3.0-11.0)*

Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. *P < 0.05 compared to baseline. Missing data in patients who discontinued dupilumab treatment during follow-up were imputed by last observation carried forward (LOCF) method.



Supplementary Figure 1. Clinician-reported outcomes and patient-reported outcomes during treatment with dupilumab.

Clinician-reported outcomes and patient-reported outcomes during dupilumab treatment were measured in 210 patients. EASI, Eczema Area and Severity Index; SD, standard deviation; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; EQ-5D-5L, five-dimension five-level EuroQoL scale.



Supplementary Figure 2. The proportion of patients achieving relative changes over time (EASI-50, EASI-75 and NRS≥ 4 points improvement from baseline) at 0/4, ≥1/4, ≥2/4, ≥3/4, and 4/4 follow-up visits.

This figure demonstrates the proportion of patients achieving relative changes over time to study the longitudinal treatment effect of dupilumab. EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; NRS, numeric rating scale.

3

Eczema control and treatment satisfaction in atopic dermatitis patients treated with dupilumab a cross-sectional study from the BioDay registry

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Abstract

Background: Eczema control is a new construct to be measured in atopic dermatitis (AD).

Objectives: Measuring patient-perceived eczema control and treatment satisfaction in AD patients, treated with dupilumab between 16 and 52 weeks.

Methods: Cross-sectional questionnaire study. Patients from the Dutch BioDay registry completed the Atopic Dermatitis Control Test (ADCT), Recap of Atopic Eczema (RECAP) and Treatment Satisfaction Questionnaire for Medication, Version II (TSQM v. II), along with other Patient Reported Outcome Measures (PROMs).

Results: 104/157 patients responded (response rate 66.2%). Median ADCT score was 4 (interquartile range [IQR] 5); median RECAP score was 5 (IQR 6); median TSQM v.II global satisfaction score was 83.3 (IQR 25.0). According to the ADCT, 38.5 – 66.3% perceived their AD was 'in control', depending on the interpretability method used. Minimally clinically important difference (MCID) of ≥ 4 points for the DLQI and POEM was achieved respectively in N=66 (84.6%) and N=63 (78.8%) patients.

Conclusion: When considering the favourable scores on other PROMs and the TSQM v. II, and comparing these to the relatively low percentage of patients perceiving control according to the ADCT, interpretability of eczema control still appears difficult. Treatment satisfaction in the studied cohort was high.

Introduction

Atopic dermatitis (AD) is one of the most common chronic and relapsing inflammatory skin diseases worldwide.[1] Because of the relapsing nature of AD, single or even repeated measures of disease severity or quality of life assessments may not be representative for 'control' of the disease. The Harmonizing Outcome Measures for Eczema (HOME) initiative explored the feasibility and acceptability of different ways to measure eczema control.[2] Therefore, two new Patient-reported outcome measures (PROM's) were developed, the Recap of atopic eczema (RECAP) questionnaire[3] and the Atopic Dermatitis Control Tool (ADCT).[4, 5]

Recent results from the BioDay registry on dupilumab treatment for AD patients in daily practice show a clinically relevant improvement of physician-reported outcome measures and patient-reported outcome measures after 3-12 months.[6, 7] Currently, there are no data on the use of the new tools measuring eczema control, ADCT and RECAP, in daily practice. Therefore, we primarily aimed to assess eczema control in patients participating in the BioDay registry by using the ADCT and RECAP. A secondary aim was to assess treatment satisfaction with dupilumab.

Methods

Study design, population and recruitment

This was a cross-sectional study carried out in patients who participate in the BioDay registry.[6] The BioDay registry is a prospective multicentre registry in which patients treated with new systemic treatments for AD in daily practice are included. For this cross-sectional study, data collection was carried out between April 10, 2020 and May 8, 2020. Patients (aged ≥ 18 years) who had been treated with dupilumab were eligible for the current study when they had been treated between 16 and 52 weeks at inclusion. This group was included because a steady state concentration of dupilumab from 16 weeks has been reported.[7, 8] On the 10th of April 2020, a digital questionnaire was sent to eligible patients, using Castor Electronic Data Capture. Two weeks later, a reminder was sent. The data were locked another two weeks later. The BioDay registry was reviewed and approved by the Medical Ethical Review Board of the University Medical Center Utrecht (METC 18/239 and 19/240).

Measurements

Demographics, severity data and PROMs collected during regular BioDay visits were used in this study, as recommended by the HOME initiative,[9] including: Eczema Area and Severity Index (EASI)[10]; Investigator Global Assessment (IGA) (range 0-5: clear, almost clear, mild, moderate, severe, very severe); Dermatology Life Quality Index (DLQI); weekly average Numerical Rating Scale (NRS) pruritus/pain (range 0-10); and Patient Oriented Eczema Measure (POEM)[11]. For an approximation of disease status at the moment of questionnaire completion, PROM data from the closest regular visit (± max. 8 weeks) in the BioDay registry were used.

Atopic Dermatitis Control Test (ADCT)

The ADCT is a validated PROM designed to assess patient-perceived control of AD in adults. It is found to have good-to-excellent content validity, construct validity, internal consistency, reliability and discriminating ability in patients with AD; as well as in a group of patients treated with dupilumab for AD.[4, 5] It is translated to Dutch.15 The ADCT includes six items with a 7-day recall period. Each item is scored from 0 (none) to 4 (extreme), with a total score of 0-24. Lower scores indicate a higher perceived control of disease. There are three methods to identify patients 'in control' and 'not in control'. For the first method, a total score of 7 or more points (derived by adding up item scores) was identified as an optimum threshold to identify patients whose AD is 'not in control'. The second and third method equally produced the highest sensitivity (0.96) and acceptable level of specificity (0.68). They are based on answering a single item above a certain threshold: one out of all six items (method 2) or one out of the first four items (method 3).[4, 12]

Recap of Atopic Eczema (RECAP)

The RECAP is a validated PROM designed to capture 'eczema control' over the past week. It includes 7 questions. Each of the questions carry equal weight and is scored from 0 to 4 (total score of 0-28), with lower scores indicating higher control.3 The RECAP has no validated cut-off scores to determine eczema control. The instrument has been translated to Dutch.[3]

Additional question

The ADCT and RECAP measure a comparable construct (eczema control). To identify patient preference, patients were asked the (global) question which of both questionnaire they preferred.

Treatment Satisfaction Questionnaire for Medication, Version II (TSQM v. II)

The TSQM was designed as a measure for treatment satisfaction with medication and was later methodologically refined into a shorter, more consistently worded version, the TSQM v. II. It includes 11 questions covering four dimensions: effectiveness, side effects, convenience, and global satisfaction. Items have varying amounts of response options. Scores ranging from 0-100 are calculated for each dimension, with higher scores indicating more satisfaction.[13]

Statistical analysis

The design of the digital questionnaire allowed for missing data. Missing data were handled in agreement with instructions by the questionnaire designers. For the RECAP and TSQM v. II missing values are allowed to a certain extent; for the ADCT missing values are not allowed.[3, 13] Due to the coronavirus disease 2019 (COVID-19) pandemic, several BioDay visits were not conducted, leading to missing values for clinical scores and PROMs.

Results

Sample characteristics

A total of 157 patients were included, with a response rate of 66.2% (N=104). Non-responder analysis showed that non-responders were significantly younger (median 46 vs 33 years) and had a significantly higher EASI score at baseline (median 12.6 vs 14.0). PROMs did not differ significantly at baseline. Ten potential eligible patients had discontinued dupilumab prior to the current study (reason of discontinuation: side effects (n=4), ineffectiveness (n=3), personal reasons (n=3)). See Table 1 for basic characteristics.

Table 1. Basic characteristics of total study population.

	n = 104
Men, n (%)	58 (55.8)
Age at questionnaire completion (y)	
Median (IQR)	46 (24.5)
Mean (SD)	46.1 (16.4)
EASI score at baseline	
Median (IQR)	12.6 (8.5)
Mean (SD)	14.1 (8.6)
Missing, n (%)	6 (5.8)
IGA score at baseline	
Median (IQR)	3 (1)
Mean (SD)	3.0 (0.8)
Missing, n (%)	1 (1.0)
DLQI score at baseline	
Median (IQR)	13 (9)
Mean (SD)	12.9 (6.9)
Missing, n (%)	5 (4.8)
POEM score at baseline	
Median (IQR)	20 (9)
Mean (SD)	19.0 (6.6)
Missing, n (%)	3 (2.9)
Weekly average pruritus NRS at baseline	
Median (IQR)	7 (2)
Mean (SD)	6.6 (2.4)
Missing, n (%)	1 (1.0)
Weekly average pain NRS at baseline	
Median (IQR)	2 (5)
Mean (SD)	3.3 (3.0)
Missing, n (%)	1 (1.0)
Atopic diseases at baseline, n (%)	
Allergic rhinitis	61 (58.7)
Asthma	53 (51.0)
Allergic conjunctivitis	58 (55.8)
Food allergy	42 (40.4)
History of ≥2 oral immunosuppressive treatments at baseline, n (%)	54 (51.9)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; SD, standard deviation.

Eczema control

Median reported values for eczema control were 4 for ADCT and 5 for RECAP. All PROMs measured within a maximum time of 8 weeks of these values differed significantly from baseline. See Table 2. The minimally clinically important difference (MCID) of ≥ 4 points for the DLQI and POEM was achieved respectively in 66 (84.6% of patients without missing values) and 63 (78.8% of patients without missing values)

patients. For ADCT, 66% of patients were 'in control' according to the first method. According to the second and third method, this number dropped to around 40% (Table 3). When asked which questionnaire was favoured by patients, 11% chose ADCT and 9% RECAP; 80% of patients indicated no preference.

Treatment satisfaction

Median global satisfaction score was 83.3 (see Table 2 and Figure 1). Notably, the median score for the side effects was 100%.

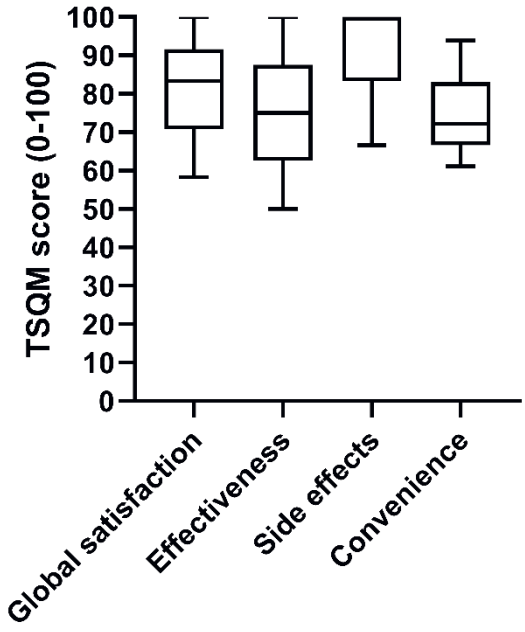

Figure 1. Treatment Satisfaction Questionnaire for Medication (TSQM) measures for dupilumab in daily practice.

Whiskers represent 10–90th percentiles.

Table 2. ADCT, RECAP and TSQM v.II values, and closest reported Patient Reported Outcome Measures.

	Total (n = 104)
ADCT score	
Median (IQR)	4 (5)
Mean (SD)	5.1 (3.7)
Missing, n (%)	7 (6.7)
RECAP score	
Median (IQR)	5 (6)
Mean (SD)	6.5 (4.7)
Missing, n (%)	5 (4.8)
TSQM v.II global satisfaction score	
Median (IQR)	83.3 (25.0)
Mean (SD)	78.9 (16.8)
Missing, n (%)	15 (14.4)
TSQM v.II effectiveness satisfaction score	
Median (IQR)	75.0 (16.7)
Mean (SD)	72.8 (20.8)
Missing, n (%)	3 (2.9)
TSQM v.II side effects satisfaction score	
Median (IQR)	100.0 (8.3)
Mean (SD)	90.9 (17.0)
Missing, n (%)	10 (9.6)
TSQM v.II convenience satisfaction score	
Median (IQR)	72.2 (16.7)
Mean (SD)	73.4 (14.7)
Missing, n (%)	12 (11.5)
Closest DLQI score	
Median (IQR)	3 (4.3)
Mean (SD)	4.1 (4.0)
Missing, n (%)	22 (21.2)
Closest POEM score	
Median (IQR)	7 (8.3)
Mean (SD)	8.5 (5.8)
Missing, n (%)	22 (21.2)
Closest weekly average pruritus NRS	
Median (IQR)	2 (3)
Mean (SD)	3.0 (2.0)
Missing, n (%)	17 (16.3)
Closest weekly average pain NRS	
Median (IQR)	0 (2)
Mean (SD)	1.1 (1.6)
Missing, n (%)	17 (16.3)

ADCT, Atopic Dermatitis Control Test; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, Numerical Rating Scale; POEM, Patient Oriented Eczema Measure; RECAP, Recap of Atopic Eczema; SD, standard deviation.

Table 3. Control according to the Atopic Dermatitis Control Tool (ADCT)

	ADCT method[1a]	ADCT method[2b]	ADCT method[3c]
In control, n (%)	69 (66.3)	40 (38.5)	42 (40.4)
Not in control, n (%)	28 (26.9)	57 (54.8)	55 (52.9)
Missing, n (%)	7 (6.7)		

Not in control: [1a]Total score on the 6 items is ≥ 7 points; [2b]One of the 6 answers is: v1 ≥ Moderate; v2 ≥ 3-4 days; v3 ≥ Moderate v4 ≥ 1 or 2 nights; v5 ≥ Moderate; v6 ≥ Moderate; [3c]One of the 4 first answers is: v1 ≥ Moderate; v2 ≥ 3-4 days; v3 ≥ Moderate; v4 ≥ 1 or 2 nights.

Discussion

In this study, between 38.5 and 66.3% of patients, using dupilumab between 16 and 52 weeks, perceived their AD as 'in control'. Treatment satisfaction of this cohort was high.

The current study showed a relatively high percentage of patients 'not in control' according to the ADCT. Taking into consideration the significant improvement from baseline for signs, symptoms and various PROMs, seen in previous studies from the BioDay registry[6, 7] resulting in low scores on these instruments after 16-52 weeks, the cut-off for 'not in control' may be too strict. In a validation paper, the interpretation of the ADCT was assessed using a patient global assessment scale as a reference. Patients indicating their AD was 'not at all controlled', 'a little controlled' or 'moderately controlled', were all categorized as being 'not in control' according to the ADCT.[4] Using the current binary cut-off values, along with the three different analysing methods, the use of the ADCT in daily practice may lead to premature discontinuation or change of treatment. Moreover, as patient perceived eczema control is an individual experience, it would be beneficial to investigate the MCID rather than a binary cut-off point for control regarding the ADCT. Future research is definitely needed.

In the current study, values for ADCT and RECAP were similar. However, no interpretability studies have been performed for the RECAP, which impedes the current interpretation of the RECAP in clinical practice and its comparison to the ADCT. It will be interesting to see how interpretability studies on the RECAP will produce values for patients perceiving their AD to be 'in control', and how this will relate to ADCT values.

The reported values for treatment satisfaction are on the higher end of the spectrum. In a large real-world study in patients on systemic therapy for AD, TSQM v.II values tended to be lower in all domains.[14] Especially the side effects satisfaction score stands out with a median of 100. A possible explanation for this is probably that many patients have had multiple treatment failures before starting dupilumab. Therefore, when treated with dupilumab, patients may trivialize their side effects if they perceive a high satisfaction regarding effectiveness of the treatment. However, a proper interpretation of the values reported here is not entirely possible due to the lack of interpretability studies for the TSQM v.II.

A limitation to our study is that the COVID pandemic resulted in various missing values. Furthermore, its cross-sectional design makes it impossible to compare the ADCT, RECAP and TSQM v.II with values at baseline or other time points. Longitudinal studies are needed.

In conclusion, our study shows that the interpretability of the ADCT and RECAP regarding eczema control and its applicability in clinical decision making may benefit from further investigation. Treatment satisfaction during dupilumab treatment in daily practice is high.

References

1. Silverberg, J.I., Atopic Dermatitis in Adults. Med Clin North Am, 2020. 104(1): p. 157-176.
2. Howells, L., et al., Defining and measuring 'eczema control': an international qualitative study to explore the views of those living with and treating atopic eczema. J Eur Acad Dermatol Venereol, 2019. 33(6): p. 1124-1132.
3. Howells, L.M., et al., Development and initial testing of a new instrument to measure the experience of eczema control in adults and children: Recap of atopic eczema (RECAP). Br J Dermatol, 2020. 183(3): p. 524-536.
4. Pariser, D.M., et al., Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin, 2020. 36(3): p. 367-376.
5. Simpson, E., et al., Validation of the Atopic Dermatitis Control Tool (ADCT(c)) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol, 2019. 19(1): p. 15.
6. Ariens, L.F.M., et al., Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry. Allergy, 2020. 75(1): p. 116-126.
7. Ariens, L.F.M., et al., Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry. J Am Acad Dermatol, 2021. 84(4): p. 1000-1009.
8. Blauvelt, A., et al., Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet, 2017. 389(10086): p. 2287-2303.
9. Leshem, Y.A., et al., Measuring atopic eczema symptoms in clinical practice: The first consensus statement from the Harmonising Outcome Measures for Eczema in clinical practice initiative. J Am Acad Dermatol, 2020. 82(5): p. 1181-1186.
10. Leshem, Y.A., et al., What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. Br J Dermatol, 2015. 172(5): p. 1353-7.
11. Charman, C.R., et al., Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol, 2013. 169(6): p. 1326-32.
12. Simpson, E., et al., The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. J Am Acad Dermatol, 2020. 83(3): p. 839-846.
13. Atkinson, M.J., et al., Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health, 2005. 8 Suppl 1: p. S9-S24.
14. Wei, W., et al., A real-world study evaluating adeQUacy of Existing Systemic Treatments for patients with moderate-to-severe Atopic Dermatitis (QUEST-AD): Baseline treatment patterns and unmet needs assessment. Ann Allergy Asthma Immunol, 2019. 123(4): p. 381-388 e2.

4

Two-year drug survival of dupilumab in a cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine and methotrexate: results from the BioDay registry

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To the editor,

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor subunit α (IL-4 Rα), the common subunit of the type 2 cytokines IL-4 and IL-13, blocking signaling of both cytokines, and consequently inhibiting the entire Th2 pathway.[1] Overall, the clinical efficacy and safety of dupilumab ± topical corticosteroids (TCS) have been demonstrated in several phase 3 clinical trials for the treatment of patients with moderate-severe AD.[2] In clinical trials, efficacy of dupilumab is tested under ideal circumstances in selected patients and therefore, results are not always generalizable to daily practice. Recent results from dupilumab treatment in daily practice show a clinically relevant improvement of physician-reported outcome measures and patient-reported outcome measures after 3-6 months, which is in line with data from clinical trials.[3, 4]

Drug survival is an analysis which gives a reflection of daily practice by analysing the time from initiation to discontinuation of therapy. Drug survival is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences.[5] Drug survival studies for dupilumab are scarce and studies comparing drug survival of dupilumab with conventional oral immunosuppressive drugs for AD are lacking.[6] In the current study, we primarily aim to assess the drug survival of dupilumab, and secondarily to compare drug survival of dupilumab with other oral immunosuppressive drugs (cyclosporine A (CsA) and methotrexate (MTX)) in two historical (previously published) daily practice cohorts of moderate to severe AD patients before the introduction of dupilumab.[7, 8] Patients treated with dupilumab were included in the BioDay registry, a prospective multicentre registry that contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both Quality of Life (QoL) as well as clinical parameters. Patients were treated with MTX, CsA and dupilumab according to national guidelines concerning dosage and follow-up. Drug survival was determined through Kaplan Meier survival curves, and analyzed for overall drug survival (discontinuation due to well-controlled disease; side effects [with/without ineffectiveness]; ineffectiveness [with/without side effects]; and other) for dupilumab, CsA and MTX and separately for treatment failure (ineffectiveness combined with side effects). Patients, who were using dupilumab/CsA/MTX at time of data lock or were lost to follow up, were censored. For each patient, data on treatment duration and reason for discontinuation was collected, as well as other detailed patient- and treatment characteristics.

The dupilumab cohort comprised of 402 patients (39.1% female, mean age 43.3 years) with a median dupilumab treatment duration of 15.1 (Interquartile range (IQR) 8.2-20.3) months at time of data lock (480 active treatment years) (Table 1). In the dupilumab cohort, 99.5% had a history of prior treatment with oral immunosuppressive drugs compared to 19.4% in the CsA- and 69.7% in the MTX cohort.

Table 1. Patient and treatment characteristics for treatment with dupilumab, cyclosporine A, and methotrexate

	Dupilumab	**Cyclosporine A**	**Methotrexate**
n	402	356	89
Female, n (%)	157 (39.1)	167(46.9)	36(40.4)
Age (years), mean (±SD)	43.3(15.8)	37.6(14.2)	50.1(17.3)
Treatment duration[a], median (IQR)	15.1(8.2-20.3)	7.9(3.2-14.4)	7.3(3.0-11.4)
Status of use[b], n (%)			
Active	358(89.1)	80(22.5)	37(41.6)
Discontinued	37(9.2)	258(72.4)	45(50.5)
Lost to follow up	7(1.7)	18(5.1)	7(7.9)

[a]In months; [b]Data lock two years after start treatment; dupilumab 15-12-2019; cyclosporine A 01-01-2014; methotrexate 01-02-2015

At the moment of data lock, 358 patients (89%) used dupilumab, 37 patients (9%) had discontinued dupilumab treatment and 7 patients (2%) were lost to follow-up. The most frequent reason for discontinuation of dupilumab was side effects (17 patients (4%)). Seven patients (2%) discontinued treatment because of ineffectiveness, two patients (0.5%) due to a combination of both side effects and ineffectiveness (Table S1). Regarding CsA, 356 patients were included with a median treatment duration of 7.9 (IQR 3.2-14.4) months. The majority of the patients (n=258 (73%)) discontinued treatment within two years after start of CsA, mostly because of well-controlled disease (n=79 (22%)) followed by side effects (n=72 (20%)) [8]. The MTX cohort included a total of 89 patients with a median treatment duration of 7.3 (IQR 3.0-11.4) months. Half of the patients (n=45 (51%)) discontinued treatment after two years of follow-up, 22 patients (25%) due side effects and 13 patients (15%) due to ineffectiveness.[7]

The overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years, respectively. In CsA treated patients drug survival rates were 37% and 20%. This was comparable to the drug survival of MTX, which was 41% and 33%, after respectively 1 and 2 years. Drug survival of dupilumab was significantly longer compared to MTX

and CsA ($p<0.0001$) (Figure 1A). Approximately, half of the patients discontinued CsA and MTX because treatment failure (ineffectiveness and/or side effects); limited dupilumab patients discontinued treatment due to treatment failure (Figure 1). Due to the low number of patients discontinuing dupilumab treatment, a prediction analysis of drug survival was not possible in the present study.

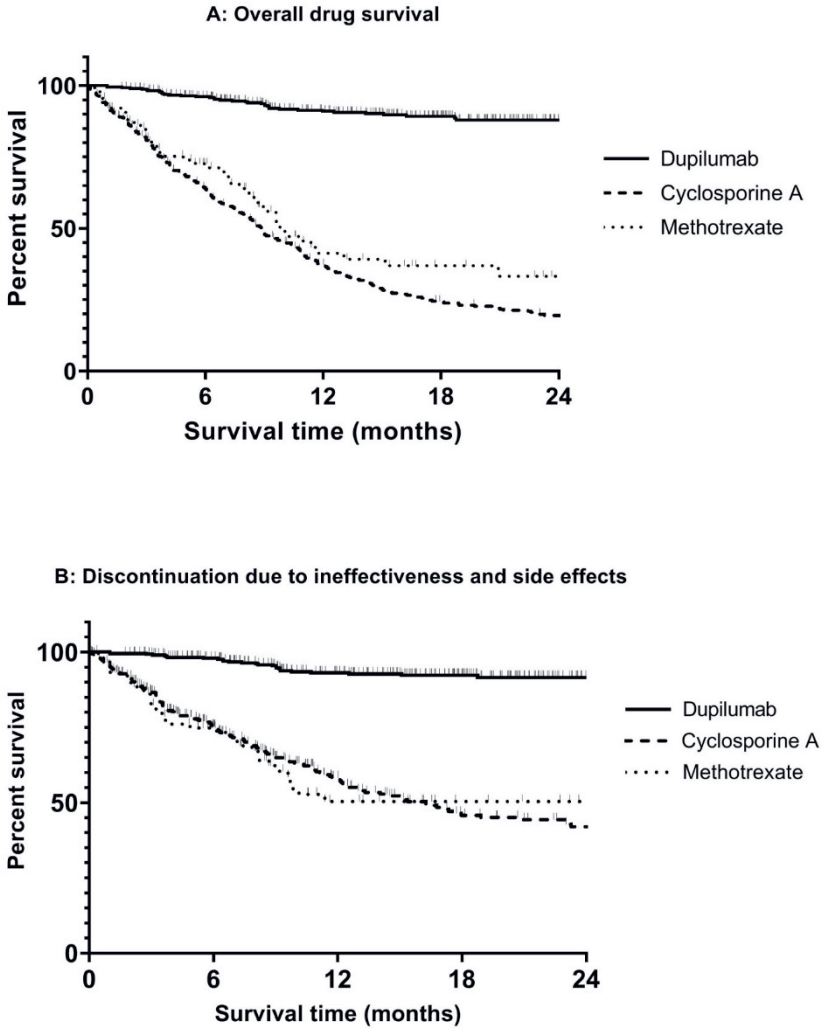

Figure 1. A: Overall drug survival for dupilumab, cyclosporine A and methotrexate. B: Drug survival related to discontinuation due treatment failure for dupilumab, cyclosporine A and methotrexate

A drug survival rate of 89% after 800 days (26.3 months) of treatment with dupilumab in a daily practice cohort (n=112) of AD patients treated at a Tertiary Care Centre in the United States (US) was reported by Khosravi et al. Reasons for discontinuation were AD flare (5/112 (5%)), conjunctivitis (3/112 (3%)), and adequate control with phototherapy (1/112 (1%)).[6] Overall drug survival rates were comparable with the results of our study, although we found a slightly lower rate of discontinuation due to ineffectiveness (2% vs. 5%).

Drug survival is influenced by the availability of alternative treatment options and changes in the population treated over time. In the dupilumab cohort, more patients had a history of prior treatment with oral immunosuppressive drugs (99.5%) compared to patients included in the CsA (19.4%) and MTX (69.7%) cohort. Patients treated with MTX and CsA, were treated before dupilumab became available on the market, and therefore the availability of dupilumab did not influence the drug survival in these cohorts. Longer drug survival of dupilumab (compared to MTX and CsA) can be explained by a persistent clinical response and lack of discontinuation due to controlled disease, but also due to the lack of availability of alternative treatment options.

In conclusion, this study shows that dupilumab has a longer drug survival compared to CsA and MTX. Only a limited number of dupilumab patients discontinued treatment due to side effects and/or ineffectiveness. Future daily practice data of dupilumab will provide further important information on the impact of the introduction of new biologic agents and small molecules for the treatment of AD on drug survival of dupilumab.

References

1. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.
2. Ariens, L.F.M., et al., *Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy.* Ther Adv Chronic Dis, 2018. **9**(9): p. 159-170.
3. Faiz, S., et al., *Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort.* J Am Acad Dermatol, 2019.
4. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2020. **75**(1): p. 116-126.
5. van den Reek, J., et al., *Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls.* J Invest Dermatol, 2015. **135**(7): p. 1-5.
6. Khosravi, H., et al., *Dupilumab Drug Survival, Treatment Failures, and Insurance Approval at a Tertiary Care Center in the United States.* J Am Acad Dermatol, 2019.
7. Politiek, K., et al., *Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis.* Br J Dermatol, 2016. **174**(1): p. 201-3.
8. van der Schaft, J., et al., *Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis.* Br J Dermatol, 2015. **172**(6): p. 1621-1627.

Supplement

Supplementary Table 1. Reason for discontinuation of dupilumab, cyclosporine A, and methotrexate

	Dupilumab	Cyclosporine A	Methotrexate
Reasons for discontinuation, n (%)			
Well-controlled disease	-	79(22.2)	4(4.5)
Ineffectiveness	7 (1.7)	55(15.4)	13(14.6)
Side effects	17 (4.2)	72(20.2)	22(24.7)
Both ineffectiveness and side effects	2(0.5)	19(5.3)	-
Other	11(2.7)	33(9.3)	5(6.7)

5

Dupilumab drug survival and associated predictors in moderate-to-severe atopic dermatitis; long-term results from the daily practice BioDay registry

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Abstract

Importance: Long-term data on dupilumab drug survival in atopic dermatitis (AD) are scarce. Furthermore, little is known about the factors influencing drug survival of dupilumab in atopic dermatitis.

Objective: To describe the drug survival for dupilumab in AD patients and to identify associated predictors.

Design: This cohort study was based on data from the multicenter prospective daily practice BioDay registry. The first patient treated with dupilumab was recorded in the BioDay registry in October 2017; data lock took place in December 2020.

Setting and participants: A total of four university and 10 non-university hospitals in the Netherlands participate in the registry. Patients (≥18 years) participating in BioDay registry with a follow-up of at least 4 weeks

Main outcome and Measure: Drug survival was analyzed by Kaplan-Meier survival curves and determinants by using univariate- and multivariate Cox regression analysis.

Results: A total of 715 adult AD patients were included with a 1-, 2- and 3-year overall dupilumab drug survival of 90.3%, 85.9% and 78.6%, respectively. Determinants for shorter drug survival related to ineffectiveness were the use of immunosuppressant at baseline (HR-2.64) and non-responders at 4-weeks (HR-8.68). Determinants for shorter drug survival related to side effects were the use of immunosuppressant at baseline (HR-2.69), age ≥65-years (HR-2.94) and Investigator Global Assessment (IGA)-score of very severe AD (HR-3.51).

Conclusion and Relevance: This study demonstrates a good overall 1-, 2- and 3-year dupilumab drug survival. Patients using immunosuppressive therapy at baseline and the absence of treatment effect at week 4 tend to discontinue treatment due to ineffectiveness more frequently. Using immunosuppressant at baseline, older age and IGA-score very severe AD were determinants for an increased risk for discontinuation due to side effects. This data provide more insight and new perspectives regarding dupilumab treatment in AD and can contribute to the optimization of patient outcomes.

Introduction

Atopic dermatitis (AD) is a multifactorial, pruritic skin disease resulting from the interaction of genetic disposition and environmental triggers with skin barrier dysfunction and a Type-2-driven immune dysregulation.[1] Dupilumab is a monoclonal antibody that targets the IL-4 receptor subunit α (IL-4Rα). This results in the blocking of signaling of T2-cytokines, IL-4 and IL-13, and consequently the inhibition of the Th2-pathway.[2, 3] Overall, the clinical efficacy and safety of dupilumab has been demonstrated in clinical trials for the treatment of patients with AD.[4-7] In these clinical trials, efficacy of dupilumab were investigated under ideal and controlled circumstances in selected patients and therefore, results are hard to generalize to daily practice.

Drug survival is an analysis that reflects daily practice by analyzing the expected duration of time until an event, discontinuation of the drug, occurs.[8] Drug survival and associated predictors are dependent on a combination of factors such as drug effectiveness, the occurrence of side-effects, patient factors and the availability of other treatment options. Our previous study showed a longer drug survival of dupilumab compared to CsA and MTX, with only a limited number of patients discontinuing treatment due to ineffectiveness and/or side effects.[9] At that time, a prediction analysis of drug survival was not feasible due to the low number of patients discontinuing dupilumab treatment. Furthermore, predictor studies regarding dupilumab drug survival are limited and not specified for the reason of discontinuation.[10] Consequently, little is known about which factors might influence the drug survival of dupilumab and whether certain clinical characteristics might be predictive for discontinuation due to either ineffectiveness and/or side effects.

The primary objective of our present study was to investigate the drug survival of dupilumab in AD patients treated in daily practice, and to identify its predictors.

Methods

Study design and patients

All patients (≥18 years) participating in BioDay registry with a follow-up of at least 4 weeks were included in this study. A total of four university and 10 non-university hospitals in the Netherlands participate in the registry. It contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both patient-reported outcomes (PRO's) as well as clinical parameters. The first patient treated with dupilumab was recorded in the BioDay registry in October 2017; data lock took place in December 2020 due to the introduction of new advanced systemic treatment in 2021.

This study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18/239) and was performed according to the declaration of Helsinki. All patients provided written informed consent.

Protocol and data collection

All patients received a loading dose of dupilumab of 600mg subcutaneously, followed by 300mg injections every other week in the first year. In cases of well-controlled AD or severe side effects, tapering of dupilumab dosage was considered.

The following patient and treatment characteristics were recorded at baseline: gender, age, body mass index (BMI), time of onset AD, history of immunosuppressive therapy, presence of atopic comorbidities and use of immunosuppressive therapy at the start of dupilumab treatment. Patients were recorded as using immunosuppressive therapy at the start of dupilumab treatment when prednisone or cyclosporine had been used within 1 week before starting dupilumab treatment and, in the case of methotrexate, within 4 weeks before the start of dupilumab treatment.

Disease severity was assessed by physician-measured clinical eczema scores, namely Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA)-score on a 6-point scale (scores range from 0 (clear AD) to 5 (very severe AD)).[11] Discontinuation due to both ineffectiveness and side effects was based on patient-clinician discussions.

Statistical analyses

Drug survival

Drug survival was analyzed with Kaplan Meier survival curves. Overall, three drug survival events were defined and analyzed separately: (I) discontinuation in overall drug survival, (II) discontinuation due to ineffectiveness and (III) discontinuation due to side effects. When patients discontinued due to both ineffectiveness and side effects, they were considered to have an event in both sub analyses (II and III). Patients were censored when still using dupilumab at time of the data lock (December 2020) or when lost to follow up. When patients discontinued for other reasons (e.g. pregnancy wish), they were included statistically in the overall drug survival analysis (I) but were censored in the sub analyses (II, III). For each included patient, only the first treatment episode of dupilumab was analyzed and treatment interruptions of less than 90 days were considered as one continuous episode.

Potential predictors

We defined the following variables as potential predictors of dupilumab drug survival: gender, age, BMI, time of onset AD, allergic asthma, allergic rhinitis, allergic conjunctivitis, food allergy, delta EASI (the absolute difference between EASI-score at week 4 and baseline), use of immunosuppressive therapy at the start of dupilumab treatment, IGA-score (as a categorical variable), weekly average Numerical Rating Scale (NRS) itch-score, eosinophils and Thymus- and activation-regulated chemokine (TARC) levels at the start of dupilumab treatment. As the effect of delta EASI was stronger than baseline EASI and we wanted to assess the effect of early response on drug survival, we included the delta EASI instead of baseline EASI. The delta EASI was dichotomized into: (a) non-responder at 4 weeks if delta EASI was ≥0 (representing equal or worsening of AD activity after 4 weeks of dupilumab treatment compared to baseline) and (b) responder if delta EASI was <0. Age at start treatment was dichotomized into (a) younger than 65 years and (b) 65 years and older. Continuous variables with a highly skewed distribution were log transformed. To increase interpretability, BMI was categorized in 5-point intervals. Late onset AD was defined as AD onset >18 years.

Prediction of discontinuation due to ineffectiveness and/or side effects

The analysis was performed in two steps. First, a univariate Cox regression analysis was performed for each variable separately. Second, a multivariate analysis, including all potential predictors (i.e. without univariate pre-selection), was performed to

assess interactions between all variables. As the number of discontinuations due to ineffectiveness and/or side effects was relatively low for the number of predictors to be evaluated, we applied Firth's correction in estimation of the multivariate Cox model. The predictive performance of the model was assessed with the c-statistic, which is similar to an area-under-the Receiver Operator Characteristic-curve for dichotomous outcomes. Validity of the proportional hazards assumption was assessed with residual analysis.[12] The assumption of a linearity of continuous predictors and the outcome was assessed with restrictive cubic spline analyses.

Prior to analyzing the data, we noted missing values on several predictors. As a complete case analysis, only analyzing patients without missing values may have resulted in bias and loss of statistical power, so we decided to use multiple imputation. Missing data were imputed with a fully conditional specification and included all potential predictors as well as the outcome. Based on the percentage of patients, we constructed 50 imputed datasets.[13, 14] The analysis was performed on each imputed dataset and the results were subsequently pooled with Rubin's rule.[12]

All data were analyzed using SPSS Statistics 26.0.0.1 (IBM, Armonk, NY, U.S.A.) and SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient and treatment characteristics

A total of 715 patients (mean age 41.8 (SD 16.0)) were included at start of dupilumab treatment. A total of 418 patients (58.5%) were male and 183 patients (25.6%) used immunosuppressive drugs at the start of treatment. The median EASI-score at baseline was 15.6 (Inter Quartile Range (IQR) 10.1-24.9). Forty-eight patients (6.7%) showed no improvement or worsening of EASI-score at week 4 (mean EASI-score increase of 57.9%) compared to baseline and were defined as 'non-responder at week-4'. 'Responders at week-4' (582/715) had a mean EASI-score decrease of 55.3%. The IGA-score was very severe AD in 8.3% (n=58) of the patients. Furthermore, patients reported a mean NRS-pruritus score of 6.8 (SD 2.3) (Table 1). During dupilumab treatment 7 patients (1.0%) started or continued concomitant immunosuppressive therapy due to ineffectiveness, at which 3 patients discontinued treatment due to ineffectiveness.

Table 1. Patient characteristics for the total cohort and differentiated for reason of discontinuation.

	Total	**Ineffectiveness**	**Side effects**
n (%)	715 (100.0)	24 (100.0)	36 (100.0)
Male, n (%)	418 (58.5)	13 (54.2)	22 (61.1)
Age, mean (SD)	41.8 (16.0)	38.7 (20.2)	46.2 (16.4)
BMI, mean (SD)	25.6 (4.5)	25.3 (3.8)	26.1 (4.8)
Age at AD onset, n (%)			
Childhood	586 (82.0)	19 (79.2)	28 (77.8)
Adolescence	43 (6.0)	3 (12.5)	4 (11.1)
Adulthood	72 (10.0)	2 (8.3)	3 (8.3)
Missing	14 (2.0)	-	1 (2.8)
Immunosuppressive drugs history, n(%)			
Naïve	27 (3.8)	0 (0)	1 (2.9)
1	351 (49.1)	8 (33.3)	10 (28.6)
2	207 (29.0)	9 (37.5)	13 (37.1)
≥3	130 (18.2)	7 (29.2)	11 (32.4)
Use of immunosuppressive therapy at BL	183 (25.6)	11 (45.8)	16 (44.4)
Missing	13 (1.8)	1 (4.2)	0 (0.0)
Atopic comorbidity			
Allergic Asthma, n (%)	396 (55.3)	10 (41.7)	21 (58.3)
Missing	15 (2.1)	-	-
Allergic Rhinitis, n (%)	469 (65.5)	13 (54.2)	25 (69.4)
Missing	37 (5.2)	-	-
Allergic Conjunctivitis, n (%)	408 (57.1)	9 (37.5)	21 (58.3)
Missing	24 (3.4)	4 (16.7)	2 (5.6)
Food allergy, n (%)	313 (43.8)	5 (20.8)	11 (30.6)
Missing	19 (2.7)	-	1 (2.8)
EASI score, median (IQR)	15.6 (10.1-24.9)	20.0 (11.0-36.8)	19.8 (12.0-32.1)
Missing	10	-	-
IGA score at BL, n (%)			
0 clear AD	0 (0.0)	0 (0.0)	0 (0.0)
1 almost clear AD	12 (1.7)	0 (0.0)	1 (2.8)
2 mild AD	104 (14.5)	5 (20.8)	6 (16.7)
3 moderate AD	289 (40.4)	6 (25.0)	10 (27.8)
4 severe AD	233 (32.6)	8 (33.3)	11 (30.6)
5 very severe AD	58 (8.1)	5 (20.8)	8 (22.2)
Missing	19 (2.7)	-	-
Weekly average pruritus NRS score at BL, mean (SD)	6.8 (2.3)	7.1 (2.8)	6.8 (2.8)
Missing	78	5	3
Eosinophils levels at BL, median (IQR), (x10*9/L)	0.3 (0.2-0.5)	0.4 (0.2-0.8)	0.4 (0.2-0.7)
Missing	46	3	2
Serum TARC levels at BL, median (IQR), (pg/mL)	1884 (829-3840)	2911 (940-5699)	2887(957-5140)
Missing	147	9	7

Table 1 (continued). Patient characteristics for the total cohort and differentiated for reason of discontinuation.

	Total	Ineffectiveness	Side effects
Response at week 4			
Non-responder at week 4, n (%)	48 (6.7)	8 (33.3)	5 (13.9)
ΔEASI week 4 vs. BL, %	-46.6	-15.7	-40.9
Clear AD (EASI=0) at week 4, n (%)	2 (0.3)	0 (0)	0 (0)
Almost clear AD (EASI≤1.1) at week 4, n (%)	24 (3.4)	0 (0)	3 (8.3)
Mild AD (EASI≤7) at week 4, n (%)	318 (44.5)	3 (12.5)	14 (38.9)
Missing	85 (11.9)	4 (16.7)	4 (11.1)

BL, baseline; SD, standard deviation; IQR, interquartile range, BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; NRS, Numerical Rating Scale; TARC, Thymus- and activation-regulated chemokine.

Reasons for discontinuation

At the moment of data lock, December 2020, 614 patients (85.9%) were still using dupilumab, 90 patients (12.6%) had discontinued dupilumab treatment and 11 patients (1.5%) were lost to follow-up (Table 2). Eighteen patients (2.5%) discontinued treatment due to ineffectiveness. As shown in Table 2, 30 patients (4.2%) terminated dupilumab due to side effects, with Dupilumab Associated Ocular Surface Disease (DAOSD) being the largest group (n=17, 2.4%). The majority of these patients (n=6), who discontinued treatment due to DAOSD, had an IGA-score of very severe AD at start of dupilumab treatment. The second largest group of side effects were cutaneous side effects (n=10), these skin lesions developed over a longer time period with a median dupilumab treatment duration of 63 weeks (IQR 46-83) before discontinuation (Table 2). Six patients (0.8%) discontinued treatment due to a combination of both side effects and ineffectiveness. Eleven patients (1.5%) discontinued treatment due to wish for pregnancy and 25 patients due to other reasons (3.5%) (Table 2 and supplementary Table 1).

Table 2. Treatment characteristics and reasons for discontinuation of dupilumab

	n (%)	**Treatment duration weeks,** median (IQR)
Status of dupilumab treatment by data lock		
Active	614 (85.9)	84 (43-131)
Discontinued	90 (12.6)	36 (18-66)
Lost to follow up	11 (1.5)	71 (30-87)
Reasons for discontinuation[a]		
Ineffectiveness	18 (2.5)	28 (17-33)
Side effects	30 (4.2)	40 (24-69)
Both ineffectiveness and side effects	6 (0.8)	36 (30-46)
Pregnancy wish	11 (1.5)	70 (19-108)
Other	25 (3.5)	32 (18-66)
Side effects as reason for discontinuation		
Ocular related complaints	20 (2.8)	32 (17-41)
Conjunctivitis (DAOSD)	14 (2.0)	31 (18-41)
Uveitis	3 (0.4)	28 (4-97)
Limbitis (DAOSD)	2 (0.3)	39 (39-39)
Cornea perforation (DAOSD)	1 (0.1)	4 (4-4)
Skin related complaints	10 (1.4)	63 (46-83)
Atypical lymphomatoid reaction	3 (0.4)	54 (27-85)
Worsening of Mycosis Fungoides (MF)[b]	1 (0.1)	60 (60-60)
Psoriasiform lesions	3 (0.4)	65 (16-83)
Rosacea	3 (0.4)	81 (46-91)
Muscle- and joint pain	2 (0.3)	47 (39-54)
Eosinophilia	1 (0.1)	40 (40-40)
Combination of headache/chest pain/tiredness	1 (0.1)	30 (30-30)
Systemic T-cell lymphoma	1 (0.1)	159 (159-159)
Agitation	1 (0.1)	133 (133-133)

[a]None of the patients discontinued treatment due to controlled disease. [b]In retrospect patient was misdiagnosed and appeared to have MF prior to start dupilumab and worsened after start of dupilumab. IQR, interquartile range; DAOSD, Dupilumab Associated Ocular Surface Disease.

Drug survival analysis

The 1-, 2- and 3-year overall drug survival of dupilumab was 90.3%, 85.9% and 78.6% respectively and was mostly determined by side effects. The drug survival with side effects as an event were 96.3%, 93.2% and 92.6% after 1, 2 and 3 years, respectively (Figure 1).The drug survival with ineffectiveness as an event were 96.5%, 95.7% and 95.7% after 1-, 2- and 3 years, respectively. This indicates that after two years of dupilumab treatment no additional patients discontinued dupilumab treatment due to ineffectiveness.

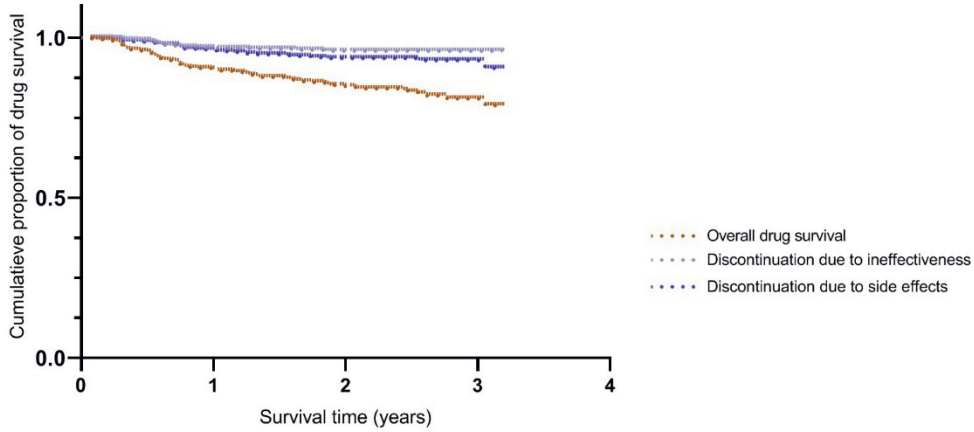

Figure 1. Dupilumab drug survival and split for reasons for discontinuation.

Predictors for discontinuation due to ineffectiveness

Results from the univariate analyses showed that the use of immunosuppressive drugs at start of dupilumab treatment (Hazard ratio (HR) 2.47, 95% CI 1.09-5.60), non-responders at week 4 (HR 7.95, 95% CI 3.32-19.07) and IGA-score very severe AD (HR 3.95, 95% CI 1.20-12.95) were associated with an increased hazard to discontinue treatment due to ineffectiveness, while presence of a food allergy (HR 0.31, 95% CI 0.12-0.84) was associated with a lower probability to discontinue treatment due to ineffectiveness (Table 3).

Results from the multivariate model are shown in Figure 2. Patients using immunosuppressive therapy at start of dupilumab treatment showed shorter drug survival (HR 2.64, 95% CI 1.10-6.37). Furthermore, being a non-responder at week 4 (HR 8.68, 95% CI 2.97-25.35) was also associated with shorter drug survival. The C-statistic was 0.85, indicating reasonably good discriminative properties of the model to predict discontinuation of dupilumab due to ineffectiveness (Figure 2 and supplementary Table 2).

Table 3. Predictors of discontinuation due to ineffectiveness and side effects determined by univariate Cox regression analysis

	Ineffectiveness		**Side effects**	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Gender (female)	1.32 (0.59-2.95)	0.49	1.02 (0.52-2.00)	0.95
Age start treatment ≥65 years[a]	1.97 (0.67-5.76)	0.22	2.07 (0.86-4.97)	0.11
BMI[b]	0.94 (0.54-1.62)	0.82	1.14 (0.77-1.68)	0.51
Late onset AD[c]	0.76 (0.18-3.23)	0.71	0.85 (0.26-2.77)	0.78
Allergic Asthma	0.52 (0.23-1.17)	0.11	0.99 (0.51-1.92)	0.97
Allergic Rhinitis	0.59 (0.26-1.31)	0.19	1.08 (0.53-2.19)	0.84
Allergic Conjunctivitis	0.59 (0.25- 1.36)	0.21	1.16 (0.58-2.31)	0.67
Food allergy	0.31 (0.12-0.84)	0.02	0.52 (0.25-1.05)	0.07
Immunosuppressant BL	2.47 (1.09-5.60)	0.03	2.16 (1.11-4.17)	0.02
Non-responder week 4[d]	7.95 (3.32-19.07)	0.00	2.44 (0.94-6.34)	0.07
IGA 1 or 2	2.16 (0.66-7.00)	0.20	1.95 (0.74-5.13)	0.18
IGA 3[e]	Ref.		Ref.	
IGA 4	1.78 (0.62-5.12)	0.29	1.42 (0.60-3.36)	0.42
IGA 5	3.95 (1.20-12.95)	0.02	3.76 (1.48-9.53)	0.01
NRS pruritus score	1.06 (0.86-1.30)	0.59	0.99 (0.85-1.15)	0.90
Eosinophils levels	1.12 (0.68-1.84)	0.64	1.18 (0.80-1.72)	0.40
Serum TARC levels	1.24 (0.87-1.78)	0.24	1.03 (0.77-1.39)	0.83

[a]Reference category <65 years; [b]BMI 5-points interval; [c]Late onset AD was defined as AD onset >18 years; [d]Non-responder at week 4 was defined as no EASI improved at week 4 compared to baseline; [e]Reference category IGA moderate. CI, confidence interval; BMI, body mass index; IGA, Investigator Global Assessment Scale; NRS, Numerical Rating Scale; TARC, Thymus- and activation-regulated chemokine.

Predictors for discontinuation due to side effects

The determinant of an increased risk for discontinuation due to side effects from univariate analysis was using immunosuppressive therapy at baseline (HR 2.16, 95% CI 1.11-4.17) and an IGA-score of very severe AD (HR 3.76, 95% CI 1.48-9.53) (Table 3).

Multivariate analysis showed the presence of immunosuppressive therapy at baseline (HR 2.69, 95% CI 1.32-5.48), older age (≥65 years) (HR 2.94, 95% CI 1.10-7.87) and an IGA-score of very severe AD (HR 3.51, 95% CI 1.20-10.28) were independent determinants of an increased risk for discontinuation of dupilumab due to side effects. The C-statistic was 0.72, which indicates reasonable discriminative properties of the model to predict discontinuation of dupilumab due to side effects (Figure 2 and supplementary Table 2).

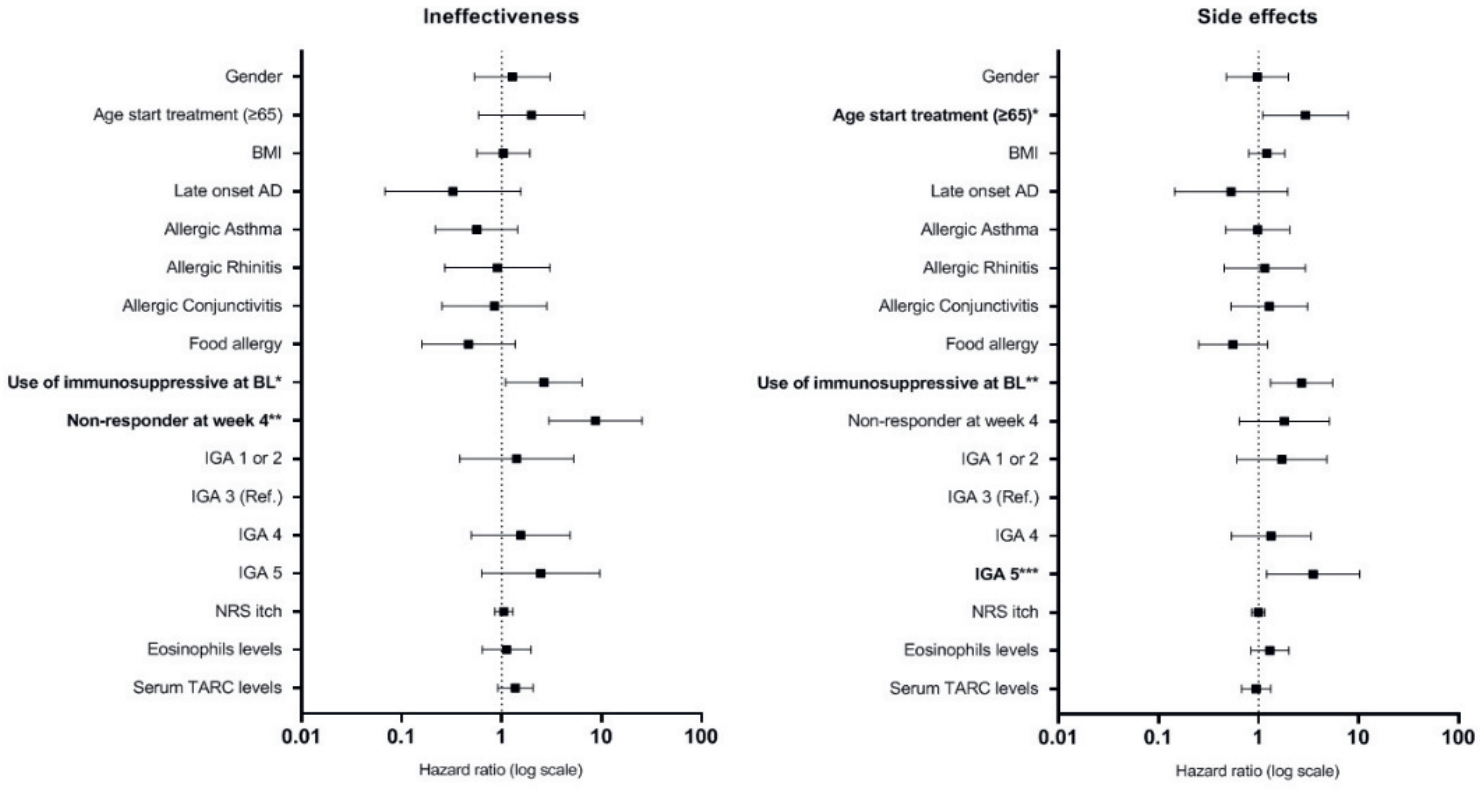

Figure 2. Predictors of drug survival for discontinuation due to ineffectiveness and side effects (hazard ratios) determined by multivariate Cox regression analysis.

*p-value<0.05; **p-value<0.05; ***p-value<0.05.

Discussion

Overall, dupilumab showed a good drug survival of 90.3%, 85.9% and 78.6% after 1-, 2- and 3-years of treatment respectively, and was predominantly determined by side effects. Use of immunosuppressive therapy at baseline, older age (≥65 years) and an IGA-score of very severe AD were independent risk factors for shorter drug survival related to side effects. Use of immunosuppressive therapy at baseline and no response after 4 weeks of dupilumab treatment were independent risk factors for shorter drug survival related to ineffectiveness.

Reasons for discontinuation of dupilumab in this study (90/715, 12.6%) were: ineffectiveness (18/715, 2.5%), side-effects (30/715, 4.2%), combination of ineffectiveness and side-effects (6/715, 0.8%), other reasons (25/715, 3.5%) and pregnancy wish (11/715, 1.5%). Khosravi et al. showed, in 2017-2019, an overall drug survival of dupilumab in 112 adult AD patients after 2.2 years of 89%. A total of 9 patients (8.0%) discontinued dupilumab: 5 (4.5%) due to AD-flare, 3 (2.7%) due to side effects (conjunctivitis) and 1 (0.9%) patient due to ineffectiveness.[15] Overall, the number of patients who discontinued dupilumab treatment are consistent with our results.

Georgakopoulos et al. assessed the 2-year drug survival of dupilumab in real-world patients with AD.[16] Drug survival of dupilumab was 83% and 80% after 1- and 2-years of treatment. Of 139 patients, treatment was discontinued in 14 patients (10.1%) due to ineffectiveness and in 14 patients due to side effects (10.1%), and among those in whom treatment failed, the median time to discontinuation was 20 weeks. Overall, higher discontinuation rates and shorter treatment duration was observed compared to our results. One explanation for this difference could be that this study was conducted when another new advanced targeted therapy for AD (e.g. baricitinib) was already available, which might have led to higher discontinuation rates for dupilumab due to availability of an alternative treatment. In our study, the data lock was set before the introduction of other new advanced systemic treatment; in this way dupilumab drug survival could be assessed without the interference of other new advanced systemic treatments. Considering that drug survival is a comprehensive outcome covering efficacy, safety, and patients' and doctors' preferences, new advanced targeted therapies will influence dupilumab drug survival. In the coming years it will be interesting to compare the drug survival of dupilumab to other advanced systemic treatment options when they are longer on the market.

Prior to this study, only one study regarding predictors for dupilumab drug survival had been conducted. Dal Bello et al. investigated drug survival of dupilumab, reasons for discontinuation, and predictive parameters of drug survival in daily practice (n=149). Sixteen months (1.3 years) from baseline, 82.0% of patients receiving dupilumab were still on treatment.[10] Reasons for discontinuing dupilumab were ineffectiveness (4.7%), remission (7.4%), and cutaneous adverse effects (2.0%). Older age at diagnosis and shorter AD duration predicted shorter overall dupilumab survival. A direct comparison to our study was not possible as we used categories for onset AD and differentiated for reason of discontinuation. However, in our study, late onset AD (>18 years) was not a significant determinant in the Cox regression analysis for the prediction of discontinuation.

No other prediction studies of dupilumab drug survival, which differentiated in the reason of discontinuation, are available in literature yet. Use of immunosuppressive therapy at baseline, older age (≥65 years) and IGA-score very severe AD at baseline were independent risk factors for shorter drug survival related to side effects. Older patients were often excluded from previous clinical studies, therefore limited data is available for this specific age group. Our results suggest that older patients are more susceptible to developing side effects compared to younger patients. The effect of an IGA-score of very severe AD as risk factor for discontinuation due to side effects might be explained by the higher risk of developing DAOSD in these patients. 22.2% (8/36) of the patients who discontinued treatment due to side effects had an IGA-score of very severe AD, with the majority of these patients (6/8) discontinuing treatment due to DAOSD. DAOSD is a frequently reported side effect of dupilumab treatment[6] and is associated with higher disease activity at baseline.[17, 18] Additionally, use of immunosuppressive therapy at baseline and the absence of response after 4 weeks of dupilumab treatment were found as independent risk factors for shorter drug survival related to ineffectiveness. Interestingly, patients who did not respond at week 4 (EASI week-4 ≥ EASI-baseline, observed in 48/715 patients (6.7%)) had an approximately 8.7-fold increased tendency to discontinue treatment due to ineffectiveness compared to patients who did respond to dupilumab in the first 4 weeks of treatment. Blauvelt et al. showed that after 4 months of dupilumab treatment, a steady state is achieved and therefore 16 weeks of treatment is considered as an important time-point to evaluate treatment response.[4] This study showed for the first time that no response/worsening of AD at week 4 is highly predictive for discontinuation of dupilumab due to ineffectiveness in the longer-term. Because of this new finding, additional analysis was performed by using

Spearman correlation. A strong correlation of 0.74 was found between EASI-score week 4 and 16 for non-responders at week 4, indicating that the EASI-score after 4 weeks of treatment will likely result in a similar EASI-score at week 16. As the availability of more new advanced systemic treatments grows, it would be beneficial for clinical practice if decision-making regarding discontinuation of a drug could be set earlier than after 4 months of treatment.

An important strength of this study is the large volume of patient data sourced from the prospective BioDay registry. We applied very few exclusion criteria to ensure the data was representative of current clinical practice and reflects a real-life situation.

Some limitations of this study need to be addressed. First, the predictive analysis for ineffectiveness and side effects was performed with a limited number of discontinuations. We applied Firth's correction to obtain bias corrected estimates of HRs, nevertheless, statistical power was limited, in particular in the multivariate analyses. Consequently, potential useful predictors may have shown insignificant p-values, and such predictors need to be evaluated in future drug survival studies.

In conclusion, this daily practice study demonstrates a good overall 1-, 2- and 3-year drug survival of dupilumab. Predictors for dupilumab drug survival showed that patients using immunosuppressive therapy at baseline and the absence of treatment effect at week 4 tend to discontinue treatment due to ineffectiveness more frequently. In addition, using immunosuppressive therapy at baseline, older age (≥65 years) and an IGA-score of very severe AD were predictors of an increased risk for discontinuation due to side effects. In the coming years daily practice registry data will provide longer follow-up data of the new advanced systemic treatments, which will give information on the dupilumab drug survival compared to these new systemic treatments.

References

1. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.
2. Sastre, J. and I. Davila, *Dupilumab: A New Paradigm for the Treatment of Allergic Diseases.* J Investig Allergol Clin Immunol, 2018. **28**(3): p. 139-150.
3. Serra-Baldrich, E., et al., *Changing perspectives in atopic dermatitis.* Allergol Immunopathol (Madr), 2018. **46**(4): p. 397-412.
4. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. **389**(10086): p. 2287-2303.
5. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE).* Br J Dermatol, 2018. **178**(5): p. 1083-1101.
6. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
7. Beck, L.A., et al., *Dupilumab treatment in adults with moderate-to-severe atopic dermatitis.* N Engl J Med, 2014. **371**(2): p. 130-9.
8. van den Reek, J., et al., *Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls.* J Invest Dermatol, 2015. **135**(7): p. 1-5.
9. Spekhorst, L.S., et al., *Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: Results from the BioDay registry.* Allergy, 2020. **75**(9): p. 2376-2379.
10. Dal Bello, G., et al., *Drug survival of dupilumab compared to cyclosporin in moderate-to-severe atopic dermatitis patients.* Dermatol Ther, 2020. **33**(6): p. e13979.
11. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.
12. Harrell, F., *Regression modelling strategies*. 2001: Springer.
13. Bodner, T.E., *What Improves with Increased Missing Data Imputations?* Structural Equation Modeling: A Multidisciplinary Journal, 2008. **15**(4): p. 651-675.
14. Graham, J.W., A.E. Olchowski, and T.D. Gilreath, *How many imputations are really needed? Some practical clarifications of multiple imputation theory.* Prev Sci, 2007. **8**(3): p. 206-13.
15. Khosravi, H., et al., *Dupilumab drug survival, treatment failures, and insurance approval at a tertiary care center in the United States.* J Am Acad Dermatol, 2020. **82**(4): p. 1023-1024.
16. Georgakopoulos, J.R., et al., *Two-year efficacy, safety, and drug survival of dupilumab for atopic dermatitis: A real-world Canadian multicenter retrospective study.* JAAD Int, 2021. **4**: p. 67-69.
17. Nahum, Y., et al., *Dupilumab-induced ocular surface disease (DIOSD) in patients with atopic dermatitis: clinical presentation, risk factors for development and outcomes of treatment with tacrolimus ointment.* Br J Ophthalmol, 2020. **104**(6): p. 776-779.
18. Treister, A.D., C. Kraff-Cooper, and P.A. Lio, *Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis.* JAMA Dermatol, 2018. **154**(10): p. 1208-1211.

Supplement

Supplementary Table 1. Description of other reasons as reasons for discontinuation of dupilumab

	n	**Duration of treatment in weeks**, median (IQR)
Own initiative	15	32 (20-66)
Patient died (cause of dead: COVID-19 and unknown)	2	58 (6-109)
Inconclusive diagnosis of AD	1	18 (18-18)
Alopecia areata	1	44 (44-44)
Corneal detachment	1	98 (98-98)
Erythema nodosum	1	15 (15-15)
Cervical myelopathy	1	42 (42-42)
Polymyalgia rheumatica	1	30 (30-30)
Suspected systemic T-cell lymphoma[a]	1	9 (9-9)
Severe thrombocytopenia	1	127 (127-127)

[a]Dupilumab was discontinued due to possibility of a systemic T-cell lymphoma but was restarted after additional diagnostics. IQR, interquartile range

Supplementary Table 2. Predictors of discontinuation due to ineffectiveness and side effects determined by multivariate Cox regression analysis

	Ineffectiveness		**Side effects**	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Gender (female)	1.28 (0.53-3.07)	0.58	0.97 (0.48-1.99)	0.94
Age start treatment ≥65y[a]	1.99 (0.59-6.74)	0.27	2.94 (1.10-7.87)	0.03
BMI[b]	1.04 (0.57-1.91)	0.90	1.21 (0.80-1.83)	0.38
Late onset AD[c]	0.33 (0.07-1.56)	0.16	0.53 (0.14-1.95)	0.34
Allergic Asthma	0.56 (0.22-1.44)	0.23	0.98 (0.47-2.05)	0.95
Allergic Rhinitis	0.90 (0.27-3.04)	0.87	1.15 (0.45-2.93)	0.77
Allergic Conjunctivitis	0.85 (0.25-2.81)	0.78	1.28 (0.53-3.11)	0.58
Food allergy	0.47 (0.16-1.37)	0.16	0.56 (0.28-1.23)	0.15
Immunosuppressant at BL	2.64 (1.10-6.37)	0.03	2.69 (1.32-5.48)	0.01
Non-responder at week 4[d]	8.68 (2.97-25.35)	0.00	1.81 (0.64-5.11)	0.26
IGA 1 or 2	1.41 (0.38-5.26)	0.61	1.71 (0.61-4.81)	0.31
IGA 3[e]	Ref.		Ref.	
IGA 4	1.55 (0.50-4.83)	0.45	1.33 (0.54-3.32)	0.54
IGA 5	2.46 (0.63-9.60)	0.20	3.51 (1.20-10.28)	0.02
NRS pruritus score	1.05 (0.85-1.29)	0.65	0.99 (0.86-1.16)	0.94
Eosinophils levels	1.12 (0.64-1.96)	0.69	1.30 (0.84-2.00)	0.24
Serum TARC levels	1.37 (0.91-2.06)	0.13	0.94 (0.67-1.32)	0.74

[a]Reference category <65 years; [b]BMI 5-points interval; [c]Late onset AD was defined as AD onset >18 years; [d]Non-responder at week 4 was defined as no EASI improved at week 4 compared to baseline; [e]Reference category IGA moderate. CI, confidence interval; BMI, body mass index; IGA, Investigator Global Assessment Scale; NRS, Numerical Rating Scale; TARC, Thymus- and activation-regulated chemokine.

6

Association of serum dupilumab levels at 16-weeks with treatment response and side effects in atopic dermatitis; a prospective, observational cohort study from the BioDay registry

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*Contributed equally

Abstract

Importance: The registered dose of dupilumab for adult atopic dermatitis (AD) patients is 300mg every other week (Q2W). At present, it is unknown whether serum dupilumab levels are associated with treatment response or side effects.

Objective: To evaluate serum dupilumab levels after 16 weeks of treatment in patients with AD, and to explore its association with treatment response and side effects.

Methods: This study consecutively included adult AD patients who started dupilumab and in whom a serum sample was available at 16 weeks of treatment. Patients received a loading dose of dupilumab 600mg subcutaneously, followed by 300mg Q2W. Patients who had a dose adjustment or discontinued treatment before 16 weeks of treatment were excluded. Disease severity was assessed at baseline and at week 16 and 52 using the Eczema Area and Severity Index (EASI)-score. Side effects were recorded during the first year. At 16-weeks the relation between dupilumab serum levels and treatment response was analyzed. Multivariate logistic regression modelling was used to determine the prediction of response (EASI90; EASI≤7) and side effects after 52-weeks, with serum dupilumab levels at 16 weeks in the presence of covariates age and gender.

Results: A total of 295 patients were included with median drug level of 86.6 µg/mL (IQR=64.6-110.0; range 10.1-382.0) after 16 weeks of treatment. No significant differences were found in serum dupilumab levels between responder statuses (<EASI50/EASI50/EASI75/EASI90) at week 16. Multivariate logistic regression analysis showed non-significant odds ratio's (ORs) for serum dupilumab levels at 16 weeks regarding prediction of long-term response (≥EASI90, OR 0.96 (95%CI:0.90-1.04), p=0.34; EASI≤7, OR 1.03 (95%CI:0.93-1.14), p=0.55) and side effects (OR 1.01 (95%CI:0.95-1.07), p=0.83).

Conclusion and Relevance: This real-world study in AD patients found a broad range of serum dupilumab levels at 16 weeks of treatment, with no association to treatment response and side effects during first year of treatment. It might be that response is dependent on target availability of the IL-4Rα, with an inter-patient variability leading to heterogeneity in response.

Introduction

Dupilumab is a human monoclonal antibody that targets the interleukin (IL)-4 receptor subunit-α (IL-4Rα), thereby blocking the signaling of IL-4 and IL-13, and consequently inhibiting the entire T2-pathway.[1] Overall, the effectiveness and safety of dupilumab have been demonstrated for the treatment of patients with atopic dermatitis (AD).[2, 3] However, not all AD patients respond equally to dupilumab treatment and some patients develop side effects. This heterogeneity may partly be explained by differences in the bioavailability of dupilumab at the target tissue, which in turn is influenced by adherence, drug dose, and pharmacokinetic (PK) covariates.[4] In other diseases, e.g. Inflammatory Bowel Disease (IBD) and psoriasis, a correlation between serum TNFα-inhibitor levels and treatment response has been described.[5, 6] At present no data is available whether measuring serum dupilumab levels can help optimizing AD treatment. Therefore, this study evaluated serum dupilumab levels after 16 weeks of treatment in AD patients, and explored its association with treatment response and side effects.

Methods

This prospective, observational cohort study consecutively included adult AD patients who started dupilumab and in whom a serum sample was available at 16 weeks of treatment. All patients participated in the BioDay registry.[3] At baseline, patients received a loading dose of dupilumab 600mg subcutaneously, followed by 300mg every other week. Patients who had a dose adjustment or discontinued treatment before 16 weeks of treatment were excluded. The BioDay registry was considered non-interventional by the local medical ethics committee (METC 18/239) and was performed according to the Helsinki Declaration. All patients provided written informed consent.

Outcome Measures

Disease severity was assessed at baseline and at week 16 and 52 using the Eczema Area and Severity Index (EASI)-score. Treatment responses were defined as the percentage of reduction in EASI-score compared with baseline (e.g. EASI90= 90% reduction in EASI-score compared to baseline) and as an absolute cut-off score of EASI-score≤7, indicating controlled AD.[7] Furthermore, side effects during the first year of dupilumab treatment were recorded, with a special focus on dupilumab-associated ocular surface disease (DAOSD).

Serum dupilumab levels

Serum dupilumab levels were measured after 16 weeks of treatment using an enzyme-linked immunosorbent assay as described previously.[8]

Statistical analysis

The AD outcome measures were calculated after 16- and 52 weeks of dupilumab treatment. Boxplots were used to visually compare drug levels by responder status at week 16. A multivariate logistic regression model was used to explore the role of serum dupilumab levels at 16 weeks in predicting response (≥EASI90; EASI≤7) at 52 weeks and to explore the association of serum dupilumab levels and the development of side effects, with a special focus on DAOSD, adjusted for age and gender. Missing data were imputed with a fully conditional specification. The analysis was performed on each imputed dataset and the results were subsequently pooled. In an additional step we added restrictive cubic splines to the model for serum dupilumab levels. Any significant non-linear effect that we observed was most likely due to a small number of patients with high serum dupilumab levels and splines were therefore not included in the model. All data were analyzed using SPSS (Version 26.0.0.1, SPSS Inc) and SAS (Version 9.4).

Results

Patient and baseline characteristics

A total of 295 patients were included, the mean age was 41.5 years (Standard Deviation (SD) 15.9) and the median EASI-score at baseline was 14.1 (Inter Quartile Range (IQR) 10.0-20.2) (Table 1). Two patients were retrospectively excluded due to non-adherence (serum dupilumab level of 0.0 µg/mL).

Table 1. Patient and treatment characteristics

	Total (n=295)
Sex, male, n (%)	170 (57.6)
Age start treatment, mean (SD)	41.5 (15.9)
Age at AD onset, n (%)	
Childhood	254 (86.1)
Adolescence	15 (5.1)
Adulthood	26 (8.8)
Use of immunosuppressive therapy at BL, n (%)	87 (29.5)
Atopic comorbidity	
Allergic Asthma, n (%)	163 (55.3)
Allergic Rhinitis, n (%)	201 (68.1)
Missing	2 (0.7)
Allergic Conjunctivitis, n (%)	197 (66.8)
Missing	2 (0.7)
Food allergy, n (%)	140 (47.5)
EASI-score at BL, median (IQR)	14.1 (10.0-20.2)
IGA score at BL, median (IQR)	3.0 (3.0-4.0)
Eosinophils levels at BL (x10*9/L), median (IQR)	0.34 (0.18-0.60)
Missing, n (%)	9 (3.1)
Serum TARC levels at BL (pg/mL), median (IQR)	1765.0 (896.3-3542.8)
Missing, n (%)	7 (2.4)
Response after 16 weeks of treatment, n	295
<EASI50	47 (15.9)
EAISI50	101 (34.2)
EASI75	109 (36.9)
EASI90	38 (12.9)
Controlled AD (EASI≤7)	241 (81.7)
Response after 52 weeks of treatment, n	248/295
<EASI50	24 (11.3)
EAISI50	43 (20.3)
EASI75	86 (40.6)
EASI90	59 (27.8)
Controlled AD (EASI≤7)	179 (84.4)
Missing, n (%)	36 (14.5)

In case of missing not shown there were no missing values. BL, baseline; SD, standard deviation; IQR, interquartile range, EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; TARC, Thymus- and activation-regulated chemokine. <EASI50, less than 50% reduction from baseline in Eczema Area and Severity Index score; EASI50, 50% reduction from baseline in Eczema Area and Severity Index score; EASI75, 75% reduction from baseline in Eczema Area and Severity Index score; EASI90, 90% reduction from baseline in Eczema Area and Severity Index score; Controlled AD, EASI≤7.

The association of serum dupilumab levels with response and side effects

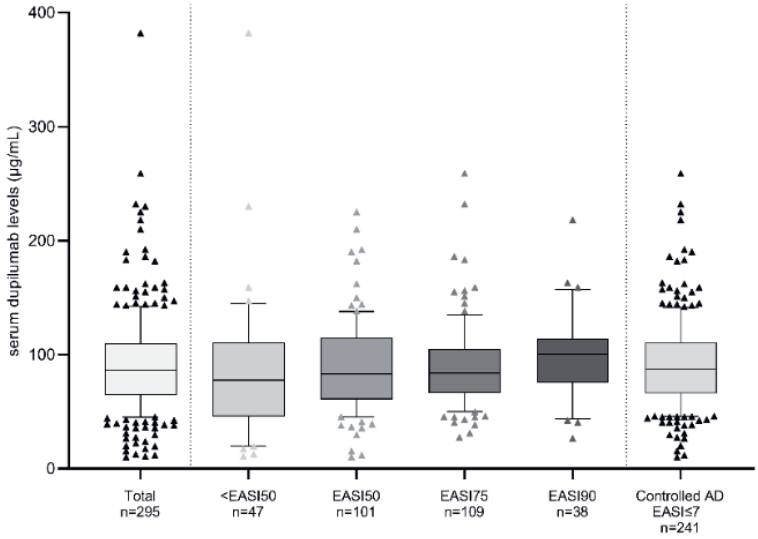
After 16 weeks of treatment median dupilumab level in the total cohort was 86.6 µg/mL (IQR=64.6-110.0; range 10.1-382.0) (Figure 1A). Furthermore, no significant differences were found in median serum dupilumab levels between responder statuses (<EASI50/EASI50/EASI75/EASI90) at week 16 (p=0.18) (Figure 1A) or in the distribution of responders statuses between the serum dupilumab levels quartiles (p=0.06) (Figure 1B).

At time of data lock 248/295 (84.1%) patients reached the 52-week time point. Patients who discontinued treatment after 16 weeks due to ineffectiveness (n=6) had median serum dupilumab levels of 91.2 µg/mL (IQR=59.3-144.0). Multivariate logistic regression analysis showed non-significant odds ratio's for serum dupilumab levels at week 16 and predicting response after 52 weeks of treatment (≥EASI90, OR 0.96 (95%CI:0.90-1.04), p=0.34; EASI≤7, OR 1.03 (95%CI:0.93-1.14), p=0.55). Side effects during the first year of dupilumab treatment were reported in 216 (73.2%) patients, of which 137 (46.4%) patients developed DAOSD. Similarly, multivariate logistic regression analysis showed non-significant ORs for serum dupilumab levels at 16 weeks for the prediction of side effects (OR 1.01 (95%CI:0.95-1.07), p=0.83) and specifically DAOSD (OR 1.02 (95%CI:0.97-1.08), p=0.46) during the first year of treatment (Table 2).

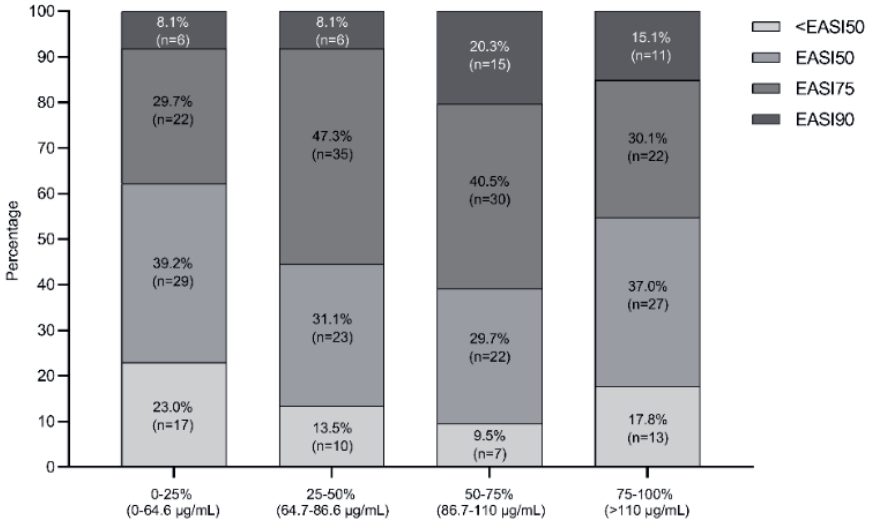
Table 2. Odds ratios of serum dupilumab levels at 16 weeks in 10-point interval for predicting long-term response and side effects; with focus on dupilumab-associated ocular surface disease.

	Odds ratio (95% CI)	**p-value**
EASI90 after one year of treatment	0.96 (0.90-1.04)	0.34
Controlled AD (EASI≤7) after one year of treatment	1.03 (0.93-1.14)	0.55
Side effects during first year of treatment	1.01 (0.95-1.07)	0.83
DAOSD during first year of treatment	1.02 (0.97-1.08)	0.46

The multivariate logistic regression model was corrected for age and gender. To increase interpretability, serum dupilumab levels were categorized in 10-point intervals. Missing data were imputed with a fully conditional specification and included all potential predictors as well as the outcome. For the response statuses a total of 15 imputed datasets were constructed. The analysis was performed on each imputed dataset and the results were subsequently pooled. Abbreviations: OR, odds ratio; CI, confidence interval; EASI90, 90% reduction from baseline in Eczema Area and Severity Index score; Controlled AD, Eczema Area and Severity Index score ≤7; DAOSD, dupilumab-associated ocular surface disease.



(A) Responder statuses vs. serum dupilumab levels



(B) Percentiles serum dupilumab levels vs. responder statuses

Figure 1. A: Serum dupilumab levels at week 16 for the total cohort and differentiated for responder statuses at week 16 using Eczema Area and Severity Index (EASI). B: The distribution of responders statuses by EASI per percentile of serum dupilumab levels at week 16.

Outliers were included in the analyses; serum dupilumab levels were categorized into quartiles and the distribution of the responder statutes in each quartile is shown. Boxplots represents median serum dupilumab levels with interquartile ranges, and whiskers represent 10th and 90th percentile.

Discussion

This study measured serum dupilumab levels in a large population of AD patients treated in daily practice. A broad range of serum dupilumab levels at week 16 was found in the total cohort, and these levels were substantially higher compared to serum levels of monoclonal antibodies used in other diseases, such as IBD and psoriasis.[5, 9] High dosing, resulting in high drug levels, might be explained by the saturable target-mediated clearance pathway of dupilumab. Li et al. described the PK profile for dupilumab from 6 phase-1 studies and concluded that when the concentration is high enough to saturate the IL-4Rα, the PK of dupilumab follows a linear/dose-proportional PK profile.[10] In AD, maximum efficacy was observed at doses that yielded dose-proportional PK profiles, which was established by high serum levels, and thus achieved saturation of the IL-4Rα.[4] Interestingly, our study suggests that observed serum dupilumab levels are not related to treatment response. This is in contrast to certain monoclonal antibodies used in other diseases (i.e. TNF-inhibitor in other autoimmune diseases).[6, 11-13] It might be that response is dependent on target availability of the IL-4Rα, with an inter-patient variability leading to heterogeneity in response. However, since serum dupilumab levels are relatively high, this likely results in full saturation of the IL-4Rα in all patients at week 16. This is supported by our previous data showing full saturation of the IL-4Rα on circulating B- and T-cells at week 16.[14] This would explain why serum dupilumab levels are not related to effectiveness, although we cannot rule out differential effects in the tissue related to heterogeneity in serum dupilumab levels. Additionally, our study showed that serum dupilumab levels at 16 weeks were not associated with side effects, specifically not with DAOSD. However, a previous study showed that prolonging the dupilumab interval, thereby lowering serum dupilumab levels, can improve DAOSD.[15] Maybe the development of DAOSD is more associated with differences in IL-4Rα expression between patients. More research is necessary to confirm the hypothesis of inter-patient variability of the IL-4Rα and pharmacokinetics of dupilumab. A limitation of the study is that the serum dupilumab measurements were performed independent of dupilumab administration, which may have affected the range of serum dupilumab levels and may have influenced the prediction model.

Conclusion

In this real-world study in AD patients, a broad range of serum dupilumab levels was found after 16 weeks of treatment, with no relation to treatment response and side effect during the first year of dupilumab treatment.

References

1. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.
2. Thaci, D., et al., *Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.* Lancet, 2016. **387**(10013): p. 40-52.
3. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
4. Kovalenko, P., et al., *Exploratory Population PK Analysis of Dupilumab, a Fully Human Monoclonal Antibody Against IL-4Ralpha, in Atopic Dermatitis Patients and Normal Volunteers.* CPT Pharmacometrics Syst Pharmacol, 2016. **5**(11): p. 617-624.
5. Gibson, D.J., et al., *Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease.* Aliment Pharmacol Ther, 2020. **51**(6): p. 612-628.
6. Wilkinson, N., et al., *Defining the Therapeutic Range for Adalimumab and Predicting Response in Psoriasis: A Multicenter Prospective Observational Cohort Study.* J Invest Dermatol, 2019. **139**(1): p. 115-123.
7. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.
8. Spekhorst, L.S., et al., *Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis.* Allergy, 2022.
9. Menting, S.P., et al., *The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting.* Br J Dermatol, 2015. **173**(3): p. 855-7.
10. Li, Z., et al., *Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Dupilumab in Healthy Adult Subjects.* Clin Pharmacol Drug Dev, 2020. **9**(6): p. 742-755.
11. Chaparro, M., et al., *Systematic review: antibodies and anti-TNF-alpha levels in inflammatory bowel disease.* Aliment Pharmacol Ther, 2012. **35**(9): p. 971-86.
12. Nakae, K., et al., *Potential application of measuring serum infliximab levels in rheumatoid arthritis management: A retrospective study based on KURAMA cohort data.* PLoS One, 2021. **16**(10): p. e0258601.
13. Moore, C., G. Corbett, and A.C. Moss, *Systematic Review and Meta-Analysis: Serum Infliximab Levels During Maintenance Therapy and Outcomes in Inflammatory Bowel Disease.* J Crohns Colitis, 2016. **10**(5): p. 619-25.
14. Bakker, D.S., et al., *Early and Long-Term Effects of Dupilumab Treatment on Circulating T-Cell Functions in Patients with Moderate-to-Severe Atopic Dermatitis.* J Invest Dermatol, 2021. **141**(8): p. 1943-1953 e13.
15. Achten, R., et al., *Long-term follow-up and treatment outcomes of conjunctivitis during dupilumab treatment in patients with moderate-to-severe atopic dermatitis.* J Allergy Clin Immunol Pract, 2021. **9**(3): p. 1389-1392 e2.

7

Predicting long-term treatment response of patients treated with dupilumab for moderate-to-severe atopic dermatitis

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Abstract

Background: Due to heterogeneity of atopic dermatitis (AD) and differences between patients, treatment effectiveness varies across individuals. Little is known about clinical characteristics that might be predictive for long-term effectiveness of dupilumab.

Objective: The aim of this study was to identify factors that are associated with the long-term treatment response (effectiveness at 52 weeks by using % change in Eczema Area and Severity Index (EASI) score) of dupilumab in a larger daily practice cohort of AD patients. Secondly, to examine if these characteristics can be combined to accurately predict long-term treatment response to dupilumab.

Methods: A cohort study was performed at the National Expertise Centre of Atopic Dermatitis, Department of Dermatology, UMC Utrecht. All patients (≥18 years) participating in BioDay registry who completed the 52-week follow-up period up were included in this study. The dataset was divided randomly into a derivation (3/4) and validation (1/4) sample. Treatment response was defined as the improvement in EASI-score (%) at 52 weeks compared to baseline. The final model was obtained using bootstrap resampling with a backward selection applied on the full model in the derivation sample. Shrunken coefficients were validated in the validation sample.

Results: A total of 552 patients were included in the analysis and were divided over either derivation (n=409) or validation (n=143) sample. Eight potentially predictor variables were found for long-term treatment response: initial response (delta EASI score 0-4 weeks) ($p < 0.01$), age at dupilumab initiation ($p = 0.10$), time of AD onset ($p = 0.05$), medical history of skin infections ($P < 0.01$), Body Mass Index (BMI) ($p = 0.08$), eosinophils count ($p = 0.11$), Investigator Global Assessment (IGA) score ($p < 0.01$) and gender ($p = 0.12$). The calibration slope of the model was 0.3059 in the validation sample versus 1 in the derivation sample.

Conclusion: Our study identified eight variables as potential predictors for long-term treatment response to dupilumab. The results of our research are an important first step towards the development of a prediction model. Further research should be focused on finding more variables with predictive value and exploring other paths including combining clinical predictors with biomarkers.

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, affecting approximately 10-20% of the adults in developed countries.[1] AD is a heterogeneous disease with a multifactorial pathogenesis, which is not quite understood yet.[2] AD is characterized by a damaged skin barrier function, skin inflammation and chronic pruritus.[3] Furthermore, patients are known to have an increased risk for skin infections, other atopic diseases and report more psychological difficulties and interpersonal issues. As a consequence, AD causes a great burden and has a substantial impact on both the quality of life and work productivity.[1, 4]

Knowledge of the immunological pathogenesis of AD has expanded in the past decade leading to development of new targeted treatments.[5] One of these treatments is dupilumab, a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor α (IL-4Rα), thereby inhibiting IL-4 and IL-13 cytokine pathways.[2, 6] IL-4 and IL-13 are type 2 inflammatory cytokines and key drivers in Th2 immune response, which is considered to play a central role in the pathogenesis of AD.[5] Dupilumab entered the Dutch market in January 2018, and AD patients are eligible to receive dupilumab when they present with an insufficient response to topical therapy and failure of at least one systemic immunosuppressive therapy. Dupilumab has shown clinically relevant improvements in signs and symptoms of AD and an acceptable safety profile in both clinical trials and daily practice studies.[7-10] However, due to heterogeneity of AD and differences between patients, treatment response varies across individuals. Results from phase 3 trials demonstrated that 40% of subjects reached the endpoint of no or almost no disease activity at week 52, resulting in 60% of patients still experiencing some symptoms.[2] This demonstrates that uncertainty in long-term effectiveness remains for these AD patients in daily practice.

Little is known about factors that may influence the treatment response to dupilumab and if certain clinical characteristics might be predictive for long-term effectiveness. Previous studies of predictive clinical characteristics are rather limited and mainly focussed on the early response.[11, 12] They showed that the early treatment response to dupilumab was associated with the initial response at four weeks of treatment, younger age, female gender, early age of AD onset, absence of hyper-eosinophilia and less severe disease at baseline (Eczema Area and Severity Index (EASI) score

<24.5).[11, 12] In this current era of new upcoming systemic treatment options for patients with moderate-to-severe AD, knowledge about predicting long-term effectiveness of (dupilumab) treatment would be essential for sufficient clinical decision making.

Therefore, the aim of this study is to identify factors that are associated with the long-term treatment response (effectiveness at 52 weeks by using % change in EASI score) of dupilumab in a larger daily practice cohort of AD patients. Secondly, to examine if these characteristics can be combined to accurately predict long-term treatment response to dupilumab.

Methods

Data source and study design

A historical cohort study was performed at the National Expertise Centre of Atopic Dermatitis, Department of Dermatology, UMC Utrecht. All patients (≥18 years) participating in BioDay registry who completed the 52-week follow-up period up were included in this study. The BioDay registry is a prospective multicentre registry that contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both Quality of Life (QoL) as well as clinical parameters. Data were extracted between 20 October 2017 and 25 March 2021 concerning patients' baseline characteristics, treatment duration and effectiveness, as well as other detailed patient- and treatment characteristics. Patients were excluded if they did not complete the 52-week follow-up period and missed ≥3 additional visits at either baseline, week 4, 16, 28 or 40.

This study did not fall under the scope of the Medical Research Involving Human Subjects Act which was confirmed by the local Medical Research Ethics Committee (METC 18/239). The study has been performed according to the declaration of Helsinki.

Outcome measurement

The percentage change in EASI score between baseline and week 52 was selected as outcome variable. The EASI score consists of four items: swelling, excoriation, erythema and lichenification at four body sites.[13] A patient can be scored from 0-72 (0: clear and 72: very severe disease).[14] The calculation was done as follows: ((EASI score at week 52 - EASI at baseline) / EASI at baseline) * 100%.

Statistical analysis

The dataset was randomly divided in samples for derivation (3/4) and narrow validation (1/4). Data were monitored on missing variables for derivation and validation samples separately. Missing data were imputed with single stochastic imputation with predictive mean matching, in both derivation and validation sample.[15] In the imputation, the set of potential predictors, outcome variable and additionally longitudinal variables of week 4, 16, 28, 40 and 52 visits were included. Longitudinal variables with ≥30% missing were excluded. Furthermore, the variable indicating whether a patient is a drop-out was also included in the imputation.

Multivariable linear regression

Multivariable linear regression was used to estimate the regression weight for each predictor of treatment response in the derivation set. Restricted Cubic Splines (RCS) or quadratic terms were added, where linear model assumption was not met, to investigate whether this improved model likelihood. Furthermore, the residual plot of the full model was inspected for outliers and they were removed from the analysis when considered overly influential on the results. Multicollinearity was assessed in line with recommendations from Kleinbaum et al. using 0.8 as threshold.[16] Using Akaike Information Criterion (AIC) as a model selection criterion, the final model was obtained using bootstrap resampling (n=600) with a backward selection applied on the full model in the imputed datasets (n=10). AIC as selection criterion is equivalent to using a p-value of 0.157 for a predictor with one degree of freedom.[17] The combination of variables that most frequently remained from the backward selection bootstrap samples were included in the prediction model. Final estimates of the model coefficients were obtained using pooling with Rubin's rules across the imputed datasets.[18]

Predictive accuracy and model validation

Predictive accuracy was assessed in the derivation set and validation set by calibration plot and the R-Square statistic. The calibration plot was used to assess the agreement between the predicted and observed change in EASI score (%). A Bland and Altman plot was used to evaluate the magnitude and direction of the model deviates from observed EASI % improvements for which 0 (no difference) is ideal. With the R-Square statistic we assessed in which degree the variation in change in EASI score (%) could be explained by the identified predictors. We re-fitted the final (multiple imputed) model on the derivation set and used this model to asses predictive accuracy in both derivation and validation set. Secondly, in order to calibrate the model in the validation set, we shrunk the model coefficients using the calibration slope revealed from the bootstrap analysis and re-estimated the intercept. Subsequently, the calibration slope was assessed and tested for identity (calibration slope equals 1) using linear regression with observed % EASI improvement as dependent variable, and predicted EASI % improvement as independent variable. All statistical analyses were performed in R version 4.0.3.

Results

Patient population

A total of 552 patients with a minimum follow-up period of 52 weeks were included and were divided over either derivation (n=409) or validation (n=143) sample (Figure 1). At dupilumab treatment initiation, the mean age was 41.7 (SD 15.7) and the median EASI was 16.4 (IQR 10.9 – 25.5). A total of 105 patients (24.6%) also used prednisolone at start dupilumab treatment. Furthermore, patients reported a median Patient Orientate Eczema Measure (POEM) score of 20.0 (IQR 16.0 – 24.0), Dermatology Life Quality Index (DLQI) score of 13.0 (IQR 8.0 – 26.0) and pruritus Numeric Rating Scale (NRS) score of 7.0 (IQR 6.0 – 8.0). All baseline characteristics are displayed in Table 1. Dupilumab treatment was discontinued in 39 patients during the 52 weeks of follow-up, reasons for discontinuation were: ineffectiveness (n=8), side effects (n=20), both ineffectiveness and side effects (n=2), pregnancy wish (n=2), lost to follow-up (n=2) or other (n=5). For 13 of these patients, follow-up data after discontinuation were available. Moreover, a total of 103 patients were missing the week 52 visit mostly caused due to the Covid-19 pandemic (Figure 1).

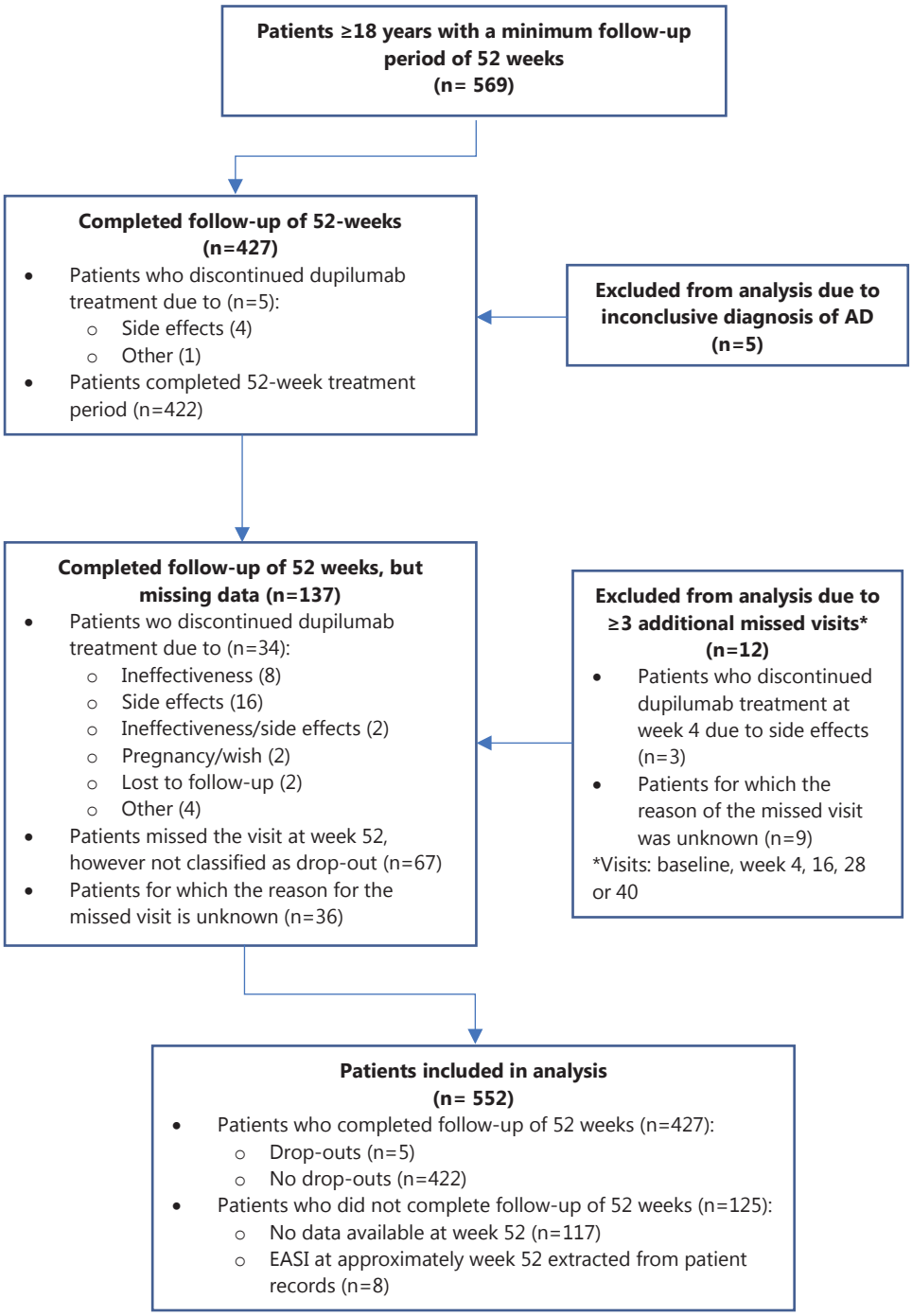

Figure 1. Flowchart of study design and patient selection for analysis

Table 1. Baseline characteristics

	Total (n=552)
Age at start dupilumab (years), mean (SD)	41.7 (15.7)
Male, n (%)	337 (61.2)
BMI, mean (SD)	25.8 (4.5)
Age at AD onset, n (%)	
Childhood	449 (83.3)
Adolescence	30 (5.6)
Adulthood	60 (10.9)
Medical history of skin infections[a], n (%)	39 (7.1)
Allergic contact dermatitis, n (%)	157 (32.8)
Localization facial, n (%)	311 (87.1)
Atopic diseases	
Allergic asthma, n (%)	311 (57.6)
Allergic rhinitis, n (%)	360 (66.3)
Allergic conjunctivitis, n (%)	317 (59.4)
Food allergy, n (%)	245 (45.6)
Concomitant use of prednisolone, n (%)	105 (24.6)
TARC, median (IQR)	1850.0 (830.5-4055.0)
Eosinophils count, median (IQR)	0.3 (0.2-0.6)
IGA score, median (IQR)	3.0 (3.0-4.0)
EASI score (0-72), median (IQR)	16.4 (10.9-25.5)
POEM score (0-28), median (IQR)	20.0 (16.0-24.0)
PGAD score[b], n (%)	
Poor	97 (26.9)
Fair	173 (48.1)
Good	81 (22.5)
Very good	6 (1.7)
Excellent	3 (0.8)
NRS itch score (0-10), median (IQR)	7.0 (6.0-8.0)
DLQI score (0-30), median (IQR)	13.0 (8.0-26.0)

[a]Consist of the combination of the following skin infections: cellulitis, erysipelas, molluscum contagiosum, tinea versicolor, herpes zoster, mycosis, eczema herpetica, herpes labialis, folliculitis and impetigo; [b]PGAD score: PGAD scores 'Good', 'Very good' and 'Excellent' were combined in the analysis due to the low number of responses in the categories 'Very good' and 'Excellent.'

Additionally, we excluded four patients during the analysis due to outlying values distorting the results. For two patients, the EASI score at week 52 consisted of a mixed image of both AD and Mycosis Fungoides (MF) which was developed during the follow-up period. This could be a possible explanation for the outlying result. In the other two patients one temporarily discontinued dupilumab treatment and one suffered from mental illnesses which could possible caused the outlying result.

Predictor variables

Variables included in the analysis

Literature search identified 20 predictor variables possibly associated with treatment response: age at start dupilumab initiation, gender, body mass index (BMI), time of AD onset, dermatologic medical history, atopic comorbidities asthma, allergic rhinitis, allergic conjunctivitis, symptomatic food allergy, allergic contact dermatitis, facial AD, concomitant use of prednisolone, lab values TARC and eosinophil count, clinical scores IGA and EASI and patient reported outcomes POEM, Patient Global Assessment of disease (PGAD), NRS itch and DLQI. Clinical scores and patient reported outcomes were analysed both as baseline score and initial response between week 0 and 4 (delta scores; e.g. EASI week 4 – EASI week 0). Because there were too much missing data on the DLQI score at week 4, the delta DLQI could not be included in our analysis.

Age at dupilumab initiation and delta EASI score at week 4 did not meet model assumptions and therefore a quadratic term was added. TARC did also not meet model assumptions despite a log transformation and addition of RCS leading to the choice to remove TARC from further analysis. We found some collinearity between predictor variables. However, this did not exceed the predefined threshold (0.8) and was therefore considered to not impact the analysis. Furthermore, the analyses of the delta scores only revealed that initial response in EASI score (delta between week 4 and baseline) as a possible predictor for long-term treatment response. Therefore, we decided to continue with the model of baseline scores and added the delta EASI score at week 4 to this model. The full model of variables that were included in the backward selection analysis is displayed in Table 2.

Table 2. Relevant predictor variables for long-term treatment response included in the analysis (full model) in derivation sample (n=405)

Variables	Coefficients	SE	P-value
Model intercept	-57.8297	16.9610	0.0007
Delta EASI score[a]			
Linear term	0.5849	0.3526	0.0980
Quadratic term	0.0060	0.0086	0.4856
Age at dupilumab initiation[b]			
Linear term	-0.7002	0.5420	0.1972
Quadratic term	0.0084	0.0060	0.1613
Time of AD onset			
Childhood	Ref	Ref	Ref
Adolescence	-9.2463	6.3552	0.1465
Adulthood	-6.3923	5.0357	0.2051
BMI	0.4416	0.3377	0.1917
Medical history of skin infections (no/yes)	6.8496	4.0840	0.0943
AD allergic contact dermatitis	0.5861	3.2806	0.8583
AD localization facial	-2.8692	3.9262	0.4654
Allergic asthma	3.0343	3.1863	0.3416
Allergic rhinitis	-2.3009	3.8919	0.5547
Allergic conjunctivitis	2.6079	3.4234	0.4467
Food allergy	2.0403	2.8160	0.4692
Concomitant use of prednisolone	-3.6921	3.8098	0.3331
Eosinophils count	-5.3678	3.9749	0.1777
NRS itch score at baseline	-0.5559	0.7031	0.4297
IGA score at baseline[c]			
Almost clear/mild	Ref	Ref	Ref
Moderate	-16.2073	4.8787	0.0010
Severe	-16.5274	5.5996	0.0034
Very severe	-15.5943	6.3667	0.0148
POEM score at baseline	-0.0261	0.2568	0.9192
DLQI score at baseline	0.2850	0.2528	0.2602
Sex, male	5.1328	3.5585	0.1500
PGAD score at baseline[d]			
Poor	Ref	Ref	Ref
Fair	2.4692	3.5328	0.4850
Good, very good and excellent	3.7745	4.4830	0.4003

[a]Delta EASI score at week 4(EASI week 4 – EASI at baseline): quadratic term added; [b]Age at start of dupilumab initiation: quadratic term added; [c]IGA score: no responses for 'Clear.' Categories 'Almost clear' and 'Mild' were combined in the analysis due to the low number of responses in both categories; [d]PGAD scores 'Good', 'Very good' and 'Excellent' were combined in the analysis due to the low number of responses in the categories 'Very good' and 'Excellent.'

Variables that remained after backward selection

Eight predictors for long-term treatment response remained after backward selection: initial response (delta EASI score at week 4) ($p < 0.01$), age at dupilumab initiation ($p = 0.10$), time of AD onset ($p = 0.05$), medical history of skin infections ($P < 0.01$), BMI ($p = 0.08$), eosinophils count ($p = 0.11$), IGA score ($p < 0.01$) and gender ($p = 0.12$). A greater initial response (delta EASI score at week 4), higher eosinophil count, adolescence or adulthood disease AD onset and higher IGA score predict a higher percentage of AD improvement. Increase of age at dupilumab initiation, BMI, medical history of skin infections and male gender predict a lower percentage of AD improvement. The selected variables are displayed in Table 3.

Table 3. Predictor variables for long-term treatment response that remained after backward selection in derivation sample (n=405)

Variables	Coefficients	SE	P-value
Model intercept	-56.176876	13.210050	< 0.01
Delta EASI score[a]			
Linear term	0.481535	0.319295	< 0.01
Quadratic term	0.003616	0.007772	
Age at dupilumab initiation[b]			
Linear term	-0.769166	0.495226	0.10
Quadratic term	0.008373	0.005461	
Age at AD onset[c]			
Childhood	Ref	Ref	0.05
Adolescence	-10.995821	5.555213	
Adulthood	-5.616389	4.401317	
BMI	0.541081	0.307789	0.08
Medical history of skin infections (no/yes)	9.826862	3.701779	< 0.01
Eosinophils count	-5.952732	3.747646	0.11
IGA score at baseline[d]			
Almost clear/mild	Ref	Ref	
Moderate	-16.705994	4.492083	< 0.01
Severe	-17.597192	5.099141	
Very severe	-14.744171	5.959779	
Sex, male	4.418394	2.883145	0.12

[a]Delta EASI score at week 4 (EASI week 4 – EASI at baseline): quadratic term added; P-value for Delta EASI score at week 4 as variable obtained by comparing two models when one included this predictor and the other did not; [b]Age of dupilumab initiation: quadratic term added; P-value for Age of dupilumab initiation as variable obtained by comparing two models when one included this predictor and the other did not; [c]P-value for time of AD onset in as variable obtained by comparing two models where one included this variable and the other did not; [d]P-value for IGA score as variable obtained by comparing two models where one included this variable and the other did not.

Predictive accuracy and model validation

The eight predictors of the final model explained 17% of the variation in change of EASI scores (%) between baseline and week 52 (Table 4). In the derivation sample, the median difference between predicted and observed values in change of EASI scores (%) was 3.5% (IQR -8.4 – 12.3).

In the validation sample, the median difference between predicted values in change of EASI scores (%) was 1.1% (IQR -11.6 – 11.9). The calibration slope of the model in the validation sample was 0.3059 versus 1 in the derivation sample (Table 4).

Table 4. Predictive accuracy and model validation in derivation (n=405) and validation sample (n=143)

	Derivation sample	**Validation sample**
	n=405	n=143
Calibration slope	1.0000	0.3059
R squared	16.9%	2.4%
Median difference[a]	3.4 (IQR -8.4 – 12.4)	1.1 (IQR -11.6 – 11.9)

[a]Between predicted and observed change

Discussion

This large daily practice cohort study of AD patients treated with dupilumab identified eight variables potentially predicting long-term treatment response to dupilumab (% change in EASI score at week 52). Our results suggest that more severe AD (higher IGA scores at baseline) is associated with a better long-term response to dupilumab treatment. Our findings also demonstrates that an initial response (delta EASI at week 4) possibly predicts a better long-term treatment response. Along with this, we identified six clinical characteristics at baseline as potential predictors. Whereas younger age, female gender, onset of AD during adolescence or adulthood and higher eosinophil count seems to be predictive for a better long-term treatment response, higher BMI and medical history of skin infections predicted less improvement of AD.

This is the first study aiming to find predictors for long-term treatment response in a large group of AD patients in daily practice (n=552). The prospective study of Olesen et al. (2019) investigated the effectiveness and safety of dupilumab treatment in a real-life setting in a small group of patients (n=43).[11] Specifically, they investigated the association between early treatment response, defined as 75% improvement on EASI score (EASI-75) after four and twelve weeks of treatment, and

several baseline characteristics (e.g. age, age of AD onset, gender, age, BMI, medical history). They found that treatment response after four and twelve weeks was likely to be associated with gender, as females showed better responses at both time points. As well as that an association between treatment response after four weeks and younger age at treatment initiation was found. Furthermore, they found that a significant reduction in EASI scores, pruritus score, sleep score and DLQI was achieved after four weeks of treatment. No significant difference was observed between four and twelve weeks indicating that the largest improvement is achieved in the first four weeks of treatment.[11] Firstly, our results also demonstrate that younger age at treatment initiation and female gender are possible predictors suggestive that these characteristics might be of importance in the prediction of response to dupilumab treatment. Secondly, we also found that the improvement of the EASI score in the first four weeks of dupilumab treatment (delta EASI score at week 4) is significantly associated with a better long-term treatment response. This suggests that the treatment response observed in the first four weeks is indeed an important indicator for long-term effectiveness.

Where we found that AD onset during adolescence and adulthood and higher eosinophil count are predictors for long-term treatment response, Ferruci et al. came to different conclusions in their retrospective chart review (n=117).[12] The aim of this review was to identify potential predictors for treatment response (defined as reaching EASI-75) after four and sixteen weeks of dupilumab treatment. They found that early AD onset and absence of hyper-eosinophilia (≥500 eosinophiles) were potential predictors for treatment response after four weeks of treatment, no significant associated predictive parameters were found at week 16.[12] The difference in results can possibly be explained by three elements. First, this difference in outcome could be due to a difference in measurement levels for time of AD onset between both studies. In our study three categories childhood, adolescence and adulthood were used, while Ferrucci et al. used the variable dichotomised at the age of 18. Therefore, early onset AD as defined in the study of Ferrucci et al. has the category adolescence included. Secondly, we inspected the correlation between time of AD onset and other predictive variables. We found some significant associations with IGA score ($p=0.02$), age at dupilumab initiation ($p < 0.01$), delta EASI score at week 4 ($p < 0.01$) and blood eosinophils ($p < 0.01$) suggesting that any predictive value of time of AD onset was incorporated in these variables. Further research is necessary to examine the contribution of time of AD onset to long-term treatment

response. Thirdly, in contrast to the results of Ferrucci et al., we found that a higher eosinophil count predicted a better long-term treatment response. Our findings, however, seems to correspond with the pathogenesis of AD in which patients often show a higher eosinophil count which appears to be correlated with disease activity.[19, 20]

An attempt to combine the eight variables identified in this study to predict long-term treatment response in clinical practice did not turn out be able to provide an accurate prediction due to two reasons. First, these eight variables only explained 17% of the variation in change of EASI scores between baseline and week 52 (%) leading to 83% of the variation remaining unexplained. Secondly, the model has no optimal validation as demonstrated by the calibration slope of 0.3059 meaning that there is no optimal agreement between predicted and observed values.

Limitations

Our study is not without limitations. Firstly, approximately 20% of the patients did not complete the follow-up period of 52-weeks, and data on predictor variables (ranging between 1% and 44%) were missing. This is mostly explained due to both the observational character as well as the Covid-19 pandemic, as patients were not able to visit the hospital on their regular schedule. Due to the amount of missing data, we tried to optimise the missing data imputation process as far as possible by including longitudinal visit data of all visits up to week 52. Secondly, some variables concerning the dermatologic medical history (psoriasis, rosacea, prurigo nodularis and photosensitive AD) were also identified as potentially relevant. However, these variables had very low responses (≤5) in one of the two categories and were therefore not included in the analysis.

Clinical relevance and future directions

The finding of eight variables potentially predicting long-term response to dupilumab treatment in AD patients could be the first step towards a prediction model to support clinicians in their clinical decision making. Currently, many disease specific therapies (small molecules and biologics) are in development for AD, promising an increase in marketed personalised medicine in the near future.[5, 23] Due to heterogeneity of the disease, it is unlikely that any of these therapies will be effective in all AD patients.[5] Clinicians will therefore have to evaluate benefits, risks and costs, of an increasing number of treatments, and could be supported in clinical

decision making by long-term prediction models.[23] On top of that, it is important to keep in mind that clinical characteristics alone may not be predictive enough. This could be caused by the heterogeneity of the disease reflecting underlying biological differences.[24] Thijs et al. identified four different biomarker clusters that demonstrates clearly the biological heterogeneity of atopic dermatitis and implies that there is a difference in the pathogenic pathway and endotype.[24] Biomarkers might therefore be crucial for assigning the right treatment to the right patient and pave the way for precision medicine.[25]

Conclusion

This study identified initial response (delta EASI score at week 4), age at dupilumab initiation, time of AD onset, medical history of skin infections, BMI, eosinophils count, IGA score and gender as potential predictors for long-term treatment response to dupilumab in AD. These results could be an important first step towards the development of a prediction model.

To establish a well-validated prediction model, which can be used to predict long-term treatment response to dupilumab in daily practice, further research on finding more variables with predictive value and e.g. combining clinical predictors with biomarker profiles of AD patients is needed.

References

1. Ariens, L.F.M., et al., *Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy.* Ther Adv Chronic Dis, 2018. **9**(9): p. 159-170.
2. Rodrigues, M.A., M. Nogueira, and T. Torres, *Dupilumab for atopic dermatitis: evidence to date.* G Ital Dermatol Venereol, 2019. **154**(6): p. 696-713.
3. Furue, M., et al., *Pathogenesis of Atopic Dermatitis: Current Paradigm.* Iran J Immunol, 2019. **16**(2): p. 97-107.
4. Ariens, L.F.M., et al., *Economic Burden of Adult Patients with Moderate to Severe Atopic Dermatitis Indicated for Systemic Treatment.* Acta Derm Venereol, 2019. **99**(9): p. 762-768.
5. Moyle, M., et al., *Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches.* Exp Dermatol, 2019. **28**(7): p. 756-768.
6. Seegraber, M., et al., *Dupilumab for treatment of atopic dermatitis.* Expert Rev Clin Pharmacol, 2018. **11**(5): p. 467-474.
7. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2020. **75**(1): p. 116-126.
8. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. **389**(10086): p. 2287-2303.
9. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
10. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE).* Br J Dermatol, 2018. **178**(5): p. 1083-1101.
11. Olesen, C.M., et al., *Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre.* J Eur Acad Dermatol Venereol, 2019. **33**(8): p. 1562-1568.
12. Ferrucci, S., et al., *Clinical Response and Quality of Life in Patients with Severe Atopic Dermatitis Treated with Dupilumab: A Single-Center Real-Life Experience.* J Clin Med, 2020. **9**(3).
13. Chopra, R., et al., *Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis.* Br J Dermatol, 2017. **177**(5): p. 1316-1321.
14. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.
15. Buuren, S.v.O., K., *Flexible multivariate imputation.* 1999: p. 1-20.
16. Kleinbaum, D.G., Kupper, L. L., Nizam, A. & Rosenberg, E. S., *Applied Regression Analysis and Other Multivariable Methods.* . 2013: Cengage Learning.
17. Heinze, G., C. Wallisch, and D. Dunkler, *Variable selection - A review and recommendations for the practicing statistician.* Biom J, 2018. **60**(3): p. 431-449.
18. Royston, P., Carlin, J. B. & White, I. R., *Multiple imputation of missing values: New features for mim.* Stata J., 2009(9, 252–264).
19. Simon, D., L.R. Braathen, and H.U. Simon, *Eosinophils and atopic dermatitis.* Allergy, 2004. **59**(6): p. 561-70.
20. Celakovska, J., et al., *Evaluation of Peripheral Blood Eosinophilia in Adolescent and Adult Patients Suffering from Atopic Dermatitis and the Relation to the Occurrence of Allergy to Aeroallergens.* Indian J Dermatol, 2019. **64**(1): p. 34-40.
21. Chowdhury, M.Z.I.T., T. C. , *Variable selection strategies and its importance in clinical prediction modelling.* am. Med. Community Heal., 2020.

22. Frank E. Harrell, J., *Regression modeling strategies. With applications to linear models, logistic regression, and survival analysis.* 2015: Springer International Publishing Switzerland.
23. van der Schaft, J., et al., *Towards personalized treatment in atopic dermatitis.* Expert Opin Biol Ther, 2019. **19**(5): p. 469-476.
24. Thijs, J.L., et al., *Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis.* J Allergy Clin Immunol, 2017. **140**(3): p. 730-737.
25. Breiteneder, H., et al., *Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma.* Allergy, 2020. **75**(12): p. 3039-3068.

8

Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis

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Abstract

Background: At present no real-world studies are available on different dupilumab dosing regimens in controlled atopic dermatitis (AD). The aim of this study was to clinically evaluate a patient-centered dupilumab dosing regimen in patients with controlled AD and to relate this to serum drug levels and serum biomarkers.

Methods: Ninety adult AD patients from the prospective BioDay registry were included based on their dupilumab administration interval according to a predefined patient-centered dosing regimen. Group A (n=30) did not fulfill the criteria for interval prolongation and continued using the standard dupilumab dosage (300mg/2 weeks), group B (n=30) prolonged dupilumab interval with 50% (300mg/4 weeks) and group C (n=30) prolonged dupilumab interval with 66-75% (300mg/6-8 weeks). AD severity score, patient-reported outcomes, serum dupilumab levels, and serum biomarkers were analyzed over time.

Results: Disease severity scores did not significantly change over time during the tapering period in any of the groups. In group B and C, the Numeric Rating Scale (NRS)-pruritus temporarily significantly increased after interval prolongation but remained low (median NRS-pruritus≤4). Median dupilumab levels remained stable in group A (standard dosage), but significantly decreased in group B and C (24.1mg/L (IQR=17.1-45.6); 12.5mg/L (IQR=1.7-22.3)) compared to the levels during the standard dosage (88.2mg/L (IQR=67.1-123.0, $p<0.001$)). Disease severity biomarker levels (CCL17/CCL18) remained low in all study groups during the whole observation period.

Conclusions: This study showed that dose reduction was successful in a subgroup of patients with controlled AD by using a patient-centered dosing regimen. These patients showed stable low disease activity and low severity biomarkers over time.

Introduction

Atopic dermatitis (AD) is one of the most common chronic and relapsing inflammatory skin diseases worldwide.[1] Better understanding of the underlying immune pathogenesis of AD has led to the development of new, more targeted therapies.[2] Dupilumab, a fully human monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4Rα), thereby blocking the IL-4 and IL-13 pathway. It is the first antibody-based treatment that became commercially available for the treatment of AD.[3] The registered dose of dupilumab for adult patients is a loading dose of 600mg subcutaneously, followed by 300mg every other week (Q2W). Results from dupilumab treatment in clinical trials[2, 4, 5] and daily practice[6, 7] show a clinically relevant improvement in physician-reported outcome measures and patient-reported outcome measures (PROMs). During long-term treatment with the standard dosage of dupilumab (Q2W) most of the patients AD remained controlled.[8] Continuing the standard dosage in patients with persistently controlled AD might lead to overtreatment and an increase in adverse events (e.g. injection side reactions, conjunctivitis).[9] Previous literature has shown a positive effect of interval prolongation in case of conjunctivitis.[10] The question arises whether interval prolongation in the case of stable disease can reduce costs and the risk of side effects, while maintaining clinical effectiveness. At present, no literature is available for different dupilumab dosing regimens in the case of persistently controlled AD. Only one daily practice study is published regarding the effectiveness of starting dupilumab Q4W, in this study the decision for dupilumab Q4W was based on economic capacity of patients instead of controlled disease.[11] Most of the current evidence on different biologic dosing regimens in case of controlled disease in daily practice includes biologic tapering in rheumatologic diseases and psoriasis. The European recommendations for rheumatoid arthritis (RA) already described tapering strategies for biologic treatments in RA patients with persistent remission.[12] In a recent tapering study with biologics in psoriasis, tight dose reduction did not lead to persistent flares or safety issues.[13] Based on these findings, a pragmatic daily practice patient-centered dupilumab dosing regimen was developed for patients with controlled AD during dupilumab treatment. The primary aim of this study was to clinically evaluate a patient-centered dupilumab dosing regimen in patients with controlled AD in daily practice and to relate this to serum drug levels. Our secondary aim was to provide insight into the course of biomarkers in the context of individual dosing of dupilumab.

Methods

Study design

This observational cohort study was performed at the department of Dermatology of the University Medical Center Utrecht and University Medical Center Groningen, the Netherlands. Ninety adult AD patients treated with dupilumab, who followed the patient-centered dosing regimen, were selected based on their dupilumab administration interval. All included patients participated in the prospective BioDay registry, which contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both patient-reported outcomes (PRO's) as well as clinical parameters. This study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18/239) and was performed according to the declaration of Helsinki. All patients provided written informed consent.

Patients and patient-centered dosing regimen

All patients received a loading dose of dupilumab 600mg subcutaneously administered by a clinician (treatment baseline, T0), followed by a standard maintenance dose of dupilumab 300mg Q2W subcutaneously administered during the first year of treatment. All patients were seen once every three months. A patient-centered dosing regimen for the treatment of dupilumab was developed and introduced from the beginning of 2019. This regimen was based upon tapering protocols of biological treatment in other diseases (e.g. psoriasis, RA)[13-15] and clinical experience. The injection intervals were stepwise prolonged guided by the Eczema Area and Severity Index (EASI) score. Patients were eligible for dose reduction after 52 weeks of dupilumab treatment (tapering baseline, T1) when the disease activity was controlled: EASI≤7, indicating mild disease activity or less[16], for at least six months. The actual decision for dose reduction of dupilumab was based on shared-decision making between patient and physician. First, the dosage was reduced to 66% of the standard dosage, by prolonging the interval to every three weeks (Q3W). If patients remained in a state of controlled disease (EASI score ≤7), the dosage was further reduced to 50% of the standard dosage, by doubling the original interval to every four weeks (Q4W). Subsequently, in case of persistently controlled disease, the dose was further reduced by gradually extending the interval to every six weeks (Q6W) (33% of the standard dosage) followed by every eight weeks (Q8W) (25% of the standard dosage). The interval was shortened in case of increased pruritus scores

reported by the patient, or increased physician-reported disease severity scores. Patients were divided after 52 weeks of treatment (based on their dupilumab administration interval) into three groups, A, B, and C (Figure 1).

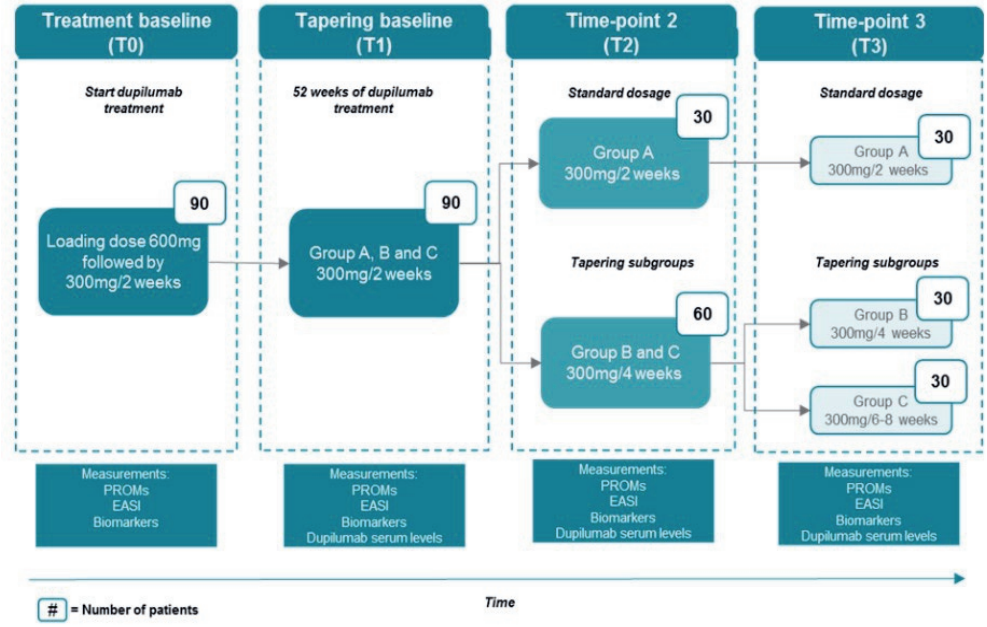


Figure 1. Study design with patient-centered dupilumab dosing regimen.

At T2 and T3 the dupilumab dose adjustment was at least 3 months prior to the measurements. PROMs, patient reported outcome measurements; EASI, Eczema Area and Severity Index.

Group A did not fulfill the criteria for dose reduction (e.g. uncontrolled disease or patients wish to continue standard dosage) and therefore continued standard dupilumab dosage (Q2W) throughout the whole observation period. Group B was able to prolong dupilumab interval with 50% (Q4W), and group C was able to prolong dupilumab interval with 66-75% (Q6W/Q8W) of the standard dosage. Due to the small number of patients who were able to taper to Q6W or Q8W, these two dosing groups were combined. Time point 2 (T2) and time point 3 (T3) differ individually due to the pragmatic approach of the patient-centered dosing regimen and daily practice setting with differences in treatment duration. However, the time of dose adjustment was at least 3 months prior to the measurements of disease severity, dupilumab serum levels, and serum biomarkers.

Outcome measures

In order to investigate the proportion of patients with persistently controlled disease despite dose reduction of dupilumab treatment, EASI score and weekly average Numeric Rating Scale (NRS)-pruritus were measured during every visit. Controlled AD in this study was defined as an EASI score ≤7[16]; NRS pruritus ≤4 was considered as a second treatment goal.[17]

Serum dupilumab levels

Serum dupilumab levels were measured at T1, T2 and T3 using an enzyme-linked immunosorbent assay (ELISA). Maxisorp microtiter plates were coated overnight at room temperature (RT) with 1 µg/mL monoclonal anti-dupilumab (clone 1G11). This is a chimeric antibody of rabbit origin, with a mouse IgG2b Fc, recombinantly expressed as described before.[18] After five times washing with PBS/ 0.02% Tween (PT), plates were incubated for 1 h at room temperature with patient serum samples, diluted 100-fold and 2000-fold in high performance ELISA buffer (HPE, Sanquin). Subsequently, the plates were washed with PT and incubated for 1 h with 0.5 µg/mL mouse monoclonal antihuman IgG4 (clone MH164.4, Sanquin). After washing, the ELISA was developed with 1-step ultra TMB-ELISA Substrate Solution (thermoFischer) diluted with MilliQ water (ratio 3:1). The reaction was stopped with 0.2 M HCl. Delta of the absorption at 450 and 540 nm was determined and compared to a titration curve of dupilumab in each plate. Lower Limit of Quantification is 0.3 µg/mL; accuracy and precision ranged from 87% to 102% and 4.4% CV to 12.2% CV.

Serum biomarkers

Serum biomarkers were measured at T0, T1, T2, and T3 using multiplex immunoassays as previously described.[19] Nineteen biomarkers associated with different disease pathways were measured: disease severity-associated markers (IL-22, pulmonary and activation-regulated chemokine (PARC/CCL18), thymus- and activation-regulated chemokine (TARC/ CCL17), periostin (OSF-2) and soluble interleukin-2 receptor alpha (sIL-2Rα)), Th2-associated markers (IL-4, IL-5, IL-13), Th17-associated markers (IL-6, IL-17, IL-22, IL-23), Th22-associated marker (IL-22), Th1-associated markers (IL-12 and IP-10), inflammatory markers (IL-1b, IL-10, GCSF, MCP1) and eosinophil markers (IL-5, eotaxin-1, eotaxin-3).

Statistical analysis

Data were analyzed for each study group at initiation of dupilumab treatment (T0), after 52 weeks of treatment (T1), and at the two time points (T2 and T3) after implementing the patient-centered dosing regimen. Differences in clinical outcome measures and biomarker levels between treatment baseline (T0) and tapering baseline (T1), and between tapering baseline (T1) and subsequent time points T2 and T3 were compared for each group separately using the paired Wilcoxon signed-rank test. Additionally, serum dupilumab levels at T2 and T3 were compared with tapering baseline (T1) using the paired Wilcoxon signed-rank test for the groups separately.
Serum dupilumab levels from group A (Q2W) were used as reference category for groups B and C to assess the effect of dose reduction on serum dupilumab levels. Differences in serum dupilumab levels were compared between the subgroups B and C vs. standard dosage group A at T1, T2 and T3 using the Mann Whitney test. Serum biomarker levels were compared between the subgroups A, B and C at each time point using the Wilcoxon signed-rank test. Serum biomarker levels were normalized by a log-transformation for the radar plots. False Discovery Rate was used to correct for multiple testing. P-values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc), Prism (version 7.4; GraphPad) and R (Version 1.3.1093).

Results

Patient population and patient-centered dosing regimen

A total of 90 adult AD patients with a follow-up of at least 91 weeks were included based on their dupilumab administration intervals. At dupilumab treatment initiation, the mean age was 42.4 (SD 16.4) and the majority of patients were male (65.6%, n=59). A total of 23 patients (25.6%) used immunosuppressive drugs at the start of dupilumab treatment (Table 1). The median EASI score at start of dupilumab (T0) was 17.9 (IQR=12.4-25.3) with no significant differences between the three subgroups (p=0.29). At T0, patients reported a median NRS pruritus score of 7.0 (IQR=5.0-8.0) with no significant differences between the three subgroups (p=0.15).

Table 1. Patient characteristics per study group

	Total	Group A Q2W	Group B Q4W	Group C Q6W/Q8W	p-value
n	90 (100)	30 (100)	30 (100)	30 (100)	
Gender (male), n (%)	59 (65.6)	18 (60.0)	23 (76.7)	18 (60.0)	0.38
Age, mean (SD)	42.4 (16.4)	36.2 (15.9)	47.6 (17.2)	43.3 (14.3)	0.29
BMI, mean (SD)	26.1 (5.4)	28.3 (6.1)	25.7 (6.2)	24.8 (3.2)	0.29
Missing	26 (28.9)	11 (36.7)	8 (26.7)	7 (23.3)	
Age at AD onset[a], n (%)					0.66
Childhood	80 (88.9)	28 (93.3)	26 (86.7)	26 (86.7)	
Adolescence	3 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	
Adulthood	7 (7.8)	1 (3.3)	3 (10.0)	3 (10.0)	
Atopic comorbidity[a], n(%)					
Allergic Asthma	54 (60.0)	19 (63.3)	21 (70.0)	14 (46.7)	0.29
Allergic Rhinitis	66 (73.3)	22 (73.3)	25 (83.3)	19 (36.3)	0.31
Allergic Conjunctivitis	56 (62.2)	20 (66.7)	21 (70.0)	15 (50.0)	0.31
Food allergy	46 (51.1)	19 (63.3)	11 (36.7)	16 (53.3)	0.29

[a]No missings were found for age at AD onset and atopic comorbidities. SD, Standard deviation; BMI, body mass index.

Clinical outcome measures

Differences in EASI score within study groups over time (Figure 2)

Dupilumab treatment led to a significant decrease of disease severity during the first year of treatment ($p<0.001$) with a median EASI score of 17.9 (IQR=12.4-25.3) at treatment baseline (T0) compared to a median EASI score of 2.7 (IQR=1.0-5.4) after one year of treatment (T1) in the total cohort. In group A (not fulfilling dose reduction criteria and continued standard dosage) disease severity was stable over time, with no significant differences observed in EASI scores comparing T1 with T2 and T3 ($p=0.27$ and $p=0.87$). At T1, T2 and T3 a total of 50.0%, 40.0% and 50.0% of the patients in group A had controlled AD (EASI ≤7), respectively. The most frequently reported reasons for continuation of standard dosage despite controlled disease were severe asthma and patient's wish (e.g. high pruritus score or fear for reoccurrence of symptoms). Additionally, the proportion of patients in whom AD remained controlled (EASI ≤7) despite dose reduction of dupilumab treatment was analyzed. At T2 (dosage Q4W for at least three months), 83.3 % (n=25) of the patients in group B, and 86.7% (n=26) of the patients in group C had controlled AD. No significant differences in EASI score were observed between T1 and T2 in both subgroups ($p=0.17$ and $p=0.79$).

At T3, an extended dosing interval of Q6W/Q8W had been applied in group C of which 28 patients (93.3%) had controlled AD, and no significant difference in EASI score was observed compared to T1 (p=0.19) (see Table 2 and Figure 2).

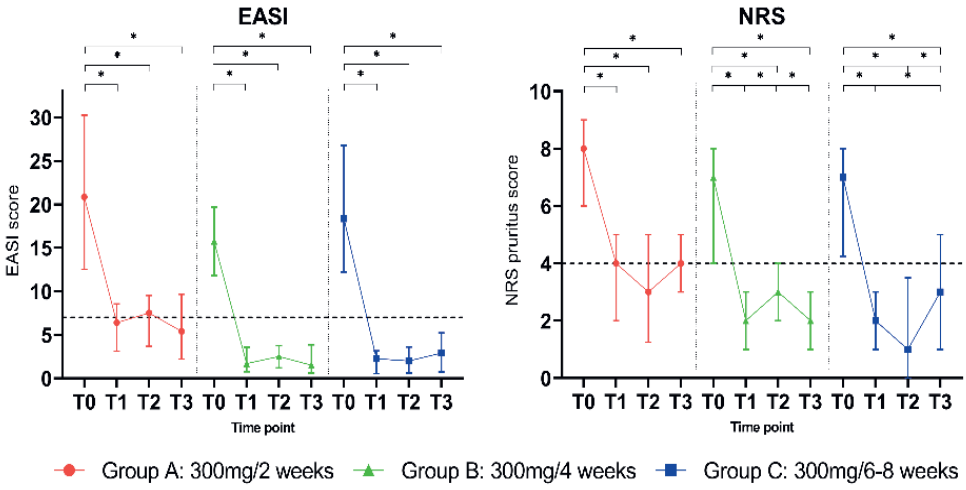


Figure 2. EASI and NRS scores per study group per time point.

Cut-off value EASI score of ≤7 indicating controlled AD; NRS-pruritus score of ≤4 is considered as a treatment goal. * p-value<0.05. Symbols represent medians with interquartile range (vertical lines).

Differences in NRS pruritus within study groups over time (Figure 2)

Dupilumab treatment significantly decreased NRS pruritus during the first year of treatment (p<0.001) with a median score of 7.0 (IQR=5.0-8.0) at treatment baseline (T0) compared to a median score of 2.0 (IQR=1.0-4.0) after one year of treatment (T1) in the total cohort. At T1, T2 and T3 a total of 65.4%, 70.0% and 68.8% of the patients in group A had NRS pruritus ≤4, respectively. In group A, NRS pruritus was stable over time, and no significant differences were observed in NRS pruritus comparing T1 with T2 and T3 (p=0.88 and p=0.47). At T2 (dosage Q4W for at least three months), 79.2% of the patients in group B, and 88.0% of the patients in group C had NRS pruritus ≤4. In the dose tapering group B, the median NRS pruritus score at T2 (median 3.0; IQR=2.0-4.0) was significantly higher compared to T1 (median 2.0; IQR=1.0-3.0; p=0.03). No significant difference for group B was found between T1 (median 1.7; IQR=0.75-3.6)) and T3 (median 1.5; IQR=0.6-3.9) (p=0.92). At T3 (dosage Q6W/Q8W for at least 3 months) 66.7% of the patients in group C had NRS pruritus ≤4. In group C, the median NRS pruritus score at T3 was significantly higher (median 3.0; (IQR=1.0-5.0) compared to T1 and T2, respectively, 2.0 (IQR=1.0-3.0), p=0.01 and 1.0 (IQR=0.0-3.5), p=0.03 (Table 2 and Figure 2).

Table 2. Treatment characteristics per study group for each time point

	Treatment BL (T0)	Tapering BL (T1)	Time point 2 (T2)	Time point 3 (T3)
Group A: Q2W, n	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.4 (3.7)	84.5 (8.6)	115.3 (15.7)
Immunosuppressant use, n (%)	8 (26.7)	2 (6.7)	2 (6.7)	2 (6.7)
Missing	1 (3.3)	9 (30.0)	11 (36.7)	7 (23.3)
EASI score, median (IQR)	20.9 (12.5-30.3)	6.4 (3.1-8.6)	7.5 (3.7-9.5)	5.4 (2.2-9.7)
Missing	0 (0)	1 (3.3)	4 (13.3)	1 (3.3)
Weekly average pruritus NRS, median (IQR)	8.0 (6.0-9.0)	4.0 (2.0-5.0)	3.0 (1.3-5.0)	4.0 (3.0-5.0)
Missing	5 (16.7)	4 (13.3)	10 (33.3)	14 (46.7)
Serum TARC levels, median (IQR)	2890 (1086-8040)	418.0 (315-951)	371 (180-685)	556 (298-817)
Missing	0 (0)	2 (6.7)	4 (13.3)	5 (16.7)
Serum dupilumab levels, median (IQR)	n.a.	95.4 (40.6-108.8)	71.4 (44.2-101.2)	73.6 (38.0-118.0)
Missing	n.a.	0 (0)	4 (13.3)	0 (0)
Group B: Q4W, n	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.1 (4.0)	115.5 (22.6)	141.0 (22.5)
Immunosuppressant use, n (%)	6 (20.0)	2 (6.7)	1 (3.3)	1 (3.3)
Missing	0 (0)	10 (33.3)	7 (23.3)	3 (10.0)
EASI score, median (IQR)	15.8 (11.8-19.7)	1.7 (0.75-3.6)	2.5 (1.2-3.8)	1.5 (0.6-3.9)
Missing	0 (0)	1 (3.3)	0 (0)	0 (0)
Weekly average pruritus NRS, median (IQR)	7.0 (4.0-8.0)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	2.0 (1.0-3.0)
Missing	1 (3.3)	1 (3.3)	6 (20.0)	7 (23.3)
Serum TARC levels, median (IQR)	1414 (900-2949)	291.0 (211-438)	301.0 (211-427)	291 (203-407)
Missing	0 (0)	2 (6.7)	0 (0)	2 (6.7)
Serum dupilumab levels, median (IQR)	n.a.	88.9 (65.3-127.0)	24.1 (17.1-45.6)	28.6 (11.7-47.9)
Missing	n.a.	1 (3.3)	0 (0)	0 (0)

Table 2 (continued). Treatment characteristics per study group for each time point

	Treatment BL (T0)	Tapering BL (T1)	Time point 2 (T2)	Time point 3 (T3)
Group C: Q6W/Q8W, n	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.7 (3.4)	95.7 (20.2)	139.6 (22.1)
Use of immunosuppressive drugs, n (%)	9 (30.0)	0 (0)	2 (6.7)	1 (3.3)
Missing	0 (0)	10 (33.3)	13 (43.3)	7 (23.3)
EASI score, median (IQR)	18.4 (12.2-26.8)	2.3 (0.6-3.1)	2.0 (0.6-3.6)	2.9 (0.7-5.2)
Missing	0 (0)	0 (0)	3 (10.0)	0 (0)
Weekly average pruritus NRS, median (IQR)	7.0 (4.3-8.0)	2.0 (1.0-3.0)	1.0 (0.0-3.5)	3.0 (1.0-5.0)
Missing	2 (6.7)	2 (6.7)	5 (16.7)	3 (10.0)
Serum TARC levels, median (IQR)	2948 (1186-6945)	364.0 (204-476)	281.0 (213-578)	296 (185-570)
Missing	0 (0)	1 (3.3)	3 (10.0)	2 (6.7)
Serum dupilumab levels, median (IQR)	n.a.	82.0 (66.8-101.0)	25.8 (20.3-48.8)	12.5 (1.7-22.3)
Missing	n.a.	0 (0)	3 (10.0)	0 (0)

BL, baseline; IQR, Interquartile range; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; TARC, Thymus- and activation-regulated chemokine. n.a. non-applicable.

Serum dupilumab levels

In the standard dosage group A, serum dupilumab levels remained stable over time. The median dupilumab levels in the individual dosing groups B and C decreased significantly from a median of 88.9 mg/L (IQR=65.3-127), and 82.0 mg/L (IQR=66.8-101.0) at T1 to 24.1 mg/L (IQR=17.1-45.6), and 25.8 mg/L (IQR=20.3-48.8) at T2 ($p<0.001$, $p<0.001$). In patients tapering dupilumab to Q6W/Q8W (group C) serum dupilumab levels further decreased to 12.5 mg/L (IQR=1.7-22.3) at T3 ($p< 0.001$) (Figure 3). As expected, significantly higher serum dupilumab levels were observed in the standard dosage group (A) compared to the study groups B and C at T2 and T3 ($p<0.001$ and $p<0.001$).

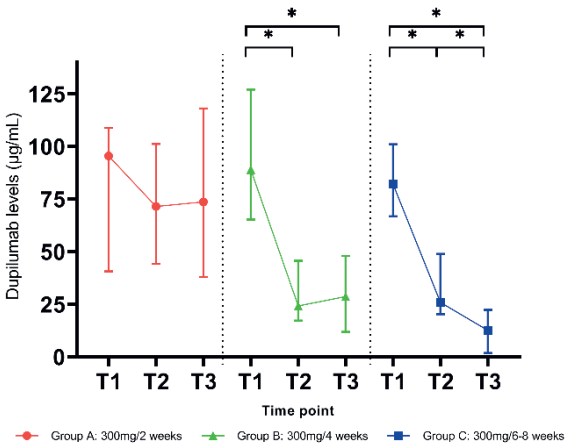


Figure 3. Serum dupilumab levels per study group at each time point.

* p-value<0.05. Symbols represent medians with interquartile range (vertical lines).

Serum biomarker levels

A total of 19 serum biomarkers were measured via multiplex immunoassays. Extreme outliers (n=4 patients) were excluded due to possible detection errors. In all subgroups, severity-related serum biomarkers PARC/CCL18 ($p=0.001$) and TARC/CCL17 ($p=0.001$) significantly decreased during the first year of dupilumab treatment (all patients using Q2W) (Figure 4). During the tapering period PARC/CCL18 and TARC/CCL17 remained low in all groups at all time points (T1, T2 and T3). Looking at the effect of tapering on the other serum biomarkers levels, no relevant significant differences were found for other severity-associated biomarkers and Th1, Th2, Th17-related markers in group A (only MCP1 had a significant difference at T3 compared to T1), group B, and group C at T2 and T3 compared to

T1 (Supplementary Figure 1). Radar plots were used to visualize differences in biomarker levels between groups A, B and C for each time point (Supplementary Figure 2). The biomarker profiles of the different dupilumab dosing groups were largely overlapping at each time point with no significant differences between the study groups. This indicates that the biological markers were stably low during tapering of dupilumab in AD with no effect of interval prolongation on biological activity regarding the selected biomarkers.

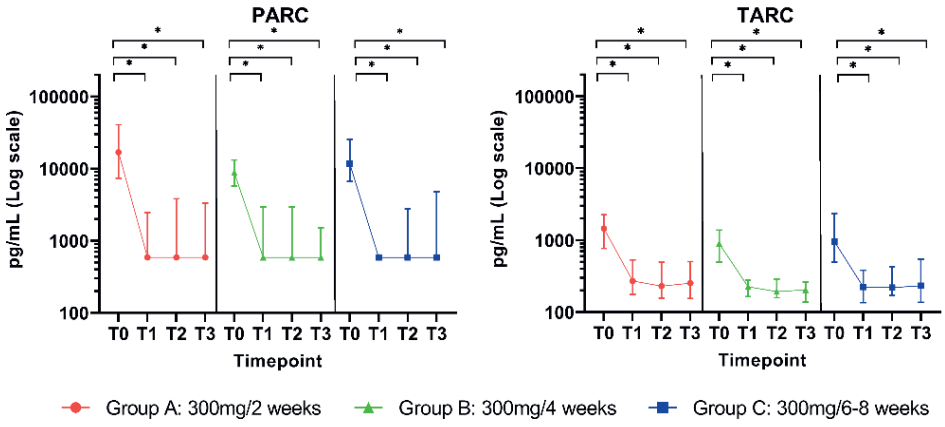


Figure 4. Significant differences over time in serum levels of disease severity biomarker TARC and PARC within study groups.

*p-value<0.05. In the clustered graphs, symbols represent medians with interquartile range (vertical lines). PARC/CCL18, pulmonary and activation-regulated chemokine; TARC/CCL17, Thymus- and activation-regulated chemokine.

Discussion

In this study dose reduction was successful in a subgroup of patients with controlled AD by using a patient-centered dupilumab dosing regimen. Disease activity and severity biomarkers remained low and stable over time. Although, NRS scores temporarily increased after interval prolongation, the changes in NRS scores were small and NRS scores remained low (median NRS scores ≤4).

To our knowledge, only one study (SOLO-continue) has investigated the effect of different dupilumab dosing regimens on disease activity.[20] This randomized controlled trial was a continuation of the SOLO study, in which patients continued dupilumab treatment in different dose regimens. High-responding dupilumab-

treated patients at week 16 (reaching EASI-75 or IGA 0-1) in the SOLO-continue study were re-randomized 2:1:1:1 to continue their original regimen of dupilumab (Q1W or Q2W) or to receive dupilumab Q4W or Q8W or a placebo for 36 weeks. In contrary to our study, the authors in the SOLO-continue study concluded that dose reduction resulted in a diminution of response for all endpoints (including EASI and NRS pruritus) and therefore recommended the approved regimen of dupilumab Q2W for long-term treatment.[20] Dose reduction was applied based on IGA or relative delta EASI at an early point in the treatment (16 weeks) without the possibility of tapering slowly over time. In our study, a patient-centered dosing regimen was used based on absolute EASI score (mild disease) for at least 6 months and shared-decision making, and started after a much longer treatment period of 52 weeks. In addition, the dosing interval was gradually prolonged and every dose adjustment lasted at least 3 months before initiating the next dose adjustment. Since our study was a daily practice study, all cases were evaluated individually at all time points. The shared-decision making and tapering after persistent controlled disease might explain why prolonging the dupilumab dosing interval was more successful in our study compared to the SOLO-continue study. Additionally, Lee et al. analyzed clinical practice data on the clinical efficacy of dupilumab Q4W and concluded that monthly dupilumab therapy was clinically effective and safe in adult patients with moderate-to-severe AD.[11] The dosing of dupilumab Q4W was not decided by disease activity or patient characteristics but by the patients themselves and mainly based on their economic capacity (due to lack of reimbursement of dupilumab in their country). Additionally, 70.2% (40/57) of the AD patients who received dupilumab Q4W had concomitant treatment with weekly methotrexate. Lee et al. showed EASI-50 and EASI-75 responses in 84.2% and 47.4% of the AD patients using dupilumab Q4W at week 16[11] compared to EASI-50 (85.7%–98.1%) and EASI-75 (60.6%–81.5%) response rates for patients using dupilumab Q2W at week 16 in other recently published real-world studies.[21-24] These results indicate that starting dupilumab treatment with a prolonged dosing interval may result in an overall less favorable treatment outcome, which was not the case in our individual dose reduction protocol based on disease activity. Although AD remained controlled in the majority of patients in groups B and C (EASI≤7), NRS scores temporarily increased after dose reduction. The clinical relevance of these differences are questionable as the changes in NRS scores were small and inconsistent and median NRS scores remained ≤4, which is also considered as a treatment target.[17]

In our study, serum dupilumab levels (Q2W) were comparable to levels described in clinical trials.[25-27] While serum dupilumab levels decreased significantly over time in the dose reduction groups (group B and C), the EASI score remained remarkably stable and low in these study groups. Although the precise mechanism of action of dupilumab has not been completely elucidated[28], binding of dupilumab to (skin homing) T- and B-cells seems to be able to reduce Th2-related cytokines and IgE production.[29-32] Sufficient clinical response despite dose reduction might be explained by persistent IL-4Rα saturation by dupilumab due to a relatively high concentration of dupilumab in sera or inter-patient variability in the target receptor (IL-4Rα) availability. Perhaps IL-4Rα saturation by dupilumab can also be achieved with lower serum dupilumab levels, and full IL-4Rα saturation might not even be needed to achieve maximum clinical effectiveness. Therefore, more research is necessary to determine inter-patient variability and the pharmacokinetics of dupilumab in different dosing regimens[33] and to determine how drug levels are related to IL-4Rα saturation and clinical effectiveness.

The biomarker profiles of the different dupilumab dosage groups were largely comparable over time. Additionally, the severity markers PARC/CCL18 and TARC/CCL17 remained significantly lower at every time point for all subgroups compared to severity marker levels at the time of start of dupilumab treatment. Previous studies observed significantly suppressed type-2 inflammatory biomarkers in serum, including TARC/CCL17 and PARC/CCL18, after 16 weeks of dupilumab treatment.[30,32] After 52 weeks of dupilumab treatment, Bakker et al. found that dupilumab treatment completely blocked IL-4Rα expression, accompanied by a decrease in serum TARC/CCL17 levels, and a rapid decrease of Th2 and Th22 cytokine production.[29] In our study disease severity markers also remained low during a follow-up of at least 91 weeks, despite dose reduction of dupilumab. Other biomarkers also did not change while tapering dupilumab in persistently controlled AD compared to standard dosage (dupilumab Q2W) suggesting stable disease over time despite dose tapering.

Limitations

This study has some limitations. Firstly, the included patients were divided into three study groups based on their dupilumab administration interval. As a result, this study subscribes the ability of dose reduction on an individual level but more research is needed to determine the percentage of successful (and unsuccessful) dose reduction

in daily practice as patients who shortened interval after dose reduction were not included. Secondly, the patient-centered dosing regimen was based on controlled AD. Patients in group A, who were not eligible for or did not agree with dose tapering, showed higher disease severity scores compared to the groups B and C. Therefore, a direct comparison between standard dosing and dose reduction was not feasible in this study design.

Conclusion

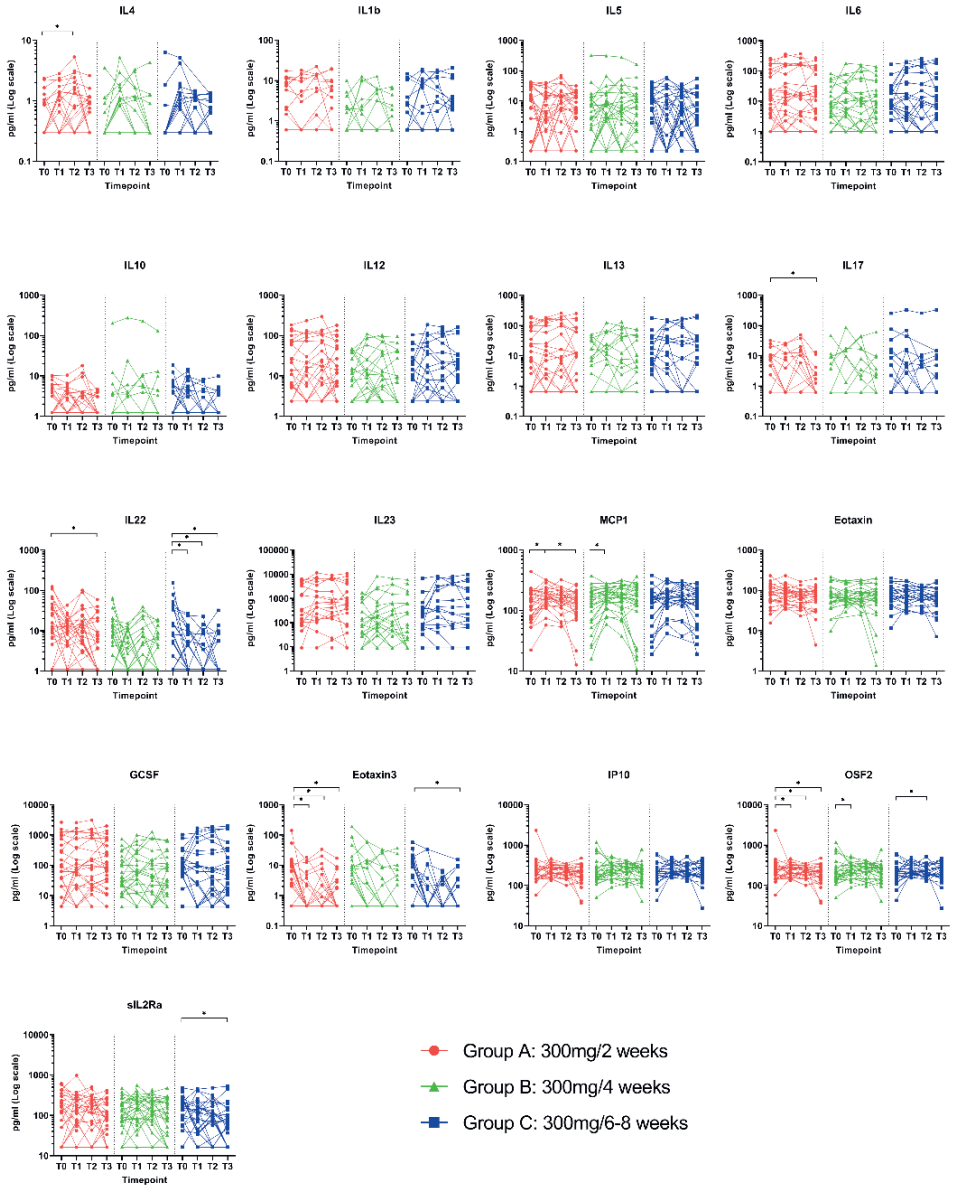
This study showed that patient-centered dose reduction after 52 weeks of dupilumab was successful in a subgroup of patients with persistently controlled AD. Despite significantly lower dupilumab levels, the EASI score and disease severity biomarkers (TARC/CCL17 and PARC/CCL18) in group B (Q4W) and C (Q6W/Q8W) remained low and stable. These findings are the first step towards personalized dupilumab treatment for controlled AD patients in clinical practice.

References

1. Weidinger, S. and N. Novak, *Atopic dermatitis.* Lancet, 2016. **387**(10023): p. 1109-1122.
2. Thaci, D., et al., *Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.* Lancet, 2016. **387**(10013): p. 40-52.
3. Beck, L.A., et al., *Dupilumab treatment in adults with moderate-to-severe atopic dermatitis.* N Engl J Med, 2014. **371**(2): p. 130-9.
4. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
5. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE).* Br J Dermatol, 2018. **178**(5): p. 1083-1101.
6. de Wijs, L.E.M., et al., *Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data.* Br J Dermatol, 2020. **182**(2): p. 418-426.
7. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
8. Wu, J.J., et al., *Dupilumab Maintains Long-Term Disease Control in Adults with Moderate-to-Severe Atopic Dermatitis as Measured by Well-Controlled Weeks: Results From the LIBERTY AD CHRONOS Clinical Trial.* Dermatol Ther (Heidelb), 2021. **11**(2): p. 327-330.
9. Deleuran, M., et al., *Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study.* J Am Acad Dermatol, 2020. **82**(2): p. 377-388.
10. Achten, R., et al., *Long-term follow-up and treatment outcomes of conjunctivitis during dupilumab treatment in patients with moderate-to-severe atopic dermatitis.* J Allergy Clin Immunol Pract, 2021. **9**(3): p. 1389-1392 e2.
11. Lee, Y., M.E. Kim, and D.H. Nahm, *Real Clinical Practice Data of Monthly Dupilumab Therapy in Adult Patients With Moderate-to-Severe Atopic Dermatitis: Clinical Efficacy and Predictive Markers for a Favorable Clinical Response.* Allergy Asthma Immunol Res, 2021. **13**(5): p. 733-745.
12. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update.* Ann Rheum Dis, 2020. **79**(6): p. 685-699.
13. Atalay, S., et al., *Comparison of Tightly Controlled Dose Reduction of Biologics With Usual Care for Patients With Psoriasis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(4): p. 393-400.
14. van Herwaarden, N., et al., *Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity.* Clin Exp Rheumatol, 2014. **32**(3): p. 390-4.
15. van Herwaarden, N., et al., *Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity.* Cochrane Database Syst Rev, 2014(9): p. CD010455.
16. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.
17. De Bruin-Weller, M., et al., *Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies.* Acta Derm Venereol, 2021. **101**(2): p. adv00402.
18. Grosserichter-Wagener, C., et al., *Biased anti-idiotype response in rabbits leads to high-affinity monoclonal antibodies to biologics.* MAbs, 2020. **12**(1): p. 1814661.
19. Bakker, D.S., et al., *Confirmation of multiple endotypes in atopic dermatitis based on serum biomarkers.* J Allergy Clin Immunol, 2021. **147**(1): p. 189-198.

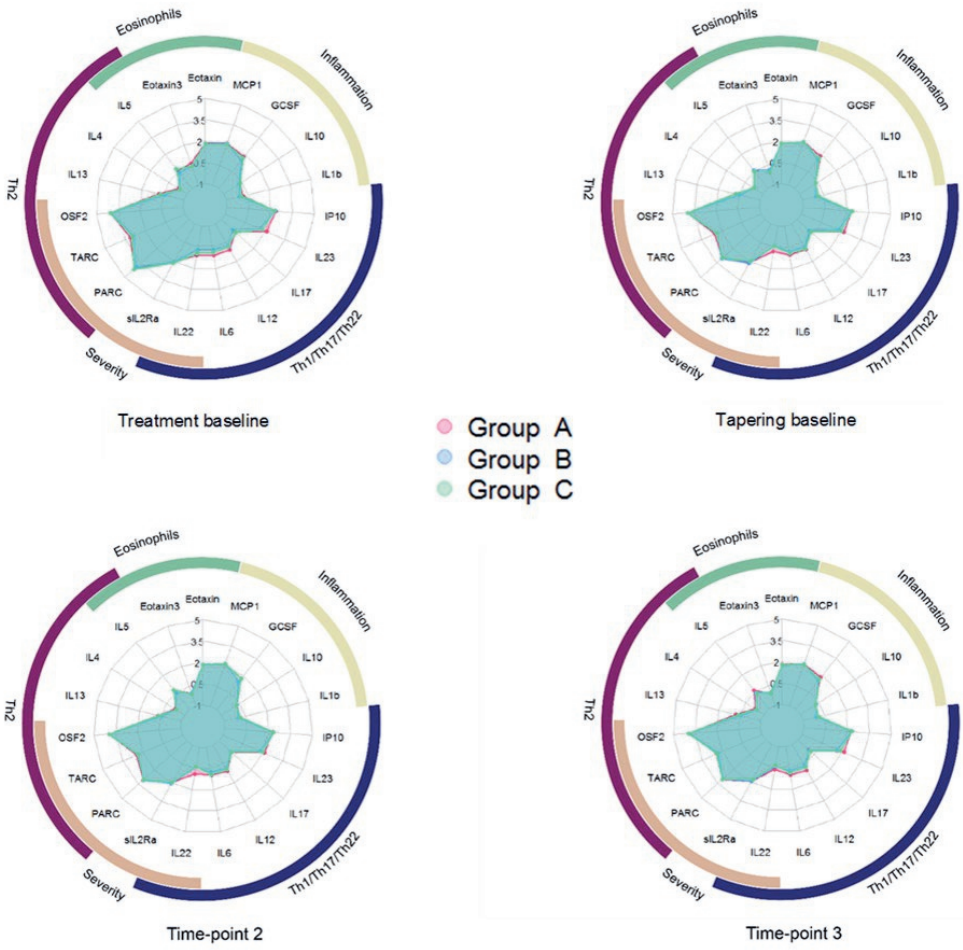
20. Worm, M., et al., *Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(2): p. 131-143.
21. Halling, A.S., et al., *Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis.* J Am Acad Dermatol, 2021. **84**(1): p. 139-147.
22. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2020. **75**(1): p. 116-126.
23. Nettis, E., et al., *Use of Dupilumab for 543 Adult Patients with Moderate-To-Severe Atopic Dermatitis: A Multicenter, Retrospective Study.* J Investig Allergol Clin Immunol, 2020: p. 0.
24. Fargnoli, M.C., et al., *Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis.* J Dermatolog Treat, 2021. **32**(5): p. 507-513.
25. *HIGHLIGHTS OF PRESCRIBING INFORMATION DUPILUMAB*. 2017 December 2021; Available from: https://www.regeneron.com/downloads/dupixent_fpi.pdf.
26. Matera, M.G., et al., *Monoclonal antibodies for severe asthma: Pharmacokinetic profiles.* Respir Med, 2019. **153**: p. 3-13.
27. Clot, P.F., et al., *Dupilumab pharmacokinetics in Chinese healthy subjects and patients with atopic dermatitis: Results of two randomized, double-blind, placebo-controlled studies*. Int Immunopharmacol, 2021. **99**: p. 107985.
28. Harb, H. and T.A. Chatila, *Mechanisms of Dupilumab.* Clinical and Experimental Allergy, 2020. **50**(1): p. 5-14.
29. Bakker, D.S., et al., *Early and Long-Term Effects of Dupilumab Treatment on Circulating T-Cell Functions in Patients with Moderate-to-Severe Atopic Dermatitis.* J Invest Dermatol, 2021. **141**(8): p. 1943-1953 e13.
30. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.
31. Punnonen, J., et al., *Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells.* Proc Natl Acad Sci U S A, 1993. **90**(8): p. 3730-4.
32. Le Floc'h, A., et al., *Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Ralpha antibody, is required to broadly inhibit type 2 inflammation.* Allergy, 2020. **75**(5): p. 1188-1204.
33. Weidinger, S., et al., *Atopic dermatitis.* Nat Rev Dis Primers, 2018. **4**(1): p. 1.

Supplement



Supplementary Figure 1. Other serum biomarker levels over time.

*p-value<0.05. Individual biomarkers serum levels are presented on a Log-scale to increase interpretability. The following biomarkers are shown: disease severity-associated markers (IL-22, periostin (OSF-2), soluble interleukin-2 receptor alpha (sIL-2Rα)), Th2-associated markers (IL-4, IL-5, IL-13), Th17-associated markers (IL-6, IL-17, IL-22, IL-23), Th22-associated marker (IL-22), Th1-associated markers (IL-12, IP-10), inflammatory markers (IL-1b, IL-10, GCSF, MCP1) and eosinophil markers (IL-5, eotaxin-1, eotaxin-3).



Supplementary Figure 2. Biomarker levels per study group for each time point.

Averages of log-transformed serum biomarker data compared per study group: A (pink), B (blue), C (green) for all time points, to evaluate the effect of tapering on serum biomarkers. Radar plots show biomarker profiles per study group for selected markers of different pathways. Spoke lengths represent means of log-transformed data per biomarker. The study groups A, B, and C are plotted simultaneously and almost entirely overlap. The radar plots show no differences in the biomarker profile at each time point between the study groups.

9

Successful tapering of dupilumab in atopic dermatitis patients with low disease activity: a large pragmatic daily practice study from the BioDay registry

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Abstract

Background: Limited data is available on patient-centered dosing of dupilumab for atopic dermatitis (AD) in daily practice.

Objective: To evaluate our patient-centered dupilumab dosing regimen in daily practice. Secondary, to assess predictors for successful tapering and to estimate cost savings.

Methods: This prospective study included adult AD patients treated with dupilumab for at least 1.3 years and participating in the BioDay registry. Interval prolongation was considered in case of dupilumab standard dose for ≥1year and persistent controlled AD (Eczema Area and Severity Index (EASI≤7); ≥six months). Primary endpoints were the mean EASI-score and Numeric Rating Scale (NRS)-pruritus after start of tapering. Predictors for successful tapering were analyzed with logistic regression and a cost saving analysis was performed.

Results: A total of 595 patients were included, of which 401 patients (mean EASI-score 2.5 (Standard deviation (SD) 2.3); NRS pruritus of 2.4 (SD 1.9) at start tapering) prolonged dupilumab interval. In 83.3% of the patients tapering was successful; most patients used dupilumab every 3 or 4 weeks (Q3W/Q4W). A significant effect over time was observed for EASI-score ($p<0.0001$; highest mean 3.5) and NRS pruritus ($p<0.0001$; highest mean 3.2), however scores remained low. Predicting successful tapering showed non-significant odds ratios for all incorporated variables. The total estimated cost saving was 3,977,033.98 EUR for 401 patients between January 2019 and June 2022.

Conclusions: Our patient-centered dosing regimen was successful in 83.3% of the patients while maintaining controlled disease, with the majority using dupilumab Q3W/Q4W. In total, 401 patients tapered dupilumab with an estimated cost saving of 3,977,033.98 EUR between January 2019 and June 2022.

Introduction

Atopic dermatitis (AD) is a complex and heterogeneous skin disorder characterized by a disrupted epidermal barrier function, skin inflammation and chronic pruritus. Knowledge of the immunological pathogenesis of AD has expanded in the past decade leading to development of new advanced targeted treatments. One of these treatments is dupilumab, a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor α (IL-4Rα), thereby inhibiting IL-4 and IL-13 cytokine pathways. Based on clinical trials, the label recommends a loading dose of dupilumab 600milligrams (mg) subcutaneously followed by a maintenance dose of 300mg every other week (Q2W).[1] Results from dupilumab treatment in daily practice showed a clinically relevant improvement of physician- and patient-reported outcome measures and the majority of patients maintain controlled AD in the long-term using the standard dosage of 300mg Q2W.[2]

Despite dupilumab's effectiveness, antibody-based treatment can have some disadvantages such as adverse events (AEs) and high costs.[3] Experience with dose reduction of dupilumab while maintaining clinical effectiveness enables individual dosing, which will benefit the patient as well as lowering budget impact. We recently investigated the safety and effectiveness of a patient-centered dosing regimen on individual patient level.[4] This study showed that dose reduction was successful and safe in a subgroup of patients with controlled AD. However, more research is needed to determine the percentage of successful (and unsuccessful) dose reduction in daily practice and to identify predictors for successful tapering.

Therefore, the aim of this study was to evaluate our patient-centered dupilumab dosing regimen in a large daily practice cohort. Our secondary aim was to identify clinical characteristics for successful tapering and to estimate the cost savings.

Methods

Study design and patient population

This study was part of the BioDay registry,[5] a prospective, observational cohort study that included all consecutive AD patients who started dupilumab. In this study adult AD patients were selected who started dupilumab with a treatment duration of at least one year and three months (e.g., at least one follow-up measurement after implementing our patient-centered dosing regimen). In case of multiple treatment

episodes, the longest treatment episode was taken into consideration. The data lock of this study took place in June 2022.

Since dupilumab is also indicated for the treatment of asthma, interval prolongation might lead to an asthma exacerbation in AD patients with comorbid asthma. For this reason, patients with severe comorbid asthma (e.g. systemic prednisone use or yearly hospital admission) were advised to continue the recommended dose of dupilumab 300mg Q2W (n=5). Patients who tapered before 52 weeks due to AEs and did not have controlled disease (n=7) or used 300mg every week (n=13) were excluded as they did not fulfill the criteria for the patient-centered dosing regimen.

The BioDay registry was considered non-interventional by the local medical ethics committee (METC 18/239) and was performed according to the Helsinki Declaration. All patients provided written informed consent.

Patient-centered dosing regimen

At baseline, all patients received a loading dose of dupilumab 600mg subcutaneously, followed by dupilumab 300mg Q2W in the first year. A standardized patient-centered dosing regimen for dupilumab treatment was developed and has been applied within the BioDay registry since 2019. This protocol was based upon tapering protocols of biological treatment in other diseases (e.g., psoriasis, rheumatoid arthritis) and clinical experience. Dupilumab interval prolongation was considered in case of treatment with dupilumab Q2W for at least one year and controlled AD (absolute cut-off score EASI≤7[6]) for at least six months, as previously described.[4] Patients continued with the longest possible dosing interval. In case of disease flares and inadequate response to intensifying topical treatment, patients returned to the previous effective dose interval. During each visit the amount of topical steroids used per week was recorded with the following categories: 0/0-10/10-30/>30 grams.

Clinical outcome measures

The primary outcome measures, disease severity, was assessed at every visit with the EASI[6] and the Numeric Rating Scale (NRS) (range 0-10)[7] (average weekly pruritus). Secondary endpoints were the proportions of patients achieving absolute cutoff scores EASI≤7 (indicating controlled disease[6]), IGA ≤2 (indicating mild disease[8]), and NRS pruritus≤4 (considered as Treat-to-Target[9]).

Successful tapering

Patients, in whom the dosing interval had to be shortened to Q2W and who continued Q2W at least 50% of the follow-up time, were defined as 'tapering failures'. Patients who shortened interval but maintained a prolonged interval (e.g. every four weeks (Q4W) to every three weeks (Q3W)) or did another tapering attempt and succeeded (e.g. ≥ 50% of the follow-up time prolonged interval) were not considered as 'tapering failures'. Every patient with a dose reduction who did not adhere to the definition of 'tapering failure' was considered as successful.

Cost saving analysis

Cumulative reduced dupilumab doses and costs were compared with the standard dose during the whole observation period (patient-centered dosing regimen was implemented since 2019, data lock June 2022). The cumulative dose after tapering baseline until June 2022 was calculated for each patient and corrected for treatment duration per dose interval. Indirect costs, such as other medical costs or visit costs, were not included. Dupilumab costs were based on actual Dutch prices during the study.

Statistical analyses

Tapering baseline was defined as start of tapering. Due to the pragmatic daily practice approach of this study, the timing of the tapering baseline differed per patient. The percentage of patients per dosing interval after one year was determined by examining the distribution of different dosing intervals at every visit. The effect of the tapering protocol on the primary outcomes EASI and NRS over time was analyzed with a linear regression model. We included a residual covariance (i.e. GEE-type) matrix in the model to correct for multiple measurements over time within patients. Results were reported as means with 95% confidence intervals. Only patients who actually attempted to taper dupilumab were included. We therefore calculated one overall p-value for time with a likelihood ratio test.[10]

Lastly, predictors for successful tapering, defined as patients with a prolonged interval ≥Q3W were analyzed with logistic regression. We defined the following possible determinants for successful dose tapering: gender, age, BMI, time of onset AD, presence of atopic comorbidities (allergic asthma; allergic rhinitis; allergic conjunctivitis; food allergy), referral hospital, and EASI, IGA, NRS pruritus score, and eosinophils at start of dupilumab treatment and at start of tapering (tapering baseline). For continuous predictors (e.g. age), the assumption of linearity was

assessed with restrictive cubic splines.[11] Estimation of the logistic regression models was performed with Firth's correction, as we included a relative high number of predictors in the analysis.[12] Results were presented as odds ratios with 95% confidence intervals and p-values. Prior to the analysis, we noted missing values on multiple predictors. As a complete case analysis may result in biased results and loss of statistical power, we decided to apply multiple imputation (MI) for the logistic regression. The MI was performed with predictive mean matching for continuous variables and logistic regression for categorical variables. All the pre-specified predictors as well as the outcome were included in the imputation. Data was imputed 50 times based on the number of patients with incomplete data[13], the analysis was performed on each imputed dataset. Results were subsequently pooled with Rubin's rule. All data were analyzed using IBM SPSS Statistics 26.0.0.1 (IBM, Armonk, NY, U.S.A.) and SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline and treatment characteristics for the total cohort

A total of 595 BioDay patients (mean age 42.0, standard deviation (SD) 15.4) with a treatment duration of at least 1 year and 3 months were included, 356 patients (59.8%) were male. The mean EASI score before start of dupilumab treatment was 18.2 (SD 11.8). Patients reported a mean NRS pruritus score of 6.8 (SD 2.3) at treatment initiation (Table 1). Patients with controlled disease (EASI≤7), who tapered dupilumab before one year (e.g. due to patient wish or AEs) of treatment but continued the dosing regimen, were also included (n=34).

Table 1. Patient and baseline characteristics for the total cohort and tapering cohort.

	Total cohort (start of treatment)	**Tapering cohort (start of tapering)**
N (%)	595 (100)	401 (100)
Male, n (%)	356 (59.8)	253 (63.1)
Age, mean (SD)	42.0 (15.4)	43.1 (15.3)
Missing	0	0
BMI, mean (SD)	25.5 (4.6)	-
Missing	158	
Age at AD onset, n (%)		
Childhood	488 (84.4)	327 (83.4)
Adolescence	33 (5.7)	24 (6.1)
Adulthood	57 (9.9)	41 (10.5)
Missing	17	9
Use of immunosuppressive therapy[a]	145 (24.8)	9 (2.2)
Missing	11	66
Atopic comorbidity		
Allergic Asthma, n (%)	330 (56.6)	222 (56.5)
Missing	12	8
Allergic Rhinitis, n (%)	389 (66.6)	267 (67.8)
Missing	11	7
Allergic Conjunctivitis, n (%)	338 (58.6)	236 (60.4)
Missing	18	10
Food allergy, n (%)	264 (45.8)	178 (45.6)
Missing	18	11
EASI score, mean (SD)	18.2 (11.8)	2.5 (2.3)
Missing	13	34
IGA score, median (IQR)	3.0 (3.0-4.0)	1.0 (1.0-2.0)
Missing	19	32
Weekly average pruritus NRS score, mean (SD)	6.8 (2.3)	2.4 (1.9)
Missing	102	71
Eosinophils levels, median (IQR), (x10*9/L)	0.3 (0.2-0.5)	0.3 (0.2-0.5)
Missing	41	83

Patients were recorded as using immunosuppressive therapy when prednisone or cyclosporine had been used within 1 week before assessment of the outcome measurements, in the case of methotrexate, 4 weeks was taken into account. BMI, body mass index; BL, baseline; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; IQR, interquartile range; NRS, Numerical Rating Scale; SD, standard deviation.

Overview of dupilumab dosing interval per visit

Visit 1 year + 6 months was completed by 504 patients; 262/504 (52.0%) patients were on a prolonged dupilumab interval, mainly Q3W or Q4W *(Figure 1)*. One year after the start of the implementation of the protocol (n=392, visit 2 years), more than half of the patients (234/392, 59.7%) were on a prolonged interval. Most of these patients used dupilumab Q3W (110/392, 28.1%) or Q4W 81/392, 20.7%), while 43/392 patients (11.0%) had a dupilumab interval of 5 weeks or longer (≥Q5W). At visit 3 years (n=200), 73.5% (n=147) of the patients had a prolonged interval, 21.5% (43/200) of the patients had a dose reduction of more than 50% with a dupilumab dose interval of ≥Q5W. After 3.5 year of treatment (n=134), a quarter of all patients (34/134) was able to reduce the dose with more than 50% (≥Q5W).

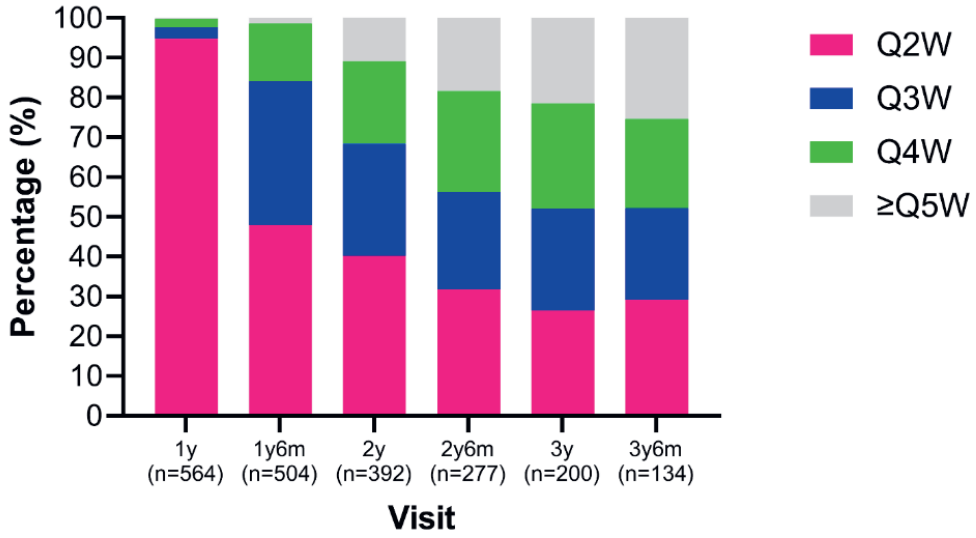


Figure 1. Overview of dupilumab dosage per visit.

Q2W, every other week; Q3W, every three weeks; Q4W, every four weeks; Q5W, every five weeks; y, year; m, month

Primary and secondary endpoints after implementing the patient-centered dupilumab dosing regimen

Over time, 401/595 (67.4%) patients prolonged dupilumab interval; mean treatment duration at start of tapering (tapering baseline) was 65.5 (SD 25.3) weeks, with a mean EASI score of 2.5 (SD 2.3) and NRS pruritus of 2.4 (SD 1.9) at start of tapering (Table 1). Mean EASI score in the tapering cohort (n=401) changed significantly over time (p<0.001) (Figure 2), with an increase to 3.1 (95% CI: 2.7-3.4) at 3 months and 3.0 (95% CI: 2.6-3.4) at 6 months after tapering. The mean EASI score remained low with the highest estimated mean being 3.5 (95% CI 2.7-4.2) after 18 months of tapering. Notably, the upper limits of all CIs remained below 7, the cut-off point for mild disease. Over time, the actual percentage of patients with EASI≤7 during tapering ranged between 79.3% and 94.3% (Table 2).

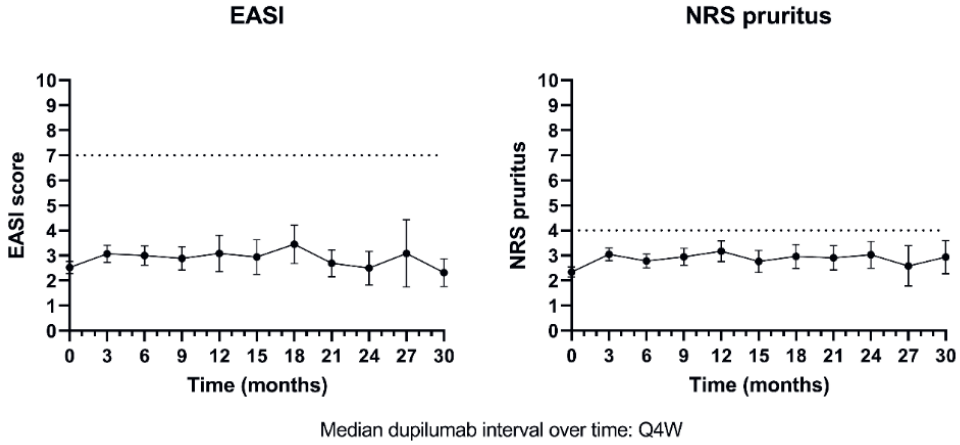


Figure 2. The course of estimated mean EASI and NRS pruritus score with 95% confidence interval in the tapering cohort (n=401).

Time point 0 is tapering baseline for each patient. Time points and follow-up duration differed between patients. To analyze the effect of implementation of the protocol, patients who shortened dupilumab to Q2W after prolonging interval are included. A significant effect is observed for both EASI and NRS over time (p-value<0.0001). However, the changes are small and the outcome measures remained low. Cut-off value EASI score of ≤7 indicating controlled AD; NRS pruritus score of ≤4 is considered as a treatment goal. Symbols represent estimated means with 95% confidence intervals (vertical lines). EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; Q4W, every four weeks.

A similar trend for the NRS-pruritus after tapering baseline was observed with a significant effect over time ($p<0.001$). At 3 months after start tapering, mean NRS showed an increase to 3.0 (95% CI: 2.8-3.3) at 3 months and 2.8 (95% CI: 2.5-3.1) at 6 months. Similarly, NRS scores remained low, with the highest estimated mean of 3.2 (95% CI 2.8-3.6) after 12 months of start tapering (Figure 2) and upper limits of the CIs remaining below 4. Over time, the actual percentage of patients with NRS pruritus ≤4 during tapering ranged between 71.3% and 81.4% (Table 2).

As shown in Table 2, due to a selection bias towards controlled AD and tapering, a relatively large group of patients using Q2W (not able or willing to taper) showed higher disease activity over time. At the start of tapering (tapering baseline, n=401), while every patient used dupilumab 300mg Q2W, 32.9% of the patients (n=107) used no topical steroids, 27.4% (n=89) used 0-10gr/week, 35.1% (n=114) used 10-30gr/week, and 4.6% (n=15) used >30gr/week (n=78 missing). At all tapering doses, the use of topical steroids was slightly higher compared to tapering baseline (Q2W). Less patients used no topical steroids, while using 0-10gr per week became the largest group in every dose group (Supplementary Figure 2).

Table 2. Treatment characteristics per dose interval for each time point

	1y (n=564)	1y6m (n=504)	2y (n=392)	2y6m (n=277)	3y (n=200)	3y6m (n=134)
Dupilumab Q2W, n	535	242	158	88	53	39
EASI score, mean (SD)	3.7 (3.6)	4.6 (4.5)	5.6 (5.8)	4.7 (5.2)	5.6 (5.3)	4.5 (3.9)
EASI score ≤7, n (%)	395 (84.4)	150 (80.6)	88 (71.5)	50 (75.8)	29 (72.5)	29 (82.4)
Missing	68	57	36	22	13	5
IGA≤2	415 (88.7)	159 (83.7)	93 (76.2)	56 (83.6)	31 (79.5)	31 (91.2)
Missing	68	53	37	21	14	5
NRS pruritus, mean (SD)	2.7 (2.1)	3.0 (2.1)	3.5 (2.3)	3.3 (2.3)	3.4 (2.4)	3.0 (2.1)
NRS pruritus≤4, n (%)	359 (80)	140 (77.3)	76 (70.4)	41 (74.5)	28 (70.0)	25 (75.8)
Missing	87	61	50	33	13	6
Dupilumab Q3W/Q4W, n	28	255	191	138	104	61
EASI score, mean (SD)	2.1 (1.3)	2.7 (2.4)	3.2 (3.3)	3.3 (3.4)	2.6 (2.6)	2.9 (3.0)
EASI score ≤7, n (%)	22 (100)	194 (93.3)	129 (89.0)	95 (88.0)	90 (93.8)	52 (94.5)
Missing	6	47	46	30	8	6
IGA≤2	22 (95.7)	195 (94.2)	127 (87.6)	92 (85.2)	88 (92.6)	53 (96.4)
Missing	6	48	46	30	9	6
NRS pruritus, mean (SD)	3.0 (2.1)	3.0 (2.2)	3.0 (2.3)	2.8 (2.3)	2.7 (1.9)	2.4 (1.9)
NRS pruritus≤4, n (%)	19 (82.6)	156 (74.3)	114 (79.2)	78 (76.5)	74 (80.4)	47 (83.9)
Missing	5	45	47	36	12	5
Dupilumab Q5W/Q6W, n	1	6	39	36	34	24
EASI score, mean (SD)	3.6 (.)	1.9 (1.8)	1.7 (1.5)	2.7 (2.7)	2.0 (2.4)	2.0 (1.8)
EASI score ≤7, n (%)	1 (100)	2 (100)	32 (100)	24 (92.3)	27 (93.1)	23 (95.8)
Missing	0	4	7	10	5	0
IGA≤2	1 (100)	2 (100)	32 (100)	24 (92.3)	27 (93.1)	21 (95.5)
Missing	0	4	7	10	5	2
NRS pruritus, mean (SD)	3.0 (.)	4.3 (4.0)	2.6 (1.9)	2.6 (2.0)	2.3 (2.2)	2.9 (2.5)
NRS pruritus≤4, n (%)	1 (100)	2 (50.0)	28 (82.4)	24 (82.8)	28 (82.4)	18 (78.3)
Missing	0	2	5	7	0	1

Table 2 (continued). Treatment characteristics per dose interval for each time point

	1y (n=564)	1y6m (n=504)	2y (n=392)	2y6m (n=277)	3y (n=200)	3y6m (n=134)
Dupilumab Q7W/Q8W, n	0	1	4	15	9	10
EASI score, mean (SD)	-	1.1 (.)	1.0 (.)	1.9 (2.3)	2.2 (2.3)	2.9 (4.0)
EASI score ≤7, n (%)	-	1 (100)	1 (100)	10 (100)	7 (100)	7 (87.5)
Missing	-	0	3	5	2	2
IGA≤2	-	1 (100)	1 (100)	10 (100)	7 (100)	6 (75.0)
Missing	-	0	3	5	2	2
NRS pruritus, mean (SD)	-	1.0 (.)	2.3 (2.5)	1.8 (1.2)	2.6 (1.5)	3.6 (3.0)
NRS pruritus≤4, n (%)	-	1 (100)	2 (66.7)	10 (100)	6 (85.7)	5 (71.4)
Missing	-	0	1	5	2	3

EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment scale; NRS, Numerical Rating Scale; Q2W, every other week; Q3W, every three weeks; Q4W, every four weeks; Q5W, every five weeks; Q6W, every six weeks; Q7W, every seven weeks; Q8W, every eight weeks; SD, standard deviation; y, year; m, month

Successful tapering

In the tapering cohort (n=401), shortening of the interval to the standard dose of 300mg Q2W after prolongation was needed in 21.2% (85/401) of the patients. At time of interval shortening the mean EASI score was 6.0 (SD 4.4) and significantly improved to 3.8 (SD 3.3) after three months of using Q2W ($p<0.05$); the mean NRS pruritus was 4.4 (SD 2.3) and significantly improved to 3.2 (SD 2.3) ($p<0.05$). A second attempt to prolong the dosing interval was successful in 18/401 (4.5%) patients with mean duration of 39.4 weeks (SD 18.4) between the first and second attempt. These patients remained for at least 50% of the follow-up time on a prolonged interval and were defined as 'successful tapering'. 67/401 (16.7%) patients who attempted tapering but shortened interval to standard dose and continued Q2W at least 50% of the whole observation period were defined as 'tapering failures'. In total, 83.3% (334/401) of the patients who attempted interval prolongation successfully continued dupilumab treatment with a prolonged interval.

Prediction of successful tapering

The determinants for successful dose reduction from univariate analysis were allergic asthma and NRS pruritus at start of dupilumab treatment, both variables were associated with lower chance to successfully taper dupilumab (Supplementary Table 1). Multivariate analysis showed non-significant odds ratios for all incorporated variables (Figure 3 and Supplementary Table 1). C-statistics was 0.71, which indicates a moderate ability of the model to predict successful tapering.

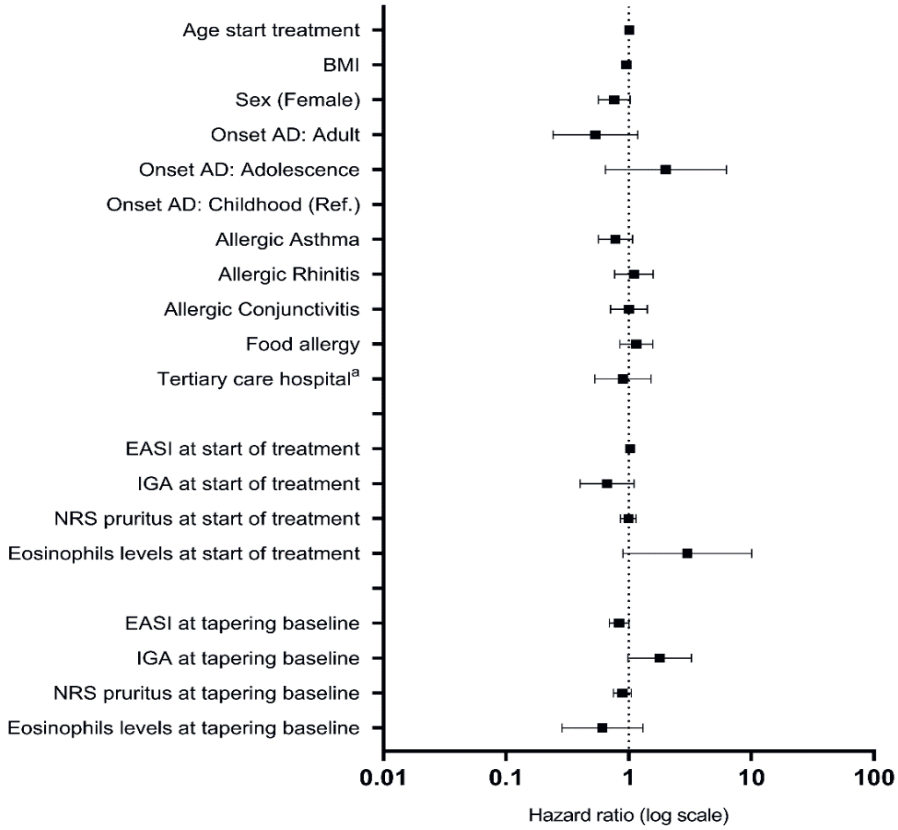


Figure 3. Non-significant predictors for successful tapering (odds ratios) determined by multivariate logistic regression analysis (n=401).

[a]Tertiary care hospital compared to secondary care hospitals. AD, atopic dermatitis; BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment scale; NRS, Numerical Rating Scale.

Cost saving of tapering dupilumab

The price of dupilumab treatment was stable throughout the study period; one year of dupilumab treatment in the Netherlands costs 16,350.88 EUR.[14] The cost savings were estimated between January 2019 and June 2022, due to the implementation of the patient-centered treatment regimen in the beginning of 2019. The cumulative dose saving after tapering baseline until June 2022 was calculated for each patient and corrected for treatment duration per dose interval. In total, 401 patients tapered dupilumab with a mean cost saving of 9,917.79 EUR per patient; total cost saving for these 401 patients was estimated to be 3,977,033.98 EUR in the period between January 2019 and June 2022 (3.5 years). The estimated annual cost saving was 1,136,295.42 EUR during this study.

Discussion

Our patient-centered dosing regimen was successful in 83.3% of the patients while maintaining controlled disease, with the majority using dupilumab Q3W/Q4W. A significant effect after start tapering was observed for EASI score (highest estimated mean 3.5) and NRS pruritus (highest estimated mean 3.2) but both remained low. In total, 401 patients had a dupilumab dose reduction with a total estimated cost saving of 3,977,033.98 EUR in the period between January 2019 and June 2022.

Only a few studies have been published on different dosing regimens of dupilumab in AD.[1, 4, 15, 16] Interestingly, while daily practice studies concluded that lower dosages were feasible in a substantial part of patients, the SOLO-continue study recommended the approved regimen of 300mg Q2W of dupilumab for long-term treatment.[1] The methodology (e.g. inclusion criteria, shared-decision making) and outcomes (e.g. definition of successful dose reduction) differ substantially between the daily practice studies and the clinical trial SOLO-continue. This probably explains the differences in outcomes and conclusions. Furthermore, it might be that prolonging interval at 16-weeks of treatment is too early, as Bangert et al. discovered that specific immune cell populations persisted for up to 1 year after clinical response while using dupilumab, which were absent in healthy controls.[17]

The effect of implementing our patient-centered dupilumab dosing regimen in daily practice on disease activity was measured by EASI score and NRS pruritus. We chose to include all patients from the tapering cohort, independent of interval shortening, to assess the direct effect of our patient-centered dosing regimen. We observed an increase in EASI and NRS scores shortly after starting the patient-centered dosing regimen and a significant effect for time. These results may suggest a negative impact of dose reduction, we nevertheless observe that differences were small and both mean observed EASI and NRS scores as well as their respective confidence intervals remained well below the clinically accepted cut-off points of 7 and 4 (resp.). This significant effect over time was most likely caused by the a relatively large number of patients combined with a large number of measurements, thus leading to high statistical power. Moreover, as the changes in EASI score and NRS pruritus were very small (max. one point deviation), they did not reach the minimal clinical important difference (MCID).[18, 19] Over time, the actual percentage of patients with controlled disease (EASI≤7) and controlled itch (NRS pruritus≤4) while tapering

ranged between 79.3% and 94.3% and 71.3% and 81.4%. Therefore, the clinical relevance of these changes over time are questionable.

The use of topical corticosteroids parallel to the treatment with dupilumab, is an important strategy in the treatment of AD.[20] In clinical trials higher efficacy was observed after 16 weeks of dupilumab treatment combined with topical steroids (percentage decline EASI score of -81.2% and 61.8% of the patients with ≥3 points reduction in NRS)[21] compared to dupilumab monotherapy (percentage decline EASI score of -71.4% and 50.3% of the patients with ≥3 points reduction in NRS).[22] A small increase in the amount of used topical steroids was observed in the tapering groups compared to tapering baseline and might have contributed to the maintenance of controlled disease during tapering. As the majority of the patients used less than 10gr/week, the use of topical steroids remained low and safe despite reducing dupilumab dose.

Due to the absence of a dose reduction protocol in literature our patient-centered dosing regimen was based upon tapering protocols of biological treatment in other diseases (e.g. psoriasis[23, 24], rheumatoid arthritis[25, 26]) and clinical experience. The present strategy was based on standardized and validated treatment goals, which was defined as low disease activity based on an EASI score of 7 or lower.[6] However, patients who shortened interval to the standard dose of 300mg Q2W in our study had an mean EASI score of 6.0 with a mean NRS pruritus score of 3.7, which was not completely in line with our protocol as in our protocol shortening should be considered in case of EASI score higher than 7. In our study, it seems that in clinical practice an EASI score of 4 or lower and/or NRS pruritus of 3 was considered as controlled disease by patient and physician.

Clinical and biological (tapering) baseline variables were analyzed for their predictive value for successful tapering. However, it was not possible to find any significant predictors in the multivariate analysis and to our knowledge no other prediction studies are available in literature yet. It might that successful dose reduction is dependent on patient motivation and/or, perhaps, physician factors. Clinical practice showed us that for successful reduction it was important to sufficiently inform the patient about the possibility of (marginal) flaring and the importance of timely using topical steroids. Furthermore, 21.2% (18/85) successfully prolonged their interval in a second attempt, indicating that a second attempt to taper is worth trying.

Considering the high costs of dupilumab (around 16.000 euros per patient per year in the Netherlands) adequate and effective usage of the drug is of great importance to reduce the budget impact. This study showed considerable cost savings, with an estimated cost saving of 3,977,033.98 EUR for 401 patients in the period between January 2019 and June 2022, which is an important finding from societal perspective.

Limitations

As our study was designed as a pragmatic daily practice study, patients fulfilling the criteria of controlled disease (EASI≤7 for 6 months) were not randomized into a dose reduction group and a standard dose group. Therefore non-inferiority could not be investigated for our patient-centered dosing regimen and consequently, results of this study are limited to a within patient comparison. Another limitation is the absence of a validated flare criteria for AD. Our flare criteria were therefore a definition based on patient and physician opinion combined with EASI and/or NRS pruritus score.

Conclusion

Our patient-centered dosing regimen was successful in 83.3% of the patients while maintaining controlled disease, with the majority using dupilumab Q3W/Q4W. In total, 401 patients tapered dupilumab with an estimated cost saving of 3,977,033.98 EUR in the period between January 2019 and June 2022.

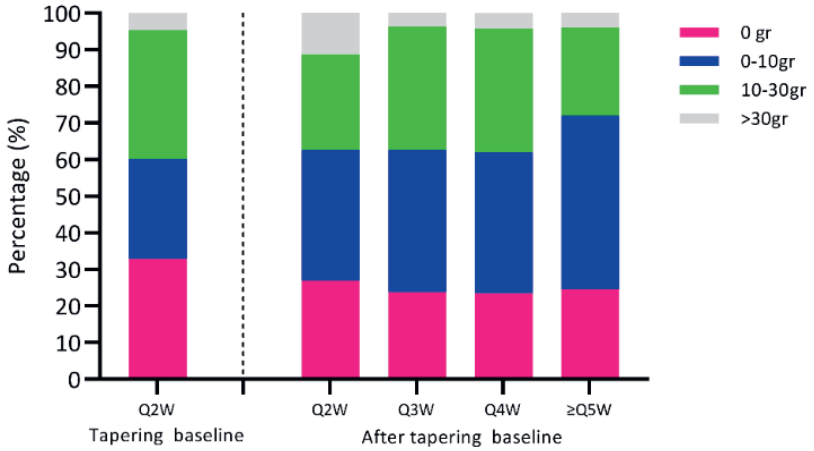
References

1. Worm, M., et al., *Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(2): p. 131-143.
2. Wu, J.J., et al., *Dupilumab Maintains Long-Term Disease Control in Adults with Moderate-to-Severe Atopic Dermatitis as Measured by Well-Controlled Weeks: Results From the LIBERTY AD CHRONOS Clinical Trial.* Dermatol Ther (Heidelb), 2021. **11**(2): p. 327-330.
3. Deleuran, M., et al., *Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study.* J Am Acad Dermatol, 2020. **82**(2): p. 377-388.
4. Spekhorst, L.S., et al., *Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis.* Allergy, 2022.
5. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
6. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.
7. Phan, N.Q., et al., *Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus.* Acta Derm Venereol, 2012. **92**(5): p. 502-7.
8. Futamura, M., et al., *A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards.* J Am Acad Dermatol, 2016. **74**(2): p. 288-94.
9. De Bruin-Weller, M., et al., *Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies.* Acta Derm Venereol, 2021. **101**(2): p. adv00402.
10. Garrett M. Fitzmaurice, N.M.L., James H. Ware. - 2nd ed. p.cm, *Applied longitudinal analysis*. 2011, John Wiley & Sons: Boston.
11. Harrell, F., *Regression modelling strategies*. 2001: Springer.
12. van Smeden, M., et al., *Sample size for binary logistic prediction models: Beyond events per variable criteria.* Stat Methods Med Res, 2019. **28**(8): p. 2455-2474.
13. Graham, J.W., A.E. Olchowski, and T.D. Gilreath, *How many imputations are really needed? Some practical clarifications of multiple imputation theory.* Prev Sci, 2007. **8**(3): p. 206-13.
14. Medicijnkosten.nl. *Zorginstituut Nederland*. 2017.
15. Lee, Y., M.E. Kim, and D.H. Nahm, *Real Clinical Practice Data of Monthly Dupilumab Therapy in Adult Patients With Moderate-to-Severe Atopic Dermatitis: Clinical Efficacy and Predictive Markers for a Favorable Clinical Response*. Allergy Asthma Immunol Res, 2021. **13**(5): p. 733-745.
16. Patruno, C., et al., *Dupilumab dose spacing after initial successful treatment or adverse events in adult patients with atopic dermatitis: A retrospective analysis.* Dermatol Ther, 2022: p. e15933.
17. Bangert, C., et al., *Persistence of mature dendritic cells, TH2A, and Tc2 cells characterize clinically resolved atopic dermatitis under IL-4Ralpha blockade.* Sci Immunol, 2021. **6**(55).
18. Schram, M.E., et al., *EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference*. Allergy, 2012. **67**(1): p. 99-106.
19. Yosipovitch, G., et al., *Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis.* Br J Dermatol, 2019. **181**(4): p. 761-769.
20. Griffiths, C., et al., *Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis and Prior Use of Systemic Non-Steroidal Immunosuppressants: Analysis of Four Phase 3 Trials.* Dermatol Ther (Heidelb), 2021. **11**(4): p. 1357-1372.
21. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year,*

randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet, 2017. **389**(10086): p. 2287-2303.
22. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
23. Atalay, S., et al., *Comparison of Tightly Controlled Dose Reduction of Biologics With Usual Care for Patients With Psoriasis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(4): p. 393-400.
24. Atalay, S., et al., *Tight controlled dose reduction of biologics in psoriasis patients with low disease activity: a randomized pragmatic non-inferiority trial.* BMC Dermatol, 2017. **17**(1): p. 6.
25. Bouman, C.A., et al., *Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial.* Ann Rheum Dis, 2017. **76**(10): p. 1716-1722.
26. van Herwaarden, N., et al., *Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity.* Clin Exp Rheumatol, 2014. **32**(3): p. 390-4.

Supplement

A.



B.

	0 gr	0-10gr	10-30gr	30-60gr	>60gr	Missing
Tapering baseline						
Dupilumab Q2W, n (%)	107 (32.9)	89 (27.4)	114 (35.1)	14 (4.3)	1 (0.3)	76
After tapering baseline						
Dupilumab Q2W, n (%)	62 (27.0)	82 (35.7)	60 (26.1)	20 (8.7)	6 (2.6)	14
Dupilumab Q3W, n (%)	206 (23.8)	337 (38.9)	292 (33.7)	28 (3.2)	4 (0.5)	51
Dupilumab Q4W, n (%)	129 (23.5)	211 (38.5)	185 (33.8)	19 (3.5)	4 (0.7)	38
Dupilumab ≥Q5W, n (%)	73 (24.6)	141 (47.5)	71 (23.9)	7 (2.4)	5 (1.7)	17

Supplementary Figure 1. The amount of used topical steroids per week at tapering baseline and after tapering baseline (n=401).

Data are shown from the tapering cohort (n=401) at start of tapering, and all follow-up visits after tapering baseline. All BioDay visits (multiple visits per patient) after start tapering are clustered per dupilumab dose interval. Q2W, every other week; Q3W, every three weeks; Q4W, every four weeks; Q5W, every five weeks; gr, gram.

Supplementary Table 1. Predictors of successful tapering determined by uni- and multivariate logistic regression analysis

	Univariate		**Multivariate**	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Sex (Female)	0.78 (0.45-1.35)	0.37	0.76 (0.57-1.03)	0.07
Age start treatment	1.00 (0.98-1.02)	0.83	1.01 (0.99-1.03)	0.33
BMI	0.95 (0.59-1.02)	0.16	0.96 (0.89-1.03)	0.24
AD onset: Adult[a]	0.92 (0.39-2.18)	0.21	0.54 (24-1.19)	0.12
AD onset: Adolescence[a]	4.35 (0.58-32.91)	0.15	2.01 (0.64-6.26)	0.23
Allergic Asthma	0.48 (0.26-0.86)	**0.01**	0.78 (0.57-1.07)	0.13
Allergic Rhinitis	1.00 (0.56-1.78)	1.00	1.10 (0.77-1.58)	0.59
Allergic Conjunctivitis	0.77 (0.43-1.36)	0.37	1.00 (0.71-1.42)	0.98
Food allergy	0.91 (0.53-1.58)	0.75	1.15 (0.85-1.57)	0.36
Tertiary care hospital[b]	0.71 (0.24-2.10)	0.54	0.90 (0.53-1.52)	0.69
At start treatment				
EASI	1.00 (0.98-1.02)	0.97	1.03 (0.99-1.07)	0.16
IGA	0.80 (0.57-1.11)	0.18	0.67 (0.40-1.10)	0.12
NRS pruritus	0.84 (0.73-0.98)	**0.02**	0.99 (0.86-1.15)	0.92
Eosinophils levels	1.70 (0.60-4.87)	0.32	3.00 (0.90-10.06)	0.07
At tapering baseline				
EASI	0.92 (0.82-1.03)	0.14	0.84 (0.69-1.01)	0.06
IGA	1.09 (0.75-1.59)	0.66	1.79 (0.98-3.26)	0.06
NRS pruritus	0.92 (0.79-1.07)	0.30	0.89 (0.75-1.05)	0.17
Eosinophils levels	0.74 (0.37-1.46)	0.38	0.61 (0.29-1.31)	0.20

[a]Reference category: Childhood. [b]Tertiary care hospital compared to secondary care hospitals. AD, atopic dermatitis; CI, confidence interval; BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; NRS, Numerical Rating Scale.

10

The positive effect of dupilumab on comorbid asthma in patients with atopic dermatitis

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Abstract

Introduction: Asthma is a common comorbid in patients with moderate-to-severe atopic dermatitis (AD), who are indicated for advanced systemic treatments, such as dupilumab.

Objective: To investigate the effect of dupilumab on asthma in patients treated with dupilumab for AD in daily practice.

Methods: Adult AD patients with comorbid asthma treated with dupilumab and at least one measurement of the Asthma Control Questionnaire (ACQ)-5 and/or Forced Expiratory Volume in 1 second (FEV1) were included. A mixed model with a random intercept was used to assess the primary effectiveness endpoints; mean change from baseline in ACQ-5 and FEV1 at 16- and 52-weeks. Secondary effectiveness endpoints were ACQ<0.5, FEV1≥80% predicted, and Fractional exhaled Nitric Oxide (FeNO) at 16- and 52-weeks.

Results: A total of 304 AD patients were included. Mean ACQ-5 was 1.32 (95% CI 1.20-1.44; n=236) at baseline, and significantly improved with -0.24 (95% CI -0.38-−0.10; n=173) at week 16 and -0.26 (95% CI -0.43-−0.09; n=110) at week 52 (p<0.00). Mean FEV1 (baseline 2.96 L (95% CI 2.79-3.13; n=104)) significantly improved over time (p<0.00) with 0.10 L (95% CI 0.03-0.16; n=81) and 0.12 L (95% CI 0.05-0.19; n=64) at week 16 and 52, respectively. At start of treatment median FeNO (n=22) was 23.43 ppb (95% CI 16.37-33.53), and significantly decreased to 13.13 ppb (95% CI 10.49-16.45; n=17) at 16-weeks and to 15.24 ppb (95% CI 12.38-18.76; n=21) at 52-weeks (p<0.00).

Conclusions: One year of dupilumab treatment primarily indicated for AD resulted in a significant improvement of comorbid asthma with the largest effect in the first 16 weeks, presenting an additional advantage of dupilumab for AD patients with comorbid asthma.

Clinical communication

IL-4 and IL-13 are Type-2 (T2) inflammatory cytokines and key drivers in T2 immune response, which is considered to play a central role in the pathogenesis of several atopic diseases such as atopic dermatitis (AD) and asthma. Dupilumab, a fully human monoclonal antibody, binds to the α-subunit of the interleukin (IL)-4 receptor and blocks the signaling pathway of IL-4 and IL-13.[1] It is the first antibody-based treatment that became available for the treatment of AD and is also registered for severe T2 asthma.[2] Several studies reported improved clinical outcomes and sustained reduction of T2 inflammatory biomarkers for AD as well as asthma by using dupilumab.[3, 4]

Since the majority of AD patients have comorbid asthma[5], the aim of this study was to investigate the effect of dupilumab on asthma in patients treated for AD with dupilumab in daily practice.

This study consecutively included adult AD patients with comorbid asthma and at least one measurement of the Asthma Control Questionnaire (ACQ)-5 (scale 0-6), and/or FEV1, who started dupilumab treatment for AD and participated in the BioDay registry from October 2017 to June 2022. The ACQ-5 was used as patient-reported outcome, consisting five questions on symptom control of asthma. Following The Global Initiative for Asthma (GINA)-guidelines controlled asthma in a real-life setting was defined as ACQ-5<0.5.[6] In a subset of patients using inhaled steroids regularly, Forced Expiratory Volume in 1 second (FEV1) was assessed, partially combined with Fractional exhaled Nitric Oxide (FeNO). Levels of NO are increased in the exhaled breath of patients with T2 asthma and provide an objective biomarker of airway inflammation, with the following cut-off points: <25 parts per billion (ppb) (low), 25-50 ppb (intermediate), ≥50 ppb (high).[7]

Primary effectiveness endpoints were the mean change from baseline in ACQ-5 and FEV1 at weeks 16 and 52. Secondary effectiveness endpoints were: ACQ-5<0.5, FEV1≥80% predicted, and FeNO at weeks 16 and 52. For the analysis of continuous outcomes, a mixed model with a random intercept was used and results were used to estimate means with 95% confidence intervals (CI). Continuous variable FeNO, with a highly skewed distribution, was log-transformed. These estimated mean log-transformed were transformed back to median FeNO values (with 95% CIs).

Descriptive analysis was used for the categorical endpoints. The role of T2-indicator blood eosinophilia (>0.4x10*9/L) at the start of dupilumab treatment on the primary endpoint FEV1 is shown in the online repository.

A total of 304 AD patients treated with dupilumab and comorbid asthma with an ACQ-5 and/or FEV1 measurement were included (see Table 1 for the baseline characteristics per cohort).

Table 1. Patient and baseline characteristics for AD patients with comorbid asthma treated with dupilumab

	ACQ cohort	**FEV1 cohort**	**FeNO cohort**
N (%)	286 (100.0)	116 (100.0)	39 (100.0)
Gender (Male), n (%)	147 (51.4)	61 (52.6)	17 (43.6)
Age, mean (SD)	41.3 (15.6)	42.2(15.2)	45.1 (14.8)
BMI, mean (SD)	26.3 (5.1)	26.9 (5.2)	26.6 (4.5)
Missing	76	29	3
Age at AD onset, n (%)			
Childhood	263 (92.9)	110 (94.8)	37 (94.9)
Adolescence	8 (2.8)	3 (2.6)	2 (5.1)
Adulthood	12 (4.2)	3 (2.6)	0 (0)
Missing	3	0	0
Use of inhalant corticosteroids, n (%)	201 (72.0)	116 (100)	39 (100)
Missing	7	0	0
Atopic comorbid			
Allergic Rhinitis, n (%)	227 (79.9)	93 (80.2)	29 (74.4)
Missing	2	0	0
Allergic Conjunctivitis, n (%)	196 (69.8)	89 (77.4)	31 (79.5)
Missing	5	1	0
Food allergy, n (%)	174 (61.7)	75 (65.2)	27 (69.2)
Missing	4	1	0
EASI score, mean (SD)	16.9 (14.4)	18.6 (11.0)	16.7 (8.8)
Missing	1	0	0
IGA score, median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)
Missing	3	0	0
Eosinophils levels (x10*9/L), median (IQR)	0.4 (0.2-0.6)	0.5 (0.2-0.6)	0.5 (0.2-0.6)
Missing	26	5	3
Eosinophilia (>0.4x10*9/L), n (%)	122 (46.9)	62 (55.9)	21 (58.3)
Missing	26	5	3

BMI, body mass index; CI, Confidence Interval; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; IQR, Interquartile range; SD, Standard Deviation.

All primary effectiveness endpoints significantly improved after 16- and 52 weeks of dupilumab treatment compared to baseline (see Figure 1 and Supplementary Table 1). Mean ACQ-5 was 1.32 (95% CI 1.20-1.45; n=236) at baseline, and

significantly improved over time (p<0.00), with -0.24 (95% CI -0.38-−0.10; n=173) at week 16 and -0.26 (95% CI -0.43-−0.09; n=110) at week 52. Mean FEV1 at start of treatment was 2.96 L (95% CI 2.79-3.13; n=104) and significantly improved over time (p<0.00) with 0.10 L (95% CI 0.03-0.16) and 0.12 L (95% CI 0.05-0.19) at week 16 (n=81) and 52 (n=64), respectively. No significant change for ACQ-5 and FEV1 was found between week 16 and 52. Secondary effectiveness endpoints are presented in Supplementary Table 1 and Figure 1. At start of dupilumab treatment median FeNO (n=22) was 23.43 ppb (95% CI 16.37-33.53) and significantly decreased over time (p<0.00), to 13.13 ppb (95% CI 10.49-16.45; n=17) at 16-weeks and to 15.24 ppb (95% CI 12.38-18.76; n=21) at 52-weeks (Figure 1). At start of treatment, 20.8% and 58.7% of the patients had an ACQ-5 <0.5 and FEV1≥80% and increased to 28.2% and 68.8% after one year of treatment, respectively (Supplementary Table 1).

In our study, ACQ-5 improved by an estimated -0.26 and FEV1 increased by an estimated 0.12 L at week 52. Overall, the effect of dupilumab on the primary endpoints was smaller than those reported in randomized controlled trials (RCTs) concerning the efficacy and safety of dupilumab in patients with uncontrolled asthma.[3] In these asthma RCTs, dupilumab showed a greater improvement in ACQ-5 (mean difference -0.48 (95% CI −0.88-−0.09)) and FEV1 (mean difference + 0.18 L (95% CI 0.11-0.25)).[3] These differences are most likely caused by differences in asthma severity of the study populations, as in the asthma RCTs, patients started dupilumab for uncontrolled severe asthma. In our AD cohort, patients started dupilumab treatment for uncontrolled moderate-to-severe AD. The majority of our patients had relatively mild asthma with a mean ACQ-5 of 1.32 and FEV1 of 2.96 L at start of treatment, making it more difficult to achieve a similar substantial improvement compared to the asthma RCTs.

As shown in the supplementary, no profound effect of T2-indicator, blood eosinophilia, at the start of treatment was found regarding the effectiveness of dupilumab on FEV1. On the contrary, in the asthma studies[3], the most robust results were observed in patients with elevated T2-indicators, including eosinophil counts. Possibly the effect of dupilumab is less dependent on T2-indicator blood eosinophilia in patients with mild asthma.

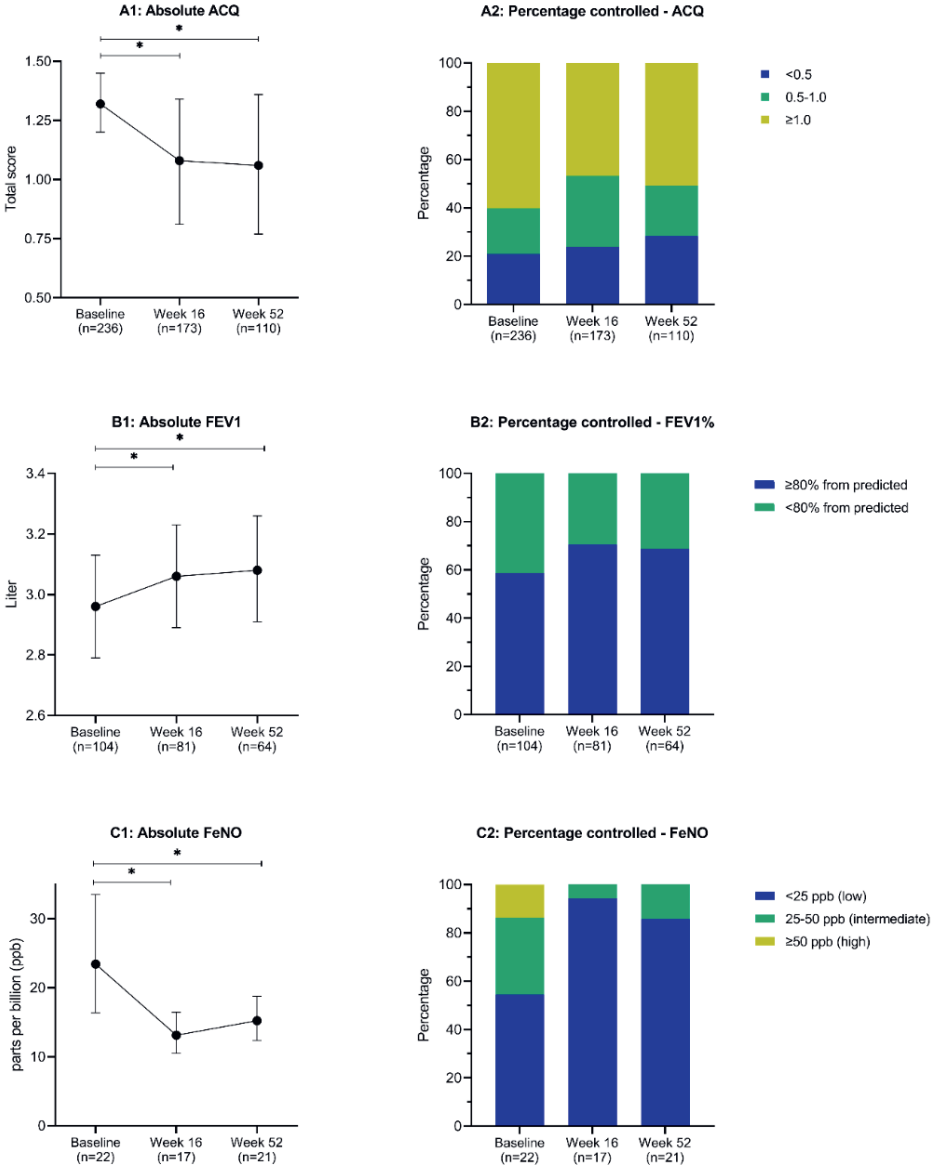

Figure 1. Effectiveness outcomes for asthma status during one year of dupilumab treatment in AD patients with comorbid asthma.

A1: Absolute change in ACQ. Bars represent mean and 95% CI; A2: Percentage controlled ACQ-5 based on cut-off points; B1: Absolute change in FEV1 in L. Bars represent mean and 95% CI; B2: Percentage controlled FEV1% from predicted; C1: Absolute change in FeNO per ppb. Bars represent median and 95% CI; C2: Percentage controlled FeNO based on cut-off points.

ACQ-5, Asthma Control Questionnaire; CI, Confidence Interval; FEV1, Forced Expiratory Volume in 1 second; FeNO, Fractional exhaled Nitric Oxide; Ppb, parts per billion. P-values based on overall likelihood ratio tests for time.*P<0.05.

A limitation of the study is the missing data due to the daily practice setting and COVID-pandemic. Additionally, spirometry measurements were only conducted in patients using inhaled corticosteroids thereby excluding patients with mild asthma.

In conclusion, one year of dupilumab treatment primarily indicated for AD resulted in a significant improvement of comorbid asthma with the largest effect in the first 16 weeks. Dupilumab treatment in AD patients provides an additional advantage for patients with comorbid asthma.

References

1. Harb, H. and T.A. Chatila, *Mechanisms of Dupilumab.* Clinical and Experimental Allergy, 2020. **50**(1): p. 5-14.
2. *Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals.* **Version 3.**
3. Agache, I., et al., *Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma.* Allergy, 2020. **75**(5): p. 1058-1068.
4. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
5. Langan, S.M., A.D. Irvine, and S. Weidinger, *Atopic dermatitis.* Lancet, 2020. **396**(10247): p. 345-360.
6. Olaguibel, J.M., et al., *Measurement of asthma control according to Global Initiative for Asthma guidelines: a comparison with the Asthma Control Questionnaire.* Respir Res, 2012. **13**: p. 50.
7. Jeppegaard, M., et al., *Validation of ATS clinical practice guideline cut-points for FeNO in asthma.* Respir Med, 2018. **144**: p. 22-29.

Supplement

A post-hoc analysis was performed to assess the role of T2-indicator blood eosinophilia (>0.4x10*9/L) at start of treatment on the effectiveness of dupilumab on the primary endpoint Forced Expiratory Volume in 1 second (FEV1). No significant differences (p=0.87) in treatment benefit was observed in patients with or without eosinophilia at start of treatment (Supplementary Table 2), with differences smaller than 0.02 L. However, patients with blood eosinophilia at baseline had a higher FEV1 at start of treatment (3.13 L (2.91-3.35)) compared to patients without blood eosinophilia (2.78 L (95% CI 2.54-3.02)).

Supplementary Table 1. Primary and secondary outcomes for asthma status during dupilumab treatment in atopic dermatitis patients.

	Baseline	Week 16	Week 52	p-value[1]
ACQ-5 score, n	236	173	110	n.a.
Spirometry, n	104	81	64	n.a.
FeNO, n	22	17	21	n.a.
Primary endpoints[2]				
ACQ-5, mean (95% CI)	1.32 (1.20-1.45)	1.08 (0.81-1.34)	1.06 (0.77-1.36)	<0.00
FEV1, mean (95% CI)	2.96 (2.79-3.13)	3.06 (2.89-3.23)	3.08 (2.91-3.26)	<0.00
Secondary endpoints[3]				
FeNO, median (95% CI)[2]	23.43 (16.37-33.53)	13.13 (10.49-16.45)	15.24 (12.38-18.76)	<0.00
FeNO, <25 ppb, n (%)	12 (54.5)	16 (94.1)	18 (85.7)	n.a.
FeNO, 25-50 ppb, n (%)	7 (31.8)	1 (5.9)	3 (14.3)	n.a.
FeNO, ≥50, n (%)	3 (13.6)	0 (0)	0 (0)	n.a.
ACQ-5 ≥1.0, n (%)	142 (60.2)	81 (46.8)	56 (50.9)	n.a.
ACQ-5 <0.5, n (%)	49 (20.8)	41 (23.7)	31 (28.2)	n.a.
FEV1 (% from predicted) ≥ 80, n (%)	61 (58.7)	57 (70.4)	44 (68.8)	n.a.

[1]P-values based on overall likelihood ratio tests for time. [2]A mixed model with a random intercept was used, results were used to estimate means with 95% confidence intervals. Continuous variable FeNO, with a highly skewed distribution, was log-transformed and were transformed back to median FeNO values (with 95% CIs). [3]Descriptive analysis was used for the categorical endpoints. ACQ-5, Asthma Control Questionnaire; CI, Confidence Interval; FEV1, Forced Expiratory Volume in 1 second; FeNO, Fractional exhaled Nitric Oxide; IQR, Interquartile range; Ppb, parts per billion; SD, Standard Deviation.

Supplementary Table 2. The role of T2-indicator, blood eosinophilia, at start of treatment on the effectiveness of dupilumab on the primary endpoint FEV1.

	Baseline FEV1	Week 16 FEV1	Week 52 FEV1	p-value[1]
Eosinophils levels >0.4 x10*9/L, mean (95% CI)	3.13 (2.90-3.36)	3.22 (2.99-3.45)	3.26 (3.02-3.49)	0.87
Eosinophils levels ≤0.4 x10*9/L, mean (95% CI)	2.76 (2.50-3.02)	2.85 (2.60-3.11)	2.89 (2.63-3.15)	

[a]Eosinophilia >0.4 x10*9/L. CI, Confidence interval. [1]P-values based on overall likelihood ratio tests for time by blood eosinophilia

11

Dupilumab has a profound effect on specific-IgE levels of several food allergens in atopic dermatitis patients

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Abstract

Background: Dupilumab is effective for the treatment of atopic dermatitis (AD) but may also exert an effect on concomitant food allergy.

Objective: To investigate the effect of dupilumab on food specific IgE (sIgE) levels in AD patients with concomitant food allergy. As secondary aim, the patient reported change in severity of food allergic symptoms during accidental allergic reactions were evaluated.

Methods: Adult AD patients treated with dupilumab with a suggestive clinical history of food allergy (resp. peanut, hazelnut, almond, cashew nut, walnut, kiwi, and apple), and a corresponding positive sIgE (≥0.35 kU/L) at the start of treatment, were included. Linear mixed models were used to model the development of sIgE values over time. Patient-reported symptoms were reassessed during dupilumab treatment.

Results: A total of 125 patients were included. An estimated sustained percentage decrease of sIgE levels was observed for all food allergens during dupilumab treatment, with a decrease of 53.0% (95% CI: 46.3-59.7) to 62.9% (95% CI: 57.0-68.8) after one year and 80.5% (95% CI: 68.9-92.1) to 86.9% (95% CI: 78.7-95.2) after three years of treatment. After three years, the lowest median sIgE levels were observed for almond (0.4, 95% CI: 0.2-0.6), while hazelnut had the highest median sIgE levels (3.0, 95% CI: 2.1-4.3). A total of 82.5% (33/40) of the patients, who accidentally ingested foods during dupilumab treatment, reported a decrease in severity of food allergic symptoms.

Conclusion: Dupilumab treatment in adult AD patients with concomitant food allergy resulted in a profound and sustained decrease in sIgE levels for several food allergens.

Introduction

Atopic dermatitis (AD) is one of the most common chronic, and often relapsing inflammatory skin diseases, with an adult prevalence of 5% in developed countries.[1] Improved understanding of the underlying immune pathogenesis of AD has led to the development of new targeted therapies. The first biological developed for AD is dupilumab, a fully human monoclonal antibody which binds to the α-subunit of the interleukin (IL)-4 receptor. Dupilumab inhibits the release of pro-inflammatory cytokines and chemokines involved in the pathophysiology of AD by blocking the signaling pathway of Type 2 (T2)-related cytokines, IL-4 and IL-13.[2] Due to the inhibition of these signaling pathways, dupilumab is also indicated for other T2-related diseases, for example eosinophilic asthma and chronic rhinosinusitis with nasal polyps.[3]

In addition, AD is associated with other atopic diseases such as allergic asthma, allergic rhinitis, allergic conjunctivitis, and food allergy.[4] AD has been shown to be a major risk factor for food sensitization and the development of immunoglobulin E (IgE)-mediated food allergy as a result of cutaneous sensitization through an increased permeability of the skin for food allergens.[5-7] Double-blind placebo-controlled food challenge is the golden standard to diagnose food allergy, but is time consuming, costly, and can only be performed in a specialized clinical setting due to the possible event of a severe allergic reaction. Therefore, in daily practice the diagnosis of food allergy is mainly based on clinical history, supported by the detection of food specific sensitization in vivo by a skin prick test, or in vitro by specific IgE (sIgE). At present, no curative therapy is available once a food allergy has been established.

Dupilumab has been shown to reduce total serum IgE in AD patients.[8] However, to our knowledge, the course of specific IgE levels during dupilumab treatment have not earlier been defined. One case report is published regarding the effect of dupilumab on food allergic reactions in patients treated with dupilumab for AD. This case report of Rial MJ et al., showed a decrease of food allergic reaction to corn and nuts after accidental food ingestion during dupilumab treatment for moderate-to-severe AD, which was objectified by an oral food challenge (OFC).[9] This case report provides some evidence for the positive effect of dupilumab in decreasing the severity of a food allergic reaction, possibly by inhibiting the IL-4/IL-13 signaling pathway. Research has shown that a decrease in sIgE levels may be indicative for a

higher tolerance for food allergens.[10-12] As a result, decreasing sIgE levels, by inhibiting the IL-4/IL-13 signaling pathway through dupilumab, could be a surrogate marker for a decrease in the severity of food allergies.

Therefore, the aim of this study was to investigate the effect of dupilumab on sIgE levels in food allergic patients with moderate-to-severe AD in daily practice. Our secondary aim was to provide insight in the patient-reported symptoms regarding food allergic reactions during dupilumab treatment.

Methods

Study design and patients

We performed a retrospective analyses of data of patients treated with dupilumab, collected prospectively by the BioDay registry at the University Medical Center Utrecht (UMCU) between October, 2017 and February, 2022. The BioDay registry is a prospective, multicenter registry collecting daily practice data on the effectiveness and safety of new systemic treatment options for AD.[13]

This study consecutively included adult AD patients who were treated with dupilumab for moderate-to-severe AD and had a concomitant clinical history of food allergy. At start of treatment, patients received a loading dose of dupilumab 600mg subcutaneously, followed by 300mg every other week. Dose reduction was considered in case of side effects or controlled AD conform the BioDay protocol. Patients with suggestive food allergic symptoms for peanut, hazelnut, almond, cashew nut, walnut, kiwi, or apple, and a corresponding positive sIgE (≥0.35 kU/L) for the respective food at the start of dupilumab treatment, were included. This study did not fall under the scope of the Medical Research Involving Human Subjects Act (METC 18/239) and has been performed according to the declaration of Helsinki. All patients provided written informed consent.

Clinical history of food allergy at start of dupilumab treatment

Data on food allergy (type of food, patient-reported symptoms, severity of the reaction) were collected by an experienced physician at the start of dupilumab treatment. The severity of food allergy related symptoms was assessed for each food separately and was classified into 5 grades applying the adapted Mueller classification; grade 0 = oral allergy symptoms, grade 1 = skin reactions, grade 2 = gastrointestinal symptoms, grade 3 = respiratory symptoms, grade 4 = cardiovascular symptoms.[14]

The most severe Mueller classification was recorded for each food separately. Foods were also referenced by their origin, namely legumes (peanut), tree nuts (hazelnut, walnut, almond, cashew nut), and fruits (kiwi, apple).

Follow-up of food allergy during dupilumab treatment

Patient-reported food allergic symptoms were reassessed after at least six months of dupilumab treatment. Reassessment included questioning whether the patient had an accidental ingestion of foods they were allergic to, and whether the food allergic symptoms improved, stabilized or worsened, compared to the symptoms before the start of dupilumab treatment. Improvement of symptoms were taken for all foods in general and were not classified per food allergen.

In vitro diagnosis

sIgE levels were measured with ImmunoCAP system (Thermo Fischer Scientific, Uppsala) and levels of ≥0.35 kU/L were considered as positive. In cases of sensitization to peanut or hazelnut, components of peanut (Ara h 2 and Ara h 8) and hazelnut (Cor a 1, Cor a 9, and Cor a 14) were additionally measured. Samples were collected at baseline and measured at least once during follow-up. Levels above 100 were defined as 101 kU/L.

Statistical analysis

A linear mixed model was used to model the development of IgE values over time. A random intercept was included to correct for multiple measurements of IgE over time in the same patient. Time (i.e. the number of weeks after inclusion that the sample was collected) was included as a continuous determinant in the model, as the moment of sample collection during treatment varied across the patients.

Validity of the model (normality assumption, linearity, homoscedasticity) was assessed by analyzing residuals.[15] Initial analysis of the IgE distribution and residual analysis indicated a deviation from normality assumption, therefore sIgE levels were log-transformed in subsequent analyses. Based on the model, the mean log-transformed IgE with 95% confidence intervals (CIs) were estimated at 13 week intervals (i.e. week 0, week 13 week 26 etc.). These estimated mean log-transformed IgE values were transformed back to the original scale for ease of clinical interpretation, thus providing median IgE values (with 95% CIs) and corresponding percentage decline.[16] All analyses were performed for each food separately. All data were analyzed using IBM SPSS Statistics 26.0.0.1 (IBM, Armonk, NY, U.S.A.) and SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient population

A total of 125 patients with a suggestive clinical history of food allergy, including sensitization for the respective foods, and treated with dupilumab for moderate-to-severe AD were included. At dupilumab treatment initiation, the mean age was 35.7 years (standard deviation (SD) 12.5) and 46.4% (n=58) of the patients were female. The mean Eczema Area and Severity Index (EASI)-score at baseline was 16.9 (SD 9.0) (Table 1). In total, 2,682 sIgE samples in 125 patients were obtained between baseline and 3.5 years of treatment with dupilumab.

Table 1. Baseline characteristics

	Total (n=125)
Gender (female), n (%)	58 (46.4)
Age, mean (SD)	35.7 (12.5)
EASI score, mean (SD)	16.9 (9.0)
Number of food allergies, n (%)	
1	42 (33.6)
2	35 (28.0)
3	15 (12.0)
4	18 (14.4)
5	12 (9.6)
6	3 (2.4)
Food allergen, n (%)	
Peanut	63 (51.2)
Hazelnut	65 (52.0)
Almond	30 (24.0)
Cashew nut	30 (24.0)
Walnut	36 (28.8)
Kiwi	38 (30.4)
Apple	44 (35.2)
Atopic comorbidity, n (%)	
Allergic Asthma	92 (73.6)
Allergic Rhinitis	102 (81.6)
Allergic Conjunctivitis	96 (76.8)
Serum TARC levels, median (IQR)	2083 (1117.3-3696.3)
Eosinophils levels, median (IQR)	0.38 (0.18-0.63)

Missing laboratory findings: serum TARC levels n=1, eosinophils levels n=1. IQR, Interquartile range; SD, Standard deviation; TARC, thymus and activation-regulated chemokine.

Clinical history of food allergy

In the 125 included patients, a total of 307 food allergies were reported. Most patients were allergic to one (n=42, 33.6%) or two foods (n=35, 28.0%) (Table 1). Peanut and hazelnut (51.2% and 52.0%) were the most common causative foods, followed by apple (35.2%). Food allergy for almond, cashew nut, walnut, and kiwi was found in 24.0%, 24.0%, 28.8%, and 30.4% of the patients, respectively. A severe allergic reaction (Mueller 3 and 4) was commonly reported for peanut (40.7%) and tree nuts (24.6%-40.0%), and was less frequently reported for fruits (13.7%-23.7%) (Table 2).

Table 2. Baseline median (IQR) sIgE levels (in kU/L) per food and per severity grade

	Total	Mueller 0	Mueller 1	Mueller 2	Mueller 3	Mueller 4
Total (n, %)	306 (100)					
Peanut, n (%)	63	10 (15.9)	14 (22.2)	13 (20.6)	22 (34.9)	3 (6.3)
Extract	22.1 (4.5-51.0)	5.2 (1.6-19.3)	6.3 (1.2-23.1)	27.4 (21.5-42.0)	40.0 (14.5-62.0)	88.0 (22.6-101.)
Ara h 2	7.7 (1.3-34.2)	1.8 (0.7-3.2)	0.9 (0.4-7.7)	14.8 (4.4-29.4)	15.6 (6.9-35.0)	49.0 (24.0-66.5)
Ara h 8	12.5 (2.8-25.8)	10.0 (0.34-40.0)	7.4 (4.0-17.8)	15.2 (1.7-31.7)	13.8 (2.4-33.1)	14.2 (7.7-53.2)
Hazelnut, n (%)	65	25 (38.5)	13 (20.0)	11 (16.9)	15 (23.1)	1 (0.8)
Extract	33.2 (16.5-62.0)	22.5 (16.4-58.0)	42.0 (10.6-57.0)	56.0 (17.7-81.0)	42.0 (17.1-54.0)	101.0 (-)
Cor a 1	41.5 (17.7-73.0)	39.5 (20.4-73.5)	41.0 (14.4-71.0)	62.0 (18.9-80.0)	29.5 (15.8-68.0)	101.0 (-)
Cor a 9	0.9 (0.1-4.4)	0.3 (0.1-1.6)	0.1 (0.1-0.2)	3.2 (1.0-13.6)	3.9 (0.2-7.3)	25.7 (-)
Cor a 14	0.4 (0.2-2.1)	0.4 (0.2-0.9)	0.2 (0.1-0.3)	1.5 (0.3-35.0)	0.6 (0.2-25.5)	101.0 (-)
Almond, n (%)	30	6 (20.0)	7 (23.3)	7 (23.3)	8 (26.7)	2 (6.7)
Extract	3.3 (1.7-5.5)	2.0 (0.9-5.5)	1.9 (1.1-6.2)	3.3 (2.0-6.1)	3.5 (2.3-5.0)	4.3 (2.8-5.7)
Cashew nut, n (%)	30	5 (16.7)	6 (20.0)	7 (23.3)	9 (30.0)	3 (10.0)
Extract	12.4 (5.0-27.4)	5.1 (1.5-5.4)	8.7 (5.0-20.8)	10.0 (8.1-25.3)	32.5 (4.8-36.0)	36.0 (17.7-78.0)
Walnut, n (%)	36	14 (38.9)	5 (13.9)	5 (13.9)	10 (27.8)	2 (5.6)
Extract	10.4 (2.3-27.3)	4.0 (2.3-17.6)	5.1 (0.9-15.2)	13.1 (2.9-15.4)	18.7 (3.9-33.2)	49.4 (0.7-98.0)
Kiwi, n (%)	38	16 (42.1)	9 (23.7)	4 (10.5)	9 (23.7)	0 (0)
Extract	5.2 (1.5-11.1)	2.3 (1.3-5.6)	7.7 (5.3-24.1)	16.2 (11.8-22.0)	4.4 (2.4-6.1)	n.a.
Apple, n (%)	44	22 (50.0)	14 (31.8)	2 (4.5)	5 (11.4)	1 (2.3)
Extract	12.9 (4.2-22.2)	14.1 (2.9-21.2)	11.9 (5.2-26.9)	2.4 (0.7-4.1)	13.6 (4.0-16.2)	30.5 (30.5-30.5)

Missing baseline severity grade: peanut n=1. Missing baseline sIgE: peanut n=2, hazelnut n=3, almond n=1, walnut=1, kiwi=1. Mueller classification: grade 0= oral allergy symptoms, grade 1= skin reactions, grade 2= gastrointestinal symptoms, grade 3= respiratory symptoms, grade 4= cardiovascular symptoms. IQR, Interquartile range.

Sensitization at the start of dupilumab treatment

Results of the baseline sIgE measurements are shown in Table 2. Median sIgE levels for the different food extracts at baseline ranged from 3.3 to 33.2 kU/L, were lowest for almond (3.3 kU/L) and kiwi (5.20 kU/L), and highest for peanut (22.1 kU/L) and hazelnut (33.2 kU/L). In peanut allergic patients, respectively 92.2% and 86.2% were sensitized for Ara h 2 and Ara h 8 with median baseline sIgE levels of 7.7 kU/L and 12.5 kU/L. In hazelnut allergic patients, sensitization for the components Cor a 1, Cor a 9 and Cor a 14 were respectively 90.3%, 52.5% and 50.0%, with median baseline sIgE levels of 41.5 kU/L, 0.9 kU/L and 0.4 kU/L.

sIgE levels during dupilumab treatment

A decrease in median sIgE levels over time was observed for all allergens during dupilumab treatment, with a steep decrease in the first year of treatment and a more flattened course in the second and third year (Figure 1). At start of dupilumab treatment, median sIgE levels for all foods ranged between 2.9 (95% CI: 1.8-4.8, for almond) and 26.8 (95% CI: 18.8-38.3, for hazelnut), and after one year of treatment the median sIgE levels for all foods ranged between 0.9 (95% CI: 0.6-1.5, for almond) and 8.6 (95% CI: 6.0-12.4, for hazelnut). After three years the lowest median sIgE levels were observed for almond (0.4, 95% CI: 0.2-0.6), while hazelnut had the highest median sIgE levels (3.0, 95% CI: 2.1-4.3).

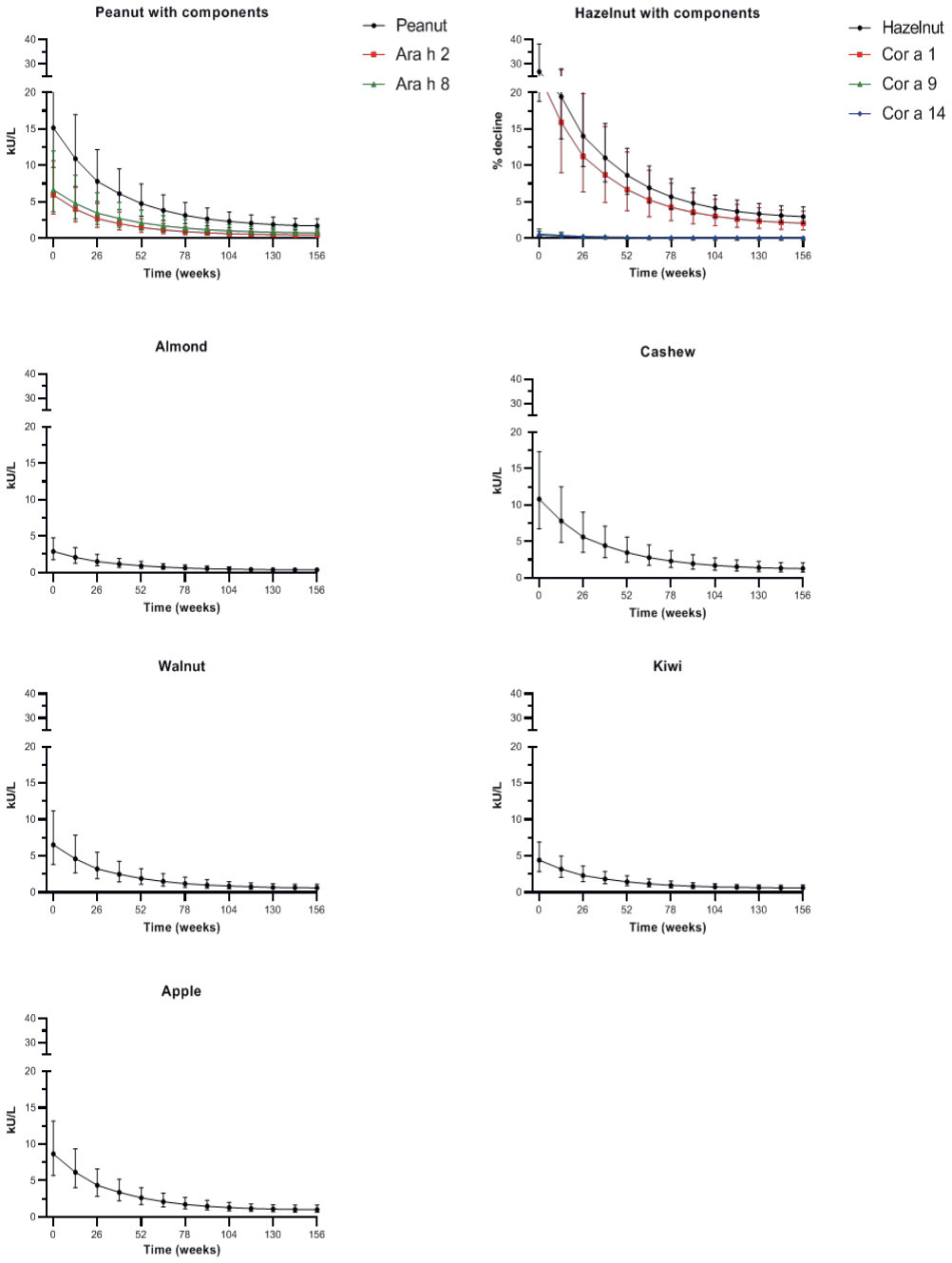

Figure 1. Estimated median decrease of sIgE levels during dupilumab treatment in patients with AD over the course of 3 years for peanut (incl. Ara h 2 and Ara h 8), hazelnut (incl. Cor a 1, Cor a 9 and Cor a 14), almond, cashew nut, walnut, kiwi, and apple.

Error bars indicate the 95% confidence interval.

Figure 2 shows the estimated percentual decrease in IgE levels for the different food allergens. The IgE levels of peanut extract decreased by 53.0% (95% CI: 46.3-59.7) after one year and by 85.3% (95% CI: 78.4-92.1) after three years of dupilumab treatment (Figure 2). The components Ara h 2 and Ara h 8 followed a similar pattern. Hazelnut-specific IgE levels decreased by 61.3% (95% CI: 56.0-66.6) after one year and by 86.1% (95% CI: 80.3-92.0) after three years, the components Cor a 1, Cor a 9, and Cor a 14 followed a similar pattern. A comparable trend was observed in the other tree nuts (cashew nut, almond, walnut); ranging from 80.5% (95% CI: 68.9-92.1) for walnut to 86.0% (95% CI: 69.1-103.0) for cashew nut after three years of treatment. Lastly, kiwi and apple showed a decrease of respectively 61.8% (95% CI: 54.5-69.0) and 62.9% (95% CI: 57.0-68.8) after one year of treatment, followed by a percentage decrease up to 86.9% (95% CI: 78.7-95.2) and 85.6% (95% CI: 78.0-93.2) after three years of treatment.

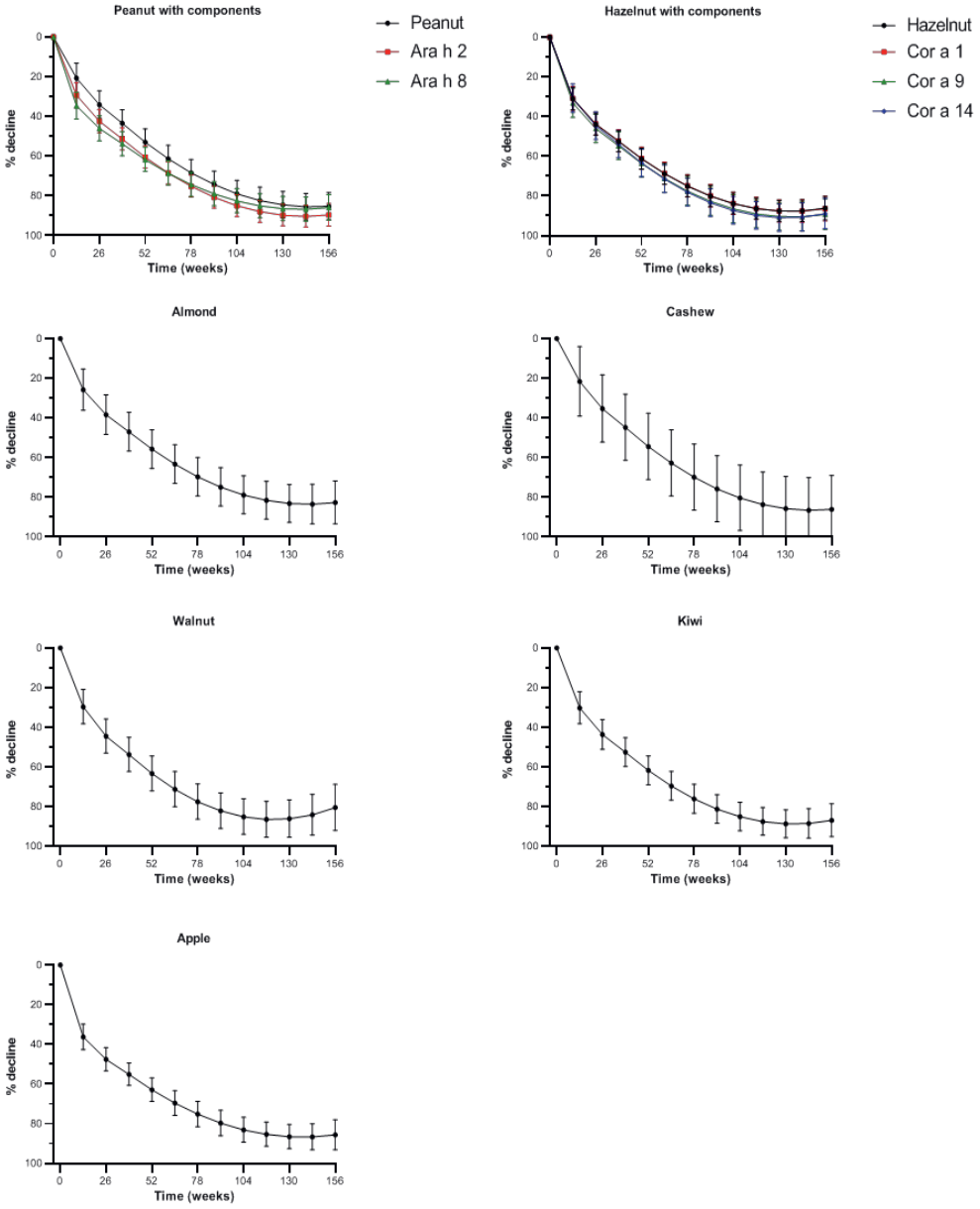

Figure 2. Estimated percentage decrease of sIgE levels during dupilumab treatment in patients with AD over the course of 3 years for peanut (incl. Ara h 2 and Ara h 8), hazelnut (incl. Cor a 1, Cor a 9 and Cor a 14), almond, cashew nut, walnut, kiwi, and apple.

Error bars indicate the 95% confidence interval.

Follow-up of food allergic symptoms during dupilumab treatment

During dupilumab treatment a total of 40 patients accidentally ingested foods they were allergic to. Of these patients, 82.5% (33/40) reported less severe food allergic symptoms during dupilumab treatment, and 17.5% (7/40) reported no change in symptoms. Patients who experienced less severe food allergic symptoms after accidental ingestion were more or less equally represented in all Mueller categories (Mueller 0 to Mueller 4), indicating that the effect of dupilumab on food allergies is observed irrespective of the severity of the initial food allergy (Table 3). At the time of reassessment of food allergies, there was no difference in median treatment duration between the patients reporting diminishing food allergic symptoms (n=33, 20 months) compared to patients without diminishing food allergic symptoms (n=7, 23 months).

Table 3. Patient-reported food allergic symptoms during treatment compared to start of dupilumab treatment in patients that accidentally ingested the food they were allergic to

	Decrease of food allergic symptoms		
	Yes (n=33)	No (n=7)	Total (n=40)
Mueller classification at baseline[a]			
Grade 0, n (%)	9 (75.0)	3 (25.0)	12 (100.0)
Grade 1, n (%)	8 (88.9)	1 (11.1)	9 (100.0)
Grade 2, n (%)	7 (87.5)	1 (12.5)	8 (100.0)
Grade 3, n (%)	8 (80.0)	2 (20.0)	10 (100.0)
Grade 4, n (%)	1 (100.0)	0 (0.0)	1 (100.0)

[a]Grade 0= oral allergy symptoms, grade 1= skin reactions, grade 2= gastrointestinal symptoms, grade 3= respiratory symptoms, grade 4= cardiovascular symptoms. SD, standard deviation.

Discussion

For the first time, this study describes the change in food allergen sIgE levels in a large population of 125 food allergic adult AD patients treated with dupilumab during an observational period up to 3.5 years. Dupilumab treatment induces a strong and sustained decrease in sIgE levels, with an estimated decrease of at least 50% for all foods after one year and more than 80% after three years of treatment. Furthermore, during dupilumab treatment, a total of 82.5% (33/40) of the patients who accidentally ingested foods to which they were allergic, reported less severe food allergic symptoms.

Presently, there is no direct evidence that a decrease in sIgE levels results in a higher threshold, less severe symptoms or tolerance, but such a relation is indirectly supported by different studies.[10-12, 17-19] Shek et al. showed that a decrease in sIgE

level was predictive for the likelihood of developing tolerance in milk and egg allergies in children.[11] Similarly, Gradman et al. presented that acquisition of tolerance of egg-white was associated with a decrease in sIgE level.[12] In addition, Peters et al. reported a significant reduction in sIgE levels in children with a resolved peanut allergy.[18] Furthermore, Saini et al. stated that a decrease in sIgE levels may be related to a higher tolerance for food allergens, as data indicated a correlation between a reduction in sIgE levels and the expression of high affinity IgE receptors on inflammatory cells.[10, 19] Additionally, Neuman-Sunshine et al. reported that higher initial peanut-specific IgE levels are associated with more severe allergic reactions.[17] Overall, these studies indicate that decreasing sIgE levels might be a surrogate marker for a diminished food allergic reaction.

In our study, we not only showed that the sIgE levels of all foods decrease during dupilumab treatment, but also that there is an indication that this might be clinically relevant. A large group of patients (33/40, 82.5%) experienced a decrease in severity during accidental ingestion of the culprit food. This effect was observed for mild, moderate as well as severe food allergies, suggesting that the effect of dupilumab does not depend on the severity of the food allergic reaction. The decrease in sIgE levels and self-reported severity of accidental food allergic reactions in AD patients treated with dupilumab, indicates that dupilumab might also have a positive effect on concomitant food allergy. However, it remains unknown whether dupilumab decreases the threshold of allergic reaction or increases the amount of the respective food that could be ingested. To evaluate this, an OFC before the start and during treatment of dupilumab is needed. Prospective studies including OFC before and during dupilumab treatment are necessary to evaluate and objectify whether treatment with dupilumab might result in a higher threshold and/or less severe symptoms in case of food allergic reaction. Studies objectifying the impact of dupilumab on food allergic symptoms are currently being conducted for peanut in pediatric AD patients.[20, 21]

We hypothesize that the effect of dupilumab on decreasing the severity of food allergic reactions might be due to inhibiting the IL-4/IL-13-pathway by blocking the IL-4Rα. Plasma cells play a major role in producing the sIgE mediating food allergic reactions and are differentiated from B-lymphocytes under influence of cytokines, IL-4, IL-5, and IL-13, respectively. Furthermore, IL-4 and IL-13 play a key role in IgE class-switching and subsequently; expansion, maintenance and activation of effector cells, including mast cells and basophils. Activation of these cells causes the release of

histamine and other mediators leading to allergic symptoms. Therefore, blocking the IL-4/IL-13 signaling pathway, by using dupilumab, might diminish food allergic reactions by interfering in the food allergic reaction cascade.

Limitations and strengths

Our study has some limitations. Firstly, clinical history of food allergy was not objectified by an OFC as the treatment was primary focused on AD in daily practice setting. However, the patient-reported symptoms were suggestive and assessed by a trained physician, and patients had sensitization to the corresponding food. Secondly, physician reassessment of food allergic symptoms during dupilumab treatment was patient-reported and not food specific without taking the threshold of the culprit allergen into account. Lastly, as patients followed the BioDay registry protocol, prolonging dupilumab administration interval was considered in case of controlled AD. This might have influenced the sIgE levels, but we decided not to correct for this phenomenon as it is reflective for clinical practice. Strengths of this study are the high number of included patients and the long follow-up time. Additionally, this study analyzed various food allergies and corresponding components, providing evidence for a broad effect.

Conclusion

In conclusion, this daily practice study shows that dupilumab treatment induces a sustained decrease in sIgE levels, showing an estimated decrease of at least 80% for all foods after three years of treatment. These findings endorse an additional advantage of dupilumab for AD patients with concomitant food allergy.

References

1. Barbarot, S., et al., *Epidemiology of atopic dermatitis in adults: Results from an international survey.* Allergy, 2018. **73**(6): p. 1284-1293.
2. Harb, H. and T.A. Chatila, *Mechanisms of Dupilumab.* Clinical and Experimental Allergy, 2020. **50**(1): p. 5-14.
3. Brazer, S.R., et al., *Using ordinal logistic regression to estimate the likelihood of colorectal neoplasia.* J Clin Epidemiol, 1991. **44**(11): p. 1263-70.
4. Silverberg, J.I., *Comorbidities and the impact of atopic dermatitis.* Ann Allergy Asthma Immunol, 2019. **123**(2): p. 144-151.
5. Rockmann, H., et al., *Food allergen sensitization pattern in adults in relation to severity of atopic dermatitis.* Clin Transl Allergy, 2014. **4**(1): p. 9.
6. Worth, A. and A. Sheikh, *Food allergy and atopic eczema.* Curr Opin Allergy Clin Immunol, 2010. **10**(3): p. 226-30.
7. Hill, D.J., et al., *Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study.* Clin Exp Allergy, 2008. **38**(1): p. 161-8.
8. Hamilton, J.D., et al., *Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases.* Clin Exp Allergy, 2021. **51**(7): p. 915-931.
9. Rial, M.J., B. Barroso, and J. Sastre, *Dupilumab for treatment of food allergy.* J Allergy Clin Immunol Pract, 2019. **7**(2): p. 673-674.
10. Saini, S.S., et al., *The relationship between serum IgE and surface levels of FcepsilonR on human leukocytes in various diseases: correlation of expression with FcepsilonRI on basophils but not on monocytes or eosinophils.* J Allergy Clin Immunol, 2000. **106**(3): p. 514-20.
11. Shek, L.P., et al., *Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy.* J Allergy Clin Immunol, 2004. **114**(2): p. 387-91.
12. Gradman, J., et al., *Relationship between specific IgE to egg components and natural history of egg allergy in Danish children.* Pediatr Allergy Immunol, 2016. **27**(8): p. 825-830.
13. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
14. Mueller, H.L., *Diagnosis and treatment of insect sensitivity.* J Asthma Res, 1966. **3**(4): p. 331-3.
15. Garrett M. Fitzmaurice, N.M.L., James H. Ware. - 2nd ed. p.cm, *Applied longitudinal analysis*. 2011, John Wiley & Sons: Boston.
16. Duan, N., *Smearing Estimate: A Nonparametric Retransformation Method. .* Journal of the American Statistical Association, 1983. **78**(September 1983): p. 605-610.
17. Neuman-Sunshine, D.L., et al., *The natural history of persistent peanut allergy.* Ann Allergy Asthma Immunol, 2012. **108**(5): p. 326-331 e3.
18. Peters, R.L., et al., *Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment.* J Allergy Clin Immunol, 2015. **135**(5): p. 1257-66 e1-2.
19. Lin, H., et al., *Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils.* J Allergy Clin Immunol, 2004. **113**(2): p. 297-302.
20. Pharmaceuticals, R., *Study in Pediatric Subjects With Peanut Allergy to Evaluate Efficacy and Safety of Dupilumab as Adjunct to AR101 (Peanut Oral Immunotherapy).*
21. Pharmaceuticals, R., *Study to Evaluate Dupilumab Monotherapy in Pediatric Patients With Peanut Allergy.*

12

General discussion

General discussion

For patients with moderate-to-severe atopic dermatitis (AD) the introduction of the first biological treatment in 2018, dupilumab, has drastically improved treatment outcomes and quality of life (QoL). This was the start of a new era in the treatment of moderate-to-severe AD, with the development of novel advanced targeted therapies including biologics and small molecules. The many emerging new advanced targeted therapeutics have already changed the current treatment of AD patients. For more patient-centered care, evidence about the effectiveness and safety of these new treatment options in daily practice is very important. The research presented in this thesis aimed to: 1) evaluate the long-term effectiveness and safety of dupilumab in daily practice; 2) move towards more personalized therapy with the use of dupilumab; 3) investigate the effect of dupilumab on the atopic comorbidities food allergy and asthma.

The implications, clinical recommendations and suggestions for future research regarding the main findings of this thesis will be discussed in this chapter.

Main findings of this thesis:

The long-term effectiveness and safety of dupilumab treatment in daily practice

- Treatment with dupilumab resulted in a rapid improvement in clinical outcome measures combined with a favourable safety profile; effectiveness further improved during the 52-week follow-up period. Conjunctivitis is more frequently reported compared to the clinical trials. **- Chapter 2**
- A total of 38.5% and 66.3% of the AD patients, using dupilumab between 16 and 52 weeks, perceived their AD as controlled by using the ADCT. Treatment satisfaction during dupilumab treatment in daily practice was high. **- Chapter 3**
- The 2-year drug survival of dupilumab was significantly longer compared to 2-year drug survival of methotrexate (MTX) and cyclosporin A (CsA). Approximately, half of the patients discontinued CsA and MTX because of treatment failure (ineffectiveness and/or side effects); limited patients (6.5%) discontinued dupilumab due to treatment failure. **- Chapter 4**

- In a cohort of 715 AD patients using dupilumab a good overall 1-, 2- and 3-year drug survival was found. Patients using immunosuppressive therapy at baseline and patient with absence of treatment effect at week 4 tend to discontinue treatment more frequently due to ineffectiveness. The use of immunosuppressant therapy at baseline, older age and an Investigator Global Assessment (IGA)-score of very severe AD were determinants for an increased risk for discontinuation due to side effects. **- Chapter 5**

Moving towards personalized AD treatment with dupilumab

- A broad range of serum dupilumab levels was found after 16 weeks of treatment in AD patients, with no relation to treatment response and side effects during the first year of treatment. **- Chapter 6**
- Eight potential predictors for long-term treatment response to dupilumab were identified: initial response (delta eczema area and severity index (EASI) score 0-4 weeks), age at dupilumab initiation, time of AD onset, medical history of skin infections, Body Mass Index (BMI), eosinophils count, IGA score, and gender. **- Chapter 7**
- Patient-centered dose reduction after 52 weeks of dupilumab was successful in a subgroup of patients with persistently controlled AD. Despite significantly lower dupilumab levels, the EASI score and disease severity biomarkers remained low and stable while using at least halve of the standard dosage. **- Chapter 8**
- Our patient-centered dosing regimen was successful in 83.3% of the patients while maintaining controlled disease, with the majority using dupilumab every other 3 or 4 weeks (Q3W/Q4W). In total, 401 patients tapered dupilumab with an estimated cost saving of 3,977,033.98 EUR between January 2019 and June 2022**- Chapter 9**

The effect of dupilumab on atopic comorbidities

- One year of dupilumab treatment, primarily indicated for AD, resulted in a significant improvement of comorbid asthma, with the largest effect in the first 16 weeks. Dupilumab treatment in AD patients provides an additional advantage for patients with comorbid asthma. **- Chapter 10**

- Dupilumab treatment induces a strong and sustained decrease in specific IgE levels in AD patients with comorbid food allergies, with an estimated decrease of at least 50% for all foods after one year and more than 80% after three years of treatment. **- Chapter 11**

Exploring daily practice performance of dupilumab in AD

The differences between clinical trials and daily practice studies

Randomized controlled trials (RCTs) are designed to measure the efficacy and safety of a single treatment in a certain disease within a homogeneous group of patients.[1] Due to the use of strict protocols in RCTs, for example the definition of the study population (strict in- and exclusion criteria), patients in RCTs differ from patients in daily clinical practice (Figure 1).[2]

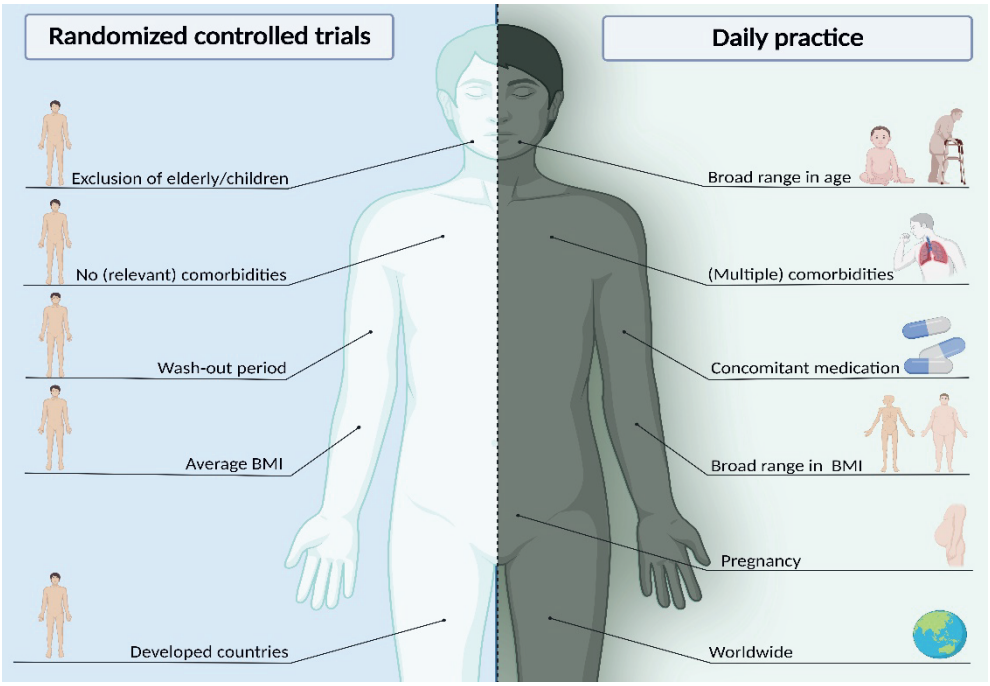

Figure 1. Differences between patient populations of clinical trials and daily practice.
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These controlled conditions in clinical trials might result in differences between the performance of the investigated drug found in clinical trials compared to daily practice studies.[3] The efficacy of an intervention can be defined as the performance under ideal and controlled circumstances, whereas effectiveness refers to its performance in 'real-world' conditions.[4, 5] To date, most clinical guidelines and recommendations concerning AD are based on clinical trial data, since real world evidence is lacking. Although efficacy research maximizes the likelihood of observing an intervention's effect if one exists, effectiveness research accounts for external patient-, provider-, and system-level factors that may moderate an intervention's

effect.[6] Therefore, effectiveness research, e.g. by using registry data, can be more relevant for health-care decisions by both health-care providers and policy-makers. An important aim of the BioDay registry is, therefore, to collect prospective data about the effectiveness and safety of new advanced targeted therapies for patients with moderate-to-severe AD in daily practice. The use of daily practice data collected by a registry, like BioDay, can bridge the gap between evidence from RCTs and daily practice.

In the first BioDay study investigating the effectiveness and safety of 16 weeks dupilumab treatment for AD in clinical practice[7], a small percentage of patients used concomitant immunosuppressant therapy at dupilumab initiation and relatively high disease activity scores at baseline were observed. Due to the relatively comparable conditions and outcome measures (absolute and relative outcome measures) between our 16-weeks daily practice study and previous dupilumab RCTs, outcomes were similar and comparable. However, over time daily practice studies reflect more and more clinical practice, as patients with multiple comorbidities, allowance of concomitant immunosuppressant therapy, and patients with lower baseline disease activity scores are included. Due to this daily practice setting it is more difficult to compare data from clinical trials and daily practice. Therefore, new comprehensive strategies are needed to define and measure clinical relevant response.

Treatment response

…How to measure?

The HOME initiative recommends that 'long-term control of eczema' is measured in all clinical trials with a duration of 3 months or longer.[8] However, little has been published on what eczema control means to those living with AD, like patients in the BioDay registry. The impact of AD is multifactorial. Due to the multifactorial character of AD, measuring multiple dimensions of treatment response by combining PROs with disease severity scores leads to a more holistic approach. However, by looking at the validated and regularly used patient-reported outcomes (PROs), none of these PROs captures the diverse signs, symptoms, and QoL impact of AD (Table 1). The ADCT seems to be the most comprehensive PRO and is designed to assess patient-perceived control of AD in adults (**Chapter 3**). Combining the ADCT with the disease severity score IGA (or EASI score) might be the most comprehensive though concise approach to assess treatment effect in daily practice.

Table 1. Overview of validated questionnaires with corresponding measured domains in atopic dermatitis.

Clinical tool	IGA [9, 10]	EASI [11, 12]	SCORAD [12, 13]	NRS itch [14]	POEM [12, 15]	DLQI [16]	TSQM [17]	ADCT [18, 19]
MCID	n/a	6.6	8.7	2–3	3.4	4	n/a	5
Clinical signs	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)
Symptoms	(-)	(-)	(+)	(-)	(+)	(-)	(-)	(+)
Pruritus	(-)	(-)	(+)	(+)	(+)	(-)	(-)	(+)
Mental health	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)
Quality of life	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(+)
Disease control	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)

Red (-) indicates the inability of measuring respective domain, green (+) indicates the possibility of measuring respective domain. ADCT, Atopic Dermatitis Control Tool; DLQI, Dermatology Life Quality Index; EASI, Eczema and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; MCID, minimum clinically important difference; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; TSQM, Treatment Satisfaction Questionnaire for Medication.

Treatment response can be measured in multiple dimensions, and can be expressed by using various types of outcome measures, e.g. absolute vs. relative differences over time or cut off points (Figure 2). In clinical trials, response is usually measured by relative change over time while using a cut-off point, for example 75%, 90%, or 100% reduction of the EASI score (i.e. EASI75, EASI90, EASI100) compared to baseline (start of therapy).

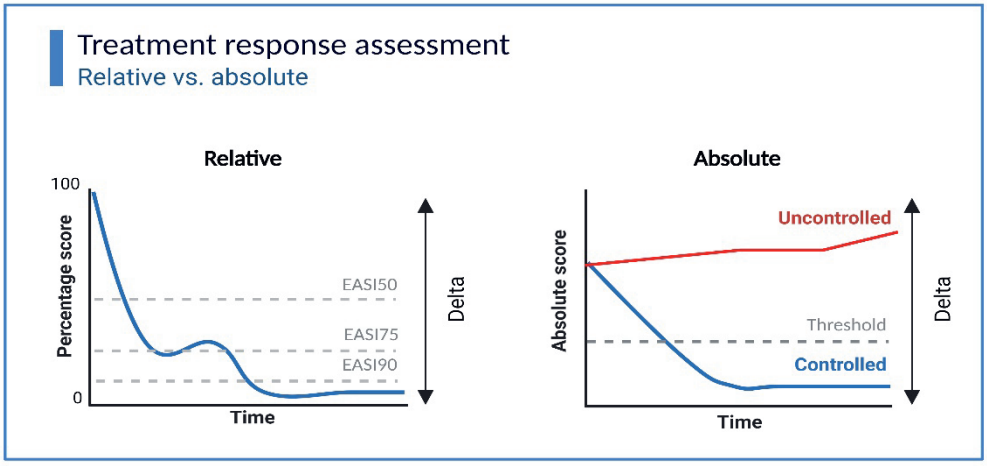


Figure 2. Different ways of treatment response assessment.

Analyses can be based on absolute vs. relative differences over time or cut-off points. A continuous scale gives more insight in response over time than relative response based on a cut-off point, such as EASI90. For example, patients achieving 89% reduction in EASI score do not achieve EASI90, while these patients have a comparable response to patients achieving 90% reduction in EASI score. In daily practice, controlled disease defined by absolute cut-off points is more and more widely used to assess response to treatment. Created with BioRender.com

The baseline measurement is an important factor influencing percentage change (e.g. patients with a low baseline EASI score are less likely to achieve EASI90 despite having a good treatment effect). In clinical trials, patients have a compulsory wash-out period of previously used systemic treatment leading to higher disease activity and clinical scores at baseline. While in daily practice multiple factors, like bridging concomitant therapy, are present and can lead to substantially lower (baseline) scores, with subsequently a smaller percentage decrease in clinical scores compared to clinical trials. As a consequence, in daily practice controlled disease defined by absolute cut-off points is more suitable to assess response to treatment. In clinical practice, controlled AD has been defined as an absolute EASI score ≤7 and Numeric Rate Scale (NRS) pruritus ≤4, and is considered as long-term outcome goal (Treat-to-Target).[20, 21] For this reason, as presented in **Chapter 6**, **8** and **9**, not only absolute and relative responses were taken into account, but cut-off points for controlled disease were assessed.

Deviating from the standard; do or don't?

As itch is one of the most important symptoms of AD, itch intensity measured by using the Peak Pruritus NRS has been endorsed by the global HOME initiative as a core symptom of AD for clinical trials.[22-25] The Peak Pruritus NRS is a single self-reported item designed to measure peak pruritus, or 'worst' itch, over the previous 24 hours. However, in BioDay itch severity is assessed by using the weekly average NRS-pruritus, which measures the average pruritus score over the last 7 days. In our opinion, weekly average NRS pruritus better reflects itch in daily practice due to the flaring character of AD compared to the Peak Pruritus NRS and therefore has greater clinical implications. As the aim of daily practice studies fundamentally differs from clinical trials, deviating from the current standard is sometimes necessary to achieve a relevant outcome.

The long-term effectiveness and safety of dupilumab treatment in daily practice

Response

….EASI and NRS

Concerning the long-term outcome of dupilumab in daily practice as described in **Chapter 2**, the effectiveness is comparable to clinical outcomes of the 52-week, randomized, double-blinded, placebo-controlled, phase 3 study that investigated long-term management of moderate-to-severe AD with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS).[26] In our study, mean percentage change in EASI after 16 weeks was –70.0% (SD 33.2) and further decreased to –76.6% (SD 30.6) after 52 weeks of treatment with median baseline EASI score of 19.0. A greater than or equal to 4-point reduction in weekly average pruritus NRS score was achieved by 62.1% (110/185) of the patients at week 52.

The treatment responses measured in other published[27-29] daily practice studies seem comparable; however, multiple factors contribute to the inability to directly compare results. The criteria for start of dupilumab differs between countries, leading to a difference in the baseline AD severity between the studies, and as stated earlier, directly influences relative response. Furthermore, outcome measures are differently presented and analyzed, for example due to the use of different statistical analyses (e.g. the last observation carried forward method vs. linear mixed-effects models) or outcome measurements. All these factors result in different outcomes which makes it often difficult to compare study results.

…Drug survival analysis

Drug survival is an overarching and holistic measure of treatment success. It depends on the effectiveness of the drug, but also for example on tolerance, general satisfaction with the treatment, as well as behavior of physician and patient.[30] In **Chapter 4** and **5** we have shown that, in general, drug survival of dupilumab treatment in AD is considered to be good, and discontinuation was most often driven by side effects. Discontinuation due to ineffectiveness was relatively uncommon.

A recent one-year drug survival study in real-world conditions in adult AD patients from various European countries, showed that 23 of 104 patients (22.1%) discontinued dupilumab treatment, mostly due to side effects (n=7, 6.7%).[31]

Drug survival analysis for dupilumab in AD in the TREATGermany registry (august 2022) showed that treatment was discontinued in only 5.0% and 11.4% of the patients after 12 and 24 months of treatment, respectively. The reasons for discontinuation are not mentioned.[32] Interestingly, data release of TREATGermany (July 2021) took place after the introduction of other new advanced targeted therapies (e.g. baricitinib) for AD. However, the discontinuation rates remain consistent with our results. This might be explained by a low prescription rate of baricitinib in Germany or by long-term effectiveness and safety of dupilumab with relatively low need for an alternative treatment. In Italy, a multicenter, retrospective study, was performed to assess drug survival of dupilumab in 247 adult AD patients.[33] After 1.4 years 14.0% (32/247) of the patients had discontinued treatment with a corresponding drug survival of 87.0%. The most frequent (13/247; 5.3%) reason for drug discontinuation was the achievement of complete disease remission, followed by side effects in 10 (4.0%) patients. Seven (2.8%) patients discontinued dupilumab due to ineffectiveness. These discontinuation rates and reasons for discontinuation are similar to our studies except for discontinuation due to controlled disease, to date none of the BioDay patients discontinued treatment due to controlled disease. As there are differences in national guidelines for initiating treatment, there might also be differences between countries in the decision-making to discontinue treatment.

In line with our results, these daily practice studies showed that dupilumab has a favorable drug survival with a low number of patients discontinuing dupilumab. In the coming years it will be interesting to re-evaluate the drug survival of dupilumab and compare the drug survival of dupilumab to other advanced systemic treatment options when they have been prescribed for a longer period. It is expected that the availability of other potent treatments for AD will lead to higher discontinuation rates of dupilumab treatment.

Safety

According to clinical trials, dupilumab treatment in moderate-to-severe AD patients is associated with a favorable safety-profile on the short-[34] and long-term[35]. The most frequently reported side effects were injection-site reactions and conjunctivitis.[36, 37] In daily practice, dupilumab has also shown to be a safe treatment option for AD, especially compared to the conventional immunosuppressive therapies (**Chapter 4**).[38] Since dupilumab is a relatively new therapy with only a few years of clinical experience (long-term) side effects, which has not been reported in clinical trials due

to their relatively short follow up, might arise in clinical practice. For example, as shown in **Chapter 5**, dupilumab-induced skin eruptions were reported after a median treatment duration of approximately one year, which is much longer compared to the follow-up duration of most clinical trials. Other side effects, including conjunctivitis, seem to occur more frequently in daily practice compared to clinical trials. Consequently, clinical experience combined with daily practice registries are needed to discover potential (long-term) side effects.

…Dupilumab Associated Ocular Surface Disease (DAOSD)

During the clinical trials, conjunctivitis adverse events were reported more often in dupilumab-treated AD patients (5%-28%) compared to placebo (2%-11%).[26, 39, 40] The first daily practice studies of AD patients treated with dupilumab showed higher incidence of dupilumab associated ocular surface disease (DAOSD) up to 38%,[7, 41-44] which was also found in our 52 week data (**Chapter 2**). This high prevalence is in line with other real-world studies[36] with a DAOSD incidence up to 70% during dupilumab treatment in a Swedish study.[45] Recently, in our prospective ophthalmological sub study from the BioDay registry a preexisting ocular surface disease (OSD) prevalence of 90% in adult patients with moderate-to-severe AD before the start of dupilumab was reported.[46] These results show higher rates of OSD in AD patients than previous studies, reporting an incidence of 32.4–55.8% of OSD in severe AD patients.[37] This strengthens the hypothesis of a possible predisposition in AD patients to develop DAOSD, since dupilumab treatment was not associated with higher conjunctivitis rates in other Th2-mediated disease (e.g. asthma and nasal polyps).[37] Additionally, higher incidence rates of OSD, both before and during dupilumab treatment, can be explained by an increased awareness and attention for ophthalmological signs and symptoms. Given the high prevalence of preexisting OSD in AD patients,[46] it might be that in these patients ocular signs and symptoms were previously suppressed by broad acting conventional therapies (e.g. CsA and MTX). Currently, the pathomechanism of the development of DAOSD in AD patients remains unclear and is being studied in ophthalmological sub-trials in our center.

In **Chapter 2** a recommendation was made to consider either artificial tears and/or off-label use of tacrolimus 0.1% eye ointment for the treatment of conjunctivitis occurring in patients with AD during dupilumab treatment. DAOSD is usually mild and responds sufficient to therapy allowing the patient to continue treatment with dupilumab. Nevertheless, 2.8% of patients discontinued dupilumab due to ophthalmic side effects (**Chapter 2** and **5**), with DAOSD being the largest group

(2.4%). So, in case of persistent severe conjunctivitis despite intensive anti-inflammatory treatment by an ophthalmologist, discontinuation or interval prolongation of dupilumab should be considered. Special attention should be paid to limbitis; a rare but severe complication of DAOSD,[47, 48] which is also described in **Chapter 5**; 0.3% of the patients (2/715) discontinued dupilumab treatment due to a limbitis, which when untreated, can lead to vision loss.[49]

…Dupilumab-induced skin eruptions

Dupilumab-induced skin eruptions were the second largest group of side effects leading to discontinuation of dupilumab (**Chapter 5**) and mostly developed after longer duration of treatment. Dupilumab-induced skin eruptions consist of four clinical phenotypes: atypical cutaneous lymphoid reaction and cutaneous T-cell lymphoma (CTCL), psoriasis-like eruption, facial dermatitis, and rosacea. Since AD is a Th2-mediated disease and the Th2-pathway is blocked by using dupilumab, antagonism of the Th2-pathway may lead to activation of the Th1- and/or Th17-pathway leading to more Th1/Th17-mediated diseases, such as psoriasis, facial dermatitis, and/or rosacea.

Due to the malignant character of CTCL, it is important to identify these patients at an early stage of the disease. Recently, multiple cases of the development of CTCL and atypical lymphoid infiltrates in AD patients treated with dupilumab have been reported.[50-54] CTCLs are a group of heterogeneous cutaneous malignancies, with mycosis fungoides (MF) as the most common type of CTCL. Because there is overlap in the clinical appearance of moderate-to-severe AD and CTCL,[55] patients with CTCL can be misdiagnosed with AD.[56-58] It was earlier proposed that dupilumab might be of benefit to CTCL patients.[56, 59] However, several case reports[53] described disease progression of CTCL while using dupilumab, which exposed the CTCL[54] and in a few cases led to death.[50-52] These case reports suggest that dupilumab-specific modulation of the immune system may cause an acceleration of disease process in CTCL. Recent analysis by Sokumbi et al. of pre-dupilumab and post-dupilumab biopsies highlighted progressive changes in the density, patterns of distribution, and composition of the lymphoid infiltrate from a reactive to a neoplastic pattern after an average of 9.8 months of dupilumab treatment.[50] At the moment, it is unknown whether dupilumab unmasks underlying CTCL by means of acceleration of the disease process, or, triggers conversion from AD to CTCL through an immunomodulatory shift. In **Chapter 5** 'CTCL-like' phenotypes were reported as well.

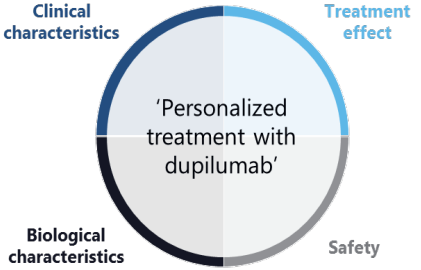
One patient had worsening of a misdiagnosed MF during dupilumab treatment and discontinued treatment, while three other patients were diagnosed with an atypical cutaneous lymphoid infiltrate which resolved after discontinuing dupilumab treatment. Additionally (unpublished data of the BioDay registry), in ten patients with atypical cutaneous lymphoid infiltrates, post-treatment biopsies showed complete clearance of the atypical lymphoid reaction in almost all patients. The exact mechanism of the immunomodulatory shift remains unknown, although most patients had an atypical clinical appearance of AD, for example late onset AD or developed a burning skin sensation instead of increased itch. For clinical practice, absence of treatment response or change in response to dupilumab should lead to a re-evaluation of AD diagnosis, preferably accompanied by a skin biopsy. Hence, these cases also highlight the need to consider CTCL as a differential diagnosis before initiating dupilumab for AD.

Moving towards personalized AD treatment with dupilumab

As the number of advanced targeted therapies registered for the treatment of AD increases, so does the need for personalized therapeutic decisions. To move towards the goal of personalized treatment, assessment of the performance of the new advanced systemic therapies for AD in daily practice is needed. In the future, the decision of which advanced targeted treatment to start for the individual patient should ideally be supported by treatment predictors for response as well as safety. This to assign patients the most optimal treatment and preventing prolonged periods of suboptimal therapy. Additionally, it is important to pursue individual dosing during treatment by finding the lowest possible dose while maintaining clinical effectiveness for each individual patient. At time of writing this thesis, only long-term data on dupilumab in daily practice is present, therefore only personalized treatment with dupilumab could be assessed (Figure 3).

Component	Key finding	Chapter
Atopic comorbidities	Positive effect of dupilumab on comorbid food allergy and asthma	10 & 11
Predictive value	Several patient characteristics were predictive for discontinuation due to ineffectiveness and/or side effects	5
Predictive value	Inability of sufficiently predicting effectiveness or successful tapering	7 & 9

Component	Key finding	Chapter
Serum drug levels	High and broad range in dupilumab levels at 16-weeks. Significantly lower dupilumab levels during tapering.	6 & 8
Serum biomarkers	Decrease of disease severity biomarkers during treatment. Disease severity biomarkers remained low during tapering.	2 & 8
Predictive value	Dupilumab levels at 16-weeks did not predict response or side effects.	6



Component	Key finding	Chapter
Outcome measures	Rapid improvement in clinical outcome measures. Treatment satisfaction was high during treatment.	2 & 3
Drug survival	Good overall drug survival compared to conventional treatment; persisted up to three year	4 & 5
Individual dosing	Tapering was successful in 83.3% of the patients while maintaining controlled disease.	9

Component	Key finding	Chapter
Incidence	Conjunctivitis was most frequently reported side effect. Induced skin eruptions developed after longer treatment duration	2 & 3
Comparison	More favorable safety profile compared conventional therapies.	4
Severity	Discontinuation was mostly driven by side effects, but rates remained low. Cave: limbitis and CTCL	4 & 5

Figure 3. Integrated approach to move towards personalized treatment with dupilumab.

To move closer to the goal of personalized AD treatment with dupilumab an approach on multiple levels is needed. Integrating all approaches will guide us towards personalized treatment with dupilumab. ADCT, Atopic Dermatitis Control Tool; DLQI, Dermatology Life Quality Index; EASI, Eczema and Severity Index; IGA, Investigator Global Assessment; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; TSQM, Treatment Satisfaction Questionnaire for Medication.

Long-term treatment success

...Predicting by clinical characteristics

Previous studies of predictive clinical characteristics are rather limited and mainly focussed on the early response (up to 16 weeks).[43, 60, 61] In **Chapter 7**, eight potential clinical predictors for long-term treatment response to dupilumab were identified: initial response (delta EASI score 0-4 weeks), age at dupilumab initiation, time of AD onset, medical history of skin infections, Body Mass Index (BMI), IGA score, and gender. However, the model did not provide an accurate prediction of response as it only explained 17% of the variation in change of EASI scores and no optimal validation was demonstrated. As a result, predicting response to dupilumab with only clinical characteristics was hardly feasible, which was also demonstrated in other inflammatory disease response prediction studies.[62-64]

... Predicting by biological characteristics

In our study described in **Chapter 6**, we investigated the role of serum dupilumab levels in predicting long-term treatment response. Although a large variation in serum dupilumab levels was found, we concluded that serum dupilumab levels at 16 weeks of treatment were not associated with treatment response during the first year of treatment. Since we studied unbound serum dupilumab levels, clinical response might be dependent on the affinity of dupilumab to the IL-4Rα and its target availability, with an inter-patient variability leading to heterogeneity in response. This is supported by our results described in **Chapter 8**, where a few patients using dupilumab every 6 or 8 weeks (Q6-8W) had serum dupilumab levels of 0, although their AD maintained controlled.

In previous studies, several biomarkers have been proposed for the prediction of response to targeted therapies in AD. The presence of high IL-22 skin expression was associated with better response to anti-IL-22 treatment with fezakinumab,[65] and high serum concentrations of the IL-13-related markers DPP4 and periostin were opposed as predictors of response to tralokinumab (anti-IL-13) treatment.[66] To date, limited serum blood biomarkers are known to predict response to dupilumab in patients with AD. Baseline serum LDH level was negatively correlated with the percentage reduction in EASI at 12 months after initiating.[67] Baseline serum thymus and activation-regulated chemokine (TARC) and IgE levels and the number of circulating eosinophils were not associated with the percentage reduction in EASI score.[67]

Mobus et al. showed that overall response to dupilumab treatment did not show marked differences between the two endotypes; eosinophil-low and eosinophil-high.[68] However, in **Chapter 7**, the level of eosinophils was found as a potential predictor for response. A study is currently conducted to explore whether biomarkers can predict clinical improvement of AD in patients treated with dupilumab.[69]

Personalized treatment in AD care could benefit from a predictive model for clinical effectiveness for dupilumab. However, as shown in above mentioned studies developing a prediction model is challenging, and clinical effectiveness might depend on a combination of clinical characteristics and serum biomarkers. Since treatment response to dupilumab is rather homogenous and the number of non-responders is low, it is rather difficult to find distinctive clinical or biological characteristics for predicting response to dupilumab.

… Predicting by focussing on side effects

As described in **Chapter 4** and **5**, the most frequently reported reason for discontinuation of dupilumab treatment was side effects. Therefore, early identification and treatment of side effects may avoid discontinuation of new advanced targeted treatment. Furthermore, early detection of patients at risk for side effects leads to more personalized treatment.

As DAOSD is one of the most frequently reported side effects of dupilumab, identifying factors which are associated with DAOSD is of great importance to distinguish patients at risk for developing DAOSD. In clinical practice studies, higher disease activity at baseline[70, 71]; history of conjunctivitis[37, 70, 72]; and eye-lid eczema[73, 74] were identified as risk factors for developing DAOSD. Reports on biomarkers as predictors for dupilumab-associated conjunctivitis are limited but serum TARC levels, blood eosinophil levels, and IgE levels[73] were significantly higher in patients who developed DAOSD. We found that DAOSD was associated with significantly higher EASI scores and serum TARC levels at baseline (**Chapter 2**). An IGA score of very severe AD was found as risk factor for discontinuation due to side effects (**Chapter 5**). This might be explained by the higher risk of developing DAOSD in very severe AD patients, as 75% of the patients with an IGA score of very severe AD discontinued treatment due to DAOSD (**Chapter 2**). For clinical practice, despite higher disease activity being a risk factor for developing DAOSD, it is not a contraindication to start dupilumab treatment. Higher disease activity does not directly imply that all patients with higher disease activity discontinue treatment due

to DAOSD. Additionally, 2.4% of the patients discontinued treatment due to DAOSD (**Chapter 2** and **5**), which indicates that only a small group of patients discontinued treatment due to DAOSD. However, as patients with high disease activity (or eye lid eczema) at start of dupilumab are at higher risk to develop DAOSD, it can be an argument to intensively ophthalmological follow-up these patients.

Contradictive results were displayed for serum dupilumab levels and the association with DAOSD. In clinical trials, an inverse relationship between serum concentrations of dupilumab and conjunctivitis was observed,[39] suggesting that conjunctivitis incidence may decrease with higher dupilumab serum concentrations.[37] This finding suggests local under treatment of the eyes, possibly due to higher target burden or lower tissue distribution. In **Chapter 9** the association of serum dupilumab levels and the development of DAOSD was explored. As opposed to the clinical trials, our study showed that serum dupilumab levels at 16 weeks were not associated with DAOSD. Furthermore, prolonging dupilumab interval, thereby lowering dupilumab serum levels, can also improve DAOSD[47], which makes it unlikely that DAOSD was undertreated. It might be possible that the development of DAOSD is associated with differences in IL-4Rα expression between patients instead of serum dupilumab levels.

Individual dosing of dupilumab

…The effect on clinical outcome measures

In **Chapter 8** and **9** our patient-centered dupilumab dosing regimen was described as successful in a subgroup of patients with controlled AD in daily practice. Tight controlled dose reduction strategy by interval prolongation while monitoring disease activity provides the possibility to determine the lowest effective dose for the individual patient. A few daily practice studies with a small sample size (≤90) and one clinical trial[75] were published concerning different dosing regimens of dupilumab.[76,77] The daily practice studies concluded that lower dosages were feasible in a substantial subset of patients, while the SOLO-continue study recommended the approved regimen of dupilumab every other week (Q2W) for long-term treatment. Additionally, a meta-analysis of RCTs was performed by Ya-Chu Shih et al. to systematically evaluate the efficacy and safety of multiple dupilumab dosing regimens in patients with moderate-to-severe AD in terms of comprehensive outcomes. In all efficacy outcomes (EASI50, IGA response, and NRS response), Q2W had no significantly better efficacy compared to Q4W. As for Q8W with an indirect comparison with Q2W, significantly reduced efficacy was noted in EASI50 compared

to Q2W; however, no significant differences were noted in IGA response and NRS response.[78] These results endorse the ability of individual dosing of dupilumab guided by disease activity in daily practice while maintaining clinical effectiveness.

…Prediction of successful tapering

Identifying predictors for (un)successful tapering leads to a weighted decision in continuing standard dosage or pursuing tapering and would limit the risk of AD flaring. In **Chapter 9**, multiple clinical and immunological variables were analysed for their predictive value, but no predictors for successful dose reduction were identified. At time of writing this thesis, no other predictive studies for successful dose reduction are published. It is possible that not only patient factors influence the ability of dose reduction, but physician factors also play a role. At start of dupilumab treatment discussing the possibility of tapering in case of controlled disease to achieve the lowest possible dose while maintaining clinical effectiveness, will improve drug adherence and contribute to individual dosing. As shown in **Chapter 9**, a small increase in the amount of used topical steroids was observed in the tapering groups. It is important to pay attention and explain the chance of marginal flaring; sufficiently informing and guiding the patient might play a key role in successful tapering. Hence, to maintain patient's personal treatment goals while reducing dupilumab dose and to improve drug adherence, shared-decision making is fundamental for personalized treatment. This might explain why our patient-centered dosing regimen was successful, while distinct clinical and immunological characteristics for successful tapering were not found.

…The potential role of the IL-4Rα

The ability of reducing dupilumab dose may be explained by differences in the bioavailability and quantity of dupilumab available at the target tissue, which in turn is influenced by adherence, drug dose, and pharmacokinetic (PK) covariates.[79, 80] As described in **Chapter 6**, a broad range of serum dupilumab levels was found after 16 weeks of treatment in AD patients and was not associated with treatment response. Overall, this broad range and high serum levels of dupilumab suggest that there might be a role for individualized dose optimization. Interestingly, dupilumab serum levels are minimally related to response in contrast to serum levels of other biologics in other diseases,[81-83] which also suggests that many patients might respond equally well with lower doses of dupilumab. This hypothesis is confirmed in **Chapter 8**, in which the pharmacological effects of dose reduction were investigated by analysing

serum drug levels over time. EASI scores remained low and stable during dose reduction, while serum dupilumab levels significantly decreased. It might be that tapering is dependent on the affinity of dupilumab to the IL-4Rα or the number of IL-4Rα with an inter-patient variability producing heterogeneity in the possibility of tapering.

….Its challenges

As shown in **Chapter 9**, in the majority of patients AD remained controlled (EASI≤7), but both EASI and NRS scores increased significantly after interval prolongation, indicating increased disease activity. The clinical relevance of these differences are questionable as the change in EASI and NRS pruritus scores were very small, did not reach the minimal clinical important difference (MCID), and stayed below the cut off values of controlled disease.[12, 24] As stated previously, due to the multifactorial character of AD, measuring different domains of disease activity by combining PROs with disease severity scores, leads to a more holistic approach. The ADCT seems to be the most comprehensive PRO and can be a valuable tool for the future to evaluate disease control (combined with IGA score) during tapering. Furthermore, 21.2% successfully prolonged their interval in a second attempt, indicating that interval prolongation should be opted out to the patient in case of persistent controlled disease even if a patient previously failed to taper. Lastly, increasing dosing interval might theoretically increase the risk of antidrug antibodies.[84, 85] In the SOLO-continue study, antidrug antibodies were found in approximately 11% of dupilumab Q8W group but also in 11% of the placebo group.[75] The possibility for increasing immunogenicity and developing antidrug antibodies after dosing interval prolongation or cessation of dupilumab was not examined in the BioDay registry. However, clinical efficacy was regained when patients switched from a prolonged interval back to Q2W.

…And timing

Our patient-centered dosing regimen was implemented after 52-weeks of treatment. However, it might be feasible to implement our dosing regimen earlier, for example after 16- or 28-weeks of treatment. This was already successfully demonstrated for tralokinumab.[86] The effect of dose reduction in tralokinumab responders at 16-weeks was assessed in a RCT comparing efficacy and safety of tralokinumab Q4W to continuation of Q2W dosing. The same inclusion criteria were used as the previously discussed SOLO-continue study.[75] A total of 89.6% and 92.5% of the patients treated

with tralokinumab Q2W, and 77.6% and 9.8% treated with tralokinumab Q4W maintained an IGA 0/1 and EASI 75 response at week 32, respectively.[86]

Based on the results of the tralokinumab tapering study, it might also be feasible to implement our patient-centered dupilumab dosing regimen at an earlier time point in case of controlled disease. However, Bangert et al. discovered that specific immune cell populations persisted for up to 1 year after clinical response while using dupilumab, which was absent in healthy controls.[87] Their data suggest that it takes at least one year of dupilumab treatment to bring immunological remission, even after having achieved clinical amelioration. Furthermore, Mobus et al. concluded that after three months of treatment with dupilumab, despite clinical improvement, the blood transcriptome displays residual signs of inflammation.[68] Future studies are needed to assess the most effective time point to reduce dupilumab dose while maintaining clinical effectiveness.

The effect of dupilumab on atopic comorbidities

The effect of dupilumab on comorbid

…Asthma

In both AD and asthma, Th2-cells producing IL-4, IL-5, IL-10, and IL-13, can further drive type 2 (T2) immune reactivity and enable eosinophilic recruitment as well as production of IgE (Figure 4).[88, 89] This underlying shared immune dysfunction, with increased T2 immunity and elevated serum IgE levels,[90] may explain some of their coexistence and the potential of dupilumab as monotherapy for these T2-associated diseases,[91] which was supported by our findings in **Chapter 10**.

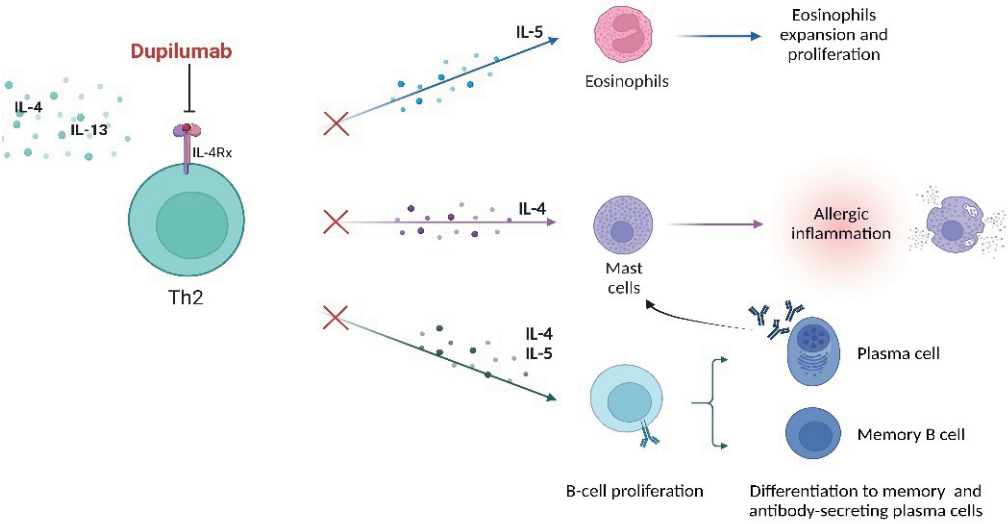


Figure 4. Blocking of IL-4 and IL-13 by dupilumab.

Dupilumab binds to the IL-4Rα on T-helper 2 (Th2)-cells, thereby blocking the effect of IL-4 and IL-13, and consequently blocking multiple Th2-related pathways. In this figure only the effect on eosinophils, mast cells, and B-cells are shown. Created with BioRender.com

Interestingly, dupilumab is the only biologic registered as treatment option for AD as well as allergic asthma. Omalizumab, a monoclonal antibody that specifically binds to the IgE Fc fragment,[92, 93] has a limited effect in patients with AD,[94] and is more effective in asthma, indicating that IgE, to a certain degree, has a secondary role in AD. Mepolizumab, a monoclonal antibody targeting IL-5, has proven to be effective in reducing disease severity in eosinophilic asthma, but failed in AD.[95] More recently, tralokinumab, a monoclonal anti-IL-13 antibody, has been investigated for both AD as well as asthma.[96, 97] While tralokinumab is now approved for the treatment of AD,

trials showed inconsistent effects on annualized asthma exacerbation rates[98] and no significant improvement of FEV1.[99] Consequently, the development of tralokinumab in severe asthma was discontinued by the producer after those studies.[96] Altogether, these studies showed that despite the common underlying immune dysfunction, AD and asthma have a distinctive response to immune-modulating treatment. This might be explained by differences in underlying immunological mechanisms, however, both atopic diseases are responsive to dupilumab treatment. Therefore, independent of eosinophilia and asthma severity, comorbid asthma in patients with AD can be an argument for opting for treatment with dupilumab (**Chapter 10**), as it targets both diseases.

…Food allergy

Exposure to a food antigen induces IgE binding to mast cells and basophils, activating these cells and triggering the release of the inflammatory mediators, IL-4, IL-5, IL-13, and Th2-related chemokines, which are responsible for tissue response and clinical symptoms (Figure 4).[100] Blocking these cytokines by using dupilumab, inhibits the IL-4/IL-13 signalling pathway and may abolish food-allergic responses, as suggested by a case report from Rial et al..[101] **Chapter 11** showed that dupilumab was able to reduce several serum food allergen-specific IgE levels in food allergic patients with AD. These findings are supported by different studies reporting on a reduction in specific IgE levels, including food- and respiratory components, by using dupilumab.[102, 103] Considering the clinical relevance of blocking the IL-4/IL-13 signalling pathway by dupilumab, a group of patients (33/40, 82.5%) experienced a decrease in severity of their allergic reactions during accidental ingestion of the culprit food during dupilumab treatment (**Chapter 11**). Additionally, multiple studies have demonstrated a significant decrease in total IgE levels during dupilumab treatment. [104, 105] It is possible that the decrease in food allergen-specific IgE levels is a result of the reduction in total IgE levels. It is unknown whether the continuous decrease in total IgE levels is also correlated with progressive clinical improvement of food allergies. By measuring specific IgE levels instead of total IgE, we can determine the changes in allergen-specific IgE antibodies and assess their correlation with clinical outcomes. This allows for a more precise assessment of the effects of dupilumab on food allergies. However, it remains unknown whether dupilumab lowers the threshold of an allergic reaction or possibly reduces the severity of the reaction. Studies objectifying the impact of dupilumab on food allergic symptoms are currently being conducted for peanut in paediatric AD patients.[106, 107]

Putting it all in perspective

Current perspectives

… On treatment options for AD in daily practice

The introduction of new advanced targeted therapies has led to a variety of licensed therapeutic options for patients with moderate to severe AD. At time of writing this thesis, two different biologics (dupilumab and tralokinumab) and three small molecules (Janus kinase (JAK)-inhibitors: baricitinib, upadacitinib, and abrocitinib) are registered for the treatment of AD in the Netherlands. As dupilumab is the first biologic that came on the market, long-term evidence of daily practice use is only available for dupilumab and provides evidence on the role of dupilumab in personalized treatment.

… On positioning dupilumab in the treatment of AD

Since 2021, JAK-inhibitors including baricitinib, upadacitinib, and abrocitinib have been approved for the treatment of AD in the Netherlands.[108-111] Those small molecules inhibit the JAK/STAT signaling pathway which is involved in several immune pathways (Th1, Th2, Th17, and Th22 cells) associated with the pathogenesis of AD.

Considering the effectiveness of JAK-inhibitors and dupilumab, the highest dose of the JAK-inhibitors upadacitinib and abrocitinib showed superiority compared to dupilumab in two previous studies.[112, 113] However, due to the short follow-up period of 12 or 16 weeks and the clinical trial setting, it might be too early to state that in the longer term these JAK-inhibitors remain superior based on these studies. Side effect profiles of dupilumab and JAK inhibitors are different: during treatment with JAK-inhibitors higher rates of cutaneous herpes infections and other infections (e.g. upper respiratory tract infections) are observed[114] compared to placebo treatment, while there is evidence that dupilumab treatment reduces the risk of cutaneous infection.[115] Acneiform eruption are frequently reported as side effect during JAK-inhibitor treatment in the AD population.[116] While conjunctivitis, the most common side effect during dupilumab treatment, is not observed during treatment with JAK inhibitors.

Tralokinumab neutralizes IL-13[117] and showed promising results in clinical trials involving patients with atopic dermatitis.[97, 118, 119] Over 2 years, tralokinumab was well-tolerated and maintained long-term control of AD signs and symptoms.[120]

Due to lack of head-to-head evidence, it is not possible to compare efficacy and safety between dupilumab and tralokinumab at this moment.

As shown in **Chapter 10** and **11** dupilumab has an additional advantage for AD patients with comorbid asthma and/or food allergy, which has not been proven for JAK inhibitors yet; considering asthma tralokinumab was proven ineffective.[96, 97] Therefore, dupilumab might be the most suitable treatment option for AD patients with atopic comorbidities (Figure 4/5).

The unmet need for patients treated with dupilumab is especially for patients with severe conjunctivitis, dupilumab-induced skin eruptions, and non-responders (Figure 5). JAK-inhibitors might be a solution for dupilumab non-responders as they inhibit the immunological pathways involved in AD pathogenesis less specific compared to dupilumab. Regarding conjunctivitis, JAK-inhibitors do not increase this risk.[109, 121, 122]

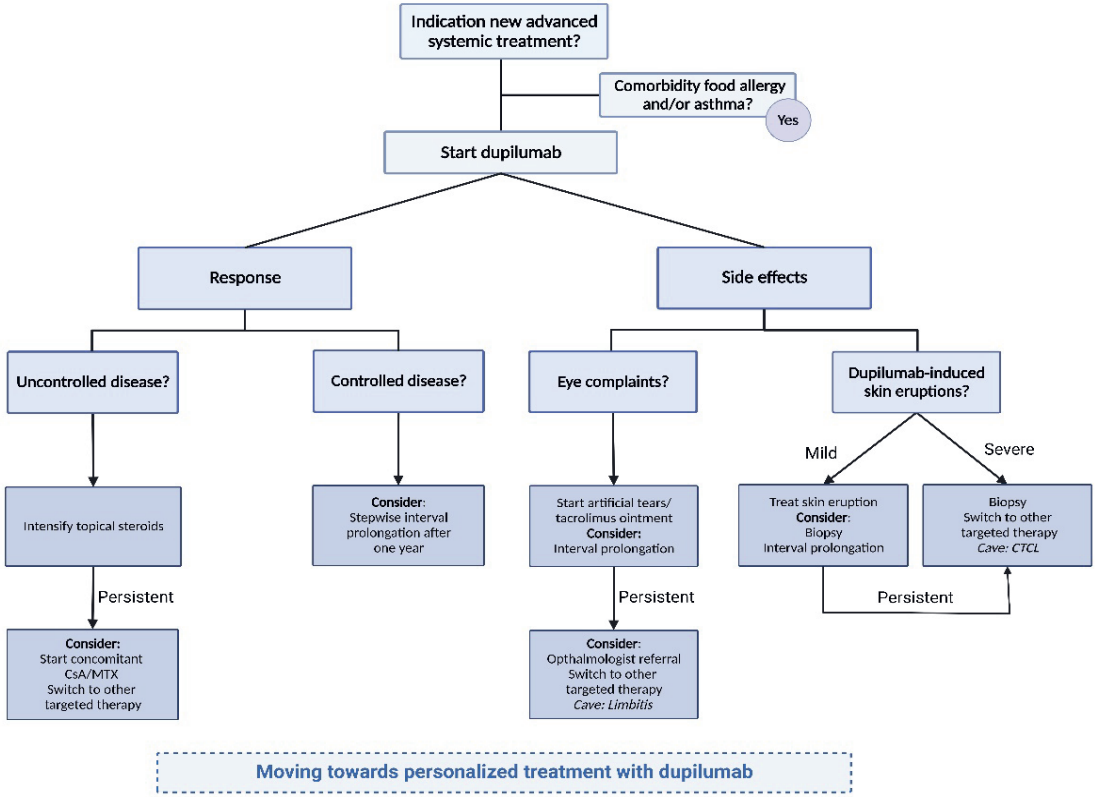


Figure 5. Treatment algorithm for dupilumab in daily practice; moving towards personalized treatment with dupilumab

CsA, Cyclosporine A; MTX, Methotrexate; CTCL, cutaneous T-cell lymphoma; Q3W, every other three weeks; Q4W, every other four weeks; Q6W, every other six weeks; Q8W, every other eight weeks. Created with BioRender.com

Future perspectives

...On real-world evidence within the BioDay registry

The dynamic situation of the subsequent introduction of new advanced targeted therapy for AD in the last years has led to a challenging situation for the analysis and interpretation of real-world data. Recognized challenges of daily practice studies are mostly of epidemiological nature, concerning e.g. data quality and definition of response. With the upcoming new generation of biologics and small molecules, treatment goals will probably shift towards lower disease severity scores and PRO's (i.e. higher effectiveness). Lastly, in daily practice a better definition for persistent controlled disease is warranted. This implicates more frequent measures of standardized PRO's between the regular visits.

...On personalized treatment in AD

With the current evidence gathered in this thesis, we hope to provide a solid foundation for the daily practice use of dupilumab in patients with AD including the introduction of personalized treatment. For example, our patient-centered dosing regimen with tapering of dupilumab could be a blueprint for dose reduction for other biologics in AD, such as tralokinumab. During JAK-inhibitor treatment personalized dosing will also be important and will prevent under- as well as overtreatment in the individual patient. In the future, predictive models, by combining clinical- and biological characteristics, might be developed to sufficiently predict response to dupilumab and other advanced systemic treatments. However, we have to consider the option that – despite emerging techniques and analysis methods – it might not be possible to accurately predict treatment response. Nevertheless, introduction of dupilumab has led to a major positive shift in the treatment paradigm of AD and has significantly improved the quality of life for many AD patients. It will be exciting to see what the future holds for the treatment of AD with subsequent introduction of new advanced targeted therapies.

References

1. Bothwell, L.E., et al., *Assessing the Gold Standard--Lessons from the History of RCTs.* N Engl J Med, 2016. **374**(22): p. 2175-81.
2. Akobeng, A.K., *Understanding randomised controlled trials.* Arch Dis Child, 2005. **90**(8): p. 840-4.
3. Powell, K. and V. Prasad, *Common misconceptions of randomized controlled trials in oncology.* Eur J Clin Invest, 2022: p. e13832.
4. Selker, H.P., S. Gorman, and K.I. Kaitin, *Efficacy-to-Effectiveness Clinical Trials.* Trans Am Clin Climatol Assoc, 2018. **129**: p. 279-300.
5. Selker, H.P., et al., *Efficacy and Effectiveness Too Trials: Clinical Trial Designs to Generate Evidence on Efficacy and on Effectiveness in Wide Practice.* Clin Pharmacol Ther, 2019. **105**(4): p. 857-866.
6. Revicki, D.A. and L. Frank, *Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies.* Pharmacoeconomics, 1999. **15**(5): p. 423-34.
7. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry.* Allergy, 2020. **75**(1): p. 116-126.
8. Chalmers, J.R., et al., *Report from the fifth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative).* Br J Dermatol, 2018. **178**(5): p. e332-e341.
9. Rehal, B. and A.W. Armstrong, *Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010.* PLoS One, 2011. **6**(4): p. e17520.
10. Futamura, M., et al., *A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards.* J Am Acad Dermatol, 2016. **74**(2): p. 288-94.
11. Hanifin, J.M., et al., *The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group.* Exp Dermatol, 2001. **10**(1): p. 11-8.
12. Schram, M.E., et al., *EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference.* Allergy, 2012. **67**(1): p. 99-106.
13. *Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis.* Dermatology, 1993. **186**(1): p. 23-31.
14. Reich, A., et al., *Tailoring the Cut-off Values of the Visual Analogue Scale and Numeric Rating Scale in Itch Assessment.* Acta Derm Venereol, 2017. **97**(6): p. 759-760.
15. Charman, C.R., A.J. Venn, and H.C. Williams, *The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective.* Arch Dermatol, 2004. **140**(12): p. 1513-9.
16. Basra, M.K., et al., *Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data.* Dermatology, 2015. **230**(1): p. 27-33.
17. Atkinson, M.J., et al., *Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers.* Value Health, 2005. **8** Suppl 1: p. S9-S24.
18. Pariser, D.M., et al., *Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT).* Curr Med Res Opin, 2020. **36**(3): p. 367-376.
19. Simpson, E., et al., *Validation of the Atopic Dermatitis Control Tool (ADCT(c)) using a longitudinal survey of biologic-treated patients with atopic dermatitis.* BMC Dermatol, 2019. **19**(1): p. 15.
20. Leshem, Y.A., et al., *What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study.* Br J Dermatol, 2015. **172**(5): p. 1353-7.

21. De Bruin-Weller, M., et al., *Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies.* Acta Derm Venereol, 2021. **101**(2): p. adv00402.
22. Leshem, Y.A., et al., *Measuring atopic eczema symptoms in clinical practice: The first consensus statement from the Harmonising Outcome Measures for Eczema in clinical practice initiative.* J Am Acad Dermatol, 2020. **82**(5): p. 1181-1186.
23. Chalmers, J.R., et al., *Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative).* Br J Dermatol, 2016. **175**(1): p. 69-79.
24. Yosipovitch, G., et al., *Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis.* Br J Dermatol, 2019. **181**(4): p. 761-769.
25. Silverberg, J.I., et al., *Validation of five patient-reported outcomes for atopic dermatitis severity in adults.* Br J Dermatol, 2020. **182**(1): p. 104-111.
26. Blauvelt, A., et al., *Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.* Lancet, 2017. **389**(10086): p. 2287-2303.
27. Bosma, A.L., et al., *Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: Results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry.* J Am Acad Dermatol, 2020. **83**(5): p. 1375-1384.
28. Fargnoli, M.C., et al., *A 48-week update of a multicentre real-life experience of dupilumab in adult patients with moderate-to-severe atopic dermatitis.* J Dermatolog Treat, 2022. **33**(2): p. 1146-1149.
29. Uchida, H., et al., *One-year real-world clinical effectiveness, safety, and laboratory safety of dupilumab in Japanese adult patients with atopic dermatitis: A single-center retrospective study.* J Am Acad Dermatol, 2021. **84**(2): p. 547-550.
30. van den Reek, J., et al., *Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls.* J Invest Dermatol, 2015. **135**(7): p. 1-5.
31. de Bruin-Weller, M., et al., *Use of systemic therapies in adults with atopic dermatitis: 12-month results from the European prospective observational study in patients eligible for systemic therapy for atopic dermatitis (EUROSTAD).* J Dermatolog Treat, 2022. **33**(5): p. 2565-2570.
32. Stolzl, D., et al., *Real-world data on effectiveness, safety and drug survival of dupilumab: An analysis from the TREATgermany registry.* Br J Dermatol, 2022.
33. Napolitano, M., et al., *Drug survival analysis of dupilumab and cyclosporin in patients with atopic dermatitis: a multicenter study.* J Dermatolog Treat, 2022: p. 1-4.
34. Thaci, D., et al., *Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.* Lancet, 2016. **387**(10013): p. 40-52.
35. Deleuran, M., et al., *Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study.* J Am Acad Dermatol, 2020. **82**(2): p. 377-388.
36. Halling, A.S., et al., *Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis.* J Am Acad Dermatol, 2021. **84**(1): p. 139-147.
37. Akinlade, B., et al., *Conjunctivitis in dupilumab clinical trials.* Br J Dermatol, 2019. **181**(3): p. 459-473.
38. Seegraber, M., et al., *Dupilumab for treatment of atopic dermatitis.* Expert Rev Clin Pharmacol, 2018. **11**(5): p. 467-474.
39. Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.* N Engl J Med, 2016. **375**(24): p. 2335-2348.
40. de Bruin-Weller, M., et al., *Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or*

when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). Br J Dermatol, 2018. **178**(5): p. 1083-1101.
41. de Wijs, L.E.M., et al., *Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data.* Br J Dermatol, 2020. **182**(2): p. 418-426.
42. Ariens, L.F.M., et al., *Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry.* J Am Acad Dermatol, 2021. **84**(4): p. 1000-1009.
43. Olesen, C.M., et al., *Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre.* J Eur Acad Dermatol Venereol, 2019. **33**(8): p. 1562-1568.
44. Faiz, S., et al., *Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort.* J Am Acad Dermatol, 2019. **81**(1): p. 143-151.
45. Ivert, L.U., et al., *Eye Complications During Dupilumab Treatment for Severe Atopic Dermatitis.* Acta Derm Venereol, 2019. **99**(4): p. 375-378.
46. Achten, R.E., et al., *Ocular surface disease is common in moderate-to-severe atopic dermatitis patients.* Clin Exp Allergy, 2022. **52**(6): p. 801-805.
47. Achten, R., et al., *Long-term follow-up and treatment outcomes of conjunctivitis during dupilumab treatment in patients with moderate-to-severe atopic dermatitis.* J Allergy Clin Immunol Pract, 2021. **9**(3): p. 1389-1392 e2.
48. Wollenberg, A., et al., *Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment.* J Allergy Clin Immunol Pract, 2018. **6**(5): p. 1778-1780 e1.
49. Le, Q., J. Xu, and S.X. Deng, *The diagnosis of limbal stem cell deficiency.* Ocul Surf, 2018. **16**(1): p. 58-69.
50. Sokumbi, O., et al., *Evolution of Dupilumab-Associated Cutaneous Atypical Lymphoid Infiltrates.* Am J Dermatopathol, 2021. **43**(10): p. 714-720.
51. Du-Thanh, A., V. Gustave, and O. Dereure, *Lethal anaplastic large-cell lymphoma occurring in a patient treated with dupilumab.* JAAD Case Rep, 2021. **18**: p. 4-7.
52. Poyner, E.F.M., et al., *Dupilumab unmasking cutaneous T-cell lymphoma: report of a fatal case.* Clin Exp Dermatol, 2022. **47**(5): p. 974-976.
53. Espinosa, M.L., et al., *Progression of cutaneous T-cell lymphoma after dupilumab: Case review of 7 patients.* J Am Acad Dermatol, 2020. **83**(1): p. 197-199.
54. Ayasse, M., et al., *Mycosis Fungoides Unmasked by Dupilumab Treatment in a Patient With a History of Atopic Dermatitis.* Dermatitis, 2021. **32**(1S): p. e88-e89.
55. Silverberg, J.I., *Atopic Dermatitis in Adults.* Med Clin North Am, 2020. **104**(1): p. 157-176.
56. Saulite, I., et al., *Sezary Syndrome and Atopic Dermatitis: Comparison of Immunological Aspects and Targets.* Biomed Res Int, 2016. **2016**: p. 9717530.
57. Newsom, M., et al., *Two cases of mycosis fungoides diagnosed after treatment non-response to dupilumab.* Dermatol Online J, 2021. **27**(1).
58. Chiba, T., et al., *Diagnosis of Mycosis Fungoides Following Administration of Dupilumab for Misdiagnosed Atopic Dermatitis.* Acta Derm Venereol, 2019. **99**(9): p. 818-819.
59. Geskin, L.J., et al., *Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation.* Blood, 2015. **125**(18): p. 2798-805.
60. Ferrucci, S., et al., *Clinical Response and Quality of Life in Patients with Severe Atopic Dermatitis Treated with Dupilumab: A Single-Center Real-Life Experience.* J Clin Med, 2020. **9**(3).
61. Nettis, E., et al., *Dupilumab in atopic dermatitis: predictors of treatment outcome and time to response.* J Eur Acad Dermatol Venereol, 2021.
62. Tavakolpour, S., et al., *A comprehensive review of rituximab therapy in rheumatoid arthritis patients.* Clin Rheumatol, 2019. **38**(11): p. 2977-2994.
63. Yiu, Z.Z.N., et al., *Meeting Report: Psoriasis Stratification to Optimize Relevant Therapy Showcase.* J Invest Dermatol, 2021. **141**(8): p. 1872-1878.

64. Warren, R.B., et al., *Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study.* Br J Dermatol, 2019. **180**(5): p. 1069-1076.
65. Brunner, P.M., et al., *Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab.* J Allergy Clin Immunol, 2019. **143**(1): p. 142-154.
66. Wollenberg, A., Howell, M. D., Guttman-Yassky, E., Silverberg, J. I., Birrell, C., Kell, C., Ranade, K., Dawson, M., & van der Merwe, R., *A Phase 2b Dose-Ranging Efficacy and Safety Study of Tralokinumab in Adult Patients with Moderate to Severe Atopic Dermatitis.* . SKIN The Journal of Cutaneous Medicine, 2018. **2(S1), S29.**
67. Kato, A., et al., *Higher baseline serum lactate dehydrogenase level is associated with poor effectiveness of dupilumab in the long term in patients with atopic dermatitis.* J Dermatol, 2020. **47**(9): p. 1013-1019.
68. Mobus, L., et al., *Blood transcriptome profiling identifies 2 candidate endotypes of atopic dermatitis.* J Allergy Clin Immunol, 2022. **150**(2): p. 385-395.
69. Nakahara, T., et al., *Exploration of biomarkers to predict clinical improvement of atopic dermatitis in patients treated with dupilumab: A study protocol.* Medicine (Baltimore), 2020. **99**(38): p. e22043.
70. Nahum, Y., et al., *Dupilumab-induced ocular surface disease (DIOSD) in patients with atopic dermatitis: clinical presentation, risk factors for development and outcomes of treatment with tacrolimus ointment.* Br J Ophthalmol, 2020. **104**(6): p. 776-779.
71. Treister, A.D., C. Kraff-Cooper, and P.A. Lio, *Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis.* JAMA Dermatol, 2018. **154**(10): p. 1208-1211.
72. Nettis, E., et al., *Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience.* J Investig Allergol Clin Immunol, 2020. **30**(3): p. 201-204.
73. Touhouche, A.T., et al., *Incidence and risk factors for dupilumab associated ocular adverse events: a real-life prospective study.* Journal of the European Academy of Dermatology and Venereology, 2021. **35**(1): p. 172-179.
74. Achten, R.E., et al., *Identification of Risk Factors for Dupilumab-associated Ocular Surface Disease in Patients with Atopic Dermatitis.* Acta Derm Venereol, 2022. **102**: p. adv00666.
75. Worm, M., et al., *Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(2): p. 131-143.
76. Lee, Y., M.E. Kim, and D.H. Nahm, *Real Clinical Practice Data of Monthly Dupilumab Therapy in Adult Patients With Moderate-to-Severe Atopic Dermatitis: Clinical Efficacy and Predictive Markers for a Favorable Clinical Response.* Allergy Asthma Immunol Res, 2021. **13**(5): p. 733-745.
77. Jendoubi, F., et al., *Longer dupilumab dosing intervals in adult patients with atopic dermatitis: experience from a French multicentre retrospective cohort study.* Br J Dermatol, 2022.
78. Shih, Y.C., et al., *Efficacy and Safety of Multiple Dupilumab Dose Regimens in Patients with Moderate-To-Severe Atopic Dermatitis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials.* Dermatology, 2022: p. 1-13.
79. Kovalenko, P., et al., *Exploratory Population PK Analysis of Dupilumab, a Fully Human Monoclonal Antibody Against IL-4Ralpha, in Atopic Dermatitis Patients and Normal Volunteers.* CPT Pharmacometrics Syst Pharmacol, 2016. **5**(11): p. 617-624.
80. Harb, H. and T.A. Chatila, *Mechanisms of Dupilumab.* Clin Exp Allergy, 2020. **50**(1): p. 5-14.
81. Edrees, A.F., S.N. Misra, and N.I. Abdou, *Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions.* Clin Exp Rheumatol, 2005. **23**(4): p. 469-74.
82. Kui, R., et al., *Presence of antidrug antibodies correlates inversely with the plasma tumor necrosis factor (TNF)-alpha level and the efficacy of TNF-inhibitor therapy in psoriasis.* J Dermatol, 2016. **43**(9): p. 1018-23.

83. Pallagi-Kunstar, E., et al., *Utility of serum TNF-alpha, infliximab trough level, and antibody titers in inflammatory bowel disease.* World J Gastroenterol, 2014. **20**(17): p. 5031-5.
84. Lio, P.A., *Considerations in Weaning or Withdrawing Dupilumab Therapy-Nothing Is Forever.* JAMA Dermatol, 2020. **156**(2): p. 119-120.
85. Hsu, L. and A.W. Armstrong, *Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response.* Expert Rev Clin Immunol, 2013. **9**(10): p. 949-58.
86. Silverberg, J.I., et al., *Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial.* Br J Dermatol, 2021. **184**(3): p. 450-463.
87. Bangert, C., et al., *Persistence of mature dendritic cells, TH2A, and Tc2 cells characterize clinically resolved atopic dermatitis under IL-4Ralpha blockade.* Sci Immunol, 2021. **6**(55).
88. Pulendran, B. and D. Artis, *New paradigms in type 2 immunity.* Science, 2012. **337**(6093): p. 431-5.
89. Andersen, Y.M.F., et al., *Burden of respiratory comorbidities in patients with atopic dermatitis and psoriasis.* Br J Dermatol, 2017. **177**(4): p. e145-e146.
90. Somanunt, S., et al., *The natural history of atopic dermatitis and its association with Atopic March.* Asian Pac J Allergy Immunol, 2017. **35**(3): p. 137-143.
91. *Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals.* **Version 3.** .
92. Schulman, E.S., *Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders.* Am J Respir Crit Care Med, 2001. **164**(8 Pt 2): p. S6-11.
93. Kawakami, T. and U. Blank, *From IgE to Omalizumab.* J Immunol, 2016. **197**(11): p. 4187-4192.
94. Wang, H.H., Y.C. Li, and Y.C. Huang, *Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis.* J Allergy Clin Immunol, 2016. **138**(6): p. 1719-1722 e1.
95. Oldhoff, J.M., et al., *Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis.* Allergy, 2005. **60**(5): p. 693-6.
96. Chung, K.F., *Tralokinumab unsuccessful for management of severe, uncontrolled asthma.* Lancet Respir Med, 2018. **6**(7): p. 480-481.
97. Wollenberg, A., et al., *Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2).* Br J Dermatol, 2021. **184**(3): p. 437-449.
98. Panettieri, R.A., Jr., et al., *Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials.* Lancet Respir Med, 2018. **6**(7): p. 511-525.
99. Russell, R.J., et al., *Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled phase 2 trial.* Lancet Respir Med, 2018. **6**(7): p. 499-510.
100. Fiocchi, A., B.P. Vickery, and R.A. Wood, *The use of biologics in food allergy.* Clin Exp Allergy, 2021. **51**(8): p. 1006-1018.
101. Rial, M.J., B. Barroso, and J. Sastre, *Dupilumab for treatment of food allergy.* J Allergy Clin Immunol Pract, 2019. **7**(2): p. 673-674.
102. Apoil P.A. TM, P.C., *In atopic dermatitis patients, dupilumab therapy reveals that IgE against food allergens decrease faster than IgE specific for respiratory allergens.* Poster presented at European Academy of Allergy and Clinical Immunology (EAACI) annual congress 2019.
103. Guttman-Yassky, E., et al., *Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis.* J Allergy Clin Immunol, 2019. **143**(1): p. 155-172.

104. Beiser, M., D. Rosenstreich, and D. Ferastraoaru, *Change in total IgE levels in inner city patients receiving monoclonal biological agents for allergic disorders.* Clin Exp Allergy, 2023. **53**(2): p. 230-232.
105. Zhou, B., et al., *The changes of IgE levels in type 2 inflammatory diseases after treatment of dupilumab: a systematic review and meta-analysis.* Expert Rev Clin Pharmacol, 2022. **15**(10): p. 1233-1242.
106. Pharmaceuticals, R., *Study in Pediatric Subjects With Peanut Allergy to Evaluate Efficacy and Safety of Dupilumab as Adjunct to AR101 (Peanut Oral Immunotherapy).*
107. Pharmaceuticals, R., *Study to Evaluate Dupilumab Monotherapy in Pediatric Patients With Peanut Allergy.*
108. Guttman-Yassky, E., et al., *Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study.* J Am Acad Dermatol, 2019. **80**(4): p. 913-921 e9.
109. Reich, K., et al., *Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2021. **397**(10290): p. 2169-2181.
110. Guttman-Yassky, E., et al., *Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial.* J Allergy Clin Immunol, 2020. **145**(3): p. 877-884.
111. Silverberg, J.I., et al., *Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatol, 2020. **156**(8): p. 863-873.
112. Blauvelt, A., et al., *Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial.* JAMA Dermatol, 2021. **157**(9): p. 1047-1055.
113. Reich, K., et al., *Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial.* Lancet, 2022. **400**(10348): p. 273-282.
114. Nogueira, M. and T. Torres, *Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis: Focus on Abrocitinib, Baricitinib, and Upadacitinib.* Dermatol Pract Concept, 2021. **11**(4): p. e2021145.
115. Fleming, P. and A.M. Drucker, *Risk of infection in patients with atopic dermatitis treated with dupilumab: A meta-analysis of randomized controlled trials.* J Am Acad Dermatol, 2018. **78**(1): p. 62-69 e1.
116. Nezamololama, N., et al., *Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib.* Drugs Context, 2020. **9**.
117. Wollenberg, A., et al., *Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb.* J Allergy Clin Immunol, 2019. **143**(1): p. 135-141.
118. Gutermuth, J., et al., *Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7).* Br J Dermatol, 2022. **186**(3): p. 440-452.
119. Silverberg, J.I., et al., *Tralokinumab Plus Topical Corticosteroids as Needed Provides Progressive and Sustained Efficacy in Adults with Moderate-to-Severe Atopic Dermatitis Over a 32-Week Period: An ECZTRA 3 Post Hoc Analysis.* Am J Clin Dermatol, 2022. **23**(4): p. 547-559.
120. Blauvelt, A., et al., *Long-term 2-Year Safety and Efficacy of Tralokinumab in Adults with Moderate-to-severe Atopic Dermatitis: Interim Analysis of the ECZTEND Open-label Extension Trial.* J Am Acad Dermatol, 2022.
121. Bieber, T., et al., *Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis.* N Engl J Med, 2021. **384**(12): p. 1101-1112.
122. Bieber, T., et al., *Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials.* J Eur Acad Dermatol Venereol, 2021. **35**(2): p. 476-485.

13

English summary, Nederlandse samenvatting

English summary

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases worldwide. AD is characterized by exacerbations and remissions of eczematous skin lesions, persistent pruritus and pain, resulting in sleep disturbance and a significantly reduced quality of life. AD is a highly heterogeneous disease on a clinical as well as a biological level. Both genetic and environmental factors contribute to the complex pathogenesis of AD, resulting in immune dysregulation and epithelial barrier disruption.

Dupilumab is the first biologic approved for the treatment of patients with moderate-to-severe AD and proved high efficacy and safety in large randomized controlled trials. However, we know that the highly regulated situations in these trials can lead to a difference in treatment effect compared to the reality in daily practice. This emphasizes the importance of observational studies in a daily practice setting in order to evaluate the advantages and disadvantages of a treatment in a large and more diverse population.

Given the heterogeneous nature of AD, it is unlikely that every patient will respond the same to a particular treatment. In contrast to the current "one-size-fits-all" approach, there will be a great need for more patient-centered treatment strategies. Furthermore, the number of targeted therapies for AD is growing which also gives the opportunity to work towards personalized treatment. As dupilumab is the first biologic that came on the market, long-term evidence of daily practice use is only available for this advanced systemic treatment option. The studies described in this thesis aimed to assess the performance of dupilumab in daily practice and to optimize dupilumab treatment for the individual patient. In the future, this information may help us choose which patient might benefit most from dupilumab treatment and may contribute to finding the most optimal treatment/dosing strategy for an individual patient during dupilumab treatment.

As shown in **Chapter 2**, treatment with dupilumab in daily practice resulted in a rapid improvement in clinical outcomes combined with a favorable safety profile. Conjunctivitis was more frequently reported as a side effect compared to the clinical trials. As shown by a patient-reported outcome, the majority of patients was satisfied with dupilumab treatment (**Chapter 3**). Looking from a different angle with a more

holistic approach, by using drug survival, dupilumab had an overall good drug survival persistent up to three years (**Chapter 4** and **5**), meaning that only few patients discontinued dupilumab treatment due to ineffectiveness and/or side effects. Using immunosuppressive therapy at baseline, absence of treatment effect at week 4, older age and an Investigator Global Assessment-score of very severe AD were found to predict discontinuation of dupilumab treatment ineffectiveness and/or side effects. Overall, above mentioned studies concluded that dupilumab was a safe and effective treatment option for the majority of patients with moderate-to-severe AD in daily practice.

Personalized treatment with dupilumab in AD could also benefit from predictive models. However, as shown in the performed prediction studies (**Chapter 5**, **7** and **9**) developing a prediction model was challenging. Since response to dupilumab was rather homogenous, the number of non-responders was low and number of patients able to taper was high, it was rather difficult to find distinctive clinical or biological characteristics for our prediction models.

A following question was whether it was possible to reduce the dose of dupilumab while maintaining clinical effectiveness. In **Chapter 6**, a broad range and relatively high serum dupilumab levels were found after 16 weeks of treatment in AD patients, with no relation to treatment response and side effects during the first year of treatment. Therefore, it might be possible that some patients can maintain clinical effectiveness with lower serum dupilumab levels by prolonging dupilumab interval. This was confirmed by our results described in **Chapter 8**. The results of **Chapter 8** were based on our patient-centered dupilumab dosing regimen; in this dosing regimen the dupilumab interval was stepwise prolonged in case of persistent controlled AD. Despite significantly lower serum dupilumab levels, the EASI scores and disease severity biomarkers remained low and stable while using at least halve of the standard dosage (**Chapter 8**). Our dosing regimen was implemented since 2019 in the BioDay registry and guided us towards more personalized treatment with dupilumab. In **Chapter 9**, we concluded that our disease activity guided dosing regimen was successful in 83.3% of the patients while maintaining controlled disease, with the majority using dupilumab Q3W/Q4W. Although a significant effect after start tapering was observed for EASI and NRS pruritus, these scores remained low and still fulfilled the criteria of mild disease.

In total, 401 patients had a dupilumab dose reduction with a total estimated cost saving of 3,977,033.98 EUR between January 2019 and June 2022.

Due to its mode of action, dupilumab treatment in AD patients might also be beneficial for other comorbid atopic diseases, such as asthma and food allergy. In **Chapter 10** and **11** we analyzed the effect of dupilumab on the atopic comorbidities food allergy and asthma in AD patients. One year of dupilumab treatment, primarily indicated for AD, resulted in a significant improvement of comorbid asthma, with the largest effect in the first 16 weeks (**Chapter 10**). Furthermore, dupilumab treatment induced a strong and sustained decrease in specific IgE levels for a variety of food allergens in AD patients with comorbid food allergies, with an estimated decrease of at least 50% for all foods after one year and more than 80% after three years of treatment (**Chapter 11**). In the context of personalizing treatment, dupilumab might be the most suitable treatment option for AD patients with atopic comorbidities.

Future perspectives

The daily practice studies described in this thesis focused on the long-term treatment effect of dupilumab, the possibility of tapering dupilumab, and the effect on atopic comorbidities asthma and food allergy. **Chapter 12** discussed this thesis' most important findings in the context of the daily performance of dupilumab while moving towards personalized treatment with dupilumab in AD.

The landscape of AD treatment is changing. At time of writing this thesis, two different biologics (dupilumab and tralokinumab) and three small molecules (Janus kinase (JAK)-inhibitors: baricitinib, upadacitinib, and abrocitinib) are registered for the treatment of AD in the Netherlands. These new drugs offer new treatment opportunities for patients with an inadequate response to dupilumab, patients with severe conjunctivitis, and dupilumab-induced skin eruptions. With the current evidence gathered in this thesis, we hope to provide a solid foundation for the daily practice use of dupilumab in patients with AD while moving towards personalized treatment. For example, our patient-centered dosing regimen could be a blueprint for dose reduction for other biologics in AD, such as tralokinumab. In the future, predictive models, by combining clinical- and biological characteristics, might be developed to sufficiently predict response to dupilumab and optimize treatment

strategies. However, we have to consider the option that – despite emerging techniques and analysis methods – it might not be possible to accurately predict treatment response.

Hence, introduction of dupilumab has led to a major positive shift in the treatment paradigm of AD, and has significantly improved the quality of life for many AD patients. It will be exciting to see what the future holds for the treatment of AD with subsequent introduction of new advanced targeted therapies.

Nederlandse samenvatting

Constitutioneel eczeem (CE) is een van de meest voorkomende chronische inflammatoire huidaandoeningen wereldwijd. CE is een heterogene ziekte op zowel biologisch als klinisch niveau en wordt gekenmerkt door periodes van opvlamming en remissie. De ziekte uit zich door middel van een rode schilferende huiduitslag met aanhoudende jeuk en pijn, wat vaak resulteert in slaapstoornissen en een aanzienlijke vermindering van kwaliteit van leven. Zowel genetische- als omgevingsfactoren dragen bij aan het complexe ontstaansmechanisme van CE, uiteindelijk leidend tot disregulatie van het afweersysteem en verstoring van de huid barrière.

Dupilumab is de eerst geregistreerde biological voor de behandeling van matig tot ernstig CE en heeft zijn effectiviteit en veiligheid aangetoond in grootschalige gerandomiseerde onderzoeken met controlegroepen. Echter, de sterk gecontroleerde situaties in deze onderzoeken kunnen soms leiden tot een verschil in behandelresultaat in vergelijking met de dagelijkse praktijk. Dit benadrukt het belang van observationele studies in een dagelijkse praktijkomgeving om de voor- en nadelen van een behandeling te evalueren in een grote en meer diverse populatie.

Vanwege de heterogene aard van CE is het onwaarschijnlijk dat elke patiënt op dezelfde wijze zal reageren op een specifieke behandeling. In tegenstelling tot de huidige "one-size-fits-all" benadering is er een grote behoefte aan meer patiëntgerichte behandelstrategieën. Bovendien groeit het aantal nieuwe specifieke geneesmiddelen (targeted therapies) voor CE, wat ook de mogelijkheid biedt om toe te werken naar meer gepersonaliseerde behandeling. Aangezien dupilumab de eerste biological is dat recentelijk (in 2017) op de markt is gekomen voor CE, zijn lange termijn dagelijkse praktijk resultaten vooralsnog alleen beschikbaar voor dit specifieke middel. De studies beschreven in dit proefschrift hebben als doel de prestaties van dupilumab in de dagelijkse praktijk te beoordelen en de behandeling met dupilumab te optimaliseren voor individuele patiënten. In de toekomst kan deze informatie ons helpen bij het bepalen welke patiënten het meeste baat zullen hebben bij behandeling met dupilumab, en kan het bijdragen aan het vinden van de meest optimale behandel- en doseringsstrategie voor elke individuele patiënt.

Zoals getoond in **Hoofdstuk 2**, resulteerde behandeling met dupilumab in de dagelijkse praktijk in een snelle verbetering van de klinische uitkomsten in combinatie met een gunstig bijwerkingsprofiel. In de dagelijkse praktijk werd

conjunctivitis vaker gemeld als bijwerking in vergelijking met de klinische gecontroleerde onderzoeken. Zoals blijkt uit de patiënt-gerapporteerde uitkomstmaten, was de meerderheid van de patiënten tevreden met de dupilumab behandeling (**Hoofdstuk 3**). Door gebruik te maken van 'drug survival' analyses, waarmee de duur dat patiënten een geneesmiddel gebruiken wordt gemeten, hebben we laten zien dat dupilumab een hoge 'drug survival' heeft. De meerderheid van de patiënten bleef dupilumab gebruiken na drie jaar behandeling (**Hoofdstuk 4** en **5**); slechts een klein aantal patiënten staakte dupilumab vanwege ineffectiviteit en/of bijwerkingen. Het gebruik van immunosuppressieve therapie bij start, het ontbreken van behandelresultaat na 4 weken, hogere leeftijd en een Investigator Global Assessment (IGA)-score van zeer ernstige CE bleken voorspellend te zijn voor het stopzetten van de dupilumab behandeling vanwege ineffectiviteit en/of bijwerkingen. Samenvattend kunnen we concluderen dat de bovengenoemde studies aantonen dat dupilumab een veilige en effectieve behandeloptie is voor de meerderheid van de patiënten met matige tot ernstige CE in de dagelijkse praktijk.

Het gebruik van voorspellende modellen kan mogelijk een positieve bijdrage leveren aan gepersonaliseerde behandeling van CE met dupilumab. Echter, zoals blijkt uit de uitgevoerde voorspellingsstudies in dit proefschrift (**Hoofdstuk 5**, **7** en **9**), was het ontwikkelen van een accuraat voorspellend model voor respons op dupilumab of de mogelijkheid tot succesvol afbouwen een uitdaging. Aangezien de respons op dupilumab vrij homogeen was, het aantal non-responders laag en het aantal patiënten dat kon afbouwen hoog, was het moeilijk om onderscheidende klinische of biologische kenmerken te vinden voor onze voorspellingsmodellen.

Om toe te werken naar gepersonaliseerde behandeling met dupilumab was de volgende vraag of het mogelijk is om de standaard dosering van dupilumab (300mg/2 weken) te verlagen met behoud van klinische effectiviteit. In **Hoofdstuk 6** werden een brede range en relatief hoge serum dupilumab spiegels gevonden na 16 weken behandeling bij CE patiënten, zonder relatie met behandelrespons en bijwerkingen gedurende het eerste jaar van de behandeling. Het is daarom wellicht mogelijk dat patiënten klinische effectiviteit kunnen behouden met lagere serum dupilumab spiegels door het interval van dupilumab te verlengen. Dit werd bevestigd door onze resultaten beschreven in **Hoofdstuk 8**. Deze resultaten waren gebaseerd op ons patiëntgerichte dupilumab-doseringsregime waarin, bij aanhoudend gecontroleerde ziekte, het toedieningsinterval stapsgewijs werd verlengd. Ondanks significant lagere serum dupilumab spiegels bleven de Eczema Area and Severity

Index (EASI)-scores en ziekteactiviteit-gerelateerde biomarkers laag en stabiel terwijl minstens de helft van de standaarddosering werd gebruikt (**Hoofdstuk 8**). Ons dupilumab-doseringsregime is sinds 2019 geïmplementeerd in het BioDay register en leidde ons naar meer gepersonaliseerde behandeling met dupilumab. In **Hoofdstuk 9** concludeerden we dat ons op ziekteactiviteit gerichte doseringsschema succesvol was bij 83,3% van de patiënten terwijl de ziekte onder controle werd gehouden, waarbij de meerderheid dupilumab elke 3 of 4 weken gebruikte. Hoewel er een significant effect werd waargenomen na het verlengen van het dupilumab interval voor de EASI score en de Numeric Rating Scale (NRS) voor jeuk, bleven deze scores laag en voldeden ze nog steeds aan de criteria voor milde ziekte. In totaal ondergingen 401 patiënten een verlaging van de dupilumab dosering, wat resulteerde in een totale geschatte kostenbesparing van 3.977.033,98 EUR tussen januari 2019 en juni 2022.

Vanwege het werkingsmechanisme kan dupilumab behandeling bij patiënten met CE ook gunstige effecten hebben op atopische comorbiditeiten, zoals astma en voedselallergieën. In **Hoofdstuk 10** en **11** hebben we het effect van dupilumab op de atopische comorbiditeiten voedselallergie en astma bij CE patiënten geanalyseerd. Eén jaar dupilumab behandeling, primair geïndiceerd voor CE, leidde tot een significante verbetering van astma controle en ziekteactiviteit, met het grootste effect in de eerste 16 weken (**Hoofdstuk 10**). Daarnaast leidde de behandeling met dupilumab tot een aanzienlijke en langdurige afname van specifieke IgE-niveaus in het bloed voor verschillende voedselallergenen bij CE patiënten met voedselallergie, met een geschatte afname van minstens 50% voor alle voedingsmiddelen na één jaar en meer dan 80% na drie jaar behandeling (**Hoofdstuk 11**). In de context van het personaliseren van de CE behandeling kan dupilumab de meest geschikte behandeloptie zijn voor CE patiënten die ook atopische comorbiditeiten hebben.

Toekomstperspectieven

De dagelijkse praktijkstudies die in dit proefschrift worden beschreven, hebben zich gericht op het beoordelen van het langetermijneffect van dupilumab, de mogelijkheid om dupilumab af te bouwen, en het effect op atopische comorbiditeiten zoals astma en voedselallergie. In **Hoofdstuk 12** worden de belangrijkste bevindingen van dit proefschrift besproken in de context van het gebruik van dupilumab in de dagelijkse praktijk en het optimaliseren van de behandeling met dupilumab voor de individuele patiënt.

Op het moment van het schrijven van dit proefschrift zijn er in Nederland twee verschillende biologische middelen (dupilumab en tralokinumab) en drie kleine moleculen (Janus kinase (JAK)-remmers: baricitinib, upadacitinib en abrocitinib) geregistreerd voor de behandeling van CE. Deze nieuwe geneesmiddelen bieden nieuwe behandelingsmogelijkheden voor patiënten met een ontoereikende respons op dupilumab, patiënten met ernstige conjunctivitis en door dupilumab geïnduceerde huid afwijkingen of andere bijwerkingen.

Dankzij de resultaten die in dit proefschrift zijn verkregen, hopen we een stevige basis te leggen voor het dagelijks gebruik van dupilumab in de behandeling van CE en streven we naar een meer gepersonaliseerde aanpak. Ons doseringsregime dat gericht is op de individuele patiënt kan dienen als een blauwdruk voor het verlagen van de dosis van andere biologische geneesmiddelen bij CE, zoals tralokinumab.

In de toekomst is het wellicht mogelijk dat voorspellende modellen worden ontwikkeld die gebruikmaken van zowel klinische als biologische kenmerken om de respons op dupilumab te voorspellen en behandelstrategieën te optimaliseren. Het streven naar gepersonaliseerde behandeling blijft belangrijk, maar we moeten rekening houden met de optie dat het – ondanks voortdurende ontwikkeling van technieken en analysemethoden –mogelijk is dat we niet in staat zijn om de behandel respons nauwkeurig te voorspellen voor elke individuele patiënt. Het is een continu proces van leren en verbeteren, waarbij we de individuele behoeften en kenmerken van elke patiënt in overweging moeten nemen bij het bepalen van de meest geschikte behandeling.

De introductie van dupilumab heeft geleid tot een belangrijke positieve verschuiving in het behandelingsparadigma van CE en heeft het de kwaliteit van leven van veel CE patiënten aanzienlijk verbeterd. Het is zeer interessant om te zien wat de toekomst in petto heeft voor de behandeling van CE met de introductie van nieuwe specifieke geneesmiddelen (targeted therapies) in de dagelijkse praktijk.

Appendix

List of abbreviations

AD	Atopic dermatitis
AKC	Atopic keratoconjunctivitis
AUC	Area under the curve
BMI	Body mass index
CI	Confidence Interval
CsA	Cyclosporine A
CTCL	Cutaneous T-cell lymphoma
DAOSD	Dupilumab Associated Ocular Surface Disease
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ELISA	Enzyme-linked immunosorbent assay
EQ-5D	Generic five-dimension five-level
FA	Food allergy
HR	Hazard ratio
IGA	Investigator Global Assessment scale
IgE	Immunoglobulin E
IL	Interleukine
IL-4Rα	Interleukin-4 receptor alpha
IQR	Interquartile range
JAK	Janus kinase
MCID	Minimal clinically important difference
METC	Medical Research Ethics Committee

MTX	Methotrexate
NRS	Numerical Rating Scale
OFC	Oral food challenges
PARC	Pulmonary and activation-regulated chemokine
POEM	Patient-Oriented Eczema Measure
PROs	Patient-reported outcomes
PROMs	Patient-reported outcome measures
Q1W	Every week
Q2W	Every other week
Q3W	Every three weeks
Q4W	Every four weeks
Q6W	Every six weeks
Q8W	Every eight weeks
RT	Room temperature
ROCcurve	Receiver Operator Characteristic-curve
SD	Standard deviation
sIgE	Specfic immunoglobulin E
T0	Treatment baseline
T1	Tapering baseline
T2	Time point 2
T3	Time point 3
TARC	Thymus and activation-regulated chemokine
Th2	T-helper 2
TCS	Topical corticosteroids

List of publications

This thesis, published

Spekhorst LS, Boesjes CM, Loman L, Zuithoff NPA, Bakker DS, Kamphuis E, Kamsteeg M, Haeck I, Oosting AJ, van Lumig PPM, van Lynden-van Nes AMT, Tupker RA, Flinterman A, Garritsen FM, Touwslager WRH, de Bruin-Weller MS, Schuttelaar ML, de Graaf M. Successful tapering of dupilumab in atopic dermatitis patients with low disease activity: a large pragmatic daily practice study from the BioDay registry. Br J Dermatol. 2023 May 13:ljad159.

Spekhorst LS, de Graaf M, van der Rijst LP, Zuithoff NPA, Schweizer RC, Kamsteeg M, Haeck I, van Lynden-van Nes AMT, van Lumig P, Romeijn GLE, Schuttelaar ML, de Bruin-Weller MS. The positive effect of dupilumab on comorbid asthma in patients with atopic dermatitis. Clin Transl Allergy. 2023 Jan;13(1):e12219.

Spekhorst LS, van der Rijst LP, de Graaf M, van Megen M, Zuithoff NPA, Knulst AC, de Bruin-Weller MS, Le TM. Dupilumab has a profound effect on specific-IgE levels of several food allergens in atopic dermatitis patients. Allergy. 2023 Mar;78(3):875-878.

Spekhorst LS, de Graaf M, Loeff F, Zuithoff NPA, Bakker D, Boesjes CM, Thijs J, Achten R, van Wijk F, Rispens T, de Bruin-Weller MS. Association of Serum Dupilumab Levels at 16 Weeks With Treatment Response and Adverse Effects in Patients With Atopic Dermatitis: A Prospective Clinical Cohort Study From the BioDay Registry. JAMA Dermatol. 2022 Dec 1;158(12):1409-1413.

Spekhorst LS, Bakker D, Drylewicz J, Rispens T, Loeff F, Boesjes CM, Thijs J, Romeijn GLE, Loman L, Schuttelaar ML, van Wijk F, de Graaf M, de Bruin-Weller MS. Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis. Allergy. 2022 Nov;77(11):3398-3407.

Spekhorst LS, de Graaf M, Zuithoff NPA, van den Reek JMPA, Kamsteeg M, Boesjes CM, Romeijn GLE, Loman L, Haeck I, Oosting AJ, de Boer-Brand A, Touwslager WRH, Flinterman A, van Lynden-van Nes AMT, Gostynski AH, de Bruin-Weller MS, Schuttelaar ML. Dupilumab Drug Survival and Associated Predictors in Patients With Moderate to Severe Atopic Dermatitis: Long-term Results From the Daily Practice BioDay Registry. JAMA Dermatol. 2022 Sep 1;158(9):1048-1056.

Oosterhaven JAF, **Spekhorst LS**, Zhang J, Voorberg AN, Romeijn GLE, Boesjes CM, de Graaf M, de Bruin-Weller MS, Schuttelaar MLA. Eczema control and treatment satisfaction in atopic dermatitis patients treated with dupilumab - a cross-sectional study from the BioDay registry. J Dermatolog Treat. 2022 Jun;33(4):1986-1989.

Ariëns LFM, van der Schaft J, **Spekhorst LS**, Bakker DS, Romeijn GLE, Kouwenhoven TA, Kamsteeg M, Voorberg AN, Oosting AJ, de Ridder I, Sloeserwij A, Haeck I, Thijs JL, Schuttelaar MLA, de Bruin-Weller MS. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry. J Am Acad Dermatol. 2021 Apr;84(4):1000-1009.

Spekhorst LS, Ariëns LFM, van der Schaft J, Bakker DS, Kamsteeg M, Oosting AJ, de Ridder I, Sloeserwij A, Romeijn GLE, de Graaf M, Haeck I, Thijs JL, Schuttelaar MLA, de Bruin-Weller MS. Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: Results from the BioDay registry. Allergy. 2020 Sep;75(9):2376-2379.

Other publications

Clabbers J, Boesjes CM, **Spekhorst LS**, van Gisbergen M, Marshall J, Maas E, Janssen R, Janssen M, Zuithoff NPA, Steijlen P, de Graaf M, van Geel M, de Bruin-Weller MS, Gostyński AH. Influence of pathogenic filaggrin variants on dupilumab treatment in atopic dermatitis. Submitted.

Boesjes CM, Kamphuis E, de Graaf M, **Spekhorst LS**, Haeck I, van der Gang LF, Loman L, Zuithoff NPA, Dekkers CC, van der Rijst LP, Romeijn MLE, Oosting AJ, Gostynksi A, van Lynden-van Nes AMT, Tupker RA, Garritsen FM, Flinterman A, Politiek K, Touwslager WRH, Christoffers WA, Stewart SM, Kamsteeg M, Schuttelaar MA, de Bruin-Weller MS. Long-term clinical effectiveness and reasons for discontinuation of dupilumab treatment in atopic dermatitis; 5-year results from the BioDay registry. Submitted.

Boesjes CM, van der Gang LF, Bakker DS, ten Cate TA, **Spekhorst LS**, de Graaf M, van Dijk MR, de Bruin-Weller MS. Dupilumab-Associated Lymphoid Reactions in Patients With Atopic Dermatitis. JAMA Dermatol. Published online October 18, 2023. doi:10.1001/jamadermatol.2023.3849

Boesjes CM, van Emst M, Bakker DS, **Spekhorst LS**, van Wijk F, de Graaf M, de Bruin-Weller MS. Muscle and joint pain during dupilumab treatment for atopic dermatitis: Lack of association with antinuclear antibodies. Clin Exp Allergy. 2023 May;53(5):582-585.

Boesjes CM, Van der Gang LF, Zuithoff NPA, Bakker DS, **Spekhorst LS**, Haeck I, Kamsteeg M, De Graaf M, De Bruin-Weller MS. Effectiveness of Upadacitinib in Patients with Atopic Dermatitis including those with Inadequate Response to Dupilumab and/or Baricitinib: Results from the BioDay Registry. Acta Derm Venereol. 2023 Feb 16;103:adv00872.

Boesjes CM, Kamphuis E, Zuithoff NPA, Bakker DS, Loman L, **Spekhorst LS**, Haeck I, Kamsteeg M, Van Lynden-van Nes AMT, Garritsen FM, Politiek K, Oldhoff M, De Graaf M, Schuttelaar MLA, De Bruin-Weller MS. Daily Practice Experience of Baricitinib Treatment for Patients with Difficult-to-Treat Atopic Dermatitis: Results from the BioDay Registry. Acta Derm Venereol. 2022 Nov 24;102.

Achten RE, Van Luijk C, Van der Rijst L, Bakker D, **Spekhorst L**, Zuithoff N, Schuttelaar M, Romeijn G, Voorberg A, Kamsteeg M, Haeck I, De Graaf M, Thijs J, De Boer J, De Bruin-Weller M. Identification of Risk Factors for Dupilumab-associated Ocular Surface Disease in Patients with Atopic Dermatitis. Acta Derm Venereol. 2022 Mar 11;102:adv00666.

Ariëns LFM, Bakker DS, **Spekhorst LS**, Van der Schaft J, Thijs JL, Haeck I, Flinterman AE, Kamsteeg M, Schuttelaar MLA, De Bruin-Weller MS. Rapid and Sustained Effect of Dupilumab on Work Productivity in Patients with Difficult-to-treat Atopic Dermatitis: Results from the Dutch BioDay Registry. Acta Derm Venereol. 2021 Oct 19;101(10).

Spekhorst LS, van den Reek JMPA, Knulst AC, Röckmann H. Determinants of omalizumab drug survival in a long-term daily practice cohort of patients with chronic urticaria. Allergy. 2019 Jun;74(6):1185-118.

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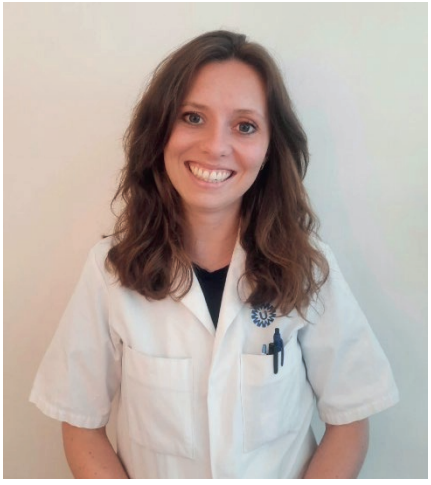
About the author



Lotte Stefanie Spekhorst was born on the 4th of February 1992 in the city of Hengelo, the Netherlands. After graduating from high school (the Grundel Lyceum Hengelo) in 2010, she started studying Biomedical science at the University of Groningen and obtained her bachelor in 2013. In 2013 she also started with the study Medicine which she completed in 5 years at the University of Groningen. Her fascination for dermatology was instigated in 2018, being part of a research project on the use of omalizumab for chronic urticaria in daily practice under supervision of dr. Heike Röckmann in the University Medical Center Utrecht. After graduation in 2018, she started her PhD at the Department of Dermatology and Allergology at the UMC Utrecht in 2018, with a main focus on the daily practice use of dupilumab in atopic dermatitis under supervision of prof. dr. de Bruin-Weller, dr. M. de Graaf and dr. D. Bakker. She played an important role in the development of the BioDay registry, and one of her studies was considered as highlight of the European Academy of Dermatology and Venereology congress in Milan 2022. After finishing the PhD trajectory and travelling the world with Daan Fernandes, she started in 2023 as physician in the Emergency Department and Surgery Department at Gelderse Vallei Hospital in Ede. In march 2024, she will start her training to become a forensic doctor.