Complex care for complex eczema in children

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ISBN: 978-90-393-6888-6

Cover, lay-out and printing: ProefschriftMaken || www.proefschriftmaken.nl

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Complexe zorg voor complex eczeem
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 22 december 2017 des middags te 2.30 uur

door

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geboren op 9 augustus 1982
te Woerden

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The DAVOS trial was funded by the European Allergy and Asthma Center Davos, patient support group ´Vereniging Nederland Davos`, and Merem Dutch Asthma Center Davos.

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1.
General introduction

Pediatric atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting up to 30% of children compared to 5 to 10% of adults.[1, 2] It is one of the most common childhood diseases with increasing prevalence in recent decades.[3] In children, AD onset occurs in 45% during the first 6 months of life, 60% during the first year and 85% are affected before the age of 5 years.[2] The clinical phenotype of AD varies with age, but dry skin, itchy red lesions on characteristic body areas and a course of disease with exacerbations and remissions are important features. Eczematous lesions may present in acute (oozing, crusted, eroded vesicles or papules on erythematous plaques), subacute (thick and excoriated plaques) and chronic (lichenified, slightly pigmented, excoriated plaques) forms.[4] Up to 70% of childhood AD disappears spontaneously before adolescence, but in other children lesions will persist into adolescence and adulthood.[2, 4] In a minority of patients AD develops in adulthood.[5] It is very likely that there are distinct AD subtypes with different genetic and immunological profiles.

Impact of pediatric AD

AD has a significant negative effect on the quality of life of affected children and their parents.[6] Increasing disease severity further reduces reported quality of life.[7] The child's lifestyle is often limited, particularly in respect to clothing, holidays, staying with friends, owning pets, swimming or the ability to play or do sports.[6] Time-consuming daily treatment regimens impact the functioning of the whole family. Social or emotional problems may occur because of the distinguished appearance.[6] Daytime itchiness that often worsens during the night, leads to disturbed sleep of the child and parents. Sleep deprivation results in tiredness, mood changes and impaired psychosocial functioning of the child but may also lead to parental anxiety and depression.[8] Children with AD are also at an increased risk of developing other mental health disorders such as attention deficit hyperactivity disorder (ADHD), depression and anxiety.[9]

Moderate to severe AD

No reliable data are available regarding the prevalence of moderate to severe AD amongst children in the Netherlands. One of the reasons is that there is no uniform way of defining mild, moderate or severe disease. At least sixteen different scoring systems to measure the severity of AD exist.[10] Large population surveys use parental estimates for disease severity, while other studies use validated scoring systems by clinicians. AD severity scoring in Dutch general practices indicate over 70% of pediatric patients have mild AD, while 20% have moderate and 2% severe disease.[11] Another study assessing the economic burden of AD in the Netherlands, estimated that 8% of children are referred to a specialist, suggesting these are the ones with more severe disease.[12] Other population surveys give similar estimates. A recent population-based estimate in the USA using the 2007 National Survey of Children's Health asked parents to self-assess their child's AD severity: 67% assessed their child's AD to be mild, 26% moderate and 7% severe.[13] In the United Kingdom, a cross-sectional survey of

1760 affected children from one to five years of age scored by a dermatologist found that 84% of cases were mild, 14% were moderate, and 2% were severe.[14]

From a clinical point of view, severe disease is eczema that is resistant to first line topical corticosteroid treatments (mild potency) and has a considerable impact on quality of life.[15] Several definitions of severe disease have been proposed. The European Taskforce on Atopic Dermatitis defined severe AD as having an eczema severity score (SCORAD) greater than 50 or "persistent" disease, whereas the NICE eczema guidelines refer to "widespread areas of dry skin, incessant itching, and skin redness".[16, 17] There is no universally agreed definition of severe AD. Furthermore, the available scoring systems for AD do not take topical treatment into account. The potency of the used preparation influences the skin symptoms and it is not possible to interrupt topical treatment in order to reliably assess AD severity each time. Currently, no measure of AD severity exists which takes both symptoms and treatment into account.

Difficult to treat AD

Approximately 10% of pediatric patients referred to secondary care (3% of all AD patients) do not respond well to daily treatment with topical corticosteroids and can be considered complex or difficult to treat.[18] These children are unable to gain sufficient disease control and often have an extensive treatment history, with frequent hospitalizations and use of systemic immunosuppressive treatment. Successful AD treatment requires several treatment management skills and lifestyle adjustments. Knowledge of AD treatment, for example regarding potency of topical corticosteroids or knowing what to do in case of flares, is essential but often poor.[19] Furthermore, the topical treatment AD requires is time-consuming which makes adherence to treatment often difficult.[20] Poor adherence to treatment is a problem since it obstructs the intended improvement in quality of life and increases the burden on the child and his family.[21, 22] It may also lead to prescription of higher quantities and/or more potent medication like systemic immunosuppressive therapy because of assumed treatment failure. Fear of using topical corticosteroids and difficulties in having the child cooperate with skin care further challenge successful AD management.[20, 23] Improving treatment management skills may therefore be very helpful for children with difficult to treat AD.

Immunological characteristics of AD

The pathogenesis of AD is unknown and seems to be multifactorial, including a genetic predisposition, impaired skin barrier and altered local and systemic immunological responses resulting in chronic inflammation.[2, 24] It has been hypothesized that a primary immunologic disturbance leads to IgE-mediated sensitization and the epithelial barrier dysfunction is regarded as a consequence of local inflammation.[2] This is also referred to as the outside-in hypothesis. However, this idea is opposed by another hypothesis suggesting that an intrinsic defect in the epithelial cells, for example associated with mutations in the filaggrin

gene, leads to barrier dysfunction and the immunologic aspects are an epiphenomenon: the inside-out hypothesis.[2] Filaggrin loss of function mutations have been found in 27% of AD patients, compared to 9% of the healthy population, and are associated with severe AD, elevated total serum IgE levels, increased allergen sensitization, food allergy, asthma, and allergic rhinitis.[25-27] Around 80% of AD patients have a predominant Th2 systemic disbalance characterized by increased IgE levels and eosinophilia.[4] Three main potential immunological phenotypes have been suggested for AD: non-lesional skin, acute disease flares, and chronic remitting relapsing disease.[28] A Th2 immune response is present in all three phenotypes, but most prominent during acute disease flares. The production of Th2 and Th17 mediated cytokines, such as IL-4, IL-5 and IL-13 can be detected in lesional and non-lesional skin during the acute phase of the disease.[4] However, during the chronic course of AD, Th2 mediated cytokines are less expressed. This phase is more characterized by a Th1/Th22 driven inflammation.[29]

Other atopic comorbidities

AD is often the first step in the development of other atopic diseases as asthma, allergic rhinitis or food allergy: the concept of the atopic march.[30] This hypothesis is based on the observation that clinical signs of atopic dermatitis and food allergy often occur earlier in life and signs of asthma and allergic rhinitis occur later in life. Studies on diagnosis of asthma in children with AD report estimates that vary between 25% to 80%.[30] These are mostly cross-sectional population-based surveys at different ages. For example, a US population-based survey from 2007 estimated prevalence of food allergies (15%), asthma (20%) and allergic rhinitis (34%) among children diagnosed with AD.[31] The same study suggested an association between AD severity and a higher prevalence of other atopic comorbidities.[31] However in daily practice, there is no systematic work-up of other atopic diagnoses when a child presents with severe AD.

A systematic review of 13 cohort studies confirmed the increased risk of developing asthma after AD and showed that one in three infants with AD develops asthma at school age.[32] Another study combining two large UK population-based cohorts demonstrates that only 16% of children with AD will develop 2 or 3 coexisting atopic comorbidities and less than 7% develop into the atopic march (AD followed by asthma and then rhinitis).[33] However, the increased prevalence of several comorbidities on the population level does not necessarily imply the same pattern on the individual level. The increased risk of other atopic comorbidities could be associated with distinct AD phenotypes (immune or genetic). Using advanced statistical approaches such as machine learning, distinct disease profiles can be distinguished over time, for example persistent AD only, persistent AD and wheeze, persistent AD with later-onset rhinitis or atopic march.[33]

AD treatment strategies in pediatric AD

Treatment of AD revolves around three aspects: anti-inflammatory treatment, hydrating topical treatment to restore the disrupted skin barrier, and avoidance of triggers. The main elements of anti-inflammatory treatment are topical corticosteroids and to a lesser extent topical calcineurin inhibitors. According to the UK potency system, there are four different potencies of topical corticosteroids: mild such as hydrocortisone 0.5%, moderate such as clobetasone butyrate 0.05%, potent such as bethamethasone valerate 0.1%, fluticasone proprionate 0.05%, mometasone furoate 0.1%, and very potent such as clobetasol propionate 0.05%. For severe disease, treatment with systemic immunosuppressive drugs such as cyclosporin A (CsA) is available from age 2 or prednisone is available from 1 month.[16, 34] However, other agents such as methotrexate (MTX), mycophenolate mofetil (MMF) or azathioprine (AZA) are also used in the treatment of severe pediatric AD.[35] Recently dupilumab (a monoclonal antibody that blocks interleukin-4 and interleukin-13) has been registered and approved by the FDA for use in adults.[36] In children > 6 years old, phase 2 studies have been completed and phase 3 studies are ongoing.[37] Oral H1 antihistamines are frequently used to reduce itch, especially at night, but do not have sufficient effect on lesions and there is no high-level evidence to support its efficacy as a monotherapy.[16, 38]

The scientific evidence for the roles of triggers in AD is limited.[39] It is very difficult to assess the roles of potential triggers due to the relapsing course of AD with frequent and unexplained fluctuations in disease severity.[39] However, several trigger factors have been identified, such as irritants (soap, sweat, clothing), allergens (aeroallergens such as pollen or house dust mite), and stress.[40] Some studies have shown an association between HDM and aeroallergen exposure and AD flares among house dust mite (HDM) sensitized subjects, indicating the possible relevance of HDM reduction measures.[41-43] However, the role of environmental triggers and the concept of allergen avoidance have been more extensively studied in asthma.[44] AD treatment guidelines are provided by national and international expert committees.[16, 45]

Multidisciplinary treatment

Because of the various skills needed to successfully manage AD, complex multidisciplinary treatment programs have been developed for children who do not respond well to regular treatment.[46, 47] Multidisciplinary educational group trainings have been developed for parents of children with AD.[48, 49] In the United States, two major hospitals have developed multidisciplinary treatment programs for children with AD. A multidisciplinary day program (ADP atopic dermatitis program) has been developed at the National Jewish Medical and Research Center in Denver, Colorado.[46] The outpatient program takes five to ten days and patients may also be observed overnight to evaluate sleep disturbance. A similar program exists at Boston Children's Hospital. The Atopic Dermatitis Center (ADC) provides multidisciplinary care for patients with severe AD who have not responded to conventional treatment.[47]

The common elements included in these programs are intensive education about AD, treatment management and psychological or behavioral interventions aimed at coping with itch. However, these programs are mostly geared towards younger children (preschool and younger) and focus on AD only. Asthma, allergic rhinitis and food allergies are not systematically assessed within in the existing programs and there are few special programs for older children and adolescents.

Alpine climate treatment

In Europe, alpine climate treatment has been used for decades to treat patients with AD and/or asthma. Important characteristics of the alpine climate are the low exposure to allergens and pollution and the increased exposure to UV radiation.[44] Specialized clinics exist for example in Switzerland, Germany and Italy, where patients are hospitalized for a period of 4 weeks to over 3 months. Observational studies have consistently shown improvement in disease activity after alpine climate treatment, with lasting effects up to 12 months after treatment.[50] However, no randomized trials have ever been conducted to provide evidence for its effectiveness compared to multidisciplinary treatment in unspecified climate zones.[51]

Pragmatic trial design

A pragmatic trial design is often used in healthcare interventions to assess effectiveness: whether an intervention works in daily practice.[52] The term 'pragmatic' was invented to help distinguish between explanatory trials, designed to test causal research hypotheses, and trials that are designed to help choose between treatment options.[53] The majority of randomized clinical trials carried out in the field of medicine are explanatory trials. In 2003, a review identified 95 pragmatic trials out of 250.000 trials listed by the US National Library of Medicine.[54, 55] However, to be able to provide evidence for a therapeutic decision, pragmatic trials are needed. A pragmatic trial is designed to answer questions about how effective one therapy is compared to the other. Its results can be directly applied to clinical practice and provides direct information to those who must choose whether or not to prescribe, use, pay for or promote particular treatments.[53] The main disadvantage of pragmatic trials is that it is not possible to determine the exact health benefits for each aspect of the provided treatment.[56]

The main differences between trials with explanatory and pragmatic designs are explained in Table 1 (adapted from Zwarenstein et al).[56]

Table 1 Key differences between trials with explanatory and pragmatic designs

	Explanatory design	Pragmatic design
Question	Efficacy—can the intervention work?	Effectiveness—does the intervention work when used in normal practice?
Setting	Well resourced, "ideal" setting	Regular clinical practice
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest Representative of patients who are likely to receive the intervention in the future
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented

Thesis outline

This thesis addresses the effectiveness of integrative multidisciplinary care for children with difficult to treat AD with a special focus on alpine climate treatment.

In chapter 2 we systematically review the current literature as a further introduction of the use of alpine climate treatment in patients with AD. So far only observational studies have been carried out providing low-quality evidence for the effectiveness of alpine climate treatment. Therefore, we performed a pragmatic randomized controlled trial using as primary outcomes the long-term (6 months post-treatment) effectiveness on quality of life, disease severity and coping with itch of a 6 week multidisciplinary treatment period either at sea level or in the alpine climate. Chapter 3 presents the study protocol of the DAVOS trial.

To achieve satisfactory treatment results, several treatment management skills are needed, including knowledge of topical therapies and life style adjustments. We studied treatment management skills in a larger group of parents of children with mild to moderate AD attending our outpatient clinic and present the results in chapter 4.

Children with AD are often diagnosed with food allergies. Microbial colonization of the human gut during infancy is important for the maturation of the immune system.[56] Several studies have shown associations between intestinal microbiota and development of atopic disease. We studied the relation between the intestinal microbiome of a larger group of children with AD and food allergy and looked for associations with microbial species in chapter 5.

The results of the DAVOS trial are presented in chapter 6. The multidisciplinary approach we have used in the trial is described in chapter 8. Furthermore, we investigated immunological

changes regarding T and B cells before and immediately after the 6 week multidisciplinary intervention in both arms of the DAVOS trial. These results are presented in chapter 7.

Children with difficult to treat AD constitute a heterogeneous patient group. At inclusion in the study, we extensively assessed the children on clinical and psychosocial parameters. In chapter 9, we explore predictors of a sustained effect of the interventions we studied in the DAVOS trial.

Finally, all findings will be discussed in chapter 10 with recommendations for clinical practice and future research.

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2.

Alpine climate treatment of atopic dermatitis: a systematic review

Karin Fieten, Geert Weststrate, Esther van Zuuren,
Carla Bruijnzeel-Koomen & Suzanne Pasmans

Allergy 2015, 70(1):12-25

Abstract

Climate therapy has been used for decades in the treatment of atopic dermatitis (AD) but evidence of its effectiveness has not yet been assessed systematically. A systematic literature search in Medline, Embase and the Cochrane library was performed to identify all original studies concerning alpine climate treatment. The risk of bias of individual studies was assessed following the Cochrane Handbook, level of evidence was rated using GRADE guidelines. Fifteen observational studies were included concerning 40148 patients. Four studies concerning 2670 patients presented follow-up data over a period of 1 year. Disease activity decreased in the majority of patients during treatment (96% of n=39006) and 12 month follow-up (64% of n=2670). Topical corticosteroid use could often be reduced or stopped during treatment (82% of n=1178) and during 12 month follow-up (72% of n=3008). Quality assessment showed serious study limitations, therefore resulting in a very low level of evidence for the described outcomes. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters, are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by subsequent exacerbations and remissions.[1] Its prevalence is increasing worldwide and AD is currently among the most common skin diseases in children.[2] Itching, disturbed sleep and time-consuming medical treatment regimens lead to a reduced experienced quality of life in AD patients.[3,4]

AD is a complex disease with several genetic and environmental factors involved.[5] A genetic predisposition leads to an atopic constitution and a disturbed immune response which results in chronic inflammation and an impaired skin barrier.[6,7] In several eczema birth cohorts, the association between AD and the subsequent development of asthma and allergic sensitization has been established.[8,9] Prevalence of allergic sensitization in children with AD varies between countries, ranging from 52% in Belgium to 83% in Australia.[8] Around 30% of children diagnosed with AD will develop asthma later in life.[10] Among adults with AD, there is also great variation in prevalence of allergic sensitization and asthma diagnosis.[11]

Exposure to irritants and allergens, changes in physical environment (pollution, humidity), infections and psychosocial or emotional factors are possible triggers for exacerbations.[12] AD treatment is based on control of inflammation, infection, skin hydration and trigger avoidance.[13,14] Treatment approaches include anti-inflammatory therapy with topical immunosuppressives (dermatocorticosteroids, calcineurin inhibitors) and anti-microbial treatment, according to current guidelines.[13,14] In more severe cases, phototherapy or systemic immunosuppressive treatment is needed. Patients are often reluctant and concerned about the use of corticosteroids and systemic immunosuppressive treatment. Because of the chronic nature of AD, alternative therapies are often considered, such as acupuncture, homeopathy, dietary supplements/restrictions and Chinese herbal medicine.[15,16] However, the efficacy of these therapies over regular therapy could not be demonstrated.[17-19]

Climate therapy has been used since the 20th century for the treatment of various chronic inflammatory dermatoses and pulmonary diseases.[20,21] It combines anti-inflammatory treatment in a trigger-free environment with being hospitalized in a specialized clinic for a period of four weeks to three months. Climate therapy at seaside or mountain resorts has shown improvement in disease activity and reduced corticosteroid use in patients with AD.[22-26] In asthma, treatment in high altitude clinics has resulted in improved asthma control, asthma-related quality of life and a reduced corticosteroid requirement.[27-30] Clinics were built specifically for the rehabilitation of patients with AD or asthma in mountain areas of Switzerland ("Dutch Asthma Center Davos", Davos 1560m, "Alexanderhausklinik" Davos, 1560m, "Hochgebirgsklinik" Davos, 1560m), Italy ("Istituto Pio XII" Misurina 1756m) and south Germany ("Santa Maria", Oberjoch 1200m, "Prinzregent Luitpolt", Scheidegg 1000m). However, it is unclear which mechanisms lead to the observed effect. Limited health care resources and further advances in evidence-based medicine have put the existence of specialized high altitude clinics under pressure. It is important to quantify the direct and long-term effects of

climate treatment, since significant improvement in AD severity is also observed after clinical treatment in unspecified climate zones.[31]

Objective

The current systematic review summarizes the existing evidence for the clinical effect of alpine climate treatment for patients with AD.

Methods

Search process

A systematic literature search was performed including original studies published until July 3rd 2013. A sensitive search strategy was designed to retrieve all relevant articles from Medline, Embase and the Cochrane library. We searched for [''atopic dermatitis'' OR ''eczema'' OR ''neurodermatitis" OR "neurodermitis"] AND [''climate'' OR ''climatology'' OR ''climatotherapy'' OR ''climatic therapy'' OR ''altitude'' OR ''mountains'' OR ''alpine''] as medical subject headings or as main key words in the title or abstract. Two researchers (KF and GW) selected potentially eligible reports independently. Any disagreement on inclusion of studies was resolved by discussion with the other author (SP) until consensus was reached. Reference lists of retrieved articles and previously published reviews were hand-searched to identify further relevant studies.

Inclusion & Exclusion Criteria

Studies were included when alpine climate treatment was mentioned in title or abstract and part of the study population was diagnosed with AD. No limitation was set on study design, age of the patients, duration of treatment or outcome measure. Studies written in English or German were included. Studies concerning climate treatment in other climate regions, such as maritime climate, or in artificial conditions, such as climate chambers, were excluded.

Outcomes

The main outcome was disease severity after climate therapy, measured with any scoring system. Secondary outcomes were topical or systemic corticosteroid use, disease severity during follow-up, corticosteroid use during follow-up and other reported outcomes.

Risk of bias assessment

We assessed the risk of bias of the included studies according to the domain-based evaluation described in Chapter 8 and 13 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[32] We evaluated selection bias, performance bias, attrition bias, detection bias, reporting bias and publication bias.

Data Extraction

The following study characteristics were collected: author and year of publication, target population of the study (including age and sample size), altitude, name and location of the clinic, treatment duration and reported outcome variables. Outcome variables direct after treatment and during follow-up were separately extracted. Not all studies reported the same outcome measures, therefore different studies contribute to the different outcomes. Data from studies with similar outcome measures were transformed and pooled. Regarding disease severity, several scoring systems were used. All PGAs (physician graded assessments) with a 4 or 5 point scale were reduced to a 3 point scale (better, same, worse) for comparability. One study used number of exacerbations during follow-up as an outcome, this was transformed to a course of disease outcome where no or less exacerbations were counted as better, more exacerbations as worse, and the same number of exacerbations as same.[33] Studies reporting SCORAD scores are reported separately. Self-assessments by patients with a 4 or 5 point scale were also transformed to a 3 point scale (better, same, worse) and pooled. Data on corticosteroid use was differentiated for topical and systemic treatment, reduced to a yes/no variable for current use and pooled.

Authors were contacted to clarify results when needed. When data extraction was not possible or when no absolute patient numbers were provided and authors did not respond to the request for additional information, studies were not included in the outcome tables. The overall quality of evidence was rated using GRADE guidelines.[34] The review was reported according to the PRISMA statement.[35]

Data analysis

For each outcome, data from the different studies was transformed and pooled, and total and relative patient numbers were calculated. It was not possible to further analyze the extracted data or to do a meta-analysis.

Results

Studies included in the review

Results of our search strategy are shown in Figure 1. The search yielded 143 hits in Medline and 112 hits in Embase of which 61 were duplicate hits. Out of a total of 200 articles, 65 were eligible for full text screening. Three were excluded because of language (two Russian, one Bulgarian).[36-38] Two were excluded because they showed duplicate data from an already included study.[33, 39] Six were excluded because they were part of two growing cohorts,[33, 39-45] the most recent publications with the largest cohorts were included.[22, 46] Three were excluded because they described only individual case reports.[47, 48] Fifteen studies were finally included concerning 40148 patients. Study characteristics are shown in Table 1. No randomized trials were identified. All studies were observational, control groups were not incorporated in

the study design. The majority of studies was written in German and published in German journals, restricting their accessibility to international readers.

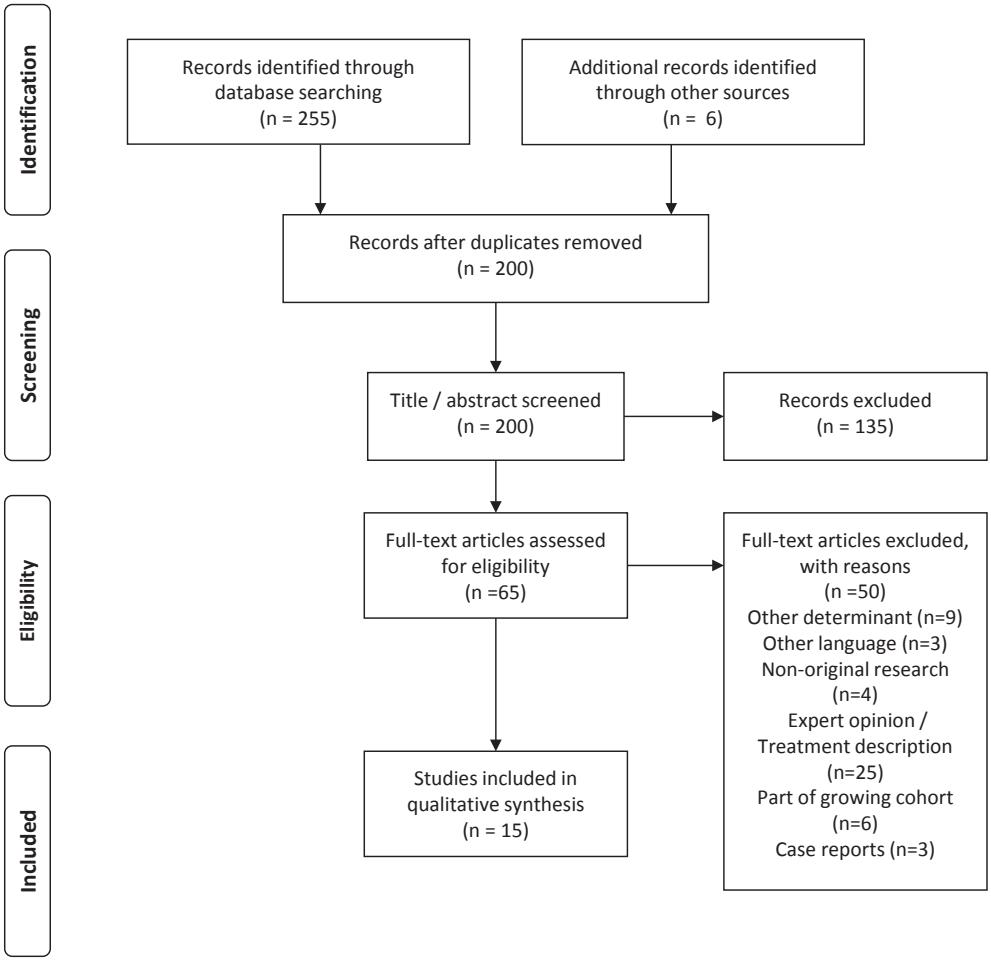

Figure 1 PRISMA Flow Diagram

Risk of bias

A risk of bias assessment was carried out and summarized in Table 2.

Selection bias

Some studies used specific inclusion criteria but most studies included AD patients who were admitted to an alpine clinic. These patients may be different from the wider population of AD patients. Patient characteristics of relevant atopic comorbidities, such as asthma and rhinitis were provided but the results of climate therapy were not differentiated accordingly.

Table 1 Characteristics of included studies

Author / Year	Period of data collection	Population(n)	Treatment center	Altitude (m)	Duration of treatment	Duration of follow-up	Outcome	Outcome during follow-up
à Porta 2000	1990 -1994	adults (n=97)	Davos: Zürcher Höhenklinik	1600m	32 days	1 year	PGA Corticosteroid use	Period until first relapse. Course of disease during followup. Start of corticosteroid use.
Borelli 1967	1966 – 1967	adolescents / adults (n=230)	Davos: Alexander-hausklinik	1560m	not mentioned	n/a	Change in eosinophils SPT	n/a
Borelli 1995	1961 – 1995	adults/children (n=31438)	Davos: Sanatorium Valbella (Alexander-hausklinik)	1560m	6 weeks	n/a	PGA Corticosteroid use	n/a
Drosner 1988	1986	adults (n=56)	Davos: Alexander-hausklinik	1560m	4-5 weeks	n/a	SPT	n/a
Drzimalla 1999	1995 - 1997	adults (n=4660)	Davos: Alexander-hausklinik	1560m	4-6 weeks	1 year	PGA	Number of flares. Skin assessment. Corticosteroid use.
Duve 1991	not mentioned	adults/children (n=624)	Davos: Alexander-hausklinik	1560m	4-8 weeks	1 year	PGA	Course of disease. Corticosteroid use
Eberlein 2009	2003 - 2004	adults/children (n=139/n=165) diagnosed with astma, AD and/or COPD	Germany: Santa Maria, Fachklinik Allgau, Asthmazen-trum Buchenhö-he	1200m 1000m 870m	3-4 weeks	n/a	SCORAD TARC IL16 eosinophils ECP	n/a

Table 1 Continued

Fuchs 1959	1958	adults (n=393)	Germany: Sachsenbaude	1130m	8 weeks	n/a	PGA	n/a
Heine 1995	1987 – 1988	children / adolescents (n=375)	Davos: Alexander-hausklinik	1560m	around 6 weeks	1 year	PGA Corticosteroid use	Course of disease Corticosteroid use
Kneist 1987	1986	adults/ children(n=1465)	Davos: Alexander-hausklinik	1560m	6 weeks	1 year	PGA Corticosteroid use	Course of disease. Corticosteroid use
Petermann 2000	not mentioned	children/ adolescents (n=102), SCORAD >25, use of systemic CS excluded	Germany: Santa Maria Prinzregent Luitpold	1200 m 1000m	4 weeks	2 years	SCORAD	Number of flares. Missed school days, doctor visits and hospitalizations.
Petermann 2004	1996 – 1998	children/ adolescents (n=55), SCORAD >25	Germany: Santa Maria	1200m	4 weeks	n/a	SCORAD ECP EPX	n/a
Simon 1999	not mentioned	adults (n=33), use of systemic CS excluded	Davos: Alexander-hausklinik	1560m	4-6 weeks	n/a	SCORAD ECP	n/a
Triebskorn 1991	not mentioned	adults (n=20)	Davos: Alexander-hausklinik	1560m	4 weeks	n/a	TEWL	n/a
Walker 1993	not mentioned	adults (n=12)	Davos: Zürcher Höhenklinik	1600m	3-6 weeks	n/a	Skin intensity score eosinophils ECP	n/a

CS = corticosteroids, PGA = Physician Graded Assessment, SPT = Skin Prick Test, SCORAD= scoring of atopic dermatitis, TARC=thymus and activation regulated chemokine, IL-16= Interleukin 16, ECP = eosinophil cationic protein, EPX = eosinophil urinary protein X, TEWL = transepidermal water loss, n/a=not applicable.

There may be further selection bias due to the language restriction on the systematic search (language bias) and because most studies were published by German research groups.

Performance bias

None of the studies mentioned an intervention protocol or any details concerning climate therapy and it was not possible to assess whether the intervention was carried out according to protocol. Duration of climate therapy varied between patients and between different clinics. Furthermore, little or no information was provided on received pharmacological interventions other than corticosteroids during climate therapy.

Detection bias

In none of the studies outcomes were assessed blinded. Outcome measures such as course of disease or exacerbations were not clearly defined and in most studies unvalidated outcome measures, such as PGA, were used. When patients and dermatologists both assessed disease severity after treatment, the treating dermatologists reported greater improvement compared to the self-assessment of the patient.

Reporting bias

Six out of fifteen included studies did not report all outcome variables that were stated in the study protocol or reported outcome variables only for a part of the cohort, without providing an explanation for the missing data. One study was designed with a follow-up period of two years, but did not report any data at this point.[49] One study did not report absolute patient numbers but only percentages during the follow-up period, whereas another study did not present numbers but vaguely described disease activity after 6 months follow-up as “disease stabilized for more than 6 months in more than 50% of patients”.[50, 51]

Attrition bias

In none of studies handling of missing data or drop-out during intervention was reported. During follow-up, either no absolute patient numbers were provided, making it impossible to assess the rate of loss-to-follow-up or only patients with complete data were included. When absolute patient numbers were provided, loss-to-follow-up increased up to 50%, making attrition bias very likely.

Publication bias

For this review only published studies were considered. None of the studies was sponsored by industry, however, most studies were carried out by alpine clinics assessing the effectiveness of their own therapy. There were no reports identified with negative results but since there were no control groups it was not possible to create funnel plots to find evidence of publication bias.

Table 2 Risk of bias assessment of studies

Risk of bias	Selection bias			Performance bias	Detection bias		Reporting bias		Attrition bias
Study	**Was AD diagnosis according to criteria?**	**Were clear inclusion/ exclusion criteria used?**	**Were detailed patient characteristics on other atopic diseases provided?**	**Were concurrent interventions or unintended exposures described?**	**Validated outcome measures**	**Blinded assessment of outcome**	**Complete study protocol stated**	**All measurements from protocol reported**	**Loss to follow-up or dropout**
à Porta 2000	Y	N	Y	N	N	N	Y	Y	8%
Borelli 1995	N	N	Y	N	N	N	Y	Y	U
Borelli 1967	N	N	Y	N	Y	N	Y	N	U
Drosner 1988	N	Y	N	N	Y	N	Y	Y	U
Drzimalla 1999	N	N	Y	N	N	N	Y	Y	49%
Duve 1991	N	N	N	N	N	N	Y	N	Y*
Eberlein 2009	Y	N	Y	N	Y	N	Y	N	U
Fuchs 1959	N	N	N	N	N	N	Y	Y	U
Heine 1995	N	N	Y	N	N	N	Y	N	50%
Kneist 1987	N	N	N	Y	N	N	Y	N	Y¥
Petermann 2000	Y	Y	Y	N	Y	N	Y	N	Y¥
Petermann 2004	Y	Y	N	N	Y	N	Y	Y	U
Simon 1999	N	N	Y	N	Y	N	Y	Y	U
Triebskorn 1991	N	Y	N	N	Y	N	Y	Y	U
Walker 1993	Y	N	Y	N	Y	N	Y	Y	U

Y=yes, N=no, U=unclear, ¥Follow-up numbers were not mentioned, *Only patients with complete data at all time points were included.

Outcomes

The quality of the evidence for the pooled outcome measures as summarized in Table 3 was rated very low. Data extraction was complicated because of incomplete reporting, therefore not all studies with relevant outcomes could be included.

Disease activity

Direct after climate treatment, disease activity was decreased in the majority of 39503 patients (included in 11 studies) as scored by a dermatologist (Table 4). Validated scoring systems, such as SCORAD, were used in four studies including 451 patients.[49, 52-54] PGA was used in seven studies including 39052 patients.[22, 46, 50, 51, 55-57] In three studies including 1922 patients, patients were asked to judge their clinical improvement and reached similar conclusions as the dermatologist, but differed on the degree of improvement.[51, 55, 57] Six studies were designed with a follow-up period, but one did not report outcomes of the 2 year follow-up period, the other mentioned percentages and no exact patient numbers during follow-up.[49, 51] Drop-out during follow-up was not addressed in any of the studies, one study simply excluded patients with incomplete data. In the remaining four studies, 2670 patients were asked to return questionnaires after 3 months, 6 months and 12 months to judge AD activity with a scoring system, a global assessment or period until first relapse.[50, 55-57] The majority (64%) of these patients reported a decreased disease activity up to 12 months after treatment and an overall improved course of disease compared to the year before treatment.

Corticosteroid use

Corticosteroid use was mentioned in six studies, but one study did not differentiate between patients with AD, psoriasis, contact dermatitis and other diagnoses and its data could therefore not be included in Table 5.[46] In one study percentages were mentioned, but these did not add up to 100%.[50] In the three studies in which exact patient numbers on topical corticosteroid use are mentioned, 1178 of 1937 patients (61%) used topical corticosteroids at start of climate therapy.[51, 55, 57] Corticosteroid use during follow-up is reported in most studies for the whole patient cohort, including patients who were not using corticosteroids during climate treatment. Only one study provided data on topical corticosteroid use during follow-up in the subgroup of patients who were able to stop corticosteroids during climate therapy.[55]

Table 3 GRADE Evidence table with summary of findings

Summary of Findings table of alpine climate treatment for atopic dermatitis[65]

Patient or population: patients with atopic dermatitis
Settings: clinics at 1000-1600 m altitude
Intervention: alpine climate treatment

Outcomes	Effect estimate		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Control	Alpine climate treatment			
Improvement of disease severity Physician's Global Assessment (better, same, worse). Scale from: 0% to 100%.	No control	88.8% to 99% of the participants improved according to the dermatologist	39006 (7 studies)	⊕⊖⊖⊖ **very low**[1,2]	Combined data showed PGA was better in 96.5%, same in 3%, and worse in 0.5% of the participants
Improvement of disease severity SCORAD. Scale from: 0 to 103.	No control	Relative decrease in SCORAD ranged from -4.3 to -25.4	201 (3 studies)	⊕⊖⊖⊖ **very low**[1]	At one location in study Eberlein 2009 baseline SCORAD was lower and the reduction was smaller. For the other locations and studies reduction ranged from -12.7 to -25.4 (see Table 4)
Improvement of disease severity during follow-up Self-assessment (better, same, worse). Scale from: 0% to 100%. Follow-up: up to 12 months.	No control	56% to 64.8% of the participants considered their disease severity to be improved during follow-up	2670 (6 studies[3])	⊕⊖⊖⊖ **very low**[2,4]	Combined data showed that according to the participants disease severity was better in 64%, same in 25% and worse in 11% of the participants
Free of topical steroid use after alpine climate treatment Scale from: 0% to 100%.	No control	70% to 84% of participants was free of corticosteroids at the end of the intervention	1178 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]	Combined data across the 3 studies showed that 964 /1178 (82%) were free of corticosteroid use

No or less topical corticosteroid use at follow-up Scale from: 0% to 100%. Follow-up: up to 12 months.	No control	26% to 87% of participants used no or less topical corticosteroids during follow-up	3008 (4 studies[5])	⨁⊖⊖⊖ **very low**[2,4]	Combined data across the 4 studies showed that 2171/3008 (72%) used no or less topical corticosteroids

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No control population; not controlled for confounding; unblinded and unvalidated assessment of outcome; reporting bias, attrition bias.
[2] The limitations of the study design did not allow to upgrade for large effect.
[3] One study, Petermann 2000, did not provide data on this prespecified outcome, and the number of participants is therefore not included, nor is this study included for treatment effect. Number of participants at follow up of Kneist 1987 is unknown, only percentages are provided.
[4] Follow-up numbers were either not mentioned or up to 50%. No control population; not controlled for confounding; unblinded and unvalidated assessment of outcome; reporting bias.
[5] Number participants at follow up of Kneist 1987 is unknown, only percentages are provided and therefore not included.

Table 4 Disease severity measured with Physician Graded Assessment or SCORAD by dermatologist or self-assessment by the patient

Author / Year	Study population (n)	Outcome (n reported for outcome)	Proportion (%) and (n)	Outcome (n reported for outcome)	Proportion(%) and (n)	Mean (SD) decrease from baseline	Follow-up	Outcome during follow-up (n reported for outcome)	Proportion (%) and (n)
à Porta 2000	adults (n=97)	PGA (better, same, worse) (n=97)	99%, 1%, 0% n=96 n=1 n=0	Self- assess-ment at discharge (n=89)	93%, 7%, 0% n=83, n=6, n=0		1 year	Course of disease 6-12 months after treatment (better, same, worse) (n=89)	56%, 35%, 9% n=50, n=31, n=8
Borelli 1995	adults/children (n=31438)	PGA (better, same, worse) (n=31438)	97.2%, 2.4%, 0.4% n=30558, n=754, n=126				n/a	n/a	
Drzimalla 1999	adults (n=4660)	PGA (better, same, worse) (n=4660)	93.6%, 5.4%, 1% n=4362, n=251, n=47				1 year	Course of disease 8-12 months after treatment (better, same, worse) (n=2392)	* 64.8%, 24.4%, 10.8% n=1550, n=584, n=258
Duve 1991	adults/children (n=624)	PGA (better, same, worse) (n=624)	97.6%, 2.2%, 0.2% n=609, n=14, n=1				1 year	Course of disease (n=624)	Not clear reported, disease stabilized more than 6 months in more than 50% of patients
Fuchs 1959	adults (n=393)	PGA (better, same, worse) (n=393)	88.8%, 9.4%, 1.8% n=349, n=37,n=7				n/a	n/a	

Heine 1995	children / adolescents (n=375)	PGA (better, same, worse) (n=329)	98.5%, 0.6%, 0.9% n=324,n=2,n=3	Self- assess-ment (better, same, worse) (n=368)	91%, 6%, 3% n=335, n=22, n=11		1 year	Course of disease 7-12 months after treatment (better, same, worse) n=189	63%, 23%, 14% n=120, n=43, n=26
Kneist 1987	adults/ children(n=1465)	PGA (better, same, worse) (n=1065)	96%, 3%, 1% n=1012 n=30 n=14	Self-assessment (better, same, worse)	¦ 95,5%, 0%, 1.5% n=1399 n=22		1 year	Course of disease 6-12 months after treatment (better, same, worse)	¥ 63.4%, 31.7%, 4.9%
Total	**n=39052**	**PGA (better, same, worse)** **(n=39006)**	**96.5%, 3%, 0.5%** **n=37719, n=1088, n=199**	**Self-assess-ment (better, same, worse)** **(n=1922)**	**¤ 95%, 1.5%, 1.7%** **n=1817, n=28, n=33**			Course of disease up to 12 months after treatment (better, same, worse) (n^{1}=2670)	**64%, 25%, 11%** **n=1720, n=658, n=292**
Eberlein 2009	children(n=43) Treatment center Oberjoch	SCORAD				-15.70 (12.57)	n/a	n/a	
	children (n<24, exact number unknown) Treatment center Berchtesgaden					-4.30 (8.04)	n/a	n/a	
	adults(n=23) Treatment center Pfronten					-25.4 (11.81)	n/a	n/a	

Table 4 Continued

	adults (n<24, exact number unknown) Treatment center Berchtesgaden		-7.50 (11.04)	n/a	n/a	
Petermann 2000	children/ adolescents (n=102), SCORAD >25	SCORAD	-22.70 (8.68)	2 years	Self-assess-ment of skin	not mentioned
Simon 1999	adults (n=33)	SCORAD	-12.7	n/a	n/a	
Walker 1993	adults (n=12)	skin intensity score	51%	n/a	n/a	

n/a = not applicable
* Percentages are deduced from graph, not mentioned in text
¥ Percentages were mentioned, but no exact patient numbers
¦ Percentages do not add up to 100%
1excluding Kneist and Duve

Table 5 Corticosteroid use

Author/ Year	Popula-tion (n)	Outcome (n reported for outcome)	Propor-tion (%) and (n)	Outcome (n reported for outcome)	Propor-tion (%) and (n)	Follow-up	Outcome during follow-up	Proportion (%) and (n)	Outcome during follow-up	Proportion(%) and (n)
à Porta 2000	adults (n=97)	Free of topical corticosteroids (n=71)	70% (50/71)	Free of systemic corticosteroids (n=13)	92% (12/13)	1 year	Topical corticosteroid use (none, less, same, more)	26% (13/50)		
Drzimalla 1999	adults (n=4660)					1 year	Topical corticosteroid use (none, less, same, more)	¤ n=2156 none or less 77%, same 15%, more 9%.	Systemic corticosteroid use after 12 months follow-up	¤ n=2156 95% none or less 3% same 2% more
Duve 1991	children and adults (n=624)	Free of topical corticosteroids (n=624)	¤ ¦ 57%	Free of systemic corticosteroids (n=624)	¤¦ 86%	1 year	Topical corticosteroid use (none, less, same, more)	¤* n=624 none 36% less 19% same 38% more 9%	Systemic corticosteroid use after 12 months follow-up	¤* n=624 90% none, 4% less, 2%same, 2% more
Heine 1995	children and adolescents (n=375)	Free of topical corticosteroids (n=188)	75% (140/188)	Free of systemic corticosteroids (n=7)	57% (4/7)	1 year	Topical corticosteroid use (none, less, same, more)	¤ n=178 none 62% less 25% same 9% more 4%	Systemic corticosteroid use	¤ n=133 none 94% less 3% same 1.5% more 1.5%
Kneist 1987	children and adults (n=1465)	Free of topical corticosteroids (n=919)	84% (774/919)	Free of systemic corticosteroids (n=82)	77% (63/82)	1 year	Topical corticosteroid use (none, less, same, more)	not mentioned in text	Topical corticosteroid use (none, less, same, more) after 6 months follow-up	¥ none 40.2% less 38.5% same 17.4% more 3.8%
Total	**n=7221**	**n[2]=1178 using topical cortico-steroids**	**82% (n=964 /1178)**	**n=102 using systemic cortico-steroids**	**77% (n=79/102)**		**n[1]=3008**	**72%[1] (n=2171/3008)**		

¥ Follow-up numbers were not mentioned in the text
¤ Data presented for entire patient cohorts and not subset of patients treated with corticosteroids
[1]Excluding Kneist [2]Excluding Duve
*Percentages are deduced from graph, not mentioned in text
¦Percentages do not add up to 100%

Other outcomes

Several studies were identified reporting biomarkers or other translational parameters (Table 6). Five studies including 634 patients measured number of eosinophils, eosinophil cationic protein (ECP) and eosinophil protein X (EPX) in urine direct after climate treatment.[52-54, 58, 59] ECP decreased in three out of four studies, EPX decreased in one study and number of eosinophils decreased in three studies paralleling the observed improvement in SCORAD. A significant correlation between SCORAD and EPX was reported in one study.[59]

Skin prick tests with intracutaneously applied histamine, serotonin, acetylcholine and bradykinin showed a decrease in skin reactivity after alpine climate therapy; statistical significance was not calculated.[58] Skin prick tests with recall antigens showed a significant increase in skin reactivity after climate therapy.[60] Transepidermal water loss decreased significantly after treatment, but remained high compared to healthy controls.[61] TARC levels were stable before and after treatment at different clinics.[52]

Table 6 Eosinophil markers

Author/Year	Population(n)	Outcome	ECP mean (SD)	Number of eosinophils mean(SD)	EPX	Remarks
Borelli 1967	adolescents /adults (n=140)	Change in number of eosinophils		n=80 less, n=15 unchanged, n=25 more.		No correlation calculated with clinical outcome. Magnitude of change not calculated. Data not reported for all patients. Statistical significance not reported.
Eberlein 2009	adults/children (n=139/n=165)	Change in number of eosinophils ECP	Berchtesgaden 24.0(15.1) to 21.7(11.7) p<0.05. Oberjoch 20.0(20.2) to 16.9(12.0) p not reported Pfronten 16.9(21.3) to 15.2(15.4) p not reported	Berchtesgaden 5.8(3.4) to 4.8(2.4) p<0.05. Oberjoch 280.0 (231.2) to 247.3(172.4). Pfronten 4.6(3) to 4.3(3.5)		Results are divided by treatment center and not by diagnosis (AD, asthma and COPD reported together).
Petermann 2004	children/adolescents (n=55), SCORAD >25	ECP EPX	No change in ECP after treatment p=0.7		Decrease in EPX after treatment p=0.000	Significant correlation between SCORAD and EPX, not ECP
Simon 1999	adults (n=33)	ECP	Median ECP 33 mcg to 17.5 mcg p=0.001			Parallel improvement in SCORAD, significant correlation with ECP calculated, p not mentioned
Walker 1993	adults (n=12)	Number of eosinophils ECP	21% decrease p<0.05	43% decrease p<0.003		

Discussion

Main findings

Our systematic search for the effect of alpine climate therapy of AD patients has identified only observational studies. The largest study is a cohort of 31480 patients treated in a clinic in Davos, Switzerland from 1961 to 1995.[46] Disease activity was decreased in 96% of patients at the end of climate therapy. Topical as well as systemic corticosteroid use could be reduced or stopped during treatment in 80% of patients. Up to 12 months after treatment, 64% of patients reported a decreased disease activity; an overall improved course of disease compared to the year before treatment and 72% reported no or reduced topical corticosteroid use. Similar results were reported for children and adults.

Risk of bias

The quality of the body of evidence for the separate outcomes was very low. All identified studies had methodological and other limitations. In most identified studies clinical improvement was scored by the physician as improved, not improved or worsened. Physician global assessments are also used nowadays, because they are fast and easy to perform and give a good indication of the course of disease when repeated over time.[62] In more recent studies, SCORAD was used to measure clinical activity during climate therapy, allowing for a more objective estimation of the treatment effect.[49, 52, 53, 59] However, the measurements were not performed by an independent and blinded physician.

The majority of available data is provided by three alpine clinics, reporting on AD patients who were treated in these clinics during a certain time period. Selection bias is a problem, because there have been no generally accepted criteria for whom alpine climate therapy should be provided.[46] Also, the position of climate therapy in the healthcare system changed over time, decreasing its availability to AD patients. The relatively low rate of topical corticosteroid use could imply that patients with mild AD or concomitant diagnoses of severe asthma and mild AD were overrepresented in the study sample. However, patient characteristics were not well described and data on other pharmacological therapy was not provided. In most studies, style of reporting was very global and details were often lacking, making it difficult to interpret the data. Six studies were designed with a follow-up period, but risk of bias was substantial due to the high drop-out rates. Clinical efficacy during follow-up is important for reasons of cost-effectiveness since long-term beneficial effects may show the added value of alpine climate therapy compared to other treatment options.

It has been hypothesized that the lack or low level of respiratory allergens may contribute to the clinical effect of alpine treatment. The results in this systematic review of alpine climate therapy for patients with AD are very similar to what was reported of alpine climate therapy for patients with AA.[20] However, the latter was no systematic review and no level of evidence was assigned to the reported findings. Also, beneficial effects of alpine climate therapy irrespective of atopic status have been reported in children and adults with AA.[30,

[59, 63] But because no trials have been conducted and no control groups were included in the observational studies, there is no reliable data on which elements of alpine climate treatment are responsible for the observed effect. Multidisciplinary evaluation and treatment in a regular outpatient setting for several days also shows reduction of disease activity, corticosteroid use and improved quality of life up to two years after the described treatment program.[31, 64] This suggests that apart from the climate other elements may be important during alpine climate therapy, for example the multidisciplinary approach or the increased adherence to treatment.

Conclusion

To our knowledge, this is the first systematic review on the outcomes of alpine climate treatment of patients with AD using the Cochrane Handbook for assessing risk of bias, GRADE guidelines for assessing level of evidence and PRISMA guidelines for reporting. The results of this systematic review provide very low quality evidence, that alpine climate therapy results in decreased disease activity and reduced corticosteroid requirement direct and up to 1 year after treatment in patients with AD. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters, are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.

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3.

Comparing high altitude treatment with current best care in Dutch children with moderate to severe atopic dermatitis (and asthma): study protocol for a pragmatic randomized controlled trial (DAVOS trial)

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Trials 2014, 15:94

Abstract

Background

About 10%-20% of children in West-European countries have atopic dermatitis (AD), often as part of the atopic syndrome. The full atopic syndrome consists also of allergic asthma, allergic rhinitis and food allergy. Treatment approaches for atopic dermatitis and asthma include intermittent anti-inflammatory therapy with corticosteroids, health education and self-management training. However, symptoms persist in a subgroup of patients. Several observational studies have shown significant improvement in clinical symptoms in children and adults with atopic dermatitis or asthma after treatment at high altitude but evidence on the efficacy when compared to treatment at sea level is still lacking.

Methods/Design

This study is a pragmatic randomized controlled trial for children with moderate to severe AD within the atopic syndrome. Patients are eligible for enrolment in the study if they are: 1) diagnosed with moderate to severe AD within the atopic syndrome 2) aged between 8 and 18 years 3) fluent in the Dutch language 4) have internet access at home 5) able to use the digital patient system Digital Eczema Center Utrecht (DECU) 6) willing and able to stay in Davos for a 6 week treatment period. All data are collected at the Wilhelmina Children's Hospital and DECU. Patients are randomized over 2 groups: the first group receives multidisciplinary inpatient treatment during 6 weeks at the Dutch Asthma Center in Davos, Switzerland; the second group receives multidisciplinary treatment during 6 weeks at the outpatient clinic of the Wilhelmina Children's Hospital, Utrecht, the Netherlands. Patients and clinicians were not blinded during the trial. The trial is designed with three components: psychosocial, clinical and translational. Primary outcomes are coping with itch, quality of life and disease activity. Secondary outcomes include asthma control, medication use, parental quality of life, social and emotional wellbeing of the child and translational parameters.

Discussion

The results of this trial will provide evidence for the effectiveness of high altitude treatment compared to treatment at sea level for children with moderate to severe AD.

Trial Registration Current Controlled Trials ISRCTN88136485.

Background

About 10%-20% of children in West-European countries are diagnosed with atopic dermatitis (AD).[1] AD and allergic asthma (AA) are the most common chronic diseases in children. They can be considered different manifestations of the atopic syndrome, also including allergic rhinitis and food allergy.[2] It has been estimated that 30% to 36% of the children diagnosed with AD aged 4 years or younger will be diagnosed with asthma aged 6 years and older.[3] The reverse has also been demonstrated; in a cohort of children diagnosed with asthma aged between 6 and 9 years, 20% had developed AD after 9 years of follow-up.[4] The majority of children with AD are currently treated on an outpatient basis. Treatment approaches include topical treatment with emollients, anti-inflammatory therapy with topical immunosuppressive-like agents (corticosteroids and calcineurin inhibitors), anti-microbial treatment and educational programs, according to current guidelines.[5, 6]

However, symptoms persist in a subgroup of children with moderate to severe AD. Often these children have an extensive treatment history and are unable to gain sufficient control of their disease. It has been shown that a multidisciplinary approach to AD treatment is beneficial for children who do not respond well to regular treatment and often results in sustained clinical improvement.[7, 8] The multidisciplinary model includes medical and psychosocial evaluation and treatment and educates the children and their parents using a stepwise approach to the management of AD.[8] Psychosocial evaluation is important, because children have to learn to cope with the specific problems associated with living with a chronic disease.[9] Furthermore, they have to learn to adhere to strict medicinal regimes, which are time consuming. Often they are restricted in activities, such as sports, swimming or outside play. Social and emotional problems may occur, because of the distinguished appearance and characteristics of AD.[10] Sleep deprivation because of nightly symptoms of itch may lead to tiredness, mood changes and impaired psychosocial functioning of the child and its family.[10] AD has a significant negative impact on the quality of life of children and their parents. With increasing AD severity, reported quality of life decreases further.[11, 12]

Since the 1950s Dutch children with asthma are referred to the Dutch Asthma Center in Davos, located at 1560m in the Swiss alps, for “high-altitude” treatment.[13] Important characteristics of the alpine climate are the dry air, the low exposure to allergens, such as house dust mite and fungi, and the increased exposure to UV-radiation.[13] Also there is a relative lack of pollution.[14] Several observational studies have shown significant improvement in quality of life and clinical symptoms (Fev1, FeNO and SCORAD, among others) in children and adults with AD and asthma after treatment at high altitude.[15-21] However, no randomized trials have been done to investigate the superiority of high altitude treatment to treatment at sea level in improving quality of life or disease activity in children with AD or asthma.

In the DAVOS-trial, we compare multidisciplinary treatment at high altitude and sea level in a pragmatic randomized design. The objective of this study is to find the most effective treatment strategy for children with difficult to treat AD. This paper describes the study design and the interventions.

Methods

Design and setting

A pragmatic randomized controlled trial was designed in collaboration with the department of Pediatric Dermatology/Allergology in the Wihelmina Children's Hospital (a national referral center in the Netherlands for children with moderate-severe AD and the atopic syndrome) and the high altitude clinic Dutch Asthma Center Davos in Switzerland. Dutch children with moderate to severe AD are either treated during 6 weeks at the Dutch Asthma Center Davos (inpatient treatment) or at the Wilhelmina Children's Hospital (outpatient treatment). All children are expected to be included in the study in a time period of 4 years.

The trial consists of three different components: psychosocial, clinical and translational. The children in the study will be extensively characterized at study inclusion and during the study period. The study period includes the actual enrollment in the study, a 6 week intervention period and follow-up measurements at 6 weeks and 6 months after the intervention (Figure 1). Enrollment and all follow-up measurements will be done at the Wilhelmina Children's Hospital. The Digital Eczema Center Utrecht (DECU) will be used for data collection and communication.[22] In this digital portal possibilities for e-consulting, self-management training and online monitoring are combined.

Ethical considerations

This study follows the Dutch Medical Research Involving Human Subjects Act (WMO) and the Helsinki Declaration's principles 2008, meaning that the (legal representatives) of all participants will sign a written informed consent, stating that participation can be withdrawn at any time without any negative consequences concerning their current or future medical treatment. All study procedures have been reviewed and approved by the Medical Ethics Committee of the Utrecht Medical Center, the Netherlands (reference 09-192/K).

Participants

The DAVOS trial is designed for children in the Netherlands with difficult to treat AD who are unable to gain sufficient control of their disease with current treatment strategies. Children are eligible for enrolment in the study if they are: 1) diagnosed with moderate to severe AD within the atopic syndrome 2) aged between 8 and 18 years 3) fluent in the Dutch language 4) have internet access at home 5) able to use the Digital Eczema Center Utrecht 6) willing and able to stay in Davos for a 6 week treatment period. Children are not eligible for enrolment if they are currently participating in another study.

Recruitment, inclusion procedure and consent

The DAVOS trial is a national trial conducted in the Netherlands. Children with moderate to severe AD will be recruited from the outpatient clinic of the Wilhelmina Children's Hospital and from other hospitals in the country. Dutch dermatologists, pediatricians, allergists,

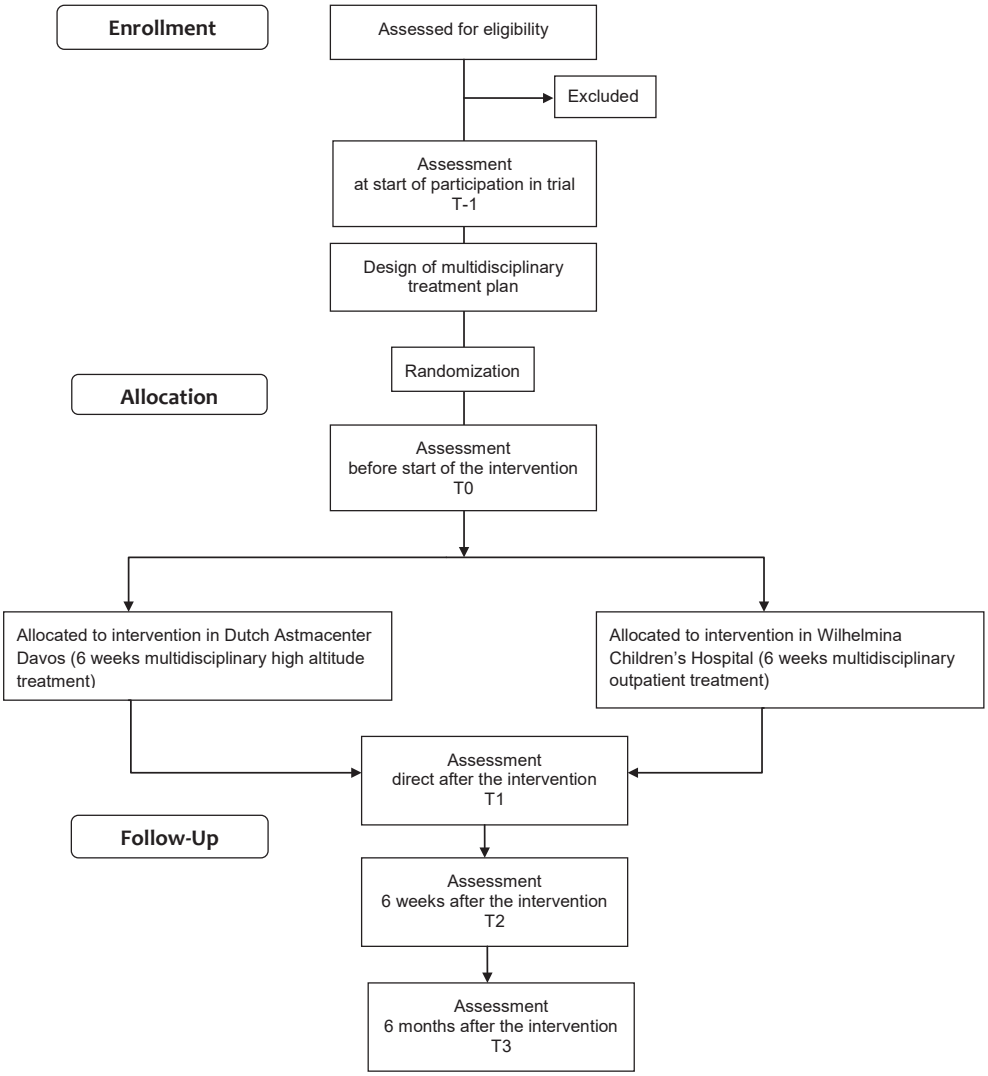

Figure 1 Flowchart of study design

general practitioners and patient support groups were informed about the trial in journals, conferences and using online media.

Children and/or their parents who are interested in the trial can register themselves directly in the DECU. A questionnaire with items regarding allergic complaints, use of (topical) immunosuppressive therapy like corticosteroids and more specific questions regarding AD activity, including a SA-EASI, questions on nightly complaints of itch and sleeping behavior and if relevant, questions on asthma, rhinitis and food allergy complaints has to be answered in order to register. Possible study participants are invited by the dermatologist in the outpatient clinic and assessed for eligibility. They are not required to stop or change their

medication at this point. Children who fulfill the inclusion criteria are then informed about the study. If they are interested in participating in the trial, they are invited for a complete evaluation by the multidisciplinary team in the Wilhelmina Children's Hospital and informed consent is signed.

Sample size

The sample size calculation for the psychosocial part is based on the primary outcome coping with itch, measured with the JUCKKI questionnaire.[23] We expect a difference of 5 points between the groups on the subscale catastrophisation (negative thoughts that have gone out of control). We based this difference on a study by Staab et al on the effect of educational programs in children and adolescents with AD.[24] In this study, the SD of both groups was 7.6. We carried out an additional sample size calculation for the clinical part of the trial. This is based on the primary outcome disease activity, measured with the SA-EASI.[25] Based on the study by Staab et al, in which SCORAD was used to measure disease activity, we expect a difference of 10 points between the groups and a SD of 15 for each group.[24,26] With a power of 80%, 36 children are needed in each group. Assuming a drop-out rate of 10%, 40 children will be assigned to each of the two study conditions.

Randomization

Children are randomly assigned to either intervention or control groups. Randomization is done with a custom made SAS program by an external data manager using a covariate-adaptive randomization method, controlled for age and diagnosis of asthma.[27]

Multidisciplinary treatment

The multidisciplinary team consists of a dermatologist, a pediatric allergist or pediatrician, psychologist and (dermatology/research) nurse. Weekly multidisciplinary evaluation during the intervention between the involved professional teams in Utrecht and Davos takes place using video conference. In this way expertise is being combined and optimal care for all included patients is guaranteed. A short summary of discussed topics is provided in the patient record in the DECU.

Before randomization and start of the intervention, a multidisciplinary treatment plan is developed with input from both multidisciplinary teams to make sure the treatment goals can be achieved under either intervention and control conditions. Based on the intake (history of received treatment, psychological questionnaires and intelligence outcomes) specific problem areas are identified and each health professional writes down the treatment goals and strategy in a treatment plan. Psychosocial as well as clinical treatment goals are formulated. Examples of treatment goals are adherence to treatment, influence and acceptance of AD in everyday life, including distinguished appearance, correct application of topical corticosteroids, coping with itch, sleep disturbances and knowing what to do during an exacerbation. Planned interventions to achieve the goals and the responsible health

professional are also specified. There are no treatment restrictions during the trial. The treatment plan is discussed with the child and his parents and may be modified if needed. External professionals who are already involved with the child, for example the referring physician, nurses or social workers, are invited to participate during the study through the DECU, with permission of the child and his parents. In this way optimal continuation of transmural treatment in the patients region is warranted after the end of the study.

The intervention in Davos

Children are admitted to the Dutch Asthma Center Davos for a period of six weeks in groups of four children. The child goes to a school integrated in the clinic. There are social workers who accommodate the group and each child has his/her own mentor.

The treatment program consists of several fixed elements. Every day a group physical activity is organized under supervision of a physiotherapist, such as fitness, swimming or outdoor activities. Weekly individual treatment sessions take place with the pediatrician, the psychologist alternating with the psychomotor therapist and the physiotherapist (if needed). The nurse monitors correct application of topical treatment in individual sessions with each child twice daily. In these individual sessions health education is provided with a weekly varying theme. The content of the individual consultations depends on the problems described in the treatment plan. Children and their parents are separated during the 6 week treatment period, but parents usually visit once.

Control condition in Utrecht

Recently a new multidisciplinary intervention has been developed for children with AD, combining education, involvement of both dermatologists, pediatricians, psychologists and nurses and the use of the Digital Eczema Center Utrecht (DECU). Children are seen half a day at the outpatient clinic on a weekly basis for a period of 6 weeks. During this period they have three consultations with the dermatologist, five consultations with the dermatological nurse, three consultations with the pediatric allergist and three consultations with the psychologist. The content of the individual consultations depends on the treatment goals described in the treatment plan.

In the third week a shared medical appointment is scheduled about coping with AD and compliance.[28] Children and their parents are separated to enable them to talk about different issues. They can put forward any subject they like within the mentioned themes, discuss their personal experiences and advice and support each other.

A description of intervention and control conditions is provided in Table 1.

Table 1 Overview of control and intervention conditions

Treatment location	Wilhelmina Children's Hospital	Dutch Asthma Center Davos
Multidisciplinary team	Dermatologist, pediatric allergist, psychologist, dermatology nurse	Pediatrician, psychologist, nurse, psychomotor therapist, physiotherapist, social workers
Treatment program	Three individual consultations with dermatologist, pediatrician and psychologist	Six individual consultations with pediatrician, four with the psychologist, three with the psychomotor therapist
	One group consultation (children and parents separate)	Physical activity program under supervision of physiotherapist
Educational program	Five individual consultations with the dermatology nurse	Twice daily individual consultations with the dermatology nurse
Treatment setting	Outpatient	Inpatient
Environment	Own home in the Netherlands	Clinic in Swiss alpine environment

Follow-up period

There is a 6 month follow-up period during which all children are assessed three times at the Wilhelmina Children's Hospital: immediately after the intervention, 6 weeks after the intervention and 6 months after the intervention, which is the end of the follow-up period. During the entire follow-up period, children are encouraged to use the self-management tools in the DECU. In case of questions and/or exacerbations, they can contact the dermatology nurse with an e-consultation and if needed an appointment with the dermatologist is made. All children are encouraged to sport for example at FitKids, a Dutch organization that facilitates physical activity programs for children with a chronic disease under supervision of a children's physiotherapist.[29]

Primary and secondary outcomes

The primary outcomes of this study are coping with itch and quality of life of the child for the psychosocial part and disease activity for the clinical part. Coping levels are measured with the JUCKKI questionnaire for children (aged 8-12 years) and the JUCKJU questionnaire for adolescents (aged 13-18 years).[23] Quality of life is assessed with the CDQLI questionnaire.[30] Disease activity is assessed with the (SA)-EASI.[25]

Secondary outcomes for the psychosocial part include social and emotional wellbeing of the child, feelings of autonomy and fear, quality of life and stress of the parents.

Secondary outcomes for the clinical part include medication use, TARC (thymus and activation-regulated chemokine, total and specific IgE, asthma control parameters such as

FeNO (fraction of exhaled nitric oxide), ACQ (asthma control questionnaire), PAQLQ (pediatric asthma quality of life questionnaire), BHR (bronchial hyperresponsiveness) and spirometric variables such as FEV1 (forced expiratory volume in 1 second), FVC(forced vital capacity) and their ratio (FEV1/FVC). During the follow-up period, the number of flares, the number of dermatologist / pediatric / psychologist appointments, e-consultations and emergency visits or hospital admissions are recorded.

At each time point in the study, questionnaires are filled in by the child and his parents, blood samples are taken from the child and lung function is assessed. A detailed overview of all parameters and measurements is provided in Table 2.

Table 2 Study assessments

Assessment	Measured with	T-1	T0	T1	T2	T3
Coping with itch and disease	JUCKKI-COPECI (8-12yr) or JUCKJU-COPEJU (13-18yr)[23]	x	x	x	x	x
Disease specific quality of life	CDQLI[30]	x	x	x	x	x
Disease activity and control (AD)	EASI[33]	x	x	x	x	x
	SA-EASI[25]	x	x	x	x	x
	Used topical corticosteroids	x	x	x	x	x
	TARC[34]	x	x	x	x	x
Disease activity and control (Asthma)	ACQ[35]	x	x	x	x	x
	PAQLQ[36]	x	x	x	x	x
	Lung function test	x	x	x	x	x
	FeNO	x	x	x	x	x
	Used medication	x	x	x	x	x
	Metacholine provocation	x				x
Serum	Total IgE		x			x
	Specific IgE: inhalation/food: CAP		x			x
	Specific IgE: inhalation/food: ISAC		x			
	Eosinophils		x	x	x	x
	Cytokine profile		x	x	x	x
Questionnaires	Social demographic information	x				
	Intelligence test[37]	x				

	SF-36[38, 39]	x				
	CBCL[40, 41]	x				
	Treatment management	x			x	x
	NPV-J[42]	x				
	TRF[40]	x				
	CBSK/CBSA [43, 44]	x		x		x
	ZBV-K[45]	x	x	x		x
	PUL (>12yr)[46]	x		x		x
	Quality of life (parents) [47]	x	x	x		x
	ZBV[48]	x		x		x
	NOSI-K[49]	x		x		x
	NOSI-events [49]	x				x
Other	Maximal cycle ergometer test	x				x
	Bacterial colonization of the skin		x	x	x	x
	Bacterial colonization of the nose		x	x	x	x
	Skin strips for protease activity		x	x	x	x

JUCKKI/JUCKJU: itching cognitions questionnaire. COPEKI/COPEJU: coping with disease questionnaire. CDQLI: the children's dermatology life quality index. EASI: eczema area and severity index. SA-EASI: self-administered eczema area and severity index. TARC: thymus and activation-regulated chemokine. ACQ: asthma control questionnaire. PAQLQ: pediatric asthma quality of life questionnaire. FeNO: fraction of exhaled nitric oxide. SF-36: short form health survey. CBCL: child behavior checklist. NPV-J: Dutch personality questionnaire-youth version. TRF: teacher report form. CBSK/A: self-perception profile for children/adolescents. ZBV-K: state-trait anxiety inventory for children. PUL: positive outcome list ZBV: state-trait anxiety inventory. NOSI-K: parental stress index- short form. NOSI-events: parental stress index-events.

Data collection and data analysis

In this study two sources of electronic data are used. The DECU gives a detailed overview of the intervention and follow-up period and contains the data from the questionnaires, assessments and e-consultations. Additional patient data is extracted from the electronic patient file in the Wilhelmina Children's Hospital. After data collection, all data will be combined into one SPSS database.

Data will be analyzed on an intention to treat basis. To examine whether there is a significant difference on the primary outcomes between the intervention and control group a mixed effects regression model will be used. Fixed effects for time, intervention group and the time*group interaction will be included in the model in order to examine the differences between the groups over time. To adjust for possible curvilinearity a squared term for time will be included in the model. A random intercept and random slope per child will be included in order to account for repeated measures within children. Baseline values of the outcome

variables are included as fixed covariates to examine their possible impact on the observed treatment effect.

Data relating to asthma outcomes will be analyzed separately for all children diagnosed with asthma. All analyses conform to a specified plan. There are no interim analyses or stopping rules.

Discussion

The DAVOS trial is a pragmatic randomized controlled trial that investigates the effect of multidisciplinary treatment at high altitude compared to sea level on coping, quality of life and disease activity in children with moderate to severe AD within the atopic syndrome. It is designed as a pragmatic trial, which fits best with our objective to find a new intervention with optimal treatment results for children with difficult to treat AD.[31]

In this study we compare inpatient treatment in a high altitude clinic in Switzerland with outpatient treatment in a national expert center in the Netherlands. We chose for outpatient treatment in the Wilhelmina Children's Hospital, because it is the current most specialized and intensive treatment in the Netherlands for this group of patients. It is most efficient to organize the involved medical disciplines to see the patients consecutively in an outpatient setting. Furthermore, we want to evaluate the best treatment for children with difficult to treat AD that minimizes its burden but maximizes the result. This means that if it is possible to reach significant clinical improvement with an intense 6 week outpatient program in the Netherlands, this is the preferred choice compared to a 6 week inpatient treatment in the Netherlands. Also, it would not be possible to extrapolate results from inpatient treatment in an academic hospital to a peripheral hospital. We believe that in this trial design, we are comparing the best options for treatment that are also likely to be carried out in practice after the end of the trial.

There are several differences between the intervention and control condition, such as the differences in setting: inpatient and outpatient, own environment and change to alpine environment. During the intervention in Davos, adherence to treatment is more likely to increase due to the clinical setting. Also, children are separated from their parents. This can be perceived as an extra burden for the child. It may also be an advantage, especially when the coping strategy of the child is negatively influenced by the coping strategies of the family.[32]

All children in both interventions are discussed in weekly videoconferencing sessions with both multidisciplinary teams. AD treatment in both interventions is supervised by a single dermatologist in the Netherlands to minimize differences. Corticosteroid use is reduced or increased according to similar stepwise plans in both treatment arms. The educational plan is co-developed by both centers and consists of similar elements in both treatment arms. It is given by the nurse and there is frequent contact between the nurses of both treatment arms. The pragmatic nature of our trial will not allow us to find out how or why the interventions work or which elements of the interventions contribute most to the observed treatment

effects. Therefore we will study effectiveness: the long-term benefit of either treatment in routine clinical practice.[31]

This study has several strengths. Children that participate come from all over the Netherlands. They often have an extensive treatment history and still experience an impaired quality of life, despite treatment according to current guidelines. In this study, children receive multidisciplinary treatment with individualized treatment goals either in their own environment or in an alpine clinical environment. The results of this trial will show which would be the most appropriate approach to provide treatment that results in sufficient long-term disease control for children with difficult to treat AD. Findings of our trial will be directly applicable in practice in the Netherlands.

The study also has potential drawbacks. It is an intense period for the study participants in which they have to visit the Wilhelmina Children's Hospital several times for the scheduled assessments. Each assessment means a missed day of work for the parents and a missed school day for the child. This may lead to a larger drop-out rate than anticipated and it may take a lot of effort to keep the study participants motivated for all assessments. In this study neither the study participants nor the health care professionals assessing outcomes were blinded to the received intervention. This may cause bias for the more subjective outcome measures, such as the SA-EASI.

To the best of our knowledge, this is the first randomized trial that compares high altitude treatment with treatment at sea level in children with difficult to treat AD. Our study provides new and detailed information on the characteristics of these children. We hope to provide evidence for an intervention that gives the best results in terms of coping, quality of life and disease activity for this group of children.

Trial status

The first patient was included in the study in September 2010. At the moment patient recruitment and data collection is in progress. We expect to complete patient recruitment by May 2014.

Acknowledgments

We like to thank Anita Beelen, PhD, Merem treatment centers for critical reading of the manuscript. We like to thank the anonymous sponsors who made the treatment of the children in the Dutch Asthma Center Davos possible. This trial can be executed thanks to grants from the European Allergy and Asthma Center Davos and the Dutch patient support group 'Vereniging Nederland Davos'. We want to acknowledge all clinicians who identified and referred possible study participants.

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4.

Parental treatment management skills in pediatric atopic dermatitis

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Clinical and Experimental Dermatology, in press

To the editor.

Atopic dermatitis (AD) is a common, pruritic inflammatory skin disease with a chronic relapsing course. Treatment usually consists of topical therapy with emollients and topical corticosteroids (TCS) requiring lifestyle adjustments. Several treatment management skills are essential for successful treatment but the complexity and time-consuming nature of treatment can be problematic for families.[1] Fear of topical corticosteroids (TCS) further complicates AD treatment.[2] This study aimed to investigate parental AD treatment management skills in a population of parents of pediatric patients with AD, attending the outpatient clinic of a Dutch academic hospital.

A cross-sectional study was carried out between 2009 and 2014. We assessed parental AD treatment management skills before the first consultation with a questionnaire developed for use in clinical practice. Multiple choice questions about knowledge and management of topical therapies, child refusal of treatment, shower behavior, reluctance to use TCS, and use of alternative therapy were included. Questions were based on literature, experience in clinical practice and through consultation with other dermatologists, pediatricians, and nurses specialized in pediatric dermatology. Parents assessed AD severity using the Self-Administered Eczema Area and Severity Index (SA-EASI).[3]

A total of 579 parents completed the treatment management questionnaire (Table 1), 10 parents did not. In this study population incorrect estimates of TCS potency (54%), uncertainty how much TCS to apply (22%), infrequent TCS application during a flare (10%), uncertainty how to phase out/step up treatment (33%), reluctance to use TCS (48%), frequent refusal of therapy (16%), use of alternative therapies (27%), unawareness of current shower advice (26%), not showering according to advice (23%), and irregular emollient use (9%) were observed (Table 2).

Several aspects of AD treatment management are well known in our study population. Other aspects such as reluctance to use TCS, knowing potency of the currently used TCS, adjusting treatment intensity and shower behavior need more attention. This study was conducted at an expert center for treatment of children with AD, so the majority of parents have been to at least a general practitioner, a dermatologist or pediatrician in a regional hospital for previous AD treatment. Quality of patient education may differ between general practitioners and specialists, but explanation of the basics of AD treatment such as the prescribed TCS potency or how to phase out AD treatment are explicitly mentioned in every AD treatment guideline. It is possible that parental AD treatment management skills are associated with line of referral or parent demographics, but this information was not available. Other limitations of this study include its cross-sectional design and the use of a questionnaire developed for use in clinical practice to assess treatment management skills.

Table 1 Patient characteristics of study population

Patient characteristics		**n = 579**
Female	n (%)	266 (46%)
Age in years	mean ± SD	5.7 ± 5.0
Disease activity		
SA-EASI	mean ± SD	28.0 ± 16.9
Mild (SA-EASI < 17)	n (%)	172 (30%)
Moderate (SA-EASI 17 – 46)	n (%)	310 (53%)
Severe (SA-EASI > 46)	n (%)	97 (17%)
Potency of currently used TCS		
Mild	n (%)	177 (31%)
Moderate	n (%)	151 (26%)
Potent	n (%)	228 (39%)
Very potent	n (%)	23 (4%)
Itch intensity		
None	n (%)	7 (1%)
Light	n (%)	29 (5%)
Moderate	n (%)	72 (12%)
A lot	n (%)	268 (46%)
Very severe	n (%)	203 (35%)
Nightly complaints of itch	n (%)	
None	n (%)	24 (4%)
Light	n (%)	89 (15%)
Moderate	n (%)	125 (22%)
A lot	n (%)	187 (32%)
Very severe	n (%)	154 (26%)
Impact on family life		
No impact	n (%)	46 (8%)
Little impact	n (%)	114 (20%)
Moderate impact	n (%)	185 (32%)
Much impact	n (%)	234 (40%)

SA-EASI: Self-administered Eczema area and Severity Index, TCS: topical corticosteroids

Table 2 Frequencies of answers to AD treatment management questionnaire

Topic	Question		Answer	Frequency n(%)
Reluctance to use TCS	Q1	Do you or your partner feel reluctance in using TCS?	No Yes, I do Yes, my partner does Yes, we both do	303 (52%) 216 (37%) 60 (10%) 0 (0%)
Knowledge of TCS	Q2	Which TCS do you apply at this moment?	Hydrocortison Triamcinolon, Emovate Cutivate, Elocon Diprosone, Topicorte, Ibaril Betnelan Dermovate	177 (31%) 151 (26%) 193 (33%) 35 (6%) 23 (4%)
	Q3	How would you rate the potency of the TCS you currently apply?	[Combined answers for all TCS] Lower Correct Higher I don't know	 73 (13%) 264 (46%) 177 (31%) 65 (11%)
	Q4	Do you know how much TCS cream you should apply per treatment moment?	Yes Yes, I use the Finger Tip Unit (FTU) No	322 (56%) 127 (22%) 130 (23%)
	Q5	How often do you apply TCS cream during worsening of AD?	Twice daily Once daily 4-6 days per week Less than 4 days per week	290 (50%) 185 (32%) 47 (8%) 57 (10%)
	Q6	Do you know how to phase out/taper off TCS treatment and how to step up TCS treatment when the AD worsens in the future?	Yes No	388 (67%) 191 (33%)
Emollients	Q7	How often do you use emollients to keep your child's skin moisturized?	At least twice daily Once daily 4-6 times per week Less than 4 times per week Seldom	360 (62%) 137 (24%) 31 (5%) 22 (4%) 29 (5%)

Shower behavior	Q8	In your opinion, what is the best way to shower for a child with AD?*	According to advice Not according to advice	427 (74%) 152 (26%)
	Q8a	Shower frequency	Daily Every other day Less than 3 times per week	38 (7%) 102 (18%) 439 (76%)
	Q8b	Shower duration	10 minutes 5 minutes 2 minutes	61 (11%) 312 (54%) 206 (36%)
	Q8d	Shower agent	Soap Showergel Showeroil Nothing	11 (2%) 60 (10%) 215 (37%) 293 (51%)
	Q9	Does your child also shower in this way?	Yes No	320 (55%) 259 (45%)
Alternative therapies	Q10	Do you use alternative therapies for the treatment of your child's AD?	No Yes, medicinal herbs Yes, homeopathy Yes, bioresonancy therapy Yes, different cream product Yes, other	425 (73%) 6 (1%) 76 (13%) 16 (3%) 10 (2%) 46 (8%)
Child refusal of therapy	Q11	Does your child refuse application of topical treatment?	Yes, often Yes, sometimes Yes, very incidental No, never	92 (16%) 111 (19%) 119 (21%) 257 (44%)

* Advice according to the local protocol: Shower frequency: Every other day or less than 3 times per week. Water temperature: lukewarm water. Shower duration: less than 5 minutes. Shower agent: shower oil or no shower agent.

Our study shows that although many parents have appropriate treatment management skills, our data support the need and importance of continued patient education. Regularly evaluating parental treatment management skills provides an important opportunity for the clinician to reinforce and improve these skills, preferable before considering more potent treatment. Future studies could address the most efficient ways to do this, for example using behavioral, nurse, e-health or multidisciplinary interventions.[4]

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5.

Fecal microbiome and food allergy in pediatric atopic dermatitis: a cross-sectional pilot study

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International Archives of Allergy and Immunology, in press

Abstract

Background

Microbial exposure might be important in the development of atopic disease. Atopic diseases have been associated with specific characteristics of the intestinal microbiome. The link between intestinal microbiota and food allergy has rarely been studied and the gold standard for diagnosing food allergy (double blind placebo controlled food challenge (DBPCFC)) has seldom been used. We aimed to distinguish fecal microbial signatures for food allergy in children with AD.

Methods

Pediatric patients with AD, with and without food allergy were included in this cross-sectional observational pilot study. AD was diagnosed according to the UK Working Party criteria. Food allergy was defined as a positive DBPCFC or convincing clinical history in combination with sensitization to the relevant food allergen. Fecal samples were analyzed using 16S rRNA microbial analysis. Microbial signature species discriminating between presence and absence food allergy were selected with elastic net regression.

Results

82 children with AD (39 girls, median age 2.5 years old) of which 20 were diagnosed with food allergy provided fecal samples. Food allergy to peanut and cow's milk was the most common. Within children with AD, six bacterial species from the fecal microbiome were identified that when combined discriminate between children with and without food allergy: *Bifidobacterium breve, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis, Escherichia coli, Faecalibacterium prausnitzii* and *Akkermansia muciniphila (*AUC 0.83, sensitivity 0.77, specificity 0.80).

Conclusions

In this pilot study, we identified a microbial signature in children with AD that discriminates between absence and presence of food allergy. Future studies are needed to confirm our findings.

Introduction

The worldwide prevalence of atopic disease has been increasing in recent decades.[1] There is no clear reason for this observed increase in prevalence, but reduced early-life exposure to different microbes is thought to be a contributing factor.[2-4] Microbial colonization of the human intestine during infancy is important for the maturation of the immune system.[5, 6] Intestinal microbiota can regulate metabolic and inflammatory responses and also modulate changes in the intestinal barrier. Several studies have shown associations between intestinal microbiota and subsequent development of atopic disease, including atopic dermatitis, asthma or rhinitis. However, few studies have investigated the link between specific patterns of intestinal microbiota and food allergy. Furthermore, the gold standard for diagnosing food allergy (double blind placebo controlled food challenge (DBPCFC)) has rarely been used.[7]

The microbiome can be considered a complex ecosystem where various species interact and group-based correlations have been identified.[5] Therefore the symbiosis of the different bacterial species and their patterns should be taken into account in data analysis. To be able to identify individual species and take the existing structures within the microbiome into account, advanced statistical modelling techniques are needed. Furthermore, assessment of microbial diversity with molecular sequencing techniques, as opposed to culture-based techniques, reveals greater diversity and has shown the importance of uncultured species.[8]

We hypothesize that children have distinct microbial patterns in their fecal microbiome that are associated with a clinical diagnosis of food allergy. In this cross-sectional pilot study, we aimed to identify microbial species in children with AD, using 16S rRNA microbial analysis followed by statistical elastic net regression approaches.

Methods

Study design and study participants

Children with AD who were treated in the outpatient clinic of the Wilhelmina Children's Hospital of the University Medical Center Utrecht participated in this cross-sectional pilot study. Inclusion criteria were: diagnosis of AD, age between 0 and 18 years, parental ability to answer Dutch questionnaires and the availability of a fecal sample for microbiome analysis. All study participants participated in a randomized controlled trial that compares shared medical appointments with individual consultations (ISRCTN08506572). The medical ethical committee of the University Medical Center Utrecht approved the study and written informed consent was obtained from all participants. Clinical history and serum samples were taken on the same day, fecal samples were provided within the next days and a DBPCFC was planned within months.

Assessment of AD and food allergy

AD was diagnosed according to the criteria of Williams et al.[9] AD severity was estimated using the self-administered eczema area and severity index (SA-EASI) by the research nurse.[10] Sensitization was determined by measurement of specific IgE against common food allergens (hen's egg, cow's milk, peanut, hazelnut, fish, wheat, soy). Both total and specific IgE were measured according to manufacturer's protocol (Phadia, Uppsala, Sweden). Diagnosis of asthma and allergic rhinitis was based on clinical history.

Food allergy was defined as a positive double blind placebo-controlled food challenge (DBPCFC) or convincing clinical history in combination with sensitization to that specific food or in case of peanut allergy, a sensitization to Ara h 2 above the defined cut off level in our clinic (5.17 kU/L).[11] A convincing clinical history was defined as a reported Type I allergic reaction with acute symptoms within 2 hours after ingestion of the food. DBPCFC was considered positive and terminated when persistent objective symptoms occurred (e.g. vomiting, generalized urticaria, wheezing or a significant drop in blood pressure) or after subjective symptoms (oral allergy symptoms, nausea, abdominal discomfort) on three subsequent doses or a severe subjective symptom (abdominal pain/nausea with discomfort) lasting for more than 45 minutes, according to the international protocol.[12] Late reactions were assessed using follow-up by telephone the next day.

Fecal samples

Children collected fecal samples at home and sent the samples to the laboratory using the regular postal service. The samples were aliquoted and frozen at -20^{0}C until further processing.

Fecal DNA isolation

Approximately 150 mg of fecal material was directly transferred to the DNA isolation plate. Then 0.5 mL phenol pH8.0 (Phenol solution, catalogue P4557, Sigma-Aldrich, St Louis, MO) was added and the samples were mechanically disrupted by bead beating 2 times 3 minutes with a 96-well plate Beadbeater (Biospec Products, Bartlesville). Samples were centrifuged at 1880 rcf (4000rpm) for 10 minutes to separate the aqueous and phenolic phases. The aqueous phase was transferred to a 96-well plate and DNA was purified with the AGOWA mag Mini DNA Isolation Kit (AGOWA, LGC genomics, Berlin, Germany) in accordance with the manufacturer's recommendations. After elution, the total bacterial load in each sample was assessed by quantitative PCR using a universal bacterial primer-probe set.[13]

16S rDNA Illumina sequencing

Analysis of the fecal microbiome composition was performed by mass sequencing of the V4 hypervariable region of the 16S rRNA gene on the Illumina MiSeq sequencer (Illumina, San Diego, CA). Barcoded DNA fragments spanning the Archaeal and Bacterial V4 hypervariable region were amplified with a standardizing level of template DNA (100pg) to prevent over-

amplification. These amplicons, generated using adapted primers 533F and 806R, were bi-directionally sequenced using the MiSeq system.[14] Pre-processing and classification of sequences was performed using modules implemented in the Mothur V.1.20.0 software platform.[15] The relative abundance of unique sequences was calculated for every fecal sample. The dataset was transformed using zero mean unit variance transformation for subsequent statistical analyses. The V4 amplicon of the 16S rRNA encoding gene allows for discrimination of several Bifidobacterial species, but not all.[16] Therefore, relevant sequences were blasted in the Ribosomal Database Platform (RDP) to determine a more accurate species level. Shannon diversity indices were calculated to describe the microbial diversity.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Non-parametric tests were used to compare the groups without and with a confirmed food allergy.

Elastic net regression

Bacterial signature species discriminating between absence and presence of food allergy were selected using elastic net regression. This is a statistical machine learning approach, applicable to large scale, structured and higher dimensional data. The method is regularization-based and combines the advantages of LASSO regression (sparsity, retaining the feature selection property of reducing coefficients to exact zero values provided by LASSO) and ridge regression (smoothness, tendency of shrinking coefficients to small values for correlated trending towards each other).[17,18] All present species and the correlations between them are taken into account, which allows for the identification of patterns of species rather than individual species.[19] Using elastic net regression, it is not possible to correct for other confounding factors which is common in other types of regression analyses used in medical statistics.[19]

Randomization test and ROC/AUC

A randomization test was conducted to test the statistical validity of the results obtained with elastic net regression. Receiver-Operating-Characteristics Area-Under-Curve (ROC/AUC) scores were generated multiple times after randomly reshuffling the food allergy diagnoses, while keeping the corresponding microbial profiles intact.[20] The dataset was cross-validated by randomly hiding 30% of the children from the model and evaluating the prediction quality on that group. The predictive accuracy of the classification model was measured with the ROC/AUC score, using a critical value of 0.05.

SPSS (version 22; IBM, Armonk, NY) was used for descriptive data analysis. GraphPad Prism (version 6.01; GraphPad Software, La Jolla, CA) was used for providing graphs and figures. All other statistical analyses were performed using numerical Python (version 2.7, Python Software Foundation, https://www.python.org).

Results

AD and food allergy

We included 82 children in this cross-sectional pilot study. There were no significant differences regarding sex or age between the children who were included and those who were not (data not shown). All 82 children were diagnosed with AD, 62 children had no food allergy (AD+FA-) and 20 children had a confirmed food allergy (AD+FA+) (Table 1).

Table 1 Patient characteristics

	No food allergy (AD+FA-) (n=62)	Confirmed food allergy (n=20) (AD+FA-)	p-value
Age in years [median (IQR)]	3.0 (5)	2.2 (5.5)	0.606
Female [n (%)]	32 (52%)	7 (35%)	0.196
SAEASI [median (IQR)]	29 (32)	46 (42)	0.283
TARC (pg/ml) [median (IQR)]	1243 (2247)	2251 (5613)	0.013
Total IgE (kU/L) [median (IQR)]	66 (281)	564 (2912)	<0.001
Sensitization to any food allergen [n (%)]	27 (43%)	20 (100%)	<0.001
Elimination diet for any food [n (%)]	19 (31%)	20 (100%)	<0.001
Diagnosed with asthma [n (%)]	18 (29%)	5 (25%)	0.727
Diagnosed with rhinoconjunctivitis [n (%)]	15 (24%)	5 (25%)	0.942

Data is shown with median and interquartile range or number and percentage. AD = atopic dermatitis, FA = food allergy, SAEASI = self-administered eczema area and severity index scored by research nurse, TARC = thymus and activation regulated chemokine.

Of the 62 children without food allergy, almost half were sensitized to common food allergens without having symptoms of food allergy after ingestions. Among the 20 children with a food allergy, peanut allergy and cow's milk allergy were the most common (Table 2). Multiple food allergies were found in 2 children. On average, a DBPCFC was performed within 10 months of providing the fecal samples (minimum 1 month, maximum 27 months).

Table 2 Children with confirmed food allergies

Food allergy	Confirmed n(%)	With DBPCFC* n(%)	Obvious clinical history only n(%)	Predicted based on elevated sIgE to arah2 > 5.17 KU/L n(%) [11]
Peanut	8 (40%)	3 (15%)	1 (5%)	4 (20%)
Hazelnut	1 (5%)	1 (5%)		
Cow's milk	8 (40%)	6 (30%)	2 (10%)	
Hen's egg	4 (20%)	3 (15%)	1 (5%)	
Other nuts	2 (10%)		1 (5%) cashew nut 1 (5%) pistachio	
Soy	0			
Fish / shrimp	0			
Total n	20 (100%)			

Multiple food allergies result in multiple entries. One patient has a confirmed food allergy for cow's milk, peanut and hen's egg, another patient has a confirmed allergy for hazelnut and hen's egg. *including no late reactions

Sequence and microbiota characteristics

A total of 2.609.478 high quality sequences were obtained (mean=27.182, range=5.825 to 105.404 of sequences per sample) that could be assigned to 12 different phyla and 1.000 unique sequences. The most predominant phyla based on mean relative abundance were Firmicutes (47%), Actinobacteria (32%), Bacteroidetes (9%), Proteobacteria (8%) and Verrucomicrobia (2%), which is characteristic for the gut microbiome of children.[21] Predominant families were Bifidobacteriaceae (28%), Lachnospiraceae (27%), Ruminococcaceae (10%), Enterobacteriaceae (5%), Streptococcaceae (4%) and Coriobacteriaceae (3.5%). Median Shannon diversity indices calculated for the group of children with and without a food allergy were 3.61 (IQR 1.16) and 3.93 (IQR 1.09), respectively (p=0.430).

Identification of microbial biomarkers related to food allergy

We identified six microbial species from four families that together discriminate between the absence and presence of food allergy in children with AD: *Bifidobacterium breve, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis* (Bifidobacteriaceae), *Escherichia coli* (Enterobacteriaceae), *Faecalibacterium prausnitzii* (Ruminococcaceae) and *Akkermansia muciniphila* (Verrucomicrobiaceae). On the species level, *Bifidobacterium breve/ longum* and *Bifidobacterium pseudocatenulatum/ catenulatum/ gallicum/ kashiwanohense* could not be distinguished after additional blasting in the RDP database, and are referred to as *Bifidobacterium breve* and *Bifidobacterium pseudocatenulatum* throughout the manuscript. Figure 1 shows the relative abundance of the six identified signature species. The fecal microbiome of children with AD and food allergy harbored relatively more *E.coli* and *B.pseudocatenulatum*, and less *B.breve, B.adolescentis, F.prausnitzii,* and *A.muciniphila*,

compared to children with AD without food allergy. The randomization test indicates that the combination of these six species is significantly different between the two groups (p = 0.001), even though the relative abundance of some single species may seem similar on a group level (Figure 1). Different relative contributions from the single species towards the total distinctive properties are distinguished, with a larger influence of *B.breve*, *B.adolescentis* and *F.prausnitzii* compared to *B.pseudocatenulatum*, *E.coli* and *A.muciniphila*, expressed as importance indices based on the elastic net regression (Figure 2). The overall predictive accuracy of the classification model (area under the curve) is 0.83 (Figure 3), with a sensitivity of 0.77 and a specificity of 0.80. Supplementary figures S1 to S3 show the relative abundance of the signature species, the distribution of the 30 most abundant species and the individual distribution of the signature species.

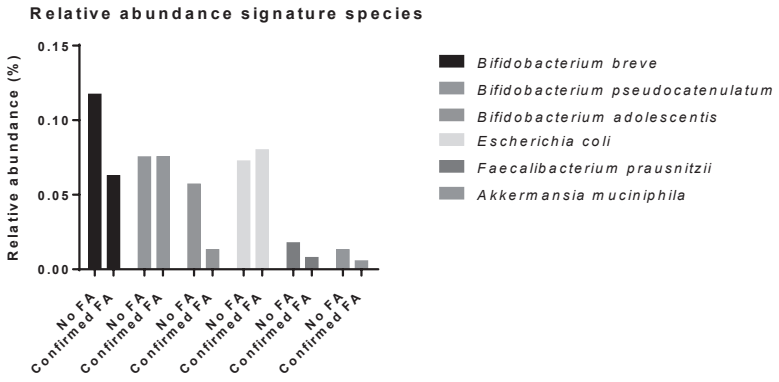

Figure 1 Relative abundance of the microbial signature species in children with AD, without and with a confirmed food allergy

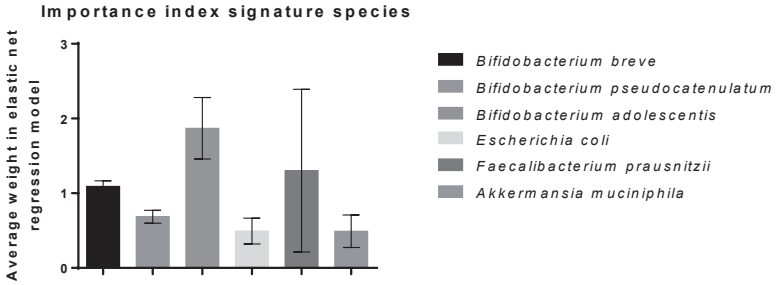

Figure 2 Importance index for signature species in the elastic net regression model

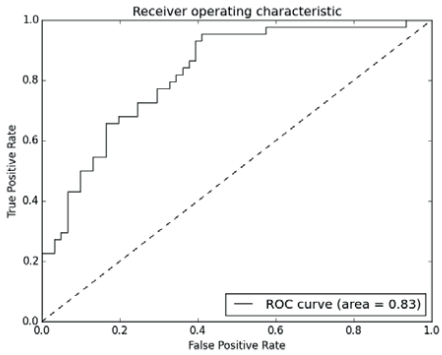

Figure 3 Receiver operating characteristic (ROC) curve of the elastic net regression model

Discussion

We analyzed the fecal microbiome of children with AD with or without a concomitant food allergy and found that a combination of six microbial species, including *E.coli*, *F.prausnitzii, A.muciniphila* and three types of *Bifidobacteria*, discriminates between the presence and absence of food allergy in children with AD (p = 0.001). The fecal microbiome of children with AD and food allergy harbored relatively more *E.coli* and *B.pseudocatenulatum* and less *B.breve*, *B.adolescentis*, *F.prausnitzii* and *A.muciniphila*, compared to children with AD without food allergy. We found no differences in microbial diversity (according to Shannon index) between the children with AD, with and without food allergy.

This is the first pilot study that identifies microbial signatures specific for food allergy in a group of children with AD using 16S rRNA sequencing techniques generating unique sequences, followed by statistical machine learning approaches. Previous studies mainly used culture-based techniques to analyze the intestinal microbiome or used 16S rRNA sequencing techniques, but subsequently simplified the data in the analysis stage by focusing on key groups of species or analyzing the data on family or genus level. However, this approach leads to less detailed information. For example the identification of *B.pseudocatenulatum*, *B.breve* and *B.adolescentis* would not have been possible when analyzing the data on a family level. Furthermore, the elastic net regression model takes group-based species interactions into account. Since interactions between species in the gut microbiome occur, this approach may lead to biologically more reliable results compared to other statistical regression approaches.[22]

Our study demonstrates that children with AD and a food allergy had significantly less *Faecalibacterium prausnitzii* and less *Akkermansia muciniphila* compared to children with AD without a food allergy. *F. prausnitzii* and *A. muciniphila* have been gaining interest more recently because of their immune-modulatory properties and possible role in mucosal tolerance. *F. prausnitzii* is the most common abundant species in the human intestinal microbiome. Its decreased abundance has been associated with several diseases, including

allergic disease and AD.[23-25] *F.prausnitzii* is the main producer of butyrate in the colon, an energy source for colonocytes with important anti-inflammatory effects. It also secretes anti-inflammatory molecules that directly modulate the host immune system, stimulates IL-10 producing regulatory T cells and is involved in the balance between effector and regulatory T cells. [26, 27] *A. muciniphila* is also involved in immunological homeostasis of the gut mucosa and gut barrier function, via an outer membrane protein that stimulates IL-10 production.[28]

Bifidobacteria and *E.coli* have been associated with food allergy and AD in other studies.[29] Less *Bifidobacteria* in the feces of children with a confirmed cow's milk allergy has been reported.[30] Cow's milk allergy was a common food allergy in our study population, so it is possible that our results regarding *Bifidobacterium breve* and *Bifidobacterium adolescentis* are mainly contributed by the cow's milk allergic children. Furthermore, we found increased relative abundance of *Escherichia coli* in the food allergic group. *E. coli* has previously been associated with diagnosis of AD, with increasing numbers of *E. coli* further increasing this risk.[31] The children in our study were all diagnosed with AD with varying severity. However, the higher TARC levels in the food allergic group suggest increased AD severity compared to the non-allergic group. This raises the possibility that the selected biomarkers also correlate with AD severity, which fits with the observation that prevalence of food allergy is higher in children with more severe disease.[32]

All microbial species resulting from our analysis have previously been correlated with atopic disease in other studies. This might raise the question whether we are looking at a food allergy specific microbial profile or a profile that is related to atopic diseases in general, as most of these children have or will develop other comorbidities within the atopic syndrome. Atopic disease has been defined differently in previous studies. In our study, all children were clinically diagnosed with AD and in addition asthma and allergic rhinitis was confirmed or ruled out based on clinical history. Food allergy was diagnosed based on DCPCFC in the majority of patients. Post-hoc analyses showed no significant differences in the presence of other atopic diagnoses between the groups with and without food allergy, suggesting that the identified species are indicating food allergy rather than general atopy.

Our study supports the hypothesis that within children with AD the intestinal microbiome differs between children with and without food allergy. Intestinal microbiota regulate the development of a diverse range of T cell functions, such as Th17, Th1, Th2 and regulatory T cells and modulate innate lymphoid cells.[33, 34] By modifying the response of the gut-associated lymphoid tissues, intestinal microbiota may influence the development of oral tolerance.[35] A recent study in humans showed that delayed colonization with Bacteroidetes is associated with a poorly developed Th1 response, which is important in immune tolerance.[36] It is also possible that disruption of the gut microbiome alters the gut epithelial integrity, thereby increasing the risk of allergic sensitization through direct uptake of allergens.[7] However, the exact mechanisms through which the intestinal microbiome influences food allergy are not elucidated yet. Furthermore, it is not clear whether a change in microbiome precedes or follows the development of food allergy.

Long-term dietary intake affects gut microbiome composition, together with host genetics, age, medication, and general lifestyle.[37] Our study population consumed a Western diet. In addition, established food allergies lead to an elimination diet, where the specific food allergen is excluded from the general diet. We cannot exclude that an elimination diet where one food is excluded from the diet also leads to detectable changes in fecal microbial composition, as has been demonstrated with increased consumption of specific foods. [38] However, in our study one third of children in the non-food allergic group also reported an elimination diet for a specific food because of various reasons. Furthermore, dietary intake varies according to personal preference. Therefore it is unlikely that the observed microbial differences are solely attributed to differences in the consumed diet. Besides a self-reported elimination diet, dietary intake was not further assessed in this study because it is very difficult to assess this accurately.

A limitation of our cross-sectional study is the heterogeneity of the study population. All the children in our study were diagnosed with AD, with varying severity, age and different food allergies, and no healthy controls were included. As expected in children, cow's milk allergy and peanut allergy were the most common food allergies in our study population, so it is possible that our results are influenced by the contribution of these food allergies. It is also plausible that distinct microbes are associated with different food allergies.[29] Due to a lack of statistical power, we were unable to select signature species for specific food allergies. Variables that are known to influence the gut microbiome, such as use of antibiotics, delivery via caesarian-section, or breast feeding, were not assessed in this study.[7] Furthermore, because of the time between the acquisition of the fecal sample and the DBPCFC, transient food allergies could have resulted in the misclassification of some children with cow's milk and hen's egg allergy.

Our findings are based on a study population of children with AD from an academic center. Identifying the microbes that are related to food allergy may help in the development of future interventions. However, future studies are needed to confirm our findings in the community population, preferably with prospective study designs using well-defined patient populations to further explore the potential of fecal microbial colonization patterns associated with specific food allergies in children with AD. Furthermore, future studies should include additional control groups: children with food allergy without AD, children with severe 'extrinsic' AD without food allergy and be of sufficient size to allow for stratification of different food allergies.

Conclusion

In this pilot study, we identified a microbial signature in children with AD that discriminates between absence and presence of food allergy. Future studies are needed to confirm our findings.

Acknowledgment

We acknowledge Ms J Beutler and Ms A Ouwens for their technical assistance.

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Supplementary figures

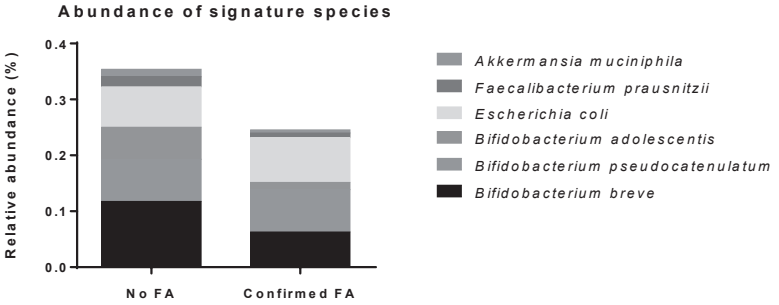

Figure S1 Relative abundance of the six signature species in children with AD, without and with food allergy

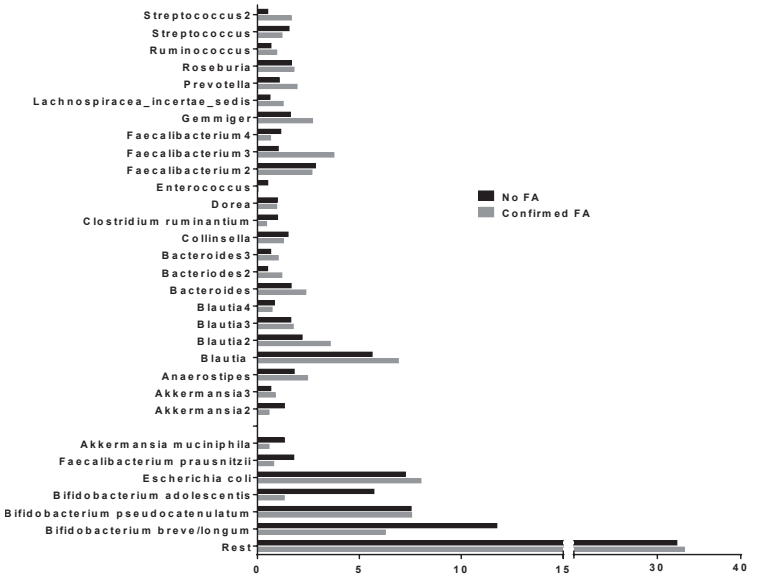

Figure S2 Distribution of 30 most abundant microbial species in children with AD, without and with food allergy

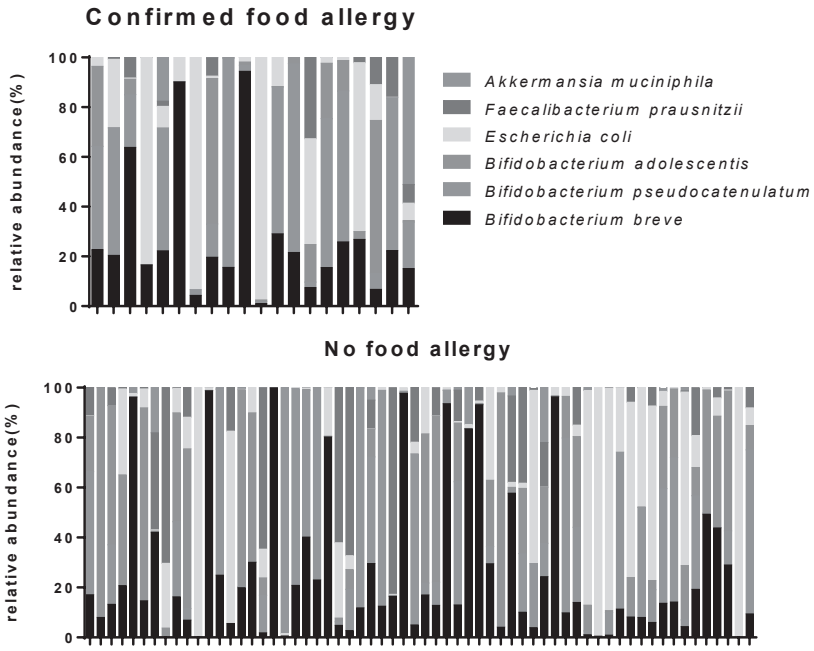

Figure S3 Distribution of six signature species in individual children with AD, without and with food allergy

6.

Effectiveness of alpine climate treatment for children with difficult to treat atopic dermatitis: results of a pragmatic randomized controlled trial (DAVOS trial)

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Clinical and Experimental Allergy, in press

Abstract

Background

Alpine climate treatment has historically been used in Europe to treat atopic dermatitis (AD), but no randomized trials have been conducted to provide evidence for its effectiveness.

Objective

To investigate the long-term effectiveness of alpine climate treatment for children with difficult to treat AD.

Materials & Methods

A pragmatic, open, randomized controlled trial was conducted. Children diagnosed with AD that was considered difficult to treat, aged between 8 and 18 years and willing to be treated in Switzerland were randomized to a six week personalized integrative multidisciplinary treatment period in a clinical setting in the alpine climate (Switzerland) or an outpatient setting in moderate maritime climate (Netherlands). Study assessments were conducted at the Wilhelmina Children's Hospital; an electronic portal was used for the collection of questionnaire data.

Primary outcomes were disease activity (SAEASI), quality of life (CDLQI), and catastrophizing thoughts (JUCKKI/JU) six months after intervention. Other assessments were immediately and six weeks after intervention. Subgroup analyses concerned asthma-related outcomes. Children were randomly assigned to either the intervention or control group using a covariate adaptive randomization method, taking age and asthma diagnosis into account. Children, parents, and health care professionals involved in treatment were not blind to group assignment. Data were analyzed according to intention-to-treat with linear mixed effects models for continuous outcomes. The trial is registered at Current Controlled Trials ISCRTN88136485.

Results

Between September 14th 2010 and September 30th 2014, 88 children were enrolled in the trial, 84 children were randomized (41 assigned to intervention, 43 to control) of whom 77 completed the intervention (38/41 (93%) intervention, 39/43 (91%) control) and 74 completed follow-up (38/41 (93%) intervention, 36/43 (84%) control). Six months after intervention there were no significant differences between the groups on disease activity (SAEASI mean difference -3.4 (95%CI -8.5 to 1.7)), quality of life (CDLQI mean difference -0.3 (95%CI -2.0 to 1.4)), and catastrophizing thoughts (JUCCKI/JU subscale mean difference -0.7 (95%CI -1.4 to -0.0)). Immediately and six weeks after intervention,

disease activity and quality of life were significantly different in favor of alpine climate treatment. Mean differences on SAEASI were -10.1 (95%CI -14.5 to -5.8) and -8.4 (95%CI -12.2 to -4.6) and on CDLQI -1.9 (95%CI -3.3 to -0.5) and -1.5 (95%CI -2.8 to -0.3) immediately and six weeks after the intervention, respectively. There were no long-term differences on asthma related outcomes. Five serious adverse events occurred during the study period, which were not thought to be related to the treatment.

Conclusions & Clinical relevance

For children with difficult to treat AD, there was no additional long-term benefit of alpine climate treatment, in contrast to the short term, compared to an outpatient treatment program in moderate maritime climate, both using a personalized integrative multidisciplinary treatment approach.

Funding

European Allergy and Asthma Center Davos, Merem Dutch Asthma Center Davos, patient support group ´Vereniging Nederland Davos`.

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by itchy lesions and subsequent exacerbations and remissions. Disease incidence has increased the last decades.[1] Currently, approximately 10% to 20% of children in Western Europe are affected.[1] The majority is diagnosed with mild AD (67%), others have moderate (26%) or severe AD (7%).[2] Approximately 10% of children with moderate to severe AD (3% of all affected children) do not respond well to regular treatment and are considered difficult to treat.[3] These children are unable to gain sufficient disease control and often have an extensive treatment history, with frequent hospitalizations and use of systemic immunosuppressive treatment. Furthermore they often have mental health problems such as anxiety and depression.[4] AD has an adverse effect on the quality of life of affected children and their families.[5] Increasing disease severity further reduces reported quality of life.[6] Furthermore, AD severity is directly related to increased prevalence of asthma, allergic rhinitis or food allergies.[7]

Multidisciplinary treatment programs, involving dermatologists, pediatric allergists, dermatology nurses and pediatric psychologists, have been developed for children who do not respond well to regular treatment and often result in clinical improvement.[8, 9] The common elements included in these programs are education, treatment management and psychological or behavioral interventions aimed at coping with disease. In addition to improving disease activity, these programs address itching and scratching, sleep disruption, challenges in disease management including adherence to treatment, psychosocial problems and education of children and their families. However, these programs are mostly geared towards younger children.[9]

Climate change to seaside or mountain resorts for the treatment of allergic diseases in children has been studied before.[10,11] Alpine climate treatment has been used for decades as a treatment option for asthma and AD in Europe.[10] Children are admitted to specialized clinics for a period of 4 weeks to 3 months, while they are treated with anti-inflammatory medication within a personalized integrative multidisciplinary approach involving simultaneous treatment by dermatologists, allergists, specialized nurses, pediatric psychologists, physiotherapists and dieticians.[10] The alpine climate environment is characterized by a reduced exposure to aeroallergens such as pollen and an absence of house dust mite, a decreased level of pollution and an increased exposure to UV radiation.[11] Observational studies have shown that alpine climate treatment improves disease activity in the long-term.[10] However, the effectiveness of alpine climate treatment has not been established in randomized trials.

In the DAVOS trial, we compare the effectiveness of inpatient alpine climate treatment with an outpatient treatment program in moderate maritime climate using a personalized integrative multidisciplinary treatment approach. The objective of this pragmatic randomized controlled trial is to investigate the long-term effectiveness of alpine climate treatment for children and adolescents with difficult to treat AD.

Methods

Study design

A pragmatic, open, randomized controlled trial was conducted in which inpatient treatment in a Dutch alpine climate clinic located at 1560 meters altitude in Switzerland (Merem Dutch Asthma Center Davos, Davos) was compared with an outpatient treatment program in moderate maritime climate in the Netherlands (Wilhelmina Children's Hospital, Utrecht) both using a personalized, integrative, multidisciplinary treatment approach. Study procedures were reviewed and approved by the institutional review board of the University Medical Center Utrecht, the Netherlands (09-192/K). The trial is registered at Current Controlled Trials ISRCTN88136485. The detailed study protocol has been published elsewhere.[12]

Participants

Dutch children and adolescents with difficult to treat AD were eligible for participation in the trial. We defined difficult to treat as use of at least a class 3 topical corticosteroid and not being able to step down, or current use of systemic immunosuppressive treatment, or repeated treatment with potent topical corticosteroids or systemic immunosuppressive treatment, or a history of use of systemic treatment, or a significant impact of AD on the child's or the families quality of life, or seemingly unresponsive to conventional therapy according to current guidelines. Dermatologists and pediatricians referred potential study participants to the outpatient clinic of the Wilhelmina Children's Hospital where they were assessed for eligibility. Inclusion criteria were: (1) diagnosis of moderate/severe AD; (2) age between 8 and 18 years; (3) fluent in the Dutch language; (4) internet access at home; (5) able to use the Digital Eczema Center and (6) willing and able to stay in Davos (Switzerland) for 6 weeks. The Digital Eczema Center is a digital patient portal with possibilities for e-consulting and online data collection with questionnaires.[13] All study participants provided written informed consent to participate in the trial. For children younger than 12 years both parents/ guardians were asked to sign, for adolescents aged 12 to 16 years both the adolescent and both parents/ guardians were asked to sign, adolescents aged 16 years or older were able to provide informed consent by themselves, in accordance with Dutch law.

Randomization

Study participants were randomly assigned 1:1 to either the intervention or control group. An external, independent data manager performed a covariate adaptive randomization method with a custom made program in SAS (statistical analysis system) to generate the randomization sequence.[14] Covariate adaptive randomization controls for imbalance between important covariates, which may result in slightly unequal groups. Consecutive groups of 8 included children were randomized, using the median age within the group as a cut-off and taking presence or absence of asthma diagnosis into account, as well as previous randomization results. Randomization results were provided to the project coordinator (FR) or the pediatric

psychologist (WZ), who informed the participants by telephone. Treatment allocation was concealed. Children, parents, and health care professionals involved in treatment were not blinded to group assignment because this was not possible.

Procedures

Both study arms used a personalized, integrative, multidisciplinary treatment approach. Different health professionals work simultaneously and with equal contributions on defined personalized treatment goals using a treatment approach involving all the relevant aspects of the child. Before randomization, a personalized treatment plan was developed for each study participant with individual treatment goals and strategies. The multidisciplinary teams consisted of a pediatric dermatologist, a pediatric allergist (control) or pediatrician trained in atopy (intervention), a pediatric psychologist, a dermatology nurse, a physiotherapist and a research nurse. The pediatric dermatologist in the control team supervised AD treatment in both study arms. A case manager assisted in the planning of study assessments and motivated the participants to attend.

There were five study assessments: inclusion in the study (T-1), immediately before (T0) and after (T1) intervention and follow-up assessments 6 weeks (T2) and 6 months (T3) after the end of the intervention. Groups of four children or adolescents started treatment simultaneously; therefore some children had to wait longer than others between T-1 and start of treatment. All study assessments were conducted at the Wilhelmina Children's Hospital. The treatment period was 6 weeks in both study arms, consisting of continuous inpatient treatment in the intervention group or 6 weekly visits to the outpatient clinic in the control group. Both study arms were protocolled to ensure consistency of treatment over time. During the follow-up period, there was no contact between the research team and study participants apart from the planned study assessments. However, in case of exacerbations or other problems, additional consultations were scheduled and recorded.

Intervention and control condition

The treatment program in Davos consisted of several fixed elements.[12] The children and adolescents attended a school within the clinic. Every day, a group physical activity was organized under supervision of a physiotherapist. Weekly individual treatment sessions were scheduled with the pediatrician, the psychologist alternating with the psychomotor therapist, and the physiotherapist (if needed). The nurse monitored correct application of topical treatment in individual sessions with each child twice daily. In these sessions health education was provided with a varying weekly theme and an AD knowledge game was played. Children or adolescents and their parents were separated during the six week treatment period, but parents usually visited once for three to four days. In addition, the parents travelled with their children to the clinic and picked them up after the end of intervention.

During the treatment program in Utrecht the children and adolescents were seen almost on a weekly basis in the outpatient clinic. They had 5 consultations with the dermatologist,

the dermatology nurse, 4 consultations with the pediatrician-allergist, and 3 consultations with the psychologist. Children and adolescents participated in a workshop in which they demonstrated how they apply topical treatment and were educated by the dermatology nurse. They also played an AD knowledge game. In the third week a group medical appointment was scheduled for the children and adolescents and their parents separately, about coping with AD and compliance. It is a substitute for an individual appointment with a clinician during which the participants discuss their personal experiences and advise and support each other.

Outcome measures

Primary outcomes were disease activity assessed with the Self-Administered Eczema Area and Severity Index (SAEASI)[15, 16], health-related quality of life assessed with the Children's Dermatology Life Quality Index (CDLQI)[17] and the subscale catastrophizing thoughts about itch assessed with the JUCCKI questionnaire (children aged 8-12 years) or the JUCKJU questionnaire (adolescents aged 13-18 years).[18] The SAEASI and CDLQI were chosen because disease activity and health-related quality of life are important outcome domains for AD. Using either domain has also been recommended by the recently published HOME initiative (Harmonizing Outcome Measures for Eczema).[19] We found a good correlation between SAEASI and EASI in our study population (r=0.66), which is in line with previous studies. The JUCKKI/JU measures catastrophizing thoughts about itch, which children with AD consider their most burdensome complaint. The timing of the primary endpoint was chosen at six months post-intervention because long-term clinical effects were thought necessary to justify the costs and the impact of alpine climate treatment.

Pre-specified subgroup analyses with asthma-related outcomes included: ACQ (Asthma Control Questionnaire), PAQLQ (Pediatric Asthma Quality of Life Questionnaire), FeNO (Fraction of exhaled Nitric Oxide), BHR (Bronchial HyperResponsiveness) with a metacholine bronchial challenge and spirometric variables FEV1 (Forced Expiratory Volume in 1 second) pre and post bronchodilator and MEF50 (Maximal Expiratory Flow at 50%). All children were examined by a pediatrician or pediatric allergist for symptoms of asthma, allergic rhinitis and food allergy. Food allergy was defined as a positive double blind placebo-controlled food challenge (DBPCFC) or convincing clinical history (a reported Type I allergic reaction with acute symptoms within 2 hours after ingestion of the food) in combination with sensitization to the specific food allergen.

Secondary outcomes were EASI (Eczema Area and Severity Index), TARC (thymus and activation regulated chemokine), pharmacological treatment, itch, nightly complaints of itch, sleep problems, BMI (body mass index), blood eosinophils, total IgE, VO2 peak/kg (maximal volume of oxygen uptake per kg), JUCKKI/JU (subscale coping), COPEKI/JU (coping with disease and itching cognitions), self-perception profile, state-trait anxiety and child autonomy. Parental secondary outcomes were disease-specific quality of life, state-trait anxiety and parenting stress.

Statistical analysis

We previously calculated that a sample size of 72 children was needed to detect a difference of 5 points on the catastrophizing thoughts subscale of the JUCKKI/JU questionnaire (assumed SD 7.6) or 10 points in SAEASI score (assumed SD 15), with 80% power and 5% significance (two-sided).[20] These differences were based on a study by Staab et al. in which long-term effectiveness of a multidisciplinary six week educational program was assessed in children and adolescents with moderate to severe AD.[20] We estimated a difference of 10 points to be clinically relevant, derived from the MCID of SCORAD and the correlation between SCORAD and SAEASI.[16, 21] To examine differences between the intervention and control group on the continuous primary and secondary outcomes, linear mixed-effects regression models were used. Missing values were not imputed. Baseline measurement was preferably T0, however when absent according to the study protocol T-1 was used. Fixed effects were included for outcomes at T0 (baseline correction), treatment group, study assessment time in weeks (6, 13 and 34 weeks corresponding to T1, T2, T3) and the interaction between treatment and assessment time. A random intercept and random slope for time per individual were included in order to account for correlation of measurements within children. Effect size Cohen's d was estimated to quantify the difference between groups at all study assessments. A p-value of 0.0167 was considered significant (after Bonferroni correction).

The JUCKKI/JU was analyzed without baseline correction, because it was assessed at fewer moments (contrary to the published protocol where T2 is falsely indicated as a study assessment for this outcome). The model used measurements from T0, T1 and T3 as outcomes, including fixed effects for treatment, assessment time in weeks, and the interaction between treatment and assessment time, and a random intercept. Data relating to asthma outcomes were analyzed separately for the subgroup of children with doctor's diagnosed asthma. Data was analyzed according to the intention-to-treat principle using IBM SPSS Statistics for Windows version 22.

Results

Children were assessed for eligibility at the outpatient clinic of the Wilhelmina Children's Hospital. Children not meeting inclusion criteria had mild AD (n=57), did not meet the age criterion (n=6), expected homesickness (n=13) or had limited Dutch language proficiency (n=2). Between September 14th 2010 and September 30th 2014, 88 children were enrolled in the trial (Figure 1). Seventy-seven children completed the intervention of whom 74 completed follow-up (12% drop-out rate). The last follow-up assessment was June 16th, 2015. Drop-out before start of the intervention was similar in both groups but different during follow-up. There were no differences in baseline characteristics between the children who dropped out and the children who completed the study (data not shown). In addition to the planned study assessments during follow-up, there were additional consultations for 10 children in the intervention group and 10 children in the control group (Supplementary table S1).

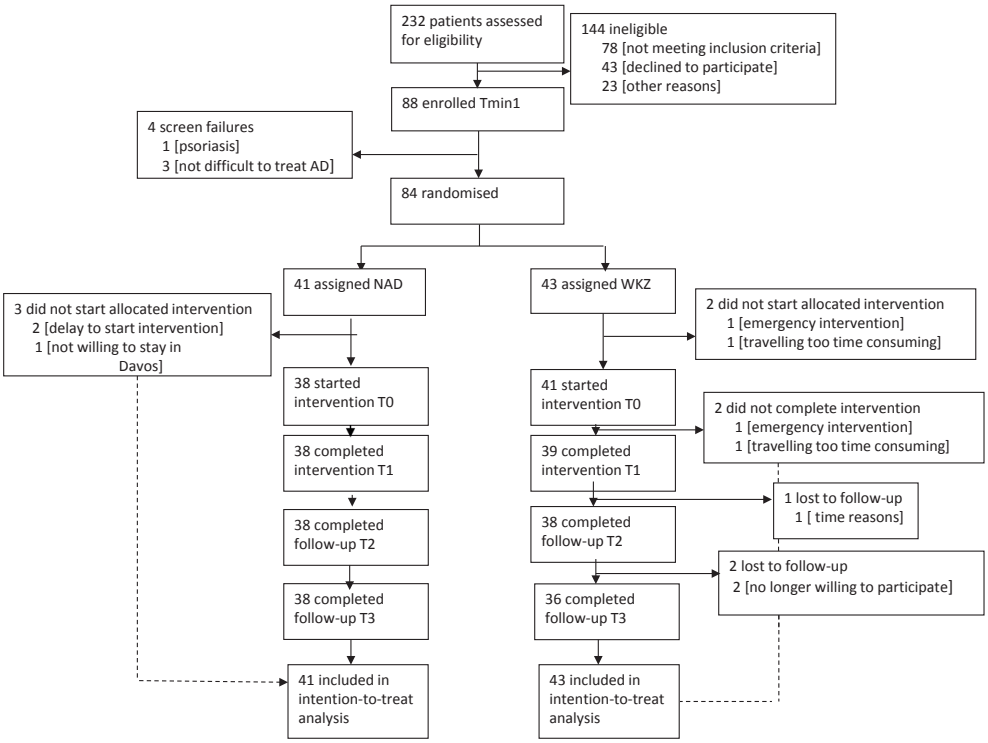

Figure 1 Trial profile

The exact time between study assessments varied because of rescheduling due to illness, holidays, or initial no-show. The mean time between study inclusion (T-1) and baseline (T0) was 19 weeks [SD 22.0], between baseline (T0) and end of intervention (T1) 6 weeks [SD 0.8], between baseline (T0) and first follow-up (T2) 13 weeks [SD 1.5], between baseline (T0) and second follow-up (T3) 34 weeks [SD 2.5]. At trial inclusion (T-1), the intervention and control group were comparable on demographic and disease characteristics (Table 1 and Table S2).

For 12 children, change of treatment (more potent topical corticosteroids or start of systemic immunosuppressives) was indicated by the pediatric dermatologist after inclusion in the study but before start of the intervention at T0, due to unacceptable disease severity. In this study population of children with difficult to treat AD, 72 (86%) were diagnosed with asthma of which 11 (13%) were diagnosed during the intervention period. Allergic rhinitis was diagnosed in 73 children (87%), with 60 (72%) children reporting persistent (year round) symptoms. Food allergy was diagnosed in 52 children (66%).

At the primary endpoint T3 (six months after the intervention), there were no statistically significant differences between the groups on the primary outcomes (Table 2). Immediately after the intervention (T1) and six weeks after the intervention (T2), there were statistically significant differences between the groups regarding disease activity and quality of life (Table 2). No differences were observed on the JUCKKI/JU subscale catastrophizing (Table 2).

Table 1 Baseline characteristics of study participants (Tmin1)

	Intervention group n=41	**Control group n=43**
Female	18 (44%)	21 (49%)
Age (years)	12.6 (2.5)	12.4 (2.4)
Aged 8 to 12 years	21 (51%)	21 (48%)
Aged 13 to 18 years	20 (49%)	22 (51%)
Age of AD onset <6 months	35 (85%)	37 (86%)
History of systemic treatment for AD (UV therapy, cyclosporine, prednisone)	26 (63%)	26 (60%)
Current use of potent or very potent topical corticosteroids*	37 (90%)	40 (93%)
Current use of cyclosporine / prednisone	2 (5%)	8 (19%)
SA-EASI (0-96)	31.2 (17.0)	28.3 (16.8)
BSA (%)	56 (21)	61 (21)
Diagnosis of asthma	35 (85%)	37 (86%)
Diagnosis of allergic rhinitis	37 (90%)	36 (84%)
Persistent symptoms of allergic rhinitis	33 (81%)	27 (63%)
Diagnosis of food allergy**	26/38 (68%)	26/41 (63%)

Data are mean (SD) or number (%) SAEASI=Self-Administered Eczema Area and Severity Index scored by caregiver. BSA=affected body surface area. AD=atopic dermatitis. *UK potency system used **food allergy was only diagnosed in children who started the intervention.

The secondary outcomes can be found in the supplementary tables S3 to S6. There were no significant long-term differences between the groups on any of the secondary outcomes. Immediately after the intervention and in the short term, there were differences in favor of alpine climate treatment on several clinical secondary outcomes.

In the subgroup of children diagnosed with asthma, there were no relevant significant differences between the groups concerning asthma related outcomes, apart from a significant difference in FeNO -14.1 (95%CI -24.3 to -3.9; p=0.007) immediately after the intervention (T1) in favor of the intervention group. Asthma varied in severity, but was mild to moderate in most cases. At baseline, asthma was not well controlled in the intervention group but improved during intervention, whereas the control group remained stable throughout the study (ACQ < 1.25).[22] There was no difference in bronchial hyperresponsiveness to metacholine (Table 3). Missing data regarding metacholine challenges occurred because of instable asthma, inappropriate technique, study planning or continuation of long-acting bronchodilators.

During the study period five serious adverse events occurred. Two children in the intervention group experienced asthma exacerbations during the first study assessment T-1 related to the metacholine challenge. During the follow-up period, one child was hospitalized for exacerbations of AD and asthma direct after study assessment T2 (control group) and one child was diagnosed with appendicitis and hospitalized between T2 and T3 (intervention group). Another child from the control group was hospitalized for AD during the intervention and subsequently dropped out of the study.

Table 2 Primary endpoints – disease activity (SAEASI), health-related quality of life (CDLQI), and catastrophizing thoughts about itch (JUCCKI/JU)

Primary endpoints	**Intervention group**		**Control group**		**Primary analysis**		
SAEASI by caregiver (range 0-96)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**p**	**Effect size (Cohen's d)**
Baseline (T0)	38	28.2 (19.9)	37	28.3 (20.5)			
End of intervention (T1)	37	3.0 (4.2)	35	14.5 (15.3)	-10.1 (-14.5 to -5.8)	0.000	0.6
First follow-up assessment (T2)	36	8.5 (8.11)	30	14.4 (12.5)	-8.4 (-12.2 to -4.6)	0.000	0.5
End of follow-up (T3)	37	11.9 (9.5)	32	15.1 (12.7)	-3.4 (-8.5 to 1.7)	0.185	0.2
CDLQI (range 0-30)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**p**	**Effect size (Cohen's d)**
Baseline (T0)	35	8.7 (5.9)	40	7.9 (5.7)			
End of intervention (T1)	34	2.9 (3.3)	31	4.8 (4.2)	-1.9 (-3.3 to -0.5)	0.008	0.4
First follow-up assessment (T2)	38	4.7 (4.3)	32	5.1 (4.6)	1.5 (-2.8 to -0.3)	0.019	0.33
End of follow-up (T3)	38	4.4 (4.3)	33	4.8 (3.7)	-0.3 (-2.0 to 1.4)	0.707	0.06
JUCKKI/JU Catastrophizing thoughts (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**p**	**Effect size (Cohen's d)**
Baseline (T0)	38	2.0 (1.1)	40	1.9 (1.0)	-0.4 (-1.0 to 0.2)	0.186	0.39
End of intervention (T1)	37	1.0 (0.7)	32	1.1 (0.9)	-0.5 (-1.2 to 0.1)	0.111	0.49
End of follow-up (T3)	38	1.1 (0.7)	31	1.2 (1.0)	-0.7 (-1.4 to -0.0)	0.047	0.66

Numbers of completed questionnaires vary due to missing data. JUCKKI/JU scores are the total scale scores divided by the number of items in each scale.

Table 3 Asthma related outcomes

Secondary endpoint	Intervention group		Control group		Statistical analysis	
ACQ 6Q	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**p**
Baseline (T0)	35	1.2 (1.1)	37	0.97 (1.03)		
End of intervention (T1)	29	0.52 (0.53)	26	0.84 (1.15)	-0.28 (-0.86 – 0.30)	0.345
First follow-up (T2)	32	0.92 (0.83)	27	0.85 (1.06)	-0.20 (-0.65 to 0.25)	0.370
End of follow-up (T3)	32	0.75 (0.74)	29	0.66 (0. 71)	0.02 (-0.25 – 0.29)	0.869
PAQLQ	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**p**
Baseline (T0)	31	5.9 (0.98)	34	6.1 (1.0)		
End of intervention (T1)	28	6.4 (0.6)	26	6.4 (0.8)	0.15 (-0.11 to 0.41)	0.258
First follow-up (T2)	32	6.2 (0.9)	27	6.3 (1.1)	0.09 (-0.12 to 0.29)	0.413
End of follow-up (T3)	32	6.3 (0.8)	29	6.4 (0.7)	-0.10 (-0.45 to 0.24)	0.553
FeNO	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**p**
Baseline (T0)	29	45.5 (29.3)	34	41.3 (37.7)		
End of intervention (T1)	31	24.6 (18.8)	34	42.7 (34.6)	-14.1 (-24.3 to -3.9)	0.007
First follow-up (T2)	31	43.9 (32.9)	32	46.6 (37.3)	-8.6 (-16.7 to -0.59)	0.036

End of follow-up (T3)	30	41.8 (25.0)	26	34.7 (27.9)	7.8 (-6.9 to 22.5)	0.292
Spirometry FEV1pre pp (%)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**P**
Baseline (T0)	29	87.0 (14.1)	34	94.0 (8.9)		
End of intervention (T1)	32	92.8 (10.5)	34	94.0 (11.4)	4.32 (0.52 to 8.12)	0.027
First follow-up (T2)	32	90.8 (11.5)	33	91.3 (11.6)	3.79 (0.37 to 7.2)	0.031
End of follow-up (T3)	31	88.9 (12.6)	26	93.8 (11.4)	2.21 (-1.98 to 6.4)	0.294
Spirometry FEV1 post pp (%)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**P**
Baseline (T0)	29	92.7 (11.8)	34	98.1 (8.76)		
End of intervention (T1)	32	96.1 (8.7)	34	98.8 (10.5)	2.28 (-0.81 to 5.38)	0.145
First follow-up (T2)	32	95.2 (9.8)	33	96.9 (11.1)	2.63 (-0.13 to 5.40)	0.061
End of follow-up (T3)	31	94.6 (11.3)	26	97.6 (11.3)	3.68 (-0.48 to -6.88)	0.025
Spirometry MEF50pre (L/s)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI) corrected for baseline**	**P**
Baseline (T0)	29	3.0 (0.98)	34	3.32 (1.12)		
End of intervention (T1)	32	3.35 (0.89)	34	3.37 (1.08)	0.26 (-0.07 to 0.59)	0.119
First follow-up (T2)	32	3.32 (0.97)	33	3.20 (1.26)	0.24 (-0.07 to 0.55)	0.131
End of follow-up (T3)	31	3.26 (0.97)	26	3.40 (1.04)	0.172 (-0.21 to 0.56)	0.375

BHR PD20 (µmol)	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**Estimated difference (95%CI) corrected for baseline***	**P**
Baseline (T-1)	21	0.38 (0.79)	29	0.28 (0.60)		
End of follow-up (T3)	18	0.28 (0.75)	19	0.07 (0.43)	0.05 (-0.27 to 0.36)	0.757

Numbers of completed questionnaires vary due to missing data. *Baseline is T-1. Asthma control questionnaire (ACQ), pediatric asthma quality of life questionnaire (PAQLQ), fraction of exhaled NO (FeNO), forced expiratory volume in 1 second (FEV1), maximal expiratory flow (MEF50pre), bronchial hyper responsiveness (BHR). Pre: before the use of bronchodilator, post: after the use of bronchodilator.

Discussion

This is the first randomized trial concerning the long-term effectiveness of alpine climate treatment for children or adolescents with difficult to treat AD (8-18 years). Other RCTs have assessed the effectiveness of climate change for treatment of allergic diseases.[23, 24] Six months after alpine climate treatment, this study demonstrated no differences in the primary outcomes disease activity, health-related quality of life, and catastrophizing thoughts about itch between children treated in the alpine climate (inpatient setting) or in moderate maritime climate (outpatient setting). This is in contrast to the immediate and short-term findings in favor of alpine climate treatment.

After six months follow-up, there were no significant differences between the groups. We hypothesize that this was caused by the personalized integrative multidisciplinary treatment the children received. It has been shown previously that multidisciplinary treatment programs result in sustained improved disease activity.[25] The use of structured education programs, behavioral interventions to improve coping with itch, the use of written action plans and the involvement of a specialized dermatology nurse have been shown to improve disease control.[20, 26, 27] The slightly better improvement of catastrophizing thoughts in the intervention group may be due to their significant clinical improvement, during which the children have experienced that it is possible to get control of their AD. The personalized, integrative treatment program that was used in this trial combined all of these elements. It is not likely that an increased duration of the intervention would have resulted in differences between the groups six months after the intervention, since optimal results were already observed after six weeks. The primary time point was chosen six months after intervention, because alpine climate treatment is a temporary treatment and patients have to return to their own environment after it has ended. To justify the costs and impact of alpine climate treatment, long-term effectiveness was thought more important as endpoint than short-term.

Immediately and six weeks after intervention, there were significant differences in terms of disease activity and health-related quality of life in favor of the alpine climate treatment group as well as in secondary outcomes. A significant reduction in eosinophil counts and FeNO was observed in the intervention group suggesting reduced inflammation. Decreased eosinophilia after alpine climate treatment has been reported before, mainly in asthma studies, and is possibly related with reduced allergen exposure.[28-30] TARC also decreased in both groups, which is in line with the observed reduction in disease activity. Besides the differences in climate, the clinical setting during alpine climate treatment guarantees maximal compliance with pharmacological treatment through nurse supervision of topical corticosteroid use. Compared to the outpatient program in the moderate maritime climate, alpine climate treatment was a more intense inpatient treatment, in which parents and children are separated during the intervention period and the children have intensive contact with peers. These elements may have contributed to the greater improvement in disease activity.

The initial significant difference in clinical improvement between the intervention group and control group was gradually lost during the follow-up period. This relapse could be explained by several factors. Alpine climate treatment combines exposure to a different climate with increased medical supervision in an inpatient setting. Apart from the change in climate, children have to apply skills they learned at the clinic in their home environment with less supervision. This transition might be difficult for children. Children and parents in the control group already learned to implement the newly acquired skills directly in their daily routine during the six week program and therefore it may be easier for them to retain these skills. Furthermore, there was maximal clinical improvement in the intervention group, which only leaves room for deterioration during follow-up. Another trial concerning climate treatment was designed with a follow-up period of three months.[23] Children with moderate to severe AD were randomized to a four week stay (with a structured day program) in subtropical climate or stayed at home in a subarctic/temperate climate. A similar improvement was described in disease activity and quality of life compared to our study, with a statistically significant effect in favor of the subtropical group after three months follow-up. However, the subtropical climate group showed a similar deteriorating trend during follow-up as our intervention group, suggesting that it is difficult to retain a long-term effect after climate treatment.

Our subgroup analyses concerning asthma-related outcomes indicated no significant differences between the groups concerning asthma control or asthma related quality of life. In our study population, asthma varied in severity, but was mild to moderate in most cases. Several children were diagnosed with asthma during the intervention period. Immediately and six weeks after intervention we found a significant reduction in FeNO in the intervention group, which is consistent with previous observational studies.[31] FEV1 in both groups was within normal range throughout the study period. Based on all these findings, we could not support an additional benefit of alpine climate treatment for children with mild to moderate asthma, consistent with current guidelines.[32] The subgroup analyses were specified in advance in the study protocol, but this trial was not specifically powered for asthma related outcomes. Other subgroup analyses were not specified in advance in the study protocol.

The main limitation of our trial is its many outcome measures. Clearly indicating the primary and secondary outcomes, pre-specifying the analyses in advance and correcting for multiple testing reduces chance findings. The primary outcome measures disease activity and quality of life have recently been endorsed by an expert panel to be used in AD trials and validated instruments were used to assess these outcomes.[19] A second limitation is that none of the health professionals assessing study outcomes were blinded and neither were the study participants; this was not possible. This might have influenced our findings, especially the questionnaire data. However, the results of the blinded assessment of the blood samples were in line with the unblinded assessments. Another limitation is that the questionnaire used to assess catastrophizing about itch was officially translated to Dutch but was not validated in the Netherlands. However, none of these limitations are likely to have led to a different conclusion of our findings. Furthermore, because this study was designed

as a pragmatic trial, it is not possible to determine what contributed most to the observed outcomes.[33] Only an explanatory trial comparing inpatient treatment in alpine climate and maritime climate could determine the effect of the climate.

Previous observational studies have described alpine climate treatment as an effective treatment for AD.[10] This is confirmed in this study. However, in both study arms clinically relevant long-term improvement in disease control and health-related quality of life was observed. Immediately and six weeks after intervention, this study found significant differences in terms of disease activity and health-related quality of life in favor of the alpine climate treatment group as well as in the other clinical secondary outcomes, suggesting that alpine climate treatment is a treatment option when immediate dramatic results are required. However it is likely that inpatient treatment in any hospital or the use of systemic immunosuppressives also results in significant short-term improvements.

In conclusion, we found no additional long-term benefit of alpine climate treatment compared to outpatient treatment in a moderate maritime climate for children with difficult to treat AD. This is in contrast to the short-term findings. In this trial using a personalized, integrative, multidisciplinary treatment approach, children in both arms improved in terms of AD disease activity, health-related quality of life and catastrophizing thoughts about AD.

Acknowledgments

We gratefully thank all children and their parents for participating in the study. We thank the Dutch patient support group VMCE for endorsing the study. We thank A. Beelen for critical reading of the manuscript. We want to acknowledge dermatologists A.H van der Willigen, A.A.J. Boonstoppel-Routheut, A.Y. Goedkoop, A.H.Preesman, C.B. Vos, J.C.R.M. Veldboer, W.A.M. Blom, Th.W.van den Akker, G.N.Relyveld, H.F.C. Rulo, J.M.Oldhoff, J.R. Wikler, J.Schuur, K.Roegies, H.C.J. Liberton, M.M.Hulshof, M.C.A. Polderman, R.G.L. Nellen, J.U. Ostertag, P.M.J.H. Kemperman, R.H.Houwing, R.I. Siphanto, R.L. van Leeuwen, R.L.P.Lijnen, M. Tijssen, W.G. Kamphof and Y.A. Faber, pediatricians J.C.D. Brevoord, E. Dompeling, A.J. Sprij, M. Gorissen, N. Arends, H.Kiezebrink-Lindenhovius, F.Croes, E.R.V.M.Rikkers-Mutsaerts, A.M.Vlieger, M.H. Biezeveld, B.L.Rottier, K. Aleman and general physicians F. Laven and I. den Boer for enabling patients to participate in our study by referring them to our hospital. This trial was supported by unrestricted grants from the European Allergy and Asthma Center Davos, the Merem Dutch Asthma Center Davos and the patient support group ´Vereniging Nederland Davos`.

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Supplementary tables

Table S1 Additional consultations in the intervention and control group during the total follow-up period (T1 to T3)

Reason for consultation	Number of additional consultations (n)	Number of patients intervention group	Number of patients control group	Number of additional e-consultations (n)	Number of patients intervention group	Number of patients control group	Number of additional telephone consultations (n)	Number of patients intervention group	Number of patients control group
AD	12	6	5	15	6	5	4	3	
AD treatment				9	4	2	4	2	2
AA	2	2	0						
AR	2	1	1				2	1	1
Mental health	1	1	0	1	1	0	1	0	1
Other	12	2	4	19	8	8	11	4	2
Total n	29	10	10	44	13	11	21	10	6

Multiple consultations per patient may be deduced by the number of patients stated per reason for the additional consultation.
AD= Atopic Dermatitis, AA = Allergic Asthma, AR = Allergic Rhinitis

Table S2 Extension of baseline characteristics

	Intervention group (n = 41)	**Control group** (n = 43)
Asthma diagnosed during study, n (%)	7 (17%)	4 (9%)
Time between study inclusion T-1 and start intervention T0, mean weeks (SD)	28.2 (28.5)	10.7 (6.9)
BMI (kg/m²)	19.2 (3.2)	21.2 (5.4)
Previously treated in Davos, n(%)	2 (5%)	1 (2%)
Child's level of education, n (%)		
Special primary education	1 (2%)	4 (9%)
Primary education	15 (37%)	16 (37%)
Practical education	1 (2%)	-
Lower general secondary education	8 (20%)	15 (35%)
Intermediate vocational education	-	1 (2%)
Higher general secondary education	10 (24%)	4 (9%)
Pre-university education	6 (15%)	3 (7%)
Child's living situation, n (%)		
Father and mother	32 (80%)	28 (65%)
Mother only	6 (15%)	13 (30%)
Father only	1 (3%)	1 (2%)
Father and mother alternately	1 (3%)	1 (2%)
Number of children in the family, n (%)		
1	4 (10%)	4 (9%)
2	24 (60%)	22 (51%)
3	7 (18%)	10 (23%)
4	5 (13%)	7 (16%)
Ethnicity mother, n (%)		
Dutch	35 (85%)	32 (74%)
Surinam	2 (5%)	3 (7%)
Antillean or Aruban	1 (2%)	2 (5%)
Moroccan	-	3 (7%)
Other	2 (5%)	3 (7%)

Ethnicity father, n (%)		
Dutch	36 (88%)	34 (79%)
Surinam	2 (5%)	-
Antillean or Aruban	1 (2%)	1 (2%)
Moroccan	-	3 (7%)
Other	2 (5%)	5 (12%)
Highest level of education mother, n (%)		
Higher vocational education/university	15 (39%)	11 (26%)
Vocational education	15 (3%)	16 (38%)
Secondary education	8 (21%)	12 (29%)
Primary education	-	3 (7%)
Highest level of education father, n (%)		
Higher vocational education/university	17 (47%)	14 (38%)
Vocational education	12 (33%)	9 (26%)
Secondary education	7 (20%)	13 (38%)
Primary education	-	1 (3%)
Employment mother, n (%)		
Fulltime work	3 (8%)	3 (7%)
Part-time work	22 (59%)	17 (40%)
Self-employed	5 (14%)	4 (10%)
Disabled	3 (8%)	2 (5%)
Unemployed	-	3 (7%)
Housewife	4 (11%)	13 (31%)
Employment father, n (%)		
Fulltime work	19 (53%)	24 (62%)
Part-time work	4 (11%)	1 (3%)
Self-employed	12 (33%)	10 (26%)
Disabled	1 (3%)	2 (5%)
Unemployed	-	2 (5%)
Family problems, n (%)	12 (32%)	28 (65%)
School absence, n (%)	6 (15%)	9 (21%)

Table S2 Continued

IQ, mean (SD)		
Total IQ	105.9 (16.3)	96.7 (14.9)
Verbal IQ	108.9 (15.6)	101.1 (13.9)
Performance IQ	101.4 (17.1)	92.9 (14.6)
Processing speed	101.2 (16.2)	96.4 (12.6)
CBCL, mean T-score (SD)	**n = 40**	**n = 42**
Total	55.3 (8.4)	54.9 (8.8)
Internalizing	58.8 (8.8)	58.6 (9.1)
Externalizing	49.8 (10.0)	49.5 (9.0)
Anxious/depressed	56.2 (7.9)	56.5 (7.1)
Withdrawn/depressed	57.9 (8.1)	56.6 (7.0)
Somatic complaints	64.5 (7.1)	63.7 (8.7)
Social problems	55.5 (7.0)	54.7 (6.8)
Thought problems	61.5 (8.2)	58.5 (7.3)
Attention problems	56.2 (5.0)	56.4 (5.9)
Rule-breaking behavior	52.9 (4.3)	52.8 (3.4)
Aggressive behavior	54.9 (6.0)	54.3 (5.4)
Personality (NPV-J), mean (SD); range 1-7	**n = 41**	**n = 43**
Inadequacy boys	3.3 (1.6)	3.5 (1.4)
Inadequacy girls	3.0 (1.7)	3.5 (1.5)
Persistence <12 years	4.1 (1.5)	4.1 (1.4)
Persistence >12 years	3.8 (1.3)	4.6 (1.3)
Social inadequacy	3.2 (1.5)	3.7 (1.8)
Recalcitrance	2.8 (1.1)	3.8 (1.7)
Dominance	4.1 (1.2)	4.1 (1.2)
SF-36 mother, mean (SD); range 0-100	**n = 40**	**n = 43**
Physical functioning	93.0 (16.0)	81.9 (20.3)
Social functioning	89.1 (17.9)	77.0 (28.5)
Role physical	80.6 (35.6)	70.9 (40.4)
Role emotional	90.8 (25.0)	82.2 (35.1)

Mental health	82.3 (13.7)	77.1 (17.1)
Vitality	72.9 (17.1)	64.5 (21.4)
Bodily pain	87.4 (18.3)	68.5 (24.9)
General health	74.4 (20.3)	61.5 (23.1)
Health transition	57.5 (15.2)	49.4 (19.3)
SF-36 father, mean (SD); range 0-100	**n = 34**	**n = 32**
Physical functioning	92.8 (10.2)	93.0 (8.0)
Social functioning	88.6 (14.9)	90.2 (18.2)
Role physical	91.9 (18.2)	89.1 (27.6)
Role emotional	89.2 (21.3)	99.0 (5.9)
Mental health	83.4 (12.6)	82.4 (13.8)
Vitality	75.7 (15.6)	71.6 (18.1)
Bodily pain	84.2 (16.5)	81.9 (20.4)
General health	73.8 (18.1)	67.5 (24.0)
Health transition	55.9 (19.5)	57.8 (18.4)

BMI Body Mass index, IQ intelligence quotient, CBCL child behavior checklist, NPV-J Dutch personality questionnaire-youth version, SF-36 short form health survey, SD standard deviation

Table S3 Clinical secondary outcome measures

	Intervention group		Control group		Statistical analysis	
EASI (range 0-72)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	33	13.4 (7.9)	20	13.8 (9.7)		
End of intervention (T1)	31	2.1 (2.6)	20	6.5 (5.8)	-4.2 (-6.4 to -2.0)	0.000
First follow-up assessment (T2)	34	3.4 (4.3)	19	5.7 (7.2)	-2.8 (- 4.7 to -0.8)	0.007
End of follow-up (T3)	31	5.5 (4.9)	16	5.4 (5.2)	-1.6 (-4.4 to 1.1)	0.229
TARC (pg/ml)	**n**	**Median (IQR)**		**Median (IQR)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	38	1110 (1703)	41	1076 (1558)		
End of intervention (T1)	38	619 (430)	38	806 (1074)	-237 (-655 to 180)	0.261
First follow-up assessment (T2)	37	722 (1038)	35	845 (645)	-250 (-601 to 100)	0.160
End of follow-up (T3)	38	921 (1013)	35	1094 (1239)	-287 (-710 to 137)	0.181
Blood eosinophils (x10^9/L)	**n**	**Median (IQR)**		**Median (IQR)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	37	0.53 (0.59)	37	0.51 (0.53)		
End of intervention (T1)	37	0.25 (0.26)	37	0.63 (0.55)	-0.27 (-0.45 to -0.09)	0.003
First follow-up assessment (T2)	38	0.47 (0.59)	34	0.49 (0.58)	-0.225 (-0.515 to 0.065)	0.128
End of follow-up (T3)	38	0.31 (0.43)	35	0.56 (0.52)	-0.098 (-0.788 to 0.592)	0.781
Use of > potent topical corticosteroids or systemic immuno-suppressives	**n**	**n% use of >potent topical corticosteroids or systemic immuno-suppressives**	**n**	**n% use of >potent topical corticosteroids or systemic immuno-suppressives**	**OR (95%CI) for lower potency**	**P**
Baseline (T0)	38	38 (100%)	41	38 (93%)		
End of intervention (T1)	38	30 (79%)	40	33 (82%)	2.98 (1.0 to 8.7)	0.046

First follow-up assessment (T2)	37	30 (81%)	39	36 (92%)	3.7 (1.5 to 9.5)	0.005
End of follow-up (T3)	38	36 (95%)	36	33 (92%)	0.46 (0.18 to 1.2)	0.114
Itch (range 0 - 4)	**n**	**n% severe itch**	**n**	**Mean (SD)**	**OR (95%CI) for less itch**	**P**
Baseline (T0)	38	25 (66%)	38	21 (55%)		
End of intervention (T1)	37	1 (3%)	35	7 (20%)	5.1 (2.2 to 11.7)	0.000
First follow-up assessment (T2)	36	3 (8%)	30	12 (40%)	3.35 (1.25 to 8.97)	0.016
End of follow-up (T3)	37	7 (19%)	32	8 (25%)	1.4 (0.6 to 3.2)	0.436
Nightly complaints of itch (range 0 - 4)	**n**	**n% a lot**	**n**	**n% a lot**	**OR (95%CI) for less complaints**	**P**
Baseline (T0)	38	15 (40%)	38	15 (40%)		
End of intervention (T1)	37	0	35	6 (17%)	2.97 (1.2 to 7.1)	0.014
First follow-up assessment (T2)	36	0	30	5 (16%)	2.5 (1.1 to 5.8)	0.03
End of follow-up (T3)	37	2 (5%)	32	5 (17%)	1.75 (0.68 to 4.49)	0.25
Sleep problems (range 0 - 3)	**n**	**n% Sleep problems**	**n**	**n% Sleep problems**	**OR (95%CI) for less sleep problems**	**P**
Baseline (T0)	36	26 (72%)	33	25 (76%)		
End of intervention (T1)	34	11 (32%)	31	23 (74%)	6.6 (2.6 to 17.1)	0.000
First follow-up (T2)	36	22 (61%)	34	25 (74%)	1.4 (0.57 to 3.62)	0.439
End of follow-up (T3)	36	21 (58%)	32	20 (62%)	1.9 (0.8 to 4.5)	0.144
BMI (kg/m^2)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	38	19.2 (3.4)	41	21.4 (5.3)		
End of intervention (T1)	38	19.1 (3.2)	39	21.7 (5.5)	-0.22 (-0.54 to 0.1)	0.181
First follow-up (T2)	38	19.5 (3.2)	38	21.2 (4.8)	-0.11 (-0.44 to 0.22)	0.493

Table S3 Continued

End of follow-up (T3)	38	19.5 (3.2)	34	21.5 (4.7)	0.20 (-0.41 to 0.81)	0.520
Total IgE (kU/L)	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	38	2851 (3332)	38	2983 (3036)		
End of follow-up (T3)	37	1776 (3793)	35	2965 (3251)	-625.7 (-1451.4 – 199.96)	0.135
VO2 peak/kg* (mL/kg/min)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	34	43.7 (8.3)	41	39.4 (9.3)	4.4 (0.5 – 8.3)	0.026
End of follow-up (T3)	36	46.7 (7.3)	34	41.9 (9.1)	5.3 (1.3 – 9.3)	0.010
					Group*Time (F = 0.3)	0.591

EASI (Eczema Area and Severity Index), TARC (thymus and activation regulated chemokine), BMI (body mass index), VO2 peak (maximal volume of oxygen uptake per kg). Statistical models are corrected for baseline (T0)

Table S4 Psychosocial secondary outcomes

		Intervention group		Control group		
JUCKKI/JU Coping with itch (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**p**
Baseline (T0)	38	1.8 (0.7)	40	1.8 (0.8)	-0.2 (-0.8 to 0.3)	0.387
End of intervention (T1)	37	1.8 (1.0)	32	1.7 (0.8)	-0.3 (-0.8 – 0.3)	0.377
End of follow-up (T3)	38	1.8 (0.8)	31	1.6 (0.6)	0.3 (-0.3 – 0.9)	0.380
					Group*Time (F = 1.3)	0.273
COPEKI social anxiety – depressive mood* (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	18	1.2 (0.9)	19	1.2 (0.8)	-0.1 (-0.6 – 0.5)	0.804
End of intervention (T1)	17	0.9 (0.7)	15	1.2 (0.8)	-0.3 (-0.9 – 0.3)	0.284
End of follow-up (T3)	15	0.7 (0.6)	14	1.1 (1.0)	-0.3 (-0.9 – 0.3)	0.280
					Group*Time (F = 0.7)	0.503
COPEKI itching-scratching circle – stress from the disease (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	18	2.0 (0.8)	19	2.1 (0.7)	-0.1 (-0.6 – 0.4)	0.728
End of intervention (T1)	17	1.6 (0.8)	15	2.1 (0.8)	-0.4 (0.9 – 0.2)	0.166
End of follow-up (T3)	15	1.8 (0.7)	14	1.8 (0.7)	0.1 (-0.5 – 0.6)	0.806
					Group*Time (F = 1.4)	0.262
COPEJU depressive mood – itching-scratching circle (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	21	2.5 (0.8)	20	1.9 (0.9)	0.4 (-0.1 – 0.9)	0.117
End of intervention (T1)	19	1.8 (0.8)	17	1.5 (0.8)	0.1 (-0.5 – 0.6)	0.829
End of follow-up (T3)	23	1.7 (1.0)	17	1.3 (0.9)	0.2 (-0.4 – 0.8)	0.478
					Group*Time (F = 1.7)	0.195

Table S4 Continued

COPEJU social anxiety (range 0-4)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	21	1.9 (1.2)	20	1.5 (1.2)	0.4 (-0.4 – 1.1)	0.327
End of intervention (T1)	19	1.3 (1.1.)	17	1.1 (1.0)	-0.0 (-0.7 – 0.7)	0.986
End of follow-up (T3)	23	1.3 (1.2)	17	0.9 (1.0)	0.2 (-0.5 – 0.9)	0.551
					Group*Time (F = 1.1)	0.345
COPEJU stress from the disease (range 0-4)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	21	2.0 (0.8)	20	1.5 (0.8)	0.5 (-0.1 – 1.0)	0.087
End of intervention (T1)	19	1.6 (1.0)	17	1.3 (0.7)	0.1 (-0.4 – 0.7)	0.669
End of follow-up (T3)	23	1.5 (0.9)	17	1.3 (0.8)	0.1 (-0.5 – 0.6)	0.774
					Group*Time (F = 2.1)	0.137
ZBV-K trait anxiety	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	37	6.2 (3.4)	36	5.5 (3.3)	0.4 (-1.1 – 2.0)	0.595
End of intervention (T1)	37	5.0 (3.3)	33	4.6 (3.2)	0.1 (-1.4 - -1.7)	0.875
End of follow-up (T3)	38	5.4 (3.3)	32	5.2 (3.4)	-0.0 (-1.6 – 1.5)	0.999
					Group*Time (F = 0.3)	0.770
ZBV-K state anxiety*	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	37	6.6 (3.4)	40	6.4 (3.1)	0.3 (-1.1 – 1.7)	0.650
End of intervention (T1)	37	4.2 (3.0)	33	5.6 (2.7)	-1.5 (-3.0 - -0.1)	0.040
End of follow-up (T3)	38	4.8 (3.2)	32	5.4 (3.2)	-0.7 (-2.2 – 0.7)	0.323
					Group*Time (F = 3.3)	0.041
CBSK/A scholastic competence	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	56.7 (33.9)	41	50.3 (35.1)	5.1 (-10.4 – 20.7)	0.513

End of intervention (T1)	37	54.5 (32.0)	35	57.9 (33.8)	-2.1 (-19.8 – 15.7)	0.818
End of follow-up (T3)	38	56.7 (30.3)	33	59.6 (32.3)	-5.8 (-25.0 – 13.5)	0.551
					Group*Time (F = 0.8)	0.440
CBSK/A social acceptance	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	55.8 (34.2)	41	48.4 (29.2)	9.4 (-4.4 – 23.3)	0.178
End of intervention (T1)	37	62.1 (29.3)	35	43.8 (26.8)	10.9 (-5.4 – 27.3)	0.188
End of follow-up (T3)	38	53.9 (32.6)	33	51.0 (32.6)	-3.9 (-22.5 – 14.7)	0.676
					Group*Time (F = 1.5)	0.230
CBSK/A athletic competence	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	52.5 (34.7)	41	37.2 (28.0)	16.6 (2.6 – 30.6)	0.020
End of intervention (T1)	37	49.5 (32.5)	35	43.6 (29.2)	6.7 (-9.2 – 22.6)	0.405
End of follow-up (T3)	38	48.6 (31.9)	33	47.2 (27.1)	-1.1 (-18.1 – 16.0)	0.901
					Group*Time (F = 2.7)	0.074
CBSK/A physical appearance	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	40.4 (30.8)	41	33.9 (26.4)	7.0 (-5.7 – 19.7)	0.276
End of intervention (T1)	37	42.9 (29.5)	35	36.3 (25.9)	8.6 (-6.6 – 23.7)	0.267
End of follow-up (T3)	38	41.6 (30.1)	33	41.6 (33.6)	1.8 (-16.4 – 20.0)	0.845
					Group*Time (F = 0.5)	0.633

Table S4 Continued

CBSK/A behavioral conduct	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	70.0 (28.9)	41	64.7 (28.8)	3.3 (-8.7 – 15.4)	0.582
End of intervention (T1)	37	67.4 (29.3)	35	62.1 (27.8)	8.7 (-6.9 – 24.3)	0.271
End of follow-up (T3)	38	68.1 (28.4)	33	63.5 (29.6)	3.4 (-13.7 – 20.5)	0.692
					Group*Time (F = 0.3)	0.748
CBSK/A global self-worth	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	47.5 (35.4)	41	42.4 (32.8)	4.3 (-10.9 – 19.5)	0.578
End of intervention (T1)	37	49.2 (33.6)	35	43.1 (34.1)	7.6 (-11.2 – 26.4)	0.424
End of follow-up (T3)	38	46.8 (34.7)	33	43.2 (30.8)	-0.6 (-20.7 – 19.4)	0.949
					Group*Time (F = 0.5)	0.632
CBSA close friendships	**n**	**Mean percentile (SD)**	**n**	**Mean percentile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	24	47.8 (28.3)	22	59.3 (30.2)	-10.9 (-28.2 – 6.4)	0.210
End of intervention (T1)	20	57.5 (24.0)	19	49.8 (29.7)	5.2 (-12.1 – 22.5)	0.553
End of follow-up (T3)	23	47.2 (25.6)	20	55.9 (29.8)	-12.9 (-30.2 – 4.3)	0.138
					Group*Time (F = 2.7)	0.077
PUL autonomy (range 7-28)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	22	23.1 (2.9)	25	22.8 (2.6)	0.1 (-1.5 – 1.8)	0.868
End of intervention (T1)	24	24.1 (3.3)	22	24.3 (3.2)	-0.1 (-2.0 – 1.8)	0.921
End of follow-up (T3)	25	23.4 (4.1)	22	24.6 (3.0)	-0.8 (-3.1 – 1.6)	0.516
					Group*Time (F = 0.4)	0.696

PUL social optimism (range 3-12)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T-1)	22	10.8 (1.3)	25	10.8 (1.3)	-0.0 (-0.8 – 0.7)	0.949
End of intervention (T1)	24	11.1 (1.1)	22	11.2 (1.1)	-0.0 (-0.7 – 0.7)	0.998
End of follow-up (T3)	25	10.6 (1.6)	22	11.0 (1.2)	-0.4 (-1.2 – 0.5)	0.381
					Group*Time (F = 0.5)	0.627

COPEKI coping with disease questionnaire for children, COPEJU coping with disease questionnaire for youth, CBSK self-perception profile for children, CBSA self-perception profile for adolescents, ZBV state-trait anxiety inventory, ZBV-K state-trait anxiety inventory for children, PUL positive outcome list. *PUL was filled in by children aged 13 or older

Table S5 Parental secondary outcome measures

QoL psychosomatic wellbeing mother (range 9-45)*	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	P
Baseline (T0)	34	33.2 (4.8)	38	31.6 (4.8)	1.8 (-0.6 – 4.2)	0.141
End of intervention (T1)	37	34.5 (5.2)	36	33.2 (5.4)	1.3 (-1.1 – 3.7)	0.274
End of follow-up (T3)	34	36.3 (6.1)	31	33.9 (5.5)	2.5 (-0.0 – 4.9)	0.047
					Group*Time (F = 0.7)	0.514
QoL effects on social life mother (range 6-30)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	34	24.8 (3.9)	38	24.6 (4.1)	0.7 (-1.2 – 2.5)	0.459
End of intervention (T1)	37	26.0 (4.0)	36	24.9 (4.4)	1.0 (-0.9 – 2.8)	0.302
End of follow-up (T3)	34	26.4 (4.4)	31	25.5 (3.9)	0.6 (-1.4 – 2.5)	0.563
					Group*Time (F = 0.2)	0.816
QoL confidence in medical treatment mother (range 5-25)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	34	19.1 (2.9)	38	18.7 (3.0)	0.5 (-0.8 – 1.8)	0.469
End of intervention (T1)	37	20.9 (3.0)	36	19.6 (2.8)	1.5 (0.2 – 2.8)	0.026
End of follow-up (T3)	34	21.6 (2.4)	31	20.6 (3.1)	1.2 (-0.1 – 2.6)	0.079

Table S5 Continued

					Group*Time (F = 1.2)	0.290
QoL emotional coping mother (range 4-20)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	34	14.8 (2.6)	38	14.5 (2.4)	0.4 (-0.8 – 1.6)	0.518
End of intervention (T1)	37	16.0 (2.7)	36	14.8 (2.8)	1.1 (-0.1 – 2.2)	0.079
End of follow-up (T3)	34	16.6 (2.6)	31	16.0 (2.7)	0.6 (-0.6 – 1.9)	0.297
					Group*Time (F = 0.9)	0.407
QoL acceptance of the disease mother (range 2-10)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	34	8.1 (1.4)	38	7.4 (2.0)	0.6 (-0.1 – 1.4)	0.111
End of intervention (T1)	37	8.6 (1.6)	36	7.9 (1.8)	0.6 (-0.1 – 1.3)	0.119
End of follow-up (T3)	34	8.7 (1.6)	31	7.8 (1.9)	0.7 (-0.1 – 1.5)	0.068
					Group*Time (F = 0.1)	0.878
QoL psychosomatic wellbeing father (range 9-45)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	32	33.6 (3.9)	24	34.7 (6.2)	-0.0 (-2.7 – 2.6)	0.971
End of intervention (T1)	30	35.2 (4.3)	21	35.5 (5.8)	0.7 (-2.0 – 3.3)	0.622
End of follow-up (T3)	21	37.9 (4.3)	17	35.9 (5.5)	1.1 (-1.7 – 4.0)	0.423
					Group*Time (F = 0.6)	0.538
QoL effects on social life father (range 6-30)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	32	25.1 (3.8)	24	26.3 (3.2)	-0.4 (-2.2 – 1.3)	0.606
End of intervention (T1)	30	25.8 (2.5)	21	27.4 (2.3)	-0.4 (-2.2 – 1.3)	0.612
End of follow-up (T3)	21	27.1 (2.2)	17	26.6 (3.9)	-0.0 (-1.8 – 1.8)	0.998
					Group*Time (F = 0.2)	0.824

QoL confidence in medical treatment father (range 5-25)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	32	18.4 (2.8)	24	18.3 (2.4)	0.4 (-1.0 – 1.8)	0.572
End of intervention (T1)	30	20.2 (2.4)	21	19.1 (2.6)	1.3 (-0.1 – 2.7)	0.078
End of follow-up (T3)	21	21.2 (2.1)	17	20.5 (2.7)	0.8 (-0.8 – 2.3)	0.317
					Group*Time (F = 0.7)	0.502
QoL emotional coping father (range 4-20)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	32	14.8 (2.4)	24	15.4 (3.0)	-0.0 (-1.3 – 1.2)	0.954
End of intervention (T1)	30	15.6 (2.1)	21	15.4 (2.7)	0.6 (-0.7 – 1.9)	0.368
End of follow-up (T3)	21	16.9 (1.8)	17	16.2 (2.4)	0.9 (-0.5 – 2.2)	0.214
					Group*Time (F = 1.4)	0.265
QoL acceptance of the disease father (range 2-10)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T0)	32	7.5 (1.7)	24	7.6 (2.0)	0.1 (-0.9 – 1.0)	0.860
End of intervention (T1)	30	7.9 (1.4)	21	7.9 (1.7)	0.1 (-0.9 – 1.1)	0.840
End of follow-up (T3)	21	8.2 (1.4)	17	8.1 (2.0)	0.3 (-0.8 – 1.4)	0.565
					Group*Time (F = 0.1)	0.909
NOSI-K parenting stress mother (range 1-7)*	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	3.8 (1.8)	44	3.7 (1.5)	0.1 (-0.6 – 0.9)	0.695
End of intervention (T1)	37	3.5 (1.8)	36	3.9 (2.0)	-0.3 (-1.1 – 0.4)	0.371
End of follow-up (T3)	34	3.2 (1.7)	32	3.6 (1.6)	-0.4 (-1.2 – 0.4)	0.284
					Group*Time (F = 2.9)	0.060
NOSI-K parenting stress father (range 1-7)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	34	4.3 (1.6)	33	3.9 (1.7)	0.3 (-0.5 – 1.1)	0.494
End of intervention (T1)	28	4.2 (1.6)	22	3.6 (1.7)	0.2 (-0.6 – 1.1)	0.590

Table S5 Continued

End of follow-up (T3)	21	3.2 (1.5)	18	4.4 (1.7)	-0.9 (-1.9 - -0.0)	0.047
					Group*Time (F = 5.9)	0.004
ZBV trait anxiety mother	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	4.5 (2.7)	44	4.9 (2.7)	-0.3 (-1.5 – 0.8)	0.560
End of intervention (T1)	37	3.7 (2.7)	37	4.3 (2.6)	-0.5 (-1.7 – 0.7)	0.407
End of follow-up (T3)	34	3.2 (2.6)	32	4.0 (2.3)	-0.9 (-2.1 – 0.3)	0.125
					Group*Time (F = 0.8)	0.436
ZBV trait anxiety father	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	34	4.2 (2.4)	34	5.0 (3.0)	-0.7 (-2.0 – 0.6)	0.276
End of intervention (T1)	29	3.8 (2.3)	22	4.6 (2.8)	-1.4 (-2.7 – 0.0)	0.050
End of follow-up (T3)	21	2.6 (1.8)	18	4.1 (2.8)	-1.6 (-3.1 - -0.2)	0.029
					Group*Time (F = 1.4)	0.242
ZBV state anxiety corticosteroid use mother	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	40	5.6 (2.5)	43	6.3 (2.2)	-0.7 (-1.7 – 0.3)	0.170
End of intervention (T1)	37	4.5 (2.3)	36	5.2 (2.3)	-0.7 (-1.7 – 0.3)	0.150
End of follow-up (T3)	34	3.9 (1.9)	31	5.2 (2.2)	-1.3 (-2.3 - -0.3)	0.015
					Group*Time (F = 0.7)	0.513
ZBV state anxiety corticosteroid use father*	**n**	**Mean decile (SD)**	**n**	**Mean decile (SD)**	**Estimated difference (95%CI)**	**P**
Baseline (T-1)	34	6.4 (2.4)	33	5.7 (3.0)	0.6 (-0.7 – 1.9)	0.350
End of intervention (T1)	29	5.5 (2.4)	21	4.9 (3.2)	-0.0 (-1.5 – 1.4)	0.964
End of follow-up (T3)	21	3.9 (2.2)	17	4.7 (2.7)	-1.5 (-3.0 – 0.0)	0.057
					Group*Time (F = 5.2)	0.007

QOL quality of life, NOSI-K parental stress index-short form, ZBV state-trait anxiety inventory *Analyzed without random slope

Table S6A Pharmacological treatment for AD during the study period (intervention group)

Intervention group						
Used topical corticosteroids / systemic immunosuppressives	**none**	**Tac /emovate /protopic**	**Cutivate/ elocon**	**Betnelan/ betamethason**	**Dermovate**	**Prednisone / cyclosporin**
Inclusion (Tmin1) n(%)	2 (5%)	2 (5%)	14 (34%)	19 (46%)	2 (5%)	2 (5%)
Baseline (T0) n(%)			17 (41%)	12 (29%)		9 (22%)
End of intervention (T1) n(%)	3 (8%)	5 (13%)	16 (42%)	13 (34%)		1 (3%)
First follow-up assessment (T2) n(%)		7 (19%)	16 (43%)	13 (35%)		1 (3%)
End of follow-up (T3) n(%)	1 (3%)	1 (3%)	16 (42%)	8 (21%)	3 (8%)	9 (24%)

See Table S3 for differences between the groups

Table S6B Pharmacological treatment for AD during the study period (control group)

Control group						
Used topical corticosteroids / systemic immunosuppressives	**none**	**Tac /emovate /protopic**	**Cultivate/ elocon**	**Betnelan/ betamethason**	**Dermovate**	**Prednisone / cyclosporin**
Inclusion (Tmin1) n(%)	1 (2%)	1 (2%)	14 (33%)	19 (44%)	0	8 (19%)
Baseline (T0) n(%)	1 (2%)	2 (5%)	10 (24%)	17 (42%)	2 (5%)	9 (22%)
End of intervention (T1) n(%)		7 (17%)	9 (23%)	15 (37%)	1 (3%)	8 (20%)
First follow-up assessment (T2) n(%)		3 (8%)	12 (31%)	15 (38%)	2 (5%)	7 (18%)
End of follow-up (T3) n(%)	1 (3%)	2 (6%)	13 (36%)	14 (39%)	3 (8%)	3 (8%)

See Table S3 for differences between the groups

7.

Treatment for moderate to severe atopic dermatitis at alpine and moderate maritime climates differentially affect helper T cells and memory B cells in children

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Submitted

Abstract

Background

Treatment of atopic dermatitis (AD) is focused on topical anti-inflammatory therapy, epidermal barrier repair and trigger avoidance. Multidisciplinary treatments in both moderate maritime and alpine climates can successfully reduce disease activity in children with AD. However, it remains unclear whether abnormalities in B- and T-cell memory normalize and if this differs between treatment strategies.

Objective

To determine whether successful treatment in maritime and alpine climates normalises B- and T-lymphocytes in children with moderate to severe AD.

Methods

The study was performed in the context of a trial (DAVOS trial) in which eighty-eight children with moderate to severe AD were randomized to 6 weeks of treatment either at sea level (outpatient treatment) or at alpine climate (inpatient treatment). Before and directly after treatment, disease activity was determined with SA-EASI and serum TARC, and T- and B-cell subsets were quantified in blood.

Results

Both treatment protocols achieved a significant decrease in disease activity, which was accompanied by a reduction in circulating memory Treg, transitional B-cell and plasmablast numbers. Alpine climate therapy had a significantly greater effect on disease activity and was accompanied by a reduction of blood eosinophils, and increases in memory B-cells, CD8+ TemRO, CD4+ Tcm and CCR7+ Th2 subsets.

Conclusion

Clinically successful treatment of AD induces changes in blood B- and T-cell subsets reflecting reduced chronic stimulation. In addition, multidisciplinary inpatient treatment at alpine climate specifically affects memory B-cells, CD8+ T cells and Th2 cells. These cell types could represent good markers for treatment efficacy.

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease, which affects up to 10-20% of children with a lifetime prevalence estimated at 15-30%.[1] The underlying pathogenesis of AD is multifactorial and includes environmental factors, genetic predisposition, skin barrier dysfunction, and altered local and systemic immune responses.[2-6] It remains unclear if reported abnormalities in the immune response are the cause of the disease, a result of reduced skin barrier function, or a combination of both. Still, it is generally accepted that AD is characterized by a skewing towards T-helper 2 (Th2) responses with increased immunoglobulin (Ig)E serum levels and eosinophilia.[6, 7]

The main principles in AD treatment are based on epidermal barrier repair with anti-inflammatory topical treatment, emollients, antimicrobial therapy and trigger avoidance.[5, 8] Only in more severe cases, or when insufficient control of AD is achieved, systemic immunosuppressive treatment may be required.[5, 8-11] Treatment at high altitude in the alpine climate has been used in children with AD and asthma for decades,[12] with long-term improvement in disease control and health related quality of life (Fieten et al. submitted). On the short term, disease activity has been shown to decrease significantly, which is accompanied by a significant reduction in eosinophils and fractional exhaled nitric oxide (FeNO) (Fieten et al. submitted). Despite the rationale of these treatments to dampen abnormal immune responses, data on underlying immunological effects are scarce.[13, 14]

In the acute phase of AD, dermal and epidermal lesions are predominated by Th2 cells and Th2 cytokines, such as interleukin (IL)-4, IL-5 and IL-13.[15, 16] This is also reflected in peripheral blood with increased numbers of CD4+ T-cells producing IL-4 and IL-13.[17-21] In children, this increase specifically concerns T cells expressing the cutaneous lymphocyte antigen (CLA).[22] In addition, expansions of CLA+ Th22 cells have been observed in adults with severe AD.[22] During chronic stages of the disease, T-helper cell skewing changes, with an increase of Th1 cells, which is referred to as the biphasic T-cell polarization.[23] The production of IL-22 induces epidermal hyperplasia through their effect on keratinocytes, whereas Th2 cytokines induce barrier disruption.[16, 24] Furthermore, regulatory T-cells (Tregs) are consistently found to be increased in blood of patients with AD.[25-27] Possibly, this is caused by chronic inflammatory signals, because numbers decline with treatment and correlate well with disease severity.[28, 29]

Under influence of the Th2 cytokines IL-4 and IL-13, activated B cells can undergo Ig class switching to IgE.[30] Indeed IgE-producing plasmablasts are increased in AD,[31] and elevated total and allergen-specific IgE serum levels are a hallmark of the disease. These B-cell responses also result in higher numbers of IgE+ memory B-cells in blood of patients with AD.[31, 32] Furthermore, numbers of transitional B-cells, which are attributed to have regulatory capacities through the production of IL-10, have been reported to be increased in AD.[31] Still it has been shown that dupilumab, an antibody blocking IL-4/IL-13 receptors, has equal potency in treatment of either extrinsic AD (with increased IgE levels) as intrinsic AD (without increased IgE levels). This can be explained by data showing that Th2 cytokines diminish

the expression of barrier proteins such as filaggrin, loricrin, involucrin and antimicrobial peptides.[33] Hence, this illustrates the clinical and immunological diversity of the disease.

Despite these insights into T-cell and B-cell abnormalities in disease, data about the effects of treatment on the immune response in patients with AD are limited. Most studies evaluated lesional skin biopsies and focused on T-cell subsets.[34-39] Evaluation of alpine climate treatment has been focused on a reduction in eosinophil numbers, but data on T- and B-cell subsets are limited.[13, 14]

We here resolve this gap in knowledge by analysis of blood T- and B-cells in children with moderate to severe AD before and after treatment. Specifically, we compared the effects of two clinically successful therapies: inpatient alpine climate treatment and an outpatient treatment program at maritime level (DAVOS trial).[40] We report on the identification of common and treatment-specific effects on blood B- and T-cell subsets.

Methods

Study design

This study is part of the DAVOS trial, ISRCTN88136485, which is a pragmatic randomized trial for children with moderate to severe difficult to treat AD.[40] In short, patients were enrolled between September 2010 and October 2014 and randomized to either personalized integrative multidisciplinary inpatient treatment at a high altitude clinic in Switzerland at 1,560 meters (NAD group), or to an integrative multidisciplinary outpatient treatment program in the Netherlands at sea level (moderate maritime climate) (WKZ group). Participants were assessed before the start of intervention (T0) and immediately after the 6 week intervention (T1). Both study assessments, including blood sampling within 72 hours after return of the NAD group participants, were performed in the Netherlands.

Children in the NAD group had weekly individual treatment sessions with a pediatrician, a psychologist (alternating with the psychomotor therapist) and a physiotherapist (if needed). A nurse monitored correct application of topical treatment in individual sessions with each child twice daily. In these individual sessions health education was provided with a varying weekly theme. During their stay at the high altitude clinic, children attended an integrated school. At outdoor activities the skin was applied with sun cream for protection of high UV exposure when necessary. Children in the WKZ group were seen during half a day at the outpatient clinic on a weekly basis for 6 weeks. During this period they had three consultations with the dermatologist, five consultations with the dermatological nurse, three consultations with the pediatric allergist and three consultations with the psychologist. In the third week a group consultation was scheduled about coping with AD and compliance, for the children and their parents separately.

Participants

All patients and their parents provided written informed consent for participation in the trial, which was reviewed and approved by the Medical Ethics Committee of the Utrecht Medical Center, the Netherlands (reference 09-192/K). Data regarding gender, age, asthma, allergic rhinitis, food allergy and use of topical or systemic medication during intervention were extracted from electronic patient files in the Wilhelmina Children's Hospital. Disease severity was measured with the objective Self-Administered Eczema Area and Severity Index (SA-EASI) by the research nurse at T0 and T1.[41]

Blood measurements

Total lymphocyte and eosinophil counts were determined with a Coulter cell counter (Beckman Coulter) within 24 hours of blood sampling. Serum Thymus- and activation-regulated chemokine (TARC) levels were measured with an Enzyme-Linked Immuno Sorbent Assay. Total serum IgE levels were measured with an ImmunoCAP 250 (Phadia) on T0. Peripheral blood mononuclear cells (PBMCs) of all patient samples were isolated by Ficoll-plaque density centrifugation, stored in liquid nitrogen, and used for 11-color flow cytometry. For this, one million PBMCs were incubated with antibody cocktails against B-cell or T-cell markers for 15 minutes on room temperature in 100µL total volume (Supplementary Table 1). Flow cytometric analyses were performed on a 4-laser LSRFortessa (BD Biosciences) using standardized measurement settings,[42] and data were analyzed using FacsDiva V8.0 (BD Biosciences). Immunophenotypic definitions of lymphocyte subsets are provided in Supplementary Table 2. The absolute lymphocyte counts obtained from fresh samples were used to calculate absolute numbers of the CD3+ T-cell and CD19+ B-cell subsets.

Statistical analysis

Statistical analysis was performed in SPSS version 21.0 (IBM Corp, Armonk, NY). The course of AD disease activity after treatment was determined by assessing the SA-EASI score on T1 versus T0 with the Paired Samples T-test. Changes in the absolute counts of T- and B-cell subsets after treatment in the total cohort or within the NAD and WKZ groups were analyzed with the Wilcoxon Signed Rank Test. Differences in kinetics of the T- and B-cell subsets before and after treatment between the NAD and WKZ groups were analyzed with Analysis of covariance. This analysis was corrected for possible pre-existing differences between the groups on T0 and the use of systemic medication during intervention. Systemic medication was defined as a dichotomous variable, with patients classified as using systemic medication when they had used prednisone and/or cyclosporine at any point during the six-week intervention. P-values of <0.05 were considered statistically significant. Data analysis was supervised by a senior statistician.

Results

Patient selection

A total of 88 patients were enrolled in the Davos trial (see Chapter 6, Figure 1). Of these, 79 started the intervention; 38 at high altitude (NAD) and 41 at sea level (WKZ). Two patients did not complete intervention, and data from one or more blood samples were lacking from 13 patients. This resulted in a total of 64 patients in this study: NAD group, n=31; WKZ group, n=33. Patient characteristics of children with missing blood samples did not differ from the study group.

Patient characteristics

Patient gender and age were equally distributed in both groups; 51.6% males in the NAD group and 51.5% males in the WKZ group with a mean age of 12.7 years in both groups (Table 1). Most patients (85.9%) had one or more additional allergic comorbidities (Table 1). The use of topical corticosteroids before the start of intervention was similar between the groups, with most patients using a class III corticosteroid. In addition, 4 patients (12.1%) in the WKZ group used cyclosporine at T0, whereas none did in the NAD group (Table 1).

Disease activity decreases after intervention

In the total study cohort (n=64), we observed a reduction of the SA-EASI score. The mean score of 37.2 out of 96 (SD 19.9) before the start of intervention (T0) decreased to a mean score of 10.0 (SD 11.7) after intervention (T1) (P <.001; Figure 1A). SA-EASI scores before treatment were similar between both treatment groups, but significantly lower at T1 (P <.01) in the NAD group (mean of 5.0; SD 6.6) than in the WKZ group (mean 14.6; SD 13.5) (Figure 1A).

Serum TARC levels varied considerably but correlated with the SA-EASI score (Supplemental Figure 2). After intervention TARC levels also decreased, but were differently affected by treatment protocols (Figure 1B). A significant decrease was observed in the NAD group with a median of 1149.0 pg/ml at T0 and a median of 610 pg/ml at T1 (P <.01), whereas the serum TARC levels were not significantly lower after intervention in the WKZ group.

Reduction of eosinophils and increase in T-cells after alpine climate treatment

Numbers of blood eosinophils decreased after alpine climate treatment; from a median of 610 cells/µL at T0 to 250 cells/µL at T1 (P <.001) (Figure 1C). The reduction in eosinophil numbers in the NAD group was accompanied by a significant increase in lymphocyte numbers, from a median of 2040 cells/µL at T0 to 2380 cells/µL at T1 (P <.01) (Figure 1D). This effect was significantly different from the WKZ group, in which both eosinophil and lymphocyte numbers did not change after intervention (Figure 1C and D). Within total lymphocytes, specifically T-cells were affected in the NAD group with an increase from a median of 1236.9 cells/µL before intervention to 1345.7 cells/µL after intervention (P <.01) (Figure 1E). Total B-cell numbers did not change following either treatment (Figure 1F). Although patients

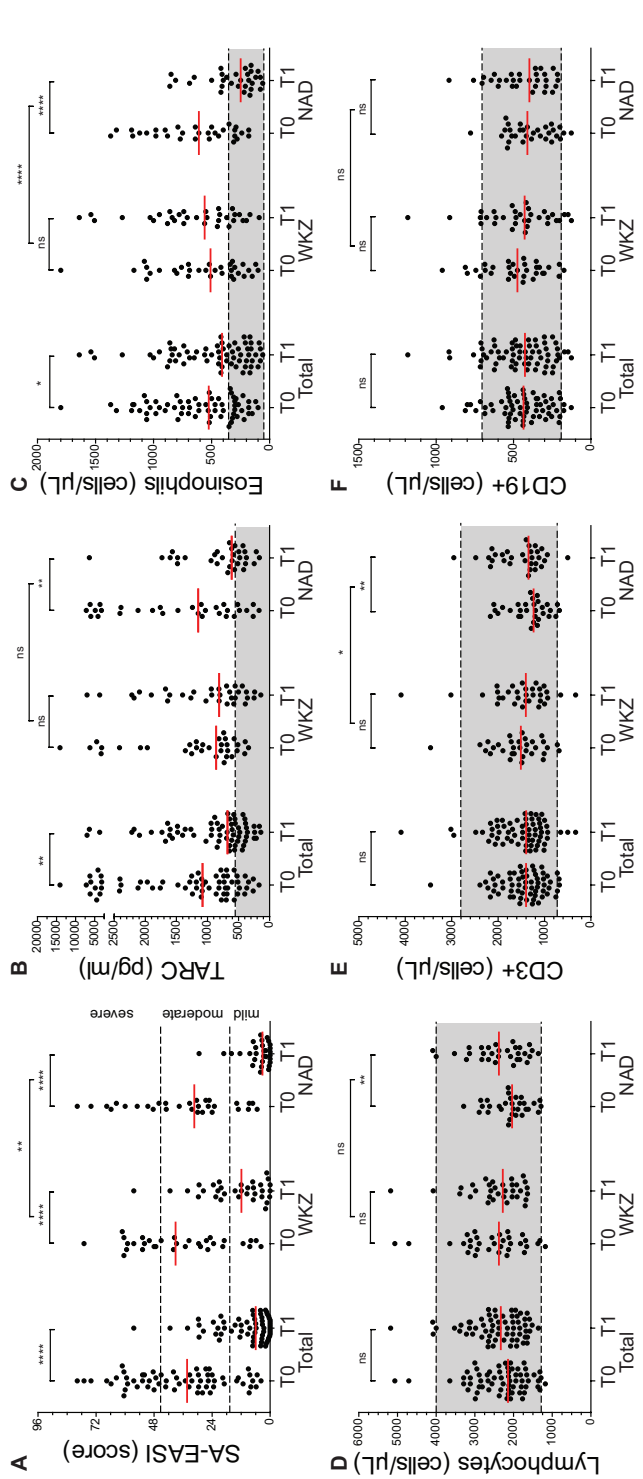

Figure 1 Disease activity and leukocyte subsets. A. Self-Administered Eczema Area and Severity Index (SA-EASI). **B.** Thymus and activation regulated chemokine (TARC). **C.** Eosinophils **D.** Total lymphocytes **E.** Total T-cells **F.** Total B-cells. Each dot represents one individual, and horizontal lines median values. Dashed lines with grey surface indicate reference values. Statistical analysis between the groups was performed with the Wilcoxon signed rank test, analysis between the groups was performed with analysis of covariance. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

Table 1 Baseline patient characteristics

Characteristics		**Total group**	**NAD group**	**WKZ group**
		(n = 64)	(n = 31)	(n = 33)
Gender				
Male	n (%)	33 (51.6)	16 (51.6)	17 (51.5)
Female	n (%)	31 (48.4)	15 (48.4)	16 (48.5)
Age (years)	mean ± SD (range)	12.7 ± 2.4 (8 – 18)	12.7 ± 2.4 (8 – 16)	12.7 ± 2.5 (8 – 18)
SA-EASI (<17 mild; 18-46 moderate; >47 severe)	mean ± SD (range)	37.2 ± 19.9 (3.8 – 79.8)	36.7 ± 20.8 (5.4 – 79.8)	37.6 ± 19.3 (3.8 – 77.0)
Other atopic diseases				
Asthma	n (%)	55 (85.9)	27 (87.1)	28 (84.8)
Allergic rhinitis	n (%)	55 (85.9)	27 (87.1)	28 (84.8)
Food allergy	n (%)	43 (67.2)	21 (67.7)	22 (66.7)
Topical corticosteroid use on T0				
No topical medication	n (%)	1 (1.6)	0 (0.0)	1 (3.0)
Hydrocortisone	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Triamcinolone/Emovate/Tacrolimus	n (%)	3 (4.7)	1 (3.2)	2 (6.1)

Cutivate/Elocon	n (%)	23 (35.9)	16 (51.6)	7 (21.2)
Betnelan/Betamethasone	n (%)	33 (51.6)	13 (41.9)	20 (60.6)
Dermovate	n (%)	4 (6.3)	1 (3.2)	3 (9.1)
Systemic medication use on T0				
No systemic medication	n (%)	59 (92.2)	29 (93.5)	29 (87.9)
Prednisone	n (%)	1 (1.6)	1 (3.2)	0 (0.0)
Cyclosporine	n (%)	4 (7.8)	0 (0.0)	4 (12.1)
serum TARC (pg/ml)	median (range)	1080.5 (170.0 – 14100.0)	1149.0 (170.0 – 7217.0)	861.0 (339.0 – 14100.0)
Eosinophils (x 10^9/L)	median (range)	0.62 (0.10 – 1.80)	0.61 (0.18 – 1.37)	0.51 (0.10 – 1.80)
Total IgE (U/ml)	median (range)	2849.0 (150.0 - 17260.0)	2872.0 (150.0 - 16718.0)	2614.0 (150.0 - 16718.0)

were randomized to a treatment protocol, the total lymphocyte counts were significantly different between the WKZ and NAD groups at T0 (*P* <.05). This difference could not be explained by patient characteristics or technical work-up as these were similar between both groups. Therefore, we corrected for pre-existing differences between the groups on T0 in our statistical analysis.

Blood T- and B-cell subsets are affected by treatment

To study the immune system in more detail we focused on total and treatment-group specific effects on subsets within the T-cell and B-cell lineages. Within the CD3+ T-cell compartment, naive (Tnaive), central memory (Tcm), CD45RA- effector memory (TemRO) and CD45RA+ effector memory (TemRA) populations were defined in both the CD4+ and the CD8+ lineages (Supplemental Figure 2). Naive T cell numbers were not affected by therapy. After treatment, absolute numbers of CD8+ TemRO T-cells were increased in the NAD group (median at T0 of 108.2 cells/μL and median at T1 of 123.5 cells/μL; *P* <.05) (Supplemental Figure 2A). Other CD8+ T-cell subsets were not affected by treatment (Supplemental Figure 2A).

Treatment affects Th2 and memory Treg cells

CD4+ Tcm were differentially affected by treatment (*P* <.05); the absolute numbers decreased slightly in the WKZ group (from a median of 189 cells/μL to 167.2 cells/μL; *P* =0.5), and significantly increased in the NAD group (median T0 136.9 cells/μL and median T1 171.9 cells/μL; *P* <.01) (Supplemental Figure 2B). Other memory CD4+ T-cell subsets did not significantly change with intervention in either of the treatment groups (Supplemental Figure 2B).

Next, we studied if Th subsets were affected by treatment. Th1, Th2 and Th17 cells were defined within the CD45RA- memory compartment based on differential expression of the chemokine receptors CCR4, CCR6 and CXCR3 (Figure 2AB). Whereas no effects of treatment were found on Th1 and Th17 cells, numbers of Th2 cells were significantly different after intervention. Importantly, treatment of the WKZ group at sea level reduced Th2 cell numbers (from a median of 84.9 cells/μL to 75.8 cells/μL; *P* <.05), whereas alpine climate treatment of the NAD group resulted in a (non-significant) increase of Th2 cells (from a median of 78.5 cells/μL to 89.0 cells/μL; *P* 0.09) (Figure 2A). As a result, the treatments also had significantly different effects on the Th1/Th2 cell ratios between the WKZ and the Davos group (*P* <.05) (Figure 2A). To further investigate the increase in Th2 cells after alpine climate treatment we analyzed the expression of the lymphoid homing receptor CCR7. We found that CCR7+ Th2 cells attributed most to the increase of peripheral Th2 cells in the NAD group (Figure 2C), in line with the total increase in CD45-CCR7+ Tcm cells (Supplementary Figure 2). The reduction of Th2 cells in the WKZ group was the result of a decrease of both the CCR7+ and CCR7- subsets (Figure 2C).

Regulatory T cells were studied based on the phenotype CD4+CD25+CD127- (Figure 3A). Numbers of total Tregs decreased slightly but not significantly after treatment (Figure 3B). However, numbers of CD45RA- memory Tregs significantly decreased following intervention,

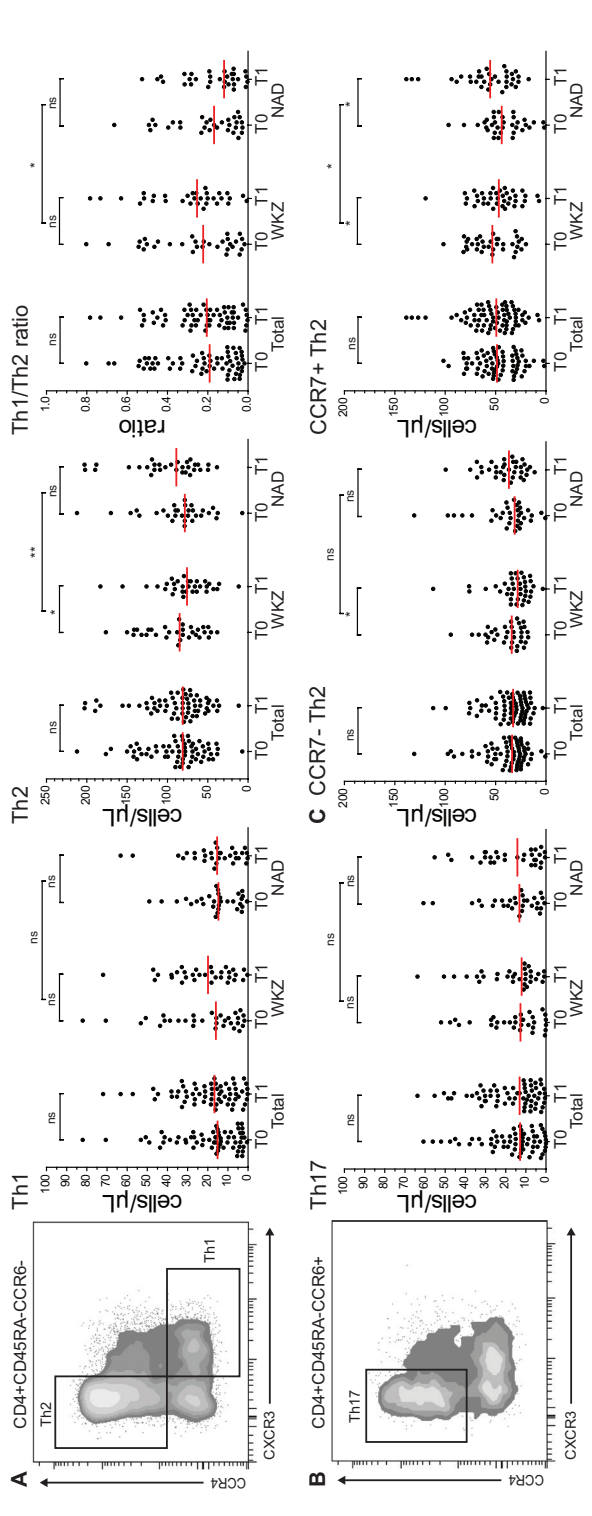

Figure 2 CD4+ T-helper subsets. A. Representative image from flow cytometric analysis of Th1 and Th2 cells and absolute counts of Th1 and Th2 cells and Th1/Th2 ratio. **B**. Representative image from flow cytometric analysis of Th17 cells and absolute counts of Th17 cells. **C**. Absolute counts of CCR7- and CCR7+ Th2 cells. Each dot represents one individual, and horizontal lines median values. Statistical analysis between the groups was performed with the Wilcoxon signed rank test, analysis between the groups was performed with analysis of covariance. *P<0.05, **P<0.01

irrespective of the type of treatment (*P* <.01; Figure 3), whereas numbers of naive Tregs did not change after treatment (Figure 3C and 3D).

Decreased transitional B-cell and plasmablast numbers after intervention

Within CD19+ B-cells, multiple naive and memory B-cell subsets and plasmablasts were defined (Figure 4A and 5A). Numbers of CD21low and naive mature B-cells did not change after intervention (Figure 4B). However, numbers of transitional B-cells (*P* <.01) and plasmablasts (*P* <.05) were significantly reduced in the total cohort (Figure 4B). From the plasmablast subsets, only IgE+ plasmablasts significantly decreased after alpine climate treatment (Supplemental Figure 3D). Transitional B-cell numbers were also solely affected by high alpine treatment (NAD; *P* <.01), whereas the slight decreases in plasmablast numbers were not significant when treatments were analyzed separately. When comparing alpine climate treatment and moderate maritime climate, an opposing effect on natural effector B-cell numbers was found (*P* <.05), with treatment at maritime climate leading to a decrease and alpine climate leading to an increase (Figure 4B).

Increased IgM, IgG and IgA memory B cell numbers following alpine climate treatment

Within the memory B-cell compartment, we defined 8 distinct subsets based on differential expression of the 5 Ig isotypes and CD27 (Figure 5A).[32, 43, 44] Of these 8 subsets, only numbers of IgG+CD27+ memory B cells were significantly increased after intervention (*P* <.05). This effect was significantly greater following alpine climate treatment than treatment at sea level (*P* <.05). In addition, alpine climate treatment led to significantly increased numbers of Natural Effector (*P* <.05), IgA+CD27- (*P* <.05) and IgA+CD27+ (*P* <.05) memory B cells subsets. No effects were found on either CD27+ or CD27- IgE-expressing memory B cells. Thus, intervention resulted in reduced transitional B cells and plasma cells, whereas alpine climate treatment specifically led to slightly increased numbers of IgA and IgG memory B cells. A summary of the significant effects of treatment on the various outcomes are displayed in Table 2.

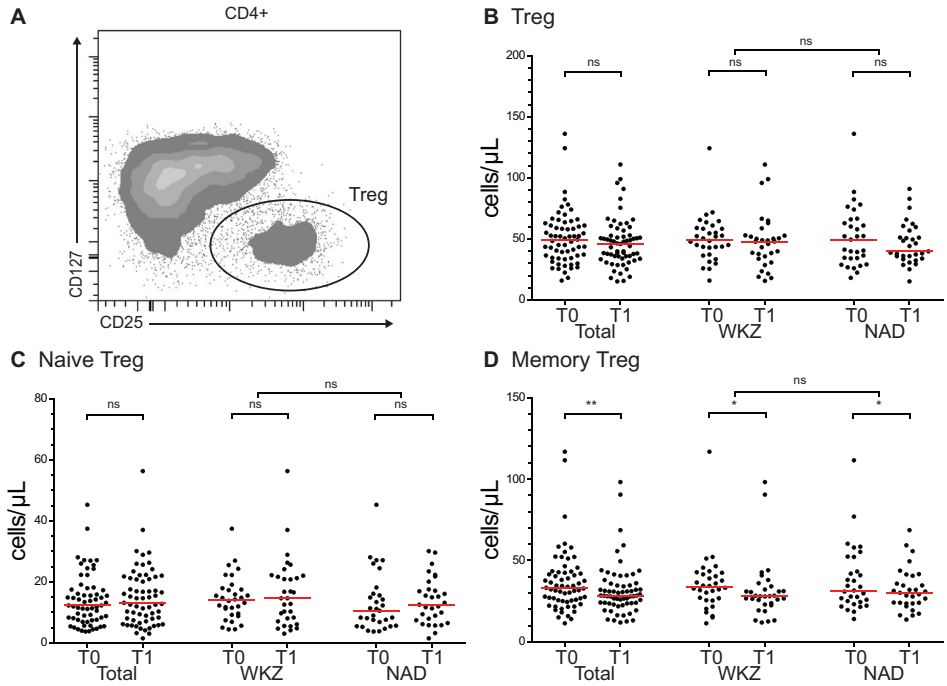

Figure 3 CD4+ Regulatory T-cell subsets. A. Representative image from flow cytometric analysis of regulatory T-cells (Tregs) **B.** Absolute counts of total Tregs **C.** Absolute counts of naive Tregs **D.** Absolute counts of memory Tregs. Each dot represents one individual and horizontal lines median values. Statistical analysis between the groups was performed with the Wilcoxon signed rank test, analysis between the groups was performed with analysis of covariance. *P<0.05, **P<0.01

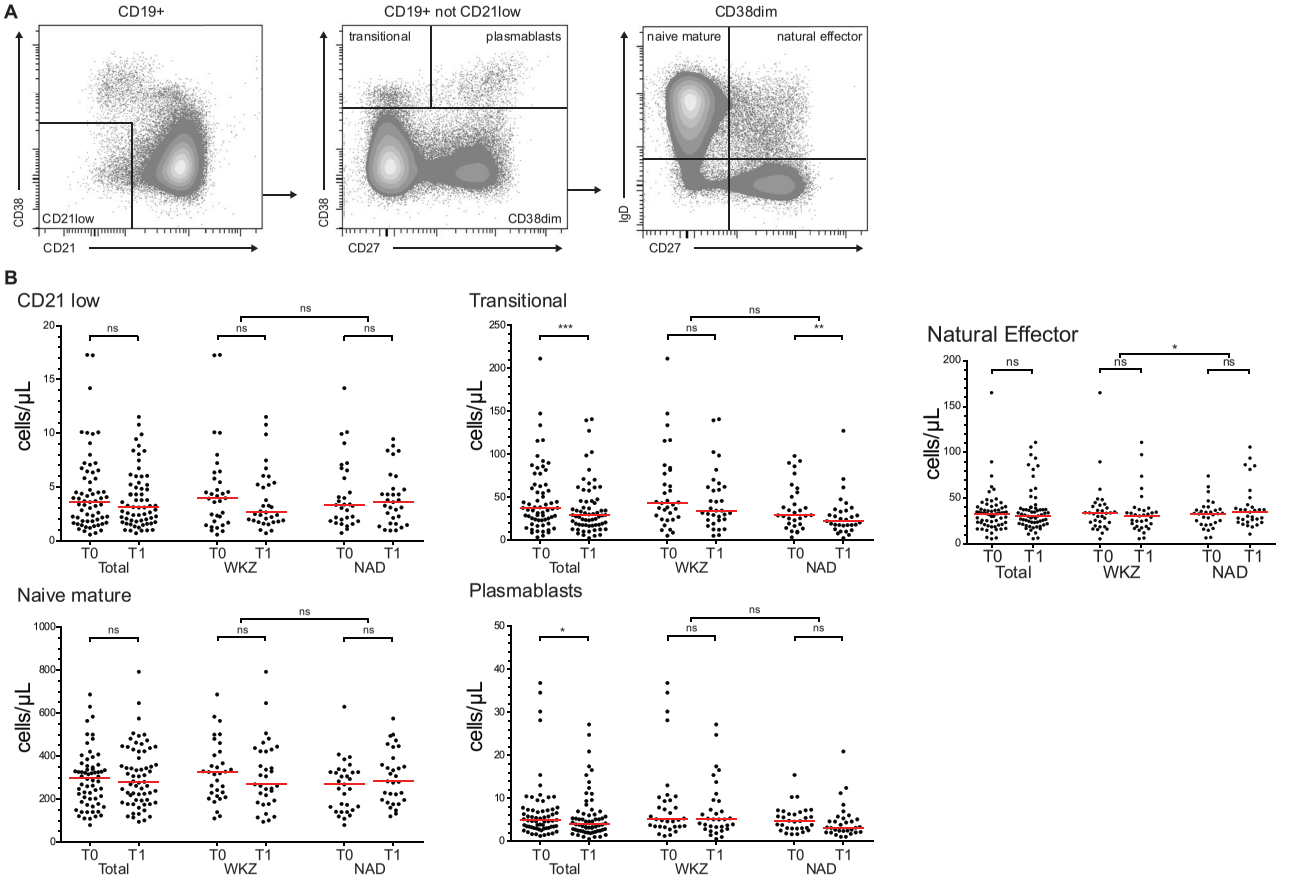

Figure 4 Major B-cell subsets. A. Representative image from flow cytometric gating strategy of major B-cell subsets. **B**. Absolute counts of major B-cell subsets. Each dot represents one individual, and horizontal lines median values. Statistical analysis within the groups was performed with the Wilcoxon signed rank test, analysis between the groups was performed with analysis of covariance. *P<0.05, **P<0.01, ***P<0.001

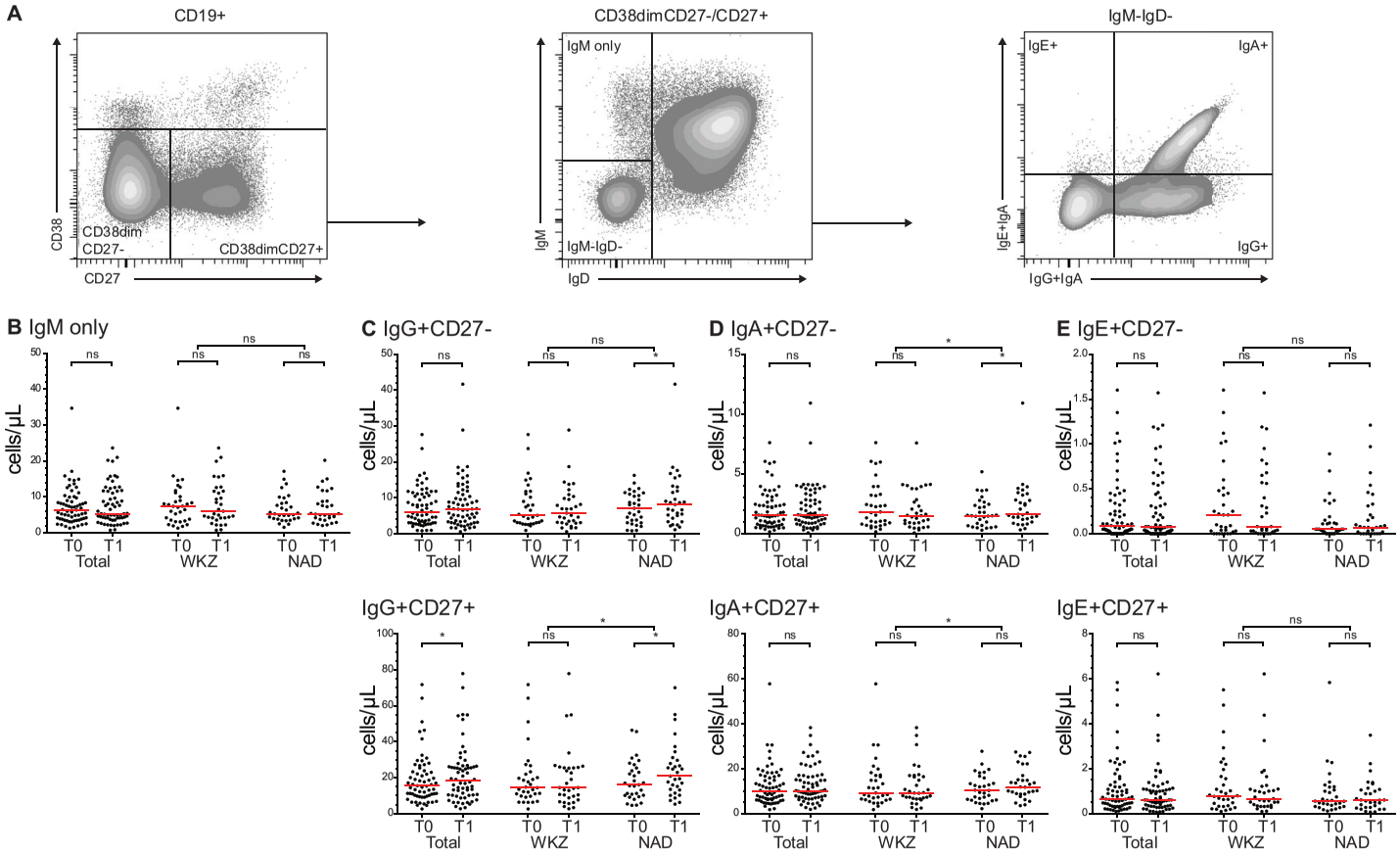

Figure 5 Memory B-cell subsets. A. Representative image from flow cytometric gating strategy of memory B-cell subsets. **B**. Absolute counts of IgM only B cells **C**. Absolute counts of CD27- and CD27+ IgG memory B-cells. **D**. Absolute counts of CD27- and CD27+ IgA memory B-cells. **E**. Absolute counts of CD27- and CD27+ IgE memory B-cells. Each dot represents one individual, and horizontal lines median values. Statistical analysis between the groups was performed with the Wilcoxon signed rank test, analysis between the groups was performed with analysis of covariance. *P<0.05

Table 2 Summary of significant effects after treatment

Parameter	WKZ	NAD	Different effects between groups
SA-EASI	↓	↓	*
TARC	-	↓	
Eosinophils	-	↓	*
T-cell subsets			
Total CD3+ T-cells	-	↑	*
CD8+	-	↑	
CD8+ TemRO	-	↑	
CD4+ Tcm	-	↑	*
Memory Tregs	↓	↓	
Th2	↓	-	*
Th2 CCR7-	↓	-	
Th2 CCR7+	↓	↑	*
B-cell subsets			
Transitional	-	↓	
IgA+CD27- memory	-	↑	*
IgG+CD27- memory	-	↑	
IgG+CD27+ memory	-	↑	*
IgE+ plasmablasts	-	↓	

↑ indicates significant increase; ↓ indicates significant decrease; - indicates no change; * indicates significant different effect between groups after treatment. WKZ, outpatient treatment at sea level; NAD, inpatient treatment at alpine climate

Discussion

We here report that clinically successful interventions of children with atopic dermatitis, either at maritime climate (outpatient treatment) or at alpine climate (inpatient treatment), differentially affect the immune system. Reduced disease activity after 6 weeks of treatment in both groups, quantified by SA-EASI and by serum TARC levels after alpine climate treatment, was accompanied by a decrease in circulating memory Tregs, transitional B-cells and plasmablasts. Moreover, 6 weeks of alpine climate treatment resulted in significantly lower disease activity scores and blood eosinophil counts than treatment at sea level, and was associated with higher numbers of Th2 and memory B cells (for summary of significant effects see Table 2). Thus, inpatient alpine climate treatment appears to have unique effects on the patient's immune system.

A notable reduction was found in memory Treg cell numbers following therapy, irrespective of the treatment protocol. Patients with AD have increased numbers of Tregs in blood as compared to healthy controls.[25-27, 45] Furthermore, Treg numbers positively correlate with AD disease activity.[29] It is thought that the increase in Treg numbers is a response to the chronic inflammation, and the numbers go down upon suppression.[28, 46] Although it cannot be excluded that therapy induces a Treg influx into the skin and thereby locally reduces skin inflammation. Still, considering the decrease in disease activity following treatment in our patients, the reduction in Treg numbers is a reflection of successful treatment. Although it is not entirely sure if Tregs migrate to skin Hence, Treg cell numbers could be a good general marker for treatment evaluation.

In addition to Tregs, transitional B-cells and plasmablasts also decreased after intervention. Transitional B-cells are recent bone marrow emigrants that can further develop into naive mature B-cells.[43] These functionally immature cells respond poorly to IgM stimulation and can exert regulatory functions via the production of IL-10, thereby dampening immune responses and inflammation.[47, 48] Transitional B-cells are reported to be expanded in patients with AD, although reports on this are not conclusive.[31, 44] Similar to memory Tregs, the decline in transitional B-cells can be the result of a decrease in disease activity. It remains to be studied if treatment directly affects survival of transitional B cells or the B-cell output from the bone marrow.

Plasmablasts are antibody producing cells that are mostly short-lived and can be precursors to long-lived plasma cells. Although our measurements were performed after freezing and thawing of cells, which could affect plasmablast numbers, there are no indications that study samples are differently affected by this. In the case of AD, where high levels of allergen specific IgE is one of the hallmarks of the disease, plasma cells are potentially important contributors to the disease.[31] Blood plasma cell numbers increase during active immune responses, as illustrated by acute infections and following vaccinations.[49, 50] Our finding that plasmablast numbers decrease upon treatment are in line with the previously established correlation with active inflammation. In addition, we stained plasmablasts for IgE, IgA and IgG and found that the largest reduction was found in IgE+ plasmablasts. However,

since surface immunoglobulin staining of plasmablasts is controversial the latter result must be interpreted with some caution, although other studies also report high numbers of IgE+ plasmablasts in patients with AD.[31]

Besides the common effects of intervention, we also observed several differences in B- and T- cell subsets between the two treatments. The significantly larger decreases in SA-EASI and serum TARC levels after alpine climate treatment were accompanied by an increase in total CD3+ T-cells. This was mainly due to increased numbers of CD8+ TemRO T-cells and T-helper 2 cells. As these are memory T cell subsets, their increased numbers could reflect increased maturation following an immune response. However, this is unlikely as the patients showed decreased disease activity and inflammation. An alternative cause for their increased numbers in blood is their re-localization from tissue. The skin harbors large numbers of immune cells, and especially Th2 cells are increased in AD lesions.[15] In addition, CD8+ T-cells have been found to infiltrate lesional skin of patients with AD.[51, 52] This can even result in decreased numbers of blood CD8+ T-cells and a higher CD4/CD8 ratio than healthy controls.[53] The increase of CD8+ TemRO and CD4+ Th2 cells following alpine climate treatment could reflect the normalization of AD skin lesions and redistribution of the memory T cells to the peripheral blood.[54-56]

Another hypothesis could be that these patients with chronic AD were skewed towards Th1 dominance prior to the intervention. Following treatment in the alpine climate with reduced disease provoking allergens, this chronic Th1 response may have subsided and the immune system could have reverted to the original state that was prone to Th2 predominance.[57] Due to the reduced allergenic pressure in the alpine climate the Th2 response is minimal and markers of the Th2 response, such as TARC and eosinophils, are reduced. This hypothesis would also explain the lack of no long-term differences between alpine climate treatment and the outpatient treatment program at moderate maritime climate (Fieten et al. submitted). Treatment in the NAD group may have dampened inflammation, but not have reset the immune system. Rather, our results show that the immune response remained skewed towards Th2, which could underlie the renewed inflammation upon return to maritime climate with higher allergen exposure.

In addition to memory T cells, alpine climate treatment also resulted in increased memory B-cell numbers. IgA+CD27-, IgG+CD27- and IgG+CD27+ memory B-cells were significantly increased, and the effects on natural effector and IgA+CD27+ memory B cells were significantly different from treatment at sea level. Since almost 80% of our patient population was additionally diagnosed with asthma, it could be speculated that the IgA+ memory B-cells may have migrated from the lungs into the peripheral circulation after clinical improvement of asthma. This is supported by additional analyses demonstrating that improvement of asthma, measured as lower exhaled nitric oxide levels, correlated with an increase of IgA+CD27- and IgA+CD27+ memory B-cells in peripheral blood. Yet, we here did not directly investigate any skin homing markers on B-cell subsets. Importantly, despite the observed effects on memory B cells, the IgE+ B-cells were not affected by either treatment. As

the CD27-IgE+ subset has been shown to be significantly increased in patients with AD,[32] the current data suggests that these numbers are not normalized following intensive treatment for 6 weeks. Since the favorable outcome of alpine climate treatment on disease severity did not persist until 6 months after treatment (Fieten et al. submitted), our observed effects on the immune system are most likely a result of reduced disease activity rather than a cause for reduction in disease severity.

The main objective of treatment comparison was to assess the effects of different climates on treatment of patients with AD. Beneficial factors ascribed to treatment in the NAD group are the characteristics of the alpine climate, which include reduced air concentrations of allergens and pollutants and a higher exposure to UV radiation.[58] In asthma, and to a lesser extent AD, reduced allergen exposure has been linked to a decrease in peripheral eosinophilia.[59-64] Indeed also in our study, after treatment, blood eosinophils were significantly lower in the NAD group. Furthermore, UV radiation exposure can lead to immunosuppressive effects, and specifically can activate local apoptosis in T and B-cells and result in decreased cytokine productions involved in lymphocyte activation and trafficking.[65-67] However, direct sunlight exposure to the skin was limited and patients were protected with sun cream.

Previous studies have reported that climate therapy can lead to reduced use of topical steroids.[12, 68] Furthermore, in our study, systemic medication, such as cyclosporine, was more frequently prescribed in the WKZ group than in the NAD group. Therefore, we have corrected for these confounding variables in our statistical analysis.

Both treatment protocols involved intensive medical supervision by multidisciplinary teams of healthcare professionals, and resulted in decreased disease activity scores after 6 weeks of treatment with sustained beneficial effects lasting for >6 months (Fieten et al. submitted). Because treatment effects were lasting, we hypothesize that treatment did not only suppress allergic responses but also altered the immune balance in the patients. As these changes had been induced during therapy, the effects present directly after treatment could be predictive of long-term treatment success. In the present study we did not investigate the long-term effects on the immune compartment, but it would be interesting to study the effects 3 months and 6 months after treatment completion and observe if treatment led to an altered peripheral immune system.

Conclusion

Intensive treatment of children with moderate to severe AD affected blood T- and B- cell subsets. In addition to changes in Treg, transitional B cells and plasmablasts upon treatment in both a moderate maritime and an alpine climate, the latter also resulted in additional changes in circulating CD8+ TemRO, Th2 and memory B-cells.

Acknowledgments

The authors are indebted to the children and their parents for participating in the study and to J. Beutler, research nurse for assistance in collection of the samples. This work was

performed in part in the Department of Immunology of the Erasmus MC in the context of the Molecular Medicine Postgraduate School. The studies were financially supported by Grant S698 from the Sophia Children's Hospital Fund (SKF), patient support group 'Vereniging Nederland Davos', European Allergy and Asthma Center Davos and Merem Dutch Asthma Center Davos.

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8.

A personalized integrative multidisciplinary treatment program (PIM) for atopic children and adolescents with difficult to treat atopic dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease with a major impact on the life of patients and their families. In moderate to severe patients, it is often accompanied by other comorbidities. We developed a personalized integrative multidisciplinary treatment program (PIM) for children and adolescents with insufficient disease control despite current treatment strategies. PIM actively involves the child and his parents and combines patient designed treatment goals with a systematic multidisciplinary approach by the involved health professionals, including assessment of AD, other atopic, pediatric and mental health comorbidities and general well-being. Throughout the integrative treatment program, multiple health professionals worked on the same treatment goals simultaneously, each using treatment strategies from their own field of expertise. We noted that significant progress can be made in a short period of time and this program was very motivating for the children and their parents. PIM is a demanding and intense program, good communication skills are essential. We encourage a treatment approach like PIM to be explored by all clinicians who are involved with children with difficult to treat AD.

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease with a major impact on the life of patients and their families. Currently up to 20% of children and adolescents in Western Europe and the US are affected.[1, 2] Estimates of disease severity vary. The majority of children have mild AD (around 70%), whereas 30% of children have moderate to severe AD.[3] Approximately 10% of children with moderate to severe AD (3% of all affected children) do not respond well to regular treatment and are considered difficult to treat.[4]

Impact of disease

AD has a significant negative effect on the quality of life of affected children and their parents/families.[5] Children suffer from intense pruritus which often worsens during the night, resulting in disturbed sleep or frequent nighttime awakenings.[5, 6] The child's lifestyle is often limited with respect to clothing, holidays, staying with friends, owning pets, swimming or the ability to play or do sports.[5] Time consuming treatment regimens further decrease quality of life.[5] From all childhood diseases, it is estimated that AD affects quality of life more than asthma, cystic fibrosis or diabetes.[7]

Current treatment

According to current guidelines, AD treatment is aimed at optimizing the skin barrier function and controlling inflammation.[4, 8, 9] The use of emollients supports the skin barrier function, whereas topical corticosteroids of varying strengths or topical calcineurin inhibitors are used to control inflammation.[10] Patient and/or parent education is essential in AD treatment and includes information about the chronic and relapsing nature of AD, exacerbating factors, therapeutic options including explanation about benefits and risks, and managing expectations. UV therapy or systemic therapy with immunosuppressive drugs or alpine climate treatment (in Europe) may be advised in children with more severe disease.[11] Alpine climate treatment combines pharmacological anti-inflammatory treatment with being hospitalized for a period of 4 weeks to 3 months in a specialized clinic located in the alpine climate.[12]

Additional treatment approaches

Because of the chronicity of AD and the significant burden of disease for children with moderate to severe AD, additional treatment approaches have been developed in the last decades. Education programs with fixed contents have been developed for children, adolescents as well as parents to be used in adjunct to standard medical care.[13-16] In Europe, therapeutic patient education (TPE) programs were developed recently that offer tailored education and explicitly focusing on the transfer of skills instead of merely providing information or advice.[17, 18] In the USA, multidisciplinary treatment programs are designed to help children and their families to successfully manage and cope with AD.[19] Besides improving disease activity, these programs also address itching and scratching, sleep disruption, parental challenges

in disease management, education of children and their families, psychosocial problems, and adherence to treatment.[20, 21] However most specialized AD programs are more suitable for younger children and their parents, and there are few possibilities for older children and adolescents that specifically address their needs.[15]

Other comorbidities

AD is very often accompanied by other atopic comorbidities, especially in the group of children with more severe disease.[3] AD severity and early AD onset directly correlate with the future risk of developing asthma, allergic rhinitis or food allergies.[22-24] The exclusion or confirmation of a food allergy is important, since children often have unproven elimination diets that are supposed to improve AD severity, but may result in nutritional deficiencies.[25] Being diagnosed with multiple atopic comorbidities increases the burden on the child and family and may negatively affect adherence to treatment and perception of symptoms. Because of the use of corticosteroids in AD treatment and its possible side effects on the adrenal function, it is important to regularly monitor the growth of the child. Obesity has been observed more frequently in children with AD compared to children without AD.[26] In children with AD exercise, heat and sweating have been identified as exacerbating factors which may contribute to reduced physical fitness.[27, 28] Children with AD also experience signficant psychosocial and behavioral problems compared to their peers.[29, 30] More recently, an association has been suggested between AD and the development of mental health disorders such as ADHD and depression, with increasing AD severity increasing the risk.[31, 32]

Aim

We developed a personalized integrative multidisciplinary treatment program (PIM) for children and adolescents with moderate to severe AD that was considered difficult to treat. Using this program in an inpatient as well as an outpatient setting, we were able to improve disease activity, quality of life and general wellbeing in a group of patients who were unable to respond sufficiently to treatment according to current guidelines.[33]

Detailed description of PIM

PIM: Evaluation of problems

Jonathan is a 14-year old boy, suffering from atopic dermatitis (AD), allergic rhinitis, asthma and food allergy. Jonathan sleeps badly mainly because of continuous itch. During the day he is tired, irritable and feels depressed. Jonathan's mother has become desperate. Jonathan's late sleep onset and frequent nightly awakenings affect her sleep and Jonathan's school performance and attendance. She is fed up with the constant fighting about his AD treatment. Jonathan is referred to PIM (a 6 week personalized integrative multidisciplinary treatment program) by his dermatologist. Before visiting our center, Jonathan and his mother completed a digital questionnaire about symptoms of AD, asthma, rhino conjunctivitis, food

allergy, and the impact of these diseases on family life as well as general wellbeing. The dermatologist and dermatology nurse assessed eligibility for participation in PIM.

PIM: Development of the treatment plan

Standardized questionnaires (available online through publishers) are used to identify problems or other aspects that may need additional attention during the intervention. At the day of the first visit Jonathan and his mother are consecutively seen by the case manager, dermatologist, dermatology nurse, pediatrician-allergist (within PIM a pediatrician trained as an allergist), pediatric psychologist and physiotherapist for an extensive assessment. This involves the skin and other atopic, pediatric and mental health comorbidities, but also general wellbeing, including school absence, physical fitness, and knowledge of treatment guidelines. Jonathan indicates which problems he experiences and what he would like to be different at the end of PIM. A detailed description of the problems Jonathan described to each health professional can be found in PIM Box 1.

At the end of the day of the first visit, the identified problems from the perspective of the child and/or the parents, and the professionals are discussed among the members of the multidisciplinary team. The professionals plan a stepped integrated intervention strategy and create a structured treatment plan using a goal-oriented approach. The treatment goals are then discussed and prioritized regardless of the nature of the problems (i.e. medical problems are not necessarily addressed first) together with Jonathan, his mother, and the members of the multidisciplinary team. Jonathan's treatment plan consists of the following goals:

- I want to get up in the morning and do my treatment without having discussions about this with my mother
- I want to sleep better and have a normal school schedule
- I want to have a better looking skin and be slimmer
- I want to have more control about my itch
- I would love to play soccer again and see my friends
- I would like to be more cheerful (less depressive)

The treatment goals and corresponding intervention strategies are evaluated continuously during and after the intervention in the team. Examples of treatment goals and strategies are shown in PIM Table 1. The dermatologist has the final responsibility for the total treatment plan.

PIM Box 1: Description of the problems Jonathan experiences

Dermatologist: Jonathan says that the itch drives him crazy. He wants his skin to look normal and he wants the itching to stop. He further mentions he feels sad about his disease and himself. Jonathan's mother mentions that the topical treatment that Jonathan received until now has not been effective. Jonathan's medication has been prescribed by the dermatologist in the past. Both the general practitioner and the pharmacist warned Jonathan's mother for the consequences of frequent use of topical corticosteroids. She tells the dermatologist that she is confused by the conflicting advice. The answers to the AD treatment management questionnaire confirm a lack of knowledge on frequency of TCS application during a flare, amount of TCS to be used and potency of the currently prescribed TCS.

Dermatology nurse: Jonathan explains that he tries to treat his skin twice a day, but it takes a lot of time. He finds it difficult to be compliant and thinks treatment will not be effective anyway. Furthermore it can be painful to apply the ointment to the skin. When the dermatology nurse asks Jonathan and his mother to assess Jonathan's skin, she notices that they recognize the severe AD spots but not the lesions with mild AD and the lesions that are lichenified. The same is seen when the nurse asks which lesions are treated. The SAEASI by Jonathan demonstrates a lower score compared to the nurse, suggesting that Jonathan underestimates his AD.

Psychologist: Jonathan says that he hopes to sleep and feel better and to experience less itch. Jonathan says he is going crazy because of his itch and sometimes wishes to be dead. His mother hopes that Jonathan will be happier; Jonathan withdraws to his bedroom many times because he feels so miserable. She also hopes that he feels more responsible for his own treatment. Jonathan is asked to imagine this situation after the end of PIM and to make a drawing of it. The questionnaire confirms Jonathan's feelings of depression. Regarding the family situation, Jonathan says that he lives with his mother. He is not in contact with his father. Jonathan is in the second class of high school and he has a few friends. Because of his sleeping problems, Jonathan usually arrives at school at 11 o'clock. If the absence does not change, Jonathan will not move to the next class, despite his average intelligence level (confirmed with an intelligence test).

Pediatrician-allergist: Jonathan says that he has quit playing soccer because of complaints of fatigue and breathlessness. His runny nose also bothers him. He doesn't consume milk, peanut, nuts and fruit products; a diet started at a very young age and was advised at that time as AD treatment.

Physiotherapist: the maximal cycle ergometer test confirms Jonathan's low physical fitness.

PIM Table 1: Examples of treatment goals addressed within PIM and corresponding intervention strategies by the professional

Treatment goal from patient perspective	Description of intervention	Health professional
I want to...		
Look better and have less itch	Optimize treatment	Dermatologist
	Discuss effects and side effects	Dermatologist
	Demonstration of topical treatment	Dermatology nurse
	Lifestyle advise (e.g. shower behavior)	Dermatology nurse
	Controlling scratching by habit reversal	Pediatric psychologist
	Relaxation techniques	Pediatric psychologist
	Strategies to improve adherence, e.g. patient education about itching-scratching circle, traffic light approach, implementation of therapy in daily schedule and general coaching	All health professionals
Stop my running nose and itchy eyes	Recognize symptoms of asthma, rhinitis	Pediatrician-allergist
	Optimize treatment of asthma, rhinitis	Pediatrician-allergist
Know what I can and cannot eat	Dietary assessment and food reintroduction	Pediatrician-allergist / Dietician
	Assessment of food allergies	Pediatrician-allergist
	Knowing how to handle in case of adverse reaction	Pediatrician-allergist
	Relation between food and AD	Dermatologist
	Treatment of fear of certain foods/ fear of adrenaline auto-injector	Pediatric psychologist
Be fit and sleep better, reduce school absence	Analysis of sleep problems	Pediatrician-allergist / Pediatric psychologist
	Medication for earlier sleep onset (melatonin) and rhinitis (anti-histamines)	Pediatrician-allergist
	Psycho-education about sleep and advices on sleep hygiene	Pediatric psychologist
	Hypnotherapy and relaxation techniques to improve sleep	Pediatric psychologist
	Assess physical fitness	Pediatrician-allergist / Physiotherapist

PIM Table 1 Continued

	Evaluate asthma, rhinitis, food allergy, condition, weight and growth	Pediatrician-allergist
	Patient education: importance of sports	All professionals
	Individual sporting advice	Physiotherapist
	Optimize all atopic comorbidities	Dermatologist / Pediatrician-allergist
	Make a daily schedule of regularity and set times for sleeping, school presence, homework etc.	Pediatric psychologist / Dermatology nurse
	Contact school and make a stepped plan for extension of school presence	Pediatric psychologist
Concentrate better	Neuropsychological /cognitive evaluation	Pediatric psychologist
	School and learning advices including planning of homework	Pediatric psychologist
	Advice about balancing mental efforts and physical/relaxing activities	Pediatric psychologist
Reduce tension about the atopic treatment with my parents	Consistent integrated treatment advice from all involved health professionals	All health professionals
	Parenting advise including autonomy of the child in his treatment	Pediatric psychologist
	Personalized daily treatment plan and lifestyle advice	Dermatology nurse
	Improve coping with disease	Pediatric psychologist
	Self-assessment with patient-oriented severity assessment tool to recognize flares	Dermatologist / dermatology nurse
Feel happy and optimistic	Reach above treatment goals	Child / parents and all health professionals
	Discuss what is needed to help the child sustain his goals	Child / parents and all health professionals

PIM: the intervention period

1. Atopic dermatitis

The dermatologist evaluates the medical history and explains the course of AD; that it is characterized by exacerbations and remissions; that it is essential to monitor the skin regularly (this can be done by Jonathan or his mother) and that appropriate action should be taken when needed. The dermatologist gives an overview of the currently available AD treatment, with careful explanation of its use and occurrence of side effects. In order to reduce the severe AD and itch, the dermatologist adjusts treatment with more potent topical

corticosteroids and provides specific instructions how to use it. The fingertip unit is explained. A personal action plan is provided which indicates how to phase out or step up treatment depending on AD severity using a traffic light approach. Within this approach, red is used for exacerbations, orange when the skin lesions improve after an exacerbation and green for the controlled phase where topical treatment continues in a lower frequency and potency. The dermatology nurse takes Jonathan's intelligence profile into account while designing his personal action plan and adds pictures of his skin to the traffic light colors to help him decide in which phase his skin is. The dermatology nurse provides a try-out of different emollients and prescribes one that has been chosen by Jonathan himself.

2. Other atopic comorbidities.

Because of the severity of AD symptoms and the focus on AD related problems, other atopic disorders might be viewed as secondary by both the children, parents as well as health care professionals. The pediatrician-allergist systematically assessed symptoms of allergic asthma, rhinitis and food allergy. The pediatrician-allergist took a detailed medical history, physical examination and additional tests (spirometry, metacholine challenge, total IgE, specific IgE for aeroallergens and food allergens, DBPCFCs for children suspected of food allergy).

Some children with severe asthma did not even notice they had difficulty breathing because of the predominant symptoms of itch. Jonathan had to quit soccer, but his mother was surprised by the bad results of the lung function test and the subsequent diagnosis of asthma. The pediatrician-allergist initiated or optimized asthma and allergic rhinitis treatment and advised to start playing soccer again. The diet was reevaluated and adjusted: milk and some fruits were reintroduced successfully in Jonathan's diet with the help of a dietician. The elimination diet for nuts and peanuts was continued, based on a positive DBPCFC.

3. Mental health comorbidities.

As a consequence of AD most patients have to cope with relapses, itch, sleeping problems and intensive treatment. This requires appropriate management skills of patients and families. Meanwhile AD can be related to psychological complaints of depression and concentration. The pediatric psychologist assesses disease management abilities, cognitive abilities, and mental health and instructs patients about therapeutic techniques. Habit reversal is used to teach Jonathan how he can control his scratching behavior. He develops an active coping strategy instead of retiring to his room. Cognitive behavioral therapy focused on coping with itch and worries about his AD, but also addressed the negative thoughts about the relation with his father and his depressive feelings.

Together with the school mentor, a plan is made to optimize school presence gradually in the next weeks. Every week school presence is increased with one hour until optimal school attendance is obtained. Meanwhile the psychologist discusses sleep hygiene advice (about regularity, doing sports/being outside, screen time, food and drinks) for better sleep,

especially earlier sleep onset. She also teaches him relaxation techniques: a combination of muscle relaxation and hypnotherapy. Hypnotic suggestions of a cool environment or a fresh breeze helped Jonathan to relax and to experience less itch before going to sleep.

4. Other pediatric comorbidities.

The pediatrician-allergist assesses the amount and side-effects of the total used medication (together with the dermatologist) and general health status, including physical activity and obesity. The chronic inflammation and the chronic use of potent topical steroids or systemic immunosuppressive drugs indicates growth monitoring of the child or the assessment of other symptoms that are related to a hypothalamic-pituitary-adrenal axis alteration.

The pediatrician-allergist concludes normal growth and no other potential side-effects of steroids used and a good general health. However Jonathan is a little overweight, probably as a consequence of quitting sports. During PIM, all children are encouraged to exercise on a regular basis using the personalized action plan of the physiotherapist, when needed under supervision of a physiotherapist near home or with special programs for children with chronic disease.

5. Adherence to treatment.

Adherence to treatment is an important treatment goal that occurred in almost every treatment plan. The dermatologist and pediatrician-allergist prescribe treatment, but the nurse helps with the organization of treatment regimens taking into account family and school life, whereas the pediatric psychologist guides the process of autonomy development. Younger children are dependent on their parents for their daily AD treatment and the correct treatment regimen, but a shared routine (for example child does front and parents do the back) gradually leads to independence where the child is responsible for his or her own treatment. The nurse made a daily therapy schedule together with Jonathan in which all medicines and activities are noted, including medication for asthma and allergic rhinitis. Jonathan was asked to keep a medication diary to give him insight into his adherence to treatment.

Discussion

Patients that may benefit from PIM

AD is in most cases treated with good results with conventional treatment strategies.[8, 9] We developed a personalized integrative multidisciplinary treatment program (PIM) for children and adolescents with insufficient disease control. PIM uses a systematic multidisciplinary treatment approach with clearly defined goals and strategies that address AD as well as other atopic, pediatric and mental health comorbidities, and general well-being. PIM is especially suitable for children or adolescents who experience a significant impact on their or their families quality of life, children with repeated treatment with potent topical corticosteroids or systemic immunosuppressive treatment, children with several atopic and non-atopic comorbidities, children who seem unresponsive to conventional therapy and children with a need for in-depth education, as has been suggested previously.[21, 34]

In case of treatment failure

In some children, obvious factors such as wrong topical application techniques cause treatment failure. However, in this group of children with difficult to treat AD, a combination of multiple medical, psychological and social factors often lead to treatment failure. Problems with acceptance of the disease, difficult family circumstances or limited cognitive abilities of the child and/or the parents may hinder proper AD management. Financial problems or mental health comorbidities such as ADHD or depression may also directly influence a child's or parent's abilities to be adherent to therapy. In daily practice, there is often no time to obtain or address these problems and/or they are too complicated for a single health professional to treat in a regular outpatient setting.

Systematic evaluation concerning all domains for example by assessing lungfunction in all children resulted in asthma diagnosis and the need to step up treatment in some children. Standardized psychological assessment in PIM revealed that itching and scratching, associated sleep problems and parental stress related to AD were very common which supports the need for integrating psychological treatment with clinical care. The importance of integrating medical and psychological health care has been stressed previously.[20] During PIM, treatment with similar potency drugs as before resulted in significant disease improvement, most likely because underlying problems were also addressed systematically. The active involvement of the child/adolescent and his family within PIM, especially when a history of treatment failure exists, contributed to the treatment results. The personalized treatment approach in PIM allowed for different intervention strategies based on the best fit for an individual child or family situation.

Working together

Several health professionals were involved in PIM: a dermatologist, pediatrician-allergist, dermatology nurse, case manager, pediatric psychologist and physiotherapist. The

consultations with the involved health professionals were framed within the integrative program and all the health professionals within the treatment team were involved with every child (there was no possibility to opt-out). Throughout the treatment program, professionals worked on the same treatment goals simultaneously, each using treatment strategies from their own field of expertise (Table 1). Multidisciplinary team meetings were used to integrate, coordinate and discuss the initiated actions. This approach allowed us to reach multiple goals at the same time more effectively and address problems on one domain that prevented progress in another domain, for example regarding adherence or itch reduction. When itch is simultaneously treated with medication, education and cognitive behavioral therapy to reduce scratching behavior, the effects of the different therapies reinforce each other.

Case management

To be able to offer this kind of integrative care, a case manager is essential (preferably an experienced senior nurse). The case manager plays an important role to guide and accompany the patient on his journey during the intervention and in the period afterwards. The case manager coordinates the intervention days and pays extra attention to children with little parental support or families with multiple problems or busy schedules. She stresses the importance of completing the intervention period and conveys the consultations with all involved professionals including the dermatology nurse and the psychologist as an essential element of the intervention. Furthermore, the case manager supports the multidisciplinary team by scheduling the team meetings and the consultations with children, and initiates the effort to coach the children to attend an appointment with phone calls or emails. Digital resources were used to support PIM. In case of questions or problems at home, children and parents could easily contact the multidisciplinary treatment team using e-consultation or access their electronic patient record.

Strengths and weaknesses of PIM

Strengths of PIM are the personalized patient-centered approach and the integrative multidisciplinary team effort. PIM can be used for children and adolescents, in an inpatient and outpatient setting. Both settings are equally effective on the long-term. Regular evaluation with the child during PIM, focusing on the treatment goals, and knowing there is a limited six week treatment period to reach the goals was motivating for the child, the parents and the treatment team.

Communication is the largest pitfall within PIM. An integrative multidisciplinary team approach requires great communication skills, concerning communication with the child and family as well as among health professionals. We made sure that all involved health professionals within the team conveyed the same message, that the impact of AD for the child and the family was acknowledged and concerns were never dismissed without proper explanation. Communication among health professionals required sharing of relevant

observations and results, and trust in the leadership of other health professionals. There was increasing synergy within the team over time which contributed to the results.
PIM is a demanding and intensive program, for the children and their parents as well as for the involved health professionals. Most children and their parents were very motivated to participate in the program and expectations were high, since it appeared to be a last resort for most families.

Outlook to the future

There were differences between children in their ability to successfully implement the offered tools, such as the personalized action plan and regular skin monitoring using the SA-EASI. Some children managed to be very successful in controlling their AD after participating in PIM. However, some children experienced more problems and were less able to sustain the improved disease activity. In the future, booster sessions during the first year after the end of PIM may be helpful. Future studies will focus on this and the most optimal way to prevent relapse. A new version of the digital platform has been developed according to the model of DermHome - a personal health record model for skin / allergic diseases adopted by the Dutch dermatologist association.[35] This platform is available for patients and involved professionals.

Conclusion

AD is the most common chronic skin disease in children and in most cases treated with good results with conventional treatment strategies. A personalized integrative multidisciplinary treatment program (PIM) was described for treatment of children and adolescents with insufficient disease control, using a systematic multidisciplinary team approach that addresses AD as well as other atopic, pediatric and mental health comorbidities and general well-being. We encourage this approach to be explored by all clinicians involved with children with difficult to treat AD.

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9.

Predictors of treatment success in children with difficult to treat atopic dermatitis using a personalized integrative multidisciplinary treatment program (PIM)

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Submitted

Abstract

A personalized integrative multidisciplinary treatment program (PIM) was developed for children who are unresponsive to conventional treatment according to current guidelines. The aim of the present study was to identify child and parent clinical and psychosocial characteristics that predict long-term treatment success after PIM. Treatment was considered successful when there was a 75% reduction on the Self-Administered Eczema Area and Severity Index and/or little impact of AD on the Children's Dermatology Life Quality Index, six months after PIM. The majority (77%) of children with difficult to treat AD demonstrated long-term treatment success with PIM. Predictors of long-term treatment success included maternal disease acceptance OR (95%CI) 1.84 (1.15 – 2.94). A small group (23%) of children, mostly girls OR (95%CI) 0.10 (0.02 – 0.54) with multiple somatic complaints OR (95%CI) 0.88 (0.80 – 0.97), from families where the mother has anxiety for the use of topical corticosteroids OR (95%CI) 0.62 (0.40 – 0.94), is less likely to obtain long-term treatment success.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Its prevalence has been increasing in recent decades, currently affecting 10% to 20% of children in Western Europe. [1] AD has a significant negative effect on the quality of life of affected children and their parents, with increasing disease severity further reducing reported quality of life.[2, 3] AD treatment is mainly aimed at controlling inflammation and optimizing the skin barrier function with topical treatment. AD is often accompanied by other atopic comorbidities, especially in the group of children with more severe disease.[4] Being diagnosed with multiple atopic comorbidities increases the burden on the child and family and may negatively affect adherence to treatment. Furthermore, children with AD experience significant psychosocial problems compared to their peers, and an association between AD and the development of mental health disorders such as ADHD and depression has been suggested. [5-7]

For most children conventional treatment according to current guidelines results in acceptable disease control. Nevertheless, approximately 3% of all affected children do not respond well to regular treatment and may be considered difficult to treat.[8] For these children additional treatment approaches have been developed, such as therapeutic education programs and multidisciplinary programs to help them successfully manage and cope with AD. [9-13] However, there are few treatment possibilities specifically for older children and adolescents.

We developed a personalized integrative multidisciplinary treatment program (PIM) for children aged 8 to 18 years with difficult to treat AD. PIM includes assessment of other atopic, pediatric, mental health comorbidities, and general well-being. It is a resource and time intensive program. Therefore, it is important to identify children who will or will not benefit from the program. The aim of this study was to identify clinical and psychosocial characteristics of children and their parents that predict long-term treatment success after treatment with PIM.

Methods

Patients

Children (8-18 years) with difficult to treat AD were referred to our academic national tertiary referral center to participate in PIM. We considered moderate to severe AD seemingly unresponsive to conventional treatment according to current guidelines difficult to treat AD. More specifically, children who were dependent on use of at least a moderate potency topical corticosteroid and were not able to step down; or with a history or current use of systemic immunosuppressive treatment; or who were treated repeatedly with high potency topical corticosteroids or systemic immunosuppressive treatment; or who experienced a significant impact of AD on the child's or the families quality of life were eligible to participate in PIM. We included 74 children who were treated with PIM during the DAVOS trial and completed the 6 month follow-up period (see chapter 6).

Study design

PIM was used as a treatment approach in the DAVOS trial, a pragmatic trial that aims to investigate the long-term effectiveness of alpine climate treatment.[14] The trial is registered at Current Controlled Trials ISRCTN88136485. All children and when appropriate their parents provided written informed consent to participate in the trial. Study procedures were reviewed and approved by the institutional review board of the University Medical Center Utrecht, the Netherlands (09-192/K).

Description of PIM

PIM is a personalized, integrative multidisciplinary treatment program with clearly defined goals and strategies, based on the perspective of the child and parents. It is suitable for children and adolescents. During PIM, AD as well as other atopic, pediatric and mental health comorbidities, and general well-being are addressed. PIM is a six week program followed by an easy access phase of six months. The dermatologist and dermatology nurse assess eligibility for participation in PIM. A roadmap describing the most important elements of PIM is shown in Table I.

At the day of the initial visit, child and parents were consecutively seen by the case manager, dermatologist, dermatology nurse, pediatrician, allergist, and pediatric psychologist. The child and his parents explicitly specified the current problems and verbalized treatment goals, which is part of the patient-centered treatment approach. At the end of the day of the first visit, the multidisciplinary treatment team discussed and prioritized the problems, regardless of the nature of the problems (i.e. medical problems were not necessarily addressed first). A structured treatment plan was created using a goal-oriented approach based on the child and parents' perspective.

During the six week intervention period the children were seen almost on a weekly basis in the outpatient clinic. In this period, children had 5 consultations with the dermatologist (30 minutes) and the dermatology nurse (30 minutes), 4 consultations with the pediatrician-allergist (30 minutes), and 3 consultations with the psychologist (45 minutes). During the six week intervention period, strategies were already developed for the period after the end of PIM. This concerned treatment goals that were addressed during the intervention period but also treatment goals that could not be completed within this period. At the end of the intervention period an evaluation of the treatment goals with child and parents was conducted by each health professional. The child, parents and health professionals specifically discussed what was needed to succeed in sustaining the treatment goals during the period after PIM has ended.

All children and parents were offered the possibility for easy-access contact with the multidisciplinary team via the nurse during the following six month period using a digital platform for AD.[15] Some children and parents were also referred to health care specialists closer to their home to address ongoing problems (for example diagnostics and treatment of ADHD or autism, help to overcome obesity, help to improve family relations).

Table I PIM Roadmap

1: Multidisciplinary treatment team	Dermatologist, dermatology nurse, pediatrician-allergist, pediatric psychologist and physiotherapist, supported by a case manager
2: Evaluation of problems	Based on the perspective of the child and parents Systematic evaluation of all possibly relevant factors Start the evaluation with a blank history, repeating previous evaluations and re-evaluate current treatment strategies
	Include assessment of AD, other atopic and pediatric comorbidities, mental health comorbidities and general well-being (school absence, physical fitness, knowledge of treatment)
3: Development of the treatment plan	Use a positive, goal-oriented approach (I want to.....) Make sure treatment goals match the problems defined by the child and parents Agree on treatment goals with child, parent and treatment team Prioritize regardless of the nature of the problems Create personalized intervention strategies, adapted to emotional and cognitive development of child and parental capabilities
4: Intervention period	Make sure to address all relevant domains: AD / other atopic comorbidities / mental health / other pediatric comorbidities / adherence Simultaneously address different domains of the same problem Develop strategies for the period after the end of PIM Systematic evaluation during PIM with child and parents
5: Results	Evaluate the treatment goals and celebrate the result of PIM Decide on what is needed to sustain the treatment goals
6: Support	Weekly multidisciplinary team meetings Case manager Digital resources to support the program Synergy within the treatment team
7: Pitfalls	Communication Sharing relevant observations and results Trust the leadership of other health professionals

Responders / non responders

Treatment was considered effective, when clinically relevant improvement was observed on disease activity (SA-EASI scored by the parents) or quality of life (CDLQI) experienced by the child after six months. A relative improvement of 75% on the SAEASI was considered a clinically relevant improvement. We used severity banding to interpret CDLQI scores.[16] A score ≤6 corresponds to a small effect on the child's life. To define long-term responders, we used data from study inclusion or baseline, and the last follow-up assessment. Six months after the end of PIM, long-term responders demonstrated a reduction of at least 75% on the SAEASI and/or scored 6 or less on the CDLQI. Children were characterized as "responders" or "non-responders" in subsequent data analysis.

Predictors

Both children and parents completed questionnaires before the start of PIM and six months after the end of PIM.[14] Demographic and social characteristics were assessed with standard questionnaires. Clinical parameters were extracted from the digital patient file. Behavioral and emotional problems were assessed with the parent-completed Child Behavior Checklist, which includes the syndrome scales anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior.[17] Children's itching cognitions and AD specific coping were measured with the Dutch translation of the German coping with disease (COPEKI/JU) and itching cognitions (JUCKKI/JU) questionnaires.[18] Both child and parents completed the Dutch version of the State-Trait Anxiety Inventory.[19, 20] For parents, state anxiety concerned the use of topical corticosteroids whilst for children, state anxiety referred to how they felt at the moment they completed the questionnaire. Parental quality of life was assessed with a German disease-specific quality of life questionnaire translated into Dutch.[21] The questionnaire consists of 26 items measuring five domains: psychosomatic well-being, effects of the disease on social life, confidence in medical treatment, emotional coping, and acceptance of the disease.

Statistical analyses

Candidate predictors were based on literature and clinical experience. Univariate logistic analyses were done to identify predictors associated with responder status. Multivariate logistic regression models were used to explore the contribution of the candidate predictors on responder status using a backward selection procedure. Data was analyzed using IBM SPSS Statistics for Windows version 22.

Results

In total, 79 children with difficult to treat AD participated in PIM and long-term treatment results were available for 74 children (see chapter 6). There were no differences in baseline characteristics between the children who did and did not complete long-term study assessments (data not shown).

Six months after the end of PIM, the majority of children (77%, n=57) showed a 75% reduction of disease activity according to a clinical scoring system and/or indicated little impact on their quality of life and were characterized as responder. Table II describes the baseline characteristics of responders and non-responders, additional characteristics are presented in supplementary Table I.

Table II Baseline demographic and clinical characteristics of responders and non-responders

	Responder n=57	Non-responder n=17	p-value
Age (years)	12.4 (2.6)	13.2 (2.0)	0.206
Girls	23 (40%)	12 (71%)	0.051
SAEASI	39 (18.5)	34.5 (16)	0.361
CDLQI	7.9 (4.4)	10.5 (5.3)	0.074
AD onset in first 6 months of life	49 (86%)	14 (82%)	0.707
Asthma diagnosis	48 (84%)	15 (88%)	1.000
Rhinitis diagnosis	49 (86%)	16 (94%)	0.675
Food allergy diagnosis	39 (68%)	11 (65%)	0.775
Psychiatric diagnosis (DSM-V)	5 (9%)	3 (18%)	0.340
CBCL somatic complaints t-score[a]	63.0 (7.7)	68.0 (7.7)	0.020
Itching cognitions – coping	1.8 (0.8)	1.9 (0.5)	0.688
Current use of potent or very potent TCS	54 (95%)	15 (88%)	0.323
History of use of systemic immunosuppressives	34 (60%)	12 (71%)	0.353
TARC (pg/ml)	1085 (1560)	1119 (1300)	0.772

Data is described as mean(SD), median (IQR) or n(%) [a]The CBCL subscales can be seen in Supplementary Table I.

Most children were diagnosed with other atopic comorbidities such as asthma, rhinitis or food allergy. A majority of children had used systemic immunosuppressives in the past and most children were currently using potent or very potent topical corticosteroids. Girls were overrepresented in the group of non-responders and there were statistically significant more somatic complaints in this group.

There were 30/57 children who demonstrated both improved disease activity and quality of life, 6/57 children who demonstrated improved disease activity but not quality of life, and 21/57 children who experienced little impact on quality of life but demonstrated less than 75% reduced disease activity. We could not identify demographic, clinical or psychosocial characteristics that differed between these children.

The majority of the long-term non-responders (70%, n=12/17) demonstrated a 75% reduction of disease activity according to a clinical scoring system and/or indicated little impact on their quality of life immediately after the end of PIM.

Parental baseline characteristics are described in Table III. Mothers of responders indicated a higher psychosomatic wellbeing and better disease acceptance. Furthermore they indicated a significantly lower general anxiety and specific anxiety for the use of topical

corticosteroids. There were no statistically significant differences between the responders and non-responders concerning paternal quality of life and anxiety.

Table III - Parental characteristics of responders and non-responders

	Responder n=57	Non-responder n=17	p-value
Parental quality of life			
QoL mother psychosomatic wellbeing	33.1 (4.9)	29.8 (4.4)	0.016
QoL mother effects on social life	24.5 (4.4)	22.3 (4.0)	0.075
QoL mother satisfaction with medical care	19.0 (3.0)	18.1 (2.1)	0.248
QoL mother emotional coping with disease	14.3 (3.0)	12.9 (2.2)	0.080
QoL mother acceptance of disease	8.1 (1.6)	6.9 (1.3)	0.007
QoL father psychosomatic wellbeing	35.3 (4.6)	33.6 (5.8)	0.266
QoL father effects on social life	25.7 (3.1)	25.2 (4.4)	0.593
QoL father satisfaction with medical care	18.4 (2.6)	18.1 (3.2)	0.710
QoL father emotional coping with disease	14.9 (2.7)	13.5 (3.1)	0.128
QoL father acceptance of disease	7.7 (1.6)	6.8 (1.9)	0.075
State / trait anxiety			
STAI mother trait anxiety	4.3 (2.5)	5.7 (2.3)	0.045
STAI mother state anxiety topical steroids	5.7 (2.3)	6.9 (1.9)	0.038
STAI father trait anxiety	4.2 (2.5)	5.3 (2.7)	0.175
STAI father state anxiety topical steroids	5.7 (2.6)	6.5 (3.1)	0.338

Univariate analysis demonstrated no statistically significant influence of clinical parameters on responder status. In the final multivariate model, sex and somatic complaints of the child, as well as maternal fear of using topical corticosteroids, and maternal difficulties with disease acceptance were significantly associated with being a long-term responder (Table IV).

Table IV logistic regression analysis for long-term responders

Predictor	Univariate analysis OR(95%CI)	Multivariate analysis (reduced model) OR (95%CI)	P value
Age	0.86 (0.68 – 1.09)		
Girls	0.28 (0.09 – 0.91)	0.10 (0.02 – 0.54)	0.007
Potency of currently used TCS	1.9 (0.63 – 5.76)		
History of use of systemic immunosuppressives	0.43 (0.11 – 1.69)		
Itching cognitions – catastrophizing	0.47 (0.22 – 0.99)		
CBCL Somatic complaints	0.92 (0.86 – 0.99)	0.88 (0.80 – 0.97)	0.012
QoL Maternal disease acceptance	1.58 (1.10 – 2.28)	1.84 (1.15 – 2.94)	0.011
QoL Maternal psychosomatic wellbeing	0.86 (0.76 – 0.98)		
STAI Maternal trait anxiety	1.25 (1.0 – 1.55)		
STAI Maternal fear of topical corticosteroids	0.76 (0.59 – 0.99)	0.62 (0.40 – 0.94)	0.025

Discussion

We provided a personalized integrative multidisciplinary treatment program (PIM) for children and adolescents with difficult to treat AD. The program offered a structured treatment approach with clearly defined goals and strategies, addressing AD as well as other atopic, pediatric and mental health comorbidities. Six months after participating in PIM, the majority of our study population (77%) demonstrated at least a 75% reduction in disease activity and/or indicated little impact of AD on their daily life. Psychosocial and family variables and not clinical variables, predicted long-term treatment success after participating in PIM.

The majority (77%, n=57) of our study population demonstrated substantial long-term improvement in disease activity and quality of life after participating in PIM. Children who participated in PIM had a history of previous treatment failure with conventional treatment according to current guidelines. Apparently, PIM is an effective treatment option for these children. Multiprofessional eczema interventions may lead to improvements in disease severity and quality of life.[13] However, little is known about the effective elements of a multidisciplinary approach. In most patients, we observed an accumulation of medical, psychological and social problems that needed tailored treatment. Studies concerning children with asthma and diabetes have shown that engagement with children's expertise about their own lives, exploring children's understandings and preferences, and avoiding age-based assumptions about children's contributions to their care are important factors for

successful patient centered care.[22] During PIM, the children and their families were actively involved in the design of the treatment goals and treatment strategies. Input from the child and parents was combined with an integrative multidisciplinary approach by the involved health professionals. Actively involving the parents may also contribute to the successful treatment results, because of the relationship between parental treatment competence and self-efficacy and child behavior.[23] Integrating knowledge by means of multidisciplinary team work and clearly defining and making use of the specific role of each team member was demonstrated important in the care for adolescents with type 1 diabetes.[24] In PIM, each health professional contributed to the treatment goals and other atopic, mental health, pediatric comorbidities, and general well-being were explicitly addressed. Because the child psychologist was a member of the treatment team, children and parents were more inclined to accept and understand the need for psychological treatment. Addressing all the relevant aspects structurally and simultaneously is a unique and probably effective aspect of PIM compared to other treatment programs.

Some children (23%, n=17) were characterized as long-term non-responders. During PIM, professionals and children developed strategies that could help them to retain treatment effects. Despite these efforts, in some families practical and psychosocial problems seem to prevent long-term treatment success. These children and the identified non-responders were characterized by female sex, multiple somatic complaints according to the CBCL, maternal anxiety for topical corticosteroids and maternal difficulties with disease acceptance. This pattern of child and family characteristics resembles that of children with functional somatic symptoms. Functional somatic symptoms are often characterized by a disproportionate burden of disease compared to the severity of the complaints. They are more common in females and more common with increasing age, ranging from 4 times more problems in adolescents to 2-9 times more problems in adulthood.[25, 26] Furthermore, functional somatic symptoms seem to have an intergenerational character, with mothers often experiencing functional symptoms themselves, as well as anxiety and depression.[27, 28] Therefore actively involving the parents when treating a child with difficult to treat AD, also in the case of adolescents, seems essential when functional somatic symptoms might be suspected. Furthermore, other treatment methods may be used for these children during intervention, such as hypnotherapy or cognitive behavioral therapy which has been shown to be effective in the treatment of functional abdominal pain.[29, 30] However, the majority of long-term non-responders (12 out of 17) demonstrated a positive response to PIM immediately after the program.

Children from families that are unlikely to achieve long-term treatment success according to the predictors that we identified, may also benefit from a more intensive follow-up period to sustain the treatment effect in the long term, for example with more intensive support to the whole family and guidance or more frequent booster visits.[31] This would be in line with the current conventional treatment for functional somatic symptoms, which consists of simultaneous and often prolonged simultaneous medical and psychological treatment.[32]

A strength of our study is that we chose stringent criteria for the definition of responders and non-responders. We expected at least 75% improvement using a clinical scoring system and/or a quality of life score corresponding with little impact of AD on the child's life. Both disease control and the impact of AD on daily life are regarded important outcomes for AD.[33] The generalizability of our study is limited. In this study, PIM was provided to children who were considered difficult to treat, which we broadly defined as children with insufficient disease control despite conventional treatment strategies according to current treatment guidelines. Furthermore, children and adolescents aged 8 to 18 years were treated with PIM. Although it is possible that younger children with difficult to treat AD also profit from PIM, this was not investigated in this study.

Identifying children and families who may benefit from certain interventions is important to increase effectiveness in health care, resulting in less overtreatment or undertreatment and a selective application of expensive treatments. PIM is indicated for a subpopulation of children with AD. Future studies are needed to confirm our findings, and to further characterize the heterogeneous population of children with difficult to treat AD and to provide earlier identification of children with difficult to treat AD.

Clinical implications

In current practice, when a child presents with difficult to treat AD, other atopic diseases, psychosocial, parent or family factors are not necessarily addressed. Our study demonstrates that treatment with an integrative program addressing AD simultaneously with other atopic, pediatric and mental health comorbidities, and general well-being, results in sustained improvement on disease activity and/or quality of life for the majority of children. Structural involvement of a pediatric psychologist within the team and attention for psychosocial problems throughout PIM was valuable. It has been reported before that the diagnosis of underlying psychological factors is essential to determine an effective AD treatment plan.[10, 34]

A small subgroup of children from families with characteristics resembling functional somatic symptoms does not respond sufficiently in the long term. Specifically addressing parental disease acceptance and parental fear of using topical corticosteroids could be helpful. A clinical approach that overemphasizes the somatic and ignores psychosocial factors including the parents is a pitfall in the treatment of functional somatic symptoms.[32, 35] An important risk that dermatologists and pediatricians should be aware of in this group is overtreatment. Due to a lack of treatment response physicians tend to intensify treatment according to the guidelines.[36] In children with functional symptoms this is usually not effective. Physicians can support these children and their parents by continuously emphasizing the inextricable link between body, brain and mind and the importance to adress all in treatment.[32, 34]

Conclusion

The majority (77%) of children with difficult to treat AD, seemingly unresponsive to conventional treatment according to current guidelines, are able to improve with PIM. Identifying children based on psychosocial and family but not clinical variables, predicted long-term treatment success after participating in PIM. Attention should be paid to a small group of children, mostly girls with multiple somatic complaints, from families where the mother has anxiety for the use of topical corticosteroids and difficulties with disease acceptance.

Acknowledgment

We acknowledge the study team that participated in the treatment of children with difficult to treat AD using PIM: Lilian Figee, Jos Beutler, Florine Raymakers, Erik Hulzebos, Joan Winkelhof, Maartje Vandewall, Carolien van Stam, and Monica Uniken Venema.

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Supplementary Table I – CBCL and COPEKI / COPEJU subscales

	Responder n=57	**Non-responder n=17**	**p-value**
CBCL social problems t-score	55.8 (7.6)	53.8 (4.4)	0.302
CBCL thought problems t-score	59.9 (7.7)	60.8 (7.8)	0.672
CBCL attention problems t-score	56.5 (5.6)	57.5 (5.1)	0.529
Internalizing behavior			
CBCL anxious/depressed t-score	56.2 (7.8)	56.1 (5.8)	0.934
CBCL withdrawn t-score	57.5 (8.0)	56.4 (6.6)	0.614
CBCL somatic complaints t-score[a]	63.0 (7.7)	68.0 (7.7)	0.020
Nightmares	12 (21%)	5 (29%)	0.472
Constipated	7 (12%)	5 (29%)	0.093
Dizzy	8 (14%)	4 (24%)	0.351
Overtired	15 (26%)	10 (59%)	0.013
Aches	10 (18%)	5 (29%)	0.285
Headaches	20 (35%)	10 (59%)	0.080
Nausea	13 (23%)	4 (24%)	0.950
Eye problems	4 (7%)	3 (18%)	0.189
Skin problems	50 (88%)	14 (82%)	0.570
Stomach aches	21 (37%)	11 (65%)	0.042
Vomiting	8 (14%)	3 (18%)	0.713
Externalizing behavior			
CBCL rule breaking behavior t-score	52.7 (4.0)	52.7 (3.4)	0.933
CBCL aggressive behavior t-score	55.1 (6.1)	53.1 (4.1)	0.228
Coping with itch – children	**(n=28)**	**(n=6)**	
COPEJU social anxiety	1.3 (1.1)	2.6 (0.8)	0.001
COPEJU stress	1.6 (0.8)	2.4 (0.7)	0.005
Coping with itch – adolescents	**(n=25)**	**(n=11)**	
COPEKI social anxiety/depressive moods	1.3 (0.7)	1.3 (1.1)	0.918
COPEKI itching-scratching circle/ stress	2.2 (0.7)	2.4 (0.7)	0.553

COPEJU depressive moods/ itching-scratching circle	1.9 (0.8)	2.8 (0.5)	0.002

[a]The answer categories 'somewhat or sometimes true' and 'very true or often true' are collapsed into one.

10.
General Discussion

The main objective of this thesis is to explore the effectiveness of integrative multidisciplinary care for children with complex difficult to treat AD, with a special focus on alpine climate treatment. Parental treatment management skills of children with mild to moderate AD and associations between intestinal microbial species and food allergy were assessed. In this thesis the results of the first randomized clinical trial investigating the effectiveness of alpine climate treatment are presented, including immunological changes before and after treatment. Furthermore a new complex treatment approach using a personalized, integrative, multidisciplinary program (PIM) is described. Children who participated in the trial were extensively characterized and predictors of a sustained treatment effect after PIM were identified. In this chapter the main conclusions of this thesis are summarized and discussed and implications for daily practice and policy makers are given.

Children with difficult to treat AD

Difficult to treat AD

Atopic dermatitis (AD) is a chronic inflammatory skin disease, varying from mild to very severe, with genetic, immunologic, and environmental factors influencing its course. In this thesis, we define difficult to treat AD as use of at least a moderately potent topical corticosteroid and not being able to step down, or current use of systemic immunosuppressive treatment, or repeated treatment with potent topical corticosteroids or systemic immunosuppressive treatment, or a history of use of systemic treatment, or a significant impact of AD on the child's or the families quality of life, or seemingly unresponsive to conventional therapy according to current guidelines. Patients with difficult to treat AD are a heterogeneous group who do not respond as expected to AD treatment. In many patients factors such as inadequate treatment regimens, non-compliance, unaddressed comorbidities or family dysfunction interfere with AD symptoms, and directly influence the ability to achieve disease control. A standard protocol for the evaluation of difficult to treat AD has never been agreed upon, but a systematic evaluation of patients with difficult to treat AD has been described by Arkwright et al. and should include a confirmation of the diagnosis, address the basics of AD management, optimize current treatment, evaluate triggers (infection, allergens, irritants), manage related diseases and assess psychosocial disturbances.[1]

Why was the AD of children in the DAVOS study cohort difficult to treat?

In the DAVOS trial, we included children (8 - 18 years) that we considered difficult to treat, with moderate to severe AD according to a clinical scoring system. Different reasons may contribute to AD being difficult to treat: severe disease, difficulty in following treatment recommendations resulting in low adherence to treatment, other atopic or mental health comorbidities (such as asthma, anxiety disorders or ADHD) which negatively impact AD and/or the treatment. In some children, obvious factors such as wrong topical application techniques cause treatment failure. However, in the group of children with difficult to treat

AD who participated in the DAVOS trial, a combination of multiple medical, psychological and social factors led to the disease being difficult to treat. Problems with acceptance of the disease, the treatment, difficult family circumstances or limited cognitive abilities of the child and/or the parents may influence AD management. Financial problems or mental health comorbidities such as ADHD or depression may also directly influence a child's or parent's abilities to be adherent to therapy. Prevalence of other atopic comorbidities such as asthma may also negatively affect AD control. Standardized psychological assessment demonstrated that itching and scratching, associated sleep problems and parental stress related to AD were very common.

Assessment of AD severity

So far there has been no international consensus/agreement on how to assess AD severity. Several clinical scoring systems have been designed to assess AD severity and there are currently 16 scoring systems available.[2] Usually assessment of the severity of the lesions and assessment of the affected body surface area are combined resulting in a total score. Some scoring systems may also take symptoms into account such as itch or nightly awakenings. The variety of scoring systems, the lack of standardization and the differences in measurement properties result in suboptimal assessment of AD severity.[3] Furthermore it complicates the comparison of outcomes across different studies, because the terms mild, moderate and severe depend on the clinical scoring system used. Defining severe AD according to the most frequently used clinical scoring systems SCORAD and EASI, corresponds to a SCORAD score > 50 or an EASI score > 21.[4, 5] The HOME initiative has now recommended EASI and POEM to be used in future clinical trials.[6] Another complication related to the use of clinical scoring systems is that the course of AD is characterized by exacerbations and remissions. Therefore a single assessment of severity has very limited meaning since it can easily overestimate or underestimate severity. Furthermore, long-term disease control is an important outcome for AD. Some effort has been made to agree on the definition of an exacerbation and proposals have been made, such as treatment escalation or use of topical anti-inflammatory medication.[7, 8] Furthermore, using a clinical scoring system, the currently used medication is not taken into account. The potency of a topical corticosteroid directly influences the aspects of the lesions and the affected body surface area. Therefore treatment with a potent topical corticosteroid will result in a lower score on a clinical scoring system, thereby suggesting less severe disease. The limitations related to the use of clinical scoring systems to assess AD severity imply the need for a different system, for example based on treatment need and response to treatment. Classifying disease severity based on treatment need and response to treatment is new for AD. However, it may give a better estimation of AD severity than a clinical scoring system, because of the reasons stated before. Ideally, AD severity should be assessed over a longer period of time and a clinical scoring system should take current treatment into account.

Difficult to treat AD and refractory AD

It is widely accepted that severe disease corresponds with a need for high-intensity treatment to treat symptoms. In the study population of the DAVOS trial with difficult to treat AD, over 90% used potent or very potent topical corticosteroids before starting the study. Despite this, their AD was considered moderate to severe according to a clinical scoring system (Figure 1A). Few estimates for the proportion of patients with difficult to treat AD are available, but approximately 10% of pediatric patients referred to secondary care (3% of all AD patients) are estimated to be difficult to treat.[1] In some of these patients, the disease remains uncontrolled even after addressing and removing all possible aggravating factors and despite high-intensity treatment. These patients have refractory AD (Figure 1B). A similar distinction between difficult to treat and refractory has been made in the field of asthma research.[9, 10] In order to find out whether a patient has difficult to treat or refractory AD, the previously mentioned other factors have to be addressed first.

In our study using PIM, in the long term 57 out of 74 patients (77%) obtained sufficient disease control, which we defined as a reduction of at least 75% on a clinical scoring system or little impact on daily life according to a quality of life questionnaire (chapter 6). Disease control was achieved using moderate to potent topical corticosteroids, which was similar treatment as before participation in the study. This illustrates that with adequate intervention patients are capable to control their AD with maintenance therapy with topical corticosteroids according to current guidelines. The majority of pediatric patients in our study population labeled with difficult to treat AD were able to achieve sufficient disease control after invention with PIM. Our findings implicate the importance of assessment of other factors possibly aggravating AD severity and suggest that addressing and treating these factors properly contributes to improved disease control. After the trial we concluded that only a small proportion (5/74; 7%) of children was not able to reach sufficient disease control neither short term nor long-term and could be considered as children with refractory AD. Comparable results were reported in a recent study in which 79 adult patients with difficult to treat AD were admitted for a structured inpatient treatment and education program.[11]

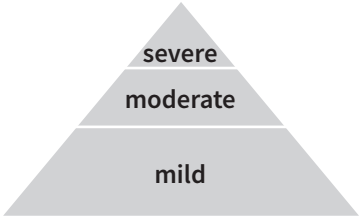

Figure 1A Estimated relative prevalence of mild, moderate, severe AD based on a clinical scoring system

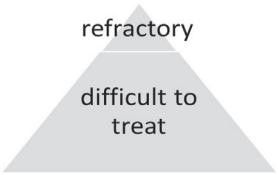

Figure 1B Estimated relative prevalence based on response to treatment according to current guidelines of difficult to treat AD and refractory AD

Treatment strategies for difficult to treat AD and refractory AD

It is important to distinguish between difficult to treat AD and refractory AD because the proposed treatment strategy that follows should be different. The patient with refractory disease is the patient who may benefit from novel treatment strategies. Patients with difficult to treat AD may not be candidates for innovative anti-inflammatory therapies like biologics, initially because it is very likely their disease will be under control with topical immunosuppressive treatment, after addressing other factors such as disease acceptance, reluctance to use topical corticosteroids, or treatment refusal independent of whether they used systemic medication in the past. In daily practice, there is often no time to obtain or thoroughly address the above mentioned disease influencing factors. Furthermore these factors are too complex for a single health professional to treat in a regular outpatient setting.

Using a personalized integrative, multidisciplinary treatment approach as described in chapter 8, treatment goals based on the problems experienced by the child, the parents and/or the health professionals were designed (chapter 8). Treatment goals usually focused on disease control and itch, sleeping problems, tension about AD treatment within the family, other atopic disorders, general physical fitness, and feelings of anxiety, depression, autonomy. There was great similarity among the defined treatment goals, suggesting these are the main issues children and parents are struggling with. Minimal impact of AD on the child's daily life could be summarized as the ultimate treatment goal.

Characteristics of difficult to treat children in the DAVOS study cohort

Atopy

Several longitudinal studies have identified associations with other atopic conditions, where AD onset in early life is followed by food allergies, asthma and allergic rhinitis (atopic march).[12] Looking at the baseline characteristics of the children in the DAVOS trial, we observed some very striking similarities, but also heterogeneity, mainly regarding the psychosocial assessments (chapter 6). The most striking features are the age of AD onset, which was before 6 months of age in 85% of children, and the high prevalence of other atopic diseases, such as asthma (86%), rhinitis (87%) and food allergy (66%) of children. A 2007 US population-based survey estimated prevalence of food allergies (15%), asthma (20%) and allergic

rhinitis (34%) among children diagnosed with AD and suggested a positive association between AD severity and the presence of other atopic comorbidities.[13] Almost all children were sensitized to common aeroallergens (99%), the majority to food allergens (75%) and all children had a total IgE above 150 KU/L, 56% had elevated blood eosinophil counts, and TARC was elevated (above 848 pg/ml) in 60% of children. Interestingly, a group of adult AD patients with poorly controlled AD despite the use of topical and oral corticosteroids, topical calcineurin inhibitors, antibiotics, and antihistamines has also been characterized as highly atopic in another study.[14] A higher perennial allergen sensitivity, a higher rate of food allergen sensitization, and elevated total IgE was observed in that study compared to patients with active disease who were responsive to topical treatment. This suggests that distinct atopic characteristics may be typical for patients with difficult to treat AD.

Mental health

Children with AD seem to be at an increased risk of developing other mental health disorders such as attention deficit hyperactivity disorder (ADHD), depression, anxiety or autism spectrum disorder.[15-17] Children with more severe AD had higher rates of ADHD compared with those with less severe AD or without AD.[15] In our study cohort, AD had a significant impact on quality of life and clinically relevant sleeping problems were reported in the majority of children. We also found higher prevalence of feelings of fear and depression, withdrawn behavior, social problems and thought problems, compared to the general population. This was an unexpected finding. It has recently been suggested that prevalence of mental health comorbidities is higher in patients with more severe disease, but this was after the start of our study.[15] In 13 children diagnoses of ADD or ADHD were suspected, and ADHD was confirmed in 5 children. The underlying mechanisms of these associations are not clear, but could be related to the significant impact of AD on quality of life, the chronic itch or increased sleep disturbance.[18-20] Itch often increases in the evening or at night, which negatively affects sleeping patterns.[21] Children and adolescents with eczema often have difficulty falling asleep, frequently awake during the night and experience an overall reduction in sleeping time.[22] It has been hypothesized that sleeping problems mediate the relation between AD and behavioral problems.[23, 24] However, other chronic diseases in childhood also increase the risk of emotional and behavioral problems.[25] Regardless of the working mechanism, our findings and those from other studies support the need for the systematic assessment of mental health disorders in children with more severe AD.

AD treatment management skills

Patient education is important in the management of all chronic diseases, but especially in AD. The topical treatment AD requires is time-consuming requires more effort from the patient and/or parent and the changing treatment regimens (stepping up and phasing out) require good patient self-management skills and the ability to assess disease activity.[26] Regarding knowledge of AD treatment, we found that the parents of children participating

in the DAVOS trial were well informed. 65% provided a correct estimation of the potency of the currently used TCS, 91% know how much TCS to apply (49% use the FTU), 87% increase the frequency of TCS application to once or twice daily during a flare, 93% know how to step up and phase out TCS. Alternative therapy is used by 11%, and 84% use emollients once or twice daily. We only observed room for improvement regarding parental reluctance to use TCS (44% of parents); shower behavior (29% of children do not shower according to advice) and treatment refusal by the child (indicated "often" by 17% and "sometimes" by 34%). Comparing these outcomes with data describing treatment management skills of an unselected AD population attending our outpatient clinic between 2009 and 2014, described in chapter 4, knowledge of TCS regarding correctly estimated TCS potency (65% vs 54%), how much to apply (91% vs 78%), how to step up / phase out (93% vs 67%), application frequency during a flare (87% vs 82%), and shower behavior (71% vs 45%) seemed better and use of alternative treatment lower (11% vs 27%). Another main difference between these groups seemed to concern treatment refusal by the child, which was higher in the DAVOS group (51% vs 35%). Parental reluctance to use TCS was high in both groups (44% vs 48%). Assessing these factors individually for each patient may provide valuable input to define unmet education needs. Furthermore, when there are multiple diagnoses, it is important that education is provided concerning all relevant diagnoses and especially the combination thereof. Handling multiple diseases, for example AD, asthma, rhinitis and ADHD requires other treatment management skills than handling AD only. A personalized intervention in which patient education is completely adapted to the patients' needs could be very valuable for children with difficult to treat AD.

Microbial characteristics

AD flares are associated with increased Staphylococcus aureus and decreased microbial diversity, and S. aureus is cultured from up to 90% of AD lesions.[27, 28] In a mice model for AD, microbial dysbiosis has been shown to directly affect skin inflammation whereas increasing microbial diversity improves the inflammation.[29, 30] Apart from the cutaneous microbiome, our findings from chapter 5 suggest that the intestinal microbiome may be deviant in AD as well. We demonstrated that within a group of children with varying AD severity, differences in prevalence of several microbial species were associated with a diagnosis of food allergy. However, our study was a small pilot study with a cross-sectional study design. Confirming the results prospectively is necessary to confirm whether the identified microbial profile is independent of changes in AD activity. Furthermore, we assessed the association with a diagnosis of food allergy, but were not able to assess different food allergens, because of statistical limitations. It could be that transient or persistent food allergies are associated with different microbial profiles or that the microbial profile differs depending on the specific food allergen. This has to be studied in future prospective studies with larger well characterized patient populations. However, confirming an absence of food allergy might be even more important for the AD population, since children with AD are often subjected to

unnecessary elimination diets in order to improve AD severity.[31] Apart from the epidermal barrier dysfunction in AD, the intestinal epithelial integrity may also be affected. This could increase the risk of allergic sensitization through direct uptake of allergens in the intestine.[32] More severe AD has previously been associated with a higher prevalence of food allergy.[13] It is possible that the relation between AD severity and food allergy is mediated by the intestinal microbiome. Several microbial species have been shown to secrete anti-inflammatory molecules or directly modulate cytokine production.[33-35] However, the exact mechanisms through which the intestinal microbiome might influence oral tolerance are not elucidated yet. Furthermore, it is not clear whether a change in microbiome precedes or follows the development of food allergy. However, deliberately modifying the intestinal microbiota might be a valuable treatment strategy for AD or other allergic diseases.[36]

Alpine climate treatment: the DAVOS trial

Rationale of the DAVOS trial

Current treatment strategies for pediatric AD are not sufficient for a subgroup of children with difficult to treat AD. In daily practice, there is currently no systematic work-up of other atopic diagnoses or assessment of mental health problems when a child presents with difficult to treat AD. During the DAVOS trial, we provided children aged 8 to 18 years with a new personalized, integrative, multidisciplinary treatment approach (PIM) as described in chapter 8. In addition, the intervention group was treated in an inpatient setting in the alpine climate. Historically, climate treatment has been used in Europe for decades for the treatment of various chronic inflammatory dermatoses and pulmonary diseases, but no randomized trials have been conducted to demonstrate its effectiveness.[37, 38] Concerning alpine climate treatment for AD, so far only observational studies have been conducted.[38] Even though the available data is quite positive (decrease of disease activity in 96% of patients, reduction or no need for the use of topical or systemic corticosteroids in 80% of patients), there was considerable risk of bias in the available studies resulting in very low quality evidence. Furthermore, because of the lack of control groups and the lack of trials there are no reliable data on which elements are responsible for the observed positive effect. Therefore a randomized controlled trial was needed to provide evidence regarding the effectiveness of alpine climate treatment.

Methodological considerations

The primary study aim of the DAVOS trial was to investigate the long-term effectiveness of alpine climate treatment. To perform this we choose a pragmatic trial design. In a pragmatic trial the whole package of care is under investigation and not a single treatment element.[39] This is in contrast to the more frequently encountered explanatory trial, which is designed to test a causal research hypothesis and therefore can only address one element at the time. The differences in study design between explanatory and pragmatic trials have consequences for the study population, the intervention and the validity of the results. Regarding the study

population, an explanatory trial has a homogeneous population and strict inclusion criteria whereas a pragmatic trial selects patients who would be representative of patients who are likely to receive the intervention in the future. Concerning the intervention, treatment is carried out under selected conditions for a selected group of patients, which is needed to provide an answer to the question of efficacy. In a pragmatic design, the natural variations that occur between patients and between treatments reflect the real life situation to which the trial results will apply. Treatment changes or additional treatments are allowed and left to the decision of the clinician. Another main difference is the external validity or generalizability of the trial results. In explanatory trials there can be great differences between the setting in which the trial was carried out and the health care setting in which the intervention will be implemented, which may lead to limited applicability to clinical practice.[40]

Pragmatic trials provide results that are directly relevant to clinical practice, because they are usually designed in a regular clinical care setting. Because alpine climate treatment consists of several elements that may reduce disease activity and because it is difficult to separate these elements we choose a pragmatic study design. One of the elements that coincide is the inpatient setting and the alpine climate where the inpatient clinic is located. In order to investigate the effect of the climate, children from the control group would have to be treated in an inpatient setting as well. However, current best practice in the Netherlands at the time of designing the trial was care in an outpatient setting. With a pragmatic study design we would be able to provide evidence for the effectiveness of a treatment that is directly applicable to clinical practice and would benefit children with difficult to treat AD the most. We reasoned that, depending on the results provided by the pragmatic trial, explanatory trials could then be carried out in the future.

Main findings of the DAVOS trial

Short term results and immunological changes

Immediately after alpine climate treatment and after six weeks follow-up, we found significantly greater improvement in disease activity, health-related quality of life and other clinical secondary outcomes, confirming the effectiveness of alpine climate treatment on the short term. This is in line with the results of previous observational studies.[38] The pharmacological treatment patients received during treatment (eg potent topical corticosteroids and systemic immunosuppressives when needed) was comparable in both groups. In chapter 7, we assessed immunological changes in peripheral blood samples to get insight in the underlying immune mechanisms that might explain why children treated in the alpine climate have a better outcome immediately after intervention compared to children from the control group. Observed changes in circulating inflammatory cells are described before and immediately after the intervention. The most striking difference between the groups is the significant reduction in eosinophils in the intervention group, but not the control group. A decrease in peripheral eosinophilia has been demonstrated in most studies regarding alpine climate

treatment.[41-46] Serum TARC also decreased significantly in the intervention group, but not in the control group. These findings might be explained by the greater reduction in disease activity in the alpine climate group. Compared to baseline, both groups demonstrated a reduction in memory regulatory T cells (CD45RA- memory Tregs) which is line with the observed reduced disease activity. Concerning the plasmablast subsets, IgE+ plasmablasts significantly decreased after alpine climate treatment, but no effects were found on either CD27+ or CD27- IgE-expressing memory B cells. Slightly increased numbers of IgA and IgG memory B cells (IgG+CD27+, IgA+CD27-, IgA+CD27+) were observed. These differences could be explained by the unique regulatory mechanisms characteristic of IgE+ B cells.[47]

Several of the T and B cell subsets moved in contrary directions in the intervention and control group. For example, the number of total CD3+ T-cells in the intervention group increased after the end of intervention, but decreased in the control group, mainly because of increased numbers of T helper 2 cells and CD8+TemRO cells. As a consequence the ratios of Th1/Th2 between the groups are also different. This was an unexpected finding. A previous study demonstrated a significant reduction of the IL-2 receptor alpha-chain expression within the CD4+ lymphocyte population after only 3 weeks of alpine climate treatment.[41] However, high expression of IL-2 receptor is also directly related to regulatory T cells, which were found to be decreased in our study. We did not specifically observe IL-2 specific T cells in our study. A possible explanation for the increased Th2 cells in blood could be its recompartmentalization from tissue, however this is difficult to quantify.[48 49] Another possibility is that these patients were skewed towards Th1 dominance prior to alpine climate treatment, and that the chronic Th1 response may have subsided and reverted to the original Th2 dominance due to the intervention, characteristic for atopic disease. All blood samples were taken in the Wilhelmina Children's Hospital on a Tuesday and children usually travelled during the weekend. Therefore it cannot be excluded that the remaining Th2 skewing in the intervention group underlies the renewed inflammation upon return to the Netherlands, with higher allergen exposure. Furthermore, it cannot be excluded that the lag between leaving the alpine climate and taking the blood sample has annulled some of the changes that were present during alpine climate treatment. Therefore, future studies might include blood sampling and analysis already in Davos prior to leaving the alpine climate. In our study we have chosen to sample in the Netherlands to guarantee the standardization of both the sampling and the analysis.

Overall there was wide data dispersion in the different T and B cell subsets and most changes were small in magnitude. Therefore it is not directly clear how these small changes could be responsible for the biological effects, reflected in the observed significant reduction of disease activity. Furthermore the significantly larger clinical improvement we observed in the intervention group was not reflected in the immunological findings. It cannot be excluded that a longer treatment period in the alpine climate would lead to more sustained immunological changes and would possibly also contribute to a more sustained treatment effect. In future studies it might be helpful to assess blood samples more frequently during

alpine climate treatment, to be able to study possible changes in more detail. Ideally the inflammatory process should also be studied in the affected tissue by taking skin biopsies to assess the local inflammatory processes. For this, analysis of inflammatory cells, i.e. dendritic cells, as well as the molecular signature would be of great interest.[50] To study the effective immune response, PBMCs could be isolated and T cell proliferation could be measured after polyclonal or house dust mite specific stimulation. Furthermore, biomarkers reflecting AD severity could be measured in addition to other cytokines.[51]

Alpine climate treatment

Alpine climate treatment is a total care package which consists of several elements. Each of these elements separately may also contribute to an improved disease activity. The characteristics of the alpine climate (low allergen exposure, low pollution and high UV exposure) are thought to be beneficial for atopic patients. However, the inpatient setting in Davos guarantees optimal compliance with pharmacological treatment through nurse supervision of topical immunosuppressive treatment, which could also have been responsible for the favorable short term outcome. Although health-related quality of life is directly related to AD symptoms the greater improvement in quality of life might also be affected by the structured day program with school, outdoor activities and sports in the intervention group. Parents and children are separated during the intervention period and the children have intensive contact with peers. This separation can be perceived as an extra burden for the child, but may also be an advantage, especially when the coping strategy of the child is negatively influenced by the coping strategies of the parents.[52] The positive effect of being away from home in a relaxing environment has been demonstrated before in a retrospective study in children with severe AD.[53] We hypothesized that these are the most probable elements that could have contributed to the increased disease control at 6 weeks in the intervention group.

Environmental characteristics of the alpine climate

Allergen avoidance

Historically, the reasons for the positive treatment results of climate treatment were mainly contributed to the characteristics of the alpine climate environment (low allergen exposure, especially house dust mite allergen (HDM), low pollution rates and high UV exposure) which are thought to be beneficial for atopic patients. It has been suggested that indoor avoidance of HDM and molds could possibly enhance management of refractory AD.[14] However, several placebo controlled studies with HDM reducing measures found significant reduction in exposure to HDM, especially the main allergen Der p 1, but no obvious improvement in AD severity.[54-56] Furthermore, the studies indicating low HDM allergen exposure in the alpine climate are relatively old.[57, 58] A more recent study carried out in Ecuador found relevant concentrations of mite species up to 2800m altitude.[59] Another study carried out in alpine

regions in Germany and Austria has demonstrated that there is no significant change in HDM concentration with increasing altitude and clinically relevant concentrations of HDM allergens were also detected in regions located above 1500 m altitude.[60] There is no reason to assume this would be different in Switzerland where the DAVOS trial was carried out. Other aeroallergens such as birch or grass pollen are less prevalent in the alpine climate as well.[61] It could be that allergen avoidance would only be relevant for sensitized patients, but subgroup analyses from our trial did not show a different effect of alpine climate treatment for HDM sensitized patients compared to non-HDM sensitized patients, also suggesting allergen avoidance was not the driving mechanism for clinical improvement in our study.

Pollution and UV radiation

Air pollutants are well-known risk factors for asthma and have recently been gaining more interest in AD.[62] Some studies suggest that outdoor air pollutants may act as risk factors for development or exacerbations of AD.[63, 64] The alpine climate is characterized by lower levels of PM10 and other traffic-related pollution.[65] However, there are likely multiple mechanisms for the harmful effects of different pollutants and these have not been elucidated yet. Furthermore, the duration of the intervention in the alpine climate was six weeks and it is not clear if this period is long enough to contribute to a reduction in AD severity because of reduced exposure to air pollutants.

Another environmental characteristic of the alpine climate is its increased UV exposure. Phototherapy using narrowband UVB and UVA1 are used in AD treatment.[66] Therefore it seems logical to assume that increased exposure to UV radiation could contribute to improved disease severity. However, studies assessing the relation between AD prevalence and UV exposure show conflicting results.[67, 68] Furthermore, the actual individual UV exposure also depends on the hours spent outside, clothing, season, and on the use, quality, and potency of the used sunscreen products. Children in the intervention group were not explicitly instructed to expose their lesional skin to the sun.

Clinical setting

Alpine climate treatment takes place in a clinical setting. Usually patients with AD require hospital admission because of complications such as eczema herpeticum, systemic bacterial infection or erythroderma.[69] However in severe AD that has not responded to standard outpatient treatment, hospital admission provides an excellent opportunity to assess self-management and to improve disease control.[69] The clinical setting in which alpine climate treatment takes place offers the same opportunity. Maximal compliance with pharmacological treatment is guaranteed through nurse supervision and assistance with topical treatment. Furthermore, the clinical stay can be combined with a structured treatment and education program, including various sessions. In the identified observational studies concerning alpine climate treatment, very little is described about the actual therapy patients have received. Furthermore there is a large variety of psychological treatment

possibilities, individual or in groups and physiotherapy; sports therapy and massages are also mentioned. However, no further details or examples are given, so it is not clear how intense the treatment program a patient receives actually is. However, it is very likely that these factors also contribute to the reported reduction in disease severity. In the DAVOS trial, we used a standardized treatment program which was comparable in both study arms. We cannot exclude that the advantages of the inpatient setting contributed to the better short term treatment results in the intervention group.

Long-term results

The follow-up period of six months allowed for assessment of long-term results, which is important for children, their parents and society to justify the impact of alpine climate treatment, and in terms of resources. We found no significant differences between the intervention and control group regarding disease activity, health-related quality of life, catastrophizing thoughts and coping with itch after six months follow-up. Compared to baseline, there was statistically significant improvement regarding these outcomes in both groups, except for coping with itch. The majority of children in both groups were able to reach acceptable disease control using moderate to potent topical corticosteroids and topical calcineurin inhibitors. The psychological treatment the children received may have contributed to the comparable improvement in catastrophizing thoughts. Coping with itch is a personal trait, less situation specific and more difficult to influence which may explain why there was no change in either group. However, we expected to see improvement on coping with itch in both groups.

During the follow-up period, the initially larger improvement in the intervention group is gradually lost whereas the control group remained stable. It is likely that if there is a positive influence of the alpine climate, this effect can only be exerted whilst you are present in the climate. The same pattern of loss of effect is visible in the only other trial concerning a change in climate from a subarctic/temperate to a sunny subtropical climate.[70] The intervention group in that study shows a similar deteriorating trend up to three months follow-up as our intervention group, suggesting that it is difficult to retain a long-term effect after climate treatment. Another explanation might be the change in setting for children in the intervention group. They have to apply the skills they learned in the clinic in their home environment whereas children in the control group already learned to implement the newly acquired skills directly in their daily routine during the six week program. Therefore it may be easier for them to retain these skills. It could be that offering booster sessions to the intervention group or providing more guidance in the initial follow-up with more frequent office visits could be helpful for the intervention group to retain the effect. However, it is also possible that sustained disease control is related to other factors. About 77% of children from the DAVOS study cohort (equally distributed among both groups) were able to reach sustained long-term disease control. The main predictive factors for long-term disease control we identified were maternal disease acceptance, whereas psychosomatic complaints, being a girl and

maternal fear of using topical corticosteroids reduced the likelihood of long-term treatment success. This pattern of child and family characteristics resembles that of children with functional somatic symptoms. However, most of these children (12 out of 17) did reach short term disease control, according to the same definition, suggesting that it is possible for them to improve but they probably need a different and more personalized follow-up. It could be that psychosocial characteristics of these children prevent a more sustained disease control. However, when behavioral changes are required for sustained disease control, it is possible that the duration of the intervention was too short or not optimal. The intervention in the DAVOS trial was 6 weeks and there was very limited guidance to help the children adjust to their home situation after the intervention. Furthermore, when family factors are important in the ability to sustain the effect, it is essential that these are explicitly addressed during the treatment program and support is also provided during follow-up. Another possibility is that children who are unable to reach sustained disease control constitute a distinct phenotype of refractory disease. There were only 5 children who did not reach sufficient short term nor long-term disease control and we were not able to distinguish them from the other children. Future studies are needed to investigate this further.

Comorbidities should be taken into account when evaluating AD control. AD is rarely a single disease entity, especially when it is moderate or severe. Recently, it has been suggested that AD severity could be linked directly to the severity of other atopic disorders.[13] In the DAVOS study cohort, about 20% of patients were using oral immunosuppressives (CsA or prednisone) throughout the study, with significant differences in favor of the alpine climate treatment group immediately after intervention and during initial follow-up. Out of the 12 patients that required oral immunosuppressives during the final follow-up period, only 2/12 required CsA for their AD, the others 10/12 required prednisone bursts because of asthma exacerbations. This data indicates that even though the patient's AD was well-controlled, control of comorbidities is also important in the total amount of medication used. This is also important when AD severity is assessed based on treatment need, because the simultaneous use of prednisone for asthma also decreases AD severity and AD treatment may influence asthma severity. Therefore in children with difficult to treat AD with several atopic diagnoses, it is important to take all the relevant diagnoses and treatments into account.

Our study results implicate that there is limited effectiveness of alpine climate treatment, because the main additional value of alpine climate treatment would be in its effectiveness on the long-term. An intervention that minimizes the burden but maximizes the result is preferred for children, suggesting that if it is possible to reach significant clinical improvement with a six week outpatient treatment program close to home, this would be the preferred choice, of course depending on the family and personal circumstances of the child.

PIM: a personalized integrative multidisciplinary intervention for children with difficult to treat AD

In chapter 8 we described a personalized integrative multidisciplinary treatment approach (PIM) which was used between 2010 and 2014 for children with moderate to severe difficult to treat AD during the DAVOS trial. PIM was used in two settings: an inpatient setting for the alpine climate treatment group and an outpatient setting for the control group. PIM actively involves both the child and his parents and combines patient designed treatment goals with a systematic multidisciplinary approach by the involved health professionals, including assessment of AD, other atopic, pediatric and mental health comorbidities and general well-being. This assessment is done in a systematic way, includes psychosocial questionnaires and parental assessment, and there are no possibilities to opt-out on parts of the program. Throughout the integrative treatment program, multiple health professionals work simultaneously on the same treatment goals, each using treatment strategies from their own field of expertise. Intervention strategies are chosen based on the best fit for an individual child or family situation. Because PIM uses a personalized approach based on the problems experienced by the child, it is specifically suitable for older children. The systematic approach including all comorbidities is another unique feature of PIM.

Education

Because of the significant burden of disease for children with moderate to severe AD, several additional treatment approaches have been developed in the last decades. Education programs with fixed contents have been developed for children, adolescents as well as parents to be used in adjunct to standard medical care.[71-74] In Europe, therapeutic patient education (TPE) programs were developed recently that distinguish themselves from conventional education programs by offering tailored education and explicitly focusing on the transfer of skills instead of merely providing information or advice.[75, 76] Indeed education should be the highest priority in disease management, especially for children with milder disease. However in our group of difficult to treat patients, education could improve some issues but generally knowledge of AD treatment was satisfactory.

Multidisciplinary treatment

Multidisciplinary treatment programs exist to help children and their families to successfully manage and cope with AD using a personalized treatment approach.[77] Examples of multidisciplinary treatment programs are the Atopic Dermatitis Program at National Jewish Medical and Research Center in Denver and the Atopic Dermatitis Center at Children's Hospital Boston.[78, 79] Besides education of children and their families, these programs also address itching and scratching, sleep disruption, parental challenges in disease management, psychosocial problems and adherence to treatment in order to improve disease activity. However the approach used in these programs seems less integrative compared to PIM, even though the importance of integrating medical and psychological

health care in AD treatment has been stressed previously.[20] In one program in Boston, access to a child psychologist within the program was not offered to all participants, but had to be requested.[78] Parent's initial request for a meeting with the program psychologist was not related to disease severity, but associated with sleep problems and parental emotional and practical challenges in the management of the child's condition (more specifically, the parent feeling overwhelmed with managing the child's AD and the parent finding it difficult to follow treatment recommendations). In the other program in Denver, the psychosocial interventions are tailored to the needs, goals and strengths of the family and varied from brief psychoeducation to daily therapy sessions focusing on parenting, relaxation techniques and other techniques to minimize scratching, such as distraction, behavior replacement, cognitive therapy, biofeedback and hypnosis.[79] In our PIM program, the sessions with a child psychologist were mandatory and were mostly used to address coping with disease, relaxation and itching and scratching. Offering the sessions as an integrated part of the treatment program removed resistance by the parents or child. If needed, additional psychosocial or psychiatric assessments, short interventions or referrals were organized. Furthermore, most specialized AD programs are more suitable for younger children and their parents, and there are fewer possibilities for older children and adolescents that specifically address their needs.

Multiple comorbidities

Assuming that a child with difficult to treat AD will have or will develop several comorbidities in the future, it seems wise to involve a multidisciplinary treatment team from an early stage, preferably across different disciplines, so that clinical and mental health issues may be addressed properly and as early as possible. During the DAVOS trial we have experienced that there are many similarities in the way a certain child or family is coping with several disorders and that it is important to guide and support the often extensive medical treatment regimens in the daily schedule. When for example a child is diagnosed with AD, asthma, seasonal allergic rhinitis, and ADHD, it is very helpful to design a single schedule for the child and family involving all medications and treatment regimens. This gives a clear overview and supports adherence. Furthermore it is important that the applicability of a treatment regimen is evaluated and that actual adherence is monitored. However in daily practice, there is no treatment guideline for difficult to treat AD including other comorbidities; but each disease is addressed in its own treatment guideline. Furthermore a systematic approach as described in PIM, which often revealed that the lack of progress was caused by another unaddressed problem, helps to get to the root of the problem. We noticed that because of the presence of simultaneous atopic diseases, multiple complaints appeared to lead to a distorted perception of complaints. For example, some children with severe dyspnea hardly noticed that they had difficulty breathing. Systematic evaluation by assessing lungfunction in all children resulted in a diagnosis of asthma in several children and the need to intensify asthma treatment in others.

Possible mechanisms of effect

PIM is a demanding and intensive program, for the children and their parents as well as for the involved health professionals. Therefore PIM is only necessary and suitable for a subgroup of children with difficult to treat AD. We included children aged 8 to 18 years in the DAVOS study, which is already a smaller group compared to the younger age groups. Most children and their parents were very motivated to participate in the program and expectations were high, since it appeared to be a last resort for most families. During PIM, treatment with similar potency drugs as before resulted in significant disease improvement, most likely because underlying problems were also addressed systematically. The personalized approach, the integrative multidisciplinary team efforts and the simultaneous treatment processes contributed to the significant progress in a fixed relatively short period of time. It was extremely motivating for the children and their parents to experience progress in an often hopeless situation. For most children, participation in the trial resulted in a remarkable improvement in disease activity. Another explanation could be that PIM was used in a trial and trial participation usually leads to improved adherence to treatment.[80]

An integrative multidisciplinary team approach requires great communication skills, concerning communication with the child and family as well as among health professionals. This requires sharing of relevant observations and results in multidisciplinary meetings, and trust in other health professionals. The support among health professionals in a multidisciplinary team can be very valuable. Different behavior displayed by the child or family members towards different health professionals could be observed and could provide valuable input on how to best address a certain problem, for example with additional support regarding communication skills by a psychologist for the treatment team. Furthermore it is important that all involved health professionals within the team convey the same message to the child and family.

Because of the systematic stepwise approach in the same way by all professionals in all patients, it is difficult to state which elements are essential and which could be superfluous. PIM is a six week program during which a systematic evaluation takes place, but it is mostly centered on patient preference regarding treatment goals and outcomes. This personalized approach makes it unique, but it also makes it difficult to explore possibilities to condense the program further, since this may vary depending on the problems experienced by the patient.

Positioning of PIM and alpine climate treatment among other treatments for AD

There is a clear stepwise approach for AD treatment, in which climate therapy and psychosomatic counseling is indicated for moderate or recurrent AD in the 2015 European position paper.[5] However, in the 2014 Dutch treatment guidelines, alpine climate treatment is not recommended for AD treatment because of limited evidence for its effectiveness. Furthermore, it is currently not reimbursed for patients with AD by Dutch health insurance.

In the US treatment guidelines, climate treatment or multidisciplinary interventions are not mentioned at all.[81] However the importance of education and psychosocial consequences is recognized in every guideline. An overview of treatment options for AD is provided in Figure 2.

Based on the results of the DAVOS trial, alpine climate treatment could be an option for children that urgently need fast improvement or with a difficult family situation. The greatest reduction in disease activity in the intervention group was observed in the first two to three weeks. However, alpine climate treatment has not been directly compared to inpatient treatment in the Netherlands using PIM. Therefore it cannot be excluded that both interventions are equally effective. On the long-term, we demonstrated that there are no differences between children who were treated in the alpine climate and children who were treated in an outpatient setting, both with a personalized integrative multidisciplinary (PIM) treatment program. Unless future studies demonstrate possibilities to retain the initial, significantly larger effect on disease activity and quality of life on the long-term, there is currently not sufficient evidence to support alpine climate treatment as a treatment option for difficult to treat AD.

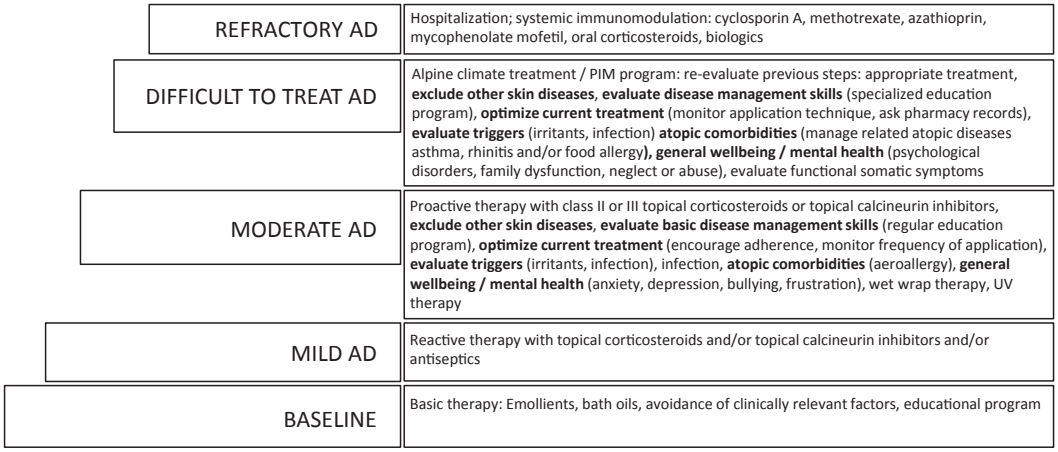

Figure 2 Suggested positioning of PIM and alpine climate treatment among other treatments for AD

Suggested treatment options may be used in a stepwise manner, according to AD severity and treatment need. Based on Arkwright et al., Wollenberg et al. and the findings of this thesis.

In current guidelines, systemic immunomodulation and inpatient treatment are indicated as treatment options for severe AD according to a clinical scoring system.[5] Several systemic immunomodulatory drugs are available for severe AD, of which only cyclosporin A (CsA) is officially registered in the Netherlands and others (methotrexate (MTX), mycophenolate mofetil (MMF) or azathioprine (AZA)) are used off-label. In general, management of AD with systemic corticosteroids only, should be avoided due to short and long-term adverse effects, risk of rebound upon discontinuation and an overall unfavorable risk-benefit profile.[82] There

is a lack of comparative studies on the available systemic immunomodulating therapies and there are few studies on optimal dose, duration and long-term use in AD.[83] Furthermore, there were significantly less trials in pediatric patients compared to adults. Based on the findings of this thesis, PIM may reduce the need for the use of systemic immunomodulatory drugs in pediatric AD, if it is applied timely, because it may provide the necessary skills and support resulting in sufficient disease control.

Currently there is very limited evidence regarding the effectiveness of inpatient treatment.[11, 69] Most likely hospitalization is effective because adherence is optimized and trigger factors are reduced. Therefore it could be an effective treatment option for patients with difficult to treat AD. However, on the long term, it would be more efficient if hospitalization could be prevented for example by further improving the treatment management skills of the patient with a PIM like program in an outpatient setting. In an observational study with adult patients diagnosed with difficult to treat AD, exhaustion and psychological disturbance were a reason for hospitalization in half of the patients.[11] Offering support with a program like PIM, in which psychological care is integrated, could possibly prevent hospitalization for this reason. Psychosomatic counseling is also advised in the European guidelines from step 3 (moderate AD). The high prevalence of children with increased feelings of depression and anxiety in our study cohort also supports the importance of integrated psychological care. Because in patients with difficult to treat AD symptoms are mainly determined by other aggravating factors, a systematic treatment approach as described before with a PIM like program, would likely improve AD symptoms in the majority of patients and possibly prevent the use of systemic immunomodulatory drugs or hospitalization. Based on the findings of this thesis, we suggest that personalized integrative multidisciplinary treatment programs could be added to the treatment options for moderate to severe AD. Using a PIM like approach, the children with difficult to treat AD can be identified and the majority of children can be treated successfully with regularly available topical corticosteroids. Children who remain with refractory disease would still need another treatment approach. For children with functional somatic complaints, overtreatment is an important risk since physicians tend to intensify treatment due to a lack of treatment response, according to treatment guidelines. Current conventional treatment for functional somatic symptoms consists of simultaneous and often prolonged medical and psychological treatment.[84] In the DAVOS study cohort, 5/74 children were not able to reach neither short term nor long-term disease control, according to our stringent definition (disease reduction of at least 75% using a clinical scoring system and quality of life score indicating little impact on the child's life). It is very likely that this group of children constitutes a distinct phenotype of refractory disease. For these children, other types of treatment are needed. Further detailed characterization of these children is needed to determine the most effective treatment strategy.

Currently several systemic immunomodulatory drugs are available for AD treatment. However, there are children who do not respond well to for example CsA (around 20%).[85, 86] The new biologic dupilumab, which can be administered once every two weeks and later

once per month, has been shown to improve AD severity dramatically and has recently been approved for use by the FDA for adults.[87-89] Depending on the results of the current phase 3 trials in Europe, dupilumab likely becomes available in Europe as well.[90] Several other biologics for AD are currently in phase 2 / phase 3 trials for adults and might become available for children in the future as well.[91]

An integrative multidisciplinary treatment program such as PIM could be beneficial for children with all degrees of AD severity, but is only necessary for a small proportion of pediatric patients. Because of the costs and intensity of the program, and the requirement of a team in which the dermatologist, pediatrician, allergist, (dermatology) nurse, and pediatric psychologist work together, we suggest that PIM like programs are carried out in a limited number of expert centers with special interest and experience in the management of AD patients. Education, adherence to treatment and treatment management skills remain important issues and should be evaluated continuously. Furthermore, family aspects such as maternal disease acceptance and maternal fear of using corticosteroids have been identified as important factors for long-term treatment success with PIM. Therefore, addressing these issues and explicitly incorporating the family as well as the child in treatment are essential for long-term treatment success. However, one should keep in mind that in general it may be difficult to learn several abilities simultaneously. Therefore prioritizing and setting realistic (sub) goals stepwise is important.

Recommendations and future research

Even though caregivers /parents of children with AD have expressed their desire in qualitative studies for a less complicated AD treatment with convenient medications that can be administered infrequently and have minimal side-effects, the essence of AD treatment still requires topical anti-inflammatory treatment with topical corticosteroids / calcineurin inhibitors and emollients.[81,92] Systemic immunomodulatory drugs might be more convenient for the patient, but strict monitoring is required and its long-term use is not recommended. Multidisciplinary intervention programs have been developed to provide patients with the needed skills to manage and cope with AD.[93] However, no randomized trials have been done to assess whether PIM treatment programs are superior to other regular treatment options or to assess its cost-effectiveness.

Future studies should also include other age groups, since we now focused on children aged 8 to 18 years. Future studies may also compare the effect of PIM like programs with interventions using systemic immunomodulatory drugs. No explanatory studies have been done to investigate the efficacy of alpine climate treatment. Comparing inpatient treatment in the alpine climate with inpatient treatment in moderate maritime climate will provide evidence for the role of the climate. If such a study would demonstrate differences, additional explanatory studies could determine which factor is characteristic of the alpine climate and responsible for the observed differences.

However it is important that future studies not only use clinical outcomes, but also psychosocial outcomes that may also be related to long-term adherence to treatment, such as coping behavior or depression, and patient reported outcomes. Future studies may also focus on the children who did not respond well to PIM, either on the short term or also on the long term and identify which treatment strategies would be needed for them. Furthermore, clinical severity scoring systems do not capture long-term disease control, current treatment or response to treatment so other ways to assess AD severity could be developed in future studies. In general, more pragmatic trials should be carried out in regular clinical care settings, since these types of trials provide results that are directly relevant to clinical practice.

Precision medicine

Multidisciplinary treatment programs but also systemic treatment (CsA, biologic) is costly. Therefore it is very important to decide which patient is the best candidate for which type of treatment. Without appropriately phenotyping the patient, it is difficult to predict which patient will profit the most from a certain treatment. Furthermore the identification of patient subgroups aids in the decision for whom tailored prevention or new therapeutic strategies have to be developed.[94] It is very likely that different AD phenotypes can be characterized by different clinical, immunological, microbial or mental health features. Apart from the clinical phenotypes based on age of onset, disease severity or presence of other atopic diseases, serological biomarkers constitute a more objective way of phenotyping.[95, 96] More recently, four distinct clusters of patients have been identified based on a combination of serum biomarkers that could represent specific AD endotypes with distinct biological mechanisms.[97] It is unlikely that newly developed biologics that target highly specific biological axes will be equally effective in all patients with AD.[97] With a systems medicine approach more insight in the heterogeneity of AD can be gained. The identification of specific AD endotypes will aid clinical decision making and predict the effect of a certain intervention in advance.[94] This will allow interventions to be concentrated on the patients that will most likely benefit, which is also called precision medicine.

Final conclusions

AD is a heterogeneous and complex disease. Classifying disease severity based on treatment need and response to treatment over time instead of clinical scoring systems may represent a more uniform and representative way of scoring that also eases comparison across studies. For some children with moderate to severe AD, current treatment options are not sufficient. We have shown that it is possible for most of these children (8-18 years) to improve using the interventions that were presented in this thesis and that a personalized integrative multidisciplinary treatment approach (PIM) seems to be effective for most children with difficult to treat AD. An additional value of alpine climate treatment could not be demonstrated on the long-term. Identifying and phenotyping difficult to treat children and refractory children with AD as accurately as possible are essential steps for successful disease management.

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11.
Summary / Samenvatting

Summary

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting up to 30% of children. It is one of the most common childhood diseases with increasing prevalence in recent decades. AD has a significant negative effect on the quality of life of affected children and their parents. Estimations of the prevalence of mild, moderate to severe AD amongst children in the Netherlands vary, but are estimated at 70% mild AD, 20% moderate AD and 2% severe AD. One of the reasons of the varying estimates is that there is no uniform way of defining mild, moderate or severe disease. Treatment of AD revolves around three aspects: anti-inflammatory treatment, topical treatment with emollients to restore the disrupted skin barrier, and avoidance of triggers such as irritants, allergens or stress. Patients with difficult to treat AD are a heterogeneous group who do not respond as expected to AD treatment. Different reasons may contribute to AD being difficult to treat: severe disease, difficulty in following treatment recommendations resulting in low adherence to treatment, inadequate treatment regimens, other atopic or mental health comorbidities (such as asthma, anxiety disorders or ADHD) or family dysfunction which negatively impact AD and/or the effect of treatment. In this thesis, we define difficult to treat AD as use of at least a moderately potent topical corticosteroid and not being able to step down, or current use of systemic immunosuppressive treatment, or repeated treatment with potent topical corticosteroids or systemic immunosuppressive treatment, or a history of use of systemic treatment, or a significant impact of AD on the child's or the families quality of life, or seemingly unresponsive to conventional therapy according to current guidelines. Because of the various skills needed to successfully manage AD, multidisciplinary treatment programs have been developed for children who do not respond sufficiently to regular treatment. In Europe, alpine climate treatment has been used for decades to treat patients with AD and/or asthma. However, no randomized trials have ever been conducted to provide evidence for its effectiveness.

Chapter 2 describes the results of a systematic review of the literature on the effectiveness of alpine climate treatment that identified observational studies only. Despite the positive outcome data, there was considerable risk of bias in the available studies resulting in very low quality evidence. Therefore we concluded that a randomized controlled trial is needed to provide evidence regarding the effectiveness of alpine climate treatment.

In chapter 3 the study protocol of a pragmatic randomized trial to investigate the long-term effectiveness of alpine climate treatment is described. Children with moderate to severe AD that was considered difficult to treat were eligible for participation in the DAVOS trial. They were randomized to a six week treatment period either in an alpine clinic in Switzerland or in an outpatient setting in the Netherlands, followed by a six month follow-up period.

In chapter 6 the characteristics of the children who participated in the trial are described. We observed an early age of onset and a high prevalence of other atopic comorbidities (asthma, rhinitis, food allergy) in the majority of children. Furthermore sleeping problems were present in the majority of children and we found higher prevalence of feelings of fear/depression, withdrawn behavior, social problems and thought problems, compared to the

general population. Several children were diagnosed with ADHD. Regarding knowledge of AD treatment, we found that the parents of children participating in the DAVOS trial were well informed regarding knowledge of TCS. There was room for improvement regarding parental reluctance to use TCS, shower behavior, and refusal of treatment by the child. Comparing these outcomes with data describing treatment management skills of an unselected AD population attending our outpatient clinic between 2009 and 2014, as described in chapter 4, we observed less use of alternative treatment and more treatment refusal by the child in the difficult to treat group. Furthermore we observed that in case of multiple diagnoses, it is important that education is provided concerning all relevant diagnoses and especially in handling the combination, including the therapy strategies. In chapter 5 we demonstrate in a pilot study that differences in prevalence of several intestinal microbial species were associated with a diagnosis of food allergy in a group of children with varying AD severity. However, this was a small study with a cross-sectional study design. Confirming the results and assessment of different food allergies is necessary, preferably in prospective studies with larger well characterized patient populations.

In chapter 6 the results of the DAVOS trial are described. Immediately after alpine climate treatment and after six weeks follow-up, we found significantly greater improvement in disease activity, health-related quality of life and other clinical secondary outcomes in the alpine climate treatment group. This is in line with the results of previous observational studies. In chapter 7, we assessed immunological changes in peripheral blood samples to get insight in the underlying immune mechanisms that explain why children treated in the alpine climate have a better outcome than children from the control group. The most striking difference between the groups is the significant reduction in eosinophils in the intervention group, which is in line with previous studies. Clinically successful AD treatment induces changes in blood B- and T-cell subsets reflecting reduced chronic stimulation. However, the wide data dispersion in the different T and B cell subsets before and after the intervention did not coincide with the significant reduction of disease activity observed in the intervention group.

At the primary endpoint after six months follow-up, we found no significant differences between the intervention and control group regarding disease activity, health-related quality of life, catastrophizing thoughts and coping with itch. Long-term effectiveness is important for children, their parents and society to justify the impact of alpine climate treatment, and in terms of resources. Therefore our study results implicate that there is limited additional effectiveness of alpine climate treatment, because the main additional value of alpine climate treatment would be in its effectiveness on the long-term. Using a personalized, integrative, multidisciplinary treatment approach, children in both study arms improved in terms of AD disease activity, health-related quality of life and catastrophizing thoughts about AD.

In chapter 8 the personalized, integrative, multidisciplinary treatment approach (PIM) that was used in both study arms is described in more detail. PIM actively involves both the child and his parents and combines patient designed treatment goals with a systematic

multidisciplinary approach by the involved health professionals, including assessment of AD, other atopic, pediatric and mental health comorbidities and general well-being. This assessment is done in a systematic way and there are no possibilities to opt-out on parts of the program. These are unique features of PIM compared to other multidisciplinary treatment programs. During PIM, multiple health professionals work simultaneously on the same treatment goals, each using treatment strategies from their own field of expertise. Intervention strategies are chosen based on the best fit for an individual child and/or family situation. Because PIM uses a personalized approach based on the problems experienced by the child, it is specifically suitable for older children (8-18 years).

In chapter 9 we show that for the majority (77%) of children with difficult to treat AD, participation in the trial using PIM resulted in remarkable improvement in disease activity. This was defined as a 75% reduction in disease severity according to a clinical scoring system and little impact of AD on daily life, six months after the end of PIM. Predictors for long-term treatment success included maternal disease acceptance. A small group of children, mostly girls with multiple somatic complaints, from families where the mother has anxiety for the use of topical corticosteroids is less likely to obtain long-term treatment success. These characteristics resemble children with functional somatic symptoms. Most of the children who were unable to reach long-term disease control (70%, 12 out of 17) did reach short-term disease control, according to the same definition. This suggests that it is possible for them to improve but they might be in need of a different and more personalized follow-up.

In chapter 10 the main findings of this thesis are summarized and discussed. Because only a small proportion (estimated 3%) of the total pediatric population with AD is considered difficult to treat, we suggest that the evaluation and treatment of children with difficult to treat AD should be carried out in a limited number of expert centers with special interest and experience in the management of these patients. In this thesis, we have shown that a personalized integrative multidisciplinary treatment approach (PIM) seems to be effective for the majority of children aged 8 to 18 years with difficult to treat AD. PIM addresses other factors that may interfere with AD symptoms, such as inadequate treatment regimens or unaddressed comorbidities or family dysfunction. These factors are important to address because they directly influence the ability to achieve disease control. An additional value of alpine climate treatment could not be demonstrated on the long term. Identifying and phenotyping difficult to treat and refractory children with AD as accurately as possible, are essential steps for future successful disease management.

Samenvatting

Constitutioneel eczeem (CE) is een chronische inflammatoire huidaandoening, die ongeveer 30% van de kinderen betreft. Het is een van de meest voorkomende aandoeningen op de kinderleeftijd en komt de afgelopen decennia steeds vaker voor. CE heeft een grote negative impact op de kwaliteit van leven van de betroffen kinderen en hun ouders. Schattingen van de prevalentie van matig tot ernstig CE bij Nederlandse kinderen lopen uiteen. Een van de redenen hiervoor is dat er geen eenduidige manier is om mild, matig of ernstig CE vast te stellen. De behandeling van CE bestaat uit drie onderdelen: anti-inflammatoire behandeling, gebruik van indifferente middelen om de verstoorde huidbarrière te herstellen en vermijding van uitlokkende factoren. Patiënten met moeilijk behandelbaar CE vormen een kleine, heterogene groep die niet zoals verwacht reageren op de ingezette behandeling. In veel patiënten spelen andere factoren een belangrijke rol, zoals onvoldoende behandeling, moeilijkheden bij het opvolgen van de voorgeschreven behandeling wat leidt tot lage therapie trouw, onbehandelde comorbiditeiten, andere atopische of psychosociale aandoeningen (zoals asthma, angststoornissen of ADHD) die een negative impact hebben op het CE of de behandeling, of een ingewikkelde thuissituatie. Deze factoren beïnvloeden direct de mate waarin de gewenste ziekte controle bereikt kan worden. In dit proefschrift, wordt moeilijk behandelbaar CE als volgt gedefinieerd: gebruik van tenminste een klasse 3 dermatocorticosteroïd waarbij afbouwen niet lukt, gebruik of een geschiedenis van gebruik van systemische immunosuppressieve therapie, herhaalde behandeling met klasse 3 dermatocorticosteroïden of systemische immunosuppressieve therapie, onvoldoende reageren op de reguliere behandeling voor CE volgens de richtlijn en/of een grote invloed van CE op de kwaliteit van leven van het kind of de ouders. Er zijn verschillende vaardigheden nodig om goed met CE en de behandeling te kunnen omgaan. Voor kinderen die niet goed reageren op de reguliere behandeling zijn multidisciplinaire behandelprogramma's opgezet. In Europa wordt tevens hooggebergtebehandeling gebruikt voor patienten met CE en/of astma. Er zijn echter geen gerandomiseerde studies gedaan die bewijs geven voor de doelmatigheid van deze behandeling.

In hoofdstuk 2 worden de resultaten van een systematische review van de wetenschappelijke literatuur beschreven waarin alleen observationele studies zijn gevonden. Ondanks de positieve bevindingen, was er in alle studies sprake van een risico op vertekening van de studieresulaten (bias). Hierdoor is de kwaliteit van de bewijsvoering laag. Daarom is het nodig om een gerandomiseerde studie uit te voeren om hiermee de doelmatigheid van hooggebergtebehandeling te kunnen onderzoeken.

In hoofdstuk 3 wordt het studie protocol van een pragmatische gerandomiseerde studie naar de lange termijn effectiviteit van hooggebergtebehandeling beschreven. Kinderen uit Nederland met matig tot ernstig moeilijk behandelbaar CE konden meedoen aan de DAVOS studie. Ze werden gerandomiseerd voor een 6 weekse behandelperiode in een kliniek in het hooggebergte in Zwitserland of poliklinisch in Nederland, gevolgd door een follow-up periode van 6 maanden.

In hoofdstuk 6 worden de kinderen die aan de DAVOS studie hebben meegedaan in detail beschreven. De meeste kinderen hadden een CE dat al in de vroege kinderleetijd begon met veel atopische comorbiditeiten (astma, rinitis, voedselallergie). De meeste kinderen hadden slaapproblemen en vergeleken met de gemiddelde bevolking kwamen gevoelens van angst en depressie, teruggetrokken gedrag, sociale problemen en denkproblemen veel voor. Een aantal kinderen was gediagnosticeerd met ADHD. De meeste ouders van kinderen waren goed op de hoogte van de behandelvoorschriften met dermale corticosteroiden. Terughoudendheid bij het gebruik van corticosteroiden, douche gedrag en weigeren van insmeermomenten door het kind konden nog verbeterd worden. Vergeleken met de vaardigheden van een grotere groep kinderen met CE die tussen 2009 en 2014 de polikliniek bezocht, beschreven in hoofdstuk 4, was er minder gebruik van alternatieve behandelmethoden en meer weigeren van de behandeling door het kind in de groep met moeilijk behandelbaar CE. Als er sprake is van meerdere aandoeningen tegelijkertijd, is het belangrijk dat er voldoende voorlichting wordt gegeven over alle bekende aandoeningen en vooral ook in het omgaan met de combinatie hiervan.

In hoofdstuk 5 wordt beschreven dat voedselallergie vaak geassocieerd is met ernstiger CE en dat kinderen met voedselallergie en CE een onderscheidende combinatie van bacteriën in hun darmen hebben vergeleken met de kinderen zonder voedselallergie met CE. Echter, de uitgevoerde studie was klein en met een cross-sectionele studie opzet. Bevestiging in grotere prospectieve studies met grote goed gekarakteriseerde patiëntengroepen is wenselijk.

In hoofdstuk 6 worden de resultaten van de DAVOS studie beschreven. Direct na hooggebergtebehandeling en na 6 weken follow-up, is er significant meer verbetering in ziekte activiteit, gezondheidsspecifieke kwaliteit van leven en andere klinische secundaire uitkomstmaten in de hooggebergte groep. Dit komt overeen met de resultaten van eerder gepubliceerde observationele studies. In hoofdstuk 7 hebben we gekeken naar immunologische veranderingen in perifeer bloed om een idee te krijgen welke onderliggende immunologische mechanismen verantwoordelijk kunnen zijn voor de gevonden uitkomsten. Het meest opvallende verschil tussen de groepen is de significante daling in eosinofielen in de interventie groep, wat overeenkomt met eerdere studies. Wat betreft de verschillende T cel en B cel subsets, was er een grote data spreiding zichtbaar en waren de meeste verschillen klein of bewogen zich in verschillende richtingen in de hooggebertegroep en controle groep. Daarom is het niet direct duidelijk hoe deze bevindingen de geobserveerde klinische effect in beide groepen verklaren.

Na 6 maanden follow-up (primaire uitkomstmaat) waren er geen significante verschillen tussen de hooggebergtegroep en de controle groep op het gebied van ziekte activiteit, gezondheidsspecifieke kwaliteit van leven, catastroferende gedachten en omgaan met jeuk. De effectiviteit van hooggebergtebehandeling op de lange termijn is belangrijk voor kinderen, hun ouders en de samenleving om de impact van hooggebergtebehadenling te kunnen verantwoorden. Onze studie resultaten impliceren dat er beperkte effectiviteit is van

hooggebergtebehandeling, omdat de belangrijkste extra toegevoegde waarde de effectiviteit op de lange termijn zou zijn.

In hoofdstuk 8 wordt de persoonlijke, integratieve, multidisciplinaire aanpak (PIM) beschreven die in beide studie armen gebruikt is. PIM betrekt zowel het kind als de ouders actief bij het behandelprocoes en combineert behandeldoelen die door de patient zijn opgesteld met een systematische multidisciplinaire aanpak door de betrokken professionals, op het gebied van CE, maar ook andere comorbiditeiten (atopisch, kindergeneeskundig en psychosociaal) en algemeen welbevinden. De assessment wordt systematisch uitgevoerd en er zijn geen mogelijkheden om bepaalde onderdelen van het programma over te slaan. Dit zijn unieke kenmerken van PIM vergeleken met andere multidisciplinaire programma's. Tijdens PIM werken de verschillende zorgprofessionals tegelijkertijd aan de behandeldoelen, ieder met zijn eigen behandelstrategieën. De behandelstrategie die het beste bij het kind of de gezinssituatie past, wordt gekozen. Omdat PIM een persoonlijke aanpak kent die gebaseerd is op de specifieke problemen die het kind ervaart, is het ook geschikt voor oudere kinderen/ adolescenten.

In hoofdstuk 9 blijkt dat voor de meeste kinderen met moeilijk behandelbaar CE die hebben meegedaan aan de DAVOS studie een dramatische verbetering heeft plaatsgevonden. Ongeveer 77% (n=56) van de kinderen die hebben meegedaan lieten een 75% afname in ziekte-activiteit al dan niet gecombineerd met een kleine impact van CE op het dagelijks leven zien, zes maanden na de interventie met PIM. De belangrijke voorspellende factor voor lange termijn behandelsucces, is een moeder die de ziekte accepteert. Meisjes met veel somatische klachten en een moeder met angst voor dermale corticosteroiden hebben minder kans op lange termijn behandel succes. Echter de meeste van deze kinderen (70%, 12 van de 17) lukte het wel om direct na de interventie behandel succes te behalen, volgens dezelfde definitie. Verbetering lijkt dus wel degelijk mogelijk voor deze kinderen, maar het is moeilijk om het behandeleffect vast te houden. Wellicht zou een meer gepersonaliseerde follow-up of een verlengde follow-up periode geschikt zijn voor deze kinderen.

In hoofdstuk 10 worden de belangrijkste bevindingen van dit proefschrift samengevat en besproken. Omdat maar een klein deel (geschat wordt 3%) van de totale populatie kinderen met CE moeilijk behandelbaar is, stellen we voor om deze kinderen te evalueren en te behandelen in een klein aantal expert centra met speciale interesse en ervaring in het behandelen van deze patiënten.

Samengevat toont dit proefschrift aan dat een persoonlijke, integratieve, multidisciplinaire behandelaanpak (PIM) effectief is voor de meeste kinderen van 8 tot 18 jaar met moeilijk behandelbaar CE. PIM neemt ook andere factoren mee die de gewenste ziekte controle kunnen beinvloeden, zoals onvoldoende behandeling, on(der)behandelde comorbiditeiten of psychosociale aspecten. Het is belangrijk om aandacht aan al deze factoren te besteden omdat ze de te behalen ziekte controle direct beïnvloeden. Op de lange termijn kon geen toegevoegde waarde van hooggebergtebehandeling worden aangetoond. Om CE met goed

resultaat te kunnen behandelen, is het nodig om kinderen met moeilijk behandelbaar CE te onderscheiden van kinderen met refractair CE.

Appendices

Abbreviations

16S rRNA 16 Svedberg units ribosomal ribonucleic acid
AA allergic asthma
AR allergic rhinitis
AD Atopic dermatitis
ADHD attention deficit hyperactivity disorder
AZA azathioprine
ADP atopic dermatitis program
ADC atopic dermatitis center
ACQ asthma control questionnaire
AUC Area-Under-the-Curve
BHR bronchial hyper responsiveness
COPEKI/COPEJU coping with disease questionnaire
CsA cyclosporin A
CBCL child behavior checklist
CBSK self-perception profile for children
CBSA self-perception profile for adolescents
CDLQI children's dermatology life quality index
DECU digital eczema center utrecht
DBPCFC double blind, placebo-controlled, food challenge
ECP eosinophil cationic protein
EPX eosinophil protein X
EASI eczema area and severity index
FDA food and drug administration
FA food allergy
FEV1 forced expiratory volume in 1 second
FeNO fraction of exhaled nitric oxide
FVC forced vital capacity
HDM house dust mite
IgE Immunoglobulin E
IQR interquartile range
JUCKKI children's itching cognitions questionnaire
JUCKJU adolescents' itching cognitions questionnaire
MTX methotrexate
MMF mycophenolate mofetil
NOSI-events parental stress index - events
NOSI-K parental stress index - short form
NPV-J Dutch personality questionnaire - youth version
PAQLQ pediatric asthma quality of life questionnaire
PGA physician graded assessment

PUL positive outcome list
ROC Receiver-Operating-Characteristics
SA-EASI self-administered eczema area and severity index
SAS statistical analysis system
SD standard deviation
SPSS Statistical Product and Service Solutions
SCORAD scoring atopic dermatitis
SF-36 short form health survey
TARC thymus and activation regulated chemokine
TCS topical corticosteroids
UV ultra violet

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everyone who contributed in any way

to the realization of this thesis

Eindelijk is het dan zover: mijn proefschrift is af! Dit zou nooit gelukt zijn zonder de hulp, het advies, het commentaar, de ideeën en de interesse van vele anderen. De volgende personen wil ik graag in het bijzonder bedanken:

Alle kinderen en hun ouders die hebben meegedaan aan de studies, zonder jullie medewerking was dit proefschrift er nooit geweest. Ik hoop dat de resultaten zullen bijdragen aan een betere behandeling voor kinderen met moeilijk behandelbaar eczeem en hun ouders.

Mijn beide promotoren: Suzanne Pasmans en Carla Bruijnzeel. Bedankt voor jullie inzet en begeleiding bij het volbrengen van mijn promotietraject. Mijn grote dank gaat uit naar Suzanne: de initiator en drijvende kracht achter dit onderzoek. Beste Suzanne, je passie en gedrevenheid hebben er voor gezorgd dat er nu een proefschrift ligt. Je lat ligt hoog, maar je enthousiasme en gedrevenheid ook, waardoor we vaak en ook vaak tot in de late uurtjes nog contact hadden. Je hebt me tijdens alle hobbels in dit lange promotietraject steeds onvoorwaardelijk gesteund, waar ik je zeer dankbaar voor ben. Dank aan Carla, die over de grote lijn waakte. Je waardevolle input heeft het onderzoek op essentiële momenten vooruit geholpen en verbeterd door het stellen van kritische vragen. Ik heb de vele discussies omtrent de interpretatie van de data achteraf zeer gewaardeerd.

Lous Rijssenbeek, zonder jou was ik nooit aan dit traject begonnen. Dank dat je me op het juiste moment hebt aangemoedigd om de eerste stap te zetten.

Yolanda Meijer, André Knulst en Rebecca Stellato, bedankt voor jullie actieve betrokkenheid bij de verschillende manuscripten.

Edward Knol en Els van Hoffen, jullie zijn vooral bij het begin en eind van dit promotietraject betrokken geweest. Dank voor de warme belangstelling gedurende al die tijd.

Onderzoek als dit kan alleen maar plaatsvinden dankzij de samenwerking tussen vele verschillende disciplines. Patiënten, psychologen, verpleegkundigen, dermatologen, allergologen, kinderartsen, kinderlongartsen, longartsen, microbiologen, longfunctieanalysten, inspanningsfysiologen, epidemiologen en statistici hebben allen een bijdrage geleverd aan dit proefschrift. Alleen al binnen het WKZ / UMC Utrecht is een samenwerking tot stand gekomen tussen de afdelingen Kinderlongziekten, Kinderpsychologie, Inspanningsfysiologie en Dermatologie / Allergologie voor dit project.

Dank aan Valesca Haneveer-van Manen en Rolien Bekkema die hebben gezorgd voor alle longfuncties, metacholine provocaties en NO metingen. Dank aan Erik Hulzebos voor de talloze inspanningstesten. Dank aan Jantine Korpel en Miranda Jacobs-Verhoef voor jullie interesse en meeleven gedurende al deze jaren.

Ook wil ik graag Frank Schuren, Evgeni Levin en Anita Ouwens van TNO bedanken.

I would like to thank Claudio Rhyner, Mattia Garbani, and Moira Prati for introducing me to the wonderful world of proteins. Thanks for teaching me all the ins and outs of working in the lab, helping me with the protein production and answering all my questions.

Cezmi and Mübeccel Akdis, thanks for supporting me and providing me with very hands-on support to continue working on this thesis. Without your help, it would not have been

possible for me to finish this thesis. Thank you very much for your support and willingness to do so. Daniela Bert, thanks for your sympathy and assistance during this process.

Professor Renner, beste Ellen, dank dat je me de mogelijkheid biedt dit proefschrift af te ronden, ook al ben ik al begonnen aan een nieuw onderzoeksproject met jou.

Mijn zeer gewaardeerde collega-onderzoekers, zonder jullie was het onderzoek doen een stuk minder leuk geweest! Bedankt voor de goede samenwerking en gezelligheid: Wieneke, Renske , Joan, Niels, Jorn, en ook Francine, Mark, Rob en Laury. Ook al was ik vaak op afstand, dankzij de moderne technieken maakte dit niet veel uit. En des te leuker als we elkaar weer in het echt zagen!

Mijn collega's en oud-collega's van het NAD: bedankt voor de gezelligheid, de gezamenlijke lunches en het meeleven met "het onderzoek".

Studenten Finola, Tara-Eileen, Ebru, Sanne, Gwenda, Geert en Marta: jullie hebben allemaal een steentje bijgedragen aan dit proefschrift, dank daarvoor.

Mijn paranimfen Monique en Joan, wat fijn om jullie achter me te hebben staan straks!

Pap en mam, zonder jullie hulp en steun was het nooit gelukt om dit proefschrift te schrijven. Mam, zelfs heen en weer vliegen naar Zwitserland om extra op te kunnen passen is niet te veel moeite voor je. Ook heb ik geregeld met de kinderen een aantal weken in jullie huis gebivakkeerd en mezelf op zolder opgesloten om flink door te kunnen werken. Wat is het fijn om zulke fantastische ouders te hebben op wie je altijd kunt terugvallen.

Lieve Florine, Hugo en Nathan; het boekje is af! Jullie hebben een hele belangrijke rol gehad tijdens deze periode en mij heel erg geholpen om de dingen in perspectief te zien. Het is geweldig om jullie te zien opgroeien en vanaf nu weer vaker samen met jullie te kunnen zijn!

Lieve Willem, eindelijk is het dan zover. Dankzij je onvoorwaardelijke steun, relativerende opmerkingen en praktische adviezen is het me gelukt dit promotietraject tot een goed einde te brengen. Nu op naar het volgende avontuur!

Curriculum vitae

Karin Berthine Fieten was born on August 9th 1982 in Woerden, the Netherlands. She graduated from high school in 2000 and moved to California to study at Orange Coast College, Costa Mesa, CA, USA. In 2001 she returned to the Netherlands and started her BSc in Biology at Wageningen University. After graduating in 2004, she worked and travelled throughout South America in 2005. She started her MSc in Science Communication at Utrecht University in 2006 and spent the most of 2007 in Costa Rica to work on her thesis concerning pesticide exposure and respiratory health of indigenous women. This resulted in her first scientific publication in the American Journal of Epidemiology and started her interest in epidemiology. She graduated in 2008 and moved to Switzerland, where she started working at the Dutch Asthma Center in Davos, on the research project Clinical and pathophsyiological features of difficult to treat asthma at high altitude. In 2011 she started her PhD project which resulted in this thesis. She performed the research described in this thesis under supervision of prof dr. C.A.F.M. Bruijnzeel-Koomen and prof. dr. S.G.M.A. Pasmans in close collaboration with the department of pediatric pulmonology and allergology, supervised by professor C.K. van der Ent en dr. Y Meijer. She obtained her second MSc degree in Clinical Epidemiology in 2015 at the University of Utrecht. She started working as a researcher at the Study Center of the Allergy Campus Davos in Switzerland in 2017. She lives in the small mountain town Davos, Switzerland with her husband and three children.