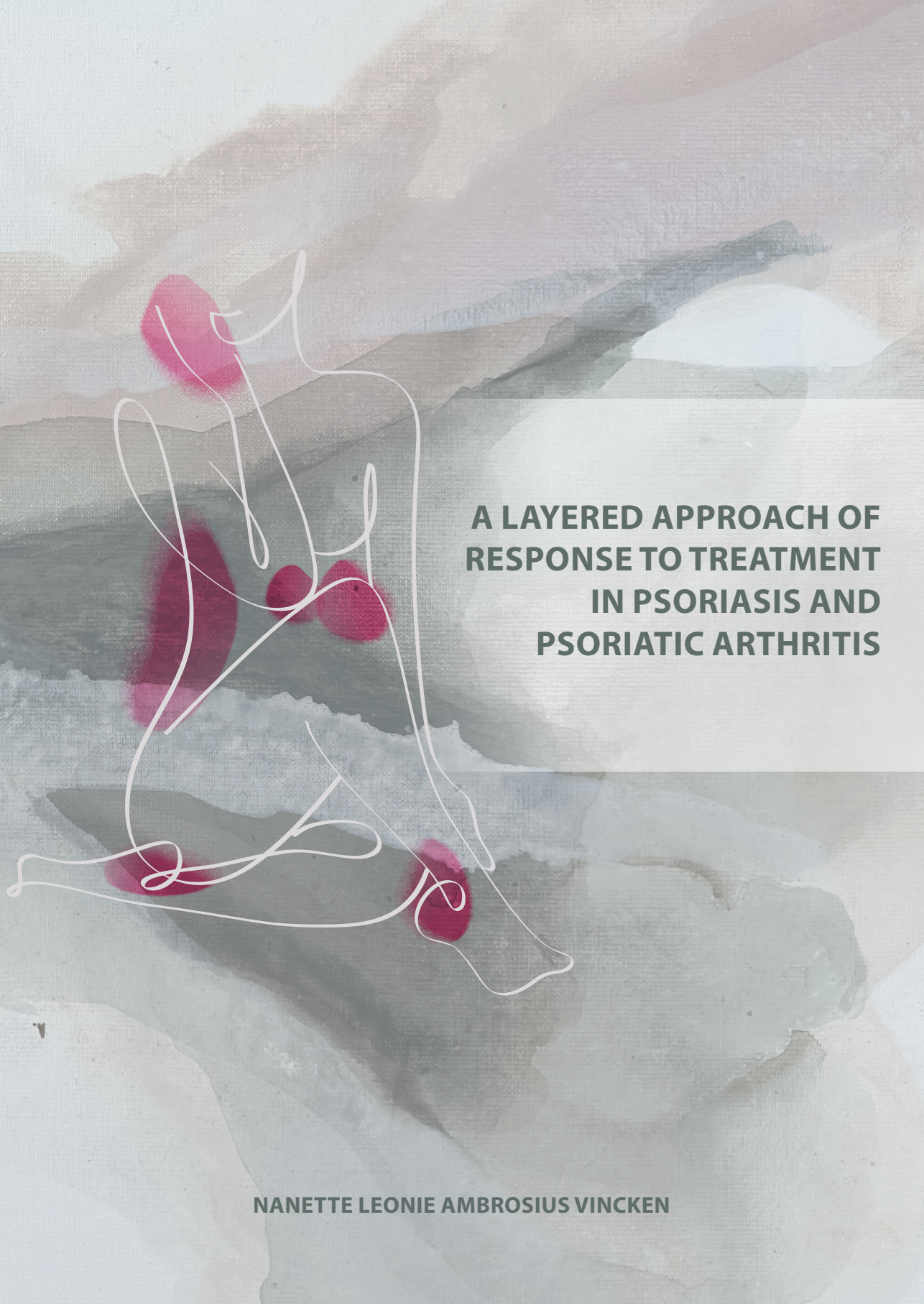
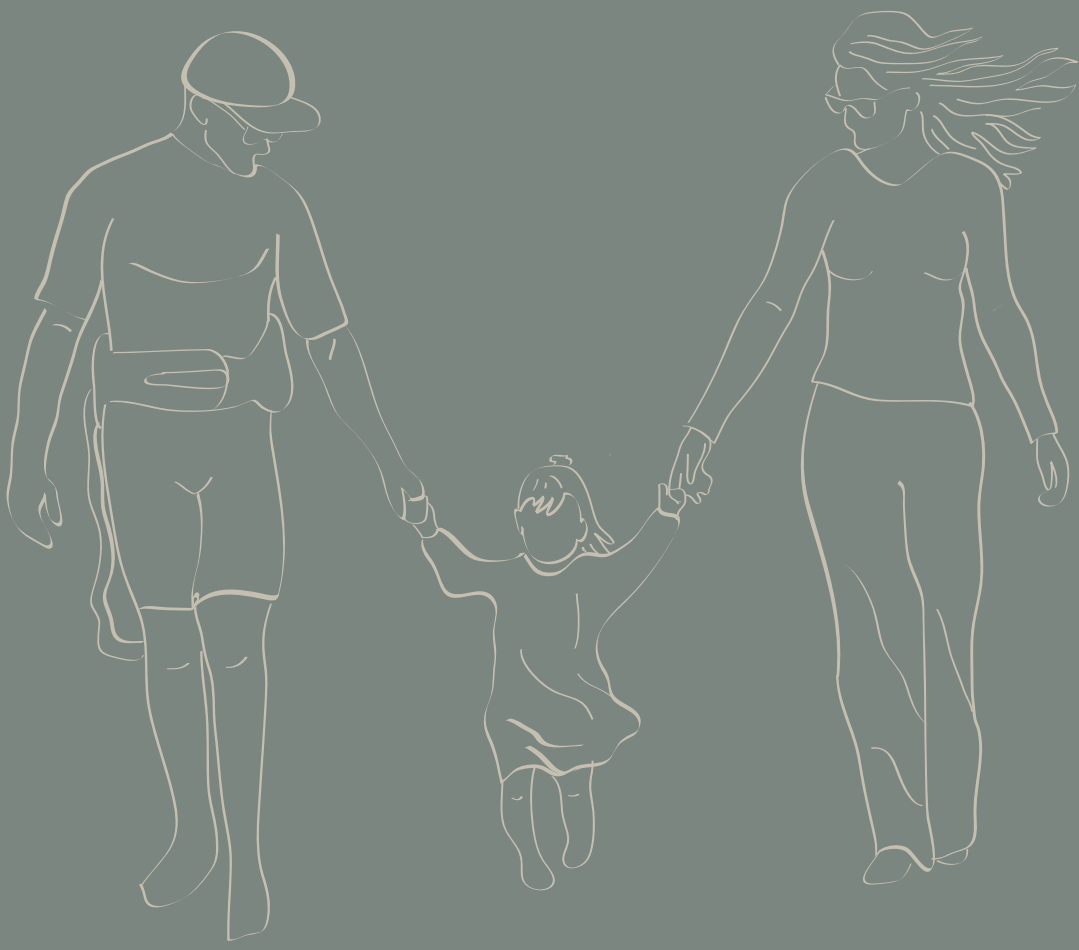


A LAYERED APPROACH OF RESPONSE TO TREATMENT IN PSORIASIS AND PSORIATIC ARTHRITIS

NANETTE LEONIE AMBROSIUS VINCKEN



A layered approach of response to treatment in Psoriasis and Psoriatic Arthritis

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A layered approach of response to treatment in Psoriasis and Psoriatic Arthritis

Een gelaagde benadering van de behandeling van psoriasis en artritis psoriatica

(met een samenvatting in het Nederlands)

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General introduction and thesis outline

1

The immune system plays a crucial role in defending against a wide variety of pathogens, cancer cells, foreign substances and by discriminating between self and nonself entities. [1,2] However, in autoimmune disorders, the response is inappropriately directed towards self-antigens, resulting in local or systemic inflammation.[3] When inflammation persists, it can cause tissue damage, ultimately leading to the manifestation of disease and symptoms. On the contrary, when the immune system is able to restore the balance of regulatory versus effector cells, natural remission can occur, albeit often requiring therapeutic treatments that boost the anti-inflammatory response **Figure 1**.[3]

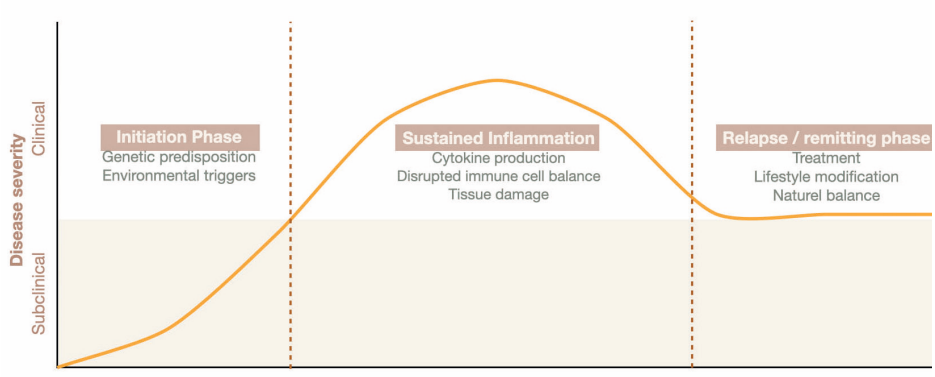

Figure 1. The three phases of autoimmunity. Image adapted from: Rosenblum 2015[3]

The care for patients with chronic autoimmune disorders, such as psoriasis, psoriatic arthritis (PsA) and atopic dermatitis (AD), poses several unmet needs that are of interest to both clinicians and researchers. These include reduction of treatment delay, improvement of quality of life (QoL), minimization of the risk of harmful side effects and identification of immunological markers that can predict patients' differential responses to certain treatment regimens. Comorbidities and psychosocial burden are also important aspects of these diseases which do not always receive sufficient attention and require more awareness in clinical practice.[4-7] These issues show the complexity of present-day care, emphasizing the need for a more personalized and individual approach. Within this thesis, some of these challenges will be addressed.

The heterogeneous nature of Psoriasis and Psoriatic Arthritis and their impact on quality of life

Psoriasis is a chronic, non-communicable and disabling disease that lacks a cure and significantly impacts the patients' QoL.[8] Around 60 million individuals, both children and adults, are affected by this condition globally. The estimated prevalence ranges from 0,51% to 11,43% in adults and from 0% to 1,37% in children, with an increasing trend observed

with more distance from the equator. The incidence is equally distributed among men and women and can manifest at any age, with the peak incidence occurring around 33 years of age.[9,10] There is a large variety in clinical manifestations that, on their own, can also vary in severity and extensiveness. Most commonly, psoriasis manifests as chronic plaque-type psoriasis (vulgaris) characterized by symmetrical, sharply demarcated erythematous plaques located on the extensor elbows and knees, intergluteal cleft and the scalp.[9,11] In more extensive forms of the disease, plaques can occur over the whole body (e.g. face, inner ears, palms soles and nails) and can commonly cause itch or painful fissures.[9]

Approximately one in five patients with psoriasis eventually develop PsA, a condition that is further characterized by clinical manifestations ranging from peripheral oligo- or poly-arthritis, axial spondyloarthritis, dactylitis, enthesitis, nail pitting and onycholysis. However, not all symptoms may necessarily manifest at once or may not develop at all, which makes the presentation of PsA very heterogeneous and sometimes difficult to diagnose.[12,13] The majority of patients present with psoriasis as the first manifestation (82,3%), or develops psoriasis within the same year (10,6%) while a minority of patients presents with arthritis (7,1%) before developing skin manifestations.[14] It is possible to speculate that psoriasis and PsA belong to the same spectrum, and that while both entities display a large heterogeneity in clinical manifestations, they share common genetic and immunological grounds.[15,16]

Clinicians should acknowledge that psoriasis and PsA are not restricted to skin and joint involvement, but rather are comprehensive diseases that can affect all aspects of a patients' life. These patients often suffer extra-articular systemic symptoms, with a higher incidence of metabolic and cardiovascular comorbidities compared to the general population.[17-19] As a result, patients report a significant disease burden contributing negatively on their QoL.[19-21] **Figure 2.**

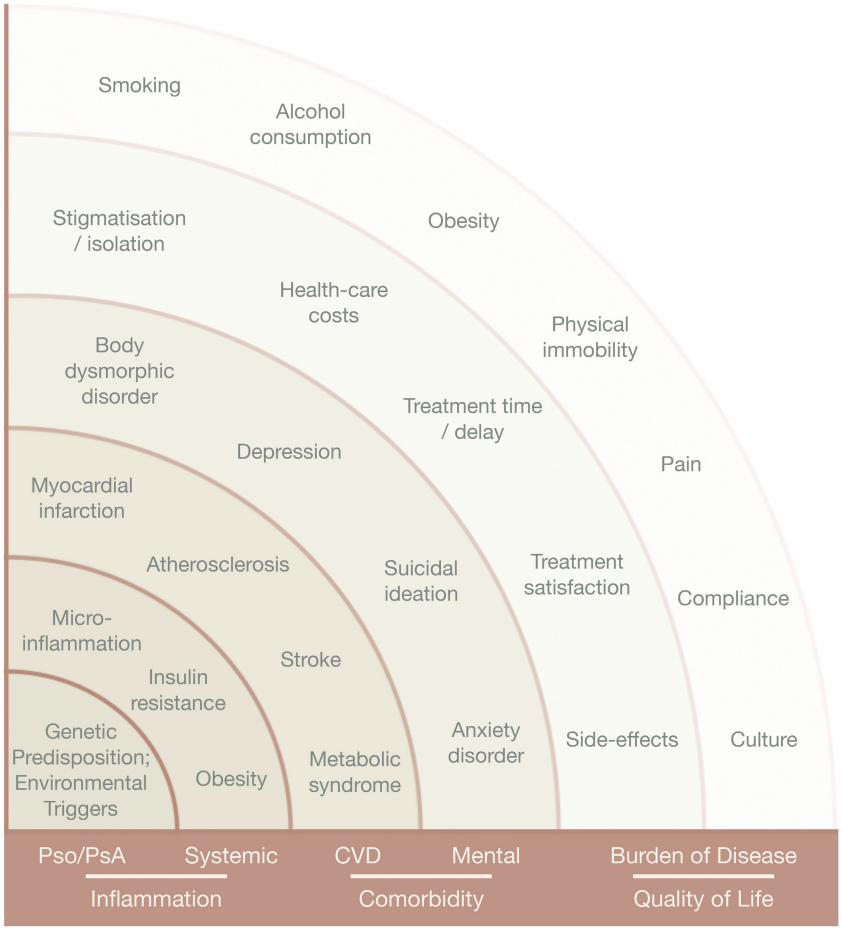

Figure 2. An overview of the different layers of psoriatic disease. Pso: psoriasis; PsA: psoriatic arthritis; CVD, cardiovascular disease. Image adapted from: Mrowietz 2014[21]

Pathogenesis and involved pathways: IL-23 and IL-12 as important drivers in psoriasis and PsA inflammation

The exact succession of events leading to the development and progression of psoriasis or PsA has not yet been elucidated. However, the general consensus is that there is a complex interplay between environmental factors and genetic predisposition that eventually triggers innate and adaptive immune responses leading to chronic inflammation.[22] Different local sites, e.g. skin or Achilles tendon, were proposed to be responsible for the initial evolution of PsA.[23] Furthermore, exogenous triggers, i.e. trauma, infection, sunlight, alcohol consumption or drug exposure can lead to the activation of key cellular players in psoriasis pathogenesis, such as keratinocytes, fibroblasts and immune cells eventually leading to chronic inflammation.[9,11,24]

Dendritic cells are important mediators between innate and adaptive immunity.[25] Among these, myeloid dendritic cells (mDC) are specialized innate immune cells which, upon activation, secrete pro-inflammatory cytokines such as interleukin (IL)-23, IL-12 and tumor necrosis factor (TNF)-α.[26,27] These cytokines play a central role in the pathogenesis of psoriasis and PsA[28-30] and drive naïve T-cells to proliferate and differentiate in to IL-17 secreting T-helper(h)17 and IFN-γ secreting Th-1 cells, respectively.[27,31] IL-17, IFN-γ and IL-22 upregulate the production of chemokines, such as neutrophil-attracting chemokines (e.g. CXCL1, CXCL2 and CXCL8) which drive immune cells to infiltrate the psoriatic skin.[24] Additionally, sustained chronic activation of mDCs and T cells will lead to the accumulation of pro-inflammatory cytokines and chemokines eventually resulting in psoriatic lesions.[24,32] **Figure 3**. Activated skin keratinocytes and fibroblasts acquire increased proliferation properties which contribute to the typical epidermal hyperplasia, parakeratosis and neovascularization of the skin observed in these patients.[9,11,30]

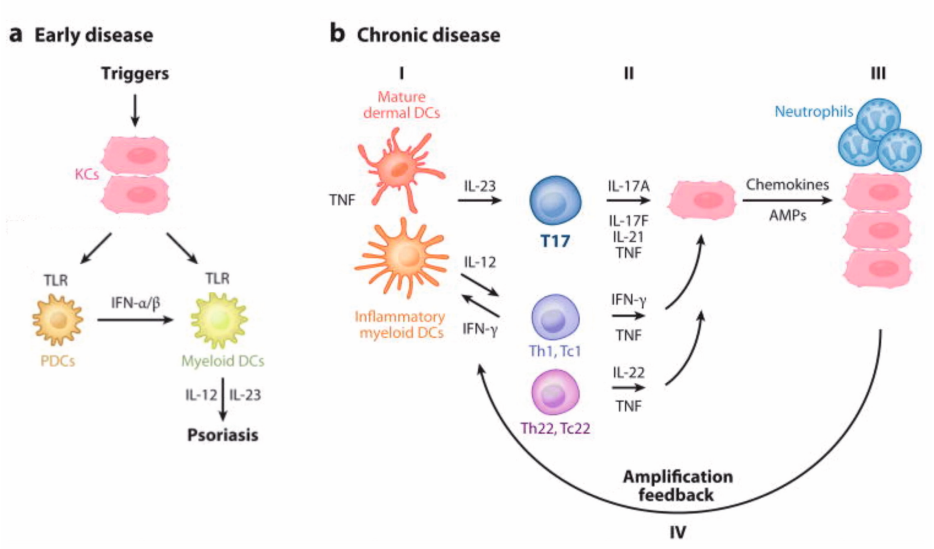

Figure 3. Pathways showing the initiation and sustained inflammation phases of psoriasis. **a**: In the early disease, triggered keratinocytes activate mDCs either directly or indirectly (via production of IFN by pDCs). Activated mDCs produce IL-12 and IL-23, key psoriatic mediators. **b**: Upon activation of (I) mDCs, IL-12 and IL-23 lead to (II) the differentiation and proliferation of naïve T-cells to the activation of pro-inflammatory effector T-cells. Cytokines produced by these cells accumulate in the skin and contribute to local inflammation. In turn (III), this stimulates keratinocytes to proliferate and form psoriatic lesions, (IV) further intensifying the cutaneous immune responses. KC: keratinocytes; TLR: toll-like-receptor; IFN: interferon; PDCs: plasmacytoid dendritic cell; IL: interleukin; TNF; tumor necrosis factor; Th: T-helper; AMPs: antimicrobial peptides. Image adapted from: Lowes 2014[24]

The two key cytokines secreted by mDCs involved in the induction, progression and maintenance of both psoriasis and PsA are IL-23 and IL-12.[33] IL-23 is made up of two subunits; IL23A (IL-23p19) and IL12B (IL-12p40), with the p40 subunit being shared with IL-12, and p19 being a unique subunit of IL-23.[33] **Figure 4.** IL-23 and IL-12 both belong to the IL-12 cytokine family and share structural and biological commonalities.[34] Given that targeting of the p40 subunit results in the inhibition of both cytokines, this subunit emerges as an interesting therapeutic target for effectively treating psoriasis and PsA. This efficacy has been substantiated through examination in clinical trials.[35]

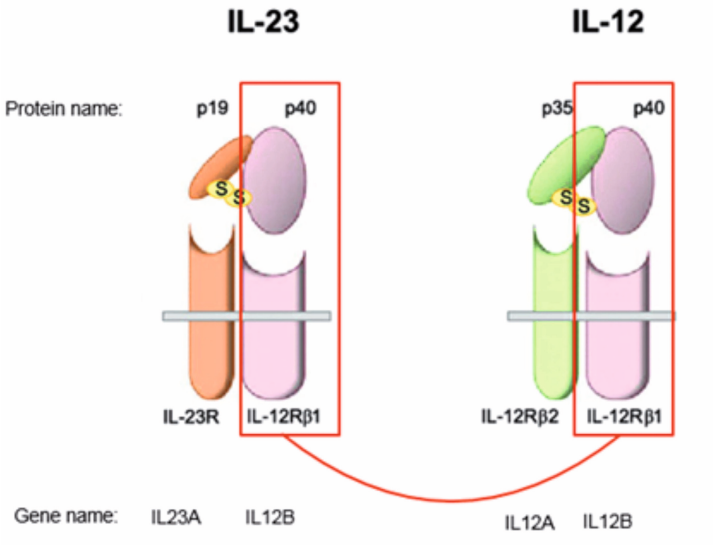

Figure 4. The biological structure of IL-23 and IL-12 and their shared sub-unit p40 binding to its receptor. IL: interleukin; R: receptor

In **Chapter 2**, we aimed to investigate whether the expression of p40 could be suppressed by tofacitinib, a highly effective second-generation small molecule inhibitor that has shown great promise in the treatment and management of psoriasis, PsA and other inflammatory and autoimmune conditions.[36]. By exploring the role of p40 in the response to tofacitinib, we aimed to unravel potential mechanisms underlying the drug's therapeutic effects in psoriasis and PsA. This is a crucial area of research, as effective treatments for these conditions are needed. **Chapter 2** shows some interesting results for our understanding of the biology and treatment of psoriasis and other inflammatory conditions, and underscores the relevance of tofacitinib as a potential therapeutic agent for these conditions.

Tofacitinib: a JAK inhibitor with promising therapeutic potential for psoriatic arthritis. A novel drug that has recently been approved and added to the therapeutic armamentarium for the treatment of PsA is tofacitinib. It is an oral small molecule inhibitor that blocks the Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway.[37] The JAK/STAT pathway is activated when cytokines (i.e. IL-12 and IL-23) bind to their corresponding receptor on the cell surface, leading to subsequent phosphorylation of JAK tyrosine kinases on the intracellular part of the receptor leading to translocation of latent cytoplasmic transcription factors (STATs) to the nucleus.[38] **Figure 5.**

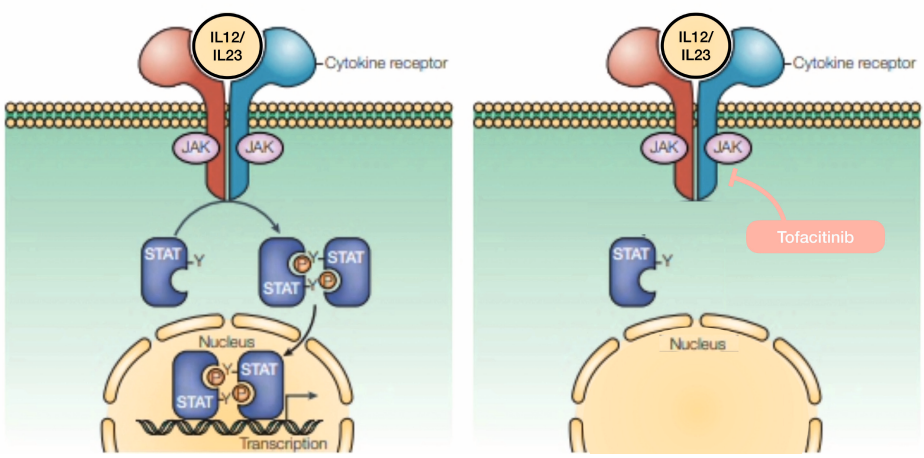

Figure 5. A schematic overview of the JAK-STAT signaling pathway: when cytokines bind to cytokine receptors, JAKs and subsequently STATs are phosphorylated. These STATs then form dimers and move into the nucleus where they can initiate the transcription of genes. Tofacitinib blocks the intracellular JAK-domain preventing phosphorylation of STATs, thus preventing gene transcription.
Image adapted from: Shuai 2003[38]

In vitro studies suggest that tofacitinib inhibits the transcription of genes that lead to immune system activation, predominantly by targeting JAK1, JAK2, JAK3 and, to a lesser extent, Tyrosine Kinase 2 (TYK2).[37] By inhibiting JAKs, tofacitinib directly suppresses multiple intracellular signaling pathways that are crucial to cytokine production and secretion. In turn, the differentiation of Th1 and Th17 cells is suppressed, along with the subsequent secretion of IFN-γ and IL-17 by these cells, respectively.[39,40] A possible explanation is the suppression of JAK2/TYK2 activation mediated by IL-12 and IL-23 binding to class I cytokine receptors, preventing STAT3 and STAT4 phosphorylation and nuclear translocation.[41] Tofacitinib has shown promising therapeutic potential in clinical trials for PsA.[36] The long term safety profile of tofacitinib appears to be broadly comparable to that of other biological treatments, except for evidence indicating a higher incidence

of herpes zoster infections in patients treated with tofacitinib compared to those treated with other biological treatments.[42] Moreover, an increased risk of major adverse cardiovascular events and venous thromboembolism has been observed in patients with rheumatoid arthritis compared to those using TNFα inhibitors. Caution should be exercised in cases where patients are 65 years or older, current or former long-term smokers, or have pre-existing cardiovascular risk factors.[43]

To address the unmet needs in the therapeutic approach for patients with psoriatic disorders, a clinical trial is currently being conducted using a multi-omics systems medicine approach. This trial aims to integrate various types of data, including clinical, transcriptomic, metabolomic, proteomic, flow cytometry, and imaging data to identify PsA patient profiles that could predict treatment response to tofacitinib, methotrexate and etanercept. The ultimate goal is to develop a tool based on patients' clinical or immunological profiles, that can aid clinicians in selecting the optimal treatment for each individual PsA patient. The protocol of this trial is described in **Chapter 3**.

Challenges in the treatment of psoriasis and psoriatic arthritis

The treatment of choice for the individual psoriasis patient very much depends on disease severity (mild – moderate – severe) and the location of the lesions. Patients with mild disease on non-functional locations can often be managed with (a combination of) topical agents, while those with more extensive disease or lesions on functional or socially debilitating areas (such as hands, feet, inguinal or face) may need a more aggressive approach such as phototherapy or systemic treatment.[44] Topical regimens can still be applied for local management of refractory lesions while receiving systemic therapy. For first-line conventional systemic treatment, acitretin, ciclosporin, fumarates or methotrexate are typically considered. If treatment success cannot be expected or inadequate response/ side effects are observed, a first-line biological or small molecule agent may be prescribed (anti-TNF; anti-IL-17; anti-IL-23; JAK inhibitors).[45] With the wide variety of available systemic non-biologic and biologic agents, clinicians may face difficulties in choosing the most suitable treatment for individual patients.[44,46]

Like psoriasis, the treatment of PsA is also highly dependent on the clinical phenotype and severity of the disease. Initially, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed. Following that, treatment options may include systemic non-biologic, biologic, or small-molecule agents. It is important to note that the effectiveness of treatment can differ based on the predominant clinical phenotype. For example, patients with mainly peripheral arthritis often find relief through disease-modifying antirheumatic drugs (DMARDs), while those with dactylitis may not experience the same level of relief.

Conversely, individuals with axial spondyloarthritis tend to benefit the most from TNF-inhibitors. Thus, tailoring the treatment approach according to the specific phenotype is crucial for effective management of PsA.[47]

As such, a "one-size-fits-all" treatment strategy does not apply for psoriasis and PsA patients, posing a challenge for clinicians to select the most appropriate regimen for each individual. With advancing techniques and new therapeutic targets being discovered, the therapeutic armamentarium is continuously being expanded, but the absence of head-to-head trials evaluating the various drugs makes it difficult to determine their relative efficacy and safety, and the optimal choice may also depend on individual patient characteristics. Consequently, treatment decision often relies on clinical judgement and trial-and-error.

While exploring treatment options, we encountered an old paradigm stating that glucocorticoids may exacerbate pre-existing psoriasis or induce a morphological shift in phenotype. Most current treatment guidelines discourage the use of these drugs in patients with psoriasis or PsA. The basis for this recommendation is a case series published in 1968[48], where several psoriasis patients developed pustular psoriasis upon glucocorticoid exposure. To critically re-appraise the restrained use and negative attitude towards systemic glucocorticoid use for psoriasis and PsA patients, we performed a systematic review, which is described in **Chapter 4**.

Psoriasis and atopic dermatitis: two sides of the same coin or distinct entities?

Just like PsA and psoriasis are related, psoriasis and AD have been considered conditions belonging to the same disease spectrum, as both are characterized by an altered growth and differentiation of epidermal keratinocytes triggered by local cytokine release and immune cell engagement.[49,50] Generally, AD is considered a Th2 and Th22-centered disease.[51] However, while European-American AD patients predominantly show a Th2 driven phenotype, Asian AD patients show a significant higher induction of the Th17 and Th22 axis together with Th2 polarization. As such, the immunological mix between psoriasis and AD, specifically in the Asian AD phenotype, suggests that the pathogenesis cannot be solely attributed to the Th2 axis.[52] Despite being a skin condition, AD is characterized by a significant amount of circulating pro-inflammatory cytokines, as compared to both psoriasis and PsA. This state of chronic systemic inflammation, often referred to as the "inflammatory skin march"[53], may eventually lead to dyslipidemia, hypertension, visceral adiposity and insulin resistance, posing a risk to develop type 2 diabetes and cardiovascular disease.[53] **Figure 6.**

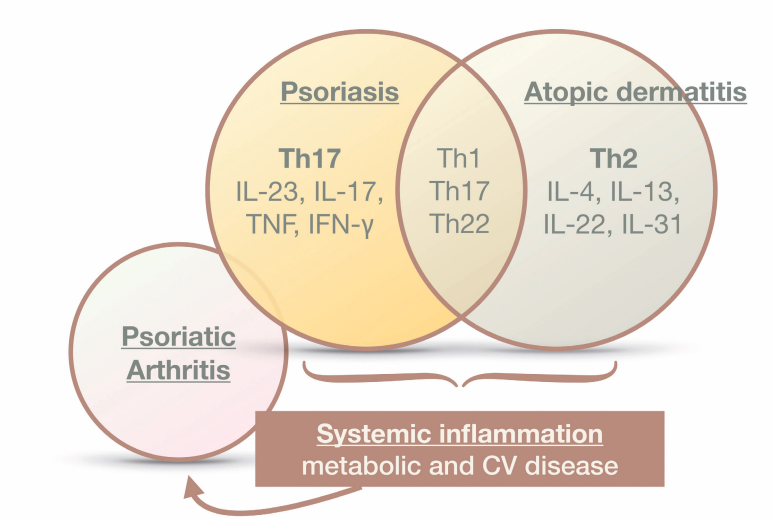

Figure 6. A schematic overview of the commonalities between psoriasis – eventually developing into psoriatic arthritis - and atopic dermatitis, two chronic inflammatory skin disorders. Chronic inflammation in both conditions has been linked to the development of metabolic and cardiovascular diseases. Th: T-helper cell; IL: interleukin; CV: cardiovascular[54,55]

Clinically, both psoriasis and AD remain clearly distinguishable in terms of anatomical skin lesion distribution (e.g. flexor and face for AD versus extensor and scalp regions for psoriasis) and the age of peak onset (early infancy and childhood for AD versus a peak incidence around 33 years for psoriasis).[56] Patients with psoriasis tend to have higher body mass index (BMI) and show more physical inactivity compared to those with AD. However, patients with severe AD tend to report worse patient-reported outcomes and disease burden than those with comparable disease severity in psoriasis.[49,56] The debate whether AD and psoriasis belong to a disease spectrum or should be considered as distinct entities remains unresolved. Despite this, the fundamental clinical challenge for both conditions remains the same: identifying the optimal treatment regimen for the individual patient while minimizing the risk of adverse effects and reducing the negative impact on patients' quality of life.

To address the unmet need for optimal treatment regimens for AD patients, our collaborators previously conducted a study that aimed to identify potential predictors of treatment response to methotrexate. This study gathered clinical and serum proteins data and identified several differentially expressed proteins in AD patients who demonstrated a positive response to methotrexate treatment (unpublished data). Out of these candidate proteins, a proof-of-concept prediction model was constructed. To determine whether

this model could be applied not only in AD, but also extended to psoriasis/PsA, we gathered clinical data and serum baseline samples from a cohort of methotrexate treated psoriasis/PsA patients and measured the same protein panel. This cohort was chosen in light of the shared immunopathogenesis between psoriasis/PsA and AD, and the fact that methotrexate is frequently used as first-line systemic treatment for these conditions.[54,57] The details of our findings are presented in **Chapter 5**.

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Suppression of IL-12/IL-23 p40 subunit in the skin and blood of psoriasis patients by tofacitinib is dependent on active interferon-γ signaling in dendritic cells: implications for the treatment of psoriasis and interferon-driven diseases

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ABSTRACT

Interleukin (IL)-12 and IL-23 are pro-inflammatory cytokines produced by dendritic cells (DCs) and associated with Psoriasis (Pso) and Psoriatic Arthritis (PsA) pathogenesis. Tofacitinib, a Janus kinase inhibitor, effectively suppresses inflammatory cascades downstream the IL-12/IL-23 axis in Pso and PsA patients. Here we investigated whether tofacitinib directly regulates IL-12/IL-23 production in DCs, and how this regulation reflects responses to tofacitinib in Pso patients. We treated monocyte-derived dendritic cells (moDCs) and myeloid dendritic cells (mDCs) with tofacitinib and stimulated cells with either lipopolysaccharide (LPS) or a combination of LPS and IFN-γ. We assessed gene expression by qPCR, obtained skin microarray and blood Olink data and clinical parameters of Pso patients treated with tofacitinib from public datasets. Our results indicate that in DCs co-stimulated with LPS and IFN-γ, but not with LPS alone, tofacitinib leads to the decreased expression of IL-23/IL-12 shared subunit *IL12B* (p40). In tofacitinib-treated Pso patients, IL-12 expression and skin severity scores (PASI) are significantly reduced in patients with higher IFN-γ at baseline. These findings demonstrate for the first time that tofacitinib suppresses IL-23/IL-12 shared subunit *IL12B* in DCs upon active IFN-γ signaling, and that Pso patients with higher IFN-γ baseline levels display improved clinical response after tofacitinib treatment.

BACKGROUND

Dendritic cells (DCs) are professional antigen-presenting cells that form the bridge between innate and adaptive immunity. Myeloid dendritic cells (mDCs) are circulating DCs[1], while monocyte-derived dendritic cells (moDCs) are tissue-resident DCs that are present at the sites of inflammation[2]. Activated DCs produce pro-inflammatory cytokines that prime naïve T-lymphocytes into specific effector phenotypes[3,4] and, when undergoing inappropriate chronic activation, can drive autoimmunity.[5]

Some of the pathways by which DCs contribute to chronic immune activation are induced by the production of IL-23 and IL-12.[6] The IL-23 cytokine consists of two subunits, *IL23A* (IL-23p19) and *IL12B* (IL-12p40). The p40 subunit is shared with IL-12, while p19 is unique to IL-23. Both IL-12 and IL-23 have an important role in the differentiation of naïve T-lymphocytes into T helper (Th) interferon (IFN)-γ-producing Th1 or IL17-producing Th17 cells, respectively.[7,8–10]

Disorders associated with deregulations of the IL-23/IL-17 and IL-12/IFN-γ immune axis include psoriasis (Pso) and psoriatic arthritis (PsA), among others.[6] Pso patients display an increased presence of inflammatory DCs expressing IL-12 and IL-23 in lesional skin.[11] Similarly, in PsA patients, elevated IL-12 expression is observed in serum and synovial fluid.[12–14]

Treatment of these diseases with Janus kinase (JAK) inhibitors has proven to be effective in recent clinical trials.[15] Specifically, tofacitinib, an oral small molecule inhibitor targeting JAK1, JAK2, JAK3 and, to a lower extent, Tyrosine Kinase 2 (TYK2)[16] significantly reduces psoriatic and arthritic manifestations, while displaying comparable benefit/risk profiles with biologicals.[17,18]

In vitro studies indicate that tofacitinib suppresses the differentiation of Th1 and Th17 T cells and the production of IFN-γ and IL-17.[19,20] A plausible mechanism of action consists in the suppression of JAK2/TYK2 activation mediated by IL-12 and IL-23 binding, which further prevents STAT3 and STAT4 nuclear translocation.[21] However, tofacitinib was also shown to reduce *IL12B* and *IL23A* mRNA levels in Pso lesional skin and in imiquimod-treated mice, suggesting a direct role in the regulation of the upstream cytokines leading to Th1 and Th17 differentiation.[22,23]

QUESTIONS ADDRESSED

Current literature indicates that tofacitinib suppresses the inflammatory cascades downstream IL-12/IL-23, key cytokines in Pso/PsA development.[6] However, whether tofacitinib is able to suppress IL-12/IL-23 production by DCs has not been documented. Here, we aimed to investigate whether tofacitinib is able to regulate the expression of IL-12 and IL-23 in DCs, and to determine how this regulation can influence responses to tofacitinib in Pso patients.

EXPERIMENTAL DESIGN

Cell isolation

Peripheral blood mononuclear cells (PBMCs) derived from either healthy control blood or buffy coats were separated with Ficoll gradient (#17-1440-02, GE Healthcare). Blood was collected following institutional ethical approval. CD1c (BDCA-1)+ mDCs and CD14+ monocytes were isolated (Miltenyi Isolation Kit #130-090-506, #130-050-201) and separated on autoMACS Pro Separator according to manufacturer's instructions. Purity was checked by flow cytometry on BD LSRFortessa™ (BD Biosciences). Before culturing, cells were washed with complete medium consisting of RPMI 1640 medium, GlutaMAX™ Supplement (#61870-036, ThermoFisher Scientific), 10% Fetal Bovine Serum (Biowest) and 1% Penicillin-Streptomycin (#15070063, ThermoFisher Scientific). mDCs were stimulated on the day of isolation, after they were rested for 1 hour at 37°C.

Generation of monocyte-derived dendritic cells

To generate moDCs, monocytes were cultured at 37°C for six days at a density of 10^6 cells/mL in the presence of 500 U/ml IL-4 and 800 U/ml GM-CSF (#204-IL-50, #215-GM-500, both from R&D Systems). Cytokines and medium were refreshed on day 3. On day 6, cells were harvested, washed with fresh complete medium and replated at a cell density of 10^6 cells/ml. Cells were left resting overnight at 37°C.

Stimulation of moDCs and mDCs

Immature moDCs and mDCs were pre-treated or not with 1µg/ml tofacitinib (CP-690550, Selleckchem) or Ruxolitinib (INCB018424, Selleckchem) for 30 minutes. After, cells were stimulated with either 10 µg/ml Lipoteichoic acid (LTA) (#L2515, Sigma Aldrich), 100ng/ml LPS, 1µg/ml R848 (#tlrl-3pelps, #tlrl-r848, Invivogen), 1000U/µL IFN-α (#CRI003B, Cell sciences) or 1000U/mL IFN-γ (#14-8319-80, eBioscience) for 4 hours.

Statistical analyses of in vitro experimental data

Statistical analyses of DCs mRNA data were performed using GraphPad Prism 8.3 Software. Non-parametric Friedman test for paired samples followed by Dunn's multiple comparisons test were computed to compare gene expression levels between 0 and 4 hours of stimulation. Values with a $p < 0.05$ were considered significant.

Details about RNA isolation and real-time PCR, GEO datasets and statistical analyses are provided in supplementary files.

RESULTS

Treatment with tofacitinib does not reduce *IL23A* and *IL12B* mRNA expression in TLR4-activated DCs

Consistent with previous reports,[24–27] we observed that the mRNA expression of IL-23p19 (*IL23A*), IL-12p40 (*IL12B*) and IL-12p35 (*IL12A*) in both mDCs and moDCs is induced by TLR2, TLR4 and TLR7/8 activation **(Supplementary Figure 1A-C)**. TLR4 was previously found upregulated in Pso PBMCs[26] and skin.[28,29] Additionally, serum and epidermal expression of S100A8 and S100A9, TLR4 ligands contributing to keratinocyte hyperproliferation, were found to be significantly higher in Pso patients in comparison to healthy controls.[30] Therefore, we chose TLR4 activation by LPS as a model to mimic DC activation in Pso blood.

In LPS-stimulated mDCs and moDCs pretreated with tofacitinib, we could not observe a reduction in the expression of *IL23A, IL12B* and *IL12A* **(Figure 1A and 1C)**. Surprisingly, the expression of *TNF*, another key cytokine playing a role in Pso pathogenesis and suppressed by tofacitinib *in vivo*[22], was also not suppressed by tofacitinib in LPS-stimulated DCs **(Figure 1B and 1D).** We could confirm that tofacitinib efficiently blocks the JAK/STAT signaling in these cells, as determined by the suppression of control *CXCL10* expression in paired samples **(Figure 1E).** We further demonstrated that lack of downregulation of IL-12/IL-23 cytokines in LPS-stimulated DCs also occurs in the presence of the JAK1/JAK2 inhibitor ruxolitinib **(Supplementary Figure 2)**, thus it is not solely attributed to tofacitinib's mode of action.

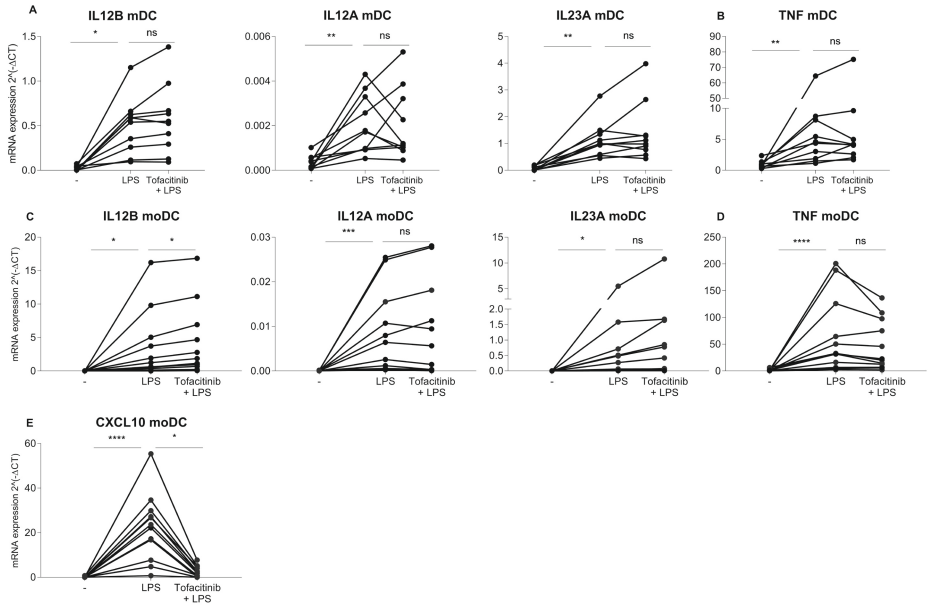

Figure 1. Cytokine gene expression in LPS-stimulated DCs treated with tofacitinib. (A-B) Gene expression of *IL12B, IL12A* and *IL23A* subunits **(A)** and *TNF* **(B)** in mDCs (n=10). **(C-E)** *IL12B*, *IL12A* and *IL23A* subunits **(C)**, *TNF* **(D)** and CXCL10 (**E**) in moDCs (n=12). mDCs and moDCs were pre-treated or not with tofacitinib for 30 minutes and stimulated with LPS for 4 hours. Gene expression was measured by real-time qPCR and represented as relative expression (2^-ΔCT). Lines connect individual donors. Significance was determined by Friedman's test followed by Dunn's multiple comparisons test.

Co-stimulation with LPS and IFN-γ leads to reduced expression of *IL12B* mRNA in DCs treated with tofacitinib

Previously, Bechera et al. reported that JAK1 inhibition in moDCs suppresses IL-23 and IL-12 expression when cells are stimulated with a combination of nickel sulfate, a TLR4 agonist, and IFN-γ.[31] We thus investigated the effects of LPS and IFN-γ stimulation on mDCs and moDCs pre-treated with tofacitinib. Co-stimulation of DCs with LPS and type II IFN-γ led to a significant reduction of *IL12B, IL12A, TNF* and *CXCL10* mRNA expression upon tofacitinib treatment **(Figure 2A-D)**. Conversely, co-stimulation with type I IFN-α did not lead to similar modulatory effects in these cells **(Supplementary Figure 3)**. These data indicate that an active type II, but not type I, IFN signaling in DCs is required for the suppression of *IL12B* and other pro-inflammatory cytokines by tofacitinib.

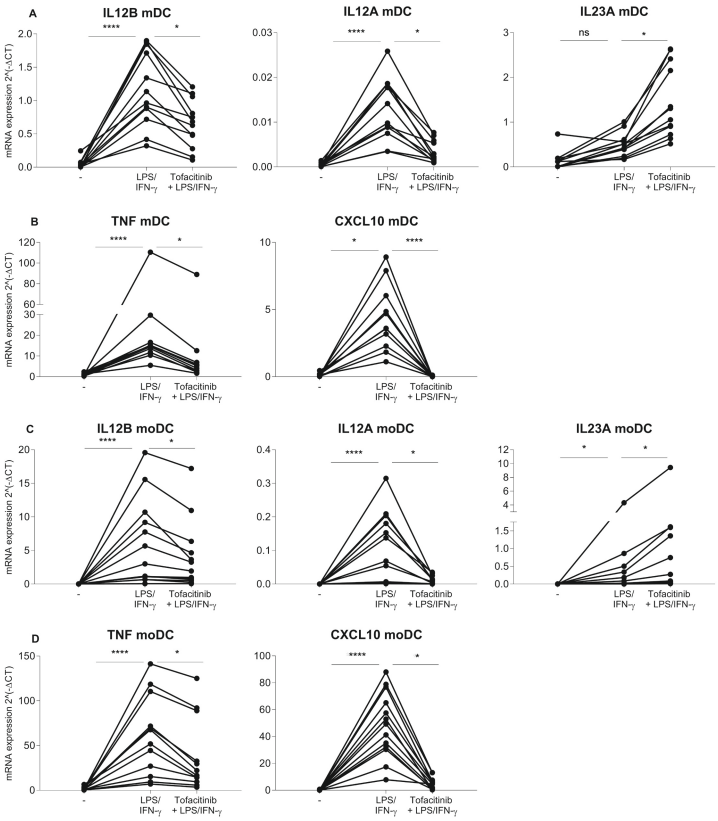

Figure 2. *IL12B* gene expression is suppressed by tofacitinib in the presence of IFN-γ in LPS-stimulated mDCs and moDCs. (A-B) Gene expression of *IL12B*, *IL12A*, *IL23A* **(A)** and *TNF* and *CXCL10* **(B)** in mDCs (n=12). **(C-D)** Gene expression of *IL12B*, *IL12A* and *IL23A* **(C)** and *TNF* and *CXCL10* **(D)** in moDCs (n=13). mDCs and moDCs were pre-treated or not with tofacitinib for 30 minutes and stimulated with a combination of LPS and IFN-γ for 4 hours. Gene expression was measured by real-time qPCR and represented as relative expression (2^-ΔCT). Lines connect individual donors. Significance was determined by Friedman's test followed by Dunn's multiple comparisons test.

Psoriasis patients with higher IFN-γ levels display reduced IL-12 expression and skin severity score after tofacitinib treatment

To test the relevance of IFN-γ stimulation in the suppression of IL-12 by tofacitinib, we analyzed publicly available data of Pso patients before and after tofacitinib treatment to assess whether higher baseline levels of IFN-γ could predict lower IL-12 production and improved Psoriasis Area and Severity Index (PASI) score after tofacitinib treatment.

From blood protein Olink data (GSE136435) we found that IL-12 levels were significantly reduced after 4 weeks of tofacitinib treatment, while more modestly reduced after 4 weeks of etanercept treatment (**Figure 3A**). IL-23 was not determined in this assay. We further assessed the baseline IFN-γ levels in the two treatment groups and defined IFN-γ-high

and IFN-γ-low patients (**Figure 3B**). We found that patients with higher IFN-γ levels at baseline also displayed higher IL-12 levels (**Figure 3C**). By calculating the difference in IL-12 levels between 4 week treatment and baseline (ΔIL-12), we identified that patients with higher IFN-γ levels better benefited from tofacitinib, but not etanercept, treatment in terms of suppression of IL-12 levels (**Figure 3D**). In order to account for the low expression of circulating IFN-γ, we performed a principal component analysis (PCA) to identify IFN-γ-clustering proteins (**Supplementary Table 1**). We found that a higher IFN-signature at baseline was related with a better reduction in PASI scores after 12 weeks of treatment with tofacitinib (unstandardized β=-2.701, p=0.033, 95% CI [-5.177, -0.226]). Conversely, In Pso patients treated for 12 weeks with etanercept, an improved PASI outcome related to higher IFN-signature was not observed (unstandardized β=0.331, p=0.735, 95% CI [-1.606, 2.268]).

From skin microarray data (GSE69967), *IL12B* mRNA levels were reduced in the lesional skin of tofacitinib-treated Pso patients **(Figure 3E**), as previously described.[22] Given the low number of patients in this study, we could only observe a trend for lower ΔIL-12 expression in individuals with higher *IFN-γ* at baseline (**Supplementary Figure 4**). However, higher basal *IFN-γ* levels correlated with a greater reduction of *IL12B* mRNA (decrease of 0.015 *IL12B* units per higher *IFN-γ* unit on average, *p*=0.039, 95% CI [-0.029, -0.001]) **(Figure 3F)**.

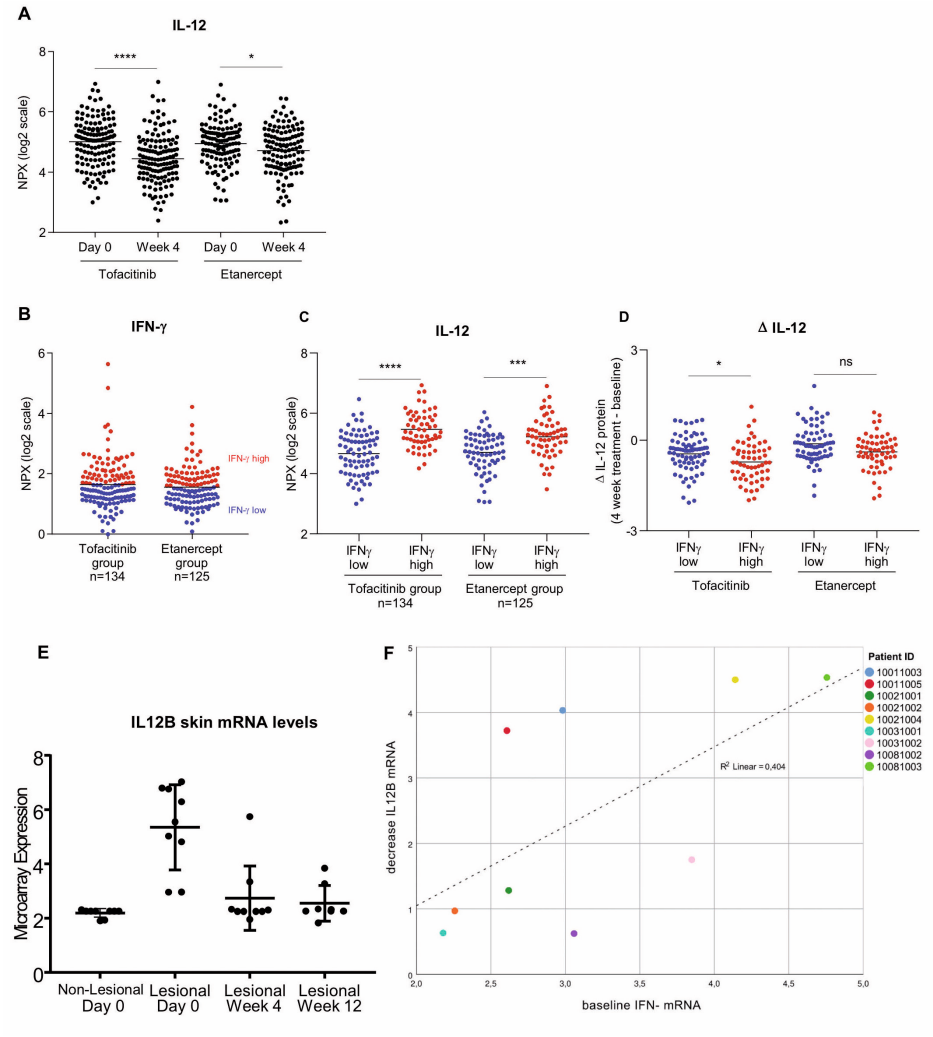

Figure 3. Patients with higher basal IFN-γ display higher basal IL-12 levels and have a significant reduction in IL-12 levels when treated with tofacitinib (A) Normalized Protein eXpression (NPX) of IL-12 protein levels in the blood of Pso patients before and after 4 weeks treatment with either tofacitinib (n=134) or etanercept (n=125). **(B)** NPX of baseline blood IFN-γ protein levels for patients treated with tofacitinib or etanercept. Treatment groups were divided by the mean IFN-γ expression to define IFN-γ high or low patients. **(C)** NPX of baseline IL-12 protein levels per treatment group for IFN-γ high or low patients. **(D)** Delta decrease of IL-12 (ΔIL-12) after 4 weeks of treatment with either tofacitinib or etanercept for IFN-γ high or low patients. Significance was determined by the Kruskal-Wallis test followed by Dunn's multiple comparisons test. Series matrix data derived from public database GSE136435. **(E)** Gene expression of *IL12B* after 0, 4 and 12 weeks of tofacitinib treatment in whole lesional psoriatic skin (n=9) compared to paired non-lesional skin. **(F)** Delta decrease of *IL12B* mRNA in relation to baseline *IFN-γ* mRNA in lesional psoriatic skin after 12 weeks of tofacitinib treatment (n=9). Data from patient 10021001 was only available until 4 weeks of treatment. Series matrix data derived from public database GSE69967.

CONCLUSIONS & PERSPECTIVES

The accumulating knowledge that IL-23 and IL-12 play a key role in the initiation and maintenance of several inflammatory diseases, such as Pso and PsA[6], led to the development of multiple selective therapeutic agents that target either specific cytokines or their downstream inflammatory events.[32] Tofacitinib is the first JAK-inhibitor registered for the indication of Pso and has shown promising results in clinical trials.[33] Studies have shown that multiple immunoregulatory pathways, such as STAT1/STAT3 in Pso skin and NF-κB in PsA synovial fibroblasts, are targeted by tofacitinib.[22,34,35] However, whether tofacitinib suppresses IL-12 and IL-23 directly, or rather indirectly through general immune suppression, has not yet thoroughly been studied.[36]

To answer this research question, we made use of mDCs and moDCs as representative models for systemic and localized inflammation.[37] We observed that both cell types increased the expression of *IL23A* and *IL12B* after TLR4 stimulation, in line with previous studies.[24,36,38] The stimulation with IFN-γ, a direct activator of the JAK/STAT-pathway, did not induce the expression of these cytokines, while potently inducing *CXCL10*, a known IFN-inducible gene **(Supplementary Figure 1B)**.

Upon LPS activation, we found that tofacitinib was not able to suppress *IL23A* and *IL12B* mRNA expression in neither mDCs nor moDCs. A similar observation was reported earlier in a model of allergic contact dermatitis by Bechara et al.[31] These results indicate that the presence of IFN-γ is needed for tofacitinib to efficiently reduce *IL12B* expression in DCs.

Unlike *IL12B*, *IL23A* expression was not potentiated by LPS+IFN-γ stimulation, nor reduced by tofacitinib. In fact, *IL23A* expression was decreased upon stimulation with LPS+IFN-γ, as compared to LPS alone **(Supplementary figure 5)**. Combined LPS+IFN-γ stimulation in DCs was previously shown to promote *IL23A* mRNA degradation, while enhancing *IL12A* and *IL12B* mRNA stabilization.[39] Thus, these findings indicate that IL-12 and IL-23 could be differentially regulated by tofacitinib in DCs.[39,40]

A differential response to tofacitinib was observed in DCs stimulated with type I or type II IFN. Type II IFN-γ signals through JAK1/JAK2, which in turn promote STAT1 homodimers and interferon regulatory factor IRF1/IRF8 complexes.[41,42] Conversely, type I IFN-α and IFN-β signal through JAK1/TYK2, which lead to STAT1/STAT2 heterodimers associating with IRF9.[43] Indeed, IRF1 and IRF8 are potently induced upon LPS+IFN-γ co-stimulation, in comparison to LPS stimulation alone.[41,44] Thus, it is plausible that tofacitinib-dependent suppression of *IL12B* expression requires inflammatory events triggered by type II, but not

type I IFN signaling, such as modulation of IRF1/IRF8 transcription factors. From the skin dataset, we could identify a distinct expression of IRF1/IRF8 in paired lesional and non-lesional samples of Pso patients and a reduced expression in lesional skin after tofacitinib treatment **(Supplementary figure 6)**.

In whole lesional Pso skin, we found that higher basal levels of IFN-γ correlated with a greater reduction in *IL12B* after 12 weeks of tofacitinib treatment. Additionally, from whole blood data, we observed that Pso patients with higher IFN-signature at basal levels displayed a better decrease in IL-12 after tofacitinib, but not etanercept, treatment which was accompanied by a significant reduction in PASI score.

Overall, our findings imply a novel role for IFN-γ in eliciting *IL12B* suppression by tofacitinib in DCs. These results can be relevant for diseases characterized by IFN-γ involvement and aid to predict therapeutic responses to tofacitinib in Pso patients.

Highlights

- IL-23/IL-12 shared subunit IL12B (p40) is expressed in TLR-activated DCs
- IL12B suppression by tofacitinib in activated DCs requires the presence of IFN-γ
- IFN-γ blood levels in psoriasis patients predict IL-12 reduction after tofacitinib
- IFN-γ levels in psoriatic skin associate with IL12B suppression after tofacitinib
- IFN-γ-related proteins in blood associate with improved PASI score after tofacitinib

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SUPPLEMENTARY INFORMATION

Supplementary experimental design

RNA isolation and real-time quantitative PCR

RNA was extracted using RNeasy Mini Kit (Qiagen) followed by cDNA preparation using SuperScript IV Reverse Transcriptase (ThermoFisher Scientific). SYBR dye (ThermoFisher Scientific) was used for real-time quantitative PCR analyses. CT values of the genes of interest were normalized to the expression of the housekeeping gene RPL35. The relative expression was calculated using the formula 2^-ΔCT. A list of primers used can be found in **Table 1.**

Table 1

Gene	Sequence (5'--> 3')
IL12B **(IL12p40)**	**Forward** TGCCGTTCACAAGCTCAAGT **Reverse** TGGGTCAGGTTTGATGATGTCC
IL23A **(IL23p19)**	**Forward** CAACAGTCAGTTCTGCTTGC **Reverse** GAAGGCTCCCCTGTGAAA AT
IL12A **(IL12p35)**	**Forward** AGGGCCGTCAGCAACATG **Reverse** TCTTCAGAAGTGCAAGGGTAAAATTC
CXCL10	**Forward** TGAAATTATTCCTGCAAGCCAA **Reverse** CAGACATCTCTTCTCACCCTTCTTT
TNF	**Forward** TCTTCTCGAACCCCGAGTGA **Reverse** CCTCTGATGGCACCACCAG
RPL35	**Forward** CATCTGGGGAAAAGTAACTCG **Reverse** AGCATCACTCGGATTCTGTG

GEO dataset

Data were retrieved from Series Matrix Files of the public dataset GSE136435 (Platform GPL27151 and GPL27152) and GSE69967 (Platform GPL570).[17,19] The dataset GSE136435 contains data from Pso patients treated with tofacitinib or etanercept (n=266 psoriasis

patients, randomized 1:1, n=1020 samples) over the course of 12 weeks. Olink Proteomics Proseek inflammatory (INF) and cardiovascular disease (CVD) Proximity Extension Assay was used to measure 157 proteins in whole blood at baseline, before start of treatment, and at 4 weeks. Response to treatment was determined at 12 weeks by assessing the Psoriasis Area and Severity Index (PASI) score, an outcome measure used in clinical trials.[19] The public dataset GSE69967 contains data from 9 Pso patients treated with tofacitinib, of which multiple biopsy specimens were taken from lesional skin over the course of treatment (baseline, day 1 and 3, and weeks 1, 2, 4, and 12). mRNA transcripts of the biopsies were quantified by Affymetrix Human Genome U133 Plus 2.0 Array.[17]

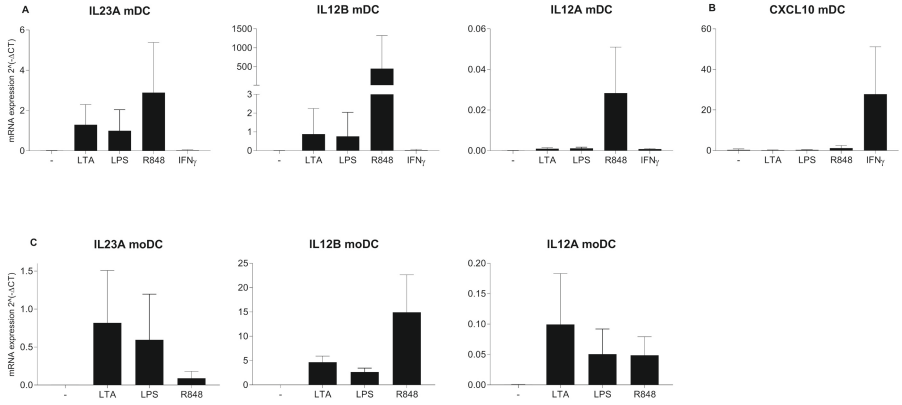
Statistical analyses of GEO dataset

In the dataset GSE136435, linear regression analysis was used to investigate the effect of the IFN-γ baseline values on the decrease in PASI score from baseline to 12 weeks in patients treated with tofacitinib . In order to account for low expression levels of circulating IFN-γ, a principal component analysis (PCA) was performed to identify IFN-γ-clustering proteins. A solution entailing 20 principal components (PC) was chosen (Supplementary table 1). Based on the inspection and eigenvalues of the PCs, one reflected IFN-signature and was used instead of the IFN-γ baseline values in a similar regression analysis as described above. The PC representing an IFN-signature was used in a separate regression analysis with PASI-scores at 12 weeks as outcome and comparing tofacitinib versus etanercept treatment groups.

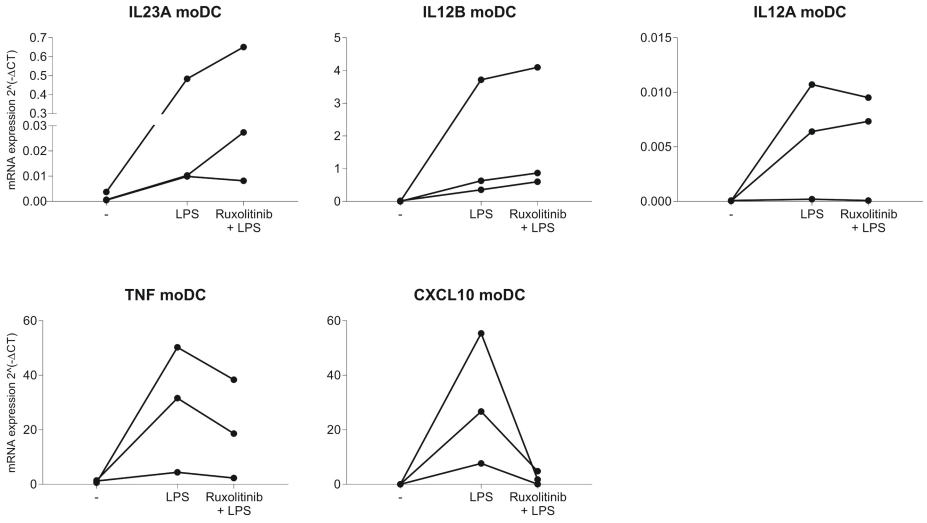
In the skin biopsy dataset (GSE69967), a linear mixed effects analysis with a random intercept at patient level was performed to account for the repeated measures of IL12B over time. The relationship between IL12B over time (outcome) and IFN-γ baseline levels was explored. IL12B at baseline was used as covariate, as well as time and the interaction between time and IFN-γ baseline levels, which were added in these models to explore whether the course over time of IL12B was influenced by IFN-γ baseline levels.

IBM SPSS Statistics for Windows, version 25.0.0.2 (IBM Corp., Armonk, N.Y., USA) was used to perform above analyses. Values with a $p < 0.05$ were considered significant.

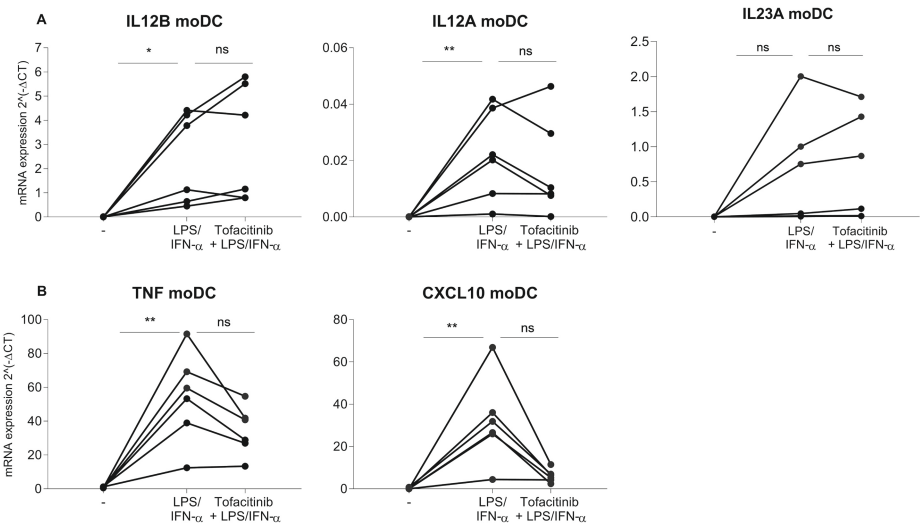
SUPPLEMENTARY FIGURES



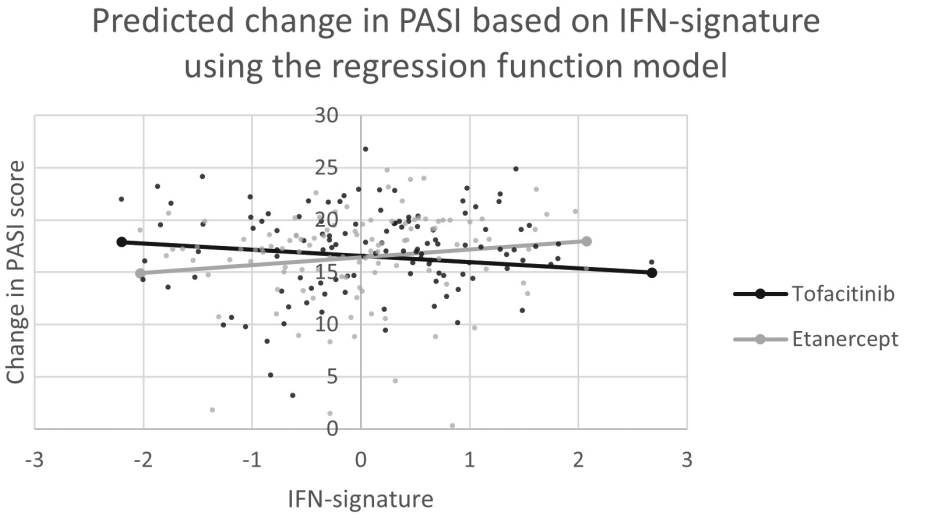
Supplementary figure 1. Expression of IL23A, IL12B and IL12A in stimulated mDCs and moDCs. (A-B) Differential gene expression in mDCs derived from buffy coats (n=4) after different TLR-agonists or IFN-γ treatment. Cells were stimulated for 4 hours. Gene expression was measured by real-time qPCR. Error bars represent the SD of the mean based upon multiple donors. (C) Differential gene expression of moDCs upon different TLR-agonists (n=2). Cells were stimulated for 4 hours. Gene expression was measured by real time qPCR. Error bars represent the SD of the mean based upon multiple donors. Note that statistical analysis were not performed due to the low sample size.



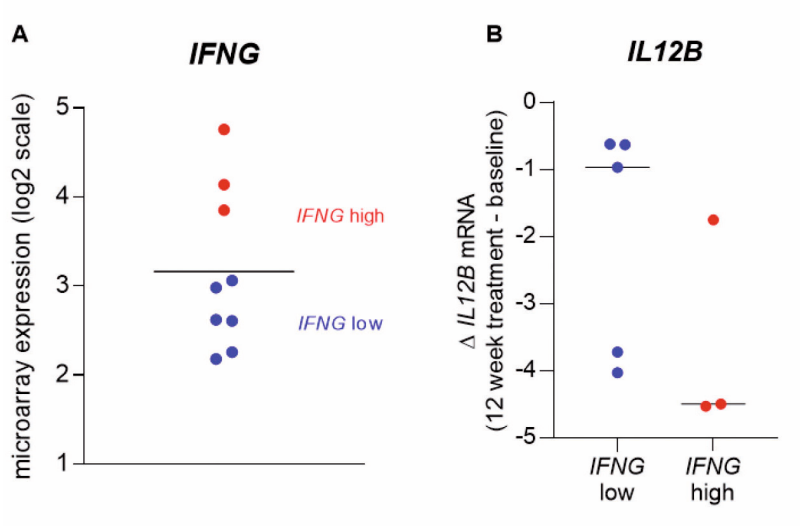
Supplementary figure 2. Induction of IL23A and IL12B in Ruxolitinib-treated moDCs. Gene expression of IL23A, IL12B and IL12A, TNF and CXCL10 in moDCs (n=3). moDCs were pre-treated with Ruxolitinib for 30 minutes and stimulated with LPS for 4 hours. Gene expression was measured by real-time qPCR and represented as relative expression (2^-ΔCT). Lines connect individual donors. Note that statistical analysis were not performed due to the low sample size.



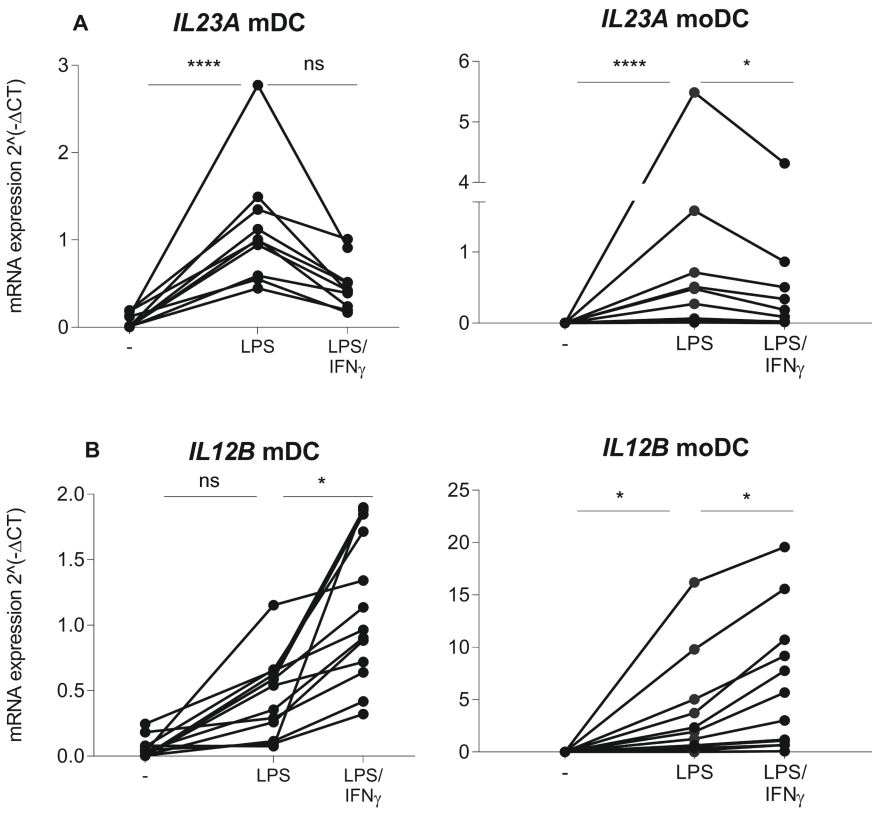
Supplementary figure 3. Suppression of IL12B by tofacitinib is not type I IFN-dependent. Gene expression of IL12B, IL12A and IL23A (A) and TNF and CXCL10 (B) in moDCs (n=6). moDCs were pre-treated or not with tofacitinib for 30 minutes and stimulated with a combination of LPS and IFN-α for 4 hours. Gene expression was measured by real-time qPCR and represented as relative expression (2^-ΔCT). Lines connect individual donors. Significance was determined by Friedman's test followed by Dunn's multiple comparisons test.



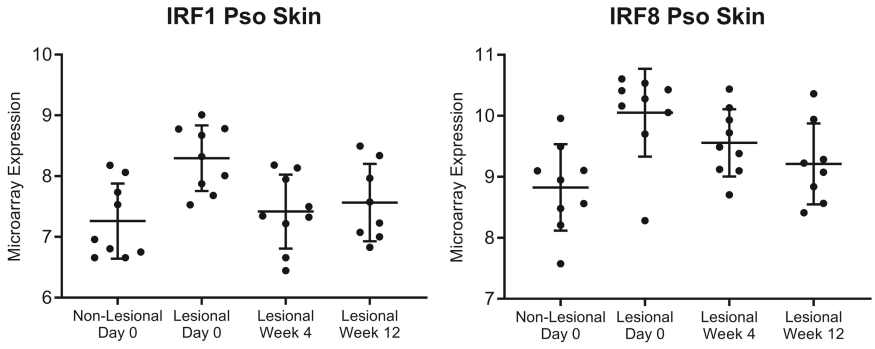
Supplementary figure 4. Increase of the IFN-signature value decreases the PASI score when treated with tofacitinib after 12 weeks. Using the regression function model (accounting for baseline PASI, age and gender for the study population) the estimated PASI scores for the average patient treated with tofacitinib or etanercept were plotted against the range of IFN-signature values. Patients' individual expected PASI scores corrected for the residuals from the regression function model are depicted as dots.



Supplementary figure 5. IFN-γ high patients show a trend towards better IL12B mRNA downregulation after tofacitinib treatment. (A) Microarray expression of IFN-γ in whole lesional Pso skin. Patients (n=9) were divided by mean expression to define IFN-γ high or low patients. (B) Delta IL12B mRNA expression after 4 weeks of treatment with tofacitinib for IFN-γ high and low patients. Series matrix data derived from public database GSE69967.



Supplementary Figure 6. Co-stimulation with LPS and IFN-γ induces IL12B but not IL23A expression in DCs. Gene expression of (A) IL23A in mDCs (n=10) and moDCs (n=13) and (B) IL12B in mDCs (n=10) and moDCs (n=13) stimulated with LPS and a combination of LPS and IFN-γ for 4 hours. Gene expression was measured by real-time qPCR and represented as relative expression (2^-ΔCT). Lines connect individual donors. Significance was determined by Friedman's test followed by Dunn's multiple comparisons test.



Supplementary figure 7. IRF1 and IRF8 expression in whole lesional psoriatic skin approximate non-lesional levels after 12 weeks of tofacitinib treatment. Gene expression of IRF1 and IRF8 after 0, 4 and 12 weeks of tofacitinib treatment in whole lesional psoriatic skin (n=9) compared to paired non-lesional skin. Series matrix data derived from public database GSE69967.

Supplementary tables

Supplementary table 1. Principal Component Matrix

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
101_IL-8	0.592	0.060	-0.016	-0.290	0.238	-0.042	-0.022	-0.059	-0.047	-0.337	0.127	-0.196	0.184	-0.015	0.122	0.017	-0.021	0.005	0.047	0.070
102_VEGF-A	0.680	0.210	0.185	-0.199	0.008	0.048	0.033	-0.074	0.030	0.109	-0.175	-0.073	-0.076	0.130	-0.026	0.038	-0.008	-0.010	0.111	0.051
103_BDNF	0.028	0.078	0.012	0.095	0.032	0.100	-0.024	0.429	0.160	0.100	-0.069	0.079	-0.061	0.282	0.311	-0.076	0.197	0.252	0.365	0.205
105_MCP-3	0.733	0.065	0.031	-0.318	0.330	0.092	-0.029	-0.046	-0.201	-0.030	0.046	-0.083	0.000	0.047	0.042	-0.001	-0.058	-0.053	0.075	-0.027
106_hGDNF	0.710	0.257	-0.317	-0.046	-0.113	-0.119	0.027	-0.106	-0.152	0.020	-0.050	-0.001	0.019	0.051	0.056	-0.122	-0.035	-0.013	-0.042	0.052
107_CDCP1	0.708	0.230	-0.185	-0.190	0.033	-0.207	0.154	-0.065	-0.068	-0.055	0.068	-0.026	-0.093	-0.010	0.105	-0.047	-0.022	-0.117	-0.003	0.046
108_CD244	0.859	0.191	-0.031	-0.097	-0.221	-0.033	-0.113	0.166	0.040	0.032	-0.019	-0.012	-0.036	0.014	0.026	0.007	-0.029	0.025	-0.045	-0.016
109_IL-7	0.568	0.195	-0.167	-0.259	-0.199	0.221	0.039	0.139	-0.165	0.000	-0.067	-0.102	0.364	-0.073	-0.103	-0.253	-0.059	-0.050	0.056	0.003
110_OPG	0.761	0.207	-0.131	-0.214	-0.144	-0.101	0.168	-0.174	0.204	0.061	0.076	-0.006	0.019	-0.066	-0.004	-0.138	0.126	0.017	0.016	0.058
111_LAP TGF-beta-1	0.795	0.207	0.103	-0.099	-0.100	0.132	-0.015	-0.066	-0.166	0.068	-0.086	-0.023	0.037	0.084	-0.062	-0.018	0.037	0.025	0.007	-0.045
112_uPA	0.864	0.154	-0.154	-0.035	-0.167	-0.053	-0.096	-0.001	0.096	-0.062	-0.054	-0.095	-0.023	-0.061	0.020	0.056	0.015	-0.078	0.038	0.030
113_IL-6	0.508	0.074	-0.228	-0.220	0.454	-0.115	0.129	-0.052	0.106	0.100	-0.131	0.005	-0.127	-0.020	-0.048	-0.144	0.079	-0.158	0.033	0.086
114_IL-17C	0.325	-0.094	-0.335	-0.212	0.516	0.212	-0.442	-0.095	-0.044	-0.050	0.179	-0.113	-0.036	0.136	-0.096	0.013	0.020	0.008	0.034	-0.014
115_MCP-1	0.769	0.108	0.064	-0.334	-0.150	-0.017	0.034	-0.107	-0.162	0.003	0.045	-0.097	0.024	-0.051	0.036	0.034	0.083	-0.083	0.091	-0.111
116_IL-17A	0.496	-0.003	-0.348	-0.166	0.476	0.251	-0.346	0.058	-0.074	0.038	0.060	-0.052	0.026	0.083	-0.121	-0.081	-0.022	0.004	0.003	0.050
117_CXCL11	0.612	0.243	0.081	-0.386	0.065	0.144	0.025	0.062	-0.040	0.048	0.063	**0.295**	0.029	-0.289	-0.058	0.008	0.030	0.128	-0.023	0.113
118_AXIN1	0.554	0.216	0.497	0.094	0.136	-0.345	-0.243	0.014	-0.036	0.069	0.079	0.172	-0.021	-0.002	-0.079	-0.024	0.013	0.040	-0.124	0.122
120_TRAIL	0.811	0.204	-0.170	0.094	-0.199	-0.038	-0.211	0.048	-0.079	0.012	-0.124	-0.062	-0.019	-0.079	0.080	0.026	-0.046	-0.033	-0.028	-0.040
121_IL-20RA	0.442	0.357	-0.041	0.448	0.134	0.012	0.134	-0.016	-0.074	-0.172	-0.081	-0.150	0.043	0.003	-0.021	0.096	-0.060	0.126	0.069	0.101
122_CXCL9	0.562	0.091	-0.347	-0.280	0.201	0.070	0.004	-0.099	0.090	-0.171	0.102	**0.338**	-0.035	-0.268	-0.006	-0.003	-0.078	0.245	0.002	-0.056
123_CST5	0.711	0.229	-0.178	0.091	-0.293	-0.028	-0.116	-0.150	-0.022	-0.023	0.081	-0.060	-0.106	-0.044	-0.010	0.080	-0.052	0.097	0.018	0.018
124_IL-2RB	0.644	0.383	-0.080	0.295	0.110	0.101	0.144	0.053	0.028	-0.074	-0.092	0.061	0.000	0.085	-0.081	0.031	-0.018	0.035	-0.045	0.127
125_IL-1 alpha	0.433	-0.020	-0.073	0.365	0.146	0.013	-0.091	0.160	0.100	-0.005	0.198	-0.253	-0.085	-0.313	0.025	0.055	0.100	-0.187	0.194	0.100

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
126_OSM	0.601	0.175	0.556	-0.212	0.187	0.107	-0.071	-0.165	0.138	0.023	-0.110	-0.046	-0.051	-0.035	0.146	0.013	-0.010	-0.034	-0.014	-0.006
127_IL-2	0.586	0.433	-0.039	0.562	0.172	0.088	0.161	-0.021	-0.036	-0.083	-0.062	-0.088	-0.065	-0.011	-0.073	0.016	0.000	0.019	0.010	0.032
128_CXCL1	0.660	0.261	0.247	-0.223	0.007	0.140	0.056	0.085	-0.044	0.130	0.043	-0.126	0.154	-0.028	-0.096	0.013	0.025	0.090	0.024	0.144
129_TSLP	0.378	0.535	0.000	0.398	0.110	0.119	0.144	0.028	-0.078	-0.028	-0.059	0.001	0.082	0.173	0.052	0.046	-0.210	0.063	-0.037	-0.031
130_CCL4	0.678	0.128	0.086	-0.283	-0.049	-0.036	0.089	0.208	-0.118	-0.244	-0.030	-0.006	0.035	-0.081	0.150	0.102	0.120	-0.034	0.107	-0.013
131_CD6	0.781	0.167	-0.150	-0.076	-0.143	-0.083	-0.090	0.201	0.023	-0.069	-0.064	0.013	-0.070	0.041	0.088	0.108	-0.108	0.011	0.020	-0.049
132_SCF	0.585	0.189	-0.070	0.120	-0.385	0.154	-0.276	-0.047	-0.060	0.005	-0.173	-0.004	-0.040	-0.062	0.074	-0.049	-0.055	0.165	0.074	-0.112
133_IL-18	0.711	0.112	-0.137	-0.248	-0.063	-0.152	0.047	0.008	0.088	-0.074	-0.074	0.013	-0.092	0.077	-0.030	-0.007	-0.030	-0.117	0.064	0.160
134_SLAMF1	0.755	0.200	-0.218	-0.145	0.047	-0.049	-0.028	0.034	-0.055	0.066	-0.025	0.096	-0.157	0.073	-0.056	-0.043	0.061	-0.123	-0.039	0.098
135_TGFA	0.659	0.132	0.459	-0.176	0.148	0.160	-0.155	-0.198	0.106	0.127	-0.080	-0.089	-0.059	0.021	0.181	-0.050	0.001	0.019	-0.006	-0.055
136_MCP-4	0.699	0.144	0.157	-0.402	-0.174	0.107	0.037	0.005	-0.195	0.156	-0.046	-0.038	-0.013	-0.055	0.000	0.022	-0.006	-0.096	-0.036	0.003
137_CCL11	0.756	0.127	-0.056	-0.200	-0.259	-0.064	-0.042	-0.244	-0.236	-0.005	0.055	-0.061	-0.047	-0.038	0.144	0.078	-0.039	0.026	-0.046	0.064
138_TNFSF14	0.653	0.183	0.622	-0.136	0.084	0.100	-0.049	-0.066	0.084	-0.025	0.063	-0.015	-0.134	0.038	0.095	0.048	-0.001	0.011	-0.023	-0.014
139_FGF-23	0.702	0.327	0.013	0.186	0.087	-0.107	0.032	-0.042	-0.083	0.276	0.007	0.098	-0.128	0.064	-0.069	0.055	0.070	0.094	0.018	0.080
140_IL-10RA	0.573	0.290	0.008	0.189	0.013	0.044	0.048	-0.037	0.031	-0.021	-0.012	0.125	0.144	0.029	0.137	0.020	-0.168	-0.254	-0.128	0.234
141_FGF-5	0.753	0.298	-0.044	0.127	-0.098	-0.003	0.112	-0.149	-0.120	0.013	0.090	-0.056	-0.033	-0.007	-0.026	-0.023	0.000	0.052	-0.042	-0.066
142_MMP-1	0.243	0.154	0.243	0.000	0.213	0.233	0.240	-0.047	-0.317	0.167	-0.035	-0.108	-0.012	-0.255	-0.207	-0.173	-0.232	-0.115	0.206	0.032
143_LIF-R	0.800	0.143	-0.182	-0.216	-0.195	-0.100	-0.044	0.035	-0.019	0.022	0.082	-0.047	0.011	0.081	0.090	-0.106	0.107	-0.047	0.010	-0.065
144_FGF-21	0.363	-0.018	-0.107	-0.257	0.161	-0.282	0.331	0.064	-0.089	0.139	0.290	-0.099	-0.044	0.244	-0.128	-0.056	0.151	0.196	0.022	-0.092
145_CCL19	0.545	0.114	-0.243	-0.261	0.018	-0.054	-0.006	0.073	0.046	0.193	-0.040	-0.029	-0.035	-0.153	0.077	0.117	0.009	0.076	-0.209	0.154
148_IL-15RA	0.812	0.306	-0.167	0.081	-0.011	-0.012	-0.030	-0.041	-0.085	0.068	-0.011	-0.047	-0.073	0.049	-0.039	-0.031	-0.082	0.097	0.062	-0.119
149_IL-10RB	0.845	0.227	-0.111	-0.075	-0.101	-0.078	-0.021	-0.015	0.162	0.114	-0.054	-0.074	-0.064	-0.015	-0.066	-0.098	-0.004	-0.054	-0.014	-0.050
150_IL-22 RA1	0.403	0.138	-0.081	0.144	-0.026	0.150	-0.014	0.052	0.045	-0.166	-0.211	-0.070	-0.245	-0.147	0.042	0.086	0.394	-0.026	-0.053	0.166
151_IL-18R1	0.732	0.177	-0.098	-0.151	-0.019	-0.080	0.143	0.160	0.168	-0.044	-0.057	0.000	-0.115	0.051	0.001	-0.132	0.028	-0.045	-0.108	0.054
152_PD-L1	0.694	0.355	-0.034	0.086	0.020	-0.027	0.047	0.002	-0.222	-0.005	0.072	0.110	0.090	0.205	0.062	-0.143	-0.123	0.025	0.061	0.036

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
153_Beta-NGF	0.638	0.334	-0.035	-0.010	-0.127	0.108	0.104	0.132	0.228	-0.171	0.086	0.001	0.053	0.019	-0.059	-0.091	0.068	-0.018	0.174	-0.017
154_CXCL5	0.491	0.184	0.140	-0.218	-0.114	0.210	0.213	0.114	0.006	0.312	-0.089	-0.165	0.307	-0.093	-0.092	0.088	0.043	0.172	-0.062	0.101
155_TRANCE	0.459	0.040	-0.212	0.001	0.097	0.026	-0.377	0.419	-0.100	0.116	-0.153	-0.037	-0.020	0.076	-0.032	0.212	-0.171	-0.152	-0.087	-0.134
156_HGF	0.824	0.171	0.248	-0.276	0.029	0.020	0.034	-0.015	0.049	0.124	-0.100	-0.074	-0.047	-0.012	0.152	-0.072	-0.024	-0.030	-0.080	-0.029
157_IL-12B	0.563	0.145	-0.341	-0.123	0.228	0.053	-0.103	0.210	0.153	0.091	-0.105	0.104	-0.179	-0.106	-0.073	0.044	-0.117	-0.023	0.115	-0.034
158_IL-24	0.529	0.305	-0.211	0.263	0.301	0.104	0.013	-0.030	0.033	-0.028	0.034	0.035	0.089	-0.012	0.000	0.019	0.084	-0.012	-0.045	-0.045
159_IL-13	0.438	0.424	-0.044	0.384	0.137	0.064	0.108	0.029	0.038	-0.063	-0.105	0.022	0.023	0.037	0.058	0.157	-0.104	-0.038	-0.059	0.131
160_ARTN	0.615	0.422	-0.028	0.438	0.132	0.089	0.152	-0.065	-0.066	0.012	0.047	-0.040	0.013	0.043	-0.047	-0.042	-0.028	0.049	-0.031	-0.070
161_MMP-10	0.626	0.148	-0.141	-0.078	-0.111	-0.058	-0.151	-0.226	0.124	-0.039	0.139	-0.017	0.018	0.037	-0.127	0.071	0.016	-0.053	0.007	-0.168
162_IL-10	0.573	0.049	-0.180	-0.283	0.001	-0.061	-0.102	-0.042	0.041	-0.063	0.024	0.099	0.069	0.043	-0.126	0.100	0.085	-0.006	0.039	-0.109
163_TNF	0.407	0.391	-0.063	0.309	0.007	0.140	0.103	0.021	-0.054	0.013	-0.014	0.016	-0.113	0.066	0.036	0.092	0.232	-0.144	-0.072	-0.211
164_CCL23	0.680	0.234	-0.215	-0.099	-0.031	-0.029	-0.085	-0.146	0.044	0.187	-0.124	0.051	0.090	0.051	0.047	-0.157	0.162	0.061	0.000	-0.021
165_CD5	0.853	0.209	-0.158	-0.023	-0.060	0.008	-0.177	0.074	0.147	0.096	-0.028	-0.024	-0.031	-0.008	0.046	0.085	-0.029	-0.003	-0.046	-0.043
166_MIP-1 alpha	0.670	0.182	0.096	-0.307	0.095	-0.190	0.142	0.132	-0.141	-0.344	0.083	-0.040	0.058	-0.020	0.184	0.080	-0.024	0.087	0.081	0.006
167_Flt3L	0.751	0.169	-0.166	-0.208	-0.123	-0.146	0.102	-0.072	0.121	0.050	0.043	-0.020	-0.077	0.013	-0.040	0.073	-0.047	-0.058	0.036	-0.041
168_CXCL6	0.694	0.171	0.232	-0.247	-0.176	0.123	-0.011	0.165	-0.038	0.196	-0.063	-0.058	0.056	-0.083	-0.026	0.042	0.124	0.033	0.001	0.164
169_CXCL10	0.568	0.151	-0.279	-0.415	0.132	0.077	0.068	0.083	-0.020	-0.102	-0.045	**0.228**	-0.018	-0.164	-0.017	-0.036	-0.041	0.167	-0.006	-0.127
170_4E-BP1	0.328	0.035	-0.007	0.095	0.119	-0.514	-0.228	-0.230	-0.319	0.163	-0.345	0.060	0.272	-0.086	0.028	0.046	0.126	-0.047	0.087	-0.076
171_IL-20	0.449	0.016	-0.321	-0.098	0.527	0.296	-0.356	0.019	-0.120	0.004	0.065	-0.055	0.061	0.128	-0.102	-0.022	0.091	-0.044	0.015	0.001
172_SIRT2	0.555	0.156	0.459	-0.001	0.081	-0.467	-0.227	0.090	0.019	-0.081	-0.100	0.039	0.171	-0.003	-0.207	0.000	0.039	0.035	0.068	-0.038
173_CCL28	0.683	0.245	-0.050	-0.069	-0.112	0.255	0.045	-0.140	-0.029	-0.039	0.104	0.003	-0.036	-0.046	-0.079	-0.054	-0.194	0.122	-0.084	0.097
174_DNER	0.824	0.253	-0.072	0.081	-0.268	-0.003	-0.126	0.056	-0.023	-0.082	0.045	-0.083	0.003	0.057	0.044	-0.069	-0.019	0.005	-0.042	-0.006
175_EN-RAGE	0.670	0.080	0.217	-0.081	0.139	-0.044	-0.222	-0.077	0.169	-0.181	-0.169	-0.146	0.037	0.107	0.121	-0.276	0.020	0.032	-0.041	-0.054
176_CD40	0.858	0.274	0.175	-0.083	-0.081	-0.137	0.008	0.030	0.053	0.056	0.077	0.012	-0.098	0.084	-0.040	-0.024	-0.024	0.016	-0.057	-0.005

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
177_IL-33	0.501	0.386	-0.050	0.453	0.108	0.066	0.180	-0.040	-0.088	-0.023	-0.092	-0.115	-0.079	0.045	-0.070	-0.025	-0.073	0.143	0.013	-0.063
178_IFN-gamma	0.467	0.276	-0.229	-0.088	0.093	0.147	0.143	0.018	0.068	-0.178	0.107	**0.445**	0.016	-0.272	-0.006	0.125	-0.061	0.113	0.172	-0.061
179_FGF-19	0.469	0.097	-0.059	0.027	-0.130	-0.217	0.034	-0.339	0.013	-0.136	0.117	-0.025	-0.005	0.164	-0.012	0.267	-0.096	-0.061	0.092	0.040
180_IL-4	0.322	0.273	-0.069	0.144	0.124	0.059	0.092	-0.028	-0.006	-0.026	0.125	0.386	0.381	0.222	0.098	0.036	0.134	-0.260	-0.042	0.015
181_LIF	0.401	0.264	-0.068	0.238	0.009	0.130	0.019	-0.112	-0.014	-0.161	0.042	0.231	0.202	-0.030	0.106	-0.035	0.304	-0.090	-0.121	-0.060
182_NRTN	0.625	0.403	-0.087	0.412	0.115	0.089	0.135	0.050	0.010	-0.109	-0.018	0.125	0.069	-0.066	0.031	0.081	-0.005	-0.171	-0.043	0.042
183_MCP-2	0.631	0.309	0.078	-0.199	-0.138	0.096	0.031	-0.002	-0.189	0.016	0.071	-0.045	-0.022	-0.087	-0.034	0.068	0.111	-0.183	0.072	-0.104
184_CASP-8	0.641	0.173	0.386	-0.034	0.169	-0.301	-0.170	0.057	0.129	-0.268	-0.133	-0.096	0.057	-0.030	-0.076	-0.032	-0.051	-0.019	0.060	-0.065
185_CCL25	0.671	0.129	-0.272	-0.209	-0.119	-0.104	-0.097	-0.177	-0.002	-0.055	0.048	-0.023	-0.016	-0.070	-0.036	0.069	-0.012	0.083	-0.066	0.095
186_CX3CL1	0.779	0.192	-0.110	-0.147	-0.203	-0.010	-0.052	-0.039	0.237	-0.019	0.053	-0.079	-0.025	0.114	-0.098	-0.036	-0.062	0.008	0.056	-0.066
187_TNFRSF9	0.832	0.109	-0.262	-0.118	0.037	0.029	-0.216	0.018	0.086	0.091	-0.090	0.026	-0.132	-0.036	0.009	0.078	-0.034	-0.024	-0.056	-0.017
188_NT-3	0.603	0.246	0.018	-0.027	-0.253	-0.022	-0.183	-0.027	0.057	-0.097	0.072	-0.007	0.205	0.159	-0.028	0.035	-0.070	0.002	-0.018	0.266
189_TWEAK	0.790	0.156	0.006	-0.159	-0.382	0.119	-0.199	0.039	0.019	-0.062	-0.068	0.036	-0.002	0.039	0.017	0.015	0.033	-0.002	-0.014	0.016
190_CCL20	0.524	0.049	-0.284	-0.298	0.387	-0.004	-0.145	-0.005	0.007	-0.019	0.220	-0.103	0.061	0.098	0.028	0.083	0.059	0.057	-0.154	0.070
191_ST1A1	0.493	0.183	0.618	0.000	0.108	-0.088	-0.005	0.029	0.035	-0.163	0.241	0.041	-0.182	0.108	-0.027	0.062	-0.082	0.072	-0.064	-0.023
192_STAMPB	0.654	0.177	0.373	0.077	0.052	-0.443	-0.187	0.096	-0.011	-0.060	-0.094	0.031	0.133	-0.036	-0.203	-0.012	0.006	0.021	0.080	-0.017
193_IL-5	0.264	0.200	0.151	0.189	0.048	0.046	0.039	-0.046	0.016	-0.072	-0.004	0.256	-0.216	0.059	0.007	-0.476	-0.049	-0.058	-0.181	-0.154
194_ADA	0.731	0.220	0.016	0.143	-0.082	-0.152	-0.092	0.110	0.068	-0.112	-0.044	-0.011	0.023	-0.079	-0.094	-0.018	0.014	0.037	-0.045	-0.118
195_TNFB	0.646	0.302	-0.138	0.084	-0.181	0.089	-0.096	0.141	0.209	0.133	-0.007	0.072	-0.031	0.096	-0.016	0.152	-0.029	-0.004	-0.020	-0.081
196_CSF-1	0.831	0.353	-0.112	0.029	0.035	0.025	0.057	-0.017	0.201	0.087	-0.023	-0.015	-0.026	0.022	0.008	-0.148	-0.033	-0.002	0.032	-0.039
103_AM	0.683	-0.098	-0.012	0.189	0.208	-0.104	0.067	-0.115	-0.237	0.345	-0.020	0.134	-0.085	0.049	0.083	0.051	0.014	0.058	0.123	0.031
105_CD40-L	0.548	-0.024	0.631	-0.172	-0.096	0.229	0.025	0.055	-0.144	0.073	0.200	0.104	-0.099	0.083	-0.062	0.053	0.013	-0.088	-0.020	-0.059
106_GDF-15	0.758	-0.318	-0.104	-0.077	0.018	-0.179	0.295	-0.249	0.021	0.083	0.097	-0.011	-0.030	-0.018	0.014	-0.043	0.000	-0.007	-0.062	0.032
107_PlGF	0.893	-0.339	-0.114	0.052	-0.054	-0.017	0.024	-0.018	0.010	0.019	-0.070	0.035	-0.041	0.003	-0.017	-0.005	-0.010	-0.030	-0.014	0.049
108_SELE	0.687	-0.364	-0.223	-0.151	0.235	0.010	0.063	0.116	-0.057	-0.065	-0.095	-0.036	0.023	0.105	-0.067	-0.077	0.016	-0.009	-0.074	0.060
109_EGF	0.527	-0.014	0.692	-0.153	-0.059	0.216	0.046	0.007	-0.129	-0.005	0.158	0.116	-0.153	0.095	-0.086	0.099	0.010	-0.045	-0.022	-0.031

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
111_SRC	0.569	-0.085	0.656	0.018	-0.027	-0.017	-0.075	0.163	0.018	0.069	0.307	0.101	-0.114	0.002	-0.044	0.048	-0.013	-0.028	-0.064	0.002
112_IL-1ra	0.715	-0.214	0.221	-0.201	0.303	-0.010	0.205	0.055	0.074	0.090	-0.103	0.044	0.098	-0.005	0.050	0.012	-0.026	-0.026	-0.005	-0.115
114_CSTB	0.861	-0.290	0.055	0.006	0.073	-0.194	0.051	-0.003	0.042	-0.012	-0.137	-0.010	0.094	0.004	-0.039	0.061	-0.009	-0.002	-0.022	-0.010
116_KLK6	0.701	-0.476	-0.204	-0.021	0.141	0.221	-0.206	0.026	-0.018	-0.047	0.046	0.016	0.021	0.056	-0.052	-0.016	-0.026	0.041	0.021	0.041
117_Gal-3	0.822	-0.316	-0.017	0.069	-0.072	-0.006	0.143	0.031	0.075	-0.111	-0.078	0.039	0.110	0.041	-0.148	-0.004	-0.001	0.045	-0.018	-0.011
118_PAR-1	0.766	-0.220	0.133	0.191	0.001	-0.158	-0.094	0.151	-0.083	0.248	0.184	0.085	0.000	-0.067	-0.092	-0.020	-0.054	0.039	-0.040	0.107
121_hK11	0.717	-0.415	-0.222	-0.001	0.150	0.211	-0.213	0.043	-0.004	-0.060	0.118	-0.030	0.008	0.024	-0.084	0.071	-0.027	-0.071	0.026	0.040
122_TIE2	0.865	-0.351	-0.060	0.100	-0.065	0.062	0.030	0.053	0.058	-0.075	-0.061	0.042	-0.018	0.030	-0.063	-0.014	0.062	-0.033	-0.011	0.056
123_TF	0.839	-0.289	-0.104	0.172	-0.191	-0.039	-0.003	-0.048	-0.020	-0.022	-0.047	0.054	0.026	0.042	-0.066	0.009	-0.062	0.016	0.078	0.027
124_TNF-R1	0.887	-0.324	-0.032	0.063	0.098	0.065	0.037	-0.041	0.060	0.038	-0.101	0.053	-0.054	-0.012	-0.019	0.023	-0.038	-0.041	0.010	-0.023
125_PDGF	0.762	-0.208	0.263	-0.043	-0.082	0.345	0.095	0.062	-0.172	-0.038	-0.039	-0.067	0.145	-0.027	-0.137	0.007	0.037	-0.029	0.016	-0.018
Subunit B																				
126_IL27-A	0.706	-0.239	-0.152	0.229	-0.020	-0.043	-0.057	0.161	0.154	0.122	0.261	0.011	0.061	-0.119	0.153	-0.166	-0.093	0.020	0.040	0.022
129_LOX-1	0.679	-0.100	0.503	0.073	0.199	0.245	-0.035	-0.183	0.079	-0.125	-0.082	-0.017	-0.019	-0.037	0.109	0.044	0.004	0.015	0.017	-0.046
130_TRAIL-R2	0.760	-0.119	-0.105	-0.030	0.000	-0.058	0.080	-0.053	0.130	0.015	-0.014	-0.160	-0.042	-0.047	0.033	-0.046	0.096	0.031	-0.046	-0.082
134_IL-6RA	0.793	-0.390	-0.074	0.130	-0.084	0.095	0.045	0.004	0.059	0.004	-0.136	0.020	-0.045	0.041	-0.043	-0.017	0.045	0.031	-0.021	0.047
135_TNF-R2	0.843	-0.342	-0.120	0.001	0.020	0.017	0.021	-0.039	0.073	0.020	-0.076	0.069	-0.092	0.010	-0.026	0.052	-0.019	0.014	-0.015	-0.049
136_MMP-3	0.668	-0.308	-0.037	0.047	-0.071	-0.090	-0.121	-0.054	-0.213	-0.199	-0.007	0.087	-0.145	0.087	-0.140	-0.165	-0.055	-0.005	0.030	0.065
137_HSP 27	0.668	-0.161	0.366	0.108	0.055	-0.404	-0.085	0.141	0.060	-0.001	0.073	0.098	0.038	-0.067	-0.154	0.030	0.072	0.032	-0.086	0.008
139_PRL	0.553	-0.218	-0.031	0.063	-0.117	0.084	0.012	-0.034	0.189	0.080	0.048	0.050	0.031	0.237	-0.088	0.155	-0.027	-0.037	0.174	-0.083
140_MPO	0.787	-0.111	0.336	0.270	0.140	0.151	-0.006	-0.073	0.024	-0.097	-0.064	-0.046	-0.064	-0.057	0.049	0.052	0.055	0.071	0.023	-0.008
141_GH	0.110	0.068	0.108	0.128	-0.048	0.090	0.055	-0.418	0.474	0.244	0.137	0.040	0.240	-0.012	-0.143	-0.063	0.008	-0.048	0.291	-0.027
143_RETN	0.733	-0.365	0.172	-0.031	0.093	0.108	-0.073	-0.134	0.171	-0.082	-0.147	-0.011	-0.053	-0.027	0.026	-0.013	0.025	0.098	-0.015	0.007
144_FAS	0.834	-0.297	-0.095	0.059	-0.054	0.007	0.115	-0.086	-0.009	-0.042	-0.139	0.026	-0.044	-0.040	-0.073	0.063	-0.012	0.048	-0.036	0.003
145_PAPPA	0.749	-0.321	-0.007	0.165	-0.088	0.000	-0.027	0.077	-0.167	-0.038	-0.015	-0.074	-0.041	0.033	0.094	-0.071	-0.034	0.099	-0.049	-0.017
148_PTX3	0.701	-0.172	0.376	0.088	0.078	0.116	-0.158	-0.099	0.224	-0.029	0.110	-0.073	0.024	-0.082	0.187	-0.071	0.019	0.004	-0.043	0.056
149_REN	0.683	-0.225	-0.022	0.076	-0.004	-0.072	0.164	0.032	-0.060	-0.002	-0.083	-0.043	-0.058	-0.124	0.053	-0.166	-0.127	-0.145	0.010	0.111

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
150_CHI3L1	0.656	-0.244	-0.047	-0.204	0.132	-0.195	0.269	-0.119	-0.050	-0.144	0.105	0.018	-0.111	0.118	0.000	-0.041	0.060	0.012	0.112	0.132
152_TIM	0.679	-0.127	-0.116	-0.051	0.005	-0.162	0.384	-0.132	0.006	-0.003	0.035	-0.101	-0.103	-0.034	-0.003	0.049	-0.074	-0.106	-0.037	0.033
154_mAmP	0.412	-0.178	-0.104	0.119	-0.089	0.115	0.099	0.035	0.090	-0.132	0.181	-0.169	0.295	0.017	-0.038	0.014	0.049	0.211	-0.386	-0.086
157_PSGL-1	0.716	-0.066	-0.005	0.329	-0.024	-0.004	-0.048	0.244	-0.031	0.144	0.270	-0.159	0.026	-0.139	0.135	-0.102	0.051	-0.039	0.034	-0.199
158_MB	0.694	-0.291	-0.132	0.040	-0.194	0.019	0.018	0.043	-0.165	-0.209	-0.159	0.123	-0.043	-0.023	-0.045	-0.037	0.115	-0.028	0.093	-0.159
159_TM	0.857	-0.383	-0.056	0.112	-0.114	0.058	-0.094	0.016	-0.007	-0.027	-0.062	0.109	-0.040	-0.023	-0.020	0.033	-0.039	-0.020	0.005	0.009
160_IL-16	0.790	-0.392	0.094	0.043	0.171	-0.056	-0.153	0.038	0.072	-0.022	-0.123	0.036	0.093	-0.034	0.024	-0.034	-0.109	-0.029	0.002	-0.046
162_U-PAR	0.791	-0.203	0.140	0.188	0.119	0.025	-0.076	-0.289	-0.078	0.125	-0.078	0.054	0.028	-0.066	0.174	0.083	-0.036	-0.023	-0.017	0.039
164_CTSD	0.849	-0.296	0.030	-0.031	0.046	-0.029	0.223	0.061	-0.022	-0.085	0.036	0.027	-0.007	0.014	-0.014	0.025	0.079	-0.048	0.049	0.024
165_RAGE	0.743	-0.358	-0.085	0.247	-0.172	0.084	-0.058	-0.037	0.079	-0.070	-0.021	-0.002	-0.034	0.033	-0.117	0.089	0.076	0.031	-0.013	0.073
166_CCL3	0.750	-0.208	0.113	-0.122	0.108	-0.133	0.127	0.204	-0.105	-0.253	0.169	-0.021	0.103	-0.078	0.224	0.045	-0.029	0.026	0.065	-0.040
167_MMP-7	0.815	-0.359	-0.127	-0.025	-0.015	0.068	0.166	-0.112	0.042	-0.042	0.024	-0.078	0.016	0.078	0.059	0.003	-0.044	-0.060	-0.053	-0.084
169_ ITGB1BP2	0.590	0.205	0.039	0.506	0.142	-0.150	-0.019	0.176	-0.086	0.051	0.158	-0.148	-0.087	-0.163	-0.157	-0.032	0.113	0.092	-0.002	0.024
170_CXCL16	0.875	-0.261	-0.030	0.169	-0.071	-0.007	0.130	-0.037	0.026	-0.027	-0.029	-0.089	-0.016	0.001	-0.084	0.001	0.077	0.055	-0.018	-0.001
171_Dkk-1	0.835	-0.224	0.217	-0.006	-0.088	0.263	0.091	-0.012	-0.143	0.049	-0.074	0.031	0.080	0.027	-0.065	-0.016	0.046	-0.031	-0.013	-0.004
173_GAL	0.629	-0.311	-0.082	0.108	-0.315	0.106	-0.090	0.042	-0.148	-0.071	0.021	0.123	0.045	0.024	0.123	-0.099	0.025	0.074	0.061	0.010
174_AGRP	0.716	-0.302	-0.004	0.232	-0.113	-0.016	-0.187	0.046	-0.076	0.251	0.139	0.098	-0.064	0.017	0.071	0.003	0.137	-0.006	0.070	0.052
177_t-PA	0.726	-0.301	-0.097	0.025	0.028	-0.119	0.205	0.197	-0.255	-0.075	-0.046	-0.047	-0.067	0.123	0.086	0.031	-0.047	-0.020	-0.005	-0.075
178_HB-EGF	0.747	-0.248	0.317	-0.084	-0.140	0.282	0.046	0.067	-0.144	0.133	-0.028	0.077	0.039	0.027	-0.040	-0.012	0.075	-0.042	-0.063	-0.048
179_ESM-1	0.774	-0.322	-0.166	0.210	-0.077	0.036	-0.078	-0.021	-0.018	0.092	0.051	0.040	0.093	0.058	0.118	-0.080	-0.019	0.062	0.053	0.035
181_VEGF-D	0.758	-0.211	0.007	0.188	-0.170	0.061	-0.040	-0.041	0.165	-0.038	0.261	-0.086	0.047	-0.075	-0.049	-0.007	-0.029	-0.116	0.042	0.073
182_MMP-12	0.707	-0.271	-0.274	0.001	0.098	0.035	0.017	-0.171	0.112	0.056	0.030	-0.042	0.000	-0.140	0.005	0.128	-0.010	-0.089	-0.107	-0.095
183_SPON1	0.807	-0.467	-0.131	0.139	-0.007	-0.035	-0.002	-0.050	-0.105	0.027	-0.042	0.004	0.000	-0.008	0.029	0.021	0.015	0.053	-0.026	0.032
185_CTSL1	0.822	-0.335	-0.049	0.114	0.001	0.010	-0.009	0.067	-0.037	-0.046	0.070	0.036	0.015	-0.040	0.098	-0.054	-0.116	-0.003	0.040	0.007
187_FABP4	0.675	-0.218	-0.100	-0.127	0.135	-0.199	0.369	0.178	0.058	0.117	-0.128	-0.040	0.111	0.053	0.004	0.133	-0.012	0.022	-0.006	-0.107
188_BNP	0.690	0.190	-0.140	0.369	0.112	-0.074	0.011	0.035	-0.100	0.049	0.214	-0.125	-0.008	-0.120	0.039	-0.012	0.124	-0.016	0.064	-0.132

Supplementary table 1. Principal Component Matrix (continued)

	Component																			
Gene	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
189_LEP	0.342	-0.019	0.031	-0.112	0.264	-0.021	0.386	0.387	0.294	0.311	-0.130	0.023	0.079	0.056	0.107	0.072	-0.086	0.019	-0.084	-0.122
191_CA-125	0.574	-0.231	0.053	0.059	-0.186	-0.093	-0.072	0.217	0.160	0.092	0.157	0.016	0.136	-0.023	0.113	-0.027	-0.239	-0.120	0.068	-0.045
192_NEMO	0.665	-0.126	0.355	0.192	0.186	-0.246	-0.258	-0.073	0.038	0.020	-0.149	0.039	0.119	-0.106	0.026	-0.090	-0.002	0.014	-0.080	0.063
193_FS	0.779	-0.328	-0.015	0.019	0.027	0.020	0.249	-0.039	0.150	-0.027	0.000	0.009	0.017	-0.011	-0.080	-0.043	0.046	-0.021	-0.050	0.052
194_PECAM-1	0.875	-0.338	0.037	0.084	-0.101	0.000	0.038	0.086	-0.041	-0.011	-0.043	0.051	-0.032	0.061	-0.088	0.009	0.021	0.004	-0.021	0.085
195_NT-pro-BNP	0.399	-0.099	-0.239	0.105	0.100	-0.210	-0.123	-0.318	-0.189	0.364	0.174	0.065	0.049	-0.011	0.230	0.082	-0.028	0.129	-0.006	-0.050
196_ECP	0.547	-0.169	0.341	0.091	0.122	0.189	0.085	-0.234	0.073	-0.060	-0.190	-0.050	0.044	0.060	0.050	0.137	-0.052	0.161	0.133	-0.085

Supplementary table 2. Baseline patient characteristics of public database cohorts.

		Sample size, n	Age, years, mean (SD or range)	Male, n (%)	BMI, kg/m2, mean (SD or range)	PASI score, mean (SD or range)
Krueger et al.						
	Tofacitinib 10mg BID	9	45.2 (11.3)	7 (77.8)	35.1 (11.5)	21.9 (8.6)
Tomalin et al.						
	Tofacitinib 10mg BID	138	43.1 (19–74)	95 (68.8%)	29.2 (17.2–52.7)	21.2 (12.0–53.1)
	Etanercept 50mg BIW	128	42.8 (18–71)	89 (69.5%)	28.7 (18.1–44.4)	21.9 (12.0–63.6)

Patient baseline characteristics derived from public database cohorts. Krueger: GEO dataset GSE69967 and Tomalin: GEO dataset GSE136435.
Abbreviations: BID: twice a day; BIW: twice a week; SD: standard deviation; BMI: body mass index; PASI: Psoriasis Area and Severity Index

TOFA-PREDICT study protocol: A stratification trial to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in psoriatic arthritis

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ABSTRACT

Introduction Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease that affects up to 30% of psoriasis patients. Current challenges in clinical care and research include personalised treatment, understanding the divergence of therapy response and unraveling the multi-factorial pathophysiology of this complex disease. Moreover, there is an urgent clinical need to predict, assess and understand the cellular and molecular pathways underlying the response to disease modifying anti-rheumatic drugs (DMARDs). The TOFA-PREDICT clinical trial addresses this need. Our primary objective is to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in PsA.

Methods and analysis In this investigator-initiated, phase III, multi-centre, open-label, four-armed, randomized controlled trial, we plan to integrate clinical, molecular, and imaging parameters of 160 PsA patients. DMARD-naive patients are randomized to methotrexate or tofacitinib. Additionally, patients that are non-responsive to csDMARDs continue their current csDMARD and are randomized to etanercept or tofacitinib. This results in four arms with each 40 patients. Patients are followed for one year. Treatment response is defined as minimal disease activity (MDA) at week 16. Clinical data, biosamples, and images are collected at baseline, 4 weeks, and 16 weeks; at treatment failure (treatment switch) and 52 weeks. For the first 80 patients, we will use a systems medicine approach to assess multi-omics biomarkers and develop a prediction model for treatment response. Subsequently, data from the second 80 patients will be used for validation.

Ethics and dissemination The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands, is registered in the European Clinical Trials Database and is carried out in accordance with the declaration of Helsinki. The study's progress is monitored by Julius Clinical, a science-driven contract research organization.

Registration details MREC reference number: NL63439.041.17; EudraCT reference number: 2017-003900-28.

ARTICLE SUMMARY

Strength and limitations of this study

Strengths:

1. Our multi-omics systems medicine approach integrates molecular, imaging, and clinical data, which facilitates identification of pre-treatment profiles that are associated with DMARD response in PsA.
2. We use a two-step data analysis approach to both discover and validate predictive profiles.
3. Sensitive imaging techniques are used to evaluate treatment response at multiple time points, enabling comparison with conventional response measures.

Limitations:

1. Although the TOFA-PREDICT includes therapies with three different mechanisms of action (MTX, a TNF inhibitor and a Janus Kinase Inhibitor), this does not cover the full therapeutic armamentarium available for PsA.
2. The two-step approach with discovery and validation bisects the cohort, leading to reduced sample size per treatment group.

INTRODUCTION

Background

Psoriatic arthritis (PsA) is a chronic, auto-inflammatory and auto–immune, musculoskeletal disease that affects up to 30% of patients with psoriasis.[1] It is considered a heterogeneous disease, as patients have a variable disease course and clinical phenotype.[1–4] The hallmarks of PsA include cutaneous psoriasis, nail dystrophy, peripheral arthritis, axial spondyloarthritis, dactylitis, and enthesitis.[1–3] PsA may also feature extra-musculoskeletal manifestations and comorbidities that impact overall morbidity and mortality, including anxiety, depression, uveitis, inflammatory bowel disease, metabolic syndrome and cardiovascular events.[5–11]

PsA can cause severe joint damage early in the disease course, contribute to functional disability and chronic pain, and as such negatively impact quality of life.[2,4,12–14] Delayed treatment initiation is associated with progression of joint erosions, decreased long-term physical function and reduced risk of medication-free remission.[13–16] A delayed diagnosis of six months may already negatively impact physical function and joint erosions.[14] These data highlight the necessity of timely initiation of effective treatment with disease-modifying anti-rheumatic drugs (DMARDs).[17,18]

Challenges in treatment and assessing response to therapy

The care for patients with PsA faces several challenges.[19] The first challenge arises in unraveling the mechanisms that underlie pathogenesis. Although over the past 15 years many researchers have studied its complex etiology, the exact molecular mechanisms underpinning PsA pathogenesis remain unknown.[3,20] It is important to improve our understanding of the genetic, environmental, and immune-mediated factors that initiate and maintain the disease, as discoveries about dysregulated immunological pathways can facilitate the development of new therapies. For example, identification of the implications of the tumor necrosis factor alpha (TNF) and interleukin (IL)-23/IL17 pathways have led to rapid development of effective therapeutic agents.[1,3] Moreover, stratification of patients with inflammatory arthritis by immunological phenotype for selection of therapy has shown promise. For example, favourable treatment response in PsA patients that were stratified based upon circulating T helper cell profiles has been reported.[21] In rheumatoid arthritis, a machine learning model based upon divergent transcriptional signatures in peripheral blood mononuclear cells (PBMCs), monocytes, and $CD4^+$ T cells, was reported to predict treatment response in adalimumab or etanercept (ETN) treated patients.[22] These examples underline how unraveling disease pathogenesis may improve clinical practice.

The second challenge comprises a lack of methods to select the optimal treatment for each patient.[4,12,23] Evidence-based treatment strategies for PsA were developed by the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). However, treatment response rates are disappointing.[24,25] Up to 40% of patients respond insufficiently to a first DMARD, and strongly divergent drug responses are observed.[3,4,12] Although conventional synthetic (cs)DMARDs are frequently used as first-line therapy, there is limited evidence available on their effectiveness in PsA.[26–28] Moreover, the number of csDMARDs, biologic (b)DMARDs and targeted synthetic (ts)DMARDs is rapidly increasing and head-to-head trials are scarce.[23,29–31] Hence, clinicians have no tools at their disposal to predict which DMARD will be effective for an individual patient.[23] This lack of precision medicine is a clinically relevant problem for a potentially aggressive disease, that may impact quality of life, affect multiple organ systems, has an economic burden on the healthcare system, and demands costly treatment that potentially causes adverse events.[12–19,21]

The third challenge comprises the wide array of novel imaging modalities and the growing number of analytical methods that have become available for the evaluation of therapy response in PsA. Conventional radiography lacks sensitivity, especially in early disease patients in whom little radiographic abnormalities are observed.[32] Furthermore, the visual interpretation of medical images is time-consuming, bound with interobserver variation and limited to semi-quantitative outcomes that may be insensitive to detect small changes over time. On the contrary, computer-based medical image analysis can generate uniform, quantitative results in a (semi)-automatic manner. Adding these techniques in trials and in clinical practice may add to unraveling mechanisms as well as improvement of treatment.

Rationale

Overall, there is an urgent clinical need to assess and understand the cellular and molecular pathways underlying DMARD treatment response in PsA. To this end the TOFA-PREDICT trial was designed. In this investor-initiated, phase III, multi-centre, four-armed, randomized trial, a multi-omics systems medicine approach is used to integrate pre-treatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging data to discover PsA patients profiles that predict response to tofacitinib (TOF), as compared to methotrexate (MTX) and etanercept (ETN). By expanding our knowledge of the underlying mechanisms, course and treatment response, the TOFA-PREDICT study also aims to identify novel biomarkers for diagnosis and disease monitoring.[3,19]

In the TOFA-PREDICT trial sensitive imaging techniques, including magnetic resonance imaging (MRI) and Fluorine-18-fluorodeoxyglucose positron emission tomography/computerized tomography (^{18}F-FDG PET/CT), are applied to monitor disease activity. The current trial can deliver important data on the value of these more advanced imaging methods. With the use of ankle MRI-scans early, possibly reversible, and inflammatory features of PsA can be visualized at the heel, which is the most frequently affected site for enthesitis in PsA.[33,34] Moreover, ^{18}F-FDG PET/CT might aid in the measurement of local and systemic inflammation in PsA, including (peri)-articular and vascular inflammation.

OBJECTIVES

Primary

- Identify pre-treatment profiles with integrated clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging data that predict response to treatment with tofacitinib, in DMARD-naïve and DMARD non-responsive PsA patients

Secondary

- Compare clinical efficacy of treatment with tofacitinib, methotrexate and etanercept in DMARD-naïve and DMARD-non responsive patients with active PsA
- Compare structural response to treatment of active PsA with tofacitinib, methotrexate, and etanercept using (semi)quantitative ankle-MRI outcomes, radiographic outcomes, and ^{18}F-FDG PET/CT outcomes
- Determine (medication specific) molecular mechanisms predicting and underlying clinical response to tofacitinib, in comparison to methotrexate, and etanercept in active PsA

METHODS AND ANALYSIS

Study setting

TOFA-PREDICT is a multicentre (seven) investigator-initiated, phase III, open-label, four-arm, randomized controlled study conducted in the Netherlands. A total of 160 PsA patients that fulfill the ClASsification criteria for Psoriatic ARthritis (CASPAR) will be included in two groups, each with two treatment arms.[35] The first group consists of DMARD-naïve patients, who are randomized to MTX (arm 1) or TOF (arm 2). The second group consists of DMARD non-responsive patients, who continue csDMARD background therapy and are randomized to addition of ETN (arm 3) or TOF (arm 4). Eligibility criteria are displayed in **Table 1**. The TOFA-PREDICT trial started on April 4, 2018 and the scheduled end date is

July 1,2025. By the end of 2022, inclusion of the first cohort of 80 patients is completed. The evaluation of the first cohort will be initiated early 2023.

Table 1: Eligibility criteria TOFA-PREDICT

INCLUSION CRITERIA	
General	
1	Patients aged 18-75 years.
2	Fulfillment of CASPAR criteria for psoriatic arthritis (PsA).
3	Psoriatic arthritis disease duration of ≥8 weeks.
4	Active arthritis based on ≥2 swollen joints AND ≥2 tender joints.
Concomitant therapies	
5	In case of oral corticosteroid use, a stable dose of ≤10 mg/day of prednisone (or equivalent) for ≥4 weeks prior to baseline visit is allowed.
6	In case of NSAID use, a stable dose one week prior to baseline visit is allowed.
7	In case of current topical treatment of psoriasis, the following regimens are allowed: • Non-medicated emollients • Topical corticosteroids ≤1% for only palms, soles, face and intertriginous areas • Tar or salicylic acid preparations and shampoos for only the scalp
Specific for DMARD non-responsive patients (arm 3 and 4)	
8	Current use of csDMARD (MTX, LEF, SSZ) • On the highest tolerable dosage (max dose 25 mg/week) • A stable dose ≥4 weeks prior to baseline • Without previous serious toxicity • In case of MTX: concomitant folate supplementation ≥5 mg/week
9	History of 1 bDMARD prior to inclusion is allowed, except: • Prior use of etanercept. • Primary failure of other TNFi than etanercept (adalimumab, golimumab, infliximab, certolizumab).
EXCLUSION CRITERIA	
General	
10	Pustular psoriasis only.
11	Diagnosis of fibromyalgia or history of any rheumatic autoimmune or inflammatory disease other than PsA.
12	Any condition possibly affecting oral drug absorption, such as gastrectomy, diabetic gastro enteropathy or bariatric surgery (e.g. gastric bypass).
13	A skin condition at the time of baseline that could interfere with evaluation of psoriasis severity.
14	Previous participation in any study with tofacitinib as IP.
15	Participation in other studies involving investigational drug(s) ≤4 weeks prior to baseline visit.
Specific for DMARD-naïve patients (arm 1 and 2)	
16	History of csDMARD, bDMARD or tsDMARD use.
Specific for DMARD non-responsive patients (arm 3 and 4)	
17	History of ≥2 bDMARDs or ≥1 tsDMARD.
Therapies	
18	Prior treatment with non-B cell-specific lymphocyte depleting therapies, alkylating agents or total lymphoid irradiation. Rituximab or other selective B-lymphocyte depleting agents are allowed, if discontinued ≥1 year prior to first dose of the IP and normal CD19/20+ counts by flow cytometry analysis.

Table 1: Eligibility criteria TOFA-PREDICT (continued)

	INCLUSION CRITERIA
19	Specific concomitant therapies, being: • Injected corticosteroids ≤4 weeks prior to baseline visit • UVB phototherapy ≤2 weeks prior to baseline visit • PUVA (psoralens and UVA) phototherapy ≤4 weeks prior to baseline visit • Topical treatments that could affect psoriasis severity (corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, retinoids) ≤2 weeks prior to baseline visit
Safety	
20	Pregnant females, females planning pregnancy, breastfeeding females and females of childbearing potential not using highly effective contraception. Women of childbearing age must test negative for pregnancy prior to enrolment.
21	Blood dyscrasias within three months prior to baseline visit, including: • Hemoglobin <10 g/dL • White blood cell count <3.0 x 10^9/L (<3000/mm^3) • Absolute neutrophil count ≤1.5 x 10^9/L (<1500/mm^3) • Absolute lymphocyte count <1.0 x 10^9/L (<1000/mm^3) • Platelet count <100 x 10^9/L (<100,000/mm^3)
22	Estimated Creatinine Clearance <40 ml/min based on Cockcroft formula.
23	Total bilirubin, AST or ALT more than two times the upper limit of normal at screening visit.
24	History of an infected joint prosthesis at any time, with the prosthesis still in situ.
25	Oral antimicrobial therapy ≤2 weeks prior to baseline visit.
26	Vaccination with live or attenuated vaccines: • ≤6 weeks prior to baseline visit • Planned during the study period • ≤6 weeks following discontinuation of the IP
27	History of alcohol or drug abuse (unless in full remission for ≥6 months prior to baseline visit).
28	Significant trauma or surgical procedure ≤1 month prior to baseline visit, or any planned elective surgery during the study period.
29	Active, latent or inadequately treated infection with Mycobacterium tuberculosis as defined by: • Positive QuantiFERON-TB Gold In-Tube test within 3 months prior to the screening visit • Suspected radiographic features on chest radiograph within 3 months prior to the screening visit • Medical history of inadequately or untreated latent or active Mycobacterium tuberculosis infection
30	Positive serologic screening for infection with human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, or history of any other chronic infection.
31	Increased risk for gastrointestinal perforation, such as diverticulitis.
32	History of any immunodeficiency or a first-degree relative with a hereditary immunodeficiency.
33	History of any lymphoproliferative disorder (such as Epstein Barr Virus related lymphoproliferative diseases), history of lymphoma, leukemia, or signs and symptoms suggestive of current lymphatic disease.
34	History of a disseminated herpes zoster or simplex infection, or recurrent (≥1 episode) herpes zoster infections.
35	History of active infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, ≤6 months prior to baseline visit.
36	Current history of lymphoma and malignancy, except for • Adequately treated or excised non-metastatic basal cell cancer of the skin, squamous cell cancer of the skin and cervical carcinoma in situ. • Adequately treated solid malignant tumors without recurrence after a minimal follow-up period of 10 years.

Table 1: Eligibility criteria TOFA-PREDICT (continued)

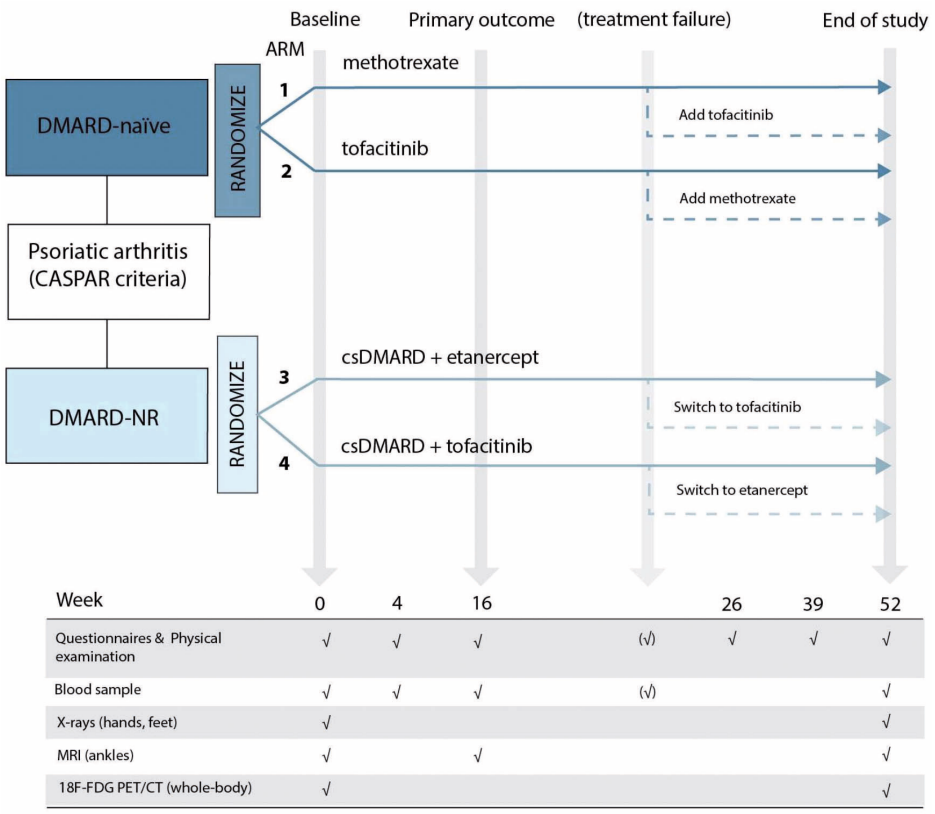
	INCLUSION CRITERIA
37	Current or recent history of a severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurologic disease.
38	Other severe acute or chronic, medical or psychiatric conditions, or laboratory abnormalities, that may • Increase the risk associated with study participation or IP administration • Interfere with interpretation of study results

Abbreviations: *ALT: alanine aminotransferase; AST: aspartate aminotransferase; bDMARD: biologic DMARD ('biological') e.g. inhibitors of tumor necrosis factor and interleukin-17A; CASPAR: ClASsification criteria for Psoriatic Arthritis; csDMARD: conventional synthetic DMARD e.g. methotrexate, leflunomide or sulfasalazine; DMARD: disease modifying anti-rheumatic drug; IP: investigational product; LEF: leflunomide; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PsA: psoriatic arthritis; SSZ: sulfasalazine; tsDMARD: targeted synthetic DMARD; TNFi: tumor necrosis factor alpha inhibitor; UVA: ultra-violet A; UVB: ultra-violet B.*

Interventions

The first group of patients are DMARD-naïve and have active PsA. Typically, these patients are at an early stage of PsA. Patients are randomized to receive either MTX monotherapy 25mg once a week, subcutaneously (standard of care therapy, arm 1) or TOF monotherapy 5mg twice daily, orally (investigational therapy, arm 2). Randomization is performed per site in computer-generated random blocks. Patients will be assessed according to a predefined schedule of regular study visits (Table 2). In case of treatment failure (see heading "Treatment failure"), combination therapy will be initiated: patients randomized to MTX will also start TOF, and vice versa. If drug intolerance warrants discontinuation of the drug, a switch will be made to the alternate drug as monotherapy (TOF to MTX and vice versa).

The second group of patients are non-responders to previous treatment with either MTX, leflunomide (LEF) or sulfasalazine (SSZ), or to previous treatment with combination therapy of a csDMARD and one previous bDMARD. A history of one bDMARD prior to inclusion is allowed, except for prior use of ETN. Prior use of a tsDMARD (Janus kinase inhibitor, abatacept) is also not allowed. Only patients who have had secondary treatment failure to a TNFi, defined as initial good response, but diminished clinical efficacy over time, are eligible to participate in the study.[36] These DMARD non-responders continue background therapy with csDMARD and are randomized to receive the addition of either ETN 50mg once a week, subcutaneously (arm 3) or TOF 5mg twice daily, orally (arm 4). ETN was chosen as it was reimbursed and no preference for a specific TNF-inhibitor is mentioned in current EULAR and GRAPPA international guidelines for the treatment of PsA.[24,25] In the event of treatment failure or drug intolerance (see heading 'Treatment failure'), a switch from ETN to TOF or vice versa will be made. **(Figure 1)**



Week	0	4	16		26	39	52
Questionnaires & Physical examination	√	√	√	(√)	√	√	√
Blood sample	√	√	√	(√)			√
X-rays (hands, feet)	√						√
MRI (ankles)	√		√				√
18F-FDG PET/CT (whole-body)	√						√

Figure 1: Study design - Treatment failure is defined as not attaining the ACR50 response on two consecutive study visits (interval four weeks), starting from week 16. **Abbreviations**: 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; CASPAR: CIASsification criteria for Psoriatic ARthritis; DMARD: disease modifying anti-rheumatic drug; NR: non-responder to conventional synthetic and a maximum of one biologic DMARD therapy; MRI: magnetic resonance imaging.

Study visits

Study visits are performed at baseline, week 4, week 16, week 26, week 39 and week 52. Each study visit comprises multiple study assessments (a schematic overview is depicted in **Table 2**). From week 16 onwards, the American College of Rheumatology (ACR)50 score is calculated every study visit, to determine treatment failure.[37] The ACR50 score is described in the outcomes section. Patients are evaluated additionally to the above-described visits according to regular clinical practice, including blood sampling for safety measurements according to regular practice. During all visits, adverse events and serious adverse events are documented with respect to safety.

Table 2: Schematic overview of study assessments

Category	Assessment	Screening	Baseline	FU	Primary endpoint	FU	FU	End of study	Treatment failure [5]
	Week number	n.a.	0	4	16	26	39	52	t.b.d.
Eligibility	Sign informed consent	√							
	Medical History	√							
	In- & exclusion criteria	√	√						
	Randomization		√						
Anamnestic	Online questionnaires [1]		√	√	√	√	√	√ [6]	√
	Patients well being	√	√	√	√	√	√	√ [6]	√
	Adverse event evaluation		√	√	√	√	√	√ [6]	√
	Medication annotation	√	√	√	√	√	√	√ [6]	√
Physical examination	Length		√						
	Weight		√	√	√	√	√	√	√
	Vital signs [2]		√	√	√	√	√	√	√
	Basic physical exam		√	√	√	√	√	√	√
	TJC (76) and SJC (78)		√	√	√	√	√	√ [6]	√
	Dactylitis evaluation		√	√	√	√	√	√ [6]	√
	Leeds enthesitis Index and enthesitis plantar fascia		√	√	√	√	√	√ [6]	√
	PASI and BSA		√	√	√	√	√	√ [6]	√
	VAS physician		√	√	√	√	√	√ [6]	√
Blood sample	Clinical chemistry & hematology [3]	√		√	√	√	√	√ [6]	
	Systems medicine approach [4]		√	√	√			√	√
Imaging	X-rays (hands, feet)		√					√ [6]	
	MRI (ankles)		√		√			√	

Table 2: Schematic overview of study assessments (continued)

Category	Assessment	Screening	Baseline	FU	Primary endpoint	FU	FU	End of study	Treatment failure [5]
	^{18}F-FDG PET/CT (whole body)		√					√	
Evaluation	Response				√	√	√	√ [6]	√

Legend: *[1] Questionnaires: Assessment of SpondyloArthritis (ASAS) health index, Dermatology Life Quality Index (DLQI), EuroQol five dimension scale (EQ-5D), Health Assessment Questionnaire (HAQ), self-administered psoriasis area and severity index (SAPASI) and the Work Productivity and Activity Impairment (WPAI) questionnaire, supplemented by the Visual Analogue Scale (VAS) for general well being and pain. [2] Vital signs: blood pressure, pulse and temperature (auricular measurement). [3] At screening visit: Hepatitis B surface antigen (HbsAg), Hepatitis B core IgG, Human Immunodeficiency Virus (HIV)-1 and 2 antibodies, p24 antigen, interferon-γ release assay (IGRA), Rheumatoid Factor (RF), Anti-citrullinated peptide/protein antibodies (ACPAs), hemoglobin (Hb), haematocrit (Ht), thrombocytes, erythrocytes, leukocytes and differentiation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glycosylated hemoglobin (HbA1c), triglycerides and cholesterol (total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)). At follow-up visits: Hb, Ht, thrombocytes, erythrocytes, leucocytes, ESR, CRP, ALT, eGFR, triglycerides and cholesterol. [4] Systems medicine approach to collect '-omics' data: proteomics, transcriptomics and metabolomics. At baseline, week 4, week 16, week 52 a total of 85 mL blood is drawn for isolation of serum, plasma, peripheral blood mononuclear cells (PBMCs), , B cells, myeloid dendritic cells (mDCs), monocytes and peripheral blood leukocytes (PBLs). In case of treatment failure only 35 mL blood is drawn for isolation of serum, plasma and PBMCs. [5] A 'treatment failure visit' is planned when the ACR50 response is not attained at a regular study visit; starting from week 16. Treatment failure is defined as again not attaining the ACR50 at this extra study visit four weeks later. [6] Selection of data obtained after resuming treatment in regular care for patients that discontinue trial medication due to (serious) adverse events, treatment failure after cross-over or other reasons.* ***Abbreviations:*** *18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; BSA: body surface area; FU: follow-up; MRI: magnetic resonance imaging; PASI: psoriasis area and severity index; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale; X-ray: conventional radiographic photograph.*

Treatment failure

Treatment failure is defined as failing to achieve an ACR50 response on two consecutive visits from week 16 onwards. If a patient does not attain the ACR50 response at a regular study visit, an additional study visit is scheduled 4 weeks later. At this 'treatment failure' visit the ACR50 response is re-assessed. In the event that the ACR50 response is again not attained, 'treatment failure' is confirmed and a cross-over to the alternate treatment protocol within that study group takes place. **(Figure 1)** A minimum washout of 1 week will be applied to patients switching from TOF to ETN (or vice versa). If the ACR50 response is attained at the 'treatment failure'-visit, regular 12-week visit intervals will continue and the patient will not switch therapy. In addition, drug intolerability that warrants discontinuation (e.g., side-effects, laboratory abnormalities) is defined as treatment failure at any time point. In the case of MTX, dosage lowering is the first step in case of drug intolerability. For ETN and TOF, dosage changes are not possible and drug intolerability indicates treatment failure. Cross-over will not take place in the last 3 months of follow-up.

MTX dosage adjustments

MTX is initiated in the DMARD-naïve arm at a dosage of 15mg/week subcutaneously. The dosage is increased to 25 mg/week after 4 weeks, unless the ACR50 response is attained or side effects prevent safe dosage escalation. By increasing the dosage to 25mg/week at week 4, the primary end point of the study can be compared between MTX and TOF at week 16 (i.e., 12 weeks of administering the maximal dosage of MTX). MTX dosage may be reduced during follow-up if ACR50 has been attained and/or if side-effects occur, in accordance with standard clinical care.

Escape medication

In accordance with standard clinical care, the following escape therapies are allowed: non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and from week 24 onwards, topical corticosteroids.

End of study

After 52 weeks of follow-up, all patients will resume regular clinical care while continuing the DMARD therapy that was initiated during the study. Treatment in regular care will also be resumed by patients that discontinue trial medication due to (serious) adverse events, treatment failure after cross-over or other reasons. From these patients, we will only collect a selection of data after 52 weeks of follow-up. (**Table 2:** footnote [6])

Data collection and samples

All collected clinical data are entered in an online database (Research online; Julius Centre UMC Utrecht) designed for the TOFA-PREDICT trial. Blood samples for the multi-omics analyses are collected at several time points throughout the study. **(Figure 1)** In addition, blood samples are taken to monitor drug safety after the start of MTX, TOF or ETN. Blood samples for the multi-omics analyses are collected at seven different study sites After protocolized transport, all blood samples are processed in a standardized way in the University Medical Center (UMC) Utrecht. The samples are pseudo-anonymized and after magnetic-activated cell sorting, peripheral blood mononuclear cell subsets are stored. Additionally, serum, plasma and peripheral blood mononuclear cell subset lysates are stored. All blood samples for multi-omics analyses are registered with Quaero Systems. The multi-omics analyses of the stored samples are performed in batches at a later stage, taking confounders such as treatment arm, visit number and demographics into account. All data are integrated at the Data Research Environment (anDREa). The omics data will be made available in public databases after primary analyses and publication.

Patient and public involvement statement

Patients were not involved in the development of the research question, the design and conduct of the study, choice of outcome measures nor recruitment.

Outcomes

Systems medicine approach

The primary objective is to discover and validate pre-treatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging profiles that predict treatment response. Response and nonresponse are defined as attaining or not attaining MDA, respectively, after 16 weeks of treatment. To define these profiles, a multi-omics systems medicine approach will be used for which transcriptomic, metabolomic, proteomic, and flow cytometry data are collected. Transcriptomic and flow cytometry analysis will be performed on peripheral blood mononuclear cell(subset)s. Proteomic and metabolomic analyses will be performed on serum and/or plasma samples. These molecular and cellular data will be added to the clinical, structural, and imaging data (ankle-MRIs, whole body ^{18}F-FDG PET/CT, and radiographs of the hands and feet). Systems medicine data analyses will be used to combine the different omics-layers in our attempt to identify profiles that predict treatment response.

Clinical efficacy measures

We use MDA at week 16 as the primary outcome for the identification of molecular and cellular profiles that predict treatment response. MDA is a validated, PsA-specific composite measure that includes evaluation of arthritis (tender and swollen joint count), skin disease (Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA)), enthesitis, and patient reported outcomes (Health assessment Questionnaire (HAQ), visual analogue scale (VAS) for pain and VAS for patient global assessment).[38,39] The clinical relevance of composite measures that include multiple disease domains has become increasingly evident over recent years.[38–40] To define treatment failure, we use the ACR50 response, because treatment effect during follow-up is most commonly detected as a change from baseline. ACR50 is a composite measure defined as 50% improvement in the number of both swollen and tender joints, next to 50% improvement in at least three of the following outcomes: HAQ, acute phase reactant (we use CRP), VAS for patient global assessment, VAS for physician global assessment and VAS for pain.[37,41,42] We calculate the ACR50 every 12 weeks starting from week 16. Moreover, we assess dactylitis, blood pressure, body mass index (BMI), laboratory parameters, additional patient-reported outcomes and calculate additional PsA-specific composite indices.[43]

Patient-reported measures

At baseline, week 4, 16, 26, 39, 52 and at treatment failure visits, patients fill out online questionnaires to monitor disease activity and their mental and physical health. TOFA-PREDICT employs the following questionnaires: Assessment of SpondyloArthritis (ASAS) health index, Dermatology Life Quality Index (DLQI), EuroQol five-dimension scale (EQ-5D), HAQ, self-administered psoriasis area and severity index (SAPASI), the Work Productivity and Activity Impairment (WPAI) questionnaire and two VAS scores to assess pain and the patients' global assessment.[44–49]

Imaging measures

Three imaging techniques are applied in the TOFA-PREDICT study: MRI-scans of both ankles, whole body ^{18}F-FDG PET/CT and conventional radiography of the hands and feet. At baseline, week 16 and 52 MRI-scans of both ankles are obtained. MRI-scans are performed using MR-equipment with a field strength of 1.5 or 3 Tesla. The ankles are scanned separately using an extremity coil. The MRI-protocol was developed in accordance with the European Society of Musculoskeletal Radiology (ESSR) recommendations and contains the following sequences: 3D proton density (PD) with fat suppression (FS), transversal T1 Turbo Spin Echo (TSE) and 3D T1 FS before and after intravenous gadolinium injection.[50] The estimated total time in the MRI room is <60 min per patient per visit. Ankle-MRIs are visually evaluated using PsAMRIS, adapted for the heel, and HEMRIS measures.[33,51] Using deep learning, quantitative outcome measures for ankle-MRIs will be developed aiming to quantify (peri)articular inflammatory joint changes such as synovitis, bone marrow oedema, and enthesitis.

At baseline and week 52, whole-body ^{18}F-FDG PET/CT-scans are obtained. ^{18}F-FDG is administered intravenously after an overnight fast. Dosing of ^{18}F-FDG depends on local guidelines. After administration of ^{18}F-FDG, the ^{18}F-FDG PET/CT is performed one hour later. A non-contrast-enhanced low-dose CT is performed for attenuation correction. In this multicentre trial, all PET/CT-reconstructions are compliant to European Association of Nuclear Medicine Research Ltd. (EARL) guidelines in order to achieve comparable quantitative outcome parameters, such as standardized uptake values (SUVs).[52] The main ^{18}F-FDG PET/CT outcome measures are vascular and (peri)articular inflammation.

At baseline and at week 52 radiographs of hands and feet are acquired. Radiographs of hands and feet are evaluated using the PsA-modified Sharp-van der Heijde score.[53] MRI, ^{18}F-FDG PET/CT and radiography observers are blinded to diagnosis and treatment.

Sample size calculation

The primary objective of TOFA-PREDICT is to predict the treatment response (attaining or not attaining MDA after 16 weeks of treatment in active PsA), using the multi-omics analysis of pre-treatment omics data. To evaluate the sample size needed to detect differentially expressed genes/proteins (DEGPs) between responders and non-responders we simulated several scenarios. These scenarios used a range of number of prognostic genes (50-500), dispersion (0.1 – 0.5), and False Discovery Rates (FDR; 0.01 – 0.1) with in each scenario assuming a minimum fold-change in DEGPs of 2, 80% power, and testing of a total of 20,000 genes with a mean expression (read count) of 50. Separate analyses were performed for an equal distribution between responders and non-responders (50:50) and for unequal distributions of responders and non-responders (40:60 and 25:75). Results in the scenario assuming 400 differentially expressed genes, an FDR of 0.05 and an unequal distribution between responders and non-responders (40:60) assuming dispersion values as found in previous RNA-seq data from our group (e.g. CD14+ monocytes, dispersion value 0.11) resulted in a sample size of 20 patients per arm. Therefore, we assumed a sample size of 80 (20 patients per arm) to be sufficient to detect relevant expression signatures. Sample size was calculated using the R package 'RnaSeqSampleSize' (version 3.6.1).[54] For other omics platforms, required sample sizes are considered smaller based on the smaller number of markers (e.g. proteins up to 180 and metabolites up to 800). To enable external validation, a similar cohort will follow the first 80 patients up to a total of 160 included patients.

Data analyses

Systems medicine approach

Different layers of baseline omics data will be analysed separately and will be integrated with clinical (e.g. gender, disease duration, etc.), patient-reported parameters, and imaging data for the discovery and validation of molecular and cellular signatures that serve as biomarkers to predict treatment response after 16 weeks of treatment (primary endpoint). Furthermore, molecular signatures will be computed using omics data collected at week 4 and 52 (or treatment failure) in addition to baseline data. We will explore the molecular signatures using bioinformatic approaches. The observations made during the exploration of the data will guide the choice of tools and algorithms for the next step of the data analysis.[55] For each analysis step, we will perform permutation analysis and k-fold cross validation to test the reliability of the molecular signature. Moreover, we will integrate multi-omics data to discover molecular signatures that are supported by different layers of data, strengthening the reliability of the discovered signature. For prediction at baseline, the expression (i.e., fold change) of the separate omics layers will be analysed. Thereafter, using resulting relevant expression signatures in addition to established clinical and imaging predictors as features, we will build integrated and internally validated machine

learning (ML) models to predict response to TOF and separately response to MTX and ETN. A final statistical analysis plan (SAP) will be defined prior to database lock using the optimal techniques for analysing expression profiles and optimal ML models to use. Genes or gene modules from these signatures and models will bring forth new hypotheses that can be verified experimentally, contributing towards a better understanding of the disease mechanisms and a predictive model for disease outcome and therapy response.

Two-step analysis

After inclusion of the first 80 patients (~20 patients per group), the first step of the predictive multi-omics analysis will be performed. Of all the available multi-omics data, predictive biomarkers are identified as either relevant (statistically significant), irrelevant (statistically insignificant) or promising (based on clinical and scientific reasons without formal statistical significance). For each –omics platform, an optimal predictive assay for treatment response will be developed. Also, all relevant biomarkers will be integrated in multi-omics approaches and added to clinical data and structural imaging data to develop an exploratory prediction model for treatment response. To externally validate the identified biomarkers, we implement a second step in the analysis. Both the relevant and promising biomarkers will be analysed in the subsequent cohort of 80 patients, to replicate the results from the first phase. The proposed –omics assays from the first cohort will be validated in the second cohort. Finally, the combined relevant and promising biomarkers of all 160 patients will be integrated in multi-omics approaches and added to structural imaging data and clinical data to develop a final and clinically applicable prediction model using pre-treatment markers. In this phase, the added predictive value of omics markers over known, easily available (clinical) baseline predictors will also be assessed.

Clinical efficacy and structural response

Efficacy of treatment and imaging outcomes will be compared between different treatment arms using logistic or linear regression analyses taking into account established prognostic indicators (such as structural damage, elevated acute phase reactants and polyarthritis, to be finalised in the SAP) and centre (as the stratification factor used in randomization). The significance level (α) will be set at 0.05, with p-values less than or equal to α considered statistically significant.

Missing data and SAEs

Cases that are lost to follow-up and other missing data will be presented descriptively. If the percentage of missing data exceeds 5%, multiple imputation will be performed, based on data type and quantity of the missing data. For binary secondary drug efficacy outcomes missing data will be defined as non-response, to prevent overestimation of the

effect. Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported descriptively.

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Systemic glucocorticoid use and the occurrence of flares in psoriatic arthritis and psoriasis: a systematic review

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ABSTRACT

Objectives

The use of systemic glucocorticoids (SGC) is traditionally discouraged in the treatment of psoriatic arthritis (PsA) and psoriasis due to risk of psoriatic flares. However, despite this recommendation, SGC are frequently prescribed for these patients. In this study we reappraise the old paradigm that SGC are contra-indicated in the treatment of PsA and psoriasis.

Methods

A systematic search of MEDLINE, EMBASE and the Cochrane Library databases was performed in November 2019 to identify articles on any SGC use compared to no use in the PsA and psoriasis population. Topical glucocorticoid treatment was excluded. Our two primary outcomes focused on prescribing characteristics and occurrence of any type of flare.

Results

Our search yielded 4,922 articles of which 21 full-text were eligible for inclusion. There were eleven retro- and prospective cohorts involving a total of 4,170,820 patients of which 6,727 (37,82%) PsA and 1,460,793 (35,17%) psoriasis patients were treated with any type of SGC. Ten observational/interventional studies did not report an increased risk or occurrence of psoriatic flares related to SGC use.

Conclusion

Our results indicate that SGC are frequently prescribed for PsA and psoriasis patients. The occurrence of psoriatic flares appears to be low upon SGC exposure. In patients with a clear indication for SGC, e.g. in need of rapid anti-inflammatory therapy or bridging of therapies, the use of SGC should be considered in view of a low risk of skin flaring. It remains of importance to weigh risks for short- and long-term SGC-related side effects in clinical decision making.

KEY MESSAGES

1. Systemic glucocorticoids are frequently prescribed for the treatment of psoriatic arthritis and psoriasis.
2. There is no solid evidence that systemic glucocorticoids increase the risk of psoriatic skin flaring.
3. Systemic glucocorticoids should not be withheld for the treatment of PsA/psoriasis patients when indicated.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, inflammatory auto-immune disease that is characterized by asymmetrical peripheral arthritis, dactylitis, enthesitis, spondyloarthritis and psoriasis of the skin and nails.(1, 2) Approximately 20-30% of all psoriasis patients will eventually develop PsA.(3) Systemic treatment with disease-modifying antirheumatic drugs (DMARD) is essential in the management of PsA in order to prevent joint damage and erosions.(4) After initiation of a DMARD, it takes up to 3 months before treatment response can be observed in approximately 40% of patients.(5) To bridge this initiation phase, systemic glucocorticoid (SGC) treatment can be given for rapid anti-inflammatory effects and to relieve pain.(6) This short-term complementary treatment has also been shown to improve long-term adherence and to improve drug survival in both psoriasis and PsA.(7) Furthermore, the addition of a SGC to current DMARD therapy give better and faster clearance of psoriatic skin lesions and prolong drug free remission period.(8)

Despite these advantages, the use of SGC for the treatment of PsA/psoriasis are traditionally discouraged by recent guidelines and textbooks due to the risks of psoriatic flares, yet they do not provide evidence to support this recommendation.(9-12) Several guidelines refer to one and the same case series written in 1968, in which 19 of 104 patients developed generalized pustular psoriasis (GPP) after withdrawal of SGC therapy.(13)

Several national health care insurance databases have shown SGC to be a frequently prescribed drug in the treatment of psoriasis in routine clinical practice. In Germany the frequency of prescriptions for SGC exceed the amount prescribed for methotrexate, fumaric acid esters or biologicals(14), and in the United States, SGC prescriptions are issued to psoriasis patients by 90% of dermatologists.(15, 16) This highlights the discrepancy between prescribing behavior and current treatment guidelines.

Mrowietz(17) has made an effort in 2012 challenging the discussion of SGC use in psoriasis patients by highlighting the widespread use of these drugs without observing an increase in psoriatic flares. However, 10 years later, a shift in this old paradigm has not yet occurred. A systematic assessment of the evidence for the recommendation against the use of SGC in psoriasis and PsA is lacking.

In this systematic review we aimed to: (1) address the general prevalence of SGC prescribing in the PsA/psoriasis population, and (2) assess the risk and occurrence of psoriatic flares in PsA/psoriasis patients treated with SGC.

METHODS

Search strategy

A systematic PICO search of MEDLINE, EMBASE and the Cochrane Library databases was performed in November 2019. The search strategy was constructed together with a medical librarian in order to identify any papers on SGC use compared to no use in the PsA/psoriasis population. Two primary outcomes of interest were: prevalence of SGC prescriptions and any type of psoriatic flare. We defined a flare as any type of reported exacerbation of the current psoriatic skin condition (e.g. using PASI, BSA, clinical examination by a physician or patients self-reporting experiencing a flare) or a morphological shift towards another phenotype (e.g. from psoriasis vulgaris towards erythrodermic psoriasis, psoriasis pustulosa etc.). Search-terms used were Psoriatic Arthritis, Psoriasis, and Glucocorticoids combined with AND. Papers on topical treatment were excluded by using NOT as Boolean operator. A limit was set to English, Dutch and German language and there was no time frame. All types of study design were considered with the exception of case reports and case series. The PICO search strategy is presented in **Supplementary Data S1.**

Study eligibility criteria

Eligibility outcome (1): studies describing the prevalence of SGC prescriptions must contain a population of unselected PsA/psoriasis patients and must report on the usage of SGC within this population. Eligibility outcome (2): studies describing the occurrence of flares in patients with PsA/psoriasis of 18 years and older starting, using or tapering SGC. All doses and administration routes were considered with the exception of topical treatment regimens. Studies in which patients concomitantly used conventional-synthetic DMARD or biological DMARD were included. Finally, they should report on any type of psoriatic flare according to the definitions described above. All flares in response to start, dose maintenance or tapering of SGC were deemed of interest.

From all articles obtained from the search strategy, titles and abstracts were screened according to the inclusion criteria. If there was uncertainty about fulfilling the criteria the article was included for full-text screening and eligibility was discussed with JvL/PW until consensus was reached. Of all included articles the references were screened to check for missing papers of interest.

Data extraction & quality assessment

Three data extraction tables were created for each research question. **Table 1** describes the general prevalence of SGC prescribing in the PsA/psoriasis population. **Table 2** describes interventional studies reporting the risk of flares associated with SGC use in PsA/psoriasis

patients compared to patients not using SGC. **Table 3** describes observational and interventional studies of PsA/psoriasis patients all using SGC and the occurrence of flares in these populations. Publication types were clustered in order to give a clear distribution. Information on aim of the study, number of patients, baseline demographics, SGC treatment regimen and indication, co-medication were extracted. Important outcomes were the amount of patients that developed a psoriatic flare and a description of the occurred flare according to the article.

The methodological quality and risk of bias was assessed using The Agency for Healthcare Research and Quality (AHRQ) methodology checklist for cross-sectional and prevalence studies.(18) This manuscript was drafted using the PRISMA guidelines.

Pooling of data

It was not possible to pool quantitative due to large heterogeneity in terms of type of SGC, administration route, dosage, treatment duration and psoriatic flare definition.

RESULTS

Study characteristics

The systematic literature search resulted in a total of 4,222 unique articles after duplicate removal. 194 full-text articles were screened for eligibility after which 21 articles fulfilled the selection criteria. **Figure 1**

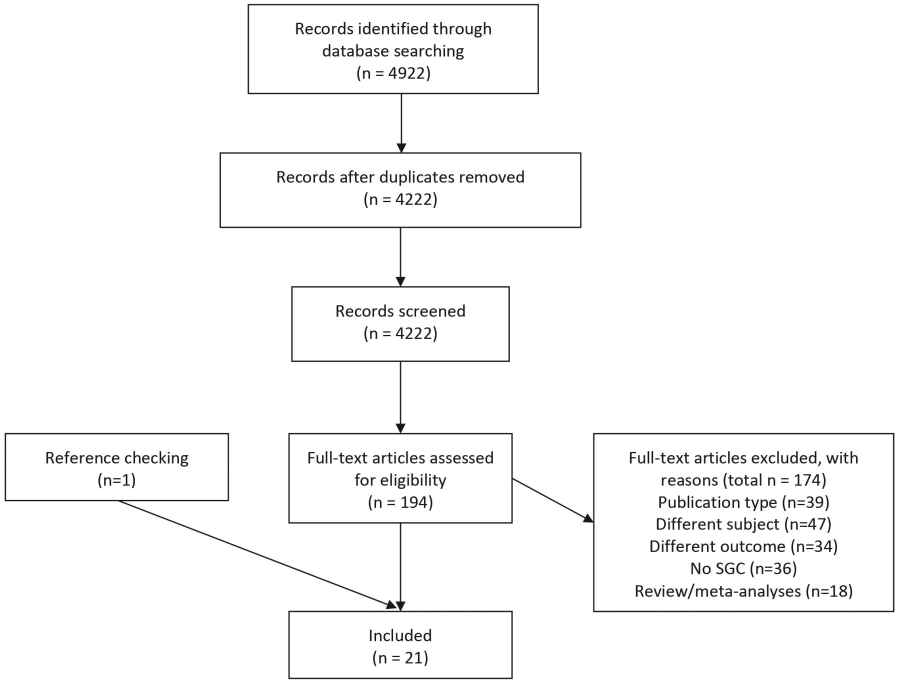

Figure 1. Prisma flow diagram of included articles

In general male and female distribution was equal. Type of SGC, treatment duration, dosage, indication for prescription and use of co-medication was heterogeneous for all included papers. Methylprednisolone (5-160mg/d given oral or intra-articular/muscular/lesional) was administered most frequently followed by triamcinolone (13-80mg/d given oral or intra-articular/muscular/lesional). Less frequently, patients were treated with prednisone, prednisolone, dexamethasone, fludrocortisone, hydrocortisone, betamethasone and deflazacort. (**Table 2** and **3** show details on all SGC used) Reporting of other possible risk factors that could contribute or lead to a psoriatic flare was lacking.

(1) Assessment of SGC prescription prevalence for PsA and psoriasis patients

Eleven retro- and prospective cohort studies were included. Data were derived from National Health Care Insurance databases or online registries specifically designed to collect demographic data regarding PsA/psoriasis. The geographic origin from articles was diverse, ranging from the United States of America, Germany, United Kingdom, Korea, Australia, Norway, Italy and Taiwan. Sample sizes ranged between 180 – 2,321,194 patients and the time period predominantly ranged from 2000 onwards. Two cohorts gathered information in the period from 1986 until 2010.

In summary, a total of 4,153,035 psoriasis and 17,785 PsA patients were analyzed in all cohorts. A substantial proportion of patients have been treated with any type of SGC over the course of their disease: 1,460,793 psoriasis (35,17%) and 6,727 PsA (37,83%) patients. Detailed study characteristics are shown in **Table 1**.

Study		Study characteristics				Medication				
1st author (year)	Publication type	Diagnosis	*n*	Follow-up duration	Gender (female, %)	Type of steroid	Route of administration	Prescribing physician	Description of SGC prescriptions	Other
Al-Dabagh 2014	retrospective cohort	Psoriasis	32.375	1989 - 2010	-	Prednisone, methylprednisolone, dexamethasone	PO, s.c.	93% by dermatologist; rest primary care physician	SGC were prescribed at 650.000 visits; (3,1% of 21.020.000 Psoriasis visits)	In 50% of cases SGC were prescribed alone; in 45% of the cases topical regimens were prescribed
Armstrong 2017	retrospective cohort	Psoriasis	1.700.000	2007 - 2012	-	Prednisone	PO	-	11,2% patients received prednisone as a first-line treatment	The amount of patients treated with SGC decreased in later lines of therapy
Augustin 2011	retrospective cohort	Psoriasis / PsA	26 338 Psoriasis; 2319 PsA	2003 - 2007	42	Betamethasone, cloprednol, cortisone, deflazacort, dexamethasone, fluocortolone, hydrocortisone, meprednisone, methylprednisolone, prednisolone, prednisone and triamcinolone	PO	1191 prescriptions by general physician; 811 by internists; 259 by dermatologists	8.15% of psoriasis patients and 5.39% of PsA patients	Followed by MTX (n=853), fumaric acid esters (n=342); leflunomide (n=168); retinoids (n=110); cyclosporine (n=105). 44.18% of psoriasis and 2.5% of PsA patients received topical treatment;
Dubreuil 2014	retrospective cohort	Psoriasis / PsA	59 281 Psoriasis; 4196 PsA	1986 - 2010	51 Psoriasis; 50 PsA	Glucocorticoid use (NOS)	PO	General physician	4.3% of Psoriasis patients and 8.2% of PsA patients	25% of Psoriasis and 35.2% of PsA patients received topical treatment;

Study		Study characteristics				Medication				
1st author (year)	Publication type	Diagnosis	*n*	Follow-up duration	Gender (female, %)	Type of steroid	Route of administration	Prescribing physician	Description of SGC prescriptions	Other
Eun 2017	retrospective cohort	Psoriasis	2.321.194	2010 - 2014	38	Methylprednisolone, prednisolone, dexamethasone, betamethasone, triamcinolone, other	PO, s.c.	General physician (93,9%), tertiary hospitals (2,2%), general hospitals (3,3%), small-sized hospitals (0,6%)	26.4% Psoriasis patients got a SGC prescriptions	
Grassi 1997	prospective cohort	PsA	180	1990 - 1992	58	Methylprednisolone, deflazacort, prednisone, betamethasone, dexamethasone, others	PO	-	24,4% PsA patients were taking SGC	72,7% were simultaneously treated with a DMARD and 88,6% with a NSAID
Kavanaugh 2018	prospective cohort	Psoriasis / PsA	7775 Psoriasis; 1719 PsA; 4315 self-reported PsA	2007 - 2015	43 Psoriasis; 49 PsA	Glucocorticoid use (NOS)	-	-	23,5% of all patients use or have used a SGC; Psoriasis 19,9%; PsA 33%; self-reported PsA 29,8%	48% of all patients use or have used an immunomodulator and 72,5% a biological. 96.9% of all patients use or have used topical therapy

Study		Study characteristics				Medication				
1st author (year)	Publication type	Diagnosis	*n*	Follow-up duration	Gender (female, %)	Type of steroid	Route of administration	Prescribing physician	Description of SGC prescriptions	Other
Lee 2016	retrospective cohort	Psoriasis	6072	2001 - 2011	46	Glucocorticoid use (NOS)	-	-	20,27% of all patients currently use SGC; 9,47% have used SGC in the past	7,32% of all patients have PsA, there is no sub analyses. 2,24% of patients are using MTX
Madland 2005	retrospective cohort	PsA	634	1999 - 2002	47	Prednisolone	PO, i.a.	Outpatient clinics	7,9% of PsA patients use oral SGC, 40% of PsA patients had an i.a. injection	40% currently uses a DMARD and 1,8% uses a biological
Rice 2018	retrospective cohort	PsA	3932	2006 - 2015	-	Glucocorticoid use (NOS)	PO	Inpatient/ outpatient clinics; general physician	All of the included PsA patients used SGC.	26,9% used SGC >60 days, the remainder used SGC intermittently
Sinnathurai 2018	prospective cohort	PsA	490	2003 - 2015	59	Prednisone, prednisolone	PO	-	25,7% of PsA patients use SGC	61% use MTX; 18,6% use leflunomide; 15,3% use SSZ; 4,1% use HCQ; 64,1% use a biological

Table 1. General prevalence of SGC prescriptions in the PsA/psoriasis population. SGC: systemic glucocorticoid; PsA: psoriatic arthritis; NOS: not otherwise specified; PO: oral s.c.: subcutaneous; i.a.: intra-articular; MTX: methotrexate; DMARD: disease modifying anti-rheumatic drug; SSZ: sulfasalazine; HCQ: hydroxychloroquine; NSAID: Non-Steroidal Anti-Inflammatory Drug

Study			Baseline characteristics			Treatment and assessment of psoriatic flare or morphological shift description					
1st author (year)	Publication type	Aim of study	Dx	*n*	Age (Y, range)	SGC [dose, RoA]	Treatment duration	Co-medication	Reason for initiation of SGC	Skin flare or morphological shift during or after tapering of SGC	Percentage of flares
Carubbi 2016	RCT	Comparing efficacy and safety between SGC and TNF IA treatment	PsA	41	42,95 (31-68)	triamcinolone [40mg/month, IA], SGC (NOS)	3 months	stable dose of anti-TNF in combination with one or more DMARDS	Refractory arthritis	no adverse events were reported during the 52-wk follow-up	0%
Gupta 2007	open label-RCT	Comparing efficacy and safety of MTX + betamethasone or MTX only	Psoriasis	40	39,63 (14-63)	betamethasone [3mg/wk, PO]	Until complete clearance of lesions: 27.13 days (24.74–29.52)	15mg MTX PO	Psoriasis	No flares after discontinuation (91.78 days in remission)	0%

Table 2. Papers directly comparing PsA and psoriasis patients using or not using SGC in RCTs. Dx: diagnosis; Y: year; RoA: route of administration; RCT: randomized controlled trial; SGC: systemic glucocorticoid; IA: intra-articular; PsA: psoriatic arthritis; NOS: not otherwise specified; DMARD: disease modifying anti-rheumatic drug; MTX: methotrexate; PO; oral.

Study			Baseline characteristics			Treatment and assessment of psoriatic flare or morphological shift description					
1st author (year)	**Publication type**	**Aim of study**	**Dx**	***n***	**Age (Y, range)**	**SGC [dose, RoA]**	**Treat-ment duration**	**Co-medication**	**Reason for initiation of SGC**	**Skin flare or morphological shift during or after tapering of SGC**	**Occurrence of flares**
Babino 2016	retrospective cohort	Efficacy and safety of combination therapy with ETN	PsA / Psoriasis	37	59,43 (42 - 83)	Prednisone [25mg/d, PO]	7 weeks (4-10 weeks)	ETN 25mg 2/wk or 50mg 1/wk, MTX	cutaneous and/or articular inefficacy of ETN monotherapy	Safety profile was assessed: no skin flares	0%
Gregoire 2021	retrospective cohort	Assess amount of any type of psoriasis flare associated with SGC use	Psoriasis	516	61,3 (SD 17,1)	Dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisone [-, PO, injectable]	18,2 weeks (SD 64,2)	MTX (30), cyclosporine (12), adalimumab (7), ETN (5), infliximab (3), ustekinumab (2)	-	16 flares: 15 mild plaque worsening, 1 erythrodermic.	1.42% (95% CI, 0.72%-2.44%)
Ganeva 2007	prospective cohort	Assess adverse drug reactions of SGC	Psoriasis	1041 (6 psoriasis)	48,9 (±18,9)	Methylprednisolone [-, PO], SGC NOS	weeks - 4 years	NSAID; ACEi	most frequently for autoimmune bullous dermatoses	none of the psoriatic exacerbation which led to hospitalization could be attributed to SGC	0%

Study			Baseline characteristics			Treatment and assessment of psoriatic flare or morphological shift description					
1st author (year)	Publication type	Aim of study	Dx	*n*	Age (Y, range)	SGC [dose, RoA]	Treat-ment duration	Co-medication	Reason for initiation of SGC	Skin flare or morphological shift during or after tapering of SGC	Occurrence of flares
Brody 1966	single-arm trial	First study assessing efficacy and safety of triamcinolone treatment	Psoriasis	23	39,8	triamcinolone [13mg/ 2-3 weeks, IM]	minimal 4 injections - 50 injec-tions over 3 years	norethynodrel, chlordiazepoxide	Psoriasis	no flares or other adverse events were reported	0%
Cohen 1959	single-arm trial	Comparing efficacy and safety of different types of SGC IL and PO	Psoriasis	25	44,92 (21-71)	triamcinolone [16mg/d]; methylprednisolone [20mg/d]; prednisolone [30mg/d]; hydrocortisone [PO, IL]	4 months (1-7)	none	Psoriasis	No adverse events; up to 200 days in remission	0%
Haroon 2018	single-arm trial	Comparing efficacy of IM triamcinolone on inflammatory back pain	Ax-PsA	40 (15 PsA/15 AS/10 control)	37,5	triamcinolone [80mg once, IA]	once	60% of patients used DMARDs	active PsA	no flares during follow-up period	0%

Study			Baseline characteristics			Treatment and assessment of psoriatic flare or morphological shift description					
1st author (year)	**Publication type**	**Aim of study**	**Dx**	***n***	**Age (Y, range)**	**SGC [dose, RoA]**	**Treat-ment duration**	**Co-medication**	**Reason for initiation of SGC**	**Skin flare or morphological shift during or after tapering of SGC**	**Occurrence of flares**
Coates 2016	RCT	Sub-analyses of TICOPA trial assessing the occurrence of SGC induced flares	PsA	206	45,5 (36-55)	methylprednisolone 40mg [5-120mg, IA]; 120mg [40-160mg, IM]	single/ multiple adminis-tration	126 patients on DMARDs (90 MTX only, 30 combination)	Not specifically mentioned / inefficacy of current treatment	No adverse events reported, no significant change in PASI: patients did not report experiencing a flare. 10 patients had a PASI increase ≥2	0%
Saviola 2007	open label - RCT	Comparing efficacy and safety of deflazacort / methylprednisolone	PsA / RA	21 (7 PsA)	60 (33-73)	methylprednisolone [4mg/d]; deflazacort [7,5mg/d] [PO]	1 year	MTX, cyclosporin	active PsA / RA	no flares during follow-up period	0%

Table 3. Papers describing PsA and psoriasis patients all being treated with SGC and the occurrence of flares in this population. Dx: diagnosis; Y: year; RoA: route of administration; SGC: systemic glucocorticoid; ETN: etanercept; PsA: psoriatic arthritis; PO; oral; MTX: methotrexate; SD: standard deviation; CI: confidence interval; NOS: not otherwise specified; NSAID: non-steroidal anti-inflammatory drugs; ACEi: ACE-inhibitor; IM: intra-muscular; IL: intra-lesional; Ax-PsA: axial psoriatic arthritis; AS: ankylosing spondylitis; IA: intra-articular; RCT: randomized controlled trial; DMARD: disease modifying anti-rheumatic drug; PASI: Psoriasis Area and Severity Index

ARHQ Methodology Checklist	Al-Dabagh et al. 2014	Armstrong et al. 2017	Augustin et al. 2011	Babino et al. 2016	Brody, 1966	Carubbi et al. 2016	Coates, 2016	Cohen, 1959	Dubreuil et al. 2014	Eun et al. 2017	Ganeva et al. 2007	Grassi, 1998	Gregoire, 2021	Gupta R, 2007	Haroon et al. 2018	Kavanaugh et al. 2018	Lee et al. 2016	Madland et al. 2005	Rice et al. 2018	Saviola et al. 2007	Sinnathurai et al. 2018
1. Define source of information (survey, record review)	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	⊕	⊕	⊕	⊕	-	⊕	⊕	-	⊕	⊕	⊕	-	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
3. Indicate time period used for identifying patients	⊕	-	⊕	⊕	-	-	⊕	-	⊕	⊕	⊕	⊕	⊕	-	-	⊕	⊕	⊕	⊕	-	⊕
4. Indicate whether or not subjects were consecutive if not population-based	⊕	-	⊕	⊕	-	⊕	⊕	-	⊕	⊕	⊕	-	⊕	-	⊕	⊕	⊕	⊕	⊕	-	⊕
5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	NA	NA	NA	-	-	⊕	-	⊕	NA	NA	-	NA	-	-	-	NA	NA	NA	NA	-	NA
6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7. Explain any patient exclusions from analysis	⊕	-	⊕	⊕	-	⊕	-	-	⊕	⊕	⊕	-	⊕	⊕	-	-	⊕	-	⊕	⊕	-
8. Describe how confounding was assessed and/or controlled	⊕	-	⊕	⊕	-	⊕	⊕	-	⊕	⊕	⊕	-	⊕	⊕	⊕	-	⊕	-	⊕	⊕	-
9. If applicable, explain how missing data were handled in the analysis	NA	NA	NA	-	-	⊕	-	-	⊕	NA	-	-	-	-	⊕	-	-	-	NA	-	-
10. Summarize patient response rates and completeness of data collection	⊕	⊕	⊕	⊕	⊕	⊕	⊕	-	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	NA	NA	NA	NA	-	⊕	⊕	-	⊕	NA	-	NA	-	-	-	NA	NA	NA	NA	⊕	NA
Total score	7	3	7	7	2	9	7	2	9	7	7	3	7	4	6	5	7	5	6	5	5

Table 4. Risk of bias. Quality of included articles was assessed using The Agency for Healthcare Research and Quality (AHRQ) methodology checklist for cross-sectional and prevalence studies. Article quality was assessed as follows: low quality = 0-3; moderate quality = 4-7; high quality = 8-11 Yes =⊕; No = -; Not applicable/Not specified = NA

(1.1) Detailed description of PsA/psoriasis populations treated with SGC

Al-Dabagh et. al reported that SGC were prescribed during 650,000 (3,1%) of the 21,020,000 total psoriasis visits, which was comparable to methotrexate (MTX), prescribed at 3,5% of all visits. When psoriasis was the sole diagnosis and no other co-morbidities were present, 50% of all these prescriptions were SGC monotherapy. No other systemic treatment was added for the prevention of skin flares. 93% of the SGC prescriptions were carried out by dermatologists.(15) In Germany SGC were the most frequently prescribed systemic drug in psoriasis patients (2,774 of 34,728 patients, 7,98%), followed by MTX (853 of 34,728 patients, 2,46%). When correcting for potential comorbidities, such as PsA or other steroid requiring comorbidities, 64% of all these prescriptions were made for the diagnosis psoriasis only. (14) In psoriasis patients naïve for either systemic drugs or biologicals, prednisone was prescribed for 75% of 254.000 patients, predominantly by primary care physicians as first-line of treatment. This frequency gradually decreases in later lines of therapy, where DMARD or biological therapy become more prominent.(16) In a Korean study, 612,248 of 2,321,194 psoriasis patients (26,4%) were treated with SGC in outpatient clinics. Patients that visited their primary care physician were more likely to be treated with SGC then patients that visited tertiary hospitals (OR 11.5, 95% CI [11.26-11.72]).(19)

A similar high frequency of SGC prescriptions is seen among PsA patients. In an international longitudinal registry 566 of 1,719 PsA patients (33%) report using SGC at time of enrollment.(20) Twenty-five percent (126 of 490) of PsA patients reported using SGC in a voluntary Australian registry.(21) In a cohort of 3,932 PsA patients, 26.9% received continuous treatment with SGC, while 73,1% received intermittent treatment.(22) In Norway the proportion of patients treated with oral SGC was lower (49 of 634 PsA patients, 7.9%), while the administration of intra-articular steroid injections remained high (247 of 634 PsA patients, 40%).(23)

(2) The risk of a SGC-induced flare: two randomized controlled trials (RCT) comparing patients using SGC with not-using SGC

Studies in which randomization occurs have a higher level of evidence. Only two RCTs were found directly comparing PsA/psoriasis patients using and not-using SGC. Both studies show no increased risk for psoriatic flaring associated with SGC exposure. One study assessed the safety and efficacy of intra-articular injections with triamcinolone 40mg or a TNFα-inhibitor in 41 PsA patients with mono-arthritis. Patients received a triamcinolone injection once a month for 3 consecutive months and were followed for 52-weeks to asses joint flaring. All patients used concomitant DMARD or biological therapy and 63,4% patients used oral SGC at the time of intervention. No flares were reported in both groups during and after SGC treatment.(24) In order to achieve faster clearance of

psoriatic lesions and prolong the remission period Gupta et al. conducted an open-label RCT including 40 patients where one arm received weekly doses of 15mg MTX and 3mg betamethasone orally and the other MTX only until complete clearance of psoriatic lesions. After clearance of the lesions treatment was ceased and remission was monitored every 4 weeks until lesions started to reappear or new lesions formed, however no flares were reported. Combination therapy was significantly better for both outcomes.(8) **Table 2** shows all details on both RCTs.

(3) Observational and interventional studies describing flare occurrence in SGC exposed PsA or psoriasis patients.

Eight observational and interventional studies were be used to explore the occurrence of SGC-related flares in PsA/psoriasis patients. **Table 3** shows relevant details of the observational and interventional studies clustered by publication type. Two papers focused primarily on the research question: are patients exposed to SGC at greater risk of developing psoriatic flares. One recently published retrospective cohort included 516 patients using SGC with a median dose of 40mg for a mean duration of 18,2 weeks. They identified a total of 16 psoriatic flares (1,42%) during or within 3 months of SGC exposure. 15 patients experienced mild worsening of plaque psoriasis and one patient developed erythrodermic psoriasis. 6 of these patients concomitantly took other medications known to induce psoriatic flares (β-blockers, hydroxychloroquine and quinacrine). The overall conclusion is that the frequency of flaring due to SGC exposure is low.(25) The other study involved a retrospective sub-analysis of a RCT in which 206 PsA patients were allowed to receive intra-articular/muscular steroids as part of a tight control treatment regimen. A total of 161 episodes of SGC use in 101 patients were documented: 50 intra-articular injections with a median dose of 40mg methylprednisolone and 111 intramuscular injections with a median dose of 120mg. A flare, defined as an increase in PASI score of ≥2, was seen in 10 patients. Overall, there was no significant PASI increase and none of these patients self-reported experiencing an exacerbation of their skin during follow-up visits.(26)

One retrospective cohort assessed the efficacy and safety of etanercept combination therapy: 4 out of 37 patients on etanercept were concomitantly treated with prednisone 25mg/day for a mean duration of 7 weeks due to cutaneous inefficacy and/or articular inefficacy. PASI scores were monitored and no flares were reported.(7) In a prospective study aimed at identifying adverse drug reactions that led to hospitalization, none of the psoriasis vulgaris exacerbations could be attributed to SGC use.(27) In two single-arm trials 23 and 25 psoriasis patients respectively, received subcutaneous triamcinolone injections every 2-3 weeks until remission occurred or oral SGC for an average of 4 months to determine the efficacy and safety. The longest treatment duration was ±3 years. None of

the participants experienced skin flaring during or after treatment.(28, 29) In an open label controlled trial, 15 PsA patients with inflammatory axial involvement received a single dose of intra-muscular triamcinolone 80mg to study the improvement of inflammatory back pain. 60% of patients concomitantly used DMARDs and no side effects were reported after a follow-up of 4 weeks.(30) In an open-label RCT studying the clinical efficacy and effects on bone metabolism of deflazacort or methylprednisolone, 7 PsA patients were enrolled. Patients were treated for six months with either deflazacort or methylprednisolone daily, after which cross-over took place to the other treatment arm. There were no flares reported during the follow-up of the study.(31)

The occurrence of psoriatic flares as reported over all studies ranged from 0 to 1,42%. This suggests that the risk of developing a flare after or during SGC exposure appears low.

Critical review of Baker's case series on SGC induced GPP

Guidelines discouraging SGC use in PsA/psoriasis mainly refer to a case series published by Baker in 1968 in which 104 patients that presented with generalized pustular psoriasis (GPP) were assessed.(13) Cases were collected from records of the authors hospital(n=24) and via questionnaires filled in by 43 dermatologists(n=80) posing high classification bias as no standardized dermatological diagnostic criteria for GPP existed. Furthermore, the correctness of the completed questionnaires depended on the physician's memory regarding his own case notes. In 19 of 104 patients that developed GPP, the suspected trigger was SGC-use, as the exacerbation developed within a few days to weeks after tapering or withdrawal of the SGC. Another 10 patients were treated with SGC because of already rapidly deteriorating psoriasis which eventually progressed to GPP. These cases might have developed into pustular psoriasis spontaneously, independent of SGC use. Six other patients had not received SGC before developing pustules, indicating that SGC might not have been the cause of flare. Other possible causes for the development of GPP described were pregnancy, hypocalcemia, infection, topical use of potent corticosteroids or idiopathic.(13) In general, this paper poses a high risk of bias and the recommendation originated from this paper is based on poor evidence and should not have been reiterated over the years without critically appraising the origin.

Risk of bias

Two studies were of high quality, most were moderate and four showed low quality. Typically, low quality studies did not systematically report on their study protocol, nor did they elaborate on their attempt to control confounding. Moderate to high quality papers clearly provided in- and exclusion criteria, source of data, elaborate on confounding and clearly presented their primary outcomes. One high quality study applied blinding.

Description of missing data was lacking in most articles. Risk of bias is summarized in **Table 4**.

DISCUSSION

In this systematic review we reappraised the old paradigm that the use of SGC in PsA/psoriasis patients increase the risk or occurrence of developing psoriatic flares. We found that SGCs are frequently used for the treatment of PsA/psoriasis in disregard of current treatment guidelines. Importantly, these data mostly arise from relatively recent papers published between 2001 and 2015. By the extent of the high usage of SGC one would assume that the reported prevalence of SGC-related psoriatic flares would be much higher. Clinically, this is not the case. Evidence advocating against the use of SGC for psoriasis and PsA patients is mostly derived from case reports or case series.(32-47) In general, these publication types have a high risk of bias and are of low-quality evidence. Therefore we feel that the original recommendation against the use of SGC in this population is based on insufficient evidence.

After the publication of the case series from Baker(13) the negative opinion regarding the use of SGC in PsA/psoriasis patients was uncritically accepted. It is however important to mention that this paper has some important methodological limitations which influence the interpretation of the study results. The use of SGC in psoriasis, and to some extent in PsA, is now traditionally discouraged and seen as malpractice. Several treatment guidelines for psoriasis and PsA directly refer to Baker or independent case reports/series as substantiation not to use SGC.(51-54) Interestingly, the EULAR PsA treatment guidelines reiterate the recommendation that the use of SGC might lead to psoriatic flaring, but mention that this recommendation is not substantiated by any evidence.(12) The GRAPPA PsA treatment guidelines indiscriminately highlight the risk of flaring without providing a direct source or critically reviewing this recommendation.(9, 10) It seems that over the years, the recommendation to avoid SGC for PsA/psoriasis patients became generally accepted and no effort has been made to critically reappraise this.

Only two papers report on flares associated with SGC use. In the paper of Coates et al.(26), where a consensus definition of a psoriasis flare is lacking, a flare was defined as an increase in PASI ≥ 2. Even though the PASI has a reliable inter-observer reproducibility (48, 49) it is not accurate for assessing mild psoriasis and thus PASI might not be the best tool to monitor flares.(50) Interestingly, all 10 patients with a PASI increase of ≥ 2 did not report experiencing a flare during follow-up visits. There seems to be a discordance between clinically defining a flare and the patients' own perception. The other retrospective cohort

specifically identified psoriasis patients exposed to SGC and found that 1,42% experienced a mild worsening of their plaque psoriasis while one patient developed erythrodermic psoriasis. An explanation for the low incidence of psoriatic flares could be that clinicians proactively take precautions to prevent flaring, for instance by initiating combination therapy with topical or systemic DMARD therapy and tapering SGC very gradually instead of acute withdrawal.

SGC are essential drugs that can rapidly reduce local or systemic inflammation in inflammatory diseases.(55) SGC, whether given intramuscular, intra-articular or oral, can be very beneficiary in the early initiation phase of DMARD therapy in PsA or psoriasis to improve quality of life and physical disability. Furthermore it has an anti-inflammatory effect by reducing pain, swelling and stiffness and induces immunosuppression that can eventually prevent permanent joint damage.(43, 56) The combination of MTX and adjunctive SGC has shown to enhance faster psoriatic skin lesion clearance and improve drug free remission period.(8) Drug survival is improved in etanercept treated psoriasis and PsA patients that experience a loss of efficacy when temporary co-treated with a SGC. (7) Besides these benefits, it is generally known that SGC also have the potential to cause adverse events such as osteoporosis and -necrosis, infections, diabetes, cardiovascular disease and suppression of the hypothalamic-pituitary-adrenal axis, especially when used for long-term treatment. However when used thoughtfully, these adverse events are partially avoidable.(57) As SGC pose multiple substantial beneficial effects it would be undesirable to exclude them from the therapeutic armamentarium for PsA and psoriasis patients.

A limitation of this review is that the SGC prescription prevalence data is derived from insurance databases and that PsA/psoriasis patients were selected based on International Classification of Diseases (ICD) codes. One cannot be certain that the SGC prescribed at that time were solely meant for the treatment of PsA/psoriasis and whether patients adhered to treatment. Even by filtering out patients with co-morbid ICD-codes that could explain SGC prescription (e.g. various rheumatologic conditions, urticaria, Crohn's disease, COPD and asthma). There is no certainty for what indication SGC were really prescribed. Since the use of SGC is traditionally discouraged for PsA/psoriasis, well conducted RCTs are scarce, providing us with heterogeneous data in terms of SGC use, making it difficult to construct an evidence based treatment recommendation. Lastly, even though the search has been performed with a medical librarian we cannot exclude the possibility that relevant articles have been missed.

This is the first systematic review questioning the old paradigm from a rheumatological and dermatological perspective. Prospective studies are needed to assess the real risk of flaring and to re-establish treatment guidelines discouraging SGC use. Considering how frequently SGC are being prescribed while the occurrence of psoriatic flares appears low and is only related with mild skin flaring, we feel that SGC should not be withheld for the treatment of PsA/psoriasis patients when necessary. In patients with a clear indication, e.g. in need of rapid anti-inflammatory therapy or bridging of therapies, SGC should be considered in view of a low risk of skin flaring. It remains of importance to weigh risks for short- and long-term SGC-related side effects in clinical decision making and possibly treat patients in combination with a DMARD, biological or topical treatment.

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Supplementary Data

PICO search strategy

Pubmed

((“Psoriasis”[Mesh] OR psoriasis[Title/Abstract] OR psoriases[Title/Abstract] OR Arthritic Psoriasis[Title/Abstract] OR psoriatic Arthritis[Title/Abstract] OR Psoriasis Arthropathica[Title/Abstract] OR Psoriatic Arthropath*[Title/Abstract]) AND (“Prednisone”[Mesh] OR “Glucocorticoids”[Mesh] OR steroid*[Title/Abstract] OR “Glucocorticoids” [Pharmacological Action] OR prednisone[Title/Abstract] OR glucocorticoid*[Title/Abstract] OR glucocorticosteroid*[Title/Abstract] OR corticosteroid*[Title/Abstract])) NOT (topical[title/Abstract] OR “Administration, Topical”[Mesh])

Embase

(‘psoriasis’/exp OR ‘psoriasis’ OR ‘psoriasis’:ti,ab,kw OR ‘arthritic psoriasis’:ti,ab,kw OR ‘psoriatic arthritis’:ti,ab,kw OR ‘psoriasis arthropathica’:ti,ab,kw OR ‘psoriatic arthropath*’:ti,ab,kw) AND (‘prednisone’/exp OR ‘prednisone’ OR ‘glucocorticoids’/exp OR ‘glucocorticoids’ OR ‘steroid*’:ti,ab,kw OR ‘prednisone’:ti,ab,kw OR ‘glucocorticoid*’:ti,ab,kw OR ‘glucocorticosteroid*’:ti,ab,kw OR ‘corticosteroid*’:ti,ab,kw) NOT (‘topical’:ti,ab,kw OR ‘administration, topical’/exp OR ‘administration, topical’)

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Treatment response to methotrexate in atopic dermatitis and psoriasis / psoriatic arthritis patients: clinical characteristics and exploration of serum proteins in responders and non-responders

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ABSTRACT

Objective To explore factors that contribute to treatment response of methotrexate (MTX) in atopic dermatitis (AD) and psoriatic arthritis/psoriasis (PsA cohort) patients using clinical characteristics and to explore serum proteins of MTX responders and non-responders.

Methods We retrospectively included 78 AD patients treated with MTX in daily practice. Patients were classified as MTX treatment responders based on the Investigators' Global Assessment. In a subgroup of 51 patients, 129 proteins were measured in pre-treatment serum samples using Luminex-based multiplex immunoassays. A proof-of-concept prediction model was constructed of the top four differentially expressed proteins. A PsA cohort (n=30) was used to see if findings could be generalized.

Results Forty-six out of 78 AD patients (59%) were classified as clinical MTX responder. Subcutaneous administration of MTX had a significant positive effect on treatment response after 6 months treatment. Significantly more non-responders (50%) were treated with oral corticosteroids at the moment of starting MTX treatment compared to the responders (20%) (p=0.005). In the Luminex subgroup, 28 patients (55%) were classified as responder. CCL5, MMP1, P-selectin and DKK1 were the top four differentially expressed proteins. CCL5 and P-selectin were significantly higher in MTX responders while MMP1 and DKK1 were significantly higher in MTX non-responders. Of these four serum proteins a proof-of-concept prediction model was created showing a sensitivity of 79%, and specificity of 83%, a positive predictive value (PPV) of 85% and negative predictive value (NPV) of 76%. In the PsA cohort the predictive model could not be generalized.

Conclusion Subcutaneous administration of MTX had a positive effect on the treatment response after 6 months treatment. CCL5, MMP1, P-selectin and DKK1 were differentially expressed among responders and non-responders. The prediction model was able to correctly classify 80,4% of AD patients, but was not generalizable to PsA patients and should therefore be prospectively validated in an AD cohort.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases worldwide. The pathogenesis of AD is multifactorial and is a complex interplay of immunologic, genetic and environmental factors.[1] The majority of AD patients can be controlled with topical corticosteroids, however a significant group of patients with refractory disease that respond insufficiently to non-systemic treatment remain.[2]

Currently, the field of AD treatment is expanding with new biologics and small molecule inhibitors being approved for the treatment of moderate-to-severe AD and many more promising therapeutics are in the pipeline.[3-8] However, biologics are still rather expensive, requiring strict reimbursement criteria. Additionally, possible long-term side effects of these therapies are still unknown. Studies in patients with inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA) have shown that, despite the availability of biologicals, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are still first-line of treatment.[9-11] Therefore it is very likely that even after the introduction of these new therapies, classic immunosuppressive drugs will still be prescribed first.

Interdisciplinary consensus-based treatment guidelines state that methotrexate (MTX) can be efficient for the treatment of AD and may be used off-label.[12] In fact, in the Netherlands, MTX is widely used in patients with severe AD and was the most commonly prescribed systemic drug for the treatment of AD between January 2012 and January 2017.[13,14] The efficacy of off-label MTX use in the treatment of AD is proven in clinical studies in terms of significant improvement in disease severity and quality of life.[14-17] Unfortunately, in daily practice MTX is discontinued in approximately half of the patients due to side-effects and/or ineffectiveness.[18]

There is a clinical unmet need in the treatment of AD to accurately predict the response to MTX therapy. Currently, a considerable number of patients are unnecessarily exposed to potential adverse effects, while others experience insufficient response to MTX, resulting in treatment delays. Therefore, the objective of this study was to identify baseline clinical predictors that can effectively distinguish responders from non-responders to MTX treatment in AD patients. Additionally, we explored the presence of differentially expressed serum proteins at baseline between MTX responders and non-responders. A proof-of-concept prediction model was constructed of the differentially expressed proteins to guide future research aimed at implementing a more personalized approach for the selection of suitable treatment options in patients with AD.

MATERIALS AND METHODS

Patients and Selection

All AD patients treated with MTX at the National Expertise Center for Atopic Dermatitis, University Medical Center Utrecht between January 2009 and January 2020 were retrospectively screened for inclusion. Patients who were treated with MTX for <6 months or patients with unclear treatment response were excluded. Patients were classified as responders to MTX treatment if they achieved an Investigators' Global Assessment (IGA) of 0-2 without the use of oral corticosteroids after 6 months of treatment. Patients with an IGA of 3-5 or still on concomitant treatment with oral corticosteroids were defined as non-responders to MTX treatment. The following data were retrospectively retrieved from the electronic patient database (EPD): sex, age, Eczema Area and Severity Index (EASI) score and IGA at moment of starting MTX, history of asthma, allergic rhinitis, allergic conjunctivitis and food allergy, therapeutic history, maintenance dose of MTX, route of MTX administration (oral or subcutaneous), hospitalization for AD at start of MTX treatment and thymus and activation regulated chemokine (TARC) levels at start of MTX treatment.

For the serum protein analysis, patients with available serum samples before starting MTX treatment were included. Serum samples were routinely collected before start of treatment and stored at -80 degrees Celsius in a biobank until analysis. To ensure a homogeneously treated subgroup, patients who had received oral immunosuppressive drugs or UV-light therapy within three months, or systemic corticosteroids within two weeks before the sampling, were excluded from the sub-analysis.

The protocol used in this study was approved by the Institutional Review Board of the University Medical Center Utrecht, adhering to the Declaration of Helsinki Principles.

Serum Protein Analysis

A panel of 143 serum proteins (all markers currently available in our center) were measured using Luminex technology at the Multiplex Core Facility of the Center for Translational Immunology (UMC Utrecht, The Netherlands), using an in-house validated panel of analytes, listed in **Table S1**. Uniquely color-coded magnetic beads (MagPlex Microsperes, Luminex, Austin, Texas) were conjugated to antibodies specific for the reported analytes and incubated with 50 µL of standard dilutions per sample for 1 hour (continuous shaking in the dark). Samples were diluted in High Performance Elisa buffer (HPE; Sanquin, The Netherlands). Pre-treatment of samples included filtration and incubation with HeteroBlock to prevent interference by binding of heterophilic antibodies. Plates were washed (Bio-Plex Pro II Wash Station; Bio-Rad, Hercules, California, USA) and a corresponding cocktail of

biotinylated detection antibodies was added for 1 hour. Repeated washings were followed by a 10 minute streptavidin-phycoerythrin (PE) incubation. Fluorescence intensity of PE was measured using a Flexmap 3D system (Luminex) and analyzed by using BioPlex Manager software version 6.1; (Bio-Rad) using 5-parameter curve fitting. Serum proteins with signals above or below the assay detection limit in >60% of the samples were excluded for further analyses, resulting in 129 unique serum proteins selected for further analysis. The top 4 differentially expressed serum proteins were plotted comparing MTX responders versus non-responders. Graphs were constructed using GraphPad Prism version 9.3.0 for Windows (GraphPad Software, San Diego, California USA).

Statistical Analysis

Data were analyzed using IBM SPSS (Statistical Package for the Social Science) software for Windows version 25.0 (SPSS Inc., Chicago, IL, USA). Differences in clinical characteristics between the two patient groups were compared using the Wilcoxon rank sum test for continuous variables, and with the chi-square test for categorical variables. P-values lower than 0.05 were considered statistically significant.

Serum samples that were above or below the assay limits of detection were given values equivalent to the lower limit divided by two or the upper limit multiplied by two. Concentration data were normalized by a log-transformation. Differences between protein levels were analyzed using the Mann-Whitney U tests. P-values lower than 0.05 were considered statistically significant.

Proof-of-Concept Protein Prediction Model

A previously developed method by Mamtani et al[19] was used to construct a prognostic model to predict treatment response of MTX. Briefly, this method consists of three steps: 1. estimating the area under the receiver characteristic curve (AUC) for each individual protein and rank these proteins individually using their Performance Index; 2. using stepwise multiple regression analysis to select the top ranked n-1 proteins; 3. combining the top-ranked proteins using a linear discriminant function analysis.

Posterior probabilities from the linear discriminant function analysis were used to define a predicted classification (group 1: 'non-responder' or group 2: 'responder') for each individual. If the posterior probability for a given patient was higher for group 1 than for group 2 the predicted classification was defined as group 1, and vice versa. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the final prediction model were calculated based on predicted and observed classifications.

Psoriatic Arthritis and Psoriasis Cohort

In order to investigate the validity/generalizability of the prognostic model, a cohort consisting of patients with psoriasis and psoriatic arthritis (PsA cohort), who received treatment with MTX, was employed since a suitable validation cohort for AD was not available. This approach is based on the observed immunological similarities in the development of AD, psoriasis, and PsA, which provide a rationale for applying a prediction model in AD to PsA/psoriasis patients.[20] 25 PsA and 5 psoriasis MTX treated patients were retrospectively selected from a study performed at the Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht (UMCU). Patients had to be naive for MTX prior to blood serum withdrawal and no concomitant biologicals were allowed. Sex, age, baseline dosage and route of administration of MTX, tender and swollen joint count scores, Psoriasis Area and Severity Index (PASI), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were collected. The distinction between responders and non-responders was based on a 6-month screening period. Patients who discontinued MTX due to inefficacy or side effects were classified as non-responders, while those who continued MTX treatment after 6 months were classified as responders. As follow-up PASI and joint count scores were not consistently documented in the Electronic Patient Database (EPD), validated composite scores such as Minimal Disease Activity (MDA) or The American College of Rheumatology (ACR) score could not be utilized to classify PsA/psoriasis patients as responders or non-responders. The top differentially expressed serum proteins identified in the PsA cohort were determined, and the analyses were carried out using the same model as described earlier.

RESULTS

Atopic Dermatitis Patients

We retrospectively included 78 AD patients treated with MTX (mean (SD) age 53.1 years (15.1); 64.1% male). Mean (SD) baseline EASI score before start of MTX treatment was 17.2 (11.5) and median (IQR) baseline IGA 3.0 (1.0). The majority of patients have previously been treated with ≥1 oral immunosuppressive drugs before starting MTX treatment (n=62 (79.5%)). The median MTX (IQR) maintenance dose was 15.0 (0.6) mg/week and 14.1% (n=11) were treated with subcutaneous injections. At the start of MTX treatment, 32.1% (n=25) were concomitantly treated with oral corticosteroids, 24.4% of the patients (n=19) were hospitalized for AD at the moment of starting MTX treatment (**Table 1**).

Clinical Responders versus Non-Responders

After a treatment period of 6 months, 59.0% (n=46) of the patients were defined as responders (IGA 0-2, without the use of oral corticosteroids after 6 months of treatment)

and 41.0% (n=32) of the patients were defined as non-responders (IGA 3-5 or still on concomitant treatment with oral corticosteroids). Significantly more patients were treated with subcutaneous injections (21.7%, n=10) among the MTX responders compared to the MTX non-responders (3.1%, n=1) (p=0.023). The mean (SD) maintenance MTX dose (mg/week) was significantly higher in the MTX-non-responders (16.2 (2.5)) compared to the MTX-responders (15.0 (0.0)) (p=0.000). Among the MTX non-responders, significantly more patients (50%, n=16) were treated with oral corticosteroids at the moment of starting MTX treatment compared to the MTX responders (19.6%, n=9). Other clinical characteristics did not significantly differ between the two groups (**Table 1**).

Protein Analysis and Prognostic Model

In total, 51 patients consisting of 28 (54.9%) clinical MTX-responders and 23 (45.1%) MTX non-responders were included in the protein sub-analysis. Serum was collected before the start of MTX treatment and 129 proteins were measured using Luminex-based multiplex immunoassays. Stepwise multiple regression analysis resulted in the selection of the top four differentially expressed serum proteins, including C-C motif chemokine ligand 5 (CCL5), P-selectin, matrix metalloproteinase-1 (MMP1) and Dickkopf-related protein 1 (DKK1). Serum levels of CCL5 and P-selectin were significantly higher in the MTX responder group compared to the MTX non-responders (**Figure 1**). Serum levels of DKK1 and MMP1 were significantly higher in the MTX non-responder group compared to the MTX responders.

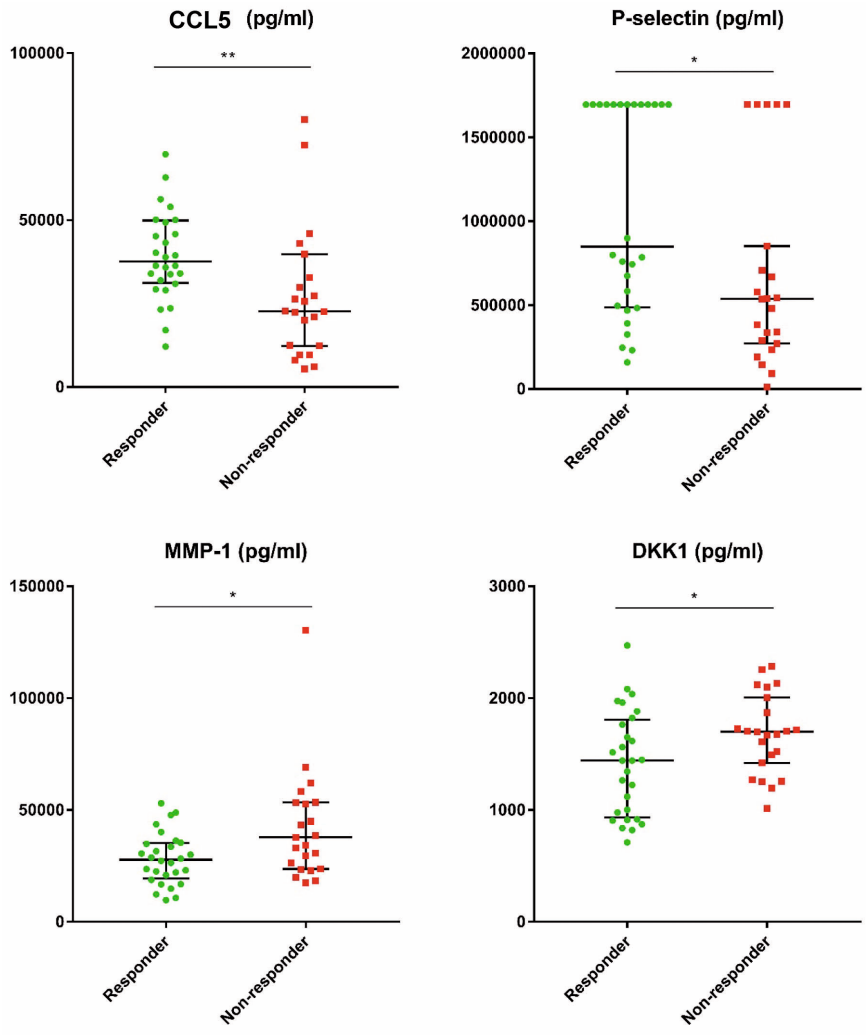

Figure 1. Differences in serum protein levels between MTX responders and MTX non-responders in the AD cohort were measured using Luminex technology. Different expression levels were compared using Mann-Whitney U tests. Horizontal bars represent median protein levels with interquartile range. *P < .05; ** P < .01.

Table 1. Clinical characteristics of the total group of MTX treated atopic dermatitis patients

	Total group (n=78)	Responders (n=46)	Non-responders (n=32)	p-value
Age at start MTX, mean (SD)	53.1 (15.1)	53.5 (14.6)	52.5 (16.0)	0.788
Men, n(%)	50 (64.1)	27 (58.7)	23 (50)	0.233
Atopic/allergic diseases at start MTX, n(%)				
Allergic rhinitis	45 (58.4)	28 (60.9)	17 (54.8)	
missing	1 (1.3)	0 (0)	1 (3.1)	0.598
Asthma	38 (49.4)	21 (45.7)	17 (54.8)	
missing	1 (1.3)	0 (0)	1 (3.1)	0.429
Food allergy	51 (66.2)	15 (32.6)	11 (35.5)	
missing	1 (1.3)	0 (0)	1 (3.1)	0.794
IGA score before treatment with MTX, median (IQR)	3.0 (1.0)	3.0 (1.0)	3.0 (1.0)	0.487
EASI score before treatment with MTX, mean (SD)	17.2 (11.5)	16.3 (11.0)	18.9 (12.5)	
missing	17 (21.8)	7 (15.2)	10 (31.3)	0.400
Therapeutic history				
No history of previous immunosuppressive treatment, n (%)	16 (20.5)	8 (17.4)	8 (25.0)	
History of ≥ 1 oral immunosuppressive treatments, n(%)	62 (79.5)	38 (82.6)	24 (75.0)	0.413
Maintenance dose (mg/week), median (IQR)	15 (0.6)	15 (0.0)	16.2 (2.5)	0.000
Subcutaneous administration, n (%)	11 (14.1)	10 (21.7)	1 (3.1)	0.023
Concomitant use of oral corticosteroids at start MTX, n(%)	25 (32.1)	9 (19.6)	16 (50.0)	0.005
Hospitalization during start MTX treatment n (%)	19 (24.4)	14 (30.4)	5 (15.6)	0.134
Serum TARC before treatment with MTX, median (IQR)	2068.0 (5168.0)	2068 (4249)	2040 (6401)	0.825

Differences in clinical characteristics between the two patient groups were compared using the Wilcoxon rank sum test for continuous variables, and with the chi-square test for categorical variables. P-values lower than 0.05 were considered statistically significant. MTX= methotrexate; IGA= Investigators' Global Assessment; EASI= Eczema Area and Severity Index; TARC=thymus and activation regulated chemokine

These serum proteins were then combined using a linear discriminant function analysis to construct a prognostic model to classify patients into 'MTX responder' or 'MTX non-responder'. CCL5 was the best individual predicting protein with an Area Under the Curve (AUC) value of 0.73. After combining the four proteins, the AUC of the final model was 0.89 (**Figure 2**). The final model had a Wilk's λ of 0.57 (p=<0.001) and predicted the classification correctly in 80.4% (n=41) out of the 51 patients. Four patients were misclassified as MTX-responder, and six patients were misclassified as MTX non-responder, resulting in a sensitivity of 79% and specificity of 83%, a positive predictive value (PPV) of 85% and negative predictive value (NPV) of 76%.

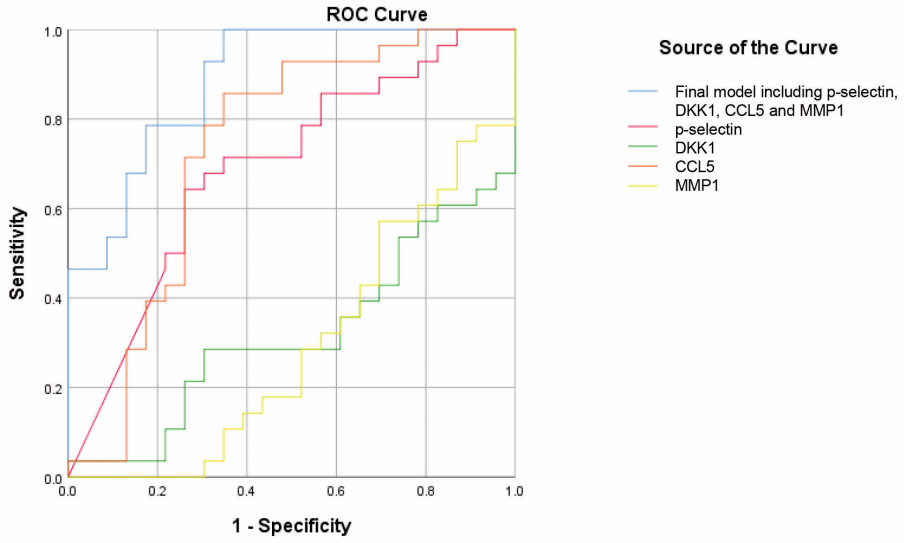

Figure 2: Receiver-operating characteristics (ROC) curve for each individual serum protein and the final model predicting MTX treatment response in the AD cohort. Method used to construct the prognostic model was previously described by Mamtani et al[19].

Psoriatic Arthritis and Psoriasis Cohort

The cohort included 25 PsA and 5 psoriasis patients treated with MTX between October 2014 and August 2018 at the department of the Rheumatology and Clinical Immunology at University Medical Center Utrecht. 63,3% (n=19) were classified as MTX responder and 36,7% (n=11) were classified as MTX non-responder after 6 months of treatment. More responders were treated with subcutaneous administration of MTX (36.8%, n=7) in comparison to non-responders (18.2%, n=2) with a clear trend in favor of subcutaneous administration (p=0.351). The median MTX (IQR) maintenance dose was 15.0 (5.0) mg/week and was comparable between both groups. In the PsA responder group the mean (SD) tender and swollen joint count scores were higher (5.4 (4.0) and 5.4 (4.1) respectively)

in comparison to non-responders (4.0 (5.0) and 3.4 (4.0) respectively), however these differences were not statistically significant (p=0.572, p=0.692). This was also true for inflammatory parameters where the mean (SD) ESR (13.2(11.2) vs 6.7 (7.4)) and CRP (8.1 (8.3) vs 6.0 (9.4)) were not significantly higher in the responder group (**Table 2**). The prognostic protein model including CCL5, P-selectin, MMP1 and DKK1 predicted the classification correctly in only 30.0% (n=9) patients. Nine patients were misclassified as MTX-responder, and 12 patients were misclassified as MTX non-responder, resulting in a sensitivity of 37% and specificity of 18.2%, a PPV of 56% and a NPV of 14%.

Table 2. Clinical characteristics of MTX treated PsA and psoriasis patients characterized by responders and non-responders

	Total (n=30)	Responders (n=19)	Non-responders (n=11)	p-value
Age at start MTX, mean (SD)	43.57 (11.4)	44.05 (10.8)	42.73 (12.8)	0.764
Men, n(%)	21 (70)	14 (73.7)	7 (63.6)	0.563
Psoriatic Arthritis, n(%)	25 (83.3)	17 (89.5)	8 (72.7)	0.236
Psoriasis, n(%)	5 (16.7)	2 (10.5)	3 (27.3)	0.236
PASI score, mean (SD)	5.7 (6.1)	5.8 (4.9)	5.6 (8.4)	
Missing (%)	3 (10)	1 (5.3)	2(18.2)	0.938
Tender Joint count[1], mean (SD)	5.0 (4.3)	5.4 (4.0)	4.0 (5.0)	
Missing (%)	1 (4.0)	-	1 (12.5)	0.474
Swollen Joint count[1], mean (SD)	4.8 (4.1)	5.4 (4.1)	3.4 (4.0)	
Missing (%)	1 (4.0)	-	1 (12.5)	0.303
ESR, mean (SD)	10.6 (10.2)	13.2 (11.2)	6.7 (7.4)	
Missing (%)	5 (16,7)	4 (21.1)	1 (9.1)	0.120
CRP, mean (SD)	7.4 (8.5)	8.1 (8.3)	6.0 (9.4)	
Missing (%)	6 (20)	3 (15.8)	3 (27.3)	0.592
Maintenance dose (mg/week), median (IQR)	15 (5.0)	15 (0.0)	15 (5.0)	0.525
Subcutaneous administration, n (%)	9 (30)	7 (36.8)	2 (18.2)	
Missing (%)	1 (3.3)	-	1 (9.1)	0.351

Differences in clinical characteristics between the two patient groups were compared using the Wilcoxon rank sum test for continuous variables, and with the chi-square test for categorical variables. P-values lower than 0.05 were considered statistically significant. [1] PsA patients only (n=25). MTX=methotrexate; PASI= Psoriasis Area and Severity Index; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein.

DISCUSSION

This is the first study showing that subcutaneous administration of MTX had a significant positive effect on treatment response in AD patients after 6 months of treatment in comparison to oral administration. These results are comparable to studies in psoriasis and RA, in which patients treated with subcutaneous MTX compared to oral MTX show improved long-term disease control, significant improved efficacy, lower visual analog scale (VAS) scores and better bioavailability.[21-24] Recently, a real-life registry study comparing psoriasis patients treated with oral (n=49) or subcutaneous MTX (n=157) showed a higher effectiveness of subcutaneous MTX (higher PASI 50 and PASI< 5 response rates at week 12), faster onset of response and more stable long-term response (higher PASI 90 rate compared with oral MTX at week 52).[25, 26] The data presented indicate that subcutaneous administration of MTX exhibits enhanced efficacy compared to oral MTX also in the AD population, potentially attributed to elevated concentrations of biologically active MTX polyglutamate.

Additionally, we found four differentially expressed serum proteins consisting of CCL5, MMP1, P-selectin and DKK1, showing significant higher baseline values of CCL5 and P-selectin for MTX-responders. A proof of concept prognostic model consisting of these four proteins was able to predict MTX treatment response correctly in 80,4% of AD patients. However, in an independent cohort of patients with PsA or psoriasis who received MTX treatment, these results could not be replicated. This indicates that the predictive model is specific to patients with AD and cannot be extrapolated to other inflammatory conditions treated with MTX. Furthermore, it suggests that the observed effect is not directly associated with the pharmacological mechanisms of MTX. It is plausible to consider that the two cohorts have distinct underlying immunological pathogenic mechanisms, thereby making the PsA cohort less suitable for direct comparison.

Among the AD cohort, the median MTX maintenance dose (mg/week) was significantly higher in the non-responders to MTX. Interestingly, more of these patients were concomitantly treated with oral corticosteroids at the initiation of MTX treatment. Although the baseline EASI scores at the moment of starting MTX treatment were similar between the MTX-responders and MTX- non-responders, the concomitant use of oral corticosteroids at baseline among the non-responders may have decreased their EASI scores. These findings suggest that this particular group may have refractory or difficult-to-treat disease partly explaining their insufficient response to MTX.

The advent of biologics and small molecule inhibitors has introduced novel therapeutic alternatives for individuals with moderate to severe AD. Nonetheless, it is anticipated that conventional immunosuppressive drugs will continue to serve as the initial preferred treatment approach, as is customary in the management of psoriasis, IBD and RA.[9-11] Unfortunately, approximately half of the AD patients have to discontinue MTX treatment due to ineffectiveness and/or side effects.[18] Since treatment response can only be assessed after three months of trial, patients may experience a delay in receiving effective treatment and may be exposed to unnecessary adverse effects. This highlights the clinical necessity to predict treatment response to MTX and advance towards more personalized therapeutic strategies for individuals with AD. Such predictive models however, whether composed of clinical characteristics and/or biological markers, do not exist yet for the treatment of AD patients.[6, 27]

Although the four identified differentially expressed proteins have not been directly implicated in AD pathogenesis, they may play a role in regulating the intricate interaction between cytokines and chemokines. For instance MMP, serves as a key protease involved in skin collagen degradation.[28] The chemokine CCL5 is upregulated in lesional skin and blood of AD patients[29-31], potentially contributing to the recruitment of eosinophils and other lymphocytes towards the affected skin.[32, 33] P-selectin may assist in the deposition of CCL5 within the skin.[34] The role of DKK1, an inhibitor of the Wnt signaling pathway, in skin disease has not extensively been studied yet.[35] Prospective validation of these differentially expressed serum proteins and the constructed prognostic protein model is necessary to determine the applicability in daily clinical practice.

This study is subject to various limitations. Firstly, the sample size of patients with AD receiving MTX treatment is small, and the study design is retrospective in nature. Furthermore, a validation cohort comprising specifically of AD patients should ideally be utilized, whereas in this study, a cohort of patients with PsA or psoriasis was employed.

In summary, this study demonstrates that subcutaneous administration of MTX exhibits a favorable impact on treatment response in patients with AD after 6-months. Furthermore, we have identified four serum proteins (CCL5, MMP1, P-selectin, and DKK1) with differential expression among MTX responders and non-responders. A proof-of-concept prediction model incorporating these four proteins has displayed the ability to predict MTX response in approximately 80% of AD patients. Notably, this prediction-model was not generalizable beyond AD in an independent PsA cohort, indicating its potential specificity for AD treatment. Prospective validation using an independent cohort of AD patients receiving MTX therapy is imperative to assess the genuine predictive capacity of this model.

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Supplementary material

Table S1. Panel of protein analytes measured using the Luminex technology at the Multiplex Core Facility of the Center for Translational Immunology.

Serum proteins measured via Luminex technology				
IL-1a	IL-8	IP-10	sVEGF-R1	BDNF
IL-1RA	IL-33	I-TAC	sSCF-R	sICAM
IL-1b	IL-37	BLC	Gal-1	sVCAM
IL-2	LIGHT	BRAK	P-sel	TNFb
IL-3	TWEAK	XCL-1	E-sel	MIG
IL-4	MIF	OPG	Cystatin C	sCD163
IL-5	OSM	OPN	SLP1	SAA-1
IL-6	TSLP	SOST	Elastase	ENA-78
IL-7	I-309	G-CSF	Trappin-2	GCP-2
IL-9	MCP-1	SCF	Endoglin	TNFa
IL-10	MIP-1a	HGF	TIM/KIM-1	TNF-R1
IL-11	MIP-1b	EGF	SDF-1a	TNF-R2
IL-12	MCP-3	FGF Basic	DKK1	sIL-2R
IL-13	MCP-2	NGF	Apelin	PAI-1
IL-15	Eotaxin	PIGF	S100A8	RBP4
IL-17	MCP-4	VEGF	Gal-9	TPO
IL-18	TARC	TREM-1	Ang-1	IFNa
IL-20	MIP-3b	Cat B	Ang-2	IFNb
IL-21	MIP-3a	sPD-1	Tie-2	IFNg
IL-22	MDC	FAS	YKL-40	
IL-23	MPIF	FAS-L	LAP	
IL-25	TECK	LAIR-1	RANTES	
IL-26	Eotaxin-3	IL-18BPa	PARC	
IL-27	C-TACK	IL-1R1	Adipsin	
IL-29	Gal-9	IL-1R2	Leptin	
IL-31	GRO-1a	ST-2	Resistin	

General discussion and Summary

6

Management of Psoriasis and Psoriatic Arthritis Patients: the Need for a Layered Approach

It is the usage of different layers in the composition of a painting that gives depth, structure, nuance and atmosphere. The making of each layer requires time, patience, and strategy, but every step will contribute to reveal the painting's final form. Similarly, the management of psoriasis and psoriatic arthritis (PsA) patients also demands a structured multi-layered approach **(Figure 1).** Such an approach is needed to uncover and to tackle the multiple facets – physical and psychosocial – that hinder the daily life of these patients.

A layered approach not solely applies to disease management but also calls for a multidisciplinary team of care-givers, such as dermatologists, rheumatologists, general practitioners, psychologist and physiotherapists.[1] Early recognition and timely, adequate treatment are of great importance to reduce physical- and mental burden, prevent irreversible joint damage [2-5] and ensure better care and management of comorbidities, ultimately improving quality of life.[6] Another important aspect of the layered approach is that both health care professionals and patients can play an important role in research, aimed at improving future care for people affected by psoriasis and PsA. Thus, it is valuable to motivate patients to contribute to this common goal as, even though it might not directly benefit them, it may lead to better care and treatment for patients similar to themselves in the future.

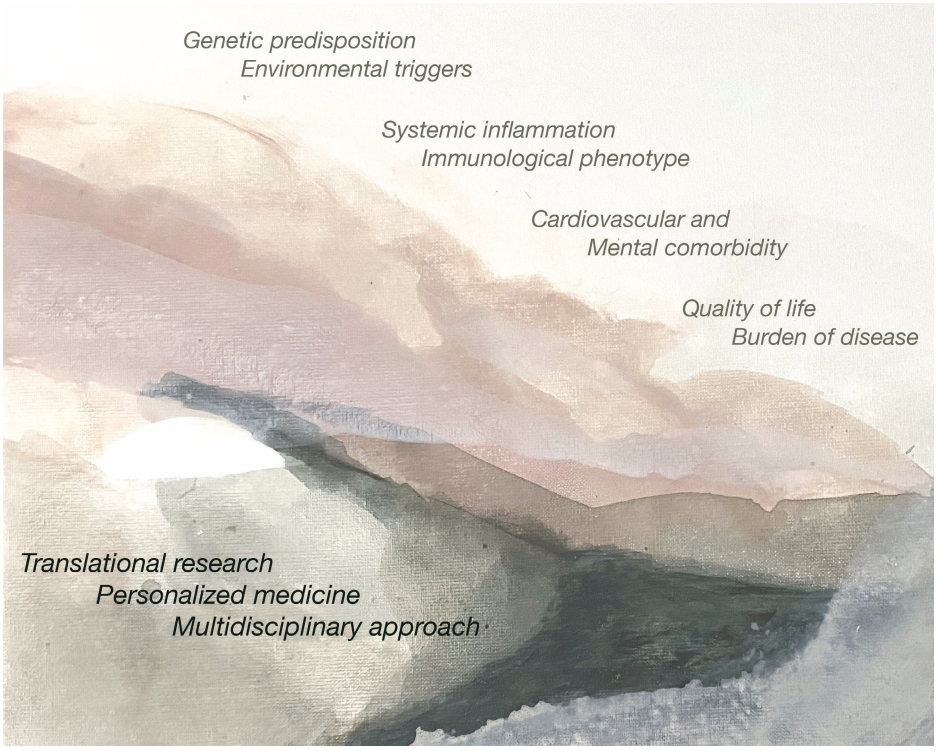

Figure 1. Abstract overview of the different layers involved in the management of psoriasis and PsA.

Genetic, Immunologic and Environmental Layers.

The precise immune events that lead to the development and progression of psoriasis or PsA are complex and not yet fully understood. Both conditions share common pathogenic mechanisms, including genetic risk alleles, environmental factors and dysfunctional immune-axis.[7, 8] However, despite these similarities, heterogeneity in disease manifestations is most characteristic for both disorders. Differential, sometimes unexplainable, treatment results are seen in patients treated for the same subtype of psoriasis or clinical manifestation of PsA.[9, 10] Thus, the lack of a "one-size fits all treatment" highlights the need of well-conducted translational science that will bring forth the tools to practice personalized medicine.

Genome-wide association studies (GWAS) and SNP arrays reveal numerous psoriatic risk alleles encoding for proteins involved in e.g. skin barrier function and immune cell signaling pathways.[11] These genes can be categorized into risk loci within the major histocompatibility complex (MHC) and non-MHC loci. Psoriasis is highly associated with HLA-Cw6 and HLA-C*06:02, being present in approximately 60% of psoriasis patients.

On the other hand, PsA is predominantly associated with HLA class I family genes. For instance, HLA-B*08:01 associates with peripheral arthritis and asymmetrical sacroiliitis, while HLA-B*27:05 is linked with axial PsA.[12, 13] There is an overlap of non-MHC genes between psoriasis and PsA, including *IL12A*, *IL12B*, *IL23R, IL23A and TNFAIP3 (*TNFα Induced Protein). While genetic variations are associated with a higher risk of developing psoriasis and PsA, their presence does not necessarily mean that disease is going to become manifest.[14] Disease onset, however, is influenced by a complex interplay between genetic predisposition, environmental factors and epigenetic alterations. Known environmental factors include smoking, obesity, alcohol use, multiple drugs like for example beta-blockers, antimalarials and lithium, biomechanical trauma, psychological stress and infections.[15]

Both psoriasis and PsA are associated with a dysregulation of the IL23/IL-17 and IL-12/IFN-γ immune axis.[16] IL-23, a heterodimeric cytokine composed of the p40*(IL12B)* and p19(*IL23A)* subunits, is conventionally secreted by dendritic cells and macrophages.[17] While the p40 subunit is shared with IL-12, the p19 subunit is unique to IL-23. Both IL-12 and IL-23 play a critical role in the differentiation of naïve T-lymphocytes into T helper (Th) interferon (IFN)-γ-producing Th1 or IL-17-producing Th17 cells, respectively.[17-20] These cytokines are major drivers of psoriatic disease and are involved in the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) signaling pathway.[21] Tofacitinib, an oral small molecule inhibitor which primarily targets JAK1 and JAK3 (followed by JAK2 and to a lower extent TYK (tyrosine kinase)2), has been shown to significantly reduce PsA and psoriasis symptoms.[22] By blocking JAK2/TYK2 activation, tofacitinib prevents the activation of STAT3 and STAT4 by IL-12 and IL-23 [23], see **Figure 2.** This further inhibits the recruitment of immune cells and the secretion of pathogenic mediators associated with chronic inflammation and tissue damage leading to clinical symptoms of psoriasis and PsA.[24]

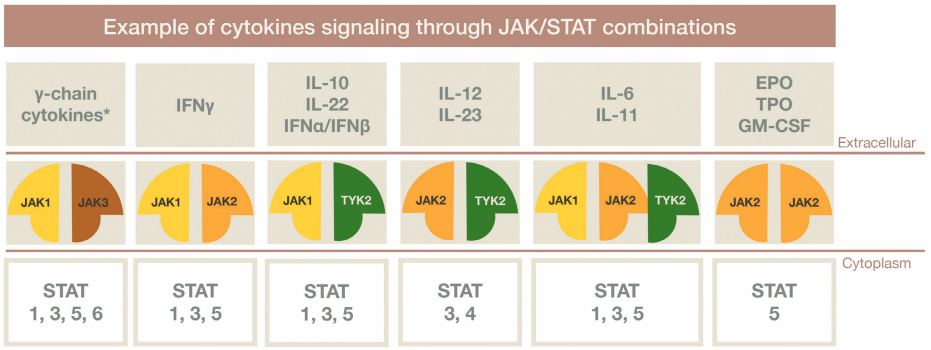

Figure 2. Cytokines signaling through JAK/STAT combinations. *γ-chain cytokines: IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. EPO: Erythropoietin; TPO: thyroid peroxidase; GM-CSF: Granulocyte/macrophage colony stimulating factor; IFN: Interferon; IL: Interleukin; JAK: Janus kinase; STAT: Signal Transducer and Activator of Transcription; TYK: Tyrosine kinase
Image modified from: Hodge 2016[25]

While the effects of tofacitinib in T cells, e.g. the inhibition of Th1 and Th17 differentiation[26] and the production of IFN-γ and IL-17[27] have been studied before, the effect on the expression and secretion of IL-23/IL12 by myeloid dendritic cells (mDC) remained uncharacterized.[28, 29] For this reason, in Chapter 2 we investigated the contribution of tofacitinib in the suppression of IL23A(IL-23p19), IL12B (IL-12p40) and IL12A (IL-12p35) production in dendritic cell models. The results of this work indicate that dendritic cells pretreated with tofacitinib and subsequently stimulated with TLR4 ligand (LPS) do not decrease the expression of IL23A, IL12B and IL12A. These results are in line with a study showing that tofacitinib rather induces IL12A and IL23A expression in both differentiating and differentiated monocyte-derived DCs (moDCs).[30]

When stimulating pre-treated mDCs with a combination of TLR4 and IFN-γ, we observed a significant downregulation of IL12B, the IL-12 shared p40 subunit. Stalder et al. also identified that IFN-γ-induced IL12A mRNA expression in moDCs can be reduced by tofacitinib treatment.[30] However, in our experiments, we observed that IFN-γ alone is a weak inducer of IL12A/B and IL23A expression in DCs (Supplementary Figure 1). Hence, we propose that combined stimulation of DCs by IFN-γ and a TLR ligand could constitute a better model to study the modulation of such cytokines by tofacitinib.

Additionally, our data suggest that the presence of an active IFN-γ signaling in DCs is important to ensure a downregulation of IL-12 and IL-23 by tofacitinib, as these cytokines are only biologically active in the presence of the p40 subunit.[31]

As we did not have a sufficiently large database of psoriasis patients treated with tofacitinib, we retrieved and analyzed data from two public databases in order to validate the clinical relevance of our findings in patient samples. Using a database containing mRNA data derived from skin-biopsy specimens taken from active psoriasis lesions in patients treated with tofacitinib, we showed that higher baseline levels of IFN-γ correlated with a greater reduction of *IL12B* after 12 weeks of treatment in comparison to patients with low IFN-γ baseline levels. The second database contained data on psoriasis patients treated with tofacitinib for 12 weeks, in which the authors performed an extensive serum protein analysis before and after 4 weeks of treatment. This database revealed that patients with a higher IFN-signature at baseline also experienced a more significant reduction in their PASI scores, together with a better reduction of IL-12 levels after tofacitinib treatment. This novel finding on the role of IFN-γ in *IL12B* suppression by tofacitinib suggests that psoriasis patients with higher levels of IFN-γ in their serum may also experience beneficial effects from tofacitinib treatment.

So far, only three additional factors have been identified that can predict a (non-)beneficial response to tofacitinib treatment.[31-33] Firstly, a randomized double-blind placebo-controlled clinical trial revealed that an early improvement in the PASI score can be used as a reliable predictor of treatment efficacy. Specifically, achieving a PASI50 at week 8 predicts a PASI75 at week 16 with an area under the receiver operating characteristic (auROC) of 87%. On the contrary, if patients do not achieve a PASI50 at week 8, only 20% of them were able to eventually achieve a PASI75 after 16 weeks, indicating a change in treatment is appropriate at this point.[31] Additionally, a pharmacokinetic study demonstrated that a higher baseline bodyweight is associated with reduced efficacy of tofacitinib, negatively impacting the likelihood of achieving a PASI75 at 12 weeks.[33] Lastly, and most interestingly, a randomized double-blind placebo-controlled clinical trial was conducted with 266 psoriasis patients either treated with tofacitinib or etanercept, in which 157 inflammatory and cardiovascular serum proteins were measured at baseline and after 4 weeks of treatment. Patients were classified as responders when achieving a PASI75 after 12 weeks of treatment. A predictive model was created using a combination of the top differentially expressed proteins (including IL12B, IL17A, IL17C and IFN- γ) at baseline and week 4, and this model was found to have an accuracy of 78.4% with an auROC of 83%. This study further confirmed the value of an early improvement in PASI score after 4 weeks of treatment with tofacitinib, with an accurate prediction of responders of 76,7%. Unfortunately the study does not further elaborate on the specific clinical applicability of the early improvement in PASI score as their main focus was the protein model.[32]

Developing a predictive model that can accurately predict early treatment response for psoriasis and PsA while minimizing unnecessary drug exposure remains a challenging task. Ideally, a model that can predict response to treatment is constructed of baseline characteristics, however to date, only models or clinical factors have been identified that can be used over a period of time for the prediction of response to tofacitinib. Overall, the improvement in PASI score over time appears to be a reliable predictor of treatment response for tofacitinib. Although this measurement has shown low levels of inter- and intraobserver variability among adequately trained and experienced clinicians [34], it should be highlighted that PASI scores are not routinely assessed by rheumatologists. This poses a certain degree of subjectivity to the PASI assessment, reducing its reliability and reproducibility making it less suitable to be a predictor of treatment response.[35] Thus, a more robust and standardized marker that can be easily interpreted is necessary to enhance the accuracy and consistency of treatment response prediction. Taken together, our findings highlight the possibility of such a new potential marker that may predict beneficial response to tofacitinib in psoriasis before treatment start, and these findings may be expanded to other inflammatory conditions associated with IFN-γ involvement.

The Layer of Quality of Life and Disease Burden

In this thesis, the anti-inflammatory properties of tofacitinib were not only studied in vitro, but a translation to clinical practice was made with the TOFA-PREDICT trial, a multi-centre investigator-initiated, phase III, randomized controlled trial. **Chapter 3** describes the TOFA-PREDICT study protocol, in which a multi-omics systems medicine approach was used to integrate pre-treatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging data trying to discover PsA patient profiles that will be able to predict response to tofacitinib, as compared to methotrexate (DMARD) and etanercept (TNF-alpha inhibitor). As previously discussed, effective treatment of PsA remains a challenging task. However, gaining a comprehensive understanding of the molecular and cellular pathways that dictate the response to therapy can greatly improve patient care. Timely initiation of appropriate treatment can lead to a reduction in pain and functional disability, while also preventing joint damage. Such outcomes would have a profound impact on the quality of life of patients with PsA. Therefore, it is crucial to continue exploring the underlying mechanisms of treatment response to enhance therapeutic strategies for PsA.[2, 36, 37] In addition to the multi-omics systems medicine approach, the Quality of Life (QoL) of patients has been given significant importance. This is achieved by collecting data from multiple questionnaires to monitor patients' mental and physical well-being. These questionnaires include the Assessment of SpondyloArthritis (ASAS) health index, Dermatology Life Quality Index (DLQI), EuroQol five dimension scale (EQ-5D), Health Assessment Questionnaire (HAQ), self-administered psoriasis area and severity

index (SAPASI) and the Work Productivity and Activity Impairment (WPAI) questionnaire and the Visual Analogue Scale (VAS) for general well-being and pain. Furthermore, two composite scores, namely the minimal disease activity (MDA) and the American College of Rheumatology (ACR)50, which both incorporate the HAQ, are utilized to assess treatment response and to determine if a patient needs a change in treatment regimen.[38, 39] Therefore, patient responder and non-responder stratification in the TOFA-PREDICT trial is partially dependent on patient reported outcomes measures (PROM).

Collectively, the TOFA-PREDICT trial provides a comprehensive, layered, approach for tailoring treatment strategies for patients with PsA and evaluating treatment efficacy by integrating QoL assessments alongside other clinical and molecular data.

Implementing Patient-Reported Outcome Measures in Clinical Practice and Research: Challenges and Recommendations

The use of Quality of Life questionnaires has changed the way we approach research and health care for over the last two decades, with a shift towards patient-centered care that considers psychosocial and cultural contexts.[40] It is a continues evolving field refining and developing more reliable and precise questionnaires to date.[41] This movement signifies a shift away from a more narrow medical only approach that focusses on disease and symptom management, towards a broader and more encompassing psychosocial and cultural context, understanding what illness means to the patient and what they need at that particular moment in their lives.[41, 42]

PROMs offer several benefits, such as facilitating multidisciplinary care, improved treatment adherence,[43, 44] quantitative monitoring of treatment response and satisfaction and act as a conversation starter for both patient and clinician regarding sensitive subjects.[43] Also, they can help stratify patients according to their results (e.g. seen by a nurse in case of stable disease or be seen by a clinician in case of worsening).[43, 45] However, there are also barriers to their usage limiting clinical implementation, including the administrative burden, the obligation to address results during consultations, the lack of awareness and experience using PROMs[43, 46], and the difficulties for people with low (computer) literacy.[47] In addition, patients have indicated that they miss questions regarding their anxieties over mortality and morbidity, as they commonly experience a fear of dying prematurely, developing cancer or experience a general uncertainty about their future.[43]

The implementation in clinical practice, especially outside research purposes, progresses slowly. To improve implementation, online PROMs should prioritize user-friendly-interfaces, be developed by experienced companies, and protect patients' privacy. The use

of paper-based PROMs should be avoided due to environmental concerns and the time-consuming manual processing. Patients should be adequately instructed and educated by, for example, (research-)nurses. Integrating PROMs with patients' electronic health records, containing pop-ups displaying cumulative scores - in comparison to previous scores – and identifying specific domains requiring attention, could help to reduce clinicians workload and lower the resistance of using PROMs. It is important to note that PROM data should serve as a complementary tool to clinical judgement.

The Layer of Comorbidities and Adverse Events in Treatment

In the field of science and medicine, paradigms serve as a theoretical framework based on experiments, theories and generalizations that provide a set of tools for approaching clinical challenges. When a paradigm becomes universally accepted, it may become enshrined as a treatment recommendation. However, when new high-throughput research, progressive insights and clinical practice contradict the current paradigm, critical re-appraisal is demanded and a gradual shift towards a new paradigm must be initiated. [48]

An example of such a paradigm shift is the emergence of systems medicine, which emphasizes a more holistic approach characterizing diseases using omics data and molecular subtypes, in contrast to the traditional way of diagnosing and treating solely relying on phenotype and symptoms.[48] Additionally, the aforementioned implementation of patient reported outcome measures (PROM) represents a shift towards a patient-centered healthcare system, where clinicians take into account patients' perception of their illness and current needs, rather than solely relying on biochemical and physical measurements.[40]

Another old paradigm discourages the use of systemic glucocorticoids for the treatment of psoriasis and PsA due to concerns over potential skin flares when initiating or discontinuing this treatment. Recent guidelines and textbooks have reiterated this recommendation without critically reassessing the evidence or providing supportive data.[49-52] In **Chapter 4** we conducted a systematic review of new insights, and evaluated the original paper from Baker and Ryan published in 1968 that influenced the negative opinion regarding glucocorticoids.[53] Our findings suggest that the evidence regarding the effects of glucocorticoids on flare risk is limited and does not warrant such a negative advice, and also the originally cited article poses a high risk of bias. Considering the frequent prescription of systemic glucocorticoids for psoriasis patients, and the infrequent occurrence of (mild) psoriatic flares upon treatment[54], we propose that systemic glucocorticoids should not be withheld when deemed necessary. In fact, these drugs are essential for rapid

reduction of local or systemic inflammation by immunosuppression[55], and subsequently reducing pain, swelling and stiffness. Also, they may prevent early damage and eventual permanent joint damage.[56] Furthermore, they are beneficial for symptom bridging in the early initiation phase of DMARD therapy where these drugs do not yet express their full effect in PsA or psoriasis, giving patients more confidence and satisfaction in the initiated treatment.[56, 57]

Chapter 4 presents a potential paradigm shift regarding the use of systemic glucocorticoids in patients with psoriasis and PsA. Following publication, the systematic review gained the attention of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), prompting an editorial by dr. L. Coates calling for a consensus statement among clinicians worldwide and urging for a decision making tool to offer clinical guidance on the use of systemic glucocorticoids.[58] This research highlights the growing need to re-evaluate the role of systemic glucocorticoids in the therapeutic armamentarium for PsA and psoriasis, while always bearing in mind the side effects and risk-benefit ratio of corticoid.

As science and medicine continue to advance, it is crucial to maintain curiosity about new ideas and insights in order to improve patient care. It is essential to critically evaluate established practices and recommendations, considering the underlying evidence and rationale for their use. While changes may be met with resistance, it is important to recognize that novel approaches do not necessarily disapprove the efficacy of our previously established methods.

The Layer of Personalized Medicine and Translational Research

Translational research is the bridge between basic science and clinical practice and has changed the way we approach medical treatment. By tailoring therapies to an individual's genetic, molecular, environmental and lifestyle factors, personalized medicine has the potential to improve treatment efficacy, reduce unnecessary drug exposure and the risk of adverse events and to reduce health care costs [59, 60] all leading to improved patient safety and improved Quality of Life.[60, 61] One of the key aims of personalized medicine is the identification of biomarkers, which can predict treatment response and aid clinicians to make informed decisions regarding therapy selection and dosing. In addition, translational research enhances drug target discovery leading to the development of new targeted therapeutics. The field of oncology is leading herein at the moment, paving the way for personalized medicine in other medical domains.[60, 61]

In **Chapter 5** clinical and molecular parameters were investigated from patients with atopic dermatitis (AD), a chronic skin disease characterized by pruritus and eczematous skin. AD is similar to psoriasis in terms of altered growth and differentiation of skin cells and the involvement of inflammatory mediators causing chronic inflammation.[62] Patients with AD face similar clinical unmet needs as psoriasis patients; finding tailored therapies fitting to the individual patient and to reduce treatment failure.[63] In light of personalized medicine, the aim of this study was to identify clinical and/or molecular predictors of treatment response to methotrexate, currently the most frequently prescribed systemic drug for AD patients in the Netherlands.[64] Retrospectively, 78 AD patients were classified as methotrexate responders or non-responders using the Investigators' Global Assessment (IGA) score, and it was found that subcutaneous administration was more beneficial for treatment response compared to oral administration in this population. Additionally, a sub-analysis was conducted on biobanked serum samples before the start of methotrexate treatment, to create a (proof of concept) prognostic baseline model for treatment response using protein markers. This prognostic model consisted four differentially expressed serum proteins and was able to predict response to methotrexate treatment with an accuracy of 80,4%. We further investigated whether these findings were specific to AD patients or reflected methotrexate's working mechanisms by using a cohort of methotrexate treated psoriasis and PsA patients. We determined the most differentially expressed proteins in this cohort, but we were not able to reproduce our findings and therefore the prognostic model was not able to correctly classify psoriasis/PsA patients. These findings implicate that the model might be uniquely correlated with methotrexate response in AD patients and is not generalizable to other conditions treated with methotrexate. Further prospective validation is needed to determine the clinical implications for AD patients of these findings.

The first PsA trial stepping over the boundaries of "proof-of-concept", paving the way for personalized medicine, was the one conducted by Miyagawa et al.[65] The study was based on the believe that an active circulating T-helper cell signature reflects the pathological basis of disease and therefore the therapeutic strategies should aim at restoring balance in these irregularities. The trial included sixty-four methotrexate-resistant PsA patients who were randomly assigned to receive either standard-of-care treatment (according to EULAR 2015 treatment guidelines[50]) or to receive personalized treatment based on lymphocyte phenotyping flow-cytometry. Patients in the 'strategic treatment-group' were stratified according to their immunophenotype, and were given either ustekinumab, secukinumab or a TNF-inhibitor depending on their Th1 or Th17 predominance. The results demonstrated that patients in the 'strategic treatment-group' had a significantly higher rate of low disease activity compared to the 'standard of care-group' (92,3% vs 55.2% of

patients respectively), thus confirming the potential of immunophenotyping to guide the selection of optimal therapy for individual patients.

Although the multi-omics approach holds great promise for personalized medicine strategies for chronic diseases, its implementation and translation into clinical practice is progressing slowly. It is important to speculate what factors are holding back its implementation. One of those factors is that advancing high-throughput technologies enable the generation of a vast amount of data from multiple omic-layers derived from different types of tissues. However, it requires advanced computational methods to identify the most useful and informative data to comprehensively understand the complex molecular processes underlying disease.[61] Also, standardization in the methods used to generate omics data is lacking, making it difficult to compare and integrate data across different studies.[66] Lastly, there is a lack of clinical validation of currently found markers or models discovered via multi-omics platforms, as well as the need to translate them in to more standardized and cost-effective laboratory protocols requests.[67] This requires a broad and extensive collaboration among researchers, clinicians and financial investors in order to conduct trials with patient populations large enough to provide solid evidence for clinical utility of multi-omics approaches.[68] Although significant progress has been made in understanding the molecular processes underlying psoriasis and PsA, there is still a long, but promising, way to go in realizing its potential for personalized medicine in clinical practice.

Future Perspective of the Layered Approach and concluding remarks: The Importance of a Multidisciplinary Team in Managing Psoriasis and Psoriatic Arthritis Patients: are Clinicians on the Same Page?

The layered approach for psoriasis and PsA care extends beyond disease and symptom management, and calls for addressing the significant comorbidities experienced by these patients. Effective management of patients with psoriasis and PsA requires a multidisciplinary approach, with general practitioners, dermatologists, rheumatologist and nurse specialists all working together to address all aspects of the patients' condition. **Figure 3.** depicts a schematic overview of the route a patient can follow and which healthcare professional may be consulted for specialized care.

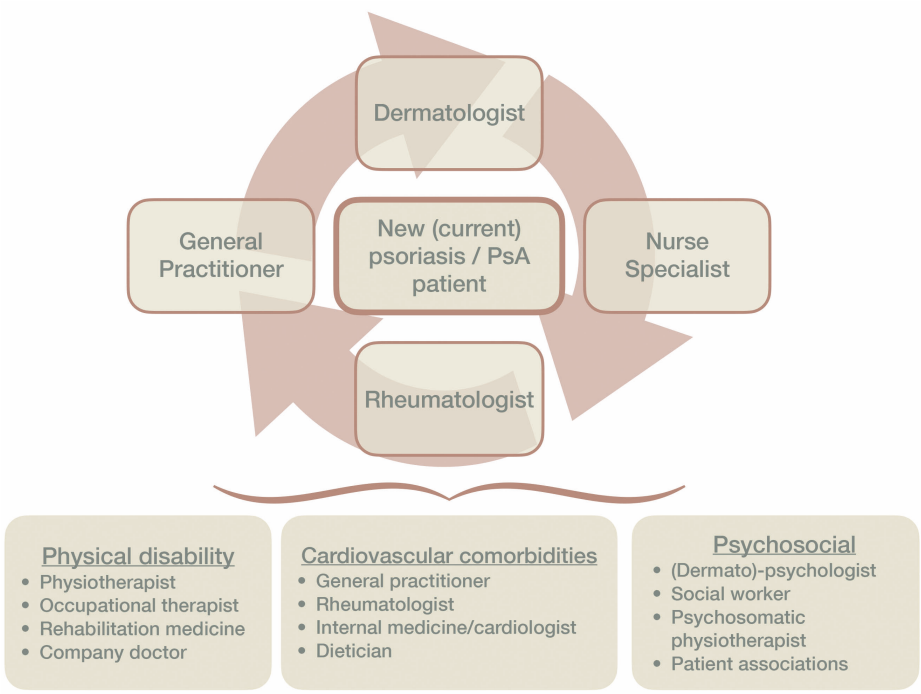

Figure 3. A schematic representation illustrating the potential healthcare professionals engaged in managing new and current psoriasis /PsA patients. The involvement of general practitioners, dermatologists, rheumatologists and nurse specialists requires close collaboration and inter-consultation amongst them should be easily accessible. In the event of co-morbidities, more sub-specialized healthcare professionals may be consulted, as shown in the boxes below.

General practitioners and dermatologists are often the first healthcare providers in contact with psoriasis patients, as many of them seek help for skin complaints, complaints of fatigue, vague musculoskeletal problems, or mental health issues, which often precede PsA.[70, 71] Thus, they have a crucial role in identifying potential PsA patients. However, a worrisome finding from a recent study revealed that approximately one-third of psoriasis patients visiting dermatology clinics remain undiagnosed with PsA.[72] The early diagnosis of PsA appears to be difficult due to the absence of clear diagnostic criteria and biomarkers, as well as the heterogeneity of the disease leading to misdiagnosis.[2, 37] Screening tools like ToPAS, PEST, PASE and EARP lack accuracy in identifying PsA patients, coupled with low awareness among clinicians regarding these tools.[73] Given that psoriasis is currently the strongest predictor of PsA, and approximately one in five psoriasis patients eventually develop PsA[74], it is essential for general practitioners and dermatologists to be aware of the condition and to educate patients to seek immediate medical attention when they experience additional symptoms. This can help prevent long term negative effects and deterioration of comorbidities.[75, 76]

In light of these comorbidities, PsA patients have a high prevalence of obesity (~45% of patients)[77] which is correlated to more severe psoriatic skin condition (OR ranging from 1.66 to 2.33 with increasing psoriasis severity).[78] Obesity negatively impacts systemic treatment responses[79] and it is significantly associated with physical (e.g. hypertension, stroke, dyslipidemia, type 2 diabetes, coronary artery disease) and mental health conditions (e.g. anxiety, depression, low self-esteem, impaired body image, eating disorder, sleep disorder).[80] Intervention by a dietician, psychologist, (psychosomatic-)physiotherapist, or a combined lifestyle intervention can prevent further deterioration. Weight loss of >5% is associated with higher rates of minimal disease activity when treating with TNFα-inhibitors[81], and long term weight loss (>1yr) has shown to significantly improve PASI scores and better outcomes in QoL questionnaires.[82] Primary care practice nurses may be involved in periodic patient monitoring for obesity or hypertension and should therefore use these opportunities to identify unhealthy vicious cycles and intervene accordingly. The above shows the importance of timely interference with unhealthy lifestyle preventing further deterioration.

The Dutch psoriasis treatment guidelines for general practitioners spend adequate attention to PsA by emphasizing the recognition of articular and extra-articular symptoms, and the need for early referral when additional treatment is necessary.[83] Additionally, the guidelines acknowledge the negative impact of psoriasis on quality of life and recommend exploring patients' hindrances in life, managing their expectations and setting realistic treatment goals. However, the relationship between psoriasis and cardiovascular/metabolic disease remains relatively understated and the guideline lacks solid literature on this topic. Two systematic reviews from 2010 and 2011 both suggest insufficient evidence is present for an independent causal relationship between psoriasis and cardiovascular disease.[84, 85] The treatment guidelines for cardiovascular disease management recommend general practitioners to consider establishing an individual risk profile for patients with PsA, but not psoriasis, and to initiate earlier treatment for cardiovascular disease.[86] However, the guideline highlights the limited availability of evidence on the association between PsA and cardiovascular disease risk, as indicated by two studies cited with low quality evidence.[87, 88] To address this gap, the guidelines suggest to compare the underlying inflammation in PsA with that of rheumatoid arthritis to justify considering PsA as a potential risk factor for cardiovascular disease.

International dermatology guidelines provide, well referenced and comprehensive information on PsA, cardiovascular disease, metabolic syndrome, mental health, lifestyle choices, inflammatory bowel disease, and malignancies. Each topic is thoroughly discussed with a corresponding paragraph emphasizing the dermatologist's role, self-management

options, and appropriate referrals for further care if necessary. These guidelines recognize the importance of a multidisciplinary approach in the management of psoriasis and its associated comorbidities.[89, 90] While the Dutch dermatology guidelines for psoriasis are comprehensive in addressing the potential occurrence of PsA and its impact on QoL, they appear to lack sufficient information on managing other associated comorbidities.[91]

Currently, there is an ongoing revision for both the Dutch general practitioner and Dermatology treatment guidelines for psoriasis. Increasing evidence supports the concept of the "inflammatory skin march," which characterizes psoriasis as a chronic inflammatory disorder affecting multiple systems.[92] Important to note is that The American Heart Association has recognized psoriasis, along with other chronic inflammatory conditions, as a risk factor for atherosclerosis and cardiovascular disease in their latest guideline.[93] While the debate on whether psoriasis is an independent risk factor for cardiovascular disease remains, there is substantial evidence indicating a higher incidence of other comorbidities, such as diabetes, metabolic syndrome, obesity, depression, and anxiety, among psoriasis patients compared to the general population.[37, 85, 87, 92, 94-98] To effectively manage psoriasis and PsA patients, healthcare professionals should be sufficiently aware of these comorbidities and allocate adequate time to prevent their deterioration. The above should be emphasized in the updated treatment protocols.

As translational research for psoriasis and PsA is still in its infancy, we must rely on our clinical view and adequately educate ourselves and other health care professionals. Awareness should be raised on all aspects of psoriatic disease. A possible solution to improve collaboration is the implementation of specialized consultations that bring together general practitioners with dermatologists or rheumatologists, an already ongoing concept called "Primary Care Plus" (Anderhalvelijnszorg). These consultations would be particularly beneficial for patients experiencing refractory symptoms and requiring more attention on specific facets of their disease, while simultaneously educating general practitioners in to more difficult-to-treat patients. The presence of a physiotherapist or psychologist, trained in the management of these diseases, would be highly valued. In instances where an organization lacks access to a specialist with the appropriate expertise, healthcare professionals should seek to establish connections with specialists outside their organizational boundaries.

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Appendices

Nederlandse samenvatting

Psoriasis is een chronische en invaliderende aandoening die geen genezing kent en aanzienlijke invloed heeft op de kwaliteit van leven van patiënten. Wereldwijd zijn ongeveer 60 miljoen mensen, zowel kinderen als volwassenen, getroffen door deze aandoening. Er is een grote verscheidenheid aan manieren waarop het ziektebeeld zich kan uiten, waarbij deze beelden op zichzelf ook weer kunnen variëren in ernst en uitgebreidheid. Meestal manifesteert psoriasis zich als het vulgaris-type, gekenmerkt door scherp begrensde rode schilferende plekken op de strekzijden van de ellebogen en knieën, tussen de billen en op de hoofdhuid. Bij meer uitgebreidere vormen van de ziekte kunnen plekken over het gehele lichaam voorkomen (bijvoorbeeld in het gezicht, in de oren, op de handen, voetzolen en nagels). Ongeveer één op de vijf patiënten met psoriasis krijgt uiteindelijk ook reumatische klachten (artritis psoriatica), met bijvoorbeeld één of meerdere ontstoken gewrichten (artritis), een bekken/wervelontsteking (axiale spondyloartritis), een ontsteking van een vinger of teen (dactylitis), peesontsteking (enthesitis) of men kan last hebben van putjesnagels of loslating van de nagel.

We weten nog niet precies hoe psoriasis en artritis psoriatica ontstaan. Beide aandoeningen delen gemeenschappelijke mechanismen, waaronder erfelijke en omgevingsfactoren en problemen in het immuunsysteem. Echter, ondanks deze overeenkomsten is de diversiteit in symptomen het meest kenmerkend voor beide aandoeningen. Patiënten die dezelfde medicatie gebruiken, ervaren vaak wisselende en soms onverklaarbare behandelresultaten. Dit benadrukt het gemis aan een universele behandelaanpak, waardoor er een dringende behoefte is aan grondig wetenschappelijk onderzoek dat kan helpen bij het ontwikkelen van gepersonaliseerde behandelingen.

Naast betrokkenheid van de huid en de gewrichten, hebben deze patiënten vaak andere gezondheidsproblemen, zoals hart- en stofwisselingsproblemen alsook psychische klachten zoals depressiviteit, een laag zelfbeeld of zelfs suïcidale gedachten. Dit alles draagt bij aan een extra grote belasting voor de patiënt en heeft een negatieve invloed op de algehele kwaliteit van leven. Zorgprofessionals zouden zich er bewust van moeten zijn dat psoriasis en artritis psoriatica aandoeningen zijn die zich niet alleen beperken tot huid- en gewrichtsklachten, maar alomvattende ziektebeelden zijn die alle aspecten van het leven kunnen beïnvloeden.

Doordat het een alomvattende aandoening is, vereist de behandeling van psoriasis en artritis psoriatica een gestructureerde, gelaagde benadering. Bij die aanpak horen meerdere disciplines betrokken te zijn, waaronder dermatologen, reumatologen,

huisartsen, psychologen en fysiotherapeuten. Vroege herkenning en tijdige adequate behandeling zijn van cruciaal belang om fysieke en psychologische belasting te verminderen, onomkeerbare schade te voorkomen en de kwaliteit van leven te verbeteren.

De rode draad in dit proefschrift is het effect van behandeling op patiënten met psoriasis en artritis psoriatica, op meerdere lagen bestudeerd. Er wordt dieper gekeken naar het werkingsmechanisme van tofacitinib, een relatief nieuw medicijn, en het bijwerkingenprofiel van systemische corticosteroïden. Ook wordt er een vergelijking gemaakt met atopisch eczeem, een soortgelijke chronische huidaandoening. De vragen die in mijn proefschrift aan bod komen zijn als volgt te omschrijven:

- Wat is het effect van tofacitinib op myeloïde dendritische cellen op celniveau en kunnen we deze bevindingen gebruiken om de behandelrespons bij patiënten met psoriasis te voorspellen?
- Kunnen we verschillen vinden in klinische kenmerken en het serum van patiënten met psoriasis/artritis psoriatica en atopisch eczeem die behandeld worden met methotrexaat en kunnen we deze gebruiken om een voorspelmodel te maken?
- Wat is de werkelijke kans op het krijgen van huid opvlammingen bij patiënten met psoriasis of artritis psoriatica als gevolg van behandeling met systemische corticosteroïden?
- Kunnen we door middel van gedegen wetenschappelijk onderzoek een voorspeller voor behandelrespons op tofacitinib, methotrexaat of etanercept vinden bij patiënten met artritis psoriatica op basis van klinische, immunologische of radiologische kenmerken?

Zowel psoriasis als artritis psoriatica worden geassocieerd met een verstoring van de IL-23/IL-17- en IL-12/IFN-γ-immuunassen. IL-23 en IL-12 zijn twee cytokines die door myeloïde dendritisch cellen worden uitgescheiden en betrokken zijn bij het ontstaan en de instandhouding van deze aandoeningen. Beide cytokines bestaan uit 2 subeenheden, waarbij de p40-subeenheid aanwezig is in zowel IL-12 en IL-23. Hierdoor vertonen beide structurele en biologische overeenkomsten, maar hebben ze aanzienlijk verschillende functionele rollen bij het reguleren van het immuunsysteem. Dit maakt p40 mogelijk een belangrijk doelwit voor de behandeling van psoriasis en artritis psoriatica, want door het medicamenteus aangrijpen van de gemeenschappelijke p40-subeenheid worden twee cruciale cytokines tegelijkertijd geremd. In **hoofdstuk 2** wordt beschreven of de expressie van p40 onderdrukt kan worden door tofacitinib, een relatief nieuw medicijn dat grote effectiviteit heeft getoond bij de behandeling van psoriasis, artritis psoriatica en andere inflammatoire ziekten. Door de rol van p40 in de respons op tofacitinib te onderzoeken,

werd geprobeerd om mogelijke mechanismen te ontrafelen die ten grondslag liggen aan de therapeutische effecten van dit geneesmiddel bij psoriasis en artritis psoriatica. Uit het onderzoek bleek dat tofacitinib de productie van deze cytokines in myeloïde dendritische cellen inderdaad kan remmen, maar alleen in de aanwezigheid van IFN-γ. Dit zou kunnen betekenen dat de aanwezigheid van een hoger niveau van IFN-γ leidt tot een meer succesvolle behandeling met tofacitinib.

Om deze theorie te bevestigen, hebben we deze bevindingen getoetst op twee databases met gegevens van psoriasispatiënten die behandeld zijn met tofacitinib. Hieruit bleek dat patiënten met hogere niveaus van IFN-γ in hun bloed beter reageerden op de behandeling met tofacitinib en een grotere vermindering van hun psoriasis symptomen lieten zien. Dit suggereert dat tofacitinib mogelijk effectiever is bij patiënten met hogere niveaus van IFN-γ in hun bloed.

In dit proefschrift zijn de ontstekingsremmende eigenschappen van tofacitinib niet alleen in vitro bestudeerd, maar is er ook een vertaalslag gemaakt naar de klinische praktijk door middel van de TOFA-PREDICT-trial, een multi-centre gerandomiseerde gecontroleerde studie. Zoals eerder besproken, blijft effectieve behandeling van artritis psoriatica een uitdaging. Echter, het verkrijgen van een uitgebreid begrip van de moleculaire en cellulaire mechanismen die de respons op therapie voorspellen, kan de zorg voor patiënten sterk verbeteren. **Hoofdstuk 3** beschrijft het TOFA-PREDICT studieprotocol, waarbij een multi-omics systems medicine-aanpak is gebruikt om verschillende gegevens te integreren om specifieke patiëntprofielen te ontdekken die respons op tofacitinib kunnen voorspellen, in vergelijking met methotrexaat (DMARD) en etanercept (TNF-alfa-remmer). Het tijdig starten van een effectieve behandeling kan leiden tot vermindering van pijn en functionele beperkingen, alsook het beperken en voorkomen van gewrichtsschade op de langere termijn. Snelle behandelresultaten hebben een gunstige impact op de kwaliteit van leven van patiënten. Samenvattend biedt de TOFA-PREDICT-trial een uitgebreide, **"layered approach"** met als cruciaal doel om de onderliggende mechanismen van behandeling te ontrafelen en om behandelstrategieën op maat voor patiënten met artritis psoriatica te ontdekken.

Een klasse medicijnen welke al langer op de markt zijn en vaak worden gebruikt bij verschillende aandoeningen vanwege hun snelle ontstekingsremmende en immunosuppressieve eigenschappen, zijn systemische corticosteroïden. Voor de behandeling van artritis psoriatica en psoriasis echter, bestaat er een algemene terughoudendheid bij het gebruik van deze middelen. Het traditionele advies, opgenomen in de hedendaagse behandelrichtlijnen, is om systemische corticosteroïden te vermijden

omdat het risico bestaat op een verergering van het huidbeeld (flare). Dit advies komt voort uit een artikel dat stamt uit 1968 waarin enkele psoriasis patiënten omschreven worden die een verergering hadden van hun huidbeeld tijdens het gebruik of na het stoppen van deze middelen. Omdat systemische corticosteroïden een belangrijk voordeel kunnen bieden tijdens de behandeling van deze aandoeningen bestaat de behoefte om de veiligheid en effectiviteit te herbeoordelen. **Hoofdstuk 4** laat door middel van uitgebreid literatuur onderzoek zien dat systemische corticosteroïden wereldwijd op grote schaal worden voorgeschreven aan patiënten met psoriasis en artritis psoriatica en dat er geen verhoogd risico lijkt te zijn op het opvlammen/verergeren van de psoriasis door het gebruik van deze middelen. Daarom stellen wij dat de terughoudendheid ongegrond is en het gebruik van deze medicijnen in overweging kan worden genomen als relevante behandeloptie. Het blijft echter van belang om de individuele risico's van korte- en lange termijn gerelateerde bijwerkingen af te wegen in de klinische besluitvorming.

Hoofdstuk 5 is gericht op het identificeren van factoren die bijdragen aan een succesvolle behandeling met methotrexaat bij patiënten met atopisch eczeem. Dit werd gedaan door het onderzoeken van klinische kenmerken en serumproteïnen uit het bloed met als doel voorspellers te vinden die bijdragen aan een betere onderverdeling van patiënten die goed (responder) of minder goed (non-responder) reageren op behandeling met methotrexaat. De resultaten toonden aan dat onderhuidse toediening van methotrexaat een positief effect heeft na 6 maanden behandeling in vergelijking met orale inname. Bovendien bleken enkele serumproteïnen (CCL5, MMP1, P-selectin en DKK1) significant te verschillen tussen responders en non-responders. Als "proof-of-concept" werden deze vier proteïnen in een voorspelmodel gegoten waarmee ~80% van de patiënten in de juiste responder/non-responder categorie kon worden geplaatst. Om te toetsen of bovenstaande bevindingen een farmacologisch effect zijn van behandeling met methotrexaat of een fenomeen is dat zich specifiek voordoet bij patiënten met atopische eczeem werden dezelfde klinische kenmerken en serumproteïnen onderzocht bij patiënten met psoriasis en artritis psoriatica. Vergelijkbaar met atopisch eczeem werd er een positief effect gezien bij een onderhuidse behandeling met methotrexaat. Het voorspelmodel met de vier serumproteïnen kon niet toegepast worden bij psoriasis en artritis psoriatica patiënten, wat maakt dat de bevindingen eerder passen bij atopisch eczeem en niet bij een farmacologisch effect van methotrexaat. Deze studie toont de mogelijkheid om een voorspelmodel te construeren en de gevonden data kunnen richting geven voor toekomstig onderzoek om de werkelijke bruikbaarheid van het model te toetsen.

About the author

Nanette Vincken was born on November 6th, 1988 in Heerlen, The Netherlands. She obtained her secondary school diploma (gymnasium at College Rolduc in Kerkrade) in 2008 and subsequently pursued her studies in Medicine at Maastricht University. In 2012, she completed an internship in Internal Medicine and Rheumatology at the Landspítali in Reykjavík, Iceland. Upon obtaining her medical degree in 2015, she worked as a clinician in the department of Internal Medicine and Nephrology in Curaçao, the Netherlands Antilles. In 2016, Nanette Vincken pursued her interest in minor surgical procedures in conjunction with internal disorders by joining the Department of Dermatology at the Mosaderma Kliniek in Hoensbroek, the Netherlands.

Despite her experience, she remained unsure about which medical specialism to pursue. Consequently, she decided to undertake a PhD trajectory in 2017 at the Laboratory of Translational Immunology, where she focused on translational research related to psoriatic arthritis and psoriasis. However, the birth of her daughter, Veerle, and a personal experience with illness caused her to re-evaluate her priorities. She realized that spending time with her loved ones was invaluable and irreplaceable. As a result, she decided to embark on a new professional journey and applied for the specialization of general practitioner. After being accepted, she commenced her training in March 2022. Nanette hopes to leverage her experience as a patient to become a doctor that guides her patients through every aspect and phase of their illness.

When not working, Nanette enjoys spending time with her partner Jakob and daughter Veerle. Her hobbies include outdoor activities such as hiking, traveling, gardening, snowboarding, and kitesurfing, as well as indoor pursuits such as painting, reading and going to the gym. Additionally, being a Limburger, she enjoys living the Burgundian lifestyle, savoring the pleasures of good food and drinks with friends and family.

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