Real-world evidence in pediatric psoriasis:

Moving towards non-invasive biomarkers and personalized care

Finola M. Bruins

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Dissertation to obtain the degree of doctor

from Radboud University Nijmegen

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according to the decision of the Doctorate Board

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Monday, June 30, 2025

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by

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Epidemiology

Psoriasis is a common chronic, immune-mediated, inflammatory skin disease. Psoriasis develops before the age of 20 years in around 30% of all psoriasis patients.[1-5] Although psoriasis in childhood is not uncommon, data on pediatric psoriasis epidemiology is limited and prevalence numbers vary slightly depending on study population, design, gender and age. De Jager et al. showed an estimated prevalence of 0.37% in children aged 0-10 years and 1.09% in patients aged 11-19 years in the Netherlands.[5] Similar rates were found in a study from the United Kingdom (0.55% in 0-9 years; 1.37% in 10-19 years) and in a German population (0.18% in 0-9 years; 0.83% in 10-19 years).[1,6] Two claims-based studies from the United States showed lower prevalence results of 0.03% in children aged 0-9 years and 0.16% for patients aged 10-17 years, with an overall prevalence of 0.09% and 0.13%.[7,8] Although psoriasis may manifest at any age, median age for childhood onset ranges between 7 and 10 years.[1,4,6,9,10] Overall, approximately one-third of (adult and pediatric) psoriasis patients have an affected first-degree relative.[4,11] In the pediatric population, patients more often have a positive family history, with percentages of children with a first- or second-degree affected family member ranging from 13.6% in Singaporean children to 73.3% and 71.0% in Dutch and Australian children.[12-15]

Clinical features

Psoriasis is a chronic disease, characterized by exacerbations and remissions and is hard to predict: while psoriasis remains mild and stable for many years in some patients, psoriasis might progress quickly in others. [16] Although the diagnosis is primarily based on clinical features, biopsy can sometimes help to confirm the diagnosis in children with atypical presentations.[17] Psoriasis is a clinically heterogeneous disease with several clinical subtypes, namely plaque psoriasis (also called psoriasis vulgaris), guttate psoriasis, inverse psoriasis, pustular psoriasis and erythrodermic psoriasis. [18]

Plaque psoriasis is the most common variant in children, accounting for at least 70-90% of all cases.[12,19-21] It is characterized by well-demarcated erythematous plaques with silvery-white scale typically involving the scalp, postauricular region, elbows, knees and umbilicus.[19,21,22] Pruritis is common and psoriasis lesions may cause pain or bleeding. In children plaques may be smaller, thinner and less scaly than in adults and psoriasis lesions tend to develop more often on the face and flexural sites.[17,19] The scalp is the most frequently involved area and often the first area of

presentation in pediatric patients.[22] Infants with psoriasis may have involvement of the diaper area, which is defined by sharply demarcated, minimally elevated erythematous plaques, often macerated, in de diaper area and inguinal folds.[15]

Guttate psoriasis is the second most common type of psoriasis in pediatric patients, ranging from 13.7-30% of cases in children.[9,12,19,21-23] This type manifests as numerous small, drop-like, erythematous, scaly papules on trunk and extremities. Guttate psoriasis is often preceded by infections, specifically group A beta hemolytic streptococcus infection of the pharynx or perianal area. A guttate psoriasis triggered by a streptococcus infections may spontaneously clear, but a proportion of patients with guttate psoriasis (with or without streptococcus infection as trigger) will eventually progress to plaque-type psoriasis.[10,12,24]

Psoriasis of the skin can be accompanied with nail involvement. The prevalence of nail psoriasis in children ranges from 10.2% to 39.2%.[10,12,14,25] Clinical features of nail psoriasis depend on the anatomical location of psoriatic inflammation within the nail unit. The effects of psoriasis on the nail matrix involve alterations of the nail plate, such as pitting, leukonychia, red spots in the lunula and crumbling.[26] Psoriasis of the nail bed may be expressed as onycholysis, oil-drop patches, dyschromia, splinter hemorrhage and nail bed hyperkeratosis.[26] The most common nail changes are pitting, onycholysis and subungual hyperkeratosis in both adults and children.[26-29]

Impact on quality of life

Pediatric psoriasis can greatly impact quality of life.[30-37] A study by Beattie et al. showed that the influence of psoriasis on the quality of life in children with psoriasis was at least equal to that of other chronic childhood diseases, such as arthritis, asthma, epilepsy and diabetes.[38] Psoriasis in children has been shown to interfere with social relationships, school and sport.[35,37] Children can experience teasing, name calling and social exclusion by peers.[19] Factors that mostly seem to influence quality of life are itch, embarrassment and difficulty with treatment regimens.[36] Effective treatment was previously shown to have a positive effect on the quality of life, with most improvement seen in itch and sleep disturbance.[36,39]

Children and adolescents are a vulnerable group since significant physical, psychological and social developmental changes take place during this period in life.[40] The development of psoriasis at an early age may therefore lead to cumulative life course impairment, in which longstanding effects of stigmatization, physical and psychological comorbidities may influence important decisions and milestones during life, such as education, jobs and relationships.[40-44] Bronckers et

al. described the impact of psoriasis on young adults (18-30 years) and found that these patients experienced impairment in daily activities, current physical health, and showed reduced productivity at work due to psoriasis.[31] Female patients, patients with higher body mass index and longer disease duration seemed to be more severely impaired.[31] Further research is needed to better understand the overall impact of psoriasis on life course and to identify risk factors for cumulative life course impairment, which ultimately may facilitate treatment decisions earlier in the disease course.[40,44]

Comorbidities

Psoriasis is known to be associated with psoriatic arthritis, occurring in 10-40% of adult psoriasis patients.[45] In pediatric psoriasis, however, prevalence seems to be lower, ranging from 1% to 10%, although this prevalence is uncertain due to juvenile psoriatic arthritis being a heterogeneous disease troubling diagnosis.[10,12] Juvenile psoriatic arthritis is believed to be a subtype of juvenile idiopathic arthritis, having overlapping but also distinctive clinical features.[46-48] It is defined following the International League of Associations for Rheumatology (ILAR) criteria as having a persistent arthritis > 6 weeks prior to the age of 16 years and the presence of psoriasis, or in case psoriasis is absent, having at least 2 of the following minor criteria: first degree relative with psoriasis, dactylitis, or fingernail abnormalities (e.g. pitting or onycholysis).[47,49]

In the pediatric psoriasis population, many studies have focused on obesity as a comorbidity and have shown a strong link between presence of psoriasis and children who were overweight, had obesity and central adiposity.[6,50-58] A recent pooled meta-analysis of pediatric psoriasis patients found odds ratio of 1.58 (95% CI 1.14-2.19, $p = .006$) for being overweight and 2.45 (95% CI 1.73-3.48), $p < .001$) for obesity compared to control patients.[50] They further demonstrated that the association with obesity is dependent on the severity of disease, with moderate-severe psoriasis patients having higher odds of obesity compared to children with mild psoriasis.[50] Koebnick et al. conducted a large cross-sectional population-based study of patients aged 2-19 years and showed that overweight and obesity were associated with increased risk of psoriasis during childhood.[59] Although studies have shown a strong link between psoriasis and obesity, the etiology of this association has not been elucidated yet.[60] It is currently thought that systemic inflammation may underlie both diseases.[60,61] However, the temporal relationship between obesity and psoriasis is uncertain. A historical Danish cohort showed that increased body mass index in adolescent females preceded the onset of psoriasis.[62] Another small pilot study of 27 patients further showed that being overweight or

obese preceded psoriasis by at least 2 years in 93% of pediatric psoriasis patients.[51] However, the relationship between psoriasis an obesity may be more complicated and may also be influenced by other factors such as genetics, race and geography or due to behavioral factors once psoriasis develops, for example less physical activity or psychosocial effects leading to weight gain.[19,60]

In addition to obesity, another comorbidity in pediatric psoriasis is metabolic syndrome.[50,53,55-58,63-66] Metabolic syndrome in children is defined as having 3 or more of the following: hypertriglyceridemia, low high-density lipoprotein (LDH) cholesterol, high fasting glucose, central obesity (waist circumference) or hypertension.[17] A large retrospective cohort study in the United States analyzed the risk for developing metabolic syndrome in children with psoriasis compared to controls without psoriasis.[53] Analysis showed that pediatric psoriasis patients had an increased risk of developing hyperlipidemia, hypertension, diabetes and metabolic syndrome compared to children without psoriasis. This increased risk was irrespective of obesity status, although obesity was a strong contributor to comorbidity development.[53] Kwa et al. additionally showed that the odds of diabetes and hypertension were approximately twofold higher in psoriasis patients aged 0-9 compared to 10-17 years.[58]

Besides physical comorbidities, studies have shown that children with psoriasis also have a higher risk of psychiatric disorders, such as depression, anxiety and bipolar disease.[57,67-71] Two U.S. and one European claim-based database studies compared pediatric psoriasis patients to matched psoriasis-free pediatric control subjects and found that children with psoriasis had an increased risk of developing psychiatric disorders, especially depression and anxiety, and receiving medication for psychiatric disorders.[57,67,70] Similarly, a case-control study in 108 children found that at least one psychiatric diagnosis was present in 70.3% of children with psoriasis versus 27.7% of children in the control group, with children with psoriasis having a 9.21-fold and 6.65-fold greater risk of respectively anxiety and depression.[71]

Immunopathogenesis

Extensive research has been conducted to elucidate the complex immunopathogenesis of psoriasis, which is an interplay of environmental factors, genetic predisposition, keratinocytes, the innate and adaptive immune system.[45,72]

Genetic predisposition is probably the main risk factor for developing psoriasis. The first studies exploring genetic background of psoriasis identified Psoriasis Susceptibility regions (PSOR), of which PSORS1 was found to have the strongest

linkage and association with susceptibility for psoriasis.[73] PSORS1 is located within the major histocompatibility complex (MHC) on chromosome 6p21.[74] The major risk allele of the PSORS1 region is HLA-C*06. This allele has been associated with early onset psoriasis, also called type I psoriasis, which refers to patients with an onset before 40 years of age, with often a more severe disease course.[45,75-77] More recently, many genome-wide association studies have identified multiple susceptibility loci across the genome, explaining approximately 30% of disease heritability to date.[45,78]

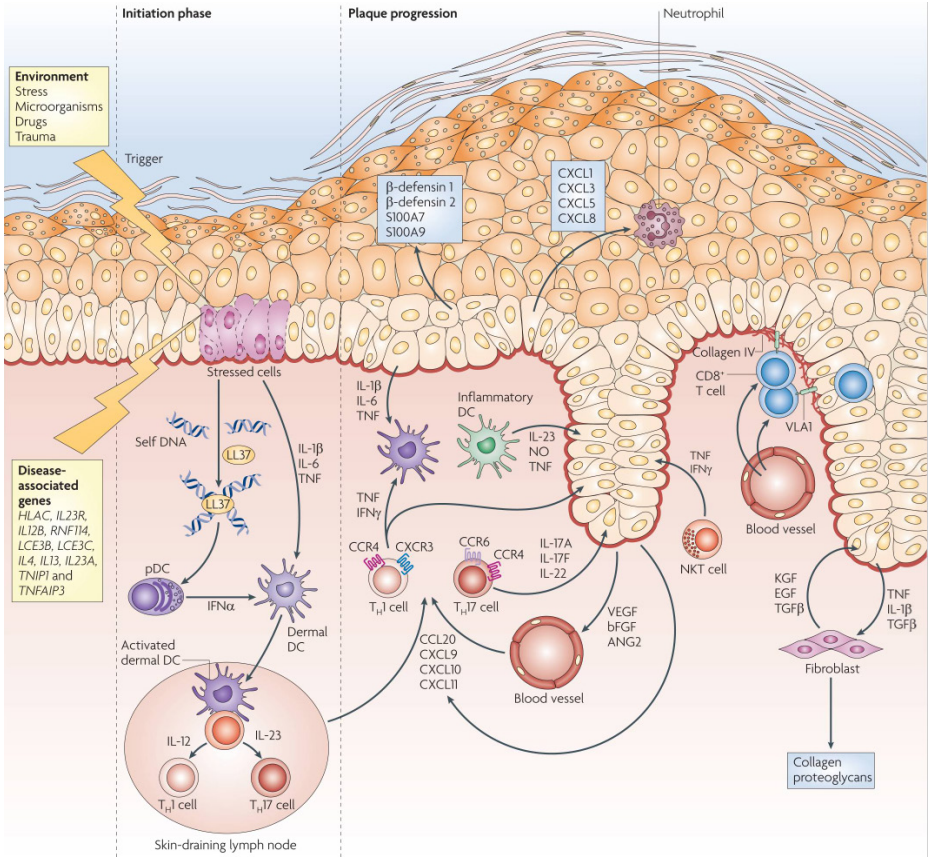

Figure 1. Immunopathogenesis of psoriasis

In psoriasis, environmental triggers may damage keratinocytes in predisposed individuals, prompting the release of various antimicrobial proteins and cytokines. These proteins and cytokines activate dendritic cells, leading to production of IL-12 and IL-23, which in turn stimulate the differentiation of naïve T-cells into T-helper (Th)-1, Th-17, and Th-22 cells. These activated T-cells subsequently release IL-17, IL-22, and TNF-α, initiating intracellular signaling in keratinocytes. This sets off an inflammatory cascade characterized by keratinocyte proliferation, angiogenesis, vasodilation, and immune cell recruitment to the skin. In the chronic phase, keratinocytes overexpress chemokines (such as CXCL9, CXCL10, CCL20) and antimicrobial peptides (including human beta defensins 1 and 2), leading to a feed-forward inflammatory response sustaining skin inflammation.

The immune system can be divided into the innate immune system, which rapidly defends the human body from microorganisms, and the adaptive immune system, which forms the second line defends, takes longer to evolve, but develops long-term memory.[79] Keratinocytes, macrophages and natural killer T-cells belong to the innate immune system. Dendritic cells form the link between innate and adaptive immunity.[79] In psoriasis, it is hypothesized that an environmental trigger in a predisposed individual may provoke or damage keratinocytes, leading to secretion the antimicrobial proteins, such as LL-37, human beta defensins 2 and 3, self-DNA fragments and cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α.[45,72,79-81] These antimicrobial proteins and cytokines activate plasmacytoid dendritic cells, which produce interferon-α leading to activation of myeloid dendritic cells, which in turn produce IL-12 and IL-23.[72] Both interleukins induce differentiation of naïve T-cells into T-helper (Th) cells. IL-12 promotes activation of Th-1 cells, whereas IL-23 has a role in proliferation and survival of Th-17 and Th-22 cells.[45] The IL-23-mediated activation of Th-17 cells is considered the most important pathway in psoriasis pathogenesis.[45,72] Th-17, Th-22 and Th-1 cells further produce IL-17, IL-22 and TNF-α, which activate intracellular signal transduction in keratinocytes, resulting in an inflammatory cascade leading to keratinocyte proliferation, angiogenesis and vasodilation and recruitment of immune cells into the skin.[72] In the chronic phase of disease, keratinocytes overexpress a number of chemokines (such as CXCL9, CXCL10, CCL20) and antimicrobial peptides (including human beta defensins 1 and 2), leading to a feed-forward inflammatory response and as such sustain skin inflammation.[80,81]

Noninvasive biomarkers

More guidance regarding the future disease course is desirable in daily clinical psoriasis care. It would be valuable for physicians to know beforehand which patients are at risk for developing severe psoriasis or which treatment is likely to be most effective, enhancing personalized medicine. This is especially true for the pediatric population, given the chronic nature of psoriasis and need for long-term care. In addition, it is hypothesized that early (aggressive) intervention might positively influence the course of the disease. Identification of children at risk for the development of severe disease would assist clinical decision making and early intervention. Biomarkers, including both clinical patient characteristics or biomarkers derived either from the skin or blood, could potentially identify those at risk for severe disease course and/or an effective treatment response. In the pediatric population, patient-friendly non-invasive methods are desirable to minimize the

development of fear for interventions and to enable regular application. In this thesis, we therefore focused on the search for clinical characteristics and non-invasive skin proteins as potential biomarkers.

Biomarkers in psoriasis

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'.[82] Biomarkers may comprise of clinical patient characteristics or blood-derived markers such as human leukocyte antigen (HLA) typing or cytokines.[83-90] Current biomarker research in psoriasis has been mainly conducted in adult patients. Multiple studies have focussed on clinical characteristics predicting treatment success or longer drug survival.[88,91,92] Most important clinical predictors for biological drug survival in adult psoriasis patients are sex, obesity and psoriatic arthritis, of which female gender and obesity were associated with a higher chance of treatment discontinuation, whereas a diagnosis of psoriatic arthritis showed lower rates of discontinuation.[88] However, although some biomarkers predicting treatment success and longer drug survival have been described, no clinical characteristics to predict the development of a severe disease have been identified. In addition to clinical biomarkers, many studies have focussed on blood-derived biomarkers to predict disease course or treatment response, including genetic markers and inflammatory cytokines, skin tissue and transcriptional biomarkers.[83-87,89,90,93] Although many efforts have been made to identify these biomarkers, none have been sufficiently able to predict disease course or treatment response in order to be translated into routine clinical practice.[93] In pediatric psoriasis, studies on either clinical predictors, blood- or tissue-derived biomarkers are lacking.[94,95]

Skin protein detection

Skin proteins can be acquired noninvasively and are therefore a promising source of biomarkers, especially in the pediatric population. Repetitive tape-stripping is the most widely used method to sample proteins from the skin and has been used in both psoriasis and atopic dermatitis.[89,96] For tape stripping, multiple tape strips are applied and removed from the skin on the same location removing part of the stratum corneum, enabling analysis of skin surface proteins from these strips.[96] Additionally, other non- or minimally invasive methods have been used, such as skin lavage, abrasion methods, reverse iontophoresis, and hair root sampling.[97-100] Recently, the transdermal analysis patch (TAP) has been introduced as a method to derive skin surface proteins.[101,102] The TAP consists of a multiplex capture-antibody microarray supported by an adhesive bandage and captures soluble proteins

that passively diffuse from the skin during a 20 minute application.[101] In previous research, TAP has shown the potential to monitor dynamic protein changes in the skin resulting from skin irritating models in healthy individuals.[103] Additionally, an advantage of TAP over tape stripping is that TAP does not damage the stratum corneum, therefore decreasing the risk of koebnerization in psoriasis patients.

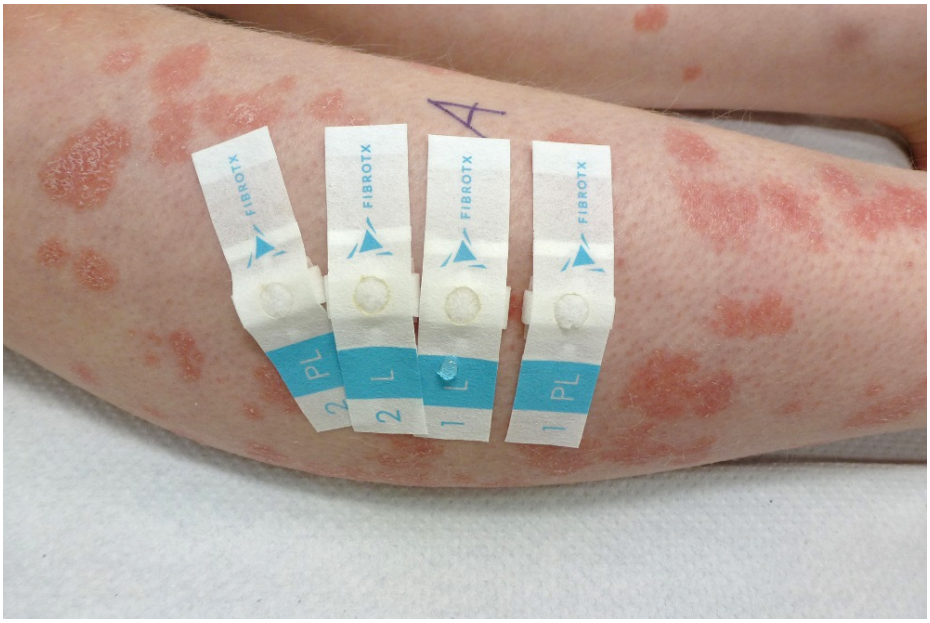

Figure 2. The Transdermal Analysis Patch (TAP)

This image shows four TAPs applied to the skin. After application, four drops of phosphate buffered saline (pH 7.4) are added to reservoir of the TAP. The TAP is applied for 20 minutes to capture skin surface proteins through immune recognition.

Treatment of psoriasis in pediatric patients

To date, no cure for psoriasis exists and treatment is therefore focused on reducing disease symptoms.[104] Several treatment modalities for the management of pediatric psoriasis exist and include topical agents, phototherapy, conventional systemic treatment and biologics.[17,19,105] Treatment choice is dependent of several factors such as age, psoriasis severity and location, impact on quality of life, previous treatments, costs, accessibility and assessment of risks versus benefit of a treatment.[19] In pediatric psoriasis, shared-decision making with the patient and family is important, especially considering the potential need for lifelong treatment.[19]

Topical treatments

Topical treatments, consisting of topical corticosteroids, vitamin D analogues and calcineurin inhibitors, are generally considered to be the first choice of treatment and the majority of children with psoriasis can be adequately managed with these agents.[17,106,107] Topical corticosteroids are most commonly prescribed and, although evidence on effectiveness and safety is limited, there is vast clinical experience and expert opinion on the use of these topical treatments.[108,109] Potential side effects include local telangiectasias, atrophy, striae and, if used extensively, suppression of the hypothalamic-pituitary-adrenal axis. It is therefore advised to apply topical corticosteroids adhering to a maximum application based on age and to use them intermittent and with rotational application, for example in combination with vitamin D analogues or calcineurin inhibitors.[17] Calcipotriol and calcitriol are both vitamin D analogues, which are often used in combination with topical corticosteroids to achieve maximal effect and a steroid-sparing effect.[17,108] Tacrolimus (0.03% and 0.1%) ointment and pimecrolimus 1% cream are calcineurin inhibitors which are used in children with psoriasis off-label and have shown to especially improve intertriginous and facial psoriasis.[110,111]

Dithranol (anthralin)

Dithranol, also known as anthralin, is one of the oldest topical antipsoriatic treatments, which has shown to be safe and effective in the treatment of moderate to severe pediatric psoriasis.[112-116] It is often applied in a day-care setting as short-contact therapy, usually given as a daily application in increasing concentrations and application time (from 15 to 45 minutes) until the skin is clear or almost clear.[112,117] The average treatment duration is around 2 months.[112] In our practice, until recently the majority of pediatric patients was treated with dithranol as a second-line topical treatment before commencing phototherapy or systemic treatment, especially considering its safe and effective profile.[106,108] However, in

more recent years, especially since dithranol has not always been available due to supply issues for several periods of time, phototherapy and/or systemic treatment have been more often initiated earlier on without using dithranol first.

Phototherapy

Phototherapy, usually narrow-band ultraviolet B (NB-UVB), has been shown to be effective in pediatric psoriasis, particularly for diffuse guttate and thin-plaque psoriasis.[118-120] Short-term side effects of phototherapy include erythema, burning, pruritus and blistering.[17] Although phototherapy has been shown to be effective, this treatment requires two to three hospital visits per week, which might be an issue for (school-aged) children and their caregivers. Anxiety may also be a significant problem in younger children.[17] Furthermore, caution is warranted in young patients and children with light skin-types due to possible long-term carcinogenic effects, even though long-term risks for (non-melanoma) skin cancer have not been assessed in the pediatric population.[106,108] Due to these concerns, phototherapy should be avoided in pre-adolescent patients.

Conventional systemic treatment

Systemic therapy is indicated for pediatric patients with a moderate to severe psoriasis which is recalcitrant to topical treatments. Choice of systemic treatment may be challenging due to limited evidence on safety and efficacy in children and treatments are often prescribed off-label. The most commonly used conventional systemic treatments for pediatric patients with moderate to severe psoriasis are methotrexate, fumaric acid esters, acitretin and cyclosporine.

Although methotrexate is the most prescribed agent for pediatric psoriasis internationally, evidence on effectiveness and safety in this population is sparse.[19] One randomized clinical trial compared methotrexate to adalimumab and found that 32.4% of 37 patients with methotrexate achieved a PASI75 at week 16.[121] Additionally only few retrospective studies[122-126] and one small (n = 25) prospective study[127] assessed methotrexate effectiveness and safety in a real-world setting. Methotrexate can be administrated either orally or subcutaneously and is usually dosed once weekly as 10-15mg/m^2/week or according to bodyweight at 0.2-0.4mg/kg/week.[123] Improvement of psoriasis may take 3 to 6 months.[17] When therapeutic control is accomplished, it is advised to taper to the lowest effective dose to minimize possible side-effects. The most common side-effects reported in children and adolescents are nausea, vomiting, transient elevation of liver enzymes and fatigue. Bone marrow suppression, pulmonary toxicity, infections and hepatotoxicity including liver fibrosis have only rarely been reported in the pediatric

population.[17,123,127] Folic acid is supplemented during methotrexate treatment, mostly to reduce gastrointestinal and hepatic side effects.[106,123,128,129] To date, there is no consensus for folic acid timing and dosing in the treatment of psoriasis.[23,106,128] It is still a matter of debate whether different folic acid regimens (ranging from 1-5mg daily to 5-10mg once a week) have an effect on the occurrence of side-effects, although few studies suggest that folic acid given 6 or 7 days per week have a more beneficial effect on gastro-intestinal side-effects when compared to supplementation once per week.[123,130,131]

Fumaric acid esters are prescribed for children with psoriasis off-label in various European countries. Few case-reports, case series and retrospective studies have been published showing that fumaric acid esters are effective and well-tolerated in children and adolescents with psoriasis.[132-135] Recently, Hamm et al. reported the results of the first randomized placebo-controlled study on the efficacy and safety of fumaric acid esters in 134 children and adolescents aged between 10 and 17 years.[136] The results show that 55% of children treated with fumaric acid esters achieved a ≥ 75% reduction of Psoriasis Area and Severity Index (PASI), which was significantly higher compared to placebo (19%).[136] Gastrointestinal adverse events and flushing were most frequently reported as side effects.[136] There is some concern about the possibility of fumaric acid esters induced lymphocytopenia and the development of progressive multifocal leukoencephalopathy (PML), which has been described in adults.[137] Although results from studies on safety and effectiveness of fumaric acid esters in children support European guidelines to consider its use as systemic treatment for pediatric psoriasis patients, laboratory abnormalities should be monitored closely.[23,106]

The use of acitretin in children has been described by only few studies to be effective and safe primarily in the treatment of (generalized) pustular, palmoplantar psoriasis and erythrodermic psoriasis.[105,138] Acitretin is usually dosed at 0.1 to 1 mg/kg/day for pediatric patients, with improvement of psoriasis generally seen after 2 to 3 months for plaque psoriasis.[128] Most frequently reported side effects are mucocutaneous, including cheilitis, xerosis, epistaxis, skin fragility and hair loss.[138] Hyperlipidemia may occur and is typical transient and dose dependent.[128] Due to teratogenicity of acitretin in combination with delayed clearance, pregnancy must be avoided until at least 3 years after discontinuation of therapy, and use in adolescent girls should be therefore considered carefully.[138]

Cyclosporine is another systemic treatment option for pediatric psoriasis. It has a rapid onset of action and is therefore considered to be a good choice if fast control

of severe psoriasis in children is required.[139] Several small retrospective studies have shown cyclosporine to be effective and generally well tolerated in pediatric psoriasis patients.[124,125,140-143] Cyclosporine it typically dosed 2 to 5 mg/kg/day in children divided in two doses.[128] Reported side effects include nephrotoxicity, hypertension and gastro-intestinal complaints. Given the potential for (long-term) renal toxicity, gradual tapering of cyclosporine to stop is advised once the psoriasis has been stabilized, with transition to another systemic agent if necessary.[128]

Biologic treatment

In recent years, several biological agents for pediatric psoriasis have been approved. Biologics selectively target cytokines or their receptor involved in the inflammatory psoriasis cascade.[144-146] These include monoclonal antibodies against TNF-α, IL-12/23, IL-17 and IL-23. At this moment, five biologics are approved by the European Medicine Agency (EMA) for moderate to severe pediatric psoriasis, namely the TNFα inhibitors etanercept (≥6 years) and adalimumab (≥4 years), IL12/23 inhibitor ustekinumab (≥ 6 years), and very recently the two IL17 inhibitors secukinumab (≥6 years) and ixekizumab (≥6 years).[144] The United States Food and Drug Administration (FDA) has not yet approved adalimumab, but has approved the other abovementioned biologics.[144] All biologics are administered subcutaneously, with injection frequency depending on the biologic administered: once weekly for etanercept, once every 2 weeks for adalimumab, once every 4 weeks for ixekizumab and secukinumab and once every 12 weeks for ustekinumab. All five biologics have been investigated in randomized controlled studies, which have shown high efficacy and a favorable side effect profile, including mostly upper respiratory tract infections, nasopharyngitis and headache.[121,145-153] Although these controlled trials have shown that the available biologics are efficacious for pediatric psoriasis patients, real-world data of the long-term effectiveness and safety in these patients is sparse.[154-159] In the future it is expected that more biologics will become available for children with psoriasis, with ongoing clinical trials testing efficacy and safety of certolizumab (NCT04123795), brodalumab (NCT03240809), guselkumab (NCT03451851), tildrakizumab (NCT03997786) and risankizumab (NCT04435600) in children at this moment.[145]

Real-world evidence

Obtaining evidence on benefits and risks of treatment in health care can be done through several types of research, roughly divided into observational studies and randomized controlled trials.[160] In the latter, the randomization balances patient

characteristics between the intervention groups being compared, and as such minimize bias so that causal conclusions regarding the study intervention can be drawn.[161,162] Although randomized controlled trials are considered to be superior to other forms of evidence, there are also some significant limitations.[161,162] Most importantly, often due to strict in- and exclusion criteria used, patients included in trials differ from the population that physicians see in daily clinical practice. A study by Phan et al. assessed the proportion of pediatric psoriasis patients that received biological treatment in daily clinical practice (BiPe cohort) that would be eligible to participate in the pediatric phase III trials of etanercept, adalimumab and ustekinumab according to the published in- and exclusion criteria.[163] Indeed, the study found that 54.5% of pediatric psoriasis patients seen in their real-life practice would be ineligible for participation in the randomized controlled trials. Main reasons for ineligibility being type of psoriasis (for example guttate psoriasis), other previous or concomitant treatments and psoriasis severity scores below those required.[163] Ineligible patients were significantly younger, had less severe psoriasis and more comorbidities than eligible patients.[163] Furthermore, studies in adult psoriasis patients have shown that effectiveness of biologics in real-life does not match efficacy found in trials.[92,164] Real-world studies, such as observational registries, could form a bridge between trial results and daily clinical practice. Especially for chronic diseases which require long-term treatment, such as psoriasis, real-world studies can provide data on treatment persistence, effectiveness, and safety over a long period of time, which is often not provided by clinical trials. In summary, at the moment of market approval of a treatment, evidence is insufficient to fully guide physicians in everyday practice to decide on the best treatment for their patients.[160] Real-world evidence is therefore needed to complement the evidence from randomized controlled trials in order to optimize treatment choices in daily clinical care.[165]

Child-CAPTURE

This thesis is based primarily on data collected in the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). This registry contains observational, longitudinal, prospective data of pediatric psoriasis patients in daily practice. The Child-CAPTURE was initiated at the Department of Dermatology at the Radboud University Medical Centre in Nijmegen in September 2008 and has been expanding ever since, now including over 600 pediatric psoriasis patients. This ongoing cohort includes all children with psoriasis (<18 years at first visit) who attend the department of Dermatology and who consent with participation in the registry. Patients already included in the registry who reach the age of 18 years are followed as young adults. Collected data includes demographics, medical history,

treatment history, disease severity scores at initiation and during treatment, safety data (according to the Common Terminology Criteria for Adverse Events)[166] and patient reported outcomes. All data is managed using the electronic data capture system CASTOR. Written informed consent is obtained from the parents or guardians and/or from the participating patients according to applicable rules. This registry was reviewed by the ethics committee of the Radboudumc before initiation and was deemed to not fall within the remit of the Medical Research Involving Human Subjects Act.

Psoriasis severity scores and patient reported outcomes

Commonly used scores to define and monitor psoriasis severity are the Psoriasis Area and Severity Index (PASI; range 0-72), the Physician Global Assessment (PGA; range 0-5) and the affected Body Surface Area (BSA).[167,168] Additionally, a severity score for single lesion severity exists: the SUM score (0-12), defined as the sum of the severity scores for erythema (0–4), induration (0-4), and desquamation (0-4). The PASI is used most often is both clinical trials and real-world studies. It is calculated by assessing four body regions: head, trunk, upper and lower extremities. For each region, subscores are determined for erythema (0-4) , desquamation (0-4), induration (0-4) and affected body surface area (0-6), eventually resulting in an overall score (0-72), with a higher score indicating more severe psoriasis.[168] In randomized controlled trials, efficacy outcomes are usually reported as relative PASI reduction in comparison to baseline. For example, a 75% or 90% reduction of baseline PASI (i.e. from a PASI 10.0 to respectively 2.5 or 1.0) would be defined as PASI75 or PASI90.[164]

To measure patient's experiences of disease severity, impact on quality of life and satisfaction of treatment, researchers and clinicians have developed patient-reported outcome measures. Several patient-reported outcome measures exist for pediatric psoriasis, such as the Children's Life Quality Index (CDLQI), Children's Scalpdex in Psoriasis (CSP), Simplified Psoriasis Index and Pediatric Quality of life Inventory.[169] The CDLQI is the most widely used outcome measure in both pediatric psoriasis real-world studies and clinical trials. In the Child-CAPTURE, the CDLQI is collected at every visit if a patient was <18 years and/or the Dermatology Life Quality Index (DLQI) if a patient was ≥16 years.[170,171] Both have a score ranging from 0-30, with a higher score indicating more impact of psoriasis on the health related quality of life. A CDLQI or DLQI score of 0 or 1 represents no effect of psoriasis on a patients quality of life.[171,172] Patient-reported outcome measures are important in both studies and clinical practice to increase insight into patient's satisfaction of their disease and treatment order to provide patient-centered care.[169]

Aims and outline of this thesis

In recent years, the treatment landscape in pediatric psoriasis is changing with the introduction of new, more effective, systemic (biologic) treatment options. There is an ongoing debate if early intervention with more effective treatment should be encouraged to limit psoriasis disease severity and course. This is especially important for pediatric psoriasis patients, considering the associated comorbidities and the cumulative effects of psoriasis on quality of life and life course. Treatment should be tailored to each individual child, considering disease presentation, comorbidities, and impact on quality of life, also considering the potential need for lifelong treatment. Ultimately, the aim is to determine the right treatment for the right child at the right time. To move closer to this goal of personalized care it is important to gain more insight in the identification of biomarkers that might predict disease course or treatment success as well as to acquire more real-world evidence on the optimal use of systemic treatments in pediatric psoriasis patients.

Therefore, this thesis consists of two parts. The first part aims to study the use of non-invasive biomarkers in pediatric psoriasis patients in daily clinical practice. In particular, we will explore the use of Transdermal Analysis Patches (TAP) and assess nail psoriasis as a potential clinical predictor. In the second part, we focus on optimization of care for pediatric psoriasis patients by assessing the real-world effect of psoriasis severity improvement on the quality of life, exploring treatment patterns, and studying effectiveness and safety of methotrexate in pediatric psoriasis patients. Specifically, the following aims are formulated:

Non-invasive biomarkers in pediatric psoriasis

1. To study the Transdermal Analysis Patch (TAP) as a non-invasive tool for biomarker detection.
    a. To explore the use of Transdermal Analysis Patch (TAP) for skin surface protein measurement in daily clinical practice.
    b. To examine the correlation of skin surface proteins measured by TAP with disease severity.
2. To study the presence of nail psoriasis as a potential predictor for more severe psoriasis disease course over time in pediatric patients.

Optimizing management of pediatric psoriasis patients

3. To gain insight in real-world treatment patterns, persistence and factors associated with switching to systemic treatment in pediatric psoriasis patients.

4. To determine if a higher degree of psoriasis improvement in fact leads to further increase of quality of life and in addition, if type of treatment (topical versus systemic) influences quality of life improvement in pediatric psoriasis patients.
5. To examine effectiveness and safety of methotrexate treatment in pediatric psoriasis in daily clinical practice.

In **chapter 2** we explore the use of the Transdermal Analysis Patch (TAP) for skin surface protein detection in pediatric psoriasis patient in daily clinical practice. In **chapter 2.1** we apply the TAP in pediatric psoriasis patients to detect soluble skin surface proteins and study its detection capability and patient-friendliness. To assess the value of the TAP in daily clinical practice, we further evaluate the use of TAP longitudinally and describe the association of skin surface proteins detected with psoriasis severity over time in **chapter 2.2.** Additionally, the marker detection capability of TAP is compared to tape stripping extraction. In **chapter 2.3** we aim to study the relationship between nail psoriasis and psoriasis severity in order to explore the predictive value of nail psoriasis on the overall psoriasis disease course over time.

In **chapter 3** we focus on optimization of care of pediatric psoriasis patients. First, we evaluate the current treatment patterns, persistence and factors associated with switching to systemic treatment in **chapter 3.1**. In **chapter 3.2** we assess if a higher degree of psoriasis improvement actually leads to a further increase of quality of life in pediatric psoriasis patients, in order to ultimately delineate a clinical meaningful treatment goal considering quality of life. We further analyze the influence of type of treatment on quality of life, independent of the psoriasis severity improvement. In **chapter 3.3** we zoom in on the conventional systemic treatment methotrexate and study its effectiveness and safety in pediatric psoriasis patients in a real-world setting, with additional focus on folic acid regimen.

Finally, this thesis closed with a general discussion in **chapter 4**, in which our findings were discussed in a broader context and future perspectives are provided.

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Chapter 2

Non-invasive biomarkers in pediatric psoriasis

2.1 Skin surface protein detection by Transdermal Analysis Patches in pediatric psoriasis

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Abstract

Introduction

Transdermal Analysis Patches (TAP) noninvasively measure soluble proteins in the stratum corneum. Ultimately, such local protein profiles could benefit the search for biomarkers to improve personalized treatment in psoriasis. This study aimed to explore the patient-friendliness and protein detection by TAP in pediatric psoriasis in daily clinical practice.

Methods

In this observational study, TAPs measuring CXC chemokine ligand (CXCL)-1/2, CC chemokine ligand (CCL)-27, interleukin (IL)-1RA, IL-23, IL-1α, IL-8, IL-4, IL-22, IL-17A, vascular endothelial growth factor (VEGF), human beta-defensin (hBD)-2, hBD-1, and kallikrein-related peptidase (KLK)-5 were applied on lesional, peri-lesional, and non-lesional skin sites of psoriasis patients aged >5 to <18 years. Discomfort during TAP removal as indicator for patient friendliness was assessed by visual analogue scale (VAS; range 0-10).

Results

Thirty-two patients (median age 15.0 years) were included, of which 19 were treated with solely topical agents and 13 with systemic treatment. The median VAS of discomfort during TAP removal was 1.0 (interquartile range 1.0). Significantly higher levels in lesional versus non-lesional skin were found for IL-1RA, VEGF, CXCL-1/2, hBD-2, and IL-8, whereas lower levels were found for IL-1α. Skin surface proteins were measured in both treatment groups, with significant higher lesional levels of KLK-5, IL-1RA, hBD-2, IL-1α, IL-23, and CCL-27 in the systemic treatment group.

Conclusion

The TAP platform holds the potential for patient-friendly and noninvasive monitoring of skin-derived proteins in pediatric psoriasis patients in daily clinical practice.

Introduction

In daily clinical psoriasis care, more guidance regarding treatment response and disease course is desirable. Predictors for disease course are scarce and mainly include clinical patient characteristics (e.g., nail psoriasis and psoriatic arthritis).[1,2] Research focusing on prediction of treatment success in psoriasis mainly targets the body mass index, genotyping, human leukocyte antigen typing, or blood-derived systemic inflammation markers.[3-7] Besides clinical biomarkers or blood-derived biomarkers, the skin itself provides a unique source of potential biomarkers, like disease-associated profiles of cytokines, chemokines, growth factors and/or antimicrobial peptides.[3,8,9]

Reported protein detection in psoriatic skin is mostly derived from punch biopsies, an invasive procedure less suitable for longitudinal follow-up with a risk for pain, scarring, and infection.[10-14] Several noninvasive or minimally invasive methods for protein detection or gene expression profiling in the skin exist. Besides the widely used application of repetitive tape stripping to study skin barrier function and regeneration mechanisms,[15,16] tape stripping is used as a sampling method for protein detection.[17-20] In addition, skin lavage, abrasion methods, reverse iontophoresis, and hair root sampling are described.[21,11,22,23] Furthermore, one microdisk-library array patch method has been used in a pilot study with 3 healthy adult volunteers.[24] The transdermal analysis patch (TAP), developed by FibroTx, is a new diagnostic tool which noninvasively quantifies proteins directly on the skin surface via spot-enzyme-linked immunosorbent assays.[25] Especially in the pediatric patient population, noninvasive methods are key to avoid discomfort and fear for interventions. Additionally, there is a great demand for biomarkers in this specific population considering the chronic aspect of the disease and need for long-term care. In previous research, TAP has shown the potential to monitor dynamic changes in the skin resulting from skin irritating models in healthy individuals.[26] Furthermore, a promising correlation of skin surface proteins sampled by the FibroTx Patch compared to tape strip samples and serum samples was shown in ten adults with atopic dermatitis.[27]

In this explorative observational study, we applied the TAP in daily clinical practice in pediatric psoriasis patients. More specifically we assessed (i) the patient friendliness of TAP, (ii) if protein detection is similar on different body locations, (iii) the TAP detection capability of inflammation-related proteins in lesional, peri-lesional and non-lesional skin and (iv) whether topical and/or systemic treatment affects TAP protein detection capability.

Materials and methods

Study design and population

This study was an explorative observational noninvasive study with internal control in a daily clinical practice setting. Participants were recruited at the outpatient clinic of the Department of Dermatology at the Radboud university medical center in Nijmegen, the Netherlands, between June 2018 and July 2019. Written informed consent and/or assent was given by all subjects and/or their legal guardian before enrollment according to applicable rules. Inclusion criteria were: age >5 and <18 years, diagnosis of psoriasis according to a dermatologist, enough psoriasis plaques to apply the TAPs at the time of enrollment and willingness to participate. Patients with another concurrent inflammatory skin disease were excluded. As study procedures occurred in a daily clinical practice setting, patients were already on a topical or systemic treatment at the moment of inclusion. There was no treatment wash out phase. The study protocol was approved by the Ethics Committee of the Radboud university medical center (NL60952.091.17).

Transdermal Analysis Patch

TAP, produced and commercialized by FibroTx, consist of a multiplex capture antibody microarray supported by an adhesive bandage for easy fixture to the skin (Figure S1).[25] One TAP antibody microarray measures up to seven proteins. The used panel was preset and consists of general skin inflammation-related proteins, of which the majority are classified as chemokines, cytokines, and antimicrobial peptides. More specifically, the following 13 proteins were analyzed by 2 independent TAPs: CXC chemokine ligand (CXCL)-1/2, CC chemokine ligand (CCL)-27, interleukin (IL)-1RA, IL-23, IL-1α, IL-8, IL-4, IL-22, IL-17A, vascular endothelial growth factor (VEGF), human beta-defensin (hBD)-2, hBD-1, and kallikrein-related peptidase (KLK)-5.

Study procedures

Patients were not allowed to use any topical medications or toiletries on the investigated sites on the day of the visit. TAPs were applied on plaques located on the arms, legs, or trunk. Lesional skin, peri-lesional skin, and non-lesional skin, with no psoriasis lesions within a distance of 10 cm, were subjected for analysis. To explore the influence of the body location on the protein profile, 2 psoriasis lesions of interest in each patient were chosen preferably on different body parts. To be able to compare protein levels between lesional, peri-lesional and non-lesional skin, TAPs were also applied peri-lesional of the 2 lesions of interest (Figure S1). After application to the skin, 4 drops of buffer (phosphate buffered saline (pH 7.4) as supplied by manufacturer) were added to the reservoir covering the microarray.

During the 20 min application time, antibodies printed on the micro-array were allowed to capture skin-derived proteins through immune recognition. After removal, the TAPs were stored at -20 °C until the captured proteins were analyzed using spot-enzyme-linked immunosorbent assay. Values outside the detection levels were regarded as not detectable. Detection levels are described in Table S1. All TAPs were applied by 2 physicians (M.J.S. or F.M.B.).

Data collection

After removal of the TAPs, experienced discomfort was rated by the subject on a 10-point visual analogue scale (VAS) as an indicator for patient friendliness. A VAS score of 0 meant no discomfort corresponding with a good patient friendliness and a score of 10 meant maximal discomfort. To assess the overall psoriasis severity, the psoriasis area and severity index (PASI; range 0-72), physician global assessment (PGA; range 0-5), and affected body surface area (BSA), with higher scores indicating more severe psoriasis, were collected. Further, a SUM score (0-12), defined as the sum of the severity scores for erythema (0–4), induration (0-4), and desquamation (0-4), was calculated in order to determine the severity of the psoriasis lesions sampled by TAPs. Additional collected data included age, sex, current treatment, and whether or not topical treatments (excluding emollients) were used on the target lesions in the past 7 days.

Statistical analysis

Demographic data were presented as numbers (percentage) for categorical variables and medians (interquartile ranges [IQR]) for continuous variables. Protein concentrations were depicted in 2 dimensions based on principal component analysis (PCA). Mann-Whitney U tests were performed to further assess differences in protein levels. To assess if protein detection was similar on different body locations (inter-donor variability), protein levels on the 2 different sites were compared by Wilcoxon signed-ranked test for both lesional and peri-lesional measurements. A sensitivity analysis with confounder correction was additionally performed and described in the supplementary material. Statistical package SPSS, version 25 (IBM), and the statistical programming language R version 3.6.2 were used to perform analyses. A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 32 patients were included with a median age of 15.0 (IQR 6.0) years and a median PASI score of 5.2 (IQR 5.1 [Table 1]). At the time of measurements, solely

topical agents were used by 19 patients, while 13 patients were on systemic therapy, with concomitant use of topical treatments if required. Patients on systemic therapy were treated with methotrexate (n=9), fumaric acid esters (n=1), or adalimumab (n=3). Overall, 12 (37.5%) patients did not use any topical treatments on the target lesions 7 days prior to the TAP applications, of which 8 (61.5%) were from the systemic treatment group. Patients on systemic therapy had significantly lower PASI scores and were significantly older compared to patients on topical agents (Table 1). One patient mentioned a burning sensation after removal of the TAP, no other adverse events were reported. The median reported VAS score for discomfort during removal was 1.0 (IQR 1.0).

Protein profiles of lesional and peri-lesional skin are similar on different Sites

Comparison of the 2 different skin sites within 1 patient with the Wilcoxon signed-ranked test showed no significant differences for each individual protein on the group level (Table S2-3). Therefore, since significant differences between different (body) sites were not found, and to improve power, measurements were combined for further analyses, resulting in 64 lesional and 64 peri-lesional samples. IL-4 and IL-17A were excluded from analyses as only one (IL-4) and no measurements (IL-17A) were above the lower detection level.

TAP detects different protein levels in lesional, peri-lesional and non-lesional skin

To explore the combinatory effect of the protein profile in lesional versus peri-lesional and non-lesional skin, a non-metric multidimensional scaling approach, that is, PCA analysis, was used. We revealed a separation between non-lesional, peri-lesional, and lesional samples in the first dimension (Figure 1). In line with known psoriasis-related expression profiles, further comparison per protein shows significantly higher levels for IL-1RA, hBD-2, IL-8, and CXCL-1/2 in lesional skin compared to both non-lesional and peri-lesional skin (Figure 2; Table S4).[17,18] VEGF showed a significantly higher level for the lesional skin compared to non-lesional skin, but not compared to peri-lesional skin. In contrast, significantly lower protein levels were found for IL-1α in lesional skin compared to both peri-lesional and non-lesional skin, which corresponds with previously reported research.[18] No significant differences between lesional, peri-lesional, and non-lesional skin were detected for IL-23, CCL-27, IL-22, hBD-1, and KLK-5, although a trend for higher levels of IL-23 and IL-22 in lesional skin compared to non-lesional skin was observed. A sensitivity analysis with confounder correction (for sex, age, body site, treatment, use of topical corticosteroids in the last 7 days, and PGA) revealed similar results (Table S5).

Table 1. Patient characteristics

Characteristics	Total (n = 32)	Patients on topical treatment (n = 19)	Patients on systemic treatment[a] (n = 13)	*p*-value
Sex, No. (%)				1.000
Male	17 (53.1)	10 (52.6)	7 (53.8)	
Female	15 (46.9)	9 (47.4)	6 (46.2)	
Age, years, median (IQR)	15.0 (6.0)	13.3 (5.9)	16.5 (2.4)	.018
Psoriasis severity, median (IQR)				
PGA	2.0 (2.0)	3.0 (2.0)	2.0 (1.0)	.114
PASI	5.2 (5.1)	7.0 (6.9)	4.3 (3.4)	.032
BSA	6.9 (6.2)	8.1 (7.5)	6.0 (3.7)	.466
SUM score[b]	5.0 (2.0)	6.0 (3.0)	4.0 (1.0)	.004
Site location, n (%)				
Site 1				.705
Leg	20 (62.5)	13 (68.4)	7 (53.8)	
Arm	6 (18.8)	3 (15.8)	3 (23.1)	
Trunk	6 (18.8)	3 (15.8)	3 (23.1)	
Site 2				.149
Leg	5 (15.6)	4 (21.1)	1 (7.7)	
Arm	18 (56.3)	12 (63.4)	6 (46.2)	
Trunk	9 (28.2)	3 (10.8)	6 (46.2)	
Non-lesional				.509
Leg	19 (59.4)	12 (63.2)	7 (53.8)	
Arm	9 (28.1)	4 (21.1)	5 (38.5)	
Trunk	4 (12.5)	3 (15.8)	1 (7.7)	
No topical treatment used on target lesions in past 7 days[c], n (%)	12 (37.5)	4 (21.1)	8 (61.5)	.018
Systemic treatment, n (%)				
Methotrexate	-	-	9 (69.2)	
Fumaric acid esters	-	-	1 (7.7)	
Adalimumab	-	-	3 (23.1)	

PGA, physician global assessment; PASI, psoriasis area and severity index; BSA, body surface area; SUM score, the sum of the severity for erythema (0–4), induration (0–4) and desquamation (0-4); IQR, interquartile range.

[a]Patients may also use topical treatments (corticosteroids and/or vitamin D derivatives).

[b]All lesions of both sites combined resulting in a total of 64 lesions (2 lesions per patient).

[c]Topical corticosteroids and/or vitamin D derivatives.

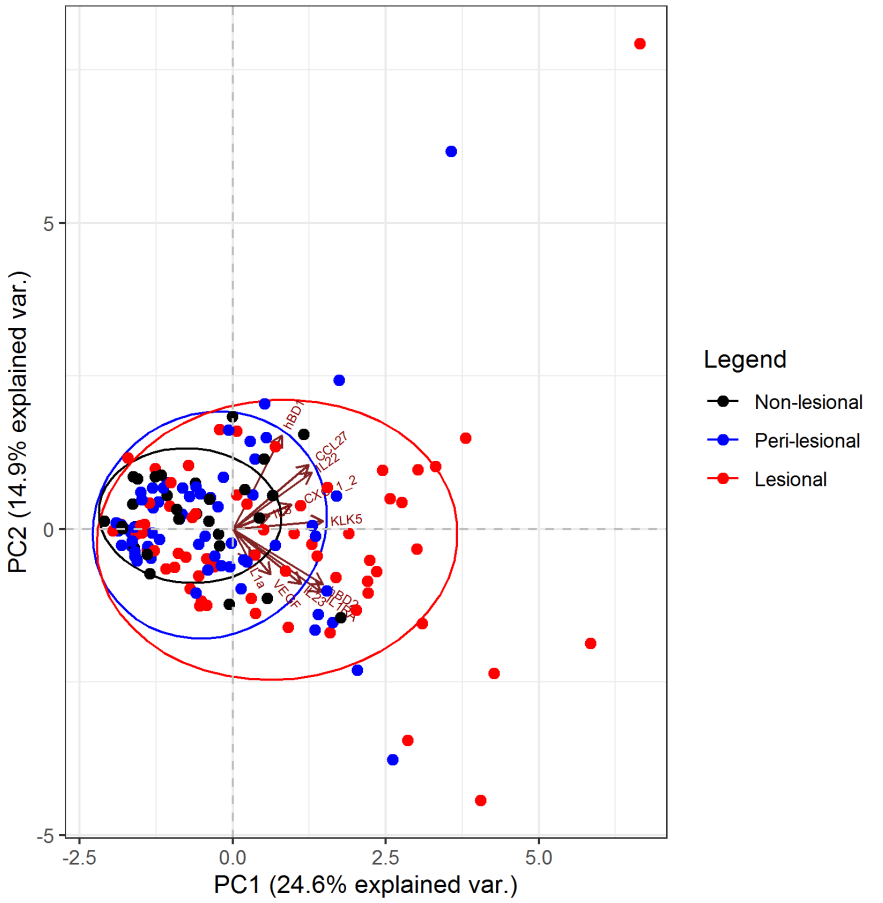

Figure 1. PCA of protein levels in lesional (n = 64 samples), peri-lesional (n = 64 samples), and non-lesional skin (n = 32 samples)

CXCL, CXC chemokine ligand; CCL, CC chemokine ligand; IL, interleukin; VEGF, vascular endothelial growth factor; hBD, human betadefensin; KLK, kallikrein-related peptidase; PCA, principal component analysis. Biplot of dimension 1 (horizontal axis) and 2 (vertical axis). Each dot represents one sample. Levels of 11 proteins were included: CXCL-1/2, CCL-27, IL-1RA, IL-23, IL-1α, IL-8, IL-22, VEGF, hBD-2, hBD-1, and KLK-5.

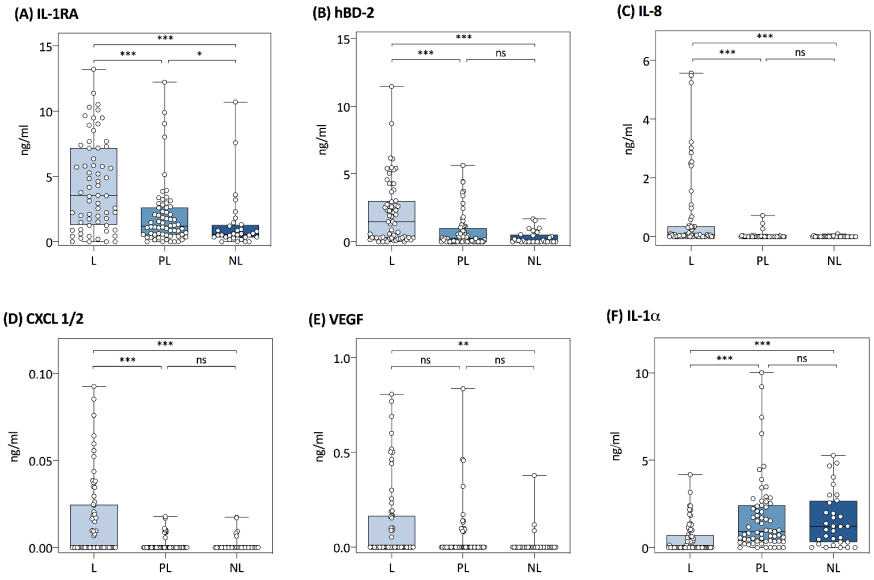

Figure 2. Absolute counts of proteins measured in lesional (n = 64 samples), peri-lesional (n = 64 samples), and non-lesional (n = 32 samples) skin by TAP

CXCL, CXC chemokine ligand; IL, interleukin; VEGF, vascular endothelia growth factor; hBD, human beta-defensin; TAP, transdermal analysis patch; L, lesional; PL, peri-lesional; NL, non-lesional. Each dot represents one measurement. The Mann-Whitney U test was used to assess differences between (i) lesional and peri-lesional skin, (ii) peri-lesional and non-lesional skin, and (iii) lesional and non-lesional skin. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ns, nonsignificant.

Protein detection in lesional skin during therapeutic regimens

As both patients on topical and on systemic treatments were included in this daily clinical practice study, the possible influence of topical and systemic treatments on the TAP protein detection was explored. PCA showed that proteins detected in the lesional skin of patients on systemic treatment are separated from those derived from patients solely on topical treatment (Figure 3). A detailed comparison between treatment groups per protein is shown in Figure 4 and Table S6. In patients on systemic treatment (n = 26 samples), significantly higher levels of IL-1α, IL-1RA, IL-23, hBD-2, CCL-27, and KLK-5 were measured compared to solely topically treated patients (n = 38 samples). After a sensitivity analysis with confounder correction (for sex, age, body site, use of topical corticosteroids on investigated lesion in last 7 days, SUM score, and PGA), levels of IL-1RA, IL-1α, and IL-23 remained higher in the lesional skin of patients on systemic treatment (Table S7).

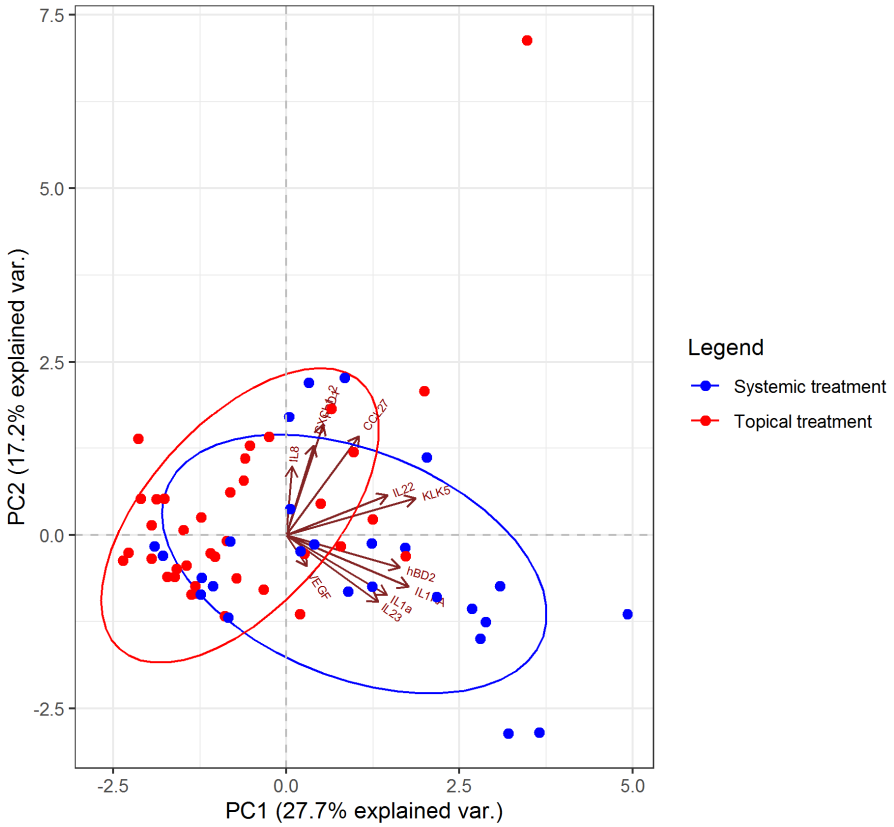

Figure 3. PCA of protein levels in the lesional skin (n = 64 samples) split for measurements of patients on solely topical treatment (n = 38 samples) versus systemic treatment (n = 26 samples)

CXCL, CXC chemokine ligand; CCL, CC chemokine ligand; IL, interleukin; VEGF, vascular endothelial growth factor; hBD, human beta-defensin; KLK, kallikrein-related peptidase; PCA, principal component analysis. Biplot of dimension 1 (horizontal axis) and 2 (vertical axis). Each dot represents 1 sample. Levels of 11 proteins were included: CXCL-1/2, CCL-27, IL-1RA, IL-23, IL-1α, IL-8, IL-22, VEGF, hBD-2, hBD-1, and KLK-5.

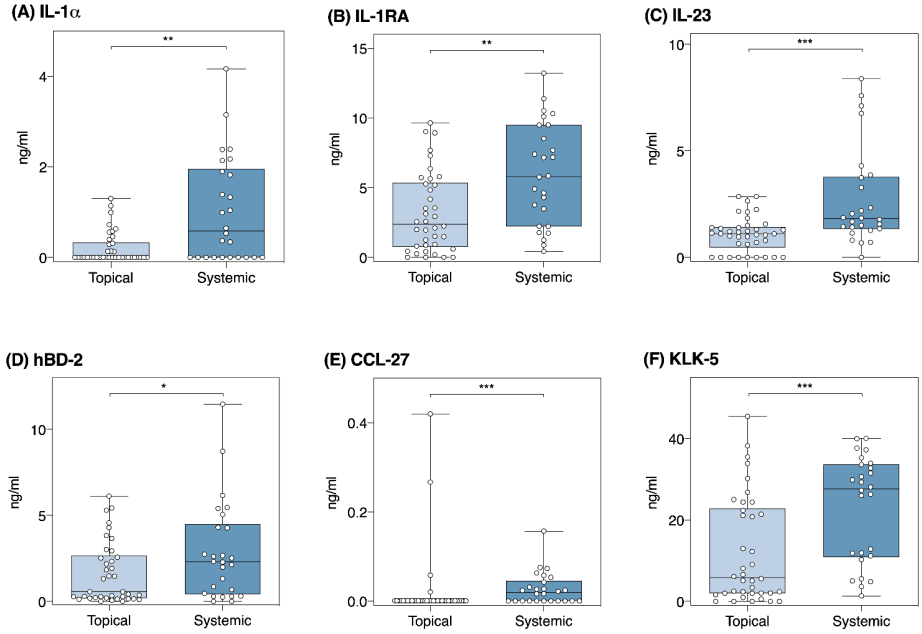

Figure 4. Absolute counts of proteins in the lesional skin (n = 64 samples) measured by TAP split for patients on solely topical treatment (n = 38 samples) versus systemic treatment (n = 26 samples)

CCL, CC chemokine ligand; IL, interleukin; hBD, human beta-defensin; KLK, kallikrein-related peptidase; TAP, transdermal analysis patch; L, lesional; PL, peri-lesional; NL, non-lesional. Each dot represents 1 measurement. The Mann-Whitney U test was used to assess differences between measurements of patients on solely topical versus systemic treatment. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ns, nonsignificant

Discussion

In our study, several key elements for the clinical applicability of TAP were identified. First, the finding that pediatric patients experienced almost no discomfort during application and removal of the TAPs supports the use of TAPs in daily clinical practice. Second, no prominent differences in protein profiles of (peri-)lesional skin were seen between different (body) sites. Although larger studies are required to confirm this, these results suggest the potential applicability of TAP on any desired (body) site. Third, both in patients on solely topical and systemic treatment, we were able to detect significant differences in protein levels between lesional and non-lesional skin, which increases the applicability of TAP in daily clinical practice. Finally, in contrast to repetitive tape stripping, TAP collects proteins from an intact stratum corneum, which reduces the risk for local skin irritation and therefore decreases the risk of koebnerization for psoriasis patients. A reduced risk for local

skin irritation might also have implications for the implementation of TAPs for the monitoring of other inflammatory skin conditions with poor barrier function, such as atopic dermatitis.

Recent studies on noninvasive skin sampling for the analysis of local skin disease signatures underscore the demand and importance of such new sampling methodologies and analyses.[19,20] This paradigm shift towards patient friendly, high end molecular disease profiling provides an alternative to the conventional use of invasive skin biopsies. Especially for the pediatric patient population these developments are of utmost importance. Similar to the RNA[20] and proteome profiling using tape strips[19] in psoriasis and atopic dermatitis, respectively, our data using TAP technology illustrates the potential of noninvasive localized sampling for quantitative investigations. The potential of skin surface protein measurement by TAP is further underlined by a recent study in 10 adult atopic dermatitis patients, which revealed a promising correlation between skin surface proteins sampled by the FibroTx Patch, tape strip skin samples, and serum samples.[27]

Although no proteome analysis studies in pediatric psoriasis patients are reported, in line with previous proteome analysis using tape stripping in adult psoriasis patients, we found higher levels of VEGF, CXCL-1/2, IL-8, and IL-23 and lower levels of IL-1α in the lesional skin.[17,18] The role of these general skin inflammatory proteins includes neutrophil infiltration and Th17-cell differentiation.[18] The reproducibility of our findings indicates the robustness of TAP for skin surface protein detection. The proteins we could include in our analysis were mostly keratinocyte-derived and enabled the differentiation between lesional and non-lesional skin. Even more subtle differences after confounder correction between non-lesional and peri-lesional skin were highlighted by the highly expressed psoriasis-associated epidermal marker protein, hBD-2 (Table S5), whose tissue and serum levels are known to correlate well to disease severity.[3] Immune cell-derived proteins IL-4 and IL-17A were excluded from analyses as only one (IL-4) and no measurements (IL-17A) exceeded the minimum detection level. According to the known psoriasis pathogenesis, it is expected that IL-4 would not be detected in the skin surface. Instead, IL-17A was anticipated to be detected being a key pro-inflammatory cytokine in psoriasis. Furthermore, IL-17A detection is described in previous tape stripping studies.[18] In our study, IL17A was measured in 15 out of 64 lesional samples, albeit values did not meet the minimum detection level. Current detection limits of the TAPs might not be sensitive enough to sufficiently measure soluble immune cell-derived proteins via diffusion through the stratum corneum, which might explain why IL-17A was not widely detected in our study.

We showed that TAP is capable to detect soluble skin proteins in patients receiving topical- and systemic treatments. Intriguingly, statistically significant lower protein levels in the lesional skin of patients on solely topicals versus those on systemic therapy were found. Even after sensitivity analysis with correction for the use of topical treatments in the last 7 days and for other possible confounders (PGA, SUM, age ,and gender) with a linear mixed model, levels of IL-1RA, IL-1α, and IL-23 remained significantly higher in patients on systemic therapy (Table S7). It has to be noted that our study design was explorative and the study was performed in daily clinical practice. Therefore, given the heterogeneity of our population, conclusions regarding the biological relevance of these differences are difficult to draw and would require a specifically designed follow up study. However, one could hypothesize that the difference in protein detection in treatment groups is due to the direct negative influence of chronic and repetitive application of topical treatments on protein levels in the stratum corneum. To explore this hypothesis, we also compared proteins between treatment groups on non-lesional skin sites, which were never treated with topical agents irrespective of the treatment group. Intriguingly, also in non-lesional skin significantly higher levels of KLK-5, IL-1RA, IL-23, and IL-1 α were seen in patients treated with systemic agents (Table S6). Experimental evidence to substantiate these findings should be gained from future studies in patient cohorts with controlled treatment regimens.

Although we ultimately search for implementation of TAP in daily clinical practice, there is still a long road ahead. Further research is needed to determine the optimal marker set for the application of TAP in (pediatric) psoriasis. Given the explorative nature of this study, a relatively small number of patients was included. It also has to be noted that the marker set captured from the skin surface was a general inflammatory preset protein panel, thus not specific for psoriasis. However, for future studies, the protein panel could be adjusted according to disease specific signature proteins, enabling the use of TAP in other inflammatory skin diseases. Our data are based on protein measurements at one time point. Longitudinal follow-up data of the present clinical practice cohort would increase insights into the consistency of the protein profile present in the skin in each individual. This could enable an understanding of the correlation with disease course and treatment response. Acquiring disease- or patient specific proteins directly from the skin surface by using TAP could enhance mapping of underlying skin disease mechanisms, personalized treatment, and ultimately prediction of disease course.

Conclusion

Protein detection in the stratum corneum of the skin by TAP is regarded patient friendly in pediatric psoriasis patients. TAP noninvasively measures proteins directly from the skin regardless of treatment and provides a promising platform for implementation of protein collection in clinical practice or research.

Funding information

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Supplementary materials

Methods

Statistical analyses (linear mixed models)

To account for correlations between measurements of the same patients and for possible confounders, we conducted a sensitivity analysis using linear mixed models to compared protein levels between (i) lesional versus peri-lesional versus non-lesional skin and (ii) between measurements of patients on solely topical versus systemic treatment. These sensitivity analyses were adjusted for the following confounders: sex, age, body site, treatment (solely topical versus systemic), use of topical corticosteroids on investigated lesion in last 7 days, SUM-score, and PGA score (mild [PGA score 1-2] versus moderate-severe [PGA score 3-4]). Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models. Estimated marginal means of protein levels were calculated and presented in Table S5 (comparison of protein levels between lesional versus peri-lesional versus non-lesional skin) and Table S7 (comparison of protein levels between measurements of patients on solely topical versus systemic treatment). Statistical package SPSS, version 25 (IBM) was used to perform these analyses. Two-sided $p < 0.05$ was considered statistically significant.

Figures

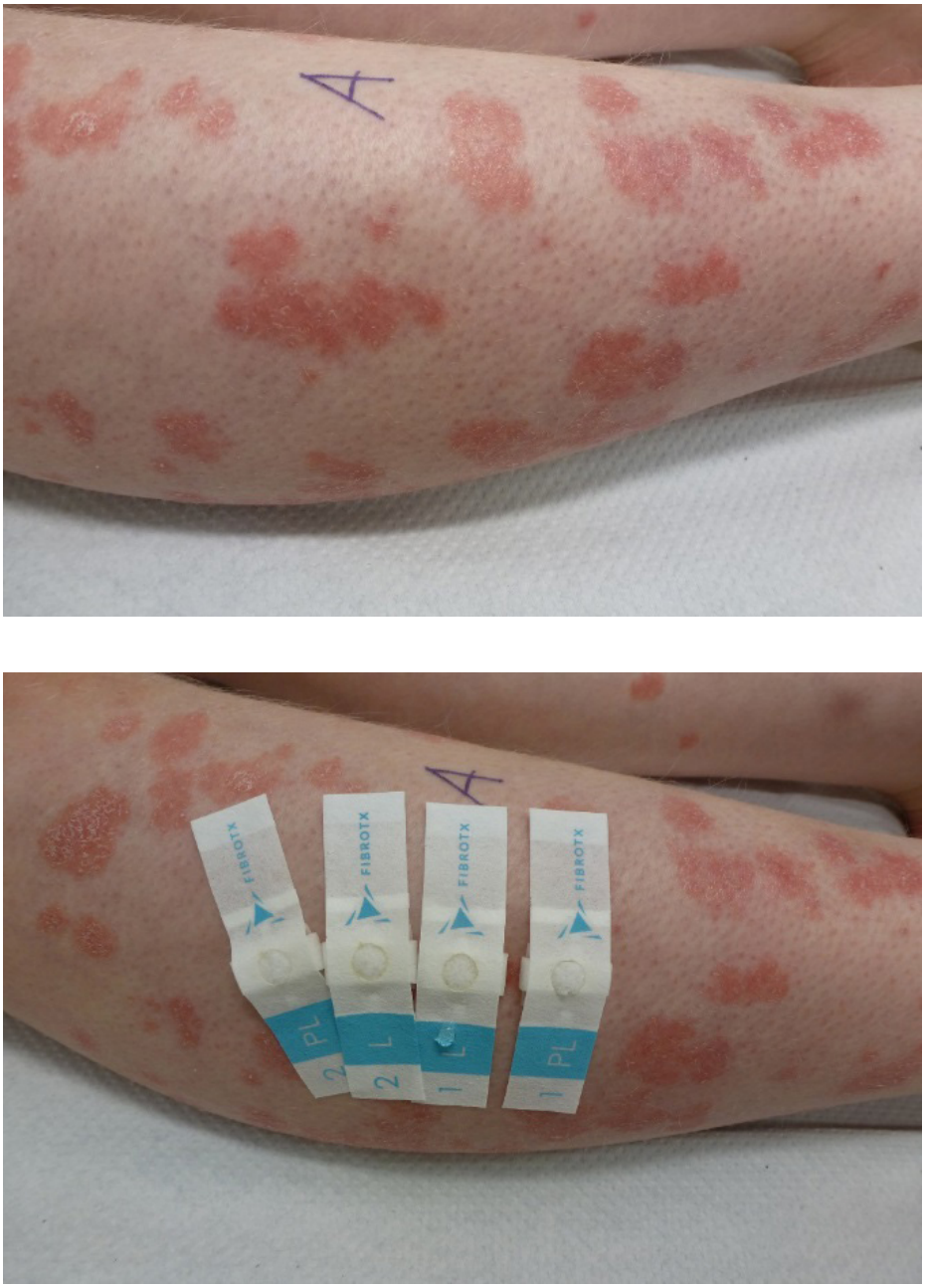

Figure S1. Test site (right lower leg) before and during FibroTx Transdermal Analysis Patches (TAP) application for protein detection

Tables

Table S1. Lower and upper protein detection levels by spot-ELISA

Protein	Minimum detection level[a]	Maximum detection level[a]
IL-1α	0.125	8.000
IL-1RA	0.083	8.000
IL-8	0.020	2.000
IL-23	0.500	25.000
VEGF	0.030	2.000
CXCL-1/2	0.005	0.500
hBD-2	0.063	4.000
CCL-27	0.015	1.000
IL-22	0.030	2.000
IL-4	0.015	2.000
hBD-1	0.015	1.000
IL-17A	0.125	8.000
KLK-5	0.390	25.000

[a]Values presented as ng/ml.

Table S2. Proteins measured on lesional skin on site 1 (n = 32 samples) versus site 2 (n = 32 samples)

Protein	Site 1	Site 2	*p*-value
IL-1RA	3.92 (3.00)	4.73 (3.89)	.443
hBD-2	2.25 (2.31)	2.01 (2.41)	.926
IL-1α	0.44 (0.98)	0.64 (0.77)	.167
IL-8	0.66 (1.42)	0.65 (1.29)	.982
VEGF	0.11 (0.19)	0.13 (0.23)	.756
CXCL-1/2	0.01 (0.02)	0.02 (0.03)	.546
IL-23	1.65 (1.85)	1.85 (2.02)	.505
KLK-5	16.76 (15.05)	16.39 (13.04)	.845
hBD-1	0.15 (0.25)	0.15 (0.17)	.382
IL-22	0.04 (0.06)	0.06 (0.10)	.435
CCL-27	0.02 (0.08)	0.02 (0.06)	.552

Values are presented as means (standard deviation) in ng/ml. Lesional protein levels from site 1 and site 2 were compared by Wilcoxon signed rank tests.

Table S3. Proteins measured on peri-lesional skin on site 1 (n = 32 samples) versus site 2 (n = 32 samples)

Protein	Site 1	Site 2	*p*-value
IL-1RA	1.85 (2.29)	2.07 (2.49)	.583
hBD-2	0.67 (1.16)	0.88 (1.41)	.201
IL-1α	1.59 (1.87)	1.87 (2.32)	.262
IL-8	0.02 (0.08)	0.04 (0.13)	.139
VEGF	0.05 (0.10)	0.06 (0.17)	.508
CXCL-1/2	0.00 (0.00)	0.00 (0.00)	.866
IL-23	1.49 (1.34)	1.41 (1.42)	.179
KLK-5	17.47 (14.03)	18.57 (14.97)	.544
hBD-1	0.12 (0.11)	0.18 (0.31)	.558
IL-22	0.04 (0.10)	0.04 (0.08)	.861
CCL-27	0.01 (0.02)	0.01 (0.02)	.674

Values are presented as means (standard deviation) in ng/ml. Peri-lesional protein levels from site 1 and site 2 were compared by Wilcoxon signed rank tests.

Table S4. Proteins measured on lesional (n = 64 samples) versus peri-lesional (n = 64 samples) versus non-lesional (n = 32 samples) skin

Protein	Lesional	Peri-lesional	Non-lesional	*p*-value[a]	*p*-value[b]	*p*-value[c]
IL-1RA	4.32 (3.47)	1.96 (2.38)	1.34 (2.25)	<.001	.022	<.001
hBD-2	2.13 (2.34)	0.77 (1.29)	0.30 (0.47)	<.001	.121	<.001
IL-1α	0.54 (0.88)	1.73 (2.10)	1.60 (1.56)	<.001	.960	<.001
IL-8	0.65 (1.35)	0.03 (0.11)	0.01 (0.02)	<.001	.294	<.001
VEGF	0.12 (0.21)	0.05 (0.14)	0.02 (0.07)	.059	.097	.004
CXCL-1/2	0.02 (0.02)	0.00 (0.00)	0.00 (0.00)	<.001	.980	.001
IL-23	1.75 (1.78)	1.45 (1.37)	1.32 (1.37)	.308	.338	.138
KLK-5	16.58 (13.97)	18.02 (14.40)	17.07 (13.02)	.575	.789	.753
hBD-1	0.15 (0.21)	0.15 (0.23)	0.12 (0.11)	.724	.904	.840
IL-22	0.05 (0.08)	0.04 (0.08)	0.03 (0.05)	.362	.969	.456
CCL-27	0.02 (0.07)	0.01 (0.02)	0.01 (0.03)	.464	.916	.441

[a]Lesional versus peri-lesional skin.

[b]Peri-lesional versus non-lesional skin.

[c]Lesional versus non-lesional skin. Values are presented as means (standard deviation) in ng/ml and were analyzed with Mann-Whitney U tests.

Table S5. Proteins measured on lesional (n = 64 samples) versus peri-lesional (n = 64 samples) versus non-lesional (n = 32 samples) skin by Linear Mixed Models

Protein	Lesional	Peri-lesional	Non-lesional	*p*-value[a]	*p*-value[b]	*p*-value[c]
IL-1RA	4.32 (3.48 – 5.16)	1.96 (1.12 – 2.80)	1.35 (0.34 – 2.35)	<.001	.207	<.001
hBD-2	2.18 (1.68 – 2.69)	0.83 (0.32 – 1.33)	0.02 (-0.68 – 0.72)	<.001	.029	<.001
IL-1α	0.54 (0.06 – 1.02)	1.73 (1.26 – 2.21)	1.60 (1.04 – 2.17)	<.001	.631	<.001
IL-8	0.62 (0.38 – 0.85)	0.06 (-0.18 – 0.30)	0.00 (-0.52 – 0.17)	<.001	.212	<.001
VEGF	0.11 (0.07 – 0.16)	0.05 (0.00 – 0.09)	0.05 (-0.02 – 0.12)	.011	.896	.102
CXCL-1/2	0.02 (0.01 – 0.02)	0.00 (0.00 - 0.01)	0.00 (0.00 – 0.01)	<.001	.921	<.001
IL-23	1.93 (1.47 – 2.39)	1.60 (1.15 – 2.06)	1.61 (1.02 – 2.19)	.029	.998	.186
KLK-5	18.16 (13.27 – 23.05)	19.58 (14.69 – 24.48)	17.81 (12.38 – 23.24)	.125	.263	.825
hBD-1	0.16 (0.10 – 0.21)	0.15 (0.10 – 0.21)	0.10 (0.01 – 0.18)	.962	.196	.185
IL-22	0.05 (0.03 – 0.07)	0.04 (0.02 – 0.06)	0.02 (-0.01 – 0.05)	.324	.164	.042
CCL-27	0.02 (0.01 – 0.04)	0.01 (0.00 – 0.03)	0.01 (-0.01 – 0.03)	.094	.623	.110

Values are presented as Estimated Marginal Means (95% CI) in ng/ml. All analysis were conducted with Linear Mixed Models and were corrected for the following confounders: sex, age, body site, treatment (solely topical versus systemic), use of topical corticosteroids on investigated lesion in last 7 days and PGA score (mild [PGA score 1-2] versus moderate-severe [PGA score 3-4]). Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models.

[a]Lesional versus peri-lesional.

[b]Peri-lesional versus non-lesional.

[c]Lesional versus non-lesional.

Table S6. Proteins measured on lesional skin, peri-lesional skin and non-lesional skin of topical treated patients versus systemic treated patients

Lesional skin			
Protein	**Topical (n = 38 samples)**	**Systemic (n = 26 samples)**	***p*-value**
KLK-5	12.18 (13.02)	23.01 (12.98)	.001
IL-1RA	3.18 (2.84)	5.99 (3.67)	.002
IL-23	1.09 (0.82)	2.72 (2.31)	<.001
hBD-2	1.62 (1.79)	2.87 (2.85)	.044
IL-1α	0.20 (0.35)	1.03 (1.17)	.003
CCL-27	0.02 (0.08)	0.03 (0.04)	<.001
IL-8	0.50 (0.91)	0.87 (1.80)	.825
hBD-1	0.19 (0.27)	0.09 (0.06)	.795
IL-22	0.03 (0.06)	0.07 (0.11)	.062
VEGF	0.13 (0.20)	0.10 (0.23)	.115
CXCL-1/2	0.02 (0.02)	0.01 (0.02)	.799
Peri-lesional skin			
KLK-5	14.39 (13.42)	23.31 (14.39)	.014
IL-1RA	1.71 (2.13)	2.33 (2.70)	.104
IL-23	1.02 (0.64)	2.09 (1.85)	.003
hBD-2	0.77 (1.15)	0.78 (1.48)	.823
IL-1α	0.97 (1.06)	2.85 (2.69)	<.001
CCL-27	0.00 (0.01)	0.02 (0.03)	<.001
IL-8	0.04 (0.14)	0.02 (0.05)	.671
hBD-1	0.13 (0.13)	0.18 (0.33)	.951
IL-22	0.02 (0.04)	0.07 (0.10)	.006
VEGF	0.03 (0.05)	0.08 (0.21)	.407
CXCL-1/2	0.00 (0.00)	0.00 (0.00)	.523
Non-lesional skin			
KLK-5	13.40 (11.60)	22.44 (13.55)	.041
IL-1RA	1.15 (2.45)	1.64 (2.00)	.022
IL-23	0.81 (0.97)	2.06 (1.56)	.016
hBD-2	0.36 (0.49)	0.21 (0.43)	.472
IL-1α	0.90 (0.91)	2.63 (1.78)	.005
CCL-27	0.01 (0.03)	0.02 (0.05)	.071
IL-8	0.01 (0.02)	0.00 (0.01)	.880
hBD-1	0.14 (0.10)	0.10 (0.12)	.195
IL-22	0.02 (0.06)	0.04 (0.05)	.287
VEGF	0.01 (0.03)	0.03 (0.10)	.940
CXCL-1/2	0.00 (0.00)	0.00 (0.00)	.970

Values are presented as means (standard deviation) in ng/ml. Samples of patients treated systemically were compared to samples of patients treated with solely topical therapy by Mann-Whitney U tests.

Table S7. Proteins measured on lesional skin of topical treated patients (n = 38 samples) versus systemic treated patients (n = 26 samples) by Linear Mixed Models

Protein	Topical	Systemic	*p*-value
KLK-5	12.93 (7.12 – 18.74)	20.89 (13.74 – 28.04)	.105
IL-1RA	3.22 (1.92 – 5.53)	5.80 (4.29 – 7.31)	.021
IL-23	0.90 (0.16 – 1.64)	2.84 (1.99 – 3.69)	.002
hBD-2	1.98 (0.83 – 3.13)	2.45 (1.11 – 3.80)	.620
IL-1α	0.11 (-0.23 – 0.46)	1.09 (0.70 – 1.48)	.001
CCL-27	0.02 (-0.01 – 0.06)	0.02 (-0.02 – 0.06)	.984
IL-8	0.50 (-0.17 – 1.16)	0.69 (-0.11 – 1.48)	.732
hBD-1	0.18 (0.10 – 0.26)	0.11 (0.01 – 0.21)	.294
IL-22	0.05 (0.02 – 0.08)	0.06 (0.02 – 0.09)	.832
VEGF	0.14 (0.05 – 0.23)	0.07 (-0.03 – 0.17)	.332
CXCL-1/2	0.02 (0.01 – 0.03)	0.01 (0.00 – 0.02)	.274

Values are presented as Estimated Marginal Means (95% CI) in ng/ml. All analysis were conducted with Linear Mixed Models and were corrected for the following confounders: sex, age, body site, use of topical corticosteroids on investigated lesion in last 7 days, SUM-score and PGA score (mild [PGA score 1-2] versus moderate-severe [PGA score 3-4]). Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models.

2.2 Challenges in noninvasive biomarker measurements in daily practice: skin surface protein detection by the Transdermal Analysis Patch in pediatric psoriasis

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Abstract

Background

Skin surface proteins are potential biomarkers in psoriasis and can be noninvasively measured with the Transdermal Analysis Patch (TAP).

Objective

To assess markers measured by TAP over time in daily clinical practice, explore their correlation with disease severity in pediatric psoriasis, and compare the TAP and tape stripping detection capability.

Methods

In this prospective observational daily clinical practice study, pediatric psoriasis patients (aged 5 to 18 years) were followed during one year. Each visit, TAPs were applied on lesional (n=2), peri-lesional (n=2), and non-lesional (n=1) sites. Post-lesional skin was sampled if all lesions on the arms, legs, or trunk cleared. Treatment and psoriasis severity data were collected. IL-1RA, hBD-2, IL-1α, IL-8, VEGF, CXCL-1/2, CCL-27, IL-23, hBD-1, IL-22, IL-17A, KLK-5, and IL-4 levels were quantified by spot-ELISA. For the statistical analysis Wilcoxon signed rank tests, Mann-Whitney U tests, and Spearman correlations were used. Detection capability of the TAP was compared to tape stripping in a separate cohort of adult psoriasis patients.

Results

32 patients (median age 15.0 years, median PASI 5.2) were followed for a mean of 11.3 (±3.4) months with a total of 104 visits. In lesional skin (n=197), significantly higher IL-1RA, hBD-2, IL-8, VEGF, CXCL-1/2, IL-23, hBD-1, IL-22, CCL-27, and IL-17A levels were found compared to non-lesional skin (n=104), while IL-1α was higher in non-lesional skin. Marker levels were highly variable over time and did not correlate with disease severity measured by PASI or SUM scores. Comparing the TAP and tape strip detection capability in adult psoriasis patients (n=10) showed that lesional hBD-2, IL1-α, IL-8, and VEGF, and non-lesional IL-1RA, hBD-2, IL-8, and VEGF were more frequently detected in tape extracts than TAPs.

Conclusion

Due to the lack of correlation with clinical disease severity and the current detection capability of the markers measured by TAP in psoriasis, its use in regular practice is still a bridge too far.

Introduction

Psoriasis is a common chronic inflammatory skin disease with an onset during childhood in almost one third of the cases.[1] The disease course is characterized by exacerbations and remissions and is unpredictable: some patients have a mild and stable disease for many years while in others it quickly progresses.[2] If biomarkers were able to predict disease course or response to treatments, their added value to daily practice would be great: they would facilitate early interventions and improve treatment decisions. The skin surface provides a unique source of potential biomarkers, as cytokines, chemokines, growth factors, and antimicrobial peptides can be measured directly at the site of the disease and are thought to reflect the underlying pathophysiology.[3-6]

Proteins in psoriatic skin are conventionally sampled through skin biopsies,[7-10] which are associated with a risk of pain, scarring, and infection.[11] Noninvasive biomarker measurements provide a patient-friendly alternative by avoiding discomfort and fear for interventions in (pediatric) patients, and can be performed repeatedly, making them more suitable for use in daily clinical practice. Tape stripping, during which corneocytes of the superficial stratum corneum are sampled with adhesive tape, is regarded the golden standard for noninvasive skin protein sampling and is widely performed. [6,12,13] Previous tape stripping studies have underlined the value and power of local biomarkers.[6,12] Recently, the Transdermal Analysis Patch (TAP) and the FibroTx Patch were described.[14-16] These methods sample soluble proteins from an intact stratum corneum. Previous research by our group revealed that the TAP can detect skin proteins in lesional, peri-lesional, and non-lesional skin in pediatric psoriasis patients treated with systemic and/or topical agents and is regarded patient-friendly.[14,15]

The consistency of proteins measured by TAP over time and the correlation with disease severity are not studied to date but are relevant to identify potential biomarkers for use in clinical practice. Additionally, the skin surface protein detection capability of the TAP might differ from tape stripping, since these methods sample at different depths of the stratum corneum and include different detection methods. In this study performed in a daily clinical practice setting, we aimed to explore the value of TAP measurements in daily practice in (pediatric) psoriasis patients by (i) comparing the marker levels measured by TAP in lesional, peri-lesional, non-lesional, and post-lesional skin, (ii) assessing the course of skin surface markers measured by TAP over time in pediatric psoriasis patients, (iii) exploring the correlation between lesional marker levels and disease severity, and (iv) comparing the marker detection capability of TAP versus tape stripping extraction.

Materials and methods

Study design and population

In this prospective observational daily clinical practice study, pediatric psoriasis patients aged 5 to 18 years were recruited between June 2018 and July 2019 at the outpatient clinic of the Department of Dermatology of the Radboud university medical center, Nijmegen, the Netherlands. Inclusion criteria were: plaque psoriasis diagnosis confirmed by a dermatologist and enough psoriasis plaques to apply the TAPs at baseline. Patients with another concurrent inflammatory skin disease or other types of psoriasis were excluded. Treatment occurred as part of regular care without a wash out phase and could consist of topical and/or systemic treatment. Patients were followed during one year, and visits were planned every three months for systemically treated patients and every six months for solely topically treated patients. However, no visits occurred between March and August 2020 due to COVID-19 restrictions. Written informed consent and/or assent was given by all participants and/or their legal guardian before enrollment. The study was approved by the ethics committee of the Radboud university medical center, region Arnhem-Nijmegen (NL60952.091.17).

Transdermal Analysis Patch

The TAP consists of a multiplex capture-antibody micro-array supported by an adhesive bandage and is described in previous publications.[14,15] Two TAPs were used with different preset protein panels. One TAP measured CXC chemokine ligand (CXCL)-1/2, interleukin (IL)-1RA, IL-23, IL-1α, IL-8, vascular endothelial growth factor (VEGF), and human beta-defensin (hBD)-2, and a second TAP measured CC chemokine ligand (CCL)-27, IL-4, IL-22, IL-17A, hBD-1, and kallikrein-related peptidase (KLK)-5. After application, four drops of phosphate buffered saline (pH 7.4) were added to microarray reservoir. TAPs were applied to the skin for 20 minutes to capture skin-derived proteins through immune recognition and were stored at -20 °C until quantification with spot-enzyme-linked immunosorbent assay (spot-ELISA). Levels within half of the lower detection limit were taken unchanged, lower values were substituted by zero. The TAP detection limits are provided in Table S1.

Study procedures

TAPs were applied on two lesional, two peri-lesional, and one non-lesional skin site (no psoriasis within a distance of 10 centimeters). The two lesions of interest were preferably located on different body parts, including the arms, legs, or trunk, with preferably a similar SUM score. TAPs were applied on the same skin sites at each visit during follow-up if possible. However, if all lesions on the arms, legs,

or trunk cleared, TAPs were applied on post-lesional skin instead of lesional skin. Patients did not use topical agents on the investigated sites on the day of the visit. After TAP removal, patients rated experienced discomfort on a 10-point Visual Analogue Scale (VAS). A VAS score of 0 and 10 corresponded to no and maximal discomfort, respectively. Psoriasis severity was measured with the Psoriasis Area and Severity Index (PASI; range 0-72), Physician Global Assessment (PGA; range 0-5), and affected Body Surface Area (BSA). SUM scores (0-12), defined as the sum of the severity scores for erythema (0–4), induration (0-4), and desquamation (0-4), were determined for the lesions of interest. Additionally, demographics and information on current treatment were collected. All procedures were performed by two physicians (MJS or FMB).

TAP versus tape stripping

Adults with plaque psoriasis diagnosed by a dermatologist, with a plaque large enough to perform both TAP and tape stripping, without a concurrent inflammatory skin disease, were recruited from September to October 2020. TAP and tape stripping were consecutively performed at one time-point in a randomized order on one lesional and non-lesional skin site. Directly after each method, experienced discomfort was rated by the patient on a 100mm VAS. TAP sampling and analysis were performed as previously described. For tape stripping, eight successive round adhesive tapes with a diameter of 2.2 cm (DSquame, CuDerm, USA) were pressed to the skin for 10 seconds using a pressure device (CuDerm, USA). Tapes were stored in cryovials at -80°C until analysis. Proteins were extracted from the tapes using ultrasonication with PBS and were either quantified by conventional ELISA (hBD-2) or Luminex multiplex based platform (CXCL-1/2, IL-1RA IL-1α, IL-8, and VEGF) and normalized to the total amount of protein. Values exceeding the detection limits were not included in the analysis. Detailed methods are provided in the Supplementary materials. All patients gave written informed consent. The study was approved by the ethics committee of the Radboud university medical center, region Arnhem-Nijmegen (NL73363.091.20).

Statistical analysis

Patient characteristics and marker levels were first analyzed with descriptive statistics and presented as frequencies and percentages, means and standard deviations (±SD), or medians and interquartile ranges (IQR). Marker levels on both the two lesional and peri-lesional sites within one patient were compared on group level with a Wilcoxon signed rank tests. Mann-Whitney U tests were performed to compare marker levels in lesional, peri-lesional, non-lesional, and post lesional skin. Mean lesional marker levels and the PASI score were plotted over time in each patient. Spearman rank correlation tests were computed for the PASI score and

mean lesional marker levels, and for lesion severity (Total SUM score, desquamation, erythema, induration) and lesional marker levels. The TAP and tape stripping detection capability was assessed by comparing the number of samples that were detected within the limits of the assay for each marker. Statistical package SPSS, version 25 (IBM, Armonk, NY) and SAS 9.4 (SAS Institute Inc, Cary, NC, USA) were used to perform analyses. A two-sided $p < 0.05$ was regarded statistically significant.

Results

Patient characteristics

32 patients were included with a median age of 15.0 years (IQR 10.9-16.9) and a median PASI score of 5.2 (IQR 3.7-8.7) at baseline (Table 1). A mean of 3.25 (±1.0) visits were performed per patient, resulting in a total of 104 visits and a mean follow-up duration of 11.3 (±3.4) months. Due to COVID-19 restrictions, 10 patients dropped out before one year of follow-up, longer visit intervals occurred towards the end of follow-up, and follow-up exceeded one year in 14 patients. At baseline, 19 patients received solely topical treatment, while 13 patients received systemic treatment. During follow up, four patients switched from topical to systemic treatment, while two patients switched from systemic to solely topical treatment (Table 1). Mild adverse events of TAP were reported during six visits, including transient local erythema (n=2), itch (n=3), and a burning sensation (n=1). The median VAS score after TAP removal was 1.0 (IQR 0.0-1.0).

Marker level differences between lesional, peri-lesional, non-lesional, and post-lesional skin

When including all samples on both the two lesional and two peri-lesional sites, marker levels were considered similar (Table S2). Therefore, all data were taken together for further analysis, resulting in 197 lesional, 197 peri-lesional, 104 non-lesional, and 6 post-lesional TAP measurements. The TAP was able to distinct lesional from non-lesional skin: significantly higher levels of IL-1RA, hBD-2, IL-8, VEGF, CXCL-1/2, CCL-27, IL-23, hBD-1, and IL-17A were found in lesional skin, whereas highest levels of IL-1α were associated to non-lesional skin (Table 2). In peri-lesional skin, IL-1RA, hBD-2, IL-8, and VEGF levels remained significantly higher compared to non-lesional skin. Only if all lesions on the arms, legs, or trunk cleared during follow-up, TAPs were applied on post-lesional skin (Figure S1). Intriguingly, post-lesional marker levels were equal to lesional levels or even significantly higher (for hBD-2 and KLK-5 [Table 2]). Moreover, compared to non-lesional skin, levels of hBD-2, IL-8, VEGF, IL-17A, and KLK-5 were significantly higher in post-lesional skin. A post-hoc

analysis solely including the patients in which post-lesional skin was sampled during follow-up revealed similar trends. IL-4 was only (and barely) detected in two lesional samples and did not show any significant relations.

Table 1. Baseline characteristics

Characteristics	All patients (n = 32[a])
Sex, male, No. (%)	17 (53.1)
Age, years, median (IQR[b])	15.0 (10.9-16.9)
Psoriasis severity, median (IQR[b])	
PASI	5.2 (3.7-8.7)
PGA	2.0 (2.0-3.8)
BSA	6.9 (4.6-10.8)
SUM score[c], median (IQR[b])	5.0 (4.0-6.0)
Site location, No. (%)	
Lesional[c]	
Leg	25 (39.1)
Arm	24 (37.5)
Trunk	15 (23.4)
Non-lesional	
Leg	19 (59.4)
Arm	9 (28.1)
Trunk	4 (12.5)
Solely topical treatment, No. (%)	19 (59.4)
Systemic treatment[d], No. (%)	
Methotrexate	9 (28.1)
Fumaric acid esters	1 (3.1)
Adalimumab	3 (9.4)
Total	13 (40.6)
Switched from therapy group during follow-up, No. (%)	
From solely topical to systemic treatment	4 (12.5)
From systemic to solely topical treatment	2 (6.3)

Abbreviations: BSA, Body Surface Area; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; SUM score, sum of the severity scores for erythema (0–4), induration (0-4), and desquamation (0-4).
[a]Unless stated otherwise.
[b]The 25th and 75th percentile are shown.
[c]All lesions of interest combined, resulting in a total of 64 lesions (2 lesions per patient) at baseline.
[d]Patients may also use topical treatments (corticosteroids and/or vitamin D derivatives).

Lesional marker levels over time and their correlation with disease severity

Detected lesional marker levels highly varied between analyzed markers (Table 2). To explore the course of marker levels during follow-up in each patient, mean lesional marker levels were plotted over time. PASI scores were added to these figures to explore if the trend of marker levels followed the overall disease severity. Regarding the association between marker concentrations and disease severity (PASI score) over time, inter- and intra-patient differences were seen. Four representative patients are depicted in Figure 1. To further explore this association, correlations between marker levels and the PASI score were calculated (Table 3). These correlations were weak (<0.30) and not statistically significant (except for KLK-5). Mostly inverse correlations were obtained, indicating lower marker levels for higher PASI scores (Table 3). On a lesional level, mostly inverse correlations between desquamation severity and marker levels were found, reaching statistical significance for IL-1α, hBD-1, and KLK-5 (Table 3). The possible association between lower markers levels and more desquamation was further substantiated by calculating mean marker levels for each local desquamation score. As the amount of lesional desquamation increased, a clear trend of decreasing IL-1α, VEGF, CCL-27, IL-23, hBD-1, IL-22, IL-17A, and KLK-5 levels was observed (Table S3). This trend was less distinct for the local erythema and induration scores (data not shown). Of note, only for IL-8 a weak positive correlation coefficient was found with lesion severity scores (<0.3; $p < .01$ [Table3]).

TAP versus tape stripping detection capability

To compare the detection capability of TAP with tape stripping, an additional study was performed including noninvasive protein profiling of stratum corneum by tapes. Both methods were performed on the same lesional and non-lesional skin site in ten adult psoriasis patients (median age 58.0, median PASI 2.0). Most patients were treated with systemic agents (n=7; 70.0%). Full population characteristics are shown in Table S4. In general, markers were more often detected or detected within the detection limits of the assay in stratum corneum extracts from tape strip samples. Specifically, lesional hBD-2, IL1-α, IL-8, and VEGF, and non-lesional IL-1RA, hBD-2, IL-8, and VEGF were more frequently detected in tape extracts (Table 4). Regarding the implementation of the sample techniques in daily practice, patients reported a low median VAS score for discomfort for both procedures: 0.0 mm (IQR 0.0-0.0 mm) for the TAP versus 0.00 (IQR 0.0-6.0 mm) for tape stripping. No adverse events were reported

Table 2. Marker concentrations measured in lesional, peri-lesional, non-lesional, and post-lesional skin samples

Marker	Lesional (n = 197)	Peri-lesional (n = 197)	Non-lesional (n = 104)	Post-lesional (n = 6)	*p*-values					
					a	b	c	d	e	f
IL-1RA	3.65 (3.33)	1.68 (2.10)	1.14 (1.73)	5.11 (2.70)	<.001	.009	<.001	<.001	.002	.178
hBD-2	2.84 (2.99)	1.21 (2.25)	0.51 (1.28)	7.63 (6.98)	<.001	.001	<.001	<.001	.001	.022
IL-1α	0.92 (1.31)	1.56 (1.81)	1.89 (2.18)	1.28 (1.18)	<.001	.123	<.001	.683	.927	.171
IL-8	0.52 (0.97)	0.03 (0.10)	0.01 (0.11)	0.09 (0.15)	<.001	.001	<.001	.002	.150	.135
VEGF	0.23 (0.43)	0.06 (0.19)	0.01 (0.06)	0.21 (0.33)	<.001	.028	<.001	<.001	.023	.714
CXCL-1/2	0.08 (0.50)	0.04 (0.35)	0.04 (0.35)	0.01 (0.02)	<.001	.163	<.001	.511	.826	.156
CCL-27	0.04 (0.09)	0.01 (0.02)	0.01 (0.02)	0.00 (0.01)	<.001	.058	<.001	.796	.699	.173
IL-23	2.30 (2.64)	1.52 (2.09)	1.56 (2.71)	2.86 (2.90)	.002	.381	.002	.213	.266	.609
hBD-1	0.22 (0.28)	0.15 (0.21)	0.13 (0.18)	0.17 (0.14)	.042	.195	.004	.245	.392	.851
IL-22	0.10 (0.25)	0.04 (0.12)	0.01 (0.04)	0.06 (0.09)	.092	.098	.004	.137	.393	.740
IL-17A	0.03 (0.13)	0.01 (0.07)	0.00 (0.01)	0.03 (0.06)	.203	.248	.049	.005	.084	.295
KLK-5	29.49 (49.98)	25.16 (29.01)	24.92 (31.40)	33.48 (7.26)	.875	.707	.814	.028	.041	.045
IL-4	0.00 (0.05)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	.156	1.000	.302	1.000	1.000	.804

All visits were included in this analysis. Values are presented as means (standard deviation) in ng/ml and comparisons were performed with Mann-Whitney U tests. Means instead of medians are displayed to improve the interpretation of the results.

[a]Lesional versus perilesional skin.

[b]Perilesional versus non-lesional skin.

[c]Lesional versus non-lesional skin.

[d]Post-lesional versus non-lesional skin.

[e]Post-lesional versus perilesional skin.

[f]Post-lesional versus lesional skin.

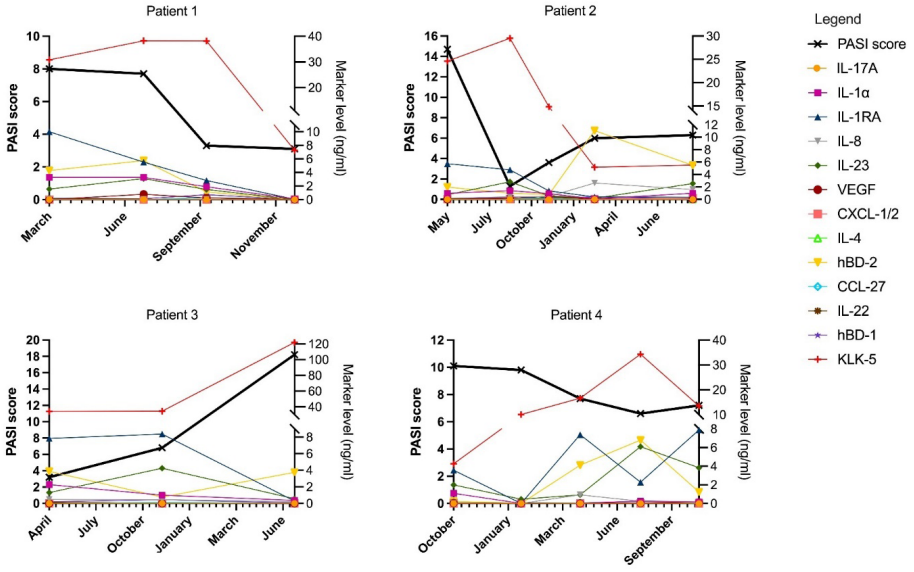

Figure 1. PASI scores and lesional marker levels measured by TAP over time

PASI scores (depicted on the left y axis) and mean lesional marker levels (depicted on the right y axis) are visualized over time for four representative patients. The follow-up duration is plotted on the x axis with intervals of 3 months. Marker levels are shown in ng/ml.

Table 3. Correlation between lesional marker concentrations and disease severity

Overall disease severity (n = 99)			Lesion severity[a] (n = 197)							
	PASI score[a]		Total SUM score		Desquamation		Erythema		Induration	
Marker	**CC**	***p*-value**	**CC**	***p*-value**	**CC**	***p*-value**	**CC**	***p*-value**	**CC**	***p*-value**
IL-1RA	0.094	.353	-0.070	.326	-0.032	.653	-0.037	.607	-0.120	.092
hBD-2	-0.140	.163	-0.026	.718	-0.133	.063	-0.025	.731	0.060	.400
Il-1α	-0.190	.058	-0.244	.002	-0.239	.001	-0.171	.016	-0.155	.030
IL-8	0.117	.247	0.217	.002	0.204	.004	0.201	.005	0.103	.149
VEGF	-0.113	.265	-0.013	.854	-0.075	.296	0.117	.100	-0.097	.176
CXCL-1/2	-0.051	.616	0.070	.331	0.069	.336	0.078	.274	0.029	.683
CCL-27	-0.111	.274	-0.069	.339	-0.129	.071	0.000	.999	-0.055	.444
IL-23	-0.003	.974	-0.101	.158	-0.125	.081	-0.077	.282	-0.059	.407
hBD-1	-0.113	.266	-0.012	.870	-0.146	.041	0.079	.270	0.018	.806
IL-22	-0.173	.088	-0.050	.485	-0.013	.855	-0.050	.487	-0.046	.518
IL-17A	-0.131	.198	-0.017	.810	-0.053	.462	0.029	.689	-0.008	.909
KLK-5	-0.211	.036	-0.111	.120	-0.179	.012	-0.026	.714	-0.105	.145
IL-4	0.044	.667	0.097	.176	0.016	.823	0.097	.176	0.102	.155

Abbreviations: CC, correlation coefficient; PASI, Psoriasis Area and Severity Index; SUM score, sum of the severity scores for erythema (0–4), induration (0-4), and desquamation (0-4).

Spearman correlations are shown for overall disease severity or lesion severity and lesional marker concentrations. All lesional data was included in this analysis. No correction for multiple measures within one patient was performed.

[a]For the correlation with the PASI score, the mean lesional protein concentration was used for each patient visit. PASI scores ranged from 1.2 to 18.2.

[b]For the correlation with lesion severity, the two lesional measurements at each patient visit were included separately and post-lesional samples were excluded, resulting in a total of 197 included measurements. Total SUM scores ranged from 2 to 9, desquamation scores ranged from 0 to 3, erythema scores ranged from 1 to 3, and induration scores ranged from 0 to 4.

Table 4. Marker levels in lesional and non-lesional skin of adult psoriasis patients (N=10) measured by TAP and tape stripping

Lesional						
	TAP[a]			**Tape stripping[b]**		
Marker	**n[c]**	**Median**	**Range**	**n[c]**	**Median**	**Range**
IL-1RA	10	7339.41	3150.50-10490.92	6[d]	36.20	23.48-50.00
hBD-2	8	3149.33	800.73-4574.33	10	295.04	20.88-767.56
IL-1α	6	319.12	222.91-896.29	10	0.28	0.00-0.84
IL-8	6	216.36	88.74-570.31	9	0.09	0.01-1.61
VEGF	2	1931.72	878.45-2984.99	8	0.07	0.03-0.11
CXCL-1/2	4	118.77	17.25-266.48	2	0.98	0.61-1.35
Non-lesional						
	TAP[a]			**Tape stripping[b]**		
Marker	**n[c]**	**Median**	**Range**	**n[c]**	**Median**	**Range**
IL-1RA	6	2413.52	256.50-3835.23	7	2.00	0.22-4.91
hBD-2	0	-	-	5	1.81	0.02-10.72
IL-1α	10	1656.17	169.12-9017.55	10	12.84	3.55-71.86
IL-8	0	-	-	1	0.04	-
VEGF	0	-	-	6	0.35	0.11-1.51
CXCL-1/2	0	-	-	0	-	-

Detection capability comparison						
	Lesional			**Non-Lesional**		
Marker	**Both, n**	**Only TAP, n**	**Only tape strip, n**	**Both, n**	**Only TAP, n**	**Only tape strip, n**
IL-1RA	10	-	-	5	1	2
hBD-2	8	-	2	-	-	5
IL-1α	6	-	4	10	-	-
IL-8	6	-	3	-	-	1
VEGF	2	-	6	-	-	6
CXCL-1/2	2	2	-	-	-	-

Only values within the detection limits were included in the analysis.

[a]Protein concentrations are presented in pg/ml.

[b]Concentrations measured in the tape strip samples were normalized to the total amount of protein and presented as pg/µg protein.

[c]Number of samples in which protein levels were within the detection limits.

[d]Other levels were above the upper detection limit.

Discussion

This study aimed to explore the value of TAP measurements in daily practice in (pediatric) psoriasis patients. We assessed skin surface proteins measured by TAP over time, determined their correlation with psoriasis severity, and compared the TAP detection capability with tape stripping. We showed that marker levels measured by TAP can differentiate between lesional and non-lesional skin. Surprisingly, marker levels in post-lesional skin were equal to or higher than lesional levels, and significantly higher than non-lesional levels. Lesional marker levels highly varied over time and no convincing correlations were found between these marker levels and PASI or SUM scores. The protein detection capability by tape stripping appeared superior to the TAP for five out of six quantified markers. In the next paragraphs, we will discuss the implication of these results.

In line with our previous publication on the baseline analysis of this cohort,[15] IL-1RA, hBD-2, IL-8, VEGF, and CXCL-1/2 levels were significantly increased in lesional skin, while the level of IL-1α was increased in non-lesional skin compared to lesional skin. In this follow-up analysis, IL-23, IL-22, hBD-1, CCL-27, and IL-17A were also significantly increased in lesional skin. In line with stratum corneum proteome profiling using tape stripping in adult psoriasis patients,[6] we found higher levels of VEGF, CXCL-1/2, IL-8, CCL-27, and IL-17A and lower levels of IL-1α in lesional skin. In contrast, we found higher levels of IL-22 in the pediatric psoriatic stratum corneum, while this was not increased in adults in the study by Mehul *et al*.[6] It has previously been suggested that IL-22 could differentiate pediatric from adult psoriasis.[7] As expected from the pathophysiology of psoriasis and previous studies,[6,15] IL-4 was barely detected: only in 2 out of 197 lesional samples.

TAPs measured lower marker concentrations as the amount of lesional desquamation increased, suggesting that excessive desquamation in psoriasis hampers sampling of soluble skin surface proteins. Our results indicate that tape stripping has a greater protein detection capability and a greater fold change between non-lesional and lesional samples, which further substantiates potential detection issues using the TAP in psoriasis. The greater protein detection capability of tape stripping could be explained by sampling deeper layers of the stratum corneum, and a greater sensitivity of quantification methods used for the tape extracts (herein used Luminex platform) than the spot-ELISA used for the TAPs. As this study solely aimed to compare the detection capability of TAP and tape stripping, statements about the potential clinical value of markers derived from tape strips in psoriasis cannot

be made. Further research is needed regarding the consistency of these marker levels over time and their correlation with disease severity.

Intriguingly, measured post-lesional marker levels were equal to or higher than lesional levels. However, we postulate that actual lesional levels were higher than post-lesional levels, but excessive desquamation resulted in an under detection of lesional marker levels. Nonetheless, hBD-2, IL-8, VEGF, IL-17A, and KLK-5 levels were significantly higher in post-lesional compared to non-lesional skin. Multiple studies have revealed that molecular and cellular imprints of psoriasis do not fully disappear in clinically cleared skin.[17-19] However, given the small number of post-lesional samples (n=6) we are unable to make valid statements regarding the presence of a residual inflammatory scar and results have to be confirmed in more post-lesional samples.

We note several limitations. Given the explorative study design, we did not perform correction for multiple measurements within one patient, since we did not want to miss any potential differences or correlations. Moreover, the marker set captured with the TAP was a preset general inflammatory panel, thus not specific for psoriasis. Hence, other psoriasis specific markers might yield better correlations with disease severity. Last, the daily practice setting resulted in uncontrolled variables (such as treatment), possibly disturbing correlations. However, it is important that correlations with disease severity are still present in a daily practice setting in order to be of value for clinical practice. Therefore, we underline the relevance of biomarker studies in a daily practice setting.

This study highlights important challenges for noninvasive biomarker measurements by TAP in pediatric psoriasis in a daily practice setting. Highly variable marker levels during the course of the disease were seen, and robust correlations between lesional marker levels measured by TAP and psoriasis severity could not be established. Moreover, detection issues related to desquamation were seen. Tape stripping may be considered instead of TAP for protein sampling of lesions with excessive desquamation, like in psoriasis. In the future, noninvasive biomarker measurements in daily practice could be of added value for managing psoriasis in the individual patient. However, in its current form, the use of biomarker measurements by TAP in pediatric psoriasis patients in daily clinical practice is still a bridge too far.

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Supplementary materials

Methods

Extraction of proteins on tape strip samples

Protein samples were obtained from tape strips by needle sonication. To do so, tape strips were placed in a tube containing 1.2ml of cold PBS/0.005% Tween with the adhesive side facing inwards. Tape strips were sonicated six times for ten seconds. After sonication, tape strips were removed from the tubes and protein concentration in the supernatant was determined using a micro BCA assay kit (Thermofisher Scientific), following manufacturer's protocol.

hBD-2 ELISA of tape strip protein samples

96-wells plates were coated overnight at 4˚C with goat-anti-human hBD2 (ABCAM) 1:500 in PBS. Plates were washed twice with PBS and blocked with 1%BSA/1% normal goat serum (Vector laboratories) in PBS for 1 hour at 37˚C. Plates were washed with PBS/0.05% Tween20 in between incubation steps. Sample incubation for 1 hour at 37˚C was followed by rabbit-anti hBD2 M47 (1:1000) incubation for 1 hour at 37˚C followed goat-anti rabbit biotinylated antibody (1:500, Vector laboratories) for 30 minutes at 37˚C. Avidine biotine complex (1:250, Vector laboratories) was incubated for 30 minutes at 37˚C followed by TMB substrate (Thermo Scientific) incubation. TMB reaction was stopped using H_2SO_4, plate absorbance was measured at 450nm.

Luminex of tape strip protein samples

Stratum corneum extracts were thawed and filtered by using a filter plate (Multiscreen, Merck KGaA, Darmstadt, Germany). Luminex assay was performed according to the manufacturer's instructions (Merck KGaA) using assay kit HCYTOMAG-60K. In short, 25 µL of extracts was used to determine the concentrations of 5 cytokines and chemokines, namely IL-1RA, IL-1α , IL-8, VEGF, and GRO (CXCL1/2). Mean fluorescence intensity of the samples was measured with a Flexmap 3D System (Luminex Corp, Austin, USA) and concentrations were calculated using Bio-Plex Manager 6.2 Software (Bio-Rad Laboratories, Veenendaal, The Netherlands).

Figures

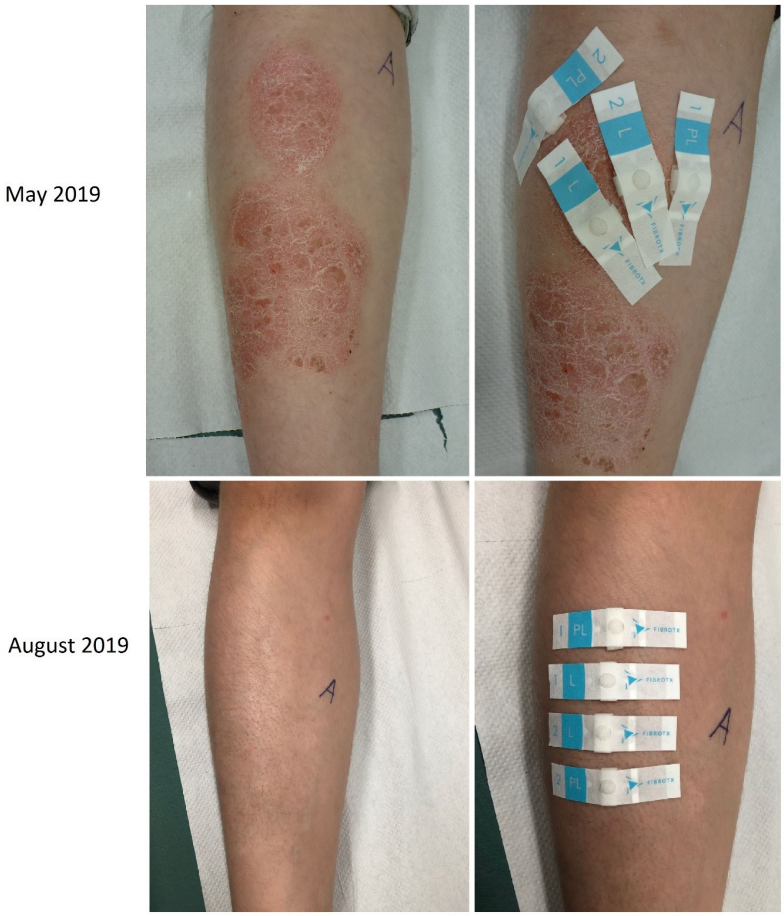

Figure S1. Example of TAP application and post-lesional sampling in a patient that started methotrexate during follow-up

Demonstration of one lesional skin site during the first two visits of one patient. Two lesional (L) and two perilesional (PL) TAPs were applied. During the second visit in august 2019, no psoriasis lesions large enough to apply the TAPs were present. Therefore, the TAPs were applied on post-lesional skin. The perilesional TAPs (PL) in august 2019 were excluded from the analysis, because they were not placed at a perilesional sample site.

Tables

Table S1. TAP lower and upper protein detection limits by spot-ELISA

Marker	Minimum detection level[a]	Maximum detection level[a]
IL-1α	0.125	8.000
IL-1RA	0.083	8.000
IL-8	0.020	2.000
IL-23	0.500	25.000
VEGF	0.030	2.000
CXCL-1/2	0.005	0.500
hBD-2	0.063	4.000
CCL-27	0.015	1.000
IL-22	0.030	2.000
IL-4	0.015	2.000
hBD-1	0.015	1.000
IL-17A	0.125	8.000
KLK-5	0.390	25.000

[a]Values are presented in ng/ml.

Table S2. Comparison of markers measured the two lesional and peri-lesional skin sites

Marker	Lesional Site A (n=98)	Lesional Site B (n=98)	*p*-value	Peri-lesional Site A (n=98)	Peri-lesional Site B (n=98)	*p*-value
IL-1RA	3.54 (3.31)	3.74 (3.39)	0.415	1.67 (2.04)	1.73 (2.18)	0.934
hBD-2	2.81 (2.98)	2.79 (3.00)	0.583	1.26 (2.40)	1.13 (2.09)	0.977
IL-1α	0.94 (1.45)	0.89 (1.16)	0.911	1.54 (1.76)	1.59 (1.87)	0.454
IL-8	0.46 (0.93)	0.57 (1.01)	0.464	0.03 (0.08)	0.04 (0.11)	0.939
VEGF	0.24 (0.48)	0.20 (0.35)	0.877	0.05 (0.17)	0.06 (0.21)	0.563
CXCL-1/2	0.09 (0.55)	0.07 (0.45)	0.962	0.04 (0.30)	0.05 (0.41)	0.661
CCL-27	0.04 (0.10)	0.05 (0.09)	0.561	0.01 (0.02)	0.01 (0.02)	0.002
IL-23	2.42 (2.89)	2.17 (2.38)	0.447	1.37 (1.45)	1.63 (2.55)	0.686
hBD-1	0.22 (0.32)	0.22 (0.24)	0.786	0.15 (0.19)	0.15 (0.23)	0.916
IL-22	0.10 (0.27)	0.09 (0.24)	0.675	0.05 (0.14)	0.02 (0.09)	0.030
IL-17A	0.02 (0.12)	0.03 (0.14)	0.594	0.01 (0.07)	0.01 (0.06)	0.893
KLK-5	28.31 (43.19)	30.57 (56.31)	0.821	27.03 (33.61)	23.27 (23.74)	0.086
IL-4	0.01 (0.07)	0.00 (0.00)	0.180	0.00 (0.00)	0.00 (0.00)	1.000

Data of all visits was included. Values are presented as means (standard deviation) in ng/ml. Lesional protein levels from site A and site B were compared by Wilcoxon signed rank tests. Visits including post-lesional measurements were excluded.

Table S3. Mean protein concentrations for each desquamation lesional severity score

Marker	Desquamation severity score				
Concentration in ng/ml, mean (SD)	**0 (n=2)**	**1 (n=116)**	**2 (n=71)**	**3 (n=8)**	**4 (n=0)**
IL-1RA	3.502 (4.494)	3.641 (3.333)	3.723 (3.254)	2.707 (4.150)	-
hBD-2	2.395 (2.563)	3.180 (3.171)	2.354 (2.761)	2.656 (2.183)	-
IL-1α	1.599 (1.461)	1.107 (1.476)	0.632 (0.969)	0.508 (0.881)	-
IL-8	0.233 (0.330)	0.296 (0.558)	0.809 (1.323)	1.318 (1.223)	-
VEGF	0.635 (0.898)	0.240 (0.446)	0.197 (0.374)	0.038 (0.082)	-
CXCL-1/2	0.292 (0.369)	0.107 (0.652)	0.024 (0.061)	0.064 (0.116)	-
CCL-27	0.190 (0.168)	0.046 (0.094)	0.038 (0.093)	0.007 (0.020)	-
IL-23	2.868 (4.055)	2.663 (3.014)	1.774 (1.933)	1.396 (1.152)	-
hBD-1	0.511 (0.185)	0.241 (0.305)	0.194 (0.254)	0.079 (0.091)	-
IL-22	0.000 (0.000)	0.104 (0.271)	0.093 (0.246)	0.028 (0.041)	-
IL-17A	0.365 (0.516)	0.025 (0.118)	0.028 (0.126)	0.000 (0.000)	-
KLK-5	37.644 (3.124)	30.180 (46.653)	30.235 (57.924)	10.950 (12.265)	-
IL-4	0.000 (0.000)	0.006 (0.063)	0.000 (0.001)	0.000 (0.000)	-

Data of all visits was included. Mean (±SD) marker levels presented for each desquamation severity score. For CCL-27, IL-22, hBD-1, KLK-5, IL-17A, hBD-2, IL-1α, IL-23, and VEGF a trend is present of lower levels as the amount of desquamation increases. Post-lesional measurements were excluded.

Table S4. Patient characteristics for the comparison of TAP and tape stripping detection capability

Characteristics	n = 10
Sex, male, n (%)	8 (80.0%)
Age, years, median (IQR[a])	58.0 (47.0-66.3)
Psoriasis severity, median (IQR[a])	
PGA	2.0 (2.0-2.3)
PASI	5.8 (3.8-7.9)
BSA	3.7 (2.5-8.9)
SUM score, median (IQR[a])	
Induration	2.0 (1.0-2.0)
Erythema	2.0 (2.0-3.0)
Desquamation	2.0 (1.8-2.0)
Total	6.0 (5.0-7.0)
Site location, n (%)	
Lesional	
Leg	7 (70.0%)
Arm	2 (20.0%)
Trunk	1 (10.0%)
Non-lesional	
Leg	5 (50.0%)
Arm	5 (50.0%)
Solely topical treatment, n (%)	3 (30.0%)
Systemic treatment[b], n (%)	
Methotrexate	1 (10.0%)
Acitretin	1 (10.0%)
Adalimumab	1 (10.0%)
Apremilast	1 (10.0%)
Guselkumab	1 (10.0%)
Ustekinumab	1 (10.0%)
Secukinumab	1 (10.0%)
Total	7 (70.0%)

IQR, interquartile range.
[a]The 25th and 75th percentile are shown.
[b]Patients may also use topical treatments.

2.3 Nail involvement as a predictor of disease severity in pediatric psoriasis: follow-up data from the Dutch Child-CAPTURE registry

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Abstract

Little is known about the relation between nail psoriasis and psoriasis severity in children, and longitudinal assessment of psoriasis severity related to nail psoriasis doesn't exist. The aim of this study was to assess whether nail psoriasis could serve as a predictor for a more severe disease course. Deidentified data were obtained from the Child-CAPTURE registry, a daily clinical practice cohort of children with psoriasis, from September 2008 to November 2015. Cross-sectional analyses were performed at baseline. Longitudinal data until 2- year follow-up were analyzed by linear mixed models. Nail psoriasis was present in 19.0% of all 343 patients at baseline and cross-sectionally associated with higher Psoriasis Area and Severity Index (PASI) ($p = .033$). Longitudinal analysis demonstrated higher PASI ($p < .001$) during two year follow-up in patients with nail involvement at baseline. These findings suggest nail psoriasis to be a potential clinical predictor for more severe disease course over time in pediatric psoriasis.

Introduction

Psoriasis develops during childhood in almost one-third of the cases, with an almost linear increase in prevalence rates until 18 years.[1-5] Nail psoriasis affects over 50% of the adult population with psoriasis, and is even more prevalent in patients with psoriatic arthritis (PsA).[6-11] Although a range of prevalence rates has been reported in children, a recent study of 4853 children revealed an overall prevalence of 15.7%[12,13]

Evidence on nail psoriasis in children and its association with psoriasis severity is scarce. A recent multicenter, cross-sectional study demonstrated more severe disease in 313 children with nail involvement compared to those without nail involvement. Nail psoriasis was also associated with male sex, palmoplantar psoriasis and PsA.[14] Two other cross-sectional studies in children reported no relation between nail psoriasis and psoriasis severity.[13,15] Remarkably, reported signs of nail psoriasis and psoriasis severity scores in these studies were based on historical information rather than physical examination of the nails and skin. In adults, studies have found nail psoriasis to be a potential clinical predictor of developing enthesitis and PsA,[16,17] and have demonstrated an association between nail psoriasis and higher psoriasis severity scores.[9,18-21] Augustin et al reported higher Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA) scores in adult patients with nail psoriasis in a cohort of 3531 patients. Based on these findings, they proposed to examine whether current nail involvement is predictive of a more severe psoriasis course in future.[20]

Approximately one-third of children with psoriasis suffer from more severe or recalcitrant disease.[5,22] Early identification of children with an increased risk for a severe disease course is essential for adequate intervention and subsequent limitation of disease progression. The presence of nail psoriasis as noninvasive, clinical predictor for a more severe disease course could contribute to this concept and become important for providing optimal treatment strategies. The aim of this prospective, observational study in a daily practice cohort of pediatric patients with psoriasis was to describe epidemiological and disease characteristics of children diagnosed with nail psoriasis at baseline, to determine the presence of nail psoriasis over time, to assess the relationship between nail psoriasis and reported psoriasis severity scores, and, ultimately, to study the predictive value of nail psoriasis for a more severe disease course over time.

Materials and methods

Patient selection and study design

This prospective, single-center study was conducted in children (aged < 18 years) diagnosed with psoriasis who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Center between September 2008 and November 2015. All available data were extracted from the Child-CAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, long-term, observational daily practice cohort of children with psoriasis. The study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Data collection and management

At baseline and during follow-up, patient, psoriasis and treatment characteristics, including presence of nail psoriasis and PsA, were collected using a standard case report form. Psoriasis severity scores (PASI, BSA and Physician Global Assessment (PGA)) and patient-reported outcome measures (Children's Dermatology Life Quality Index (CDLQI); visual analogue scales (VAS) for psoriasis severity, itch, pain, and fatigue) were also collected. Patients on topical treatment were seen at least every 6 months to 1 year; patients on systemic medication (e.g. methotrexate, dimethylfumarate, biologics) were seen every 3 months. Cross-sectional analyses were performed at baseline visit.

Nail psoriasis

The diagnosis of nail psoriasis was made by two clinicians, and exclusively based on physical examination. All twenty nails were examined. Furthermore, the target Nail Psoriasis Severity Index (NAPSI) was used as a quantitative nail assessment tool at baseline and during each follow-up visit. This tool divides the nail into imaginary quadrants and records the number of quadrants in which any manifestations of nail matrix psoriasis (pitting, leukonychia, red spots in lunula, nail plate crumbling) or nail bed psoriasis (oil drop discoloration, onycholysis, nail bed hyperkeratosis, splinter hemorrhage) are present. At each visit the most severely affected nail was assigned a nail matrix and nail bed score of 0–4, which yielded a composite score between 0 and 8.

Psoriasis severity scores

PASI, BSA and PGA scores from 0 (clear) to 5 (very severe) were reported at baseline and during each follow-up visit. All psoriasis severity scores over a period of up to 2 years were included to assess disease severity over time in patients with and without nail involvement. This timeframe was based on mean ± standard deviation

(SD) follow-up duration of 22.9 ± 23.5 months in 343 children. Two-year follow-up data were available for 40.5% of children. The percentage of patients with at least 2-year follow-up was comparable between the groups (nail psoriasis 41.5%; no nail psoriasis 40.3%, $p = .853$).

Presence of nail psoriasis over time

The presence or absence of nail psoriasis during follow-up was captured to better understand its consistence over time in children. The following categories can be distinguished: (i) patients with persistent nail psoriasis over time, (ii) patients with nail psoriasis occasionally during follow-up, and (iii) patients without nail psoriasis at any point in time.

Statistical analysis

Cross-sectional

Demographic data were summarized as medians and interquartile ranges (IQR) for continuous variables, and numbers and percentages for categorical variables. Patient and disease characteristics were presented for: (i) total number of patients, (ii) patients with nail involvement at baseline, and (iii) patients without nail involvement at baseline. Medians reported in patients with and without nail psoriasis were compared by Mann–Whitney U test. Differences between groups with regard to frequencies were analyzed by χ^2 tests for independence.

Longitudinal

PASI and PGA scores over time were both studied using linear mixed models (LMM). Psoriasis severity score was defined as dependent variable, and time (in months) from baseline visit as one of the main independent variables to model psoriasis severity over time. The occurrence of nail psoriasis at baseline and the interaction term between time and nail psoriasis were other key independent variables. The latter was included to test whether psoriasis severity scores over time are different between patients with versus without nail involvement at baseline. Sex, psoriasis severity at baseline, psoriasis duration, most intensive treatment received until first visit, concomitant antipsoriatic treatment, presence of nail matrix involvement, presence of nail bed involvement and presence of nail psoriasis over time, were incorporated as possible confounding factors. Confounders that altered the unadjusted exposure-outcome effect by ≥ 10% were kept in the model. Variance components were used as covariance type (default setting of SPSS). As a result of this model, psoriasis severity scores over time for patients with nail psoriasis vs. without nail psoriasis at baseline were shown in figure 1. Corresponding estimated marginal means (EMM) were also

calculated. In case the difference in EMM reaches significance, psoriasis severity scores over time are different between the two groups. Statistical package SPSS version 22.0 (IBM, Armonk, NY, USA) was used to perform all analyses. $p < .05$ was considered significant. Statistical package SPSS version 22.0 (IBM, Armonk, NY, U.S.A.) was used to perform all analyses. $p < .05$ was considered significant.

Results

Patient characteristics

Data from 343 de-identified patients were extracted from the Child-CAPTURE registry. Patient characteristics at baseline are shown in table 1. The majority of patients were female (58.0%), and median age and psoriasis duration were 11.0 and 1.4 years, respectively. Plaque psoriasis was the most common type of psoriasis (88.6%). Median PASI, BSA and PGA scores at first consultation were, respectively, 5.8, 5.4 and 2.0. Patients reported a median CDLQI score of 8.0. Koebnerization was observed in 78 (25.8%) patients. At baseline, 0.3% of patients were diagnosed with PsA and 3.2% had arthralgia without clinical arthritis.

Nail psoriasis is associated with male sex, higher pain score and more severe disease at baseline

A total of 65 subjects (19.0%) presented with nail psoriasis at their first visit (Table 1). The median target NAPSI was 4.0. Nail psoriasis was associated with male sex ($p = .015$), concomitant higher VAS pain score (nail psoriasis 9.0 (53.0); no nail psoriasis 3.5 (20.0), $p = .030$) and more severe psoriasis. Median PASI scores in patients with and without nail involvement were, respectively, 6.5 (6.1) and 5.6 (4.7) ($p = .033$). BSA (nail psoriasis 7.0 (13.8); no nail psoriasis 5.0 (8.1), $p = .034$) and PGA (nail psoriasis 3.0 (2.0); no nail psoriasis 2.0 (1.0), $p = .035$) scores were also higher in patients with nail psoriasis. Psoriasis patients with nail involvement more often received systemic treatment at any time before their first visit (17.6 % in patients with nail psoriasis vs. 7.3% in patients without nail psoriasis, $p = .026$). All patients with palmoplantar psoriasis (n = 5) had nail psoriasis. Although total CDLQI score was slightly higher in patients with nail involvement, this effect did not reach statistical significance ($p = .098$). Number of patients with a positive Koebner phenomenon was similar between the two groups. The presence of nail psoriasis during total available follow-up of all patients (n = 343; mean follow-up duration 22.9 months ± 23.6) was also captured. In total, 8.2% of patients had persistent nail psoriasis over time, and 22.1% occasionally had nail psoriasis. Most patients (69.7%) did not show signs of nail psoriasis at any time.

Table 1. Characteristics of pediatric psoriasis patients with and without nail involvement at baseline.

Characteristics	All patients (n = 343)	Patients with nail involvement (n = 65, 19.0%)	Patients without nail involvement (n = 278, 81.0%)	*p*-value
No. (%)				
Sex				.015
Male	144 (42.0)	36 (55.4)	108 (38.8)	
Female	199 (58.0)	29 (44.6)	170 (61.2)	
Family history				
Psoriasis in parents or siblings	112 (32.7)	20 (30.8)	92 (33.1)	.719
PsA in parents or siblings	4 (1.2)	1 (1.5)	3 (1.1)	.756
Psoriasis trigger (n = 340)				.647
No trigger	228 (66.5)	45 (70.3)	183 (66.3)	
Infection	53 (15.5)	8 (12.5)	45 (16.3)	
Stress	47 (13.7)	10 (15.6)	37 (13.4)	
Other[a]	12 (3.5)	1 (1.6)	11 (4.0)	
Koebner phenomenon[b] (n = 302)	78 (25.8)	18 (31.0)	60 (24.6)	.314
Joint involvement				.887
PsA	1 (0.3)	0 (0)	1 (0.4)	
Arthralgia[c]	11 (3.2)	2 (3.1)	9 (3.2)	
No PsA or arthralgia	331 (96.5)	63 (96.9)	268 (96.4)	
Type of psoriasis[d]				
Plaque	304 (88.6)	57 (87.7)	247 (88.8)	.791
Guttate	62 (18.1)	13 (20.0)	49 (17.6)	.654
Pustular	6 (1.7)	3 (1.1)	3 (4.6)	.050
Palmoplantar	5 (1.5)	5 (7.7)	0 (0)	<.001
Scalp	298 (86.9)	57 (87.7)	241 (86.7)	.829
Inverse	150 (43.7)	29 (44.6)	121 (43.5)	.873
Type of nail involvement (n = 64)				
Nail matrix involvement		53 (82.8)		
Nail bed involvement		27 (42,2)		
Most intensive treatment received (n = 242)				.026
Topical or intense topical[e]	219 (63.8)	42 (82.4)	177 (92.7)	
Systemic treatment	23 (6.7)	9 (17.6)	14 (7.3)	
Median (IQR)				
Age, yrs	11.0 (7.0)	11.0 (4.0)	10.0 (7.0)	.232
Psoriasis duration, yrs	1.4 (3.6)	1.8 (4.9)	1.2 (3.6)	.047
Psoriasis severity at baseline (n = 340)				
PGA, median (IQR)	2.0 (1.0)	3.0 (2.0)	2.0 (1.0)	.035
PASI, median (IQR)	5.8 (5.0)	6.5 (6.1)	5.6 (4.7)	.033
BSA, median (IQR)	5.4 (8.6)	7.0 (13.8)	5.0 (8.1)	.034

Table 1. Continued

Characteristics	All patients (n = 343)	Patients with nail involvement (n = 65, 19.0%)	Patients without nail involvement (n = 278, 81.0%)	*p*-value
Target NAPSI (0-8) median (IQR)[f]		4.0 (2.0)		
CDLQI (0-30; n = 328)	8.0 (7.0)	9.0 (8.0)	7.0 (7.0)	.098
DLQI (0-30; n = 25)	8.0 (6.0)	12.0 (5.0)	7.0 (6.0)	.101
VAS				
Psoriasis severity (n = 192)	57.5 (39.0)	51.0 (44.0)	58.0 (39.0)	.734
Itch (n = 258)	45.5 (49.0)	42.0 (65.0)	47.0 (45.0)	.724
Pain (n = 258)	5.0 (25.0)	9.0 (53.0)	3.5 (20.0)	.030
Fatigue (n = 256)	10.0 (40.0)	10.0 (41.0)	10.0 (40.0)	.916

Abbreviations: BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PsA, Psoriatic Arthritis.

[a]These included primarily trauma or surgical procedures. [b]Positive Koebner phenomenon was defined as having an isomorphic response regularly or often. [c]Arthralgia was defined as aching or pain in the joints without true arthritis. [d]Total number of patients does not equal sum of patients reporting different types of psoriasis because more than one type of psoriasis can be reported in the same patient.

[e]Intense topical treatment included dithranol treatment or UVB phototherapy. [f]The NAPSI score for most severely affected nail was calculated if nail psoriasis was present.

Nail psoriasis predicts a more severe disease course during follow-up

Longitudinal analysis of psoriasis severity scores in patients with and without nail psoriasis at baseline was performed to further investigate the role of nail psoriasis as predictor for a more severe disease course over time. LMM demonstrated an overall higher PASI score during 2-year follow-up in children with nail psoriasis compared with children without nail psoriasis at baseline (nail psoriasis at baseline, EMM 5.73 (95% confidence interval (CI) 5.00–6.46); no nail psoriasis at baseline, EMM 4.17 (95% CI 3.80–4.53), $p < .001$). This was also true for PGA scores during follow-up (nail psoriasis at baseline, EMM 2.55 (95% CI 2.35–2.76); no nail psoriasis at baseline, EMM 1.84 (95% CI 1.74–1.94), $p < .001$). Psoriasis severity scores over time are show in figure 1. Results were corrected for possible confounders at baseline, including sex, psoriasis duration and psoriasis severity score at baseline. Most intensive treatment received until first visit, concomitant antipsoriatic treatment, presence of nail matrix involvement, presence of nail bed involvement and presence of nail psoriasis over time did not alter the unadjusted exposure-outcome effect and were therefore not kept in the model. Tables 2 and 3 provide detailed information about the models used.

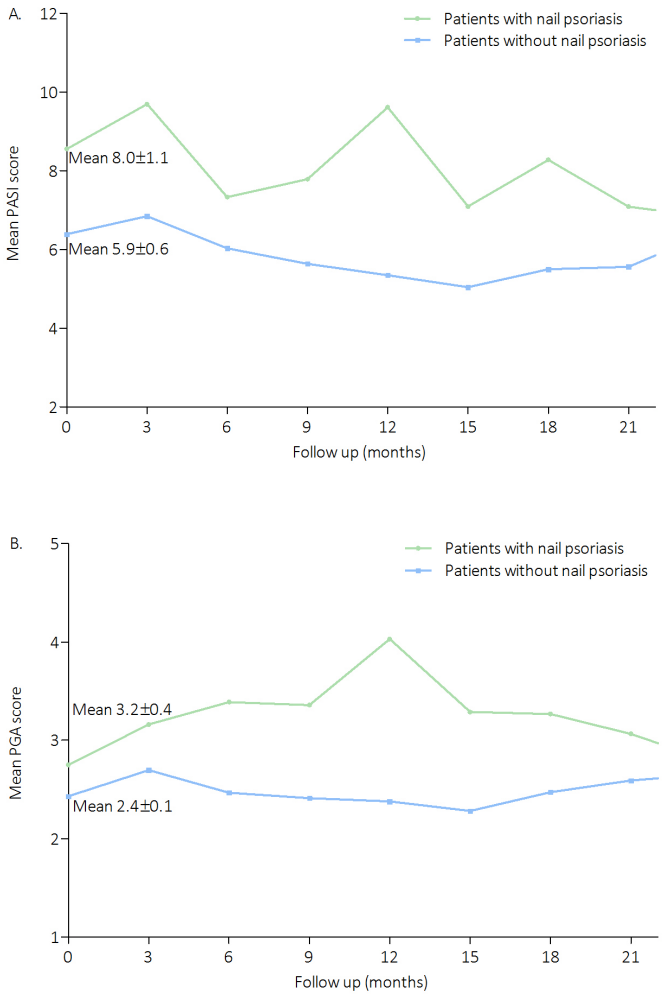

Figure 1. Estimated psoriasis severity scores during 2- year follow-up in pediatric psoriasis patients with nail involvement (n = 65) and without nail involvement (n = 278) at baseline.

A. Mean PASI score during 2- year follow-up. B. Mean PGA score during 2- year follow-up. Linear mixed models were used to predict PASI and PGA scores over time. In both models sex, psoriasis duration and severity scores at baseline were incorporated as possible confounders.

Abbreviations: PASI, psoriasis area and severity index; PGA, physician global assessment.

Graphs were presented for female subjects with a psoriasis duration of 24 months, a PASI score at baseline of 6.4 and 8.6 for subjects with and without nail psoriasis, respectively, and a PGA score at baseline of 2.43 and 2.75, respectively. Most intensive treatment received until first visit, concomitant anti-psoriatic treatment, presence of nail matrix involvement, presence of nail bed involvement and presence of nail psoriasis over time did not alter the unadjusted exposure-outcome effect by ≥10% and were therefore not kept in the model. Mean severity scores at 24 months were incorporated in our linear mixed model but could not be presented graphically due to lower numbers at this point.

Table 2. Linear mixed model used to estimate PASI scores during 2-year follow-up in pediatric psoriasis patients with nail involvement (n = 65) and without nail involvement (n = 278) at baseline

Variable	Estimate	Confidence interval		*p*-value
		lower limit	upper limit	
Intercept	1.93	0.23	3.64	0.000
Sex				0.688
Male	0.13	-0.50	0.75	
Female	0[a]	.		
Nail psoriasis at baseline				0.000
No	0.20	-1.60	1.99	
Yes	0[a]	.	.	
Time from baseline visit, months				0.000
3	2.86	1.17	4.54	
6	0.49	-1.30	2.29	
9	0.95	-0.85	2.75	
12	2.78	0.86	4.68	
15	0.26	-1.62	2.13	
18	1.44	-0.50	3.38	
21	0.25	-1.70	2.20	
24	0[a]	.	.	
Psoriasis duration, months	0.11	0.00	0.21	0.047
PASI at baseline	0.28	0.22	0.33	0.000
Interaction term between nail psoriasis at baseline visit and time from baseline visit				0.015
Nail psoriasis at baseline = no, time = 3 months	-2.44	-4.37	-0.50	
Nail psoriasis at baseline = no, time = 6 months	-0.89	-2.95	1.17	
Nail psoriasis at baseline = no, time = 9 months	-1.74	-3.83	0.34	
Nail psoriasis at baseline = no, time = 12 months	-3.85	-6.04	-1.66	
Nail psoriasis at baseline = no, time = 15 months	-1.65	-3.84	0.54	
Nail psoriasis at baseline = no, time = 18 months	-2.37	-4.63	-0.11	
Nail psoriasis at baseline = no, time = 21 months	-1.12	-3.40	1.16	
Nail psoriasis at baseline = no, time = 24 months	0[a]	.	.	

Abbreviations: PASI, Psoriasis Area and Severity Index.
[a]This parameter is set to zero because it is redundant.

Table 3. Linear mixed model used to estimate PGA scores during 2-year follow-up in pediatric psoriasis patients with nail involvement (n = 65) and without nail involvement (n = 278) at baseline

Variable	Estimate	Confidence interval		*p*-value
		lower limit	upper limit	
Intercept	1.22	0.74	1.70	0.000
Sex				0.616
Male	0.04	-0.13	0.22	
Female	0[a]	.		
Nail psoriasis at baseline				0.000
No	-0.03	-0.49	0.43	
Yes	0[a]	.	.	
Time from baseline visit, months				0.024
3	0.38	-0.04	0.80	
6	0.61	0.16	1.06	
9	0.58	0.13	1.03	
12	1.25	0.78	1,72	
15	0.51	0.04	0.97	
18	0.49	0.01	0.97	
21	0.28	-0.20	0.77	
24	0[a]	.	.	
Psoriasis duration, months	0.04	0.01	0.06	0.013
PGA at baseline	0.25	0.17	0.34	0.000
Interaction term between nail psoriasis at baseline visit and time from baseline visit				0.000
Nail psoriasis at baseline = no, time = 3 months	-0.35	-0.84	0.13	
Nail psoriasis at baseline = no, time = 6 months	-0.81	-1.32	-0.29	
Nail psoriasis at baseline = no, time = 9 months	-0.83	-1.35	-0.31	
Nail psoriasis at baseline = no, time = 12 months	-1.53	-2.08	-0.99	
Nail psoriasis at baseline = no, time = 15 months	-0.89	-10.44	-0.35	
Nail psoriasis at baseline = no, time = 18 months	-0.68	-10.24	-0.12	
Nail psoriasis at baseline = no, time = 21 months	-0.36	-0.93	0.21	
Nail psoriasis at baseline = no, time = 24 months	0[a]	.	.	

Abbreviations: PGA, Physician's Global Assessment.

[a]This parameter is set to zero because it is redundant.

Discussion

This single-center, prospective study focused on the occurrence of nail involvement in pediatric psoriasis, epidemiological and clinical characteristics of this subpopulation, and its predicting value for a more severe disease course. Whereas conflicting results were previously reported in children, we found higher psoriasis severity scores in children with nail psoriasis within a large pediatric psoriasis population, both at baseline and during follow-up. Pourchot et al, also reported more severe skin disease in children with nail psoriasis. However, psoriasis severity was defined as the use of systemic medication before or at the day of inclusion and not determined by physical examination.[14] Mercy et al did not find an association between nail involvement and severity of skin psoriasis in 181 children aged 5-17 years, but reported that a greater proportion of children with severe psoriasis had a history of nail involvement (severe psoriasis 43.7% vs mild psoriasis 33.3%, $p = .300$).[13] Previous studies in children also demonstrated nail psoriasis to be present more often in boys than girls, suggesting a possible role for koebnerization in boys.[13,14] Nail psoriasis in our population was also present more frequently in boys than in girls. However, no association was found between the koebner phenomenon and male sex by an additional χ^2 test for independence ($p = .580$). Pourchot et al. found a significant association between nail psoriasis and psoriatic arthritis ($p = .03$) in children with psoriasis.[14] The current study did not demonstrate an association between nail psoriasis and joint involvement. However, it should be noted that only one patient (0.3%) was diagnosed with PsA in our population at baseline.

Cross-sectional analyses at baseline found nail psoriasis to be present in 19.0% of children. Piraccini et al reported an overall prevalence of 15.7% in 4853 children, and respectively 19.4% and 15.5% in two centers specialized in nail disorders in Greece and Italy.[12] Prevalence rates in adult psoriasis are higher, which suggests an association with psoriasis duration, but this is still a matter of debate.[18,20,21] In our population, no significant difference in psoriasis duration between patients with versus without nail involvement was found. Moreover, almost 80% of children reported either persistent nail psoriasis (8.2%) or no signs of nail psoriasis (69.7%) during total follow-up. From a clinical perspective, the latter also suggests the presence of nail psoriasis to be a relatively stable process rather than an highly fluctuating on-off phenomenon in children. This, together with our finding that presence of nail psoriasis over time did not affect psoriasis severity scores over time, advocates nail psoriasis at baseline as a representative point in time to distinguish

between having or not having nail psoriasis and assess its predictive value for a more severe disease course until 2- year follow-up.

This study is the first to show the role of nail psoriasis at baseline as a noninvasive predictor for a more severe disease course over time. Longitudinal analysis was corrected for possible confounders at baseline, including sex, psoriasis duration and psoriasis severity score at baseline. The results revealed substantially higher PASI and PGA scores during 2-year follow-up in children with clinical signs of nail psoriasis at baseline. As such, our longitudinal findings go beyond previously reported cross-sectional findings in both children and adults, and fit within the concept of early identification of patients at risk for a more severe disease course.

Our study was limited by the use of the target NAPSI (0 – 8), in which only the most severely affected nail was scored. Further research using specific and validated nail psoriasis scoring systems of all fingernails and/or toenails is needed to further determine the role of different signs of nail psoriasis and the extent of nail involvement in predicting the severity of skin psoriasis. Mean follow- up duration of all children in our registry was about 2 years at time of analysis, limiting longitudinal analysis and the subsequent role of nail psoriasis in predicting psoriasis severity to 2-year follow-up. Whether nail psoriasis is predictive for more severe disease on the long term could not be determined. In addition, onychomycosis was clinically not suspected in any of our subjects with nail psoriasis, however, nails were not cultured to confirm its absence. Finally, although nail psoriasis proved to be relative stable over time in our population, a small percentage children without nail psoriasis at baseline still developed nail abnormalities during follow up. This may lead to underestimation of percentage of children with nail psoriasis used for longitudinal analysis.

In conclusion, nail psoriasis in children is associated with more severe psoriasis cross-sectionally as well as a more severe disease course over time. Our findings suggest nail psoriasis to be a potential clinical predictor for a more severe disease course in the pediatric population. Therefore, nail psoriasis as a clinical predictor could assist in the prompt identification of patients at risk for a more severe disease course and subsequently result in early intervention to restrict further disease progression.

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Chapter 3

Optimizing management of pediatric psoriasis patients

3.1 Treatment persistence in pediatric and adolescent patients with psoriasis followed into young adulthood. From topical to systemic treatment: a prospective, longitudinal, observational cohort study of 448 patients

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Abstract

Background

Although solely topical treatment often suffices, patients with psoriasis may require more intensive treatment (phototherapy and/or systemic treatments) to control their disease. However, in pediatric, adolescent and young adult patients, little is known about persistence of topical treatment and time until switch to systemic treatment.

Objectives

To determine the median time from psoriasis onset until (i) discontinuation of solely topical agents and (ii) switch to systemic treatment, and to identify patient characteristics associated with switching to systemic treatments.

Methods

Data were extracted from the Child-CAPTURE registry, a prospective, observational cohort of patients with pediatric-onset psoriasis followed into young adulthood from 2008 to 2018. Data prior to inclusion in the registry were collected retrospectively. Median times were determined through Kaplan–Meier survival analyses. Cox regression analysis was used to identify patient characteristics associated with switch to systemic treatment.

Results

Of 448 patients, 62.3% stayed on solely topical treatment until data lock; 14.3% switched from topicals to phototherapy, but not to systemic treatment; and 23.4% switched to systemic treatment. The median time from psoriasis onset until discontinuation of solely topical treatment was 7.3 years, and until switch to systemics was 10.8 years. Higher Psoriasis Area and Severity Index and (Children's) Dermatology Life Quality Index > 5 were independently associated with switching to systemic treatment.

Conclusions

In a population of pediatric and adolescent patients with mild-to-severe psoriasis, one-third needed more intensive treatment than solely topical therapy to control their disease. We consider the median time until switching to systemics to be long.

Introduction

Several treatment modalities for the management of psoriasis exist.[1,2] Topical treatments, consisting of topical corticosteroids, vitamin D analogues and calcineurin inhibitors, are generally considered to be the first choice of treatment.[2,3] Dithranol is a topical treatment often applied in a daycare setting as short-contact therapy, and it has been shown to be safe and effective in the treatment of moderate-to-severe psoriasis.[4,5] Short-contact dithranol therapy is usually given as a daily application in increasing concentrations and application time (from 15 to 45 min) until the skin is clear or almost clear (average duration 2 months).[4,6] In the Netherlands, the majority of pediatric patients are treated with dithranol as a second-line topical treatment before commencing phototherapy or systemic treatment.[1,7] Although solely topical treatment is sufficient for many patients with psoriasis, some patients may require more intensive treatment to control their disease, such as phototherapy or systemic therapy. Apart from a possible lack of efficacy of topical treatments, adherence to topicals is often low in patients with psoriasis, which consequently limits treatment effect, leading to insufficient disease control.[8,9] Yet, especially in pediatric patients with psoriasis, systemic therapies are commonly reserved for more severe or refractory psoriasis due to potential adverse events and/or frequent monitoring.

As systemic treatment options for patients with psoriasis are expanding, and as more data regarding the safety of systemic treatments are becoming available, a point of discussion is whether we should initiate more effective treatment earlier on. This is especially true for children, adolescents and young adults with psoriasis. As these young patients with psoriasis might have a substantial cumulative life course impairment by inadequately controlled psoriasis, they might benefit most from early and effective intervention.[10-13] It is therefore important to gain insight into how long solely topical treatments currently suffice and the duration until the start of systemic treatments in this patient group. Data on this subject are scarce, with only a few retrospective treatment pattern studies assessing these durations in adult patients with psoriasis.[14-17] Most of these studies were based on retrospective administrative databases, which have the advantage of complete coverage of the psoriasis population, but might not always accurately reflect the treatment use of patients.[14,15,17] Furthermore, due to the retrospective nature of these studies, they were unable to address the influence of psoriasis severity or the association with patient characteristics on the switch to systemic treatments.[14-17] Moreover, to the best of our knowledge, no previous study has examined the time to topical discontinuation and switch to systemics in pediatric, adolescent and young adult patients with psoriasis.

With this prospective, longitudinal, observational, single-center, daily clinical practice cohort study of young patients with psoriasis, we therefore aim to give insight into treatment persistence, taking into account psoriasis severity and patient characteristics. The following objectives were formulated. Firstly, to describe the proportions of patients who persisted on solely topical treatment, switched to phototherapy but not to systemics, or switched to systemic treatment at data lock. Secondly, to determine the median time from psoriasis onset until (i) discontinuation of solely topical treatment and (ii) switch to systemic treatment, both for all patients and split for patients with moderate-to-severe versus mild psoriasis at first visit. Additionally, we sought to identify patient characteristics associated with switching to systemic treatment.

Methods

Registry and data collection

Data for this prospective, single-center cohort study were extracted from the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, longitudinal, observational, daily clinical practice cohort of pediatric-onset patients with psoriasis. This ongoing cohort includes all patients with a diagnosis of psoriasis aged < 18 years at first visit, who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Centre between September 2008 and May 2018 (data lock). Patients included in the registry who reach the age of 18 years are followed as young adults. Patients are referred by general practitioners and dermatologists from all over the Netherlands. This study was reviewed by the ethics committee of the region of Arnhem-Nijmegen (file number CMO: 2012/383) and was deemed to not fall within the remit of the Medical Research Involving Human Subjects Act. Written informed consent was obtained from the parents or guardians and/or from the participating patients according to applicable rules.

Treatment characteristics

Treatment characteristics were collected prospectively from the moment of inclusion in the registry. Characteristics of treatments used prior to inclusion and the date of psoriasis onset (self-reported by parents and/or patients) were collected retrospectively at the first visit. For all treatments, the type of treatment (i.e. solely topical, daycare dithranol, phototherapy and systemic treatment) and the date of treatment start or switch were recorded. A treatment switch was defined as occurring when a patient switched to or added on a different type of

treatment. Regarding solely topical treatment, intermittent use of topical treatment (e.g. temporary discontinuation due to disease improvement, but restart after a psoriasis flare) was considered as continuous use of topical treatment and was not recorded as a treatment stop or switch. All patients were treated according to daily clinical care. Treatment decisions were made by the treating physician according to the Dutch evidence- and consensus-based guideline on psoriasis.[1,7,18] Patients were categorized according to treatment patterns as follows: (i) patients who stayed on solely topical treatment until data lock; (ii) patients who switched from solely topical treatment to ultraviolet B phototherapy, but not to a systemic treatment; and (iii) patients who switched to systemic treatment.

Patient characteristics

The following baseline patient characteristics were collected: sex, date of psoriasis onset and family history of psoriasis. At every visit, patient and psoriasis characteristics, including age, length and weight, psoriasis location, psoriasis severity and impact of psoriasis on quality of life were collected prospectively using a standard case report form. Psoriasis severity was measured through the Psoriasis Area and Severity Index (PASI, range 0–72) and body surface area. The impact of psoriasis on quality of life was measured with the Children's Dermatology Life Quality Index (CDLQI, range 0–30) if a patient was < 16 years old and/or the Dermatology Life Quality Index (DLQI, range 0–30) if a patient was ≥ 16 years old.[19,20]

Statistical analysis

Patient characteristics

Clinical and demographic data were presented as a mean ± SD in case of normally distributed continuous variables, as a median with interquartile range in case of non-normally distributed continuous variables, and as a number (%) for categorical variables. Patient and disease characteristics were presented for (i) all patients; (ii) patients who stayed on solely topicals until data lock; (iii) patients who switched to phototherapy, but not to a systemic treatment; and (iv) patients who switched to systemic treatment during follow-up.

Median-time analyses

To determine the median time from psoriasis onset until (i) discontinuation of solely topical treatment and (ii) switch to first systemic treatment, Kaplan–Meier survival analyses were performed. For purpose of visualization, the median time until switch to first systemic treatment was displayed as a one-minus-survival curve. In addition, to account for the use of dithranol as a second-line topical treatment in this study,

a sensitivity analysis was performed. In this sensitivity analysis the median time until topical treatment discontinuation was recalculated with dithranol considered as a next step after topical treatment (together with phototherapy and systemic treatment). Patients were censored when lost to follow-up or if no event had occurred at the moment of data lock. Subanalyses were performed split for patients with mild psoriasis, defined as PASI < 5 at the first visit, and moderate-to-severe psoriasis, defined as PASI ≥ 5 at the first visit. Log-rank tests were performed to compare Kaplan–Meier curves.

Patient characteristics associated with switching to systemic treatment

A Cox proportional hazards regression model was used to examine the association between patient characteristics and switch to systemic treatment. For this analysis only prospectively collected data were used, and therefore patients with a history of systemic treatment before inclusion in the registry were excluded. The following patient characteristics were included in the analyses: sex, first-degree family history of psoriasis, body mass index at the moment of switch, age at switch, PASI at switch, body surface area at switch, CDLQI or DLQI > 5 at switch and presence of psoriasis on either the scalp, face or nails at switch. All variables were tested with univariable analyses and were incorporated into the multivariable analysis when the *p*-value was < .20. Final determinants were selected through backward selection. Hazard ratios (HRs) with 95% confidence interval (CIs) for the determinants were calculated. As this study follows patients from childhood into young adulthood, both CDLQI and DLQI were used during follow-up. Because these scores cannot be combined into one score, a cutoff of either CDLQI > 5 or DLQI > 5 was used for analysis.[21] Body mass index was categorized into thinness, normal weight and overweight/obesity based on the extended international (International Obesity Task Force) body mass index cutoffs reported by Cole and Lobstein.[22]

Missing data were excluded from analyses. SAS (SAS for XP PRO, release 9.4 TS2 M3; SAS Institute Inc., Cary, NC, USA) and SPSS version 25 (IBM, Armonk, NY, USA) were used to perform analyses. For all statistical tests, *p*-values < .05 were considered significant.

Results

Treatment pattern and patient characteristics

The treatment pattern of all children and adolescents, and if applicable young adults, is shown in Figure 1. Of the 448 patients, 279 (62.3%) stayed on solely topical treatment (including dithranol) during follow-up, 64 (14.3%) switched

from topical to phototherapy, but not to systemic treatment, and 105 (23.4%) had eventually switched to systemic treatment at the moment of data lock. The patients' characteristics at the first visit are presented in Tables 1 and 2. Less than half of the patients were male (42.9%), and the overall mean ± SD age at psoriasis onset was 8.4 ± 4.0 years. The mean age at the last follow-up visit was 13.5 ± 4.8 years (range 2.0–24.4). The total median follow-up time was 4.2 years (interquartile range 1.8–7.5) and the mean follow-up time was 5.2 ± 4.0 years. Regarding patients who switched to systemic treatment, 70 (66.7%) switched to methotrexate and 22 (21.0%) to fumaric acid esters as first systemic treatment.

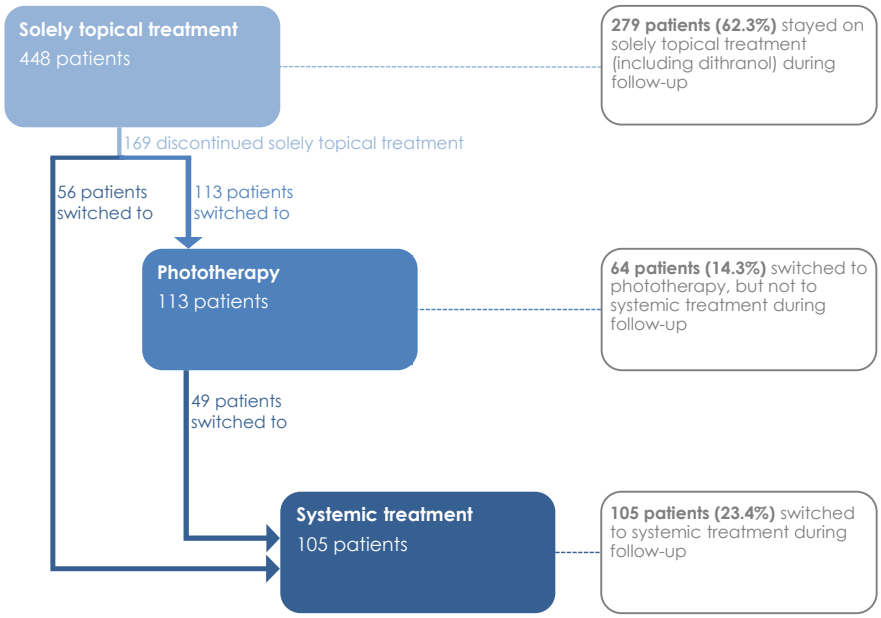


Figure 1. Treatment pattern in paediatric and adolescent patients with psoriasis followed into young adulthood

In total 448 patients initiated solely topical treatment after psoriasis onset. During follow-up 169 patients discontinued solely topical treatment and switched to a more intensive treatment: 113 patients to phototherapy and 56 to systemic treatment. Of the 113 patients who switched to phototherapy, 49 further switched to systemic treatment, giving a total of 105 patients who switched to systemic treatment during follow-up.

Table 1. Demographic and follow-up characteristics of patients with pediatric-onset psoriasis

Variable	All patients (n = 448)	Patients on solely topicals during FU (n = 279, 62.3%)	Patients that switched to phototherapy but not to systemics (n = 64, 14.3%)	Patients that switched to systemics during FU (n = 105, 23.4%)
Sex (male), no. (%)	192 (42.9)	120 (43.0)	27 (42.2)	45 (42.9)
First-degree family history, no. (%)	141 (31.5)	86 (30.8)	16 (25.0)	39 (37.1)
Age (years)				
At psoriasis onset[a], mean (SD) [range]	8.4 (4.0) [0.0 – 17.6]	7.7 (3.7) [0.0 – 16.6]	9.4 (3.8) [0.5 – 15.9]	9.4 (4.3) [0.5 – 17.6]
At switch to systemic[a], mean (SD) [range]	-	-	-	14.2 (3.3) [6.5 – 21.5]
At last follow-up visit[a], mean (SD) [range]	13.5 (4.8) [2.0 – 24.4]	11.7 (4.4) [2.0 – 24.4]	14.7 (3.5) [6.4 – 22.8]	17.5 (3.5) [7.4 – 24.4]
0 - <6 years, no. (%)	25 (5.6)	25 (9.0)	0 (0.0)	0 (0.0)
6 - <12 years, no. (%)	151 (33.7)	130 (46.6)	14 (21.9)	7 (6.7)
12 - <18 years, no. (%)	183 (40.8)	94 (33.7)	38 (59.4)	51 (48.6)
≥18 years, no. (%)	89 (19.9)	30 (10.8)	12 (18.8)	47 (19.9)
Psoriasis location at first visit[b]				
Scalp, no. (%)	349 (77.9)	217 (77.8)	48 (75.0)	84 (80.0)
Face, no. (%)	66 (14.7)	49 (17.6)	5 (7.8)	12 (11.4)
Inverse, no. (%)	171 (38.2)	111 (39.8)	23 (35.9)	37 (35.2)
Nails, no. (%)	78 (17.4)	38 (13.6)	12 (18.8)	28 (26.7)
Disease duration at first visit, median (IQR) [range]	1.7 (3.6) [0.0 – 14.1]	1.3 (2.7) [0.0 – 14.1]	2.5 (3.7) [0.0 – 13.3]	3.0 (5.2) [0.0 – 12.5]

Table 1. Continued

Variable	All patients (n = 448)	Patients on solely topicals during FU (n = 279, 62.3%)	Patients that switched to phototherapy but not to systemics (n = 64, 14.3%)	Patients that switched to systemics during FU (n = 105, 23.4%)
Follow-up time[a,c], median (IQR) [range]	4.2 (5.7) [0.0 – 19.1]	3.2 (4.7) [0.0 – 18.2]	4.5 (5.9) [0.2 – 14.4]	7.7 (6.6) [0.6 – 19.1]
Follow-up time[a,c], mean (SD) [range]	5.2 (4.0) [0.0 – 19.1]	4.1 (3.4) [0.0 – 18.2]	5.4 (3.7) [0.2 – 14.4]	8.1 (4.3) [0.6 – 19.1]
Follow-up status at data-lock, no. (%)				
Active	294 (65.6)	174 (62.4)	39 (60.9)	81 (77.1)
Referred back to GP/ dermatologist	37 (8.3)	20 (7.2)	4 (6.3)	13 (12.4)
Lost to follow-up	118 (26.1)	85 (30.5)	21 (32.8)	11 (10.5)

[a]In years. [b]Total number of patients does not equal sum of patients reporting different locations of psoriasis because more than one location of psoriasis can be reported in the same patient. [c]Follow-up time includes retrospective data. Abbreviations: FU, follow-up; GP, general practioner;

Table 2. Psoriasis outcome measures, comorbidities and treatments of patients with paediatric-onset psoriasis

Variable	All patients (n = 448)	Patients on solely topicals during FU (n = 279, 2.3%)	Patients that switched to phototherapy but not to systemics (n = 64, 4.3%)	Patients that switched to systemics during FU (n = 105, 23.4%)
Psoriasis severity at first visit, no. (%)				
Mild (PASI <5)	191 (42.6)	140 (50.2)	22 (35.5)	29 (27.6)
Moderate-Severe (PASI ≥5)	255 (56.9)	139 (49.8)	40 (64.5)	76 (72.4)
PASI (0-72), median (IQR) [range]				
at first visit	5.6 (4.9) [0.0 – 42.4]	4.9 (4.8) [0 – 31.9]	6.2 (5.4) [0.4 – 29.0]	7.0 (4.9) [0.3 – 42.4]
at switch to systemic (n = 80)	-	-	-	8.4 (4.9) [0.4 – 42.4]
BSA, median (IQR) [range]				
at first visit	5.3 (8.5) [0.0 – 76.0]	4.5 (7.4) [0.0 – 72.0]	6.2 (11.1) [0.2 – 59.5]	8.0 (11.7) [0.1 – 76.0]
at switch to systemic (n = 79)	-	-	-	9.8 (10.5) [0.1 – 72.0]
CDLQI[a] (0-30), median (IQR) [range]				
at first visit (n = 409)	7 (6) [0 – 29]	7 (7) [0 – 25] (n = 261)	7.5 (7) [0 – 29] (n = 58)	8 (6) [0 – 22] (n = 90)
at switch to systemic (n = 52)	-	-	-	11 (8) [1 – 24]
DLQI[b] (0-30), median (IQR) [range]				
at first visit (n = 32)	8 (6) [1 – 24]	7.5 (8) [1 – 15] (n = 12)	9 (9) [6 – 16] (n = 5)	9 (5) [1 – 24] (n = 15)
at switch to systemic (n = 26)	-	-	-	9 (11) [2 – 22]
BMI[c] at first visit, no. (%) (n = 398)				
Thinness	60 (15.1)	39 (15.9)	10 (18.9)	11 (11.1)
Normal weight	256 (64.3)	165 (67.1)	29 (54.7)	62 (62.6)
Overweigh/Obesity	82 (20.6)	42 (17.1)	14 (26.4)	26 (26.3)

Table 2. Continued

Variable	All patients (n = 448)	Patients on solely topicals during FU (n = 279, 2.3%)	Patients that switched to phototherapy but not to systemics (n = 64, 4.3%)	Patients that switched to systemics during FU (n = 105, 23.4%)
BMI[f] at switch to systemic, no. (%) (n = 74)				
Thinness	-	-	-	8 (10.8)
Normal weight	-	-	-	49 (66.2)
Overweigh/Obesity	-	-	-	17 (23.0)
Psoriatic Arthritis at first visit, no. (%)	2 (0.4)	0 (0.0)	0 (0.0)	2 (1.9)
First systemic treatment, no. (%)				
Methotrexate	-	-	-	70 (66.7)
Fumaric acid esters	-	-	-	22 (21.0)
Ciclosporin	-	-	-	7 (6.7)
Retinoids	-	-	-	6 (5.7)

[a]For patients <16 years old. [b]For patients ≥16 years old. [c]Cut-Offs for overweight/obesity were based on the Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity by Cole et al.[22] Abbreviations: BMI, Body Mass Index; BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; FU, follow-up; PASI, Psoriasis Area and Severity Index;

Median-time analyses

Median time until discontinuation of solely topical treatment

Figure 2(a) shows the Kaplan–Meier curve for the median time from psoriasis onset until discontinuation of topical treatment and subsequent switch to phototherapy or systemics (whichever initiated first). In total 169 patients switched from solely topical treatment. The overall median time from psoriasis onset until discontinuation of solely topical treatment was 7.3 years (95% CI 5.2–9.4), with a switching rate of 13.8% after 1 year, increasing to 27.4% after 3 years. The median time from psoriasis onset until discontinuation of solely topical treatment was significantly shorter for patients with moderate-to-severe psoriasis at the first visit at our department (5.8 years, 95% CI 4.9–6.7) than for patients with mild psoriasis at the first visit (11.2 years, 95% CI 8.6–13.9, $p < .001$). A sensitivity analysis in which dithranol was regarded as a more intensive treatment together with phototherapy and systemic treatment revealed a shorter median time (3.9 years, 95% CI 3.3–4.5) from psoriasis onset until discontinuation of solely topical treatment (including only topical corticosteroids, vitamin D analogues and/or calcineurin inhibitors) (Figure S1; see Supplementary materials).

Median time until switch to systemic treatment

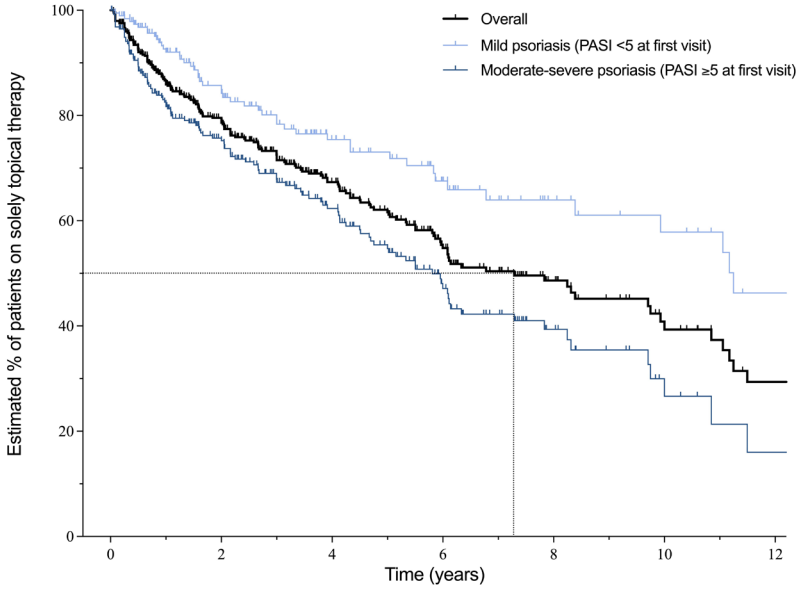
Figure 2(b) shows the Kaplan–Meier curve for the median time from psoriasis onset until switch to first systemic treatment. In total 105 patients switched to systemic treatment during follow-up. The overall median time until switch to first systemic treatment was 10.8 years (95% CI 9.8–11.9). In the first year after psoriasis onset 3.4% switched to systemic treatment, increasing to 12.0% after 3 years. The median time until first systemic treatment was shorter for patients with moderate-to-severe psoriasis than for patients with mild psoriasis at the first visit ($p = .001$).

> **Figure 2**. Median time from psoriasis onset until discontinuation of (A) solely topical therapy and (B) switch to first systemic treatment in pediatric and adolescent patients with psoriasis followed into young adulthood (n = 448).

A. During follow-up 169 patients discontinued topical treatment and switched to a more intensive treatment. The median overall time until discontinuation of topical treatment was 7.3 years [95% confidence interval (CI) 5.2–9.4]. When split for psoriasis severity at first visit, the median time was 11.2 years (95% CI 8.6–13.9) for mild psoriasis and 5.8 years (95% CI 4.9–6.7) for moderate-to-severe psoriasis ($p < .001$).

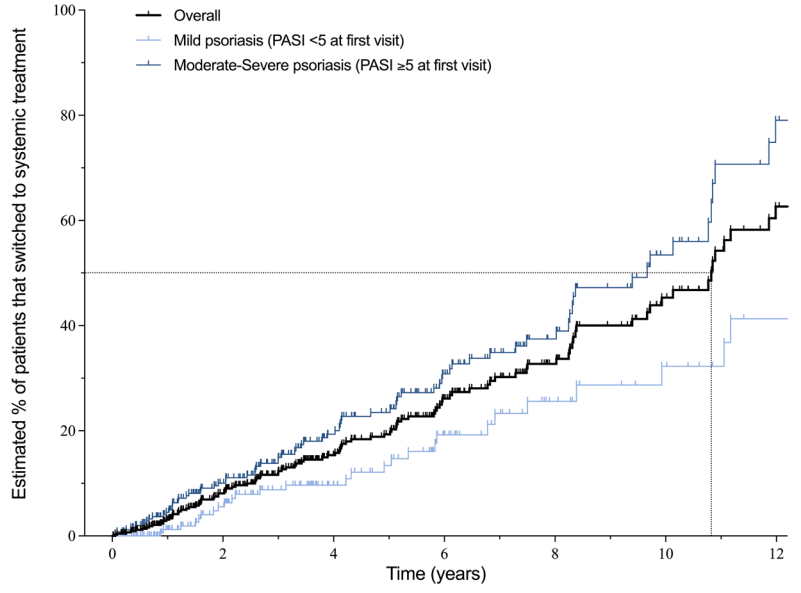
B. During follow-up 105 patients switched to systemic treatment. The median overall time until switch to (first) systemic treatment was 10.8 years (95% CI 9.8–11.9). When split for psoriasis severity at first visit, the median time was 14.8 years (95% CI 8.0–21.6) for mild psoriasis and 9.7 years (95% CI 8.1–11.3) for moderate-to-severe psoriasis ($p = .001$). PASI, Psoriasis Area and Severity Index.

Figure 2a.



No at risk							
	448	**265**	**163**	**93**	**46**	**27**	**14**
	192	113	68	43	24	18	11
	256	152	95	50	22	9	3

Figure 2b.



No at risk							
	448	**306**	**199**	**124**	**70**	**39**	**18**
	192	126	79	48	28	20	12
	256	180	120	76	42	19	6

Patient characteristics associated with switching to systemic treatment

For this analysis, 22 patients who started systemic treatment prior to inclusion in the registry were excluded, as the disease and patient characteristics at the moment of switch were unavailable. Univariable Cox regression analysis of 426 patients identified that higher PASI, higher body surface area, facial psoriasis, scalp psoriasis, nail psoriasis and CDLQI or DLQI > 5 at the moment of switch were associated with switching to systemic treatment (Table S1; see Supplementary materials). Sex, family history, age at switch and body mass index at switch were not associated with switching to systemic treatment. Multivariable Cox regression analysis showed that higher PASI (HR 1.26, 95% CI 1.13–1.42) and CDLQI or DLQI > 5 (HR 4.50, 95% CI 2.58–7.84) were independently associated with switching to systemic treatment (Table 3).

Table 3. Determinants associated with switch to first systemic treatment by multivariable Cox regression analysis (n = 426 patients)

Predictors	**Event = switch to first systemic treatment (80 events)**	
	HR [95% CI]	***p*-value**
PASI at switch[a]	1.26 [1.13 – 1.42]	<.001
CDLQI or DLQI > 5 at switch	4.50 [2.58 – 7.84]	<.001

[a]HR per 5 PASI points.

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CI, Confidence interval; DLQI, Dermatology Life Quality Index; HR, Hazard ratio; PASI, Psoriasis Area and Severity Index.

Discussion

In this prospective, longitudinal, observational cohort study of 448 pediatric and adolescent patients with psoriasis who were followed into young adulthood, 279 (62.3%) stayed on solely topical treatment until data lock, 64 (14.3%) switched to phototherapy but not to systemics and 105 (23.4%) eventually switched to systemic treatment during follow-up. The median time from psoriasis onset until discontinuation of solely topical treatment was 7.3 years, and the median time until switch to systemic treatment was 10.8 years. Both higher PASI and a CDLQI or DLQI > 5 at the moment of switch were independent characteristics associated with switching to systemic treatment.

A median time of 7.3 years from psoriasis onset until discontinuation of solely topical treatment and subsequent switch to either phototherapy or systemic treatment seems rather long. However, the use of dithranol as a second-line treatment in our cohort should be taken into consideration. In accordance with the Dutch guidelines

for pediatric psoriasis, many patients who do not respond to classical topical treatments (corticosteroids, vitamin D analogues, calcineurin inhibitors) are treated with dithranol before commencing phototherapy or systemic treatment.[1,4,23] As dithranol is a safe and effective therapy and is often given in rotation with other topical treatments, many children stay on topical treatments (including dithranol) for a considerable time.[4] However, we realize that this is not common practice in many other countries, where the availability or practicality of dithranol might be problematic. Indeed, as dithranol treatment is currently unavailable at our practice due to supply issues (not during the conduct of this study), our experience in daily practice is that phototherapy and/or systemic treatment is initiated earlier on. Therefore we carried out a sensitivity analysis in which dithranol was regarded as a more intensive treatment together with phototherapy and systemic treatment, which revealed a shorter median time until topical discontinuation of 3.9 years (Figure S1; see Supplementary materials). Probably, this median time of 3.9 years until topical discontinuation is a better reflection of practices in which dithranol is not available. Indeed, the topical discontinuation rate after 3 years in our sensitivity analysis (43.6%) is comparable with the 3-year discontinuation rate in a retrospective administrative claims database study in the USA of 49.8%.[14]

The median time from onset of psoriasis to first systemic treatment was 10.8 years in all patients in our study and 9.7 years for patients with moderate-to-severe psoriasis at first visit. Van den Reek et al. found a slightly higher median time until conventional systemic treatment of 11.0 years in a study in which treatment patterns of adult patients with severe psoriasis using a biologic agent were assessed retrospectively.[16] However, this study included only patients with severe psoriasis, all of whom switched to systemic treatment, rather than the young patients in our cohort with a severity of psoriasis ranging from mild to severe. Moreover, the fact that 76.6% of the patients in our study did not switch to systemics may have influenced the relatively long time until switch to systemic treatment, and again the use of dithranol should be taken into account. Nevertheless, as knowledge on the safety and efficacy of systemic treatments in pediatric patients with psoriasis is increasing,[24,25] daily practice will develop towards initiating systemic treatments earlier on. We consider the time until switch to systemic treatment to be long, and given the reassuring safety profile especially of biologics in (pediatric) psoriasis, our results indicate there is potential for earlier initiation of systemic treatments.

We found that a higher PASI and CDLQI or DLQI > 5 at switch were independently associated with switching to systemic treatment. The finding that a higher PASI was associated is not surprising and reflects treatment guidelines. The association with

CDLQI or DLQI > 5 reflects the importance of quality of life in treatment decisions. Additionally, the finding that facial, scalp and nail psoriasis were associated with switching in the univariate analysis suggests that psoriasis in visible areas might also influence the decision to the start systemic treatment. Interestingly, although we expected older age to influence switching to systemic treatment, both the univariable and multivariable analyses showed that age was not associated.

This study was limited by the single-center design. Although this study took place at a tertiary referral center, still 42.6% of patients had mild psoriasis (PASI < 5) at their first visit. Moreover, patients were referred by both general practitioners and dermatologists from across the Netherlands. However, as the percentage of (pediatric) patients with mild psoriasis in the general Dutch population is unknown, it is uncertain whether our study population is fully representative of the general psoriasis population in terms of psoriasis severity. Our study is strengthened by the overall large number of patients (448), the relatively long follow-up time and the fact that almost all of the data in this study were collected prospectively. Although the median times to analyses were based partly on retrospectively collected data, this study included young patients with psoriasis with only a short disease duration before inclusion in the registry (median 1.7 years). We were therefore able to record precisely all data regarding previous treatments, so the median-time analyses were probably not influenced.

In conclusion, our results give insight into the persistence of solely topical treatment and time until switch to systemic treatments in a population of children and adolescents with mild-to-severe psoriasis who were followed into young adulthood. The median times of 7.3 years until topical treatment discontinuation and of 10.8 years until switch to systemic treatment seem long, although the use of dithranol in this cohort should be taken into consideration. In this era in which reassuring safety data on methotrexate and biologics in pediatric psoriasis are emerging,[24,25] the question rises whether more effective systemic treatment should be initiated earlier on. In particular, young patients with psoriasis might benefit most from earlier intervention in terms of limiting life course impairment by uncontrolled psoriasis. This study adds to our knowledge of current prescribing patterns to further enhance the discussion about early intervention in this important subgroup of patients with psoriasis.

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Supplementary materials

Table S1. Determinants associated with switch to first systemic treatment by univariable Cox regression analysis (n= 426 patients)

Predictors	**Event = switch to first systemic treatment (80 events)**	
	HR [95% CI]	***p*-value**
Male sex	1.12 [0.71 – 1.76]	0.623
1st degree family history	1.03 [0.65 – 1.63]	0.917
Age at switch[a]	0.89 [0.67 – 1.20]	0.462
PASI at switch[b]	1.41 [1.27 – 1.56]	<.001
BSA at switch[c]	1.20 [1.13 – 1.28]	<.001
Scalp psoriasis at switch	3.54 [1.43 – 8.78]	0.006
Facial psoriasis at switch	1.49 [0.89 – 2.49]	0.149
Nail psoriasis at switch	1.68 [0.97 – 2.93]	0.065
CDLQI or DLQI > 5 at switch	5.44 [3.18 – 9.31]	<.001
Body mass index[d]		0.211
Thinness versus normal weight	1.29 [0.61 – 2.73]	0.508
Overweigh/Obesity versus normal weight	0.65 [0.37 – 1.14]	0.135

[a]Per 5 years; [b]Per 5 PASI points; [c]Per 5 BSA points;[d]Cut-Offs for body mass index weight categories were based on the Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity by Cole et al.[23]; Bold numbers illustrate hazard ratios with a *p*-value of $p < .20$ which were incorporated in multivariate analysis.

Abbreviations: BSA, Body Surface Area; CI, Confidence interval; HR, Hazard ratio; PASI, Psoriasis Area and Severity Index.

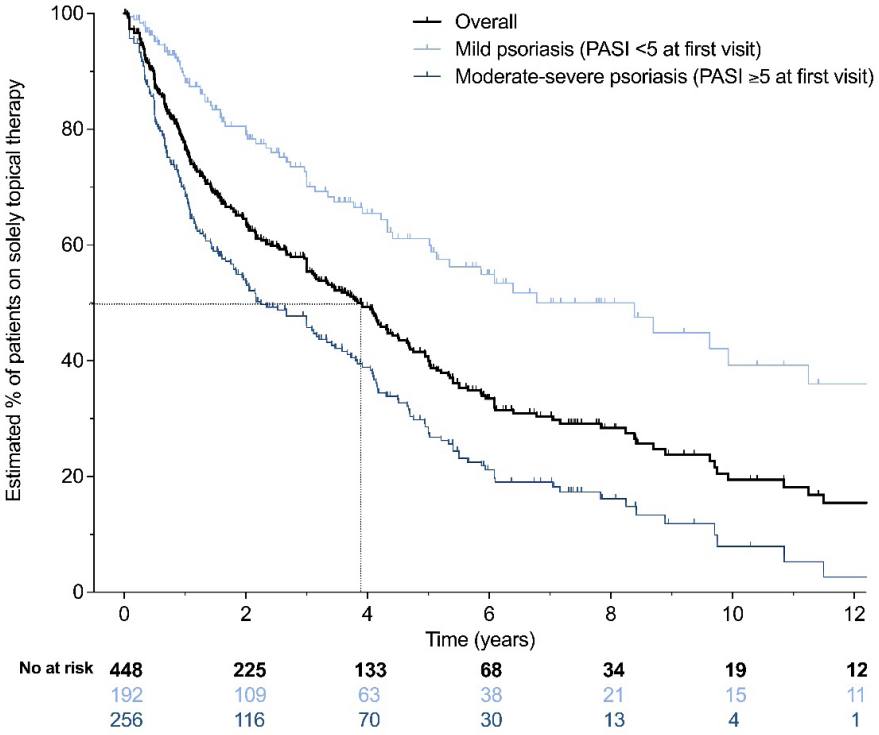

Figure S1. Median time from psoriasis onset until solely topical therapy discontinuation and switch to a more intensive treatment, including dithranol treatment, in paediatric and adolescent psoriasis patients followed into young adulthood (N=448)

During follow up 258 patients discontinued topical treatment and switched to a more intensive treatment (including dithranol, together with phototherapy/systemic). Median overall time until topical treatment discontinuation was 3.9 (95% CI 3.3 – 4.5) years. When split for psoriasis severity at first visit, median time was 8.4 (95% CI 5.3 – 11.5) years for mild psoriasis and 2.3 (95% CI 1.5 – 3.0) years for moderate-severe psoriasis (P <.001).

3.2 Association between quality of life and improvement in psoriasis severity and extent in pediatric psoriasis

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Abstract

Importance

Treatment of psoriasis is associated with improved quality of life (QOL) in those with the disease. However, in daily clinical practice, the association between the degree of psoriasis clearance and QOL has not been studied to date, especially in the pediatric population.

Objectives

To identify the association between the degree of psoriasis improvement (as measured by the Psoriasis Area Severity Index [PASI] and body surface area [BSA] response) and QOL (as measured by the Children's Dermatology Life Quality Index [CDLQI]) in pediatric psoriasis, and to assess the association of treatment type with QOL, independent of psoriasis improvement.

Design, Setting, and Participants

Data used in this single-center cohort study were extracted from the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, observational, daily clinical practice cohort of all children (aged <18 years) with a psoriasis diagnosis who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Center in Nijmegen, the Netherlands, between September 3, 2008, and May 4, 2018. All records of treatment episodes with CDLQI, PASI, and BSA scores were included in the analysis.

Exposures

Patients were treated according to daily clinical care. Treatments were clustered into topical, dithranol, conventional systemic, and biological treatments. Because of low numbers of UV-B phototherapy, this treatment was not assessed.

Main Outcomes and Measures

Primary outcomes were mean change of CDLQI scores per PASI and BSA response categories (0 to <50, 50 to <75, 75 to <90, and ≥90) and mean CDLQI change per treatment categories.

Results

In total, 319 patients (median [interquartile range] age, 10.0 [7.0] years; 183 female [57.4%]) were analyzed for PASI score improvement (399 treatment episodes) and improvement in BSA involvement (366 treatment episodes). The greatest improvements in CDLQI scores were seen in the PASI ≥90 response category,

with an estimated marginal mean change in CDLQI score of −6.6 (95% CI, −7.5 to −5.7). The greatest improvements in CDLQI scores were also observed in the BSA ≥90 response category, with an estimated marginal mean change in CDLQI score of −6.8 (95% CI, −7.5 to −6.1). Systemic treatment demonstrated a greater degree of improvement of CDLQI compared with topical treatment, independent of PASI response categories.

Conclusions and Relevance

This cohort study in a real-world setting found that the greatest improvements in QOL were associated with PASI 90 or greater, a decrease in BSA involvement of 90% or greater, and systemic treatments. These findings suggest that reaching PASI 90 or greater and decreasing BSA involvement by at least 90% may be clinically meaningful treatment goals that will help pediatric patients with psoriasis reach optimal QOL.

Introduction

Psoriasis has a negative association with quality of life (QOL) in adult and pediatric patients.[1-7] Newer, more potent biological treatments have made the achievement of PASI 90 (a reduction of 90% of the Psoriasis Area Severity Index [PASI] score) more attainable, and data from randomized clinical trials in adult patients suggest the relevance of aiming for PASI 90, which has been associated with further improvement of QOL compared with lower clinical responses.[8-15] Whether this suggestion holds true in daily clinical practice for pediatric patients with psoriasis has not been investigated to date.

In pediatric psoriasis, to our knowledge, only 1 randomized clinical trial has examined whether the degree of PASI response is associated with a greater degree of improvement in QOL.[16] Langley et al[16] evaluated the effect of etanercept on the QOL of 106 children with psoriasis and demonstrated that children treated with etanercept who achieved PASI 75 (a reduction of 75% of the PASI score) at week 12 had a greater percentage of improvements in Children's Dermatology Life Quality Index (CDLQI) score compared with nonresponders. Furthermore, although treatments are known to improve psoriasis and thus the QOL, the type of treatment (eg, topical, systemic) might also have implications for the QOL of children.[7] Whether the treatment itself is associated with QOL independent of the degree of psoriasis improvement has not been investigated to date.

In this cohort study of pediatric patients with psoriasis, we sought to identify the association between the degree of psoriasis improvement (as measured by PASI and body surface area [BSA] involvement) and QOL (as measured by CDLQI score). In addition, we examined the association of the type of treatment, independent of psoriasis improvement, with QOL.

Methods

Patient Selection and Study Design

Data for this single-center cohort study were extracted from the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, observational, daily clinical practice cohort of children and adolescents with psoriasis. The Child-CAPTURE includes all children (younger than 18 years at first visit) with the diagnosis of psoriasis who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Center in

Nijmegen, the Netherlands, between September 3, 2008, and May 4, 2018 (data lock). Patients were referred by general practitioners and dermatologists from across the Netherlands. This study was reviewed by the ethics committee of the region of Arnhem-Nijmegen and Radboud University Medical Center on the basis of the Dutch Code of Conduct for Health Research, the Dutch Code of Conduct for Responsible Use, the Dutch Personal Data Protection Act, and the Medical Treatment Agreement Act and was deemed by the ethics committee to not fall within the remit of the Medical Research Involving Human Subjects Act. Written informed consent was obtained from the parents or guardians and/or from the participating pediatric patients according to applicable rules. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Outcome Measures and Treatments

At baseline and at every visit during follow-up, patient characteristics, psoriasis severity scores (PASI range 0-72; BSA; and Physician Global Assessment [PGA] range 0-5, with the highest score indicating severe psoriasis), and treatment characteristics were collected. To quantify the association of psoriasis with QOL, we collected the validated CDLQI score at every visit.[17] The CDLQI total score ranges from 0 to 30, with a higher score indicating a greater influence on QOL. A CDLQI score of 0 or 1 represents no influence of psoriasis on a child's QOL.[18] Patients were treated according to daily clinical care. Treatment decisions were made by the treating physician. Type of treatment was recorded for each visit. Treatments were clustered into 4 categories: topical therapy (using only topical treatment, including topical corticosteroids, vitamin D analogues, and calcineurin inhibitors), dithranol (anthralin), conventional systemic therapy (methotrexate sodium and fumaric acid esters), and biological therapy (etanercept, adalimumab, or ustekinumab).

Treatment Episodes and Severity Response Categories

A treatment episode was defined as the period from the start to the end of treatment or follow-up. In systemic therapy, we considered episodes with treatment interruptions of up to 90 days as continuous episodes. Treatment episodes were included in the analysis if PASI, BSA, and CDLQI responses were available. The following were excluded from analysis: episodes with a duration less than 6 weeks, episodes with only 1 visit, and episodes with treatment other than those in the 4 categories. Given that the objective of this study was to identify the association between improvement of psoriasis and QOL, we excluded treatment episodes in which no improvement in PASI score or BSA involvement was achieved, except in the sensitivity analysis of all treatment episodes.

Clinical severity response was based on relative PASI and BSA responses, calculated using the lowest PASI and BSA scores for a treatment episode compared with the first PASI and BSA scores of that same episode. Corresponding CDLQI scores were used to assess the mean change in QOL. This approach (ie, using the lowest severity score during a treatment episode) was chosen over the approach of using the last severity scores of the treatment episode to establish an optimal severity response so that we could thoroughly analyze the association between severity score response and QOL response. Clinical severity responses were grouped into 4 response categories according to the relative PASI or BSA responses: PASI 0 to <50, 50 to <75, 75 to <90, or ≥90; or BSA 0 to <50, 50 to <75, 75 to <90, or ≥90.

Statistical Analysis

Patient characteristics were presented as medians (interquartile ranges [IQRs]) for continuous variables and numbers (percent) for categorical variables. Correlation coefficients of PASI, BSA, and PGA responses with the CDLQI score at the first visit in the Child-CAPTURE were calculated with Spearman rank-order correlation. Although analyses of patient characteristics and correlation coefficients were performed on patient level, all further analyses were conducted on treatment episode level. Consequently, a patient might have more than 1 treatment episode included in the analyses. To account for the correlations between treatment episodes of the same patient, we conducted analyses using linear mixed models and mixed-effects logistic regression models. All analyses were adjusted for the following confounders: CDLQI score or CDLQI domain scores at the start of treatment, PASI or BSA scores at the start of treatment, age, sex, psoriasis duration, and treatment duration (duration from the start of the episode to time of lowest severity score). Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models. We assessed 2 outcome measures: mean CDLQI change (assessed with linear mixed models) and percentage of CDLQI scores that reached 0 or 1 (assessed with mixed-effects logistic regression models).

In total, we performed 4 analyses to identify the (1) differences in CDLQI score changes between PASI response categories and BSA response categories; (2) differences in CDLQI domain score changes between PASI response categories; (3) differences in percentage of CDLQI 0 or 1 achievement between PASI response categories and BSA response categories; and (4) differences in CDLQI change between treatment categories. In addition, we performed a sensitivity analysis to assess the differences in CDLQI changes between PASI response categories for all treatment episodes, including episodes in which the psoriasis worsened.

Estimated marginal means were calculated with linear mixed models, and estimated percentages were calculated with mixed-effects logistic regression models. Statistical package SPSS, version 25 (IBM) and SAS, version 9.2 (SAS Institute Inc) were used to perform analyses. Two-sided $P < .05$ was considered statistically significant. All analyses were conducted from October 7, 2018, to December 13, 2018, and supervised by a senior statistician (H.M.M.G.) on our team.

Results

A total of 319 patients with 566 treatment episodes were selected; the selection of treatment episodes is shown in Figure 1. After treatment episodes with no improvement in PASI score or BSA involvement or with missing data were excluded, a total of 399 episodes were included for analysis per PASI response categories and 366 episodes were included for analysis per BSA response categories. Patient characteristics at first visit for 319 patients (median [IQR] age, 10.0 [7.0] years; 183 female [57.4%]) are presented in Table 1.

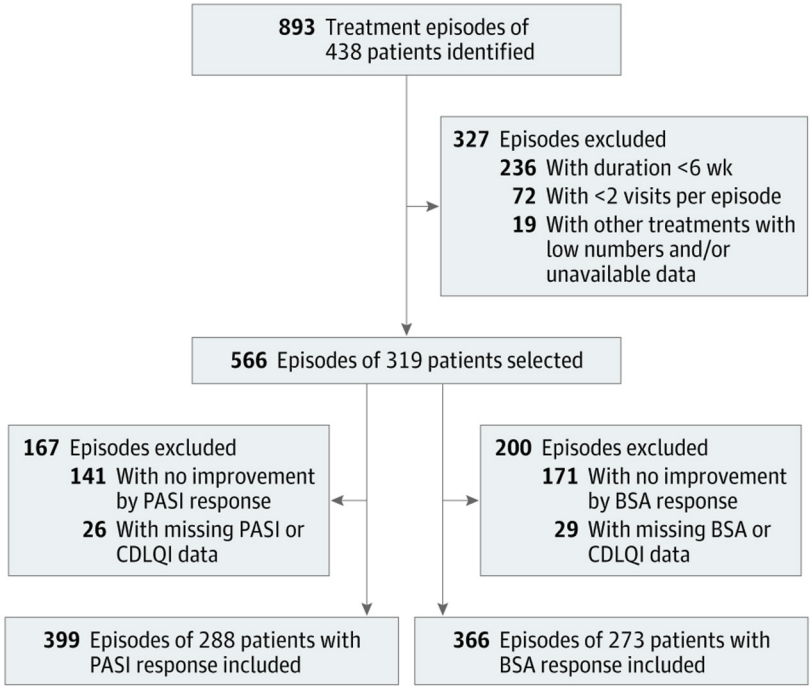

Figure 1. Selection of Treatment Episodes

BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

A statistically significant moderate positive correlation between PASI and CDLQI scores was found at first visit ($r = 0.47$; $p < .001$). Similar correlations were found for BSA and CDLQI scores ($r = 0.48$; $p < .001$) as well as PGA and CDLQI scores ($r = 0.50$; $p < .001$).

Differences in CDLQI total score change between severity response categories are presented in Figure 2A and B. Analyses showed an increasing improvement in the CDLQI score, with higher relative PASI and BSA response categories (Table S1, S3 and S4 in the Supplemental materials). The highest CDLQI total score change was seen in the PASI ≥90 response category, with an estimated marginal mean (EMM) change in CDLQI score of −6.6 (95% CI, −7.5 to −5.7). The greatest CDLQI total score changes were also observed in the BSA ≥90 response category, with an EMM change in CDLQI score of −6.8 (95% CI, −7.5 to −6.1). The sensitivity analysis of all treatment episodes, including a PASI worsening category, revealed similar results: an increasing improvement in the CDLQI score with higher relative PASI response categories (Figure S1 in the Supplemental materials).

Table 1. Characteristics of pediatric psoriasis patients at first visit (n = 319)

Characteristics	
Gender, no. (%)	
Male	136 (42.6)
Female	183 (57.4)
Family history, no. (%)	
Psoriasis in parents or siblings	106 (33.2)
Psoriatic arthritis in parents or siblings	6 (1.9)
Type of psoriasis[a], no. (%)	
Plaque	280 (87.8)
Guttate	29 (9.1)
Scalp	268 (84.0)
Inverse	115 (36.1)
Pustular	4 (1.3)
Palmoplantar	6 (1.9)
Joint involvement[b], no. (%)	
PsA	2 (0.6)
Arthralgia	10 (3.1)
Age, years, median (IQR) [range]	10.0 (7.0) [0-17]
Psoriasis duration, years, median (IQR) [range]	1.5 (3.6) [0.0-13.0]

Table 1. Continued

Characteristics	
Psoriasis severity at baseline, median (IQR) [range]	
PASI (0-72)	5.6 (5.0) [0.0-42.0]
BSA	5.3 (8.0) [0.0-72.0]
PGA (0-5)	2.0 (1.0) [0-5]
CDLQI at baseline (0-30; N=309), median (IQR) [range]	7.0 (8.0) [0-25]
CDLQI per severity category (0-30), median (IQR) [range]	
PASI 0.0 – 4.9 (N=126; 39.6%)	6.0 (6.0) [0-25]
PASI 5.0 – 9.9 (N=143; 44.9%)	8.0 (7.0) [0-23]
PASI ≥ 10.0 (N=49; 15.4%)	9.0 (7.0) [2-22]
CDLQI domain subscores, median (IQR) [range]	
Domain 'Symptoms and Feelings' (0-6)	2.0 (3.0) [0-6]
Domain 'Leisure' (0-9)	1.0 (2.0) [0-9]
Domain 'School or holidays' (0-3)	1.0 (2.0) [0-3]
Domain 'Personal relationships' (0-6)	1.0 (2.0) [0-6]
Domain 'Sleep' (0-3)	1.0 (2.0) [0-3]
Domain 'Treatment' (0-3)	1.0 (2.0) [0-3]

Abbreviations: BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PsA, Psoriatic Arthritis.
[a]Total number of patients does not equal sum of patients reporting different types of psoriasis because more than one type of psoriasis can be reported in the same patient.
[b]Arthralgia was defined as aching or pain in the joints without true arthritis.
[c]Scores for CDLQI domains were expressed as percentages of the maximum domain score.

The estimated percentages of treatment episodes in which a CDLQI score of 0 or 1 (meaning no influence of psoriasis on QOL) was achieved are presented in Figure 2C and D (Table S1, S5 and S6 in the Supplemental materials). Overall, with increasing PASI and BSA response categories, higher estimated percentages of CDLQI 0 or 1 achievement were seen. Highest CDLQI 0 or 1 achievement was seen for PASI ≥90 response category, with an estimated percentage of 65.0% (95% CI, 47.6%-78.1%), and for BSA ≥90 response category, with an estimated percentage of 65.6% (95% CI, 53.6%-78.9%).

In the assessment of CDLQI domain score changes between PASI response categories, a trend comparable with the CDLQI total score analysis was found. Results are depicted in Figure 3. The symptoms and feelings domain showed the greatest improvement with higher PASI response categories. The personal relationships domain did not show any significant changes in CDLQI score with improving PASI response categories.

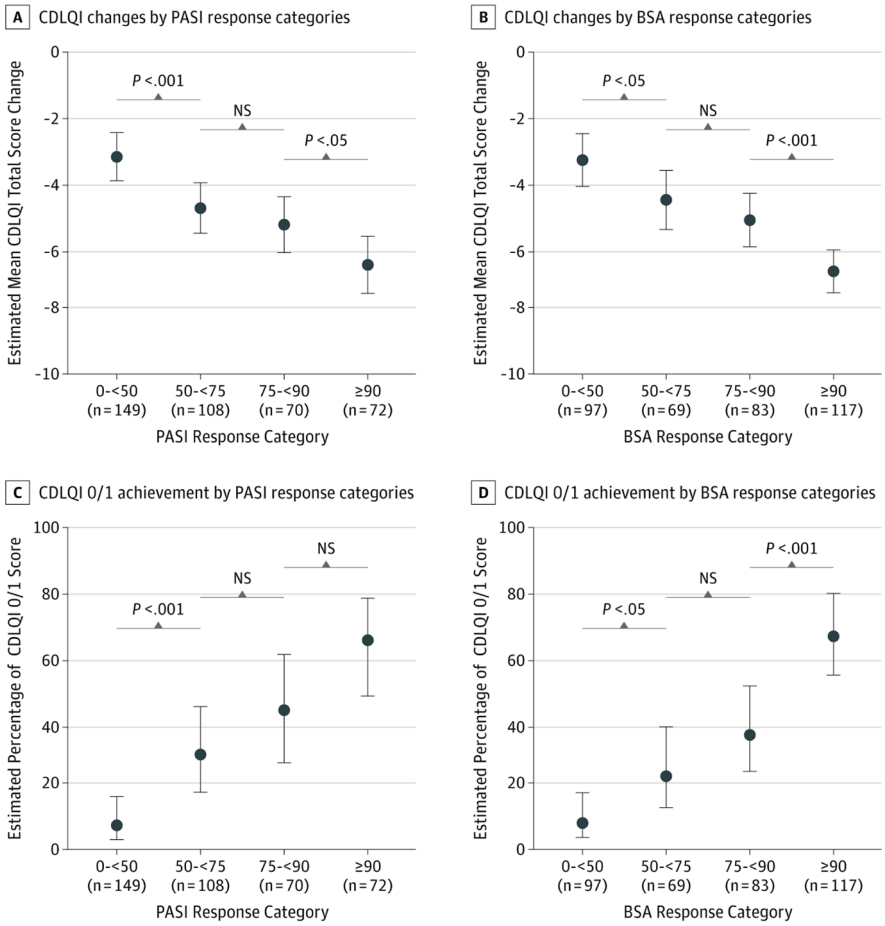

Figure 2. Estimated Mean Children's Dermatology Life Quality Index (CDLQI) Score Change and Estimated Percentages of CDLQI Score 0 or 1 Achievement by Psoriasis Area and Severity Index (PASI) and by Body Surface Area (BSA) Response Categories

A and B, Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: CDLQI, PASI, and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score, treatment, and psoriasis duration altered the unadjusted exposure outcome by 10% or higher and were kept in the models. Results are presented with a starting CDLQI score of 8.1 (the higher the score, the greater the influence on quality of life) and psoriasis duration of 3.7 years for PASI response categories, and with a starting CDLQI score of 8.2 and psoriasis duration of 3.8 years for BSA response categories. C and D, Mixed-effects logistic regression models were used for analyses. The following possible confounders were incorporated in the models: CDLQI, PASI, and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score and treatment altered the unadjusted exposure outcome of 10% or higher and were kept in the models. Results are presented with a starting CDLQI score of 8.1 and psoriasis duration of 3.7 years for PASI response categories, and with a starting CDLQI score of 8.2 and psoriasis duration of 3.8 years for BSA response categories. n, number of treatment episodes; NS, not significant.

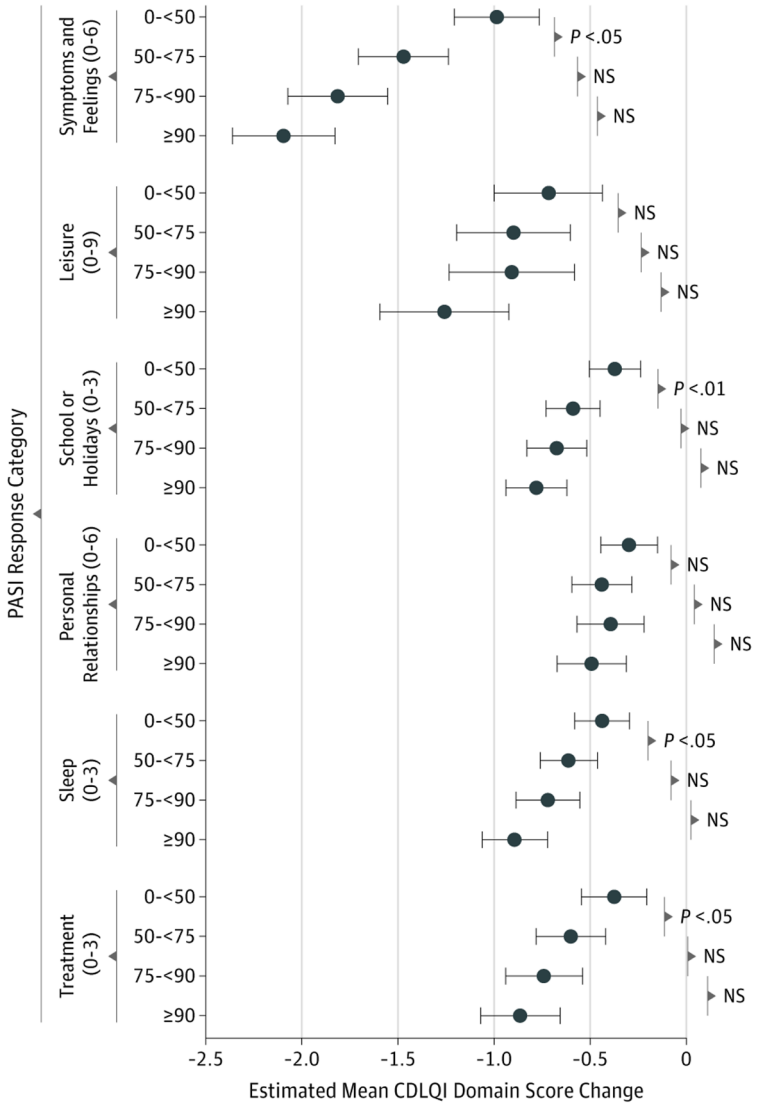

Figure 3. Estimated Mean Change of Children's Dermatology Life Quality Index (CDLQI) Domain Changes by Psoriasis Area and Severity Index (PASI) Response Categories During Follow-up

Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: CDLQI and PASI scores at the start of treatment, age, psoriasis duration, sex, treatment, and treatment duration. Only the starting CDLQI domain score, treatment, and psoriasis duration altered the unadjusted exposure outcome effect by 10% or higher and were kept in the models. Results are presented with a psoriasis duration of 3.7 years and the following starting CDLQI domain scores (with higher scores indicating a greater influence on quality of life): symptoms and feelings, 2.5 (score range, 0-6); leisure, 1.6 (score range, 0-9); school or holidays, 0.9 (score range, 0-3); personal relationships, 0.9 (score range, 0-6); sleep, 1.0 (score range, 0-3); and treatment, 1.2 (score range, 0-3). The number of treatment episodes for PASI response categories are 0 to <50, 149; 50 to <75, 108; 75 to <90, 70; and ≥90, 72. Horizontal bars and whiskers represent 95% CIs. NS indicates not significant.

Differences in CDLQI total score change between treatment categories are presented in Figure 4 (Table S2 and S3 in the Supplemental materials). A greater improvement in CDLQI score was seen for systemic therapy (conventional systemic and biological) compared with topical treatment (topical and dithranol): EMM change in CDLQI scores of −4.3 (95% CI, −4.8 to −3.8), and −4.2 (95% CI, −4.9 to −3.5) for topical and dithranol, respectively, vs EMM change in CDLQI scores of −5.8 (95% CI, −6.7 to −4.9) and −5.8 (95% CI, −7.5 to −4.1) for conventional treatment and biological treatment, respectively. The analysis of CDLQI changes between treatment groups was adjusted for confounders, including the CDLQI score at the start of treatment and psoriasis duration. Because systemic treatments are more likely to reach higher PASI responses, analysis was further adjusted for PASI response categories. The higher improvement in QOL associated with systemic therapy was, therefore, independent from the PASI response.

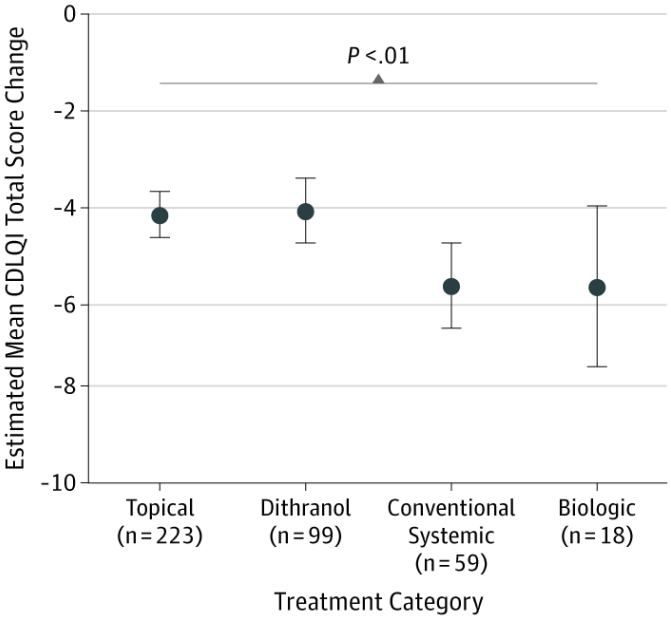

Figure 4. Estimated Mean Children's Dermatology Life Quality Index (CDLQI) Total Score Change by Treatment Categories During Follow-up

Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: age, sex, Psoriasis Area and Severity Index (PASI) score at the start of treatment, CDLQI total score at the start, PASI response categories, treatment duration, and psoriasis duration. Only PASI response categories, starting CDLQI total score, and psoriasis duration altered the unadjusted exposure outcome effect by 10% or higher and were kept in the models. Results are presented with the starting CDLQI total score of 8.1 (the higher the score, the greater the influence on quality of life) and psoriasis duration of 3.7 years. Vertical bars and whiskers represent 95% CIs.

Discussion

To our knowledge, this cohort study is the first to examine in a real-world setting the association between the degree of psoriasis improvement and QOL in pediatric patients with psoriasis. In pediatric psoriasis, only 1 randomized clinical trial to date has investigated the association between the degree of PASI response and improvement of QOL.[16] That trial found that pediatric patients treated with etanercept who achieved PASI 75 had a higher percentage of improvement in CDLQI score compared with PASI 75 nonresponders at week 12 (75.1% vs 29.8%). However, the association of reaching PASI 90 or greater with the CDLQI score was not assessed. Previous studies have demonstrated a greater degree of improvements in Dermatology Life Quality Index in adult patients who achieved PASI 90 or greater compared with lower clinical responses.[8-15] These results are in line with the findings in this present study that reaching PASI 90 or greater was associated with the highest improvement of QOL, which is reflected both in CDLQI score change and in percentage of CDLQI 0 or 1 achievement. A sensitivity analysis in which treatment episodes with worsening PASI scores were also included revealed similar results. Therefore, the results of this study seem to be robust. In addition, analysis of CDLQI domains demonstrated that the symptoms and feelings domain, which consisted of 2 items related to itch and embarrassment, seemed to be most closely associated with the improvement of PASI response. Further analysis of these 2 items showed greatest improvement in itch.

A decrease in BSA involvement of 90% or greater is also associated with a greater improvement in QOL, with similar improvement in CDLQI scores as PASI 90 or greater. We believe this result emphasizes the implication of the extent of affected area for the QOL. To our knowledge, the association between BSA decrease and QOL improvement has never been investigated in children and adults. Furthermore, a decrease in BSA involvement of 90% or greater was attained in more treatment episodes compared with PASI 90 or greater (117 episodes vs 72 episodes). These findings appear to support the use of BSA for assessing psoriasis in clinical practice.

Analysis of QOL per treatment category revealed that systemic treatments, including conventional systemic and biological therapies, are associated with greater improvements in QOL compared with topical and dithranol treatments. Because systemic treatments are more likely to reach higher PASI responses, we adjusted the analyses for PASI response categories. Thus, this positive association of systemic therapies with QOL appears to be independent of PASI score improvement. The weaker association between topical treatment and improvement in QOL might

be attributed to several characteristics of topical agents, such as time taken to apply ointments, odors, and stickiness.[19,20] However, we did not examine the factors associated with the advantages of systemic medication for QOL.

Strengths and Limitations

A strength of this study is its inclusion of 319 patients, which is a large number compared with the sample size in other pediatric psoriasis studies. In addition, all analyses were adjusted for possible confounders, including CDLQI score at the start of treatment, PASI or BSA scores at the start (to adjust for many patients who had mild-to-moderate psoriasis), age, sex, psoriasis duration, treatment, and treatment duration, and the analyses accounted for the fact that more than 1 treatment episode per patient was included. Furthermore, this study included several antipsoriatic treatments, including topical, dithranol, conventional systemic, and biological agents, rather than only biological agents, which was the case in previous (mainly adult) studies. Although UV-B phototherapy is a well-known therapy in pediatric psoriasis, we were unable to assess its association with QOL owing to low numbers. In this study, we used the CDLQI, a validated instrument for assessing the influence of psoriasis on QOL. Although the CDLQI might not capture all aspects of psychological well-being, it is commonly used in pediatric psoriasis studies and randomized clinical trials.[18]

This study also has limitations. The results are limited by the single-center study design. Furthermore, although in all analyses we adjusted for PASI, BSA, and CDLQI scores at the start of treatment, most participants had mild-to-moderate psoriasis and mild influence on QOL even before the start of treatment. Nevertheless, given that patients were referred by general practitioners and dermatologists from across the Netherlands, we believe this study cohort represents a regular pediatric psoriasis population.

Conclusions

This daily clinical practice cohort study in pediatric psoriasis demonstrates that QOL improvement is associated with higher PASI responses and improvement in BSA involvement. The greatest improvements in QOL were seen with the achievement of PASI 90 or greater and a decrease in BSA involvement of 90% or greater. Furthermore, systemic treatments are associated with a greater degree of improvement of QOL compared with topical treatments independent of PASI response. These findings suggest that a PASI 90 or greater and a decrease in BSA involvement of at least 90% may be clinically meaningful treatment goals that will help pediatric patients with psoriasis reach optimal QOL.

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Supplementary materials

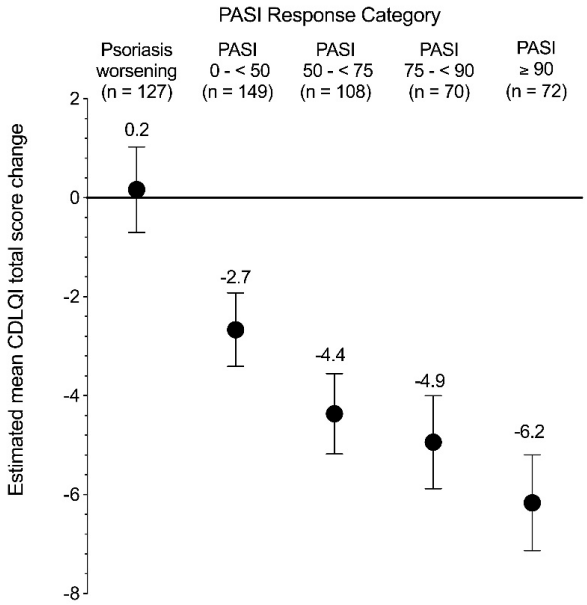

Figure S1. Estimated Mean CDLQI Change per PASI Response Categories for All Treatment Episodes (Including Treatment Episodes With Worsening of Psoriasis)

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index. Linear mixed models were used to assess the CDLQI change by PASI response categories. The following possible confounders were incorporated in the models: the start CDLQI score, the start PASI score, age at start of treatment episode, psoriasis duration, gender, treatment and treatment duration. Only start CDLQI score and treatment altered the unadjusted exposure outcome ≥10% and were kept in the models. Results are presented with a start CDLQI score of 7.7.

Table S1. Estimated mean CDLQI total score changes and CDLQI 0/1 achievement by relative PASI (n = 399 treatment episodes) and BSA response categories (n = 366 treatment episodes)

Estimated mean CDLQI total score change			
PASI response categories	**No. treatment episodes**	**Estimated marginal mean**	**95% CI**
PASI 0 - < 50	149	-3.3 [a]	-4.0 - -2.5
PASI 50 - < 75	108	-4.9 [a,b]	-5.6 - -4.1
PASI 75 - < 90	70	-5.4 [b,c]	-6.2 - -4.5
PASI ≥ 90	72	-6.6 [c]	-7.5 - -5.7
BSA response categories	**No. treatment episodes**	**Estimated marginal mean**	**95% CI**
BSA 0 - < 50	97	-3.4 [d]	-4.2 – -2.5
BSA 50 - < 75	69	-4.6 [d,e]	-5.5 – -3.6
BSA 75 - < 90	83	-5.2 [e,f]	-6.0 – -4.4
BSA ≥ 90	117	-6.8 [f]	-7.5 – -6.1

[a]PASI 0 – < 50 response versus PASI 50 – < 75 response, $p < .001$;
[b]PASI 50 – < 75 response versus PASI 75- < 90 response, $p = .328$;
[c]PASI 75- < 90 response versus PASI ≥ 90 response, $p = .032$;
[d]BSA 0 – < 50 response versus BSA 50 – < 75 response, $p = .015$;
[e]BSA 50 – < 75 response versus BSA 75- < 90 response, $p = .234$;
[f]BSA 75- < 90 response versus BSA ≥ 90 response, $p = .001$;
Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: CDLQI, PASI, and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score, treatment, and psoriasis duration altered the unadjusted exposure outcome by 10% or higher and were kept in the models. Results are presented with a starting CDLQI score of 8.1 and psoriasis duration of 3.7 years for PASI response categories, and with a starting CDLQI score of 8.2 and psoriasis duration of 3.8 years for BSA response categories.

Table S1. Continued

Estimated percentage of CDLQI 0/1 achievement			
PASI response categories	**No. treatment episodes**	**Estimated percentage**	**95% CI**
PASI 0 - < 50	149	7.5% [g]	3.1% – 16.5%
PASI 50 - < 75	108	29.5% [g,h]	17.8% – 44.4%
PASI 75 - < 90	70	43.3% [h,i]	26.9% – 60.6%
PASI ≥ 90	72	65.0% [i]	47.6% – 78.1%
BSA response categories	**No. treatment episodes**	**Estimated percentage**	**95% CI**
BSA 0 - < 50	97	7.7% [j]	3.2% - 17.1%
BSA 50 - < 75	69	22.2% [j,k]	12.5% - 37.5%
BSA 75 - < 90	83	35.0% [k,l]	23.7% - 50.2%
BSA ≥ 90	117	65.6% [l]	53.6% - 78.9%

[g]PASI 0 – < 50 response versus PASI 50 – < 75 response, p <.001;
[h]PASI 50 – < 75 response versus PASI 75- < 90 response, p =.156;
[i]PASI 75- < 90 response versus PASI ≥ 90 response, p = .064;
[j]BSA 0 – < 50 response versus BSA 50 – < 75 response, p = .011;
[k]BSA 50 – < 75 response versus BSA 75- < 90 response, p = .129;
[l]BSA 75- < 90 response versus BSA ≥ 90 response, p < .001;

Mixed-effects logistic regression models were used for analyses. The following possible confounders were incorporated in the models: CDLQI, PASI, and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score and treatment altered the unadjusted exposure outcome of 10% or higher and were kept in the models. Results are presented with a starting CDLQI score of 8.1 and psoriasis duration of 3.7 years for PASI response categories, and with a starting CDLQI score of 8.2 and psoriasis duration of 3.8 years for BSA response categories.

Table S2. Estimated mean CDLQI total score change per treatment category

Treatment categories	**No. treatment episodes**	**Estimated marginal mean**	**95% CI**
Topical	223	-4.3[a]	-4.8 - -3.8
Dithranol	99	-4.2[a]	-4.9 - -3.5
Conventional systemic	59	-5.8[a]	-6.7 - -4.9
Biologic	18	-5.8[a]	-7.5 - -4.1

[a]Systemic treatment categories (conventional systemic and biologic treatment) versus to topical treatment (topical and dithranol treatment), p = .007

Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: age, sex, Psoriasis Area and Severity Index (PASI) score at the start of treatment, CDLQI total score at the start, PASI response categories, treatment duration, and psoriasis duration. Only PASI response categories, starting CDLQI total score, and psoriasis duration altered the unadjusted exposure outcome effect by 10% or higher and were kept in the models. Results are presented with the starting CDLQI total score of 8.1 and psoriasis duration of 3.7 years.

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CI, Confidence Interval; PASI, Psoriasis Area and Severity Index.

Table S3. Linear mixed model used to estimate mean change of CDLQI total scores per PASI response groups and treatment groups

Variable	Estimate	Confidence Interval		*p*-value
		lower limit	upper limit	
Intercept	-2.01	-4.08	0.054	0.056
PASI response groups				0.000
PASI 0 - <50	3.35	2.37	4.34	0.000
PASI 50 - <75	1.76	0.71	2.81	0.001
PASI 75 - <90	1.25	0.11	2.39	0.032
PASI ≥ 90	0[a]	.	.	.
Treatment groups				0.018
Topical	1.53	-0.31	3.36	0.102
Dithranol	1.61	-0.23	3.46	0.087
Conventional systemic	0.01	-1.83	1.86	0.989
Biologic	0[a]	.	.	.
Start CDLQI total score	-0.70	-0.77	-.64	0.000
Psoriasis duration (years)	0.08	-0.04	0.20	0.199

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.
[a]This parameter is set to zero because it is redundant.
Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: CDLQI and PASI scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score, treatment, and psoriasis duration altered the unadjusted exposure outcome by 10% or higher and were kept in the models.

Table S4. Linear mixed model used to estimate mean change of CDLQI total scores per BSA response groups

Variable	Estimate	Confidence Interval		*p*-value
		lower limit	upper limit	
Intercept	-3.32	-5.33	-1.30	0.001
BSA response groups				0.000
BSA 0 - <50	3.45	2.55	4.35	0.000
BSA 50 - <75	2.21	1.23	3.19	0.000
BSA 75 - <90	1.59	0.67	2.51	0.001
BSA ≥ 90	0[a]	.	.	.
Treatment groups				0.003
Topical	2.49	0.61	4.37	0.010
Dithranol	2.83	0.95	4.71	0.003
Conventional systemic	1.22	-0.67	3.12	0.206
Biologic	0[a]	.	.	.
Start CDLQI total score	-0.67	-0.74	-0.61	0.000
Psoriasis duration (years)	0.10	-0.01	0.21	0.080

Abbreviations: BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index;
[a]This parameter is set to zero because it is redundant.
Linear mixed models were used for analyses. The following possible confounders were incorporated in the models: CDLQI and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score, treatment, and psoriasis duration altered the unadjusted exposure outcome by 10% or higher and were kept in the models.

Table S5. Mixed effects logistic regression model used to estimate CDLQI 0/1 score achievement per PASI response groups

Variable	Estimate	Confidence Interval		*p*-value
		lower limit	upper limit	
Intercept	2.21	0.90	3.52	0.001
PASI response groups				0.000
PASI 0 - <50	-3.12	-4.32	-1.93	0.000
PASI 50 - <75	-1.46	-2.37	-0.56	0.002
PASI 75 - <90	-0.87	-1.79	0.05	0.064
PASI ≥ 90	0[a]	.	.	.
Treatment groups				0.694
Topical	-0.44	-1.31	0.44	0.324
Dithranol	-0.55	-1.52	0.41	0.260
Conventional systemic	0[a]	.	.	.
Biologic	-0.10	-1.61	1.41	0.898
Start CDLQI total score	-0.15	-0.22	-0.07	0.000

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.
[a]This parameter is set to zero because it is redundant.
Mixed-effects logistic regression models were used for analyses. The following possible confounders were incorporated in the models: CDLQI and PASI scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score and treatment altered the unadjusted exposure outcome of 10% or higher and were kept in the models.

Table S6. Mixed effects logistic regression model used to estimate CDLQI 0/1 score achievement per BSA response groups

Variable	Estimate	Confidence Interval		*p*-value
		lower limit	upper limit	
Intercept	1.95	0.89	3.01	0.000
BSA response groups				0.000
BSA 0 - <50	-3.22	-4.34	-2.11	0.000
BSA 50 - <75	-1.96	-2.88	-1.04	0.000
BSA 75 - <90	-1.31	-2.05	-0.58	0.001
BSA ≥ 90	0[a]	.	.	.
Treatment groups				0.336
Topical	-0.16	-0.97	0.65	0.695
Dithranol	-0.57	-1.47	0.34	0.216
Conventional systemic	0[a]	.	.	.
Biologic	0.64	-0.89	2.17	0.410
Start CDLQI total score	-0.13	-0.19	-0.06	0.000

Abbreviations: BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index.
[a]This parameter is set to zero because it is redundant.
Mixed-effects logistic regression models were used for analyses. The following possible confounders were incorporated in the models: CDLQI, and BSA scores at the start of treatment; age; psoriasis duration; sex; treatment; and treatment duration. Only the starting CDLQI score and treatment altered the unadjusted exposure outcome of 10% or higher and were kept in the models.

3.3 Real-world methotrexate use in a prospective cohort of pediatric patients with plaque psoriasis: effectiveness, adverse events and folic acid regimen

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Abstract

In pediatric psoriasis, few studies have evaluated methotrexate effectiveness, adverse events and folic acid regimen. Therefore this study prospectively assessed methotrexate adverse events and effectiveness in pediatric patients with psoriasis in a real-world setting. Furthermore, gastrointestinal adverse events and methotrexate effectiveness were compared between folic acid regimens (5 mg once weekly versus 1 mg 6 times weekly). Data for pediatric patients with psoriasis treated with methotrexate from September 2008 to October 2020 were extracted from Child-CAPTURE, a prospective, daily clinical practice registry. Effectiveness was determined by Psoriasis Area and Severity Index (PASI). Comparison of persistent gastrointestinal adverse events between folic acid regimens were assessed through Kaplan–Meier analysis. A total of 105 pediatric patients with plaque psoriasis (41.0% male, mean age 14.1 years) were included. At week 24 and 48, an absolute PASI ≤ 2.0 was achieved by approximately one-third of all patients. During follow-up, 46.7% reported ≥ 1 persistent adverse events. After 1 and 2 years, approximately one-quarter of patients achieved a PASI ≤ 2.0 without persistent adverse events. Although non-significant, a possible trend towards lower occurrence of gastrointestinal adverse events was found for folic acid 1 mg 6 times weekly (p = .196), with similar effectiveness between folic acid regimens. These findings show that a subgroup of pediatric patients with psoriasis responded well to methotrexate treatment without considerable side-effects during a 2-year follow-up.

Introduction

Methotrexate (MTX) is frequently prescribed as a first-line systemic treatment for pediatric psoriasis patients.[1] Although it is commonly used, evidence on MTX effectiveness and safety in the pediatric psoriasis population is sparse, with only few retrospective studies[1-4] and one small (n = 25) prospective study[5] assessing MTX effectiveness and/or safety in a real-world setting. Additionally, one randomized clinical trial compared adalimumab to MTX (n = 37) in pediatric psoriasis patients.[6]

Folic acid (FA) is supplemented during MTX treatment to reduce the hepatic and gastrointestinal adverse events (AEs).[1,7-9] To date, there is no consensus for FA timing and dosing in the treatment of psoriasis. Current Dutch and European consensus is to administer FA once weekly,[7,10] whereas recent American guidelines advise FA 1 mg daily or 6 days per week.[8] Only 3 retrospective studies have compared these different FA regimens in rheumatoid arthritis patients[11,12] and in pediatric psoriasis patients,[1] which all showed a greater beneficial effect on AEs when FA was given 6 or 7 days per week compared to once weekly supplementation.

In recent years, with the approval of many biologic agents for pediatric psoriasis, the treatment landscape for pediatric psoriasis patients is changing. In view of extracutaneous comorbidities and the potential for lifelong chronicity, the pediatric psoriasis treatment paradigm is shifting towards a potentially more aggressive management in a subset of children.[13] In order to ascertain the role of MTX treatment in this changing treatment landscape, it is important to gain more prospective real-world evidence on MTX effectiveness and safety. Given the fact that absolute treatment outcomes are currently becoming increasingly important,[14-16] this study aimed to assess MTX effectiveness using both relative and absolute treatment outcomes, and safety in a large prospective, daily clinical practice cohort of pediatric psoriasis patients. Furthermore, the occurrence of gastrointestinal AEs and MTX effectiveness were compared between FA supplemented 5mg once weekly versus 1mg six times per week.

Methods

Registry and data collection

Data for this study were extracted from the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry), a single-center, observational, prospective, daily clinical practice cohort. This ongoing cohort includes all children (<18 years

at first visit) with the diagnosis of psoriasis who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Center in Nijmegen, the Netherlands, between September 2008, and October 2020 (data lock). Patients included in the registry who reach the age of 18 years are followed as young adults. This study was reviewed by the ethics committee and was deemed to not fall within the remit of the Medical Research Involving Human Subjects Act. Written informed consent was obtained from the parents or guardians and/or from the participating patients according to applicable rules.

Patient selection

All pediatric patients with plaque psoriasis that initiated MTX treatment at some point during follow-up in the Child-CAPTURE were included in this study. Patients were excluded from the study if they received any other systemic therapy concomitant with MTX, if they were treated with MTX primarily for psoriatic arthritis or if they were previously treated with MTX (before inclusion in the Child-CAPTURE). In case of multiple MTX treatment episodes during follow-up, only the first treatment episode was included in analyses. Patients with a treatment duration <12 weeks were only included if they discontinued MTX treatment before 12 weeks due to an AE.

Patient and treatment characteristics

Baseline characteristics including sex, type of psoriasis, age and psoriasis duration were collected at first visit. Psoriasis severity was measured with the Psoriasis Area and Severity Index (PASI [range 0-72]) at baseline and at every follow-up visit. In general, visits took place every 12 weeks during the first year of treatment and every 12-24 weeks thereafter. If necessary (e.g., in case of an AE or loss of effectiveness), additional patient contacts were planned. MTX treatment characteristics were captured, including start date, dose, route of administration (oral or subcutaneous), FA regimen and, if applicable, reason of discontinuation. MTX dosage was 15mg/m^2/week or 15mg/week if body surface area was >1m^2 at treatment initiation with increase during follow-up if needed until a maximum of 20mg/week for oral and 25mg/week for subcutaneous administration and a taper if tolerated. Furthermore, patients could switch from oral to subcutaneous administration during follow-up if needed.

Adverse events

All AEs were documented in preselected categories according to the Common Terminology Criteria for Adverse Events.[17] Additional AEs could be entered as free text in case it did not fit within a preselected category. In addition, date of AE onset and investigator opinion on relation of AE to MTX were reported. Each AE was

categorized as either transient, defined as an AE that was resolved before the next patient contact, or persistent, defined as an AE that was reported during at least two consecutive patient contacts. A serious AE was defined as an event that resulted in death, was life threatening, required inpatient or prolonged hospitalization or resulted in persistent or significant disability.

Folic acid regimens

At the start of the Child-CAPTURE registry in September 2008, patients with MTX received FA 5mg once weekly according to Dutch guidelines.[7] However, in reaction to our publication in which FA six times per week was associated with fewer MTX-induced gastrointestinal AEs compared to once weekly,[1] from November 2016 onwards patients that initiated MTX were given FA 1mg six times per week. Therefore we were able to compare FA regimens through a quasi-experimental design[18] with a more recent cohort (November 2016 to October 2020) using FA six times per week and a "historical" comparison cohort (September 2008 to November 2016) using FA once weekly from the same registry.

Statistical Analysis

Patient and treatment characteristics were presented as means (SD) in case of normal distributed continuous variables or medians (IQR) in case of non-normal distributed continuous variables and numbers (percent) for categorical variables. Safety data were summarized as the number (percent) of patients developing ≥1 treatment-related AE and the number (percent) of patients developing ≥1 persistent treatment-related AE (i.e., not including transient AEs).

To evaluate MTX effectiveness, percentage of patients achieving i) at least a 75% PASI reduction (PASI75), ii) at least a 90% PASI reduction (PASI90), iii) an absolute score of PASI ≤3.0 and iv) an absolute score of PASI ≤2.0 were determined at every 12 weeks up to 96 weeks. PASI scores at exact time points were obtained with interpolation using the two PASI scores closest before and after these time points. Since the inclusion of patients in the Child-CAPTURE and MTX initiation is continuously ongoing, some patients might only have a short follow-up time at time of data-lock although still being actively treated with MTX. Due to this, patients had different follow-up times at the moment of data lock, with patients that discontinued MTX or were lost to follow-up, but also patients that were active on treatment at data lock (Supplemental Figure 1). Therefore, two methods to assess effectiveness were applied: i) as treated analysis and ii) last observation carried forward (LOCF) analysis. Clopper-Pearson confidence interval was used to calculate the exact confidence intervals for the presented proportions.

Comparison of gastro-intestinal AEs occurrence between FA regimens was assessed through Kaplan-Meier survival analysis, since this analysis allows for varying follow-up times of patients in both regimens. One-minus-survival curves of the FA regimens were compared with a Cox regression analysis with correction for possible confounders. To compare effectiveness between FA regimens, the percentage of patients achieving an absolute PASI ≤3.0 and ≤2.0 in both FA groups was assessed at week 12, 24, 36 and 48. A logistic regression analysis was performed to compare effectiveness between FA regimens. For both the Cox regression analysis and logistic regression analysis the following possible confounders at start of MTX were included: sex, age, body mass index and MTX dose in mg/kg. Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models. For all statistical analyses a *p*-value <.05 was considered significant. Analyses were conducted with SPSS, version 25.0 (IBM SPSS Inc) and SAS, version 9.2 (SAS Institute Inc). All analyses were supervised by a senior statistician (HMMG).

Results

Patient and treatment characteristics

Patient and treatment characteristics of 105 pediatric patients with plaque psoriasis are shown in Table 1. The mean and median follow-up time were 1.8 (1.6) and 1.3 (1.6) (0.1 – 8.0) years respectively. Figure S1 in the Supplementary materials shows the treatment status of patients during follow-up. At time of data-lock, 66 (62.8%) patients had discontinued MTX treatment: 19 (18.1%) due to ineffectiveness, 28 (26.7%) due to AEs, 10 (9.5%) due to both ineffectiveness and AEs and 9 (8.6%) due to other reasons including remission of psoriasis (n = 5), patients's own decision (n = 2) and desire to consume alcohol (n = 2). Mean MTX dose at start of treatment was 0.27 mg/kg/week. Only 2 patients initiated MTX subcutaneously, but during follow-up 34 switched from oral to subcutaneous administration.

Forty-eight (45.7%) patients used FA 5mg once weekly, 53 (50.5%) used FA 1mg six times per week and 4 (3.8%) patients switched from FA once weekly to six times per week or vice versa during follow-up. A comparison of patient and treatment characteristics between FA regimens is shown in Table S1 in the Supplementary materials. Only the mean follow-up time differed significantly, with a shorter mean treatment duration for patients with FA six times per week (1.1 [0.8] years) versus once weekly (2.4 [2.0] years, $p < .001$).

Table 1. Patient and treatment characteristics of all paediatric patients with plaque psoriasis at start of methotrexate treatment (n = 105)

Patient characteristics	
Gender (male), no. (%)	43 (41.0)
Age[a], mean (SD) [range]	14.1 (3.1) [5.7-17.9]
BMI[b], no. (%)	
Underweight	9 (8.6)
Normal weight	74 (70.5)
Overweight/Obesity	22 (21.0)
Psoriasis location[c], no. (%)	
Scalp	104 (99.0)
Inverse	47 (44.8)
Unguium	17 (16.2)
Psoriasis duration, median (IQR) [range]	4.1 (4.8) [0.3-14.7]
PASI (0-72), mean (SD) [range]	10.2 (6.2) [3.0-42.4]
BSA (0-100), mean (SD) [range]	14.7 (13.2) [2.5-76.0]
PGA (0-5), mean (SD) [range]	3.3 (1.0) [1.0-5.0]
CDLQI (0-30), mean (SD) [range]	10.2 (5.0) [1.0-24.0]
Treatment characteristics	
Dose in mg/kg/week[d], mean (SD) [range]	0.27 (0.09) [0.02-0.51]
Administration route, no. (%)	
Oral	103 (98.1)
Subcutaneous	2 (1.9)
Folic acid regimen, no. (%)	
5mg once weekly	48 (45.7)
1mg six times per week	53 (50.5)
Both	4 (3.8)

[a]In years. [b]Cut-Offs for overweight/obesity were based on the Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity by Cole et al. [c]Total number of patients does not equal sum of patients reporting different locations of psoriasis because more than one location of psoriasis can be reported in the same patient. [d]Four patients initiated MTX at the start of the Child-CAPTURE with a test dose (<0.1 mg/kg/week) which was increased after several weeks if treatment was tolerated. All other patients initiated treatment with a dose of 15mg/m2/week or 15mg/week if BSA >1 m2.
Abbreviations: BMI, Body Mass Index; BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; SD, standard deviation.

Adverse events

Table 2 summarizes the percentage of patients experiencing ≥1 treatment-related AE and ≥1 persistent treatment-related AE. Overall, 90 (86.7%) patients experienced ≥1 AE and 49 (46.7%) experienced ≥1 persistent AE. Gastrointestinal AEs were reported most frequently, with 39.0% reporting ≥1 persistent gastrointestinal AE during follow-up. Overall, nausea (61.0%), fatigue (46.7%), abdominal pain (22.9%) and increased transaminase levels (18.1%) were noted most often. Infections regarded primarily flu like symptoms (28.6%) and upper respiratory infections (25.7%). Only one patient experienced a serious AE (pneumonia).

Table 2. Adverse events in paediatric patients with plaque psoriasis treated with methotrexate (n = 105)

Number of patients developing	**≥1 AE, no. (%)**	**≥1 Persistent AE, no. (%)**		
	All patients (n = 105)	**All patients (n = 105)**	**Patients with FA once weekly (n = 48)**	**Patients with FA six times weekly (n = 53)**
Total AEs	90 (86.7)	49 (46.7)	29 (60.4)	17 (32.1)
Gastro-intestinal AEs, total	**75 (71.4)**	**41 (39.0)**	**23 (47.9)**	**15 (28.3)**
Nausea	64 (61.0)	37 (35.2)	22 (45.8)	12 (22.6)
Abdominal pain	24 (22.9)	15 (14.3)	10 (20.8)	5 (9.4)
Vomiting	15 (14.3)	7 (6.7)	5 (10.4)	1 (1.9)
Loss of appetite	15 (14.3)	10 (9.5)	4 (8.3)	6 (11.3)
Diarrhoea	10 (9.5)	2 (1.9)	0	2 (3.8)
Dyspepsia	11 (10.5)	2 (1.9)	2 (4.2)	0
Oral ulcers	6 (5.7)	0	0	0
Dysphagia	2 (1.9)	1 (1.0)	1 (2.1)	0
Constipation	1 (1.0)	0	0	0
General AEs				
Fatigue	49 (46.7)	25 (23.8)	14 (29.2)	10 (18.9)
Headache	15 (14.3)	4 (3.8)	2 (4.2)	1 (1.9)
Dizziness	7 (6.7)	3 (2.9)	2 (4.2)	1 (1.9)
Weight loss	2 (1.9)	0	0	0
Investigations				
Increased transaminase levels	19 (18.1)	2 (1.9)	1 (2.1)	1 (1.9)
Increased bilirubin	3 (2.9)	0	0	0
Abnormal WBC count	8 (7.6)	0	0	0
Anaemia	2 (1.9)	1 (1.0)	1 (2.1)	0

Table 2. Continued

Number of patients developing	≥1 AE, no. (%)	≥1 Persistent AE, no. (%)		
	All patients (n = 105)	All patients (n = 105)	Patients with FA once weekly (n = 48)	Patients with FA six times weekly (n = 53)
Infections				
Flu like symptoms	30 (28.6)	0	0	0
Upper respiratory infections	27 (25.7)	0	0	0
Pneumonia[a]	1 (1.0)	0	0	0
Abdominal infections	5 (4.8)	0	0	0
Skin infections	4 (3.8)	0	0	0
Middle ear inflammation	4 (3.8)	0	0	0
Conjunctivitis (infective)	1 (1.0)	0	0	0
Urinary tract infections	1 (1.0)	0	0	0
Skin disorders				
Acneiform rash	5 (4.8)	2 (1.9)	2 (4.2)	0
Diffuse hair loss	6 (5.7)	2 (1.9)	0	2 (3.8)
Psychological AEs				
Agitation	2 (1.9)	0	0	0
Depressive symptoms	2 (1.9)	2 (1.9)	1 (2.1)	1 (1.9)
Suicide attempt	1 (1.0)	0	0	0

[a]Pneumonia was recorded as a serious AE. Other adverse events reported include: epistaxis, hyperhidrosis (n = 1), hyperventilation (n = 1), injection site reaction (n = 1), anal fissure (n = 1), herpes labialis (n = 1), perforation of tympanic membrane (n = 1). Abbreviations: AEs, adverse events; FA, folic acid; WBC, white blood cell.

Effectiveness

Three patients that discontinued MTX due to an AE before 12 weeks of follow-up were excluded for effectiveness evaluation as follow-up PASI scores were unavailable. Figure 1 summarizes MTX effectiveness with both absolute and relative PASI improvement every 12 weeks up to 2 year follow-up throught as treated and LOCF analyses. Both analyses showed that effectiveness tended to increase up until week 24. At week 24, the PASI75 rate was 29.4% (95% confidence interval [CI] 20.8-39.9%), PASI90 rate was 12.7% (95% CI 7.0-20.8%), an absolute PASI ≤3.0 was reached in 44.1% (95% CI 34.3-54.3%) and PASI ≤2.0 in 30.4% (95% CI 21.7-40.3%) by the LOCF analyses (Figure 1a-d). These rates increased at week 48 and 96, with respectively 37.3% (95% CI 27.9-47.4%) and 33.3% (95% CI 24.3-43.4%) achieving PASI75, 12.7% (95% CI 7.0-20.8%) and 11.8% (95% CI 6.2-19.6%) PASI90, 53.9% (95% CI

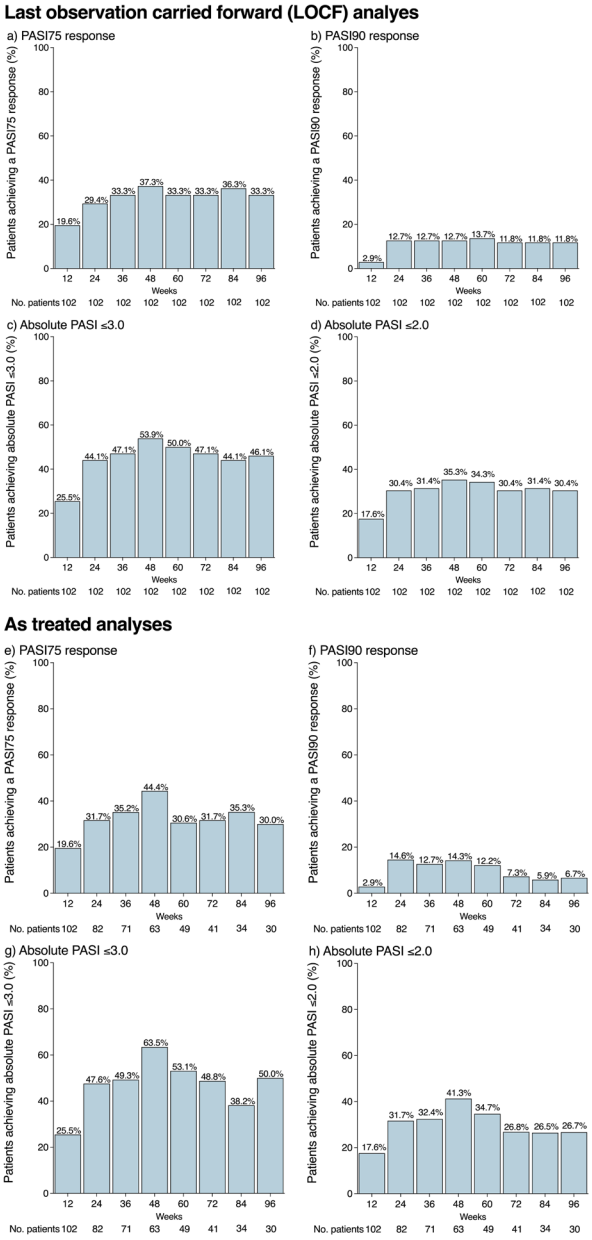

Figure 1. Percentage of pediatric patients treated with methotrexate achieving PASI75 response, PASI90 response, absolute PASI ≤3.0 and absolute PASI ≤2.0 by LOCF analyses (a, b, c, d) and as treated analyses (e, f, g, h)

Clopper-Pearson confidence interval was used to calculate the exact confidence intervals for the presented proportions. Abbreviations: PASI, Psoriasis Area and Severity Index; PASI75, at least 75% reduction in PASI; PASI90, at least 90% reduction in PAS.

43.8-63.8%) and 46.1% (95% CI 36.2-56.2%) PASI ≤3.0, and 35.3% (95% CI 26.1-45.4%) and 30.4% (95% CI 21.7-40.3%) achieving PASI ≤2.0 (Figure 1a-d). Overall, as treated analyses showed slightly higher rates (Figure 1e-h). Futhermore, to gain more insight in MTX effectiveness while also taking safety into account, we evaluated effectiveness with an additional distinction between patients with and without persistent AEs. This evaluation showed that after 1 and 2 years, respectively 39.2% (95% CI 29.7-49.4%) and 33.3% (95% CI 24.3-43.4%) of all patients achieved a PASI ≤3.0 without experiencing a persistent AE and respectively 26.5% (95% CI 18.2-36.1%) and 22.5% (95% CI 14.9-31.9%) achieved a PASI ≤2.0 without a persistent AE by LOCF analyses (Figure 2).

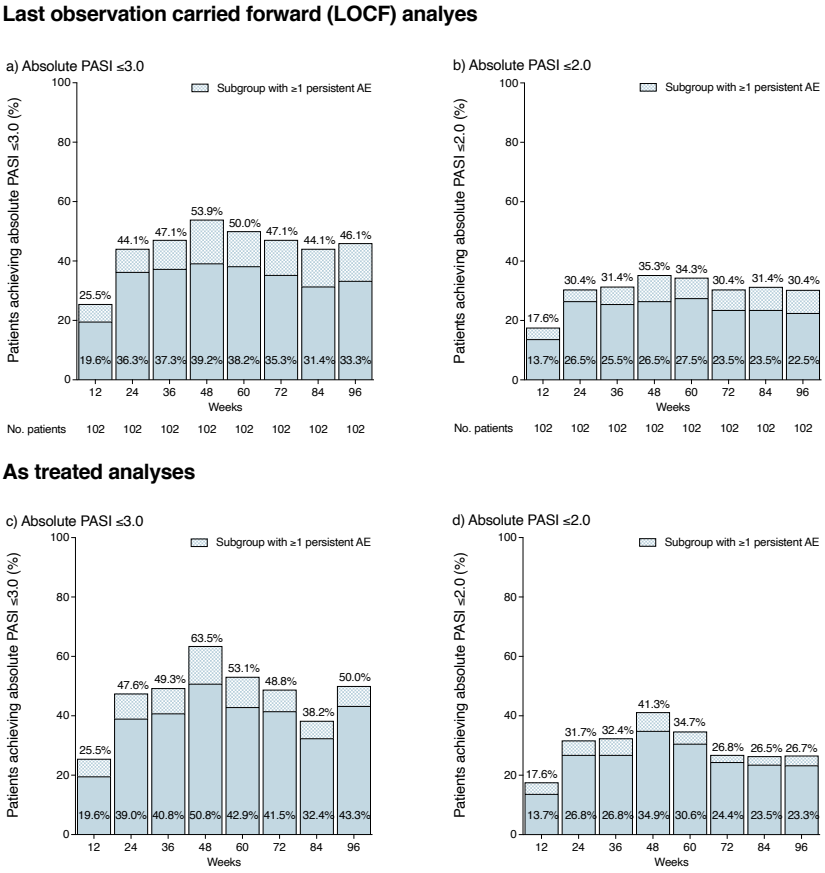

Figure 2. Percentage of paediatric patients treated with methotrexate achieving an absolute PASI ≤3.0 and PASI ≤2.0 without and with persistent adverse events by LOCF analysis (a, b) and as treated analysis (c, d)

An additional distinction was made between patients with and without persistent adverse events at all timepoints. Abbreviations: AE, adverse event; LOCF, last observation carried forward; NS, not significant; PASI, Psoriasis Area and Severity Index.

Comparison of folic acid regimens

An overview of treatment-related persistent AEs split per FA regimen is described in Table 2. Although a higher number of patients using FA once weekly experienced ≥1 persistent gastro-intestinal AE versus FA six times per week (23 [47.9%] versus 15 [28.3%]), a direct comparison of these numbers was not possible due to the difference in follow-up time between regimens. Therefore, Kaplan-Meier survival analysis was performed to compare FA regimens (Figure 3). A trend towards lower occurrence of persistent gastro-intestinal AEs over time was seen for patients with FA six times per week versus once weekly after 1 year (31.8% versus 41.7%) and 2 years (31.8% versus 51.3%), although this difference was not statistically significant (hazard ratio 0.656, 95% CI 0.346–1.243, $p = .196$) (Table S2 in the Supplementary materials). Furthermore, effectiveness between FA regimens was compared. The percentage of patients achieving an absolute PASI ≤3.0 and ≤2.0 split per FA regimen, with an additional distinction between patients with and without gastro-intestinal AEs, is presented in Figure S2 in the Supplementary materials. No statistical significant differences were found in effectiveness between FA regimens in both LOCF and as treated analyses at week 12 up to week 48 (Table S3 in the Supplementary materials).

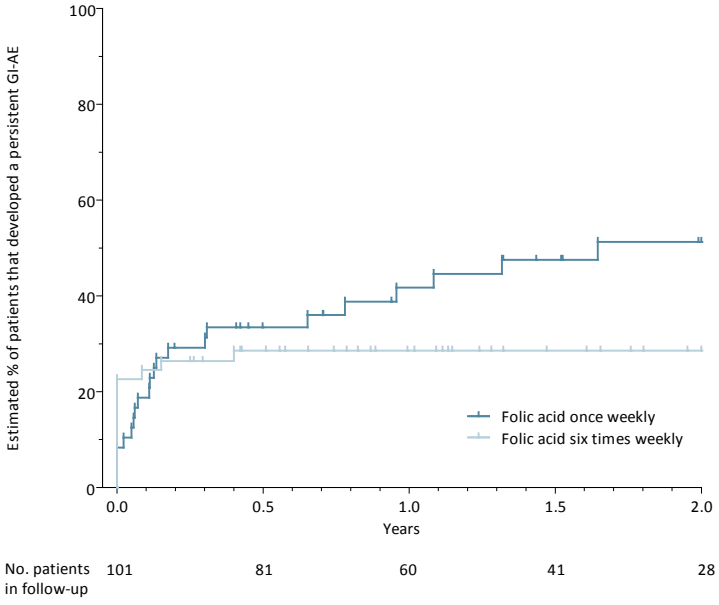

Figure 3. Rate of occurrence of persistent gastro-intestinal adverse events in paediatric psoriasis patients treated with methotrexate: folic acid once weekly versus six times per week

Kaplan-Meier curves displaying the occurrence rates of gastro-intestinal adverse events showed lower rates for patients with folic acid six times per week compared to patients with folic acid once weekly after 1-year (31.8% versus 41.7%) and 2-years (31.8% versus 51.3%), although this difference was not significant ($p = .196$).

Discussion

This prospective, single-center, cohort study of 105 pediatric patients with plaque psoriasis focused on safety and effectiveness of MTX in a real-world setting. At 24 weeks, 29.4% of patients achieved a PASI75 response and 44.1% and 30.4% achieved an absolute PASI ≤3.0 and PASI ≤2.0 respectively. Approximately one-third of all patients maintained a PASI ≤2.0 up to 2 years. Persistent AEs were common, with 46.7% patients experiencing at least 1 persistent AE during follow-up. Still, after 1 and 2 years of treatment, respectively 26.5% and 22.5% of all patients achieved a PASI ≤2.0 without any persistent adverse events.

Previous studies in a real-world setting have shown comparable results regarding effectiveness, with PASI75 response rates of 32.0% (prospective study, n = 25) to 40.0% (retrospective study, n = 30) after 24 weeks.[1,5] A randomized clinical trial comparing adalimumab with MTX found a PASI75 rate of 32.4% at week 16 (n = 37).[6] The current results go further to show that approximately one third of all patients maintained a PASI75 response up to 2 years. Furthermore, the current study assessed the number of patients achieving an absolute PASI ≤3.0 and ≤2.0. Previous studies have shown that the use of relative PASI responses, although commonly used in randomized clinical trials, seem to be less suitable in daily clinical practice studies, probably due to lower baseline PASI scores in real-life studies which challenges the achievement of a high relative PASI response.[14-16] Indeed, the current results show a higher percentage of patients achieving an absolute PASI ≤3.0 and ≤2.0 compared to a PASI90 response.

The most frequently reported AEs in the current study were nausea, abdominal pain, fatigue and increased transaminase levels. Overall, gastrointestinal AEs were common, which has been previously described in other studies regarding children treated with MTX.[1,4,5,19] Infections were frequently reported, especially flu-like symptoms (28.6%) and upper respiratory infections (25.7%); however interpretation of the relation with MTX treatment was difficult as a control group is lacking.

Although FA is supplemented during MTX treatment to reduce gastrointestinal AEs, consensus on timing and dosing of FA is lacking. In line with two previous studies in pediatric psoriasis and rheumatoid arthritis,[1,11] our results suggest a possible trend towards lower occurrence of gastrointestinal AEs with FA six times per week versus once weekly (Figure 2), however this difference did not reach statistical significance (p = .196). MTX effectiveness did not significantly differ between FA regimens during 1-year follow-up. Therefore, our results suggest there might be a

possible advantage of using FA six times per week versus once weekly in reducing gastrointestinal AEs without compromising on MTX effectiveness.

Our study was limited by the use of a quasi-experimental design with a "historical" FA regimen comparison group, which might pose a risk for time trends bias. However, since we used outcome measures that were independent of confounding due to different time-periods (e.g. PASI response, occurrence of AEs) rather than measures possibly influenced by time trends (e.g. treatment discontinuation), the different time-periods probably did not affect our results. Comparison of FA regimens was limited by relatively small subgroup numbers, possibly leading to limited power to detect differences between subgroups, with varying follow-up times. Nonetheless, the use of Kaplan-Meier analysis allowed for comparison of gastro-intestinal AEs while taking the different follow-up times into account. Although the categorization of AEs into either transient or persistent may seem arbitrary, we chose our definition of resolvement before the next patient contact based on our clinical practice, in which we have regularly patient contacts with the possibility of extra contact if necessary. Due to the single center design it is uncertain if our results are fully representative for the general pediatric psoriasis population; however our daily clinical practice study was strengthened by the prospective design, the inclusion of a relatively large number of pediatric patients (n = 105) and long follow-up time (mean 1.8 [1.6] years), which allowed us to assess MTX effectiveness up to 2 years. Furthermore, in addition to relative PASI improvement, our study also assessed absolute PASI improvement.

The treatment landscape for pediatric psoriasis is changing with increasing, more effective, biologic treatment options. Indeed, although MTX is first choice of systemic treatment in our practice according to Dutch guidelines,[7] in recent years, our daily practice experience is that a switch to biologics is initiated sooner if a (persistent) AE occurs during MTX treatment. Ideally, stratification of patients with a high probability of MTX effectiveness and low probability of development of AEs would be carried out before MTX initiation, but biomarkers to assist this stratification are still lacking. Our study showed that after 24 weeks of MTX treatment around 25% of pediatric patients with plaque psoriasis achieved a PASI ≤2.0 without any persistent AEs, with 22.5% maintaining this outcome up to 2 years. These data show that a subgroup of patients responds well to MTX without considerable side-effects. Therefore, also considering the oral administration, low costs and the possibility to stop and retreat without risk of anti-drug development, MTX might still be a good alternative to biologics for a subgroup of patients in which a delayed response (24 weeks) is clinically acceptable.

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Supplementary materials

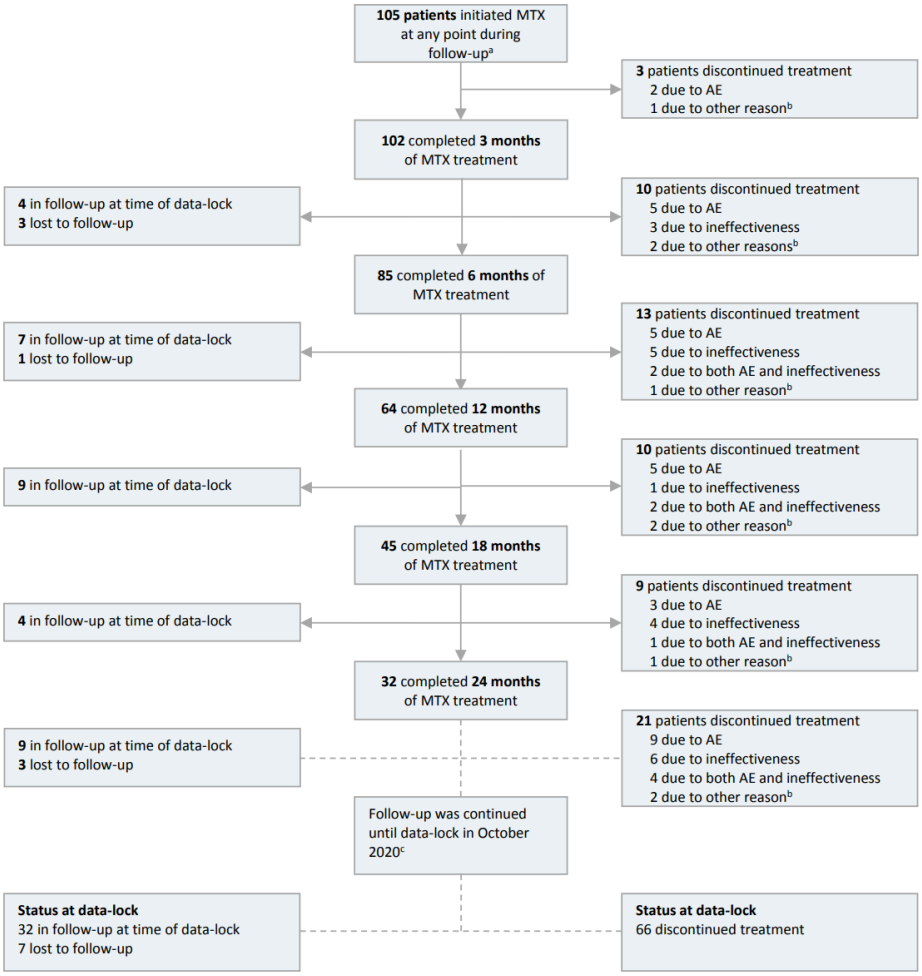

Figure S1. Flowchart of treatment status of patients during follow-up in the Child-CAPTURE

Since the inclusion of patients in the Child-CAPTURE and MTX initiation is continuously ongoing, some patients might only have a short follow-up time at time of data-lock although still being actively treated with MTX. Due to this, patients had different follow-up times at the moment of data-lock, with patients that discontinued MTX or were lost to follow-up, but also patients that were active on treatment at data-lock. This flowchart shows the number of patients that completed a certain timepoint of follow-up.

[a]Patients were included in this study if they initiated MTX at any point during the Child-CAPTURE from September, 2008 to data-lock in October, 2020.

[b]Other reasons: remission of psoriasis (n = 5), patients' own decision (n = 2) an desire to consume alcohol (n = 2).

[c]Follow-up time until either MTX discontinuation or data-lock ranges from 1 month to 96 months.

Abbreviations: AE, adverse event; MTX, methotrexate.

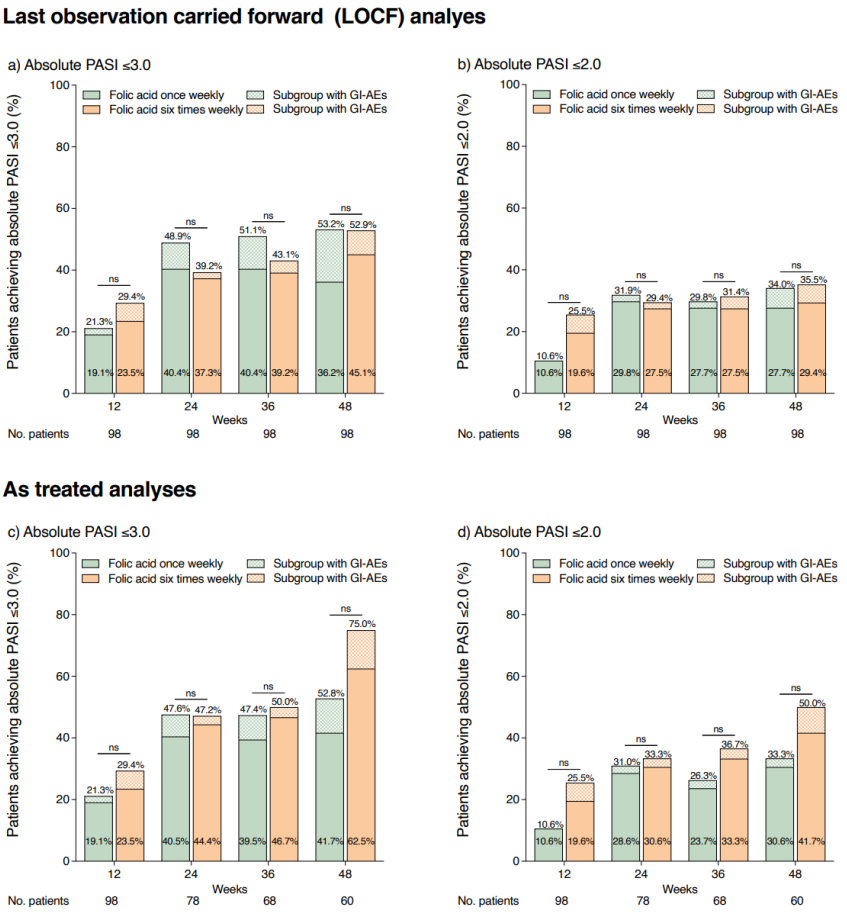

Figure S2. Percentage of pediatric patients treated with methotrexate with folic acid once weekly versus six times weekly achieving an absolute PASI ≤3.0 and ≤2.0 without and with persistent gastro-intestinal adverse events

An additional distinction was made between patients with and without persistent gastro-intestinal adverse events at all timepoints. Logistic regression models were used to compare folic acid once weekly versus six times weekly. The following possible confounders were incorporated in the models: sex, age at start of MTX, body mass index at start of MTX and dose in mg/kg at start of MTX. Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models.

Abbreviations: LOCF, last observation carried forward; NS, not significant; PASI, Psoriasis Area and Severity Index.

Table S1. Patient and treatment characteristics in all pediatric psoriasis patients at start of methotrexate treatment and split for patients with folic acid once weekly versus six times weekly

Patient characteristics	All patients[a] (N = 105)	Patients with FA once weekly (N = 48)	Patients with FA six times weekly (N = 53)	*p*-value[e]
Gender (male), N. (%)	43 (41.0)	24 (50.0)	19 (35.8)	0.217
Age[b], mean (SD) [range]	14.1 (3.1) [5.7-17.9]	14.3 (2.9) [6.5-17.9]	13.9 (3.3) [5.7-17.8]	0.724
BMI[c], N. (%)				0.063
Thinness	9 (8.6)	4 (8.3)	3 (5.7)	
Normal weight	74 (70.5)	29 (60.4)	43 (81.1)	
Overweight/Obesity	22 (21.0)	15 (31.3)	7 (13.2)	
Psoriasis location[d], N. (%)				
Scalp	104 (99.0)	47 (97.9)	53 (100.0)	0.960
Inverse	47 (44.8)	19 (39.6)	25 (47.2)	0.571
Unguium	17 (16.2)	11 (22.9)	6 (11.3)	0.197
Psoriasis duration, median (IQR) [range]	4.1 (4.8) [0.3-14.7]	4.1 (5.9) [0.3-10.8]	4.3 (4.2) [0.5-14.7]	0.778
PASI (0-72), mean (SD) [range]	10.2 (6.2) [3.0-42.4]	11.1 (6.7) [3.2-42.4]	9.5 (5.5) [3.0-32.4]	0.192
BSA (0-100), mean (SD) [range]	14.7 (13.2) [2.5-76.0]	15.8 (15.7) [2.6-76.0]	13.9 (10.8) [2.5-59.0]	0.490
PGA (0-5), mean (SD) [range]	3.3 (1.0) [1.0-5.0]	3.3 (0.8) [1.0-5.0]	3.2 (0.8) [2.0-5.0]	0.373
CDLQI (0-30), mean (SD) [range]	10.2 (5.0) [1.0-24.0]	9.9 (5.2) [1.0-19.0]	10.6 (4.8) [2.0-24.0]	0.477

Table S1. Continued

Patient characteristics	All patients[a] (N = 105)	Patients with FA once weekly (N = 48)	Patients with FA six times weekly (N = 53)	*p*-value[e]
Treatment characteristics				
Treatment duration[a], mean (SD) [range]	1.8 (1.6) [0.1-8.0]	2.4 (2.0) [0.2-8.0]	1.1 (0.8) [0.06-3.1]	<0.001
Dose in mg/kg/week, mean (SD) [range]	0.27 (0.09) [0.02-0.51]	0.26 (0.10) [0.02-0.50]	0.28 (0.09) [0.16-0.51]	0.188
Administration route, N. (%)				0.944
Oral	103 (98.1)	47 (97.9)	52 (98.1)	
Subcutaneous	2 (1.9)	1 (2.1)	1 (1.9)	

[a]All patients including 4 patients that switched from FA once weekly to six times weekly or vice versa during follow-up (these 4 patients were not included in the FA regimen groups). [b]In years. [c]Cut-Offs for overweight/obesity were based on the Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity by Cole et al. [d]Total number of patients does not equal sum of patients reporting different locations of psoriasis because more than one location of psoriasis can be reported in the same patient. [e]Comparison by Mann-Whitney U test in case of non-normal distributed continuous variables, by independent sample t-tests in case of normal continuous data and by Chi-square tests or Fisher's exact tests for categorical data.

Abbreviations: BMI, Body Mass Index; BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; IQR, interquartile range; FA, folic acid; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; SD, standard deviation.

Table S2. Cox regression model used to compare the occurrence of persistent gastro-intestinal adverse events between folic acid regimens

First model including all confounders	**Estimate**	**95% CI**	***p*-value**
Folic acid regimen			0.160
FA once per week	0[a]		
FA six times per week	0.620	0.318 – 1.207	
Sex			0.346
Male	0.728	0.376 – 1.410	
Female	0[a]		
BMI at baseline			0.999
Underweight/ normal weight	0[a]		
Overweight/obesity	1.001	0.389 – 2.577	
Age in years	0.998	0.843 – 1.181	0.980
MTX dose in mg/kg at baseline	0.592	0.002 – 209.9	0.861
Final model (after exclusion of confounders that did not alter the the unadjusted exposure-outcome effect by 10% or more)			
Folic acid regimen			0.196
FA once per week	0[a]		
FA six times per week	0.656	0.346 – 1.243	

[a]This parameter was set to zero because it is redundant.
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; FA, folic acid; MTX, methotrexate.

Table S3. Final logistic regression models for effectiveness comparison between folic acid regimens

Last observation carried forward (LOCF) analysis				
Absolute PASI ≤3.0				
	Variable	**Estimate**	**95% CI**	***p*-value**
Week 12	Folic acid regimen			0.358
	FA once per week	0[a]		
	FA six times per week	1.542	0.613 – 3.878	
Week 24	Folic acid regimen			0.333
	FA once per week	0[a]		
	FA six times per week	0.673	0.302 – 1.501	
Week 36	Folic acid regimen			0.190
	FA once per week	0[a]		
	FA six times per week	0.566	0.242 – 1.326	
	BMI at baseline			0.013
	Underweight/normal weight	0[a]		
	Overweight/obesity	0.234	0.075 – 0.732	
Week 48	Folic acid regimen			0.562
	FA once per week	0[a]		
	FA six times per week	0.783	0.341 – 1.794	
	Age in years	1.175	0.951 – 1.452	0.134
Absolute PASI ≤2.0				
Week 12	Folic acid regimen			0.065
	FA once per week	0[a]		
	FA six times per week	2.874	0.937 – 8.815	
Week 24	Folic acid regimen			0.788
	FA once per week	0[a]		
	FA six times per week	0.889	0.376 – 2.100	
Week 36	Folic acid regimen			0.621
	FA once per week	0[a]		
	FA six times per week	0.793	0.315 – 1.992	
	BMI at baseline			0.027
	Underweight/normal weight	0[a]		
	Overweight/obesity	0.173	0.036 – 0.820	
	Age in years	1.654	0.645 – 4.242	0.295
Week 48	Folic acid regimen			0.713
	FA once per week	0[a]		
	FA six times per week	0.848	0.351 – 2.046	
	Sex			0.176
	Male	0.532	0.213 – 1.328	
	Female	0[a]		

Table S3. Continued

As treated analysis				
Absolute PASI ≤3.0				
	Variable	**Estimate**	**95% CI**	***p*-value**
	Variable	Estimate	95% CI	*p*-value
Week 12	Folic acid regimen			0.358
	FA once per week	0[a]		
	FA six times per week	1.542	0.613 – 3.878	
Week 24	Folic acid regimen			0.972
	FA once per week	0[a]		
	FA six times per week	0.972	0.404 – 2.400	
Week 36	Folic acid regimen			0.818
	FA once per week	0[a]		
	FA six times per week	0.888	0.323 – 2.422	
	BMI at baseline			0.026
	Underweight/normal weight	0[a]		
	Overweight/obesity	0.157	0.031 – 0.798	
Week 48	Folic acid regimen			0.130
	FA once per week	0[a]		
	FA six times per week	2.400	0.772 – 7.459	
Absolute PASI ≤2.0				
Week 12	Folic acid regimen			0.065
	FA once per week	0[a]		
	FA six times per week	2.874	0.937 – 8.815	
Week 24	Folic acid regimen			0.822
	FA once per week	0[a]		
	FA six times per week	1.115	0.430 – 2.893	
Week 36	Folic acid regimen			0.361
	FA once per week	0[a]		
	FA six times per week	1.621	0.575 – 4.567	
Week 48	Folic acid regimen			0.199
	FA once per week	0[a]		
	FA six times per week	2.000	0.694 – 5.764	

[a]This parameter was set to zero because it is redundant.
Abbreviations: BMI, Body Mass Index; CI, Confidence interval; FA, folic acid; MTX, methotrexate.

Chapter 4

Summary and general discussion

Summary and general discussion

Psoriasis is an immune-mediated inflammatory skin disease with a chronic and unpredictable disease course, which develops during childhood in one-third of all patients. The impact of psoriasis on a child reaches beyond the skin only, with potential comorbidities and a considerable impairment of quality of life and life course. Treatment should be personalized to the individual child, considering psoriasis presentation and severity, comorbidities, impact on quality of life, and patients' and parents' preferences. Ideally, treatment choices should be supported by (clinical) predictors for a more severe disease course and/or treatment success in order to initiate the most fitting treatment at the right time for the right patient.

In this thesis, we therefore aimed to move closer to the goal of personalized treatment by gaining more insight in the identification of biomarkers that potentially predict a more severe disease course and by adding to current knowledge on systemic treatments in daily clinical care of pediatric psoriasis patients. In the first part, we therefore explored the use of the Transdermal Analysis Patches (TAP) for detecting skin surface proteins in daily clinical practice and assessed nail psoriasis as a potential predictor for overall psoriasis disease course. The second part of this thesis focused on the optimization of treatment of pediatric psoriasis patients in daily practice. We first studied current treatment patterns, persistence and factors associated with switching to systemic treatment. We further assessed if a higher degree of psoriasis improvement actually leads to a further increase of quality of life in pediatric psoriasis patients. In addition, we analyzed the influence of type of treatment (topical versus systemic) on quality of life, independent of the psoriasis severity improvement. Finally, we zoomed in on methotrexate treatment and assessed its effectiveness and safety in a real-world setting. The results of the following specific aims will be summarized and discussed below.

Non-invasive biomarkers in pediatric psoriasis

1. To study the Transdermal Analysis Patch (TAP) as a non-invasive tool for biomarker detection.
    a. To explore the use of Transdermal Analysis Patch (TAP) for skin surface protein measurement in daily clinical practice.
    b. To examine the correlation of skin surface proteins measured by TAP with disease severity.
2. To study the presence of nail psoriasis as a potential predictor for more severe psoriasis disease course over time in pediatric patients.

Optimizing management of pediatric psoriasis patients

3. To gain insight in real-world treatment patterns, persistence and factors associated with switching to systemic treatment in pediatric psoriasis patients.
4. To determine if a higher degree of psoriasis improvement in fact leads to further increase of quality of life and in addition, if type of treatment (topical versus systemic) influences quality of life improvement in pediatric psoriasis patients.
5. To examine effectiveness and safety of methotrexate treatment in pediatric psoriasis in daily clinical practice.

Non-invasive biomarkers in pediatric psoriasis

Ideally, it would be valuable for physicians to know beforehand which patients are at risk for developing severe psoriasis or which treatment is likely to be most effective for a specific patient, enhancing personalized medicine. This is especially true for the pediatric population, given the chronic nature of psoriasis and need for long-term care. Biomarkers, including both clinical patient characteristics or biomarkers derived either from the skin or blood, could potentially provide this information. In the pediatric population, patient-friendly non-invasive methods to achieve potential biomarkers are desirable to minimize the development of fear for interventions and to enable regular application in daily clinical practice. The novel Transdermal Analysis Patch (TAP) is such a non-invasive method that can detect soluble skin surface proteins from an intact stratum corneum.[1]

Aim 1a. To explore the use of Transdermal Analysis Patch (TAP) for skin surface protein measurement in daily clinical practice.

In **chapter 2.1** and **chapter 2.2** we explored the use of TAP for skin surface protein detection in 32 pediatric psoriasis patients in a daily clinical practice setting. Patients were followed for 1 year, and visits were planned every 3 months for systemically treated patients and every 6 months for solely topically treated patients. The TAP consisted of a preset panel of general inflammation-related proteins, including chemokines, cytokines and antimicrobial peptides. The following 13 proteins were captured: CXCL-1/2, CCL-27, IL-1RA, IL-23, IL-1α, IL-8, IL-4, IL-22, IL-17A, VEGF, hBD-2, hBD-1 and KLK-5 at every visit. In **chapter 2.1** we analyzed the baseline results of the TAP application in this cohort and the patient-friendliness of the TAP. In the baseline analysis, we were able to detect significant differences in protein levels between lesional and non-lesional skin in both patients on topical and systemic treatment. Specifically, higher levels were found in lesional skin for IL-1RA, hBD-2, IL-8, CXCL-1/2 and VEGF and lower levels were seen for IL-1α. Unexpectedly, IL-17A was detected in only 15 out of 64 lesional samples and levels of IL-17A were low. The rest of samples did not show any Il-17A. The TAP was regarded patient-friendly

by pediatric psoriasis patients and patients experienced almost no discomfort during the application and removal.

Aim 1b. To examine the correlation of skin surface proteins measured by TAP with disease severity.

We further evaluated the use of TAP longitudinally in **chapter 2.2** to study the consistency of the measured markers over time and to assess their correlation with disease severity. In this follow-up analysis, 32 patients were followed for a mean of 11.3 (3.4) months with a total of 104 visits, leading up to 197 lesional and 104 non-lesional measurements. This study confirmed the previously found differences in detected skin protein levels in lesional and non-lesional skin for IL-1RA, hBD-2, IL-8, CXCL-1/2, VEGF, IL-1α with now also significantly higher levels of IL-23, IL-22, hBD-1, CCL-27 and IL-17A in lesional skin compared to non-lesional skin, although overall levels of IL-17A were still low. Even though the TAP could differentiate between lesional and non-lesional skin, marker levels were highly variable over time and robust correlations between lesional marker levels and disease severity scores were absent.

To further assess the detection capability of TAP, an additional pilot study was performed in which TAP was compared with tape stripping, a widely used method for skin protein sampling.[2] Since we thought tape stripping might be less patient-friendly, we performed this study in a separate cohort of ten adult psoriasis patients to avoid unnecessary burden on children. Both TAP and tape stripping were performed in a random order on the same psoriasis lesion and non-lesional skin at a single time-point. The compared markers were IL-1RA, hBD-2, IL-1α, IL-8, VEGF and CXCL-1/2. Despite the small sample size, the pilot study revealed a higher frequency of protein marker detection in tape strip samples, with patients reporting similar low discomfort levels (visual analogue score 0.0) for both procedures.

The detected skin protein levels found in both the baseline and longitudinal analyses of our TAP study **(chapter 2.1 and 2.2)** are in line with previous proteome analyses using tape stripping in adult psoriasis patients, which also found higher levels of VEGF, CXCL-1/2, IL-8, CCL-27 and IL-23 and lower levels of IL-1α in lesional skin.[2,3] The role of these general skin inflammatory proteins include neutrophil infiltration and Th17-cell differentiation.[2] Higher levels of hBD-2 in psoriatic skin have also been previously described and additionally, studies have shown a reduction of hBD-2 with improvement of psoriasis severity suggesting a potential role of hBD-2 as biomarker to monitor or perhaps predict psoriasis disease activity.[4-7]

The results of our longitudinal study **(chapter 2.2)**, however, revealed that there was a low correlation between skin surface protein levels measured by TAP and psoriasis severity scores over time. This correlation was not only low for overall psoriasis severity, but also for lesion specific severity scores. These low correlations might be due to a low detection capability of TAP. Although the exact reasons for this lesser sensitivity are unknown, we postulate that (excessive) desquamation in psoriasis might hamper sampling of soluble skin surface (immune cell derived) proteins via diffusion through the stratum corneum by TAP. Indeed, when correlating skin protein marker levels measured by TAP with local amount of desquamation in our cohort, we found a clear trend of decreasing marker levels with increasing desquamation. This hypothesis is supported by the results from the additional pilot study in adults **(chapter 2.2)** comparing TAP to tape stripping, which showed tape stripping to have a greater protein detection capability compared to TAP. Most likely, tape stripping samples deeper layers of the stratum corneum and therefore more easily detects proteins that otherwise should first diffuse through the stratum corneum to be able to be detected by TAP. A second hypothesis for the low correlation between protein levels and psoriasis severity, is that the protein marker levels detected in the stratum corneum may show a delayed protein profile and do not reflect the actually change in proteins in the (deeper layers) of the skin.[8-10] Furthermore, our daily clinical practice study design allowed for many uncontrolled variables (such as treatment). Although it is important that correlations with disease severity can be found in a real-world setting (rather than a controlled scientific setting) to ultimately be of value for clinical practice, this design may have hampered the detection of possible correlations. Lastly, the marker set captured with the TAP was a preset general inflammatory panel, thus (mostly) not specific for psoriasis. While we did assess certain proteins previously identified in psoriatic skin, such as hBD-2, it is possible that other psoriasis-specific markers, whether currently known or yet unidentified, could establish more robust correlations with disease activity.[2,3,7] Previous studies in (adult) psoriasis patients have identified several proteins that were not assessed in our current study, such as IL-36A, IL-17A, IL-17C, IL-17F, IL-1β, IL-6, CCL4, CCL20, CXCL8, CXCL9, CXCL10, CXCL11 and S100A proteins.[2,5,11-13] Especially IL-36 seems to be an interesting protein to assess in future studies, based on a recent study showing that IL-36, found in psoriatic skin, is essential for amplifying both IL-17A and TNF response in keratinocytes.[13] Notably, the Next Generation Immunodermatology (NGID), a Dutch large-scale project involving collaboration among clinicians, biologists, bio-informaticians, statisticians, and behavioral scientists, aims to identify novel biomarkers for various skin diseases, including psoriasis to ultimately provide in patient-centered treatment.[14]

A further unexpected finding in our TAP studies that should be mentioned is the lack or low concentration of IL-17A detected in the stratum corneum of lesional psoriasis skin **(chapter 2.1 and 2.2)**. This finding is counter-intuitive since IL-17A is known to be a key pro-inflammatory cytokine in psoriasis and has been found in previous tape-strip studies in adult psoriasis patients.[2] The low concentration might be due to the previous discussed lesser detection capability of TAP. But, it should also be mentioned that almost all previous studies on proteins in psoriatic skin have been performed in adult patients. Another hypothesis might therefore be that our results differ because pediatric psoriasis patients might have a different cytokine profile compared to adult patients.[15-17] Previous research on proteins in the skin in pediatric psoriasis is very limited, with different methods used, therefore somewhat hampering adequate comparison. Nevertheless, two preliminary studies in children with psoriasis have interestingly also found lower levels of IL-17A, which is similar to our results.[15,16] The study by Kim et al. retrospectively compared skin biopsies of 22 pediatric and 25 adult psoriasis patients through immunohistochemical staining, which revealed lower levels of IL-17A in children with psoriasis compared to adults.[16] A small pilot study by Cordoro et al. compared inflammatory cell profiles in biopsies of lesional skin of 10 pediatric psoriasis patients with samples of healthy children, adult psoriasis patients and healthy adults by multiparameter flow cytometry.[15] This study found higher levels of IL-22 producing T-cells and relatively less IL-17 producing T-cells in pediatric psoriasis patients compared to adult psoriasis patients.[15] Although different methods were used, these findings are in line with our results, which showed overall low concentration of IL-17A in both baseline and longitudinal studies and higher concentration of IL-22 in the longitudinal study.

Concluding, in this chapter we set out to explore the use of TAP in children with psoriasis. This was an initial step towards the objective of identifying and utilizing skin derived biomarkers, as to ultimately assess beforehand which patients are susceptible for developing severe psoriasis. Although TAPs were able to detect soluble skin surface proteins in a patient-friendly manner in children with psoriasis, there are several hurdles to overcome. Notably, we observed a low correlation between skin surface protein levels measured by TAP and psoriasis severity scores over time. The limited detection capability of TAP and its association with desquamation warrants further investigation. Based on our findings, tape stripping might be considered in future studies, as it revealed higher protein marker levels compared to TAP, without causing additional discomfort. Furthermore, there is a scarcity of research on skin proteins in pediatric psoriasis patients. Studies conducted in a controlled setting, preferably on a larger scale, could enhance

our understanding of the skin protein and cytokine profile in pediatric psoriasis patients, providing valuable insights for future real-world studies on biomarkers. For now, the use of skin surface protein measurements by TAP as potential biomarkers in pediatric psoriasis patients in daily practice is still a bridge too far.

Aim 2. To study the presence of nail psoriasis as a potential predictor for a more severe psoriasis disease course over time in pediatric patients.

In **chapter 2.3** we described demographic and disease characteristics of pediatric psoriasis patients with versus without nail psoriasis and assessed the relationship between nail psoriasis and psoriasis severity during follow-up. Cross-sectional analysis at baseline (i.e. enrollment) of 343 pediatric psoriasis patients showed that nail psoriasis was present in 19.0% of pediatric patients and was associated with male sex, overall higher pain score and a higher psoriasis severity as measured by the Psoriasis Area and Severity Index (PASI). Further multivariable longitudinal analysis demonstrated that pediatric patients with nail involvement at baseline visit in the registry had a higher PASI during 2-year follow-up. We further assessed if the presence (or absence) of nail psoriasis was a stable process or a fluctuating phenomenon over time, as the latter would make nail psoriasis less suitable as a predictor in clinical practice. We found that 69.7% of all children reported no signs of nail psoriasis at any time during follow-up, and 8.2% reported persistent nail psoriasis over time. From a clinical perspective, this suggests that the presence or absence of nail psoriasis is a relatively stable process in around 78% of children with psoriasis, rather than a highly fluctuating on-off phenomenon in children. This, together with the results of the longitudinal analysis showing a higher PASI over 2-year follow-up in patients with nail psoriasis at enrollment, supports the potential of nail psoriasis as a clinical biomarker for a more severe disease course in pediatric psoriasis patients.

To the best of our knowledge, no previous study has investigated the role of nail psoriasis as a potential predictor for a more severe disease course over time in pediatric psoriasis patients. However, three studies in pediatric psoriasis did assess if there was a cross-sectional association between nail involvement and psoriasis severity and reported conflicting results. Similar to our study, a multicenter study by Pourchot et al. also found more severe psoriasis in 313 children with nail involvement compared to those without nail involvement.[18] However, two other cross-sectional studies reported no association between nail psoriasis and psoriasis severity in children, although Mercy et al. did report that that a greater proportion of children with severe psoriasis had a history of nail psoriasis.[19,20] Our results are in line with studies in adult psoriasis patients, which have demonstrated an association

between nail psoriasis and higher psoriasis severity scores cross-sectionally, although none of these studies longitudinally investigated the association of nail psoriasis and the course of disease severity over time.[21-28]

A seemingly limitation of this study appears to be the use of nail psoriasis at baseline visit (i.e. enrollment) of the Child-CAPTURE registry as a predictor, while this baseline visit is in fact a random moment during the psoriasis disease course of the children included in the registry (median psoriasis duration of 1.4 (3.6) years at enrollment). However, the results of our study show that nail psoriasis was a relatively stable process during follow-up. Moreover, the use of nail psoriasis at any time is applicable in daily clinical practice, since a physician will not likely see a patient when the first symptoms of nail psoriasis develop, but rather at a later point when symptoms have progressed. Our results are, however, limited by the relatively short follow-up of 2 years, which made it unable to assess whether nail psoriasis is predictive for more severe disease on the long run. More recently, our group performed a new longitudinal study to identify potential clinical predictors, including nail psoriasis, for the development of severe psoriasis in a larger group of 535 pediatric psoriasis patients with up to 10.8 years of follow-up.[29] This study identified male sex, nail psoriasis, scalp psoriasis and obesity as potential clinical predictors for the development of severe psoriasis over time.[29] Yet, given that a substantial number of children were included in both studies (inherent to data collection in a daily clinical practice registry), it is important to assess the true potential of nail psoriasis as a predictor for the development of severe psoriasis in children in other prospective pediatric psoriasis cohorts.

Optimizing management of pediatric psoriasis patients

In recent years, the treatment landscape in pediatric psoriasis is changing with the introduction of new, more effective, systemic treatment options. There is an ongoing debate if early intervention with more effective treatment should be encouraged to limit psoriasis disease progression and its impact on quality of life. To address this, it is important to gain insight into current treatment patterns and persistence. Furthermore, the question rises whether more effective treatment maximizing psoriasis improvement actually also enhances patients' quality of life, or if a certain degree of improvement suffices for children with psoriasis, potentially disregarding the need for more aggressive treatment. Last, in order to reinforce shared decision making for (potentially earlier) initiation of systemic treatment, it is important to gain more evidence on safety and effectiveness of systemic treatments in pediatric psoriasis patients in a real-world setting. Although this evidence is increasing in recent years, real-world evidence on methotrexate in pediatric patients is still

sparse. We therefore evaluated methotrexate safety and effectiveness in a large prospective cohort of children and adolescents with psoriasis.

Aim 3. To gain insight in real-world treatment patterns, persistence and factors associated with switching to systemic treatment in pediatric psoriasis patients.
In **chapter 3.1** we evaluated the current treatment patterns and persistence in a large prospective, longitudinal, observational, cohort of pediatric psoriasis patients followed from September 2008 until May 2018. Among 448 pediatric and adolescent patients (followed into young adulthood), 62.3% remained on topical treatment until data-lock, 14.3% switched to phototherapy but not to systemics, and 23.4% transitioned to systemic treatment. Median time from psoriasis onset to discontinuation of topical treatment (and subsequent switch to either phototherapy or systemics) was 7.3 years, and the overall median time to switch to systemic treatment was 10.8 years. Patient characteristics associated with switching to systemic treatment included higher PASI and (C)DLQI >5 at the moment of switch. Surprisingly, older age did not influence earlier systemic treatment initiation, as revealed by both univariable and multivariable analyses.

Since the publication of our results, additional studies assessing treatment patterns in children with psoriasis were carried out. Recently, a cross-sectional study assessed treatment patterns of 2378 pediatric psoriasis patients through a survey with dermatologists, general practitioners and pediatricians in both the United States and several European countries.[30] According to this study, 69.9% had only ever been treated with topical therapy, while 15.4% underwent phototherapy and 24.7% received systemic treatment, which is roughly similar to the results presented in this thesis.[30,31] Furthermore, a second insurance claims data study by Wan et al. assessed 13 759 pediatric psoriasis patients in the United States between 2001 and 2016. Contrary to our results they found that only 14.6% of pediatric psoriasis patients escalated treatment to phototherapy, oral systemic, or biologic therapies, leaving 85.4% of all patients treated with topical therapy or without therapy.[32]

A reason for the difference between the US study and our findings may be the claims-database versus a single (academic) center design, the latter possibly including more patients with moderate-severe psoriasis, even though many patients in our cohort were also referred by general practitioners. Then again, discrepancies in common practices or guidelines, insurance policies en availability of treatments between different regions and countries may contribute substantially to variations in treatment patterns. In this regard, the use of dithranol as a second-line treatment in our study, an uncommon treatment in many other countries, should be taken into

account. Additionally, the time period in which a study was conducted may also influence treatment patterns. The claims-database study by Wan et al. separately assessed time periods and found that from 2001-2005 to 2011-2016, the use of oral systemics and biologics in pediatric psoriasis patients both increased significantly, whereas phototherapy use declined.[32] Similarly, a study by van den Reek et al. showed that adult psoriasis patients that initiated biologic treatment between 2010-2015 received fewer conventional systemic treatments before transitioning to biologics compared to those that initiated biologic treatment between 2005-2009.[33] Several factors may explain this change over time, such as limited (or no) availability of biologics in earlier years, initial hesitance in prescribing biologics due to inexperience and lack of long-term safety data and changing reimbursement criteria and biologic labels over time.[33] Similarly, the broad time period in our study (2008-2018) therefore might have influenced our results. Although we did not assess different time periods in our study, we know from clinical practice that less patients switched to systemic treatments at the initiation of the Child-CAPTURE registry in 2008, compared to patients that were included in more recent years.

In summary, we considered both the time until topical treatment discontinuation and until switch to systemic treatment in our study to be substantial. Naturally, in clinical practice, the decision to commence systemic treatment is tailored to each patient and depends on many factors such as psoriasis severity and its impact on quality of life. It is noteworthy, however, that since the conclusion of this study, together with the growing evidence demonstrating the long-term safety profile of biologics and the lower availability of dithranol, our current clinical practice has shifted towards earlier initiation of systemic treatment in pediatric psoriasis patients. While acknowledging that this shift may come with additional costs and potential risks for the child, a sooner transition to systemic treatment may lead to more rapid and effective disease control. This is particular important for the young psoriasis population, not only considering potential comorbidities, but also in light of the cumulative effects of psoriasis on both quality of life and the life course.

Aim 4. To determine if a higher degree of psoriasis improvement in fact leads to further increase of quality of life and if type of treatment (topical versus systemic) influences quality of life improvement in pediatric psoriasis patients.
In **chapter 3.2** we explored whether a higher degree of psoriasis improvement corresponds to a significant increase in the quality of life among pediatric psoriasis patients. For this study, we included 319 patients from the Child-CAPTURE registry and compared quality of life improvement, measured using the Children's Dermatology Life Quality Index (CDLQI), across different psoriasis

response categories. These categories were defined based on Psoriasis Area and Severity Index (PASI) and body surface area (BSA) improvements: 0 to <50%, 50 to <75%, 75 to <90%, or ≥90%. The '0 to <50%' category represented a 50% or less improvement, while '≥90%' indicated a 90% or greater improvement in PASI or BSA. Our analysis revealed that the most significant increase in quality of life occurred when there was a 90% or greater improvement in both PASI (mean CDLQI decrease of −6.6) and BSA scores (mean CDLQI decrease of −6.8). Additionally, 65.0% of the patients achieving a PASI ≥90% attained a CDLQI score of 0 or 1, indicating no significant impact on their quality of life, and 65.6% achieved a similar outcome with a ≥90% improvement in BSA score. These improvements were significantly greater than in all other severity response categories, in particular the 75 to <90% response category. We further investigated the impact of treatment type on quality of life, independent of the improvement in psoriasis severity. This analysis revealed that systemic treatments, encompassing both conventional systemic and biological therapies, resulted in a greater improvement of quality of life compared to topical and dithranol treatment.

Only two other studies have explored the association between the degree of psoriasis improvement and the enhancement of quality of life in pediatric patients. Langley et al. evaluated the impact of etanercept on the quality of life in 106 children with psoriasis, demonstrating that those achieving PASI75 (a 75% or greater improvement in PASI from baseline) at week 12 experienced greater improvement in CDLQI score compared to PASI75 non-responders.[34] However, in contrast to our study, they did not investigate the influence of a PASI90 response in comparison to PASI75 and lower responses. Our findings align with a recent study by Hebert et al., which examined 171 pediatric psoriasis patients treated with ixekizumab.[35] After 12 weeks of treatment, 63.9% of patients with PASI ≥90% achieved a DLQI/CDLI of 0 or 1, compared to 59.1% in the 75 to <90% category, 33.3% in the 50 to <75% category, and 16.3% in the <50% category.[35] These results are roughly similar to our own, where 65.0% achieved CDLQI 0 or 1 in the PASI ≥90% category, compared to 43.4%, 29.5%, and 7.5% for the 75 to <90%, 50 to <75%, and <50% categories, respectively.[35,36] Previous studies in adult psoriasis patients have reported similar findings regarding improvement of psoriasis and increase in quality of life.[37-44] Yet, the abovementioned studies in both the pediatric and adult population were conducted on patients treated with biologics in controlled clinical trials, rather than our real-world setting where patients received treatment with both topical and systemic agents.

Since we included both patients receiving only topical treatments and patients on systemic treatments, our study enabled to assess the impact of treatment modality

on quality of life improvement. Our findings revealed that systemic treatments, including both conventional and biologic therapies, resulted in a significantly greater improvement of quality of life in comparison to topical treatments. Importantly, this improvement was independent of the effect of PASI improvement on quality of life. While we did not specifically assess the factors contributing to this additional benefit of systemic treatments over topicals in terms of quality of life, we hypothesize that it could be attributed to the patient-friendliness of oral medications and (even) injections. These modalities offer advantages such as reduced time consumption and less frequent application, as opposed to the less desirable characteristics associated with topical treatments, such as the time taken to apply ointments, as well as issues related to odors and stickiness. Indeed, a survey among 195 young patients showed that especially pediatric patients rated 'not sticky' to be an important characteristic of a treatment and, according to a survey performed among 666 patients and 351 caregivers in EU and US, an easy administration schedule is considered to be important.[30,45] This suggests that the convenience and user-friendly nature of systemic treatments might contribute to the observed improvement in quality of life, a factor that may be considered when optimizing treatment strategies in (pediatric) psoriasis patients.

In conclusion, our findings suggest that achieving an improvement of ≥90% in either PASI or BSA represents a clinically meaningful treatment goal concerning quality of life in pediatric psoriasis. Moreover, our study highlights that systemic treatments yield a greater enhancement in quality of life compared to topical therapies, independent of severity improvement. While acknowledging that treatment decisions are multifaceted and extend beyond consideration of quality of life alone, our results support initiation of more intensive (systemic) treatment in order to further improve psoriasis severity, and with this, aim to optimize quality of life in pediatric psoriasis patients.

Aim 5. To examine effectiveness and safety of methotrexate treatment in pediatric psoriasis in daily clinical practice.

In **chapter 3.3** we evaluated methotrexate effectiveness and adverse events in pediatric psoriasis patients in daily-clinical practice. We examined a cohort of 105 pediatric patients treated with methotrexate. Effectiveness of methotrexate improved until week 24, with 29.4% achieving a PASI75 response and 44.1% an absolute PASI ≤3.0. Approximately 46% maintained a PASI ≤3.0 up to 2 years. Persistent adverse events, including gastrointestinal complaints, fatigue, increased transaminase levels, and flu-like symptoms, were common, impacting almost 47% of patients, with nearly a quarter discontinuing methotrexate due to side

effects. Yet, there was only 1 serious adverse event (pneumonia). When stratifying effectiveness between patients with and without side effects, respectively 39.2% and 33.3% achieved a PASI ≤3.0 without any persistent adverse events after 1 and 2 years of treatment. We further performed a subanalysis to compare the occurrence of gastrointestinal adverse events between folic acid regimens (5 mg once weekly versus 1 mg 6 times per week). Although not significant, analysis showed a possible trend towards lower occurrence of gastro-intestinal adverse events with folic acid 6 times per week versus once weekly (31.8% vs 41.7% after 1 year), with similar effectiveness between regimens.

Although methotrexate has been the first choice of systemic treatment for psoriasis in pediatric patients for several decades, the evidence supporting its effectiveness in this population is limited. Our real-world study results align with two previous small studies, with PASI75 response rates of 32.0% (prospective study, n = 25) to 40.0% (retrospective study, n = 30) after 24 weeks.[46,47] A randomized clinical trial comparing adalimumab to methotrexate found a PASI75 rate of 32.4% at week 16 (n = 37). Similar efficacy patterns have been noted in adult psoriasis patients treated with methotrexate, with PASI75 responses at week 12 or 16 ranging from 33% to 45%.[48-52]

In addition to evaluating relative PASI responses, our study assessed the proportion of patients achieving absolute PASI scores of ≤3.0 and ≤2.0. Interestingly, our results revealed a substantial higher percentage of patients achieving absolute PASI <3.0 (ranging from 44.1 to 53.9%) at all time points compared to achieving PASI90 responses, which were consistently low (around 12%). Although a PASI90 response is regarded as a high clinical response in both controlled trials and daily clinical practice studies, from a clinical standpoint achieving a PASI90 response is challenging if baseline PASI scores are lower due to its relative nature. In daily clinical practice (studies) patients often have a lower baseline PASI score, since there are no stringent inclusion criteria for initiating systemic medication.[53-55] Nowadays publications also report the absolute PASI, in which the achievement of an absolute PASI ≤ 3.0 is regarded as good clinical response.[56,57] The disparity between PASI90 responses and absolute PASI ≤3.0 responses in our study underscores the importance of using absolute PASI scores to assess the effectiveness of therapeutic agents in daily clinical practice.

In our study, the safety profile of methotrexate was thoroughly assessed, revealing that adverse events were prevalent, with 46.7% of patients experiencing one or more persistent treatment-related adverse events. Among the 66 patients who discontinued methotrexate at the time of data-lock, 26.7% did so due to adverse

events. Our study focused on persistent adverse events, defined as an adverse event reported during a least two consecutive follow-up visits. Overall, nausea (61.0%), fatigue (46.7%), abdominal pain (22.9%) and increased transaminase levels (18.1%) were noted most often. Infections regarded primarily flu like symptoms (28.6%) and upper respiratory infections (25.7%). Only one patient experienced a serious adverse event (pneumonia). However, establishing a direct relationship between these events and methotrexate treatment was challenging due to the absence of a control group. Other prior studies revealed varying rates of adverse events.[46,47,58,59] Previous smaller mostly retrospective studies reported lower incidences of nausea (<1% to 20%) and fatigue (16.0%).[47,58,59] However, a large retrospective real-world study by Bronckers et al., involving European and North American children with psoriasis, showed adverse event rates more consistent with our findings, with gastrointestinal adverse events (24.0%), elevated transaminases (13.0%), fatigue (6.3%), and infections (4.4%) being the most common.[46] Despite the observed high prevalence of adverse events in our study, an evaluation of methotrexate effectiveness while accounting for these adverse events, revealed that 39.2% and 33.3% of all patients achieved a PASI of ≤3.0 without any persistent adverse events after 1 and 2 years, respectively.

Folic acid is supplemented during methotrexate treatment to reduce the hepatic and gastrointestinal adverse events (AEs).[46,60-62] While Dutch and European protocols recommend a weekly folic acid dose, American guidelines advocate for 1 mg daily or 6 days per week.[60,61,63] The international study by Bronckers et al. assessed folic acid regimen in 239 European and North American pediatric psoriasis patients treated with methotrexate and found that administering folic acid 6 out of 7 days per week was linked to a decreased likelihood of developing gastrointestinal adverse events, compared to the weekly regimen.[46] In response to this publication, we adjusted the folic acid regimen in the Child-CAPTURE registry to folic acid 1mg six times per week for patients that initiated methotrexate from November 2016 onwards. This modification enabled us to conduct a quasi-experimental study, comparing a recent cohort (November 2016 to October 2020) receiving folic acid six times per week with a 'historical cohort' (September 2008 to November 2016) receiving folic acid once weekly, both from the same registry.[64] Although our analysis did not yield statistically significant results, there was a possible trend indicating a lower incidence of gastrointestinal adverse events in the group receiving folic acid six times per week compared to the weekly regimen (31.8% vs. 41.7% after 1 year). Importantly, the efficacy of methotrexate remained consistent across both regimens. While a definitive recommendation on the folic acid regimen in pediatric psoriasis patients undergoing methotrexate treatment cannot be made, our findings suggest a potential advantage

in using a six-times-per-week folic acid regimen in reducing gastrointestinal adverse events without compromising the effectiveness of methotrexate.

In summary, our results have shown that methotrexate is effective, reaching a PASI <3.0, and safe (i.e. no persistent adverse events) in roughly a third of pediatric psoriasis patients treated with methotrexate. However, when compared to biologics, methotrexate exhibits lower effectiveness and a higher incidence of reported side effects, which raises questions about its role as the (only) first-line systemic treatment for pediatric psoriasis.[46,65-74] This is reflected by the recently updated guideline on pediatric psoriasis from the German Dermatological Society and a publication by an Italian expert group, in which both adalimumab and methotrexate are recommended as first-line treatment options.[63,75] Methotrexate, owing to its oral administration, low costs, and the possibility to discontinue and resume treatment without the risk of anti-drug development, remains a viable alternative to biologics for a subgroup of patients in which a delayed response (up to 24 weeks) is clinically acceptable and side effects are absent. But, in recent years, our clinical experience is that a switch to biologics is initiated sooner if (persistent) side effects emerge during methotrexate treatment. Ideally, identifying patients with a high likelihood of methotrexate effectiveness and a low risk of side effects before initiating treatment would be valuable. Recent studies have indicated that elevated concentrations of erythrocyte methotrexate-polyglutamates are correlated with reduced disease activity in patients undergoing methotrexate treatment for conditions such as psoriasis, rheumatoid and juvenile idiopathic arthritis, or Crohn's disease.[76,77] This suggests a potential use of erythrocyte methotrexate-polyglutamate levels for therapeutic drug monitoring and perhaps stratification of responders versus non-responders.

Main conclusions and future perspectives

Main conclusions of this thesis

Non-invasive biomarkers in pediatric psoriasis

- Skin protein sampling by TAP enabled detection of differences in protein levels between lesional and non-lesional skin in both patients on topical and systemic treatment in routine clinical practice and was regarded patient-friendly.
- However, skin protein marker levels were highly variable over time and robust correlations between lesional skin protein levels and disease severity scores were absent.
- Tape stripping appeared to have a greater skin surface protein detection capability than TAP in adult psoriasis patients.
- The presence of nail psoriasis was associated with male sex, higher pain score of skin and overall more severe psoriasis severity in 343 children.
- Longitudinal analysis revealed nail involvement to be associated with more severe psoriasis during 2-year follow-up.

Optimizing management of pediatric psoriasis patients

- Among 448 pediatric psoriasis patients followed from 2008 to 2018, 62.3% remained on topical treatment until data-lock, 14.3% switched to phototherapy but not to systemics, and 23.4% transitioned to systemic treatment.
- Median time from psoriasis onset to discontinuation of topical treatment (and subsequent switch to either phototherapy or systemics) was 7.3 years, and median time until escalation to systemic treatment was 10.8 years.
- Assessment of 319 patients revealed that the most significant increase in quality of life was seen with a ≥90% improvement in PASI (Psoriasis Area and Severity Index) and BSA (Body Surface Area) scores.
- Systemic treatments, including both conventional systemic and biological therapies, resulted in a greater improvement of quality of life compared to topical treatments, independent of psoriasis severity improvement.
- In 105 pediatric psoriasis patients treated with methotrexate, 29.4% achieved a PASI75 and 44.1% an absolute PASI ≤3.0 after 24 weeks, with approximately 46% maintaining a PASI ≤3.0 up to 2 years.
- Persistent adverse events during methotrexate treatment, including gastrointestinal complaints, fatigue, increased transaminase levels, and flu-like symptoms, were common, impacting almost 47% of patients, with nearly a quarter discontinuing methotrexate due to side effects.
- After 1 and 2 years of methotrexate treatment, respectively 39.2% and 33.3% of all patients achieved a PASI ≤3.0 without any persistent adverse events.

- Although not significant, there was a possible trend towards lower occurrence of gastro-intestinal adverse events during methotrexate treatment with folic acid administration 6 times per week versus folic acid once weekly, with similar effectiveness between regimens.

Clinical practice recommendations

In up to one-third of all psoriasis patients, the onset of psoriasis occurs before the age of 20 years.[78-82] Especially in these young patients, rapid and effective control of disease is important, not only considering systemic comorbidities, but also in light of the (cumulative) effects of psoriasis on quality of life and life course.[83-86] Treatment goals in pediatric psoriasis should therefore extend beyond merely reducing psoriasis severity, and should also prioritize improvement of quality of life. The findings presented in this thesis have shown that a higher degree of psoriasis improvement actually leads to a further increase of quality of life in pediatric psoriasis patients. Therefore, it is recommended to target a 90% or higher improvement in Psoriasis Area and Severity Index (PASI) and/or Body Surface Area (BSA). While topical therapy remains the primary treatment choice in pediatric psoriasis and may provide sufficient disease control, clinicians should contemplate transitioning to systemic treatment sooner if the psoriasis remains active or significantly impacts quality of life. This is reinforced by our findings that systemic treatments lead to a greater improvement in quality of life compared to topical treatment, irrespective of psoriasis improvement. In the context of systemic treatment choices, methotrexate is still recommended to be considered as the first choice for systemic treatment, as supported by this thesis, where one-third of patients achieved a PASI ≤3.0 without persistent side effects over a 2-year methotrexate course. This recommendation is further strengthened by the convenience of oral administration and its cost-effectiveness. However, for patients experiencing insufficient disease control, side effects, or for whom a relatively slow response (24 weeks) is clinically unacceptable, prompt consideration or switch to a biologic may be warranted, especially since accumulating safety data of biologics in pediatric psoriasis has been reassuring. Naturally, these considerations should be discussed in a shared decision-making process with patients and their parents/caregivers. Ideally, treatment decisions should also be guided by clinical predictors for a more severe disease course over time, in order to initiate the most fitting treatment at the right time for the right patient. Based on the results of this thesis and follow-up study, physicians and parents/patients, when uncertain about initiating systemic treatment, may consider the presence of nail psoriasis, scalp psoriasis, male sex and obesity as potential contributing factors in their shared decision-making process.

Future perspectives

This thesis delved into two aspects of pediatric psoriasis care: the identification of biomarkers indicative of a more severe disease trajectory and insights on treatments in the daily clinical care of pediatric psoriasis patients using data from the Dutch prospective Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry).

In addition to the clinical potential predictors that were identified in this thesis (nail psoriasis) and follow-up study (male sex, scalp psoriasis and obesity),[29] it would also be interesting to study whether certain clinical characteristics could be possible predictors for patients that will maintain a mild form of psoriasis or to identify biomarkers for non-responders or super-responders to specific treatments. Although numerous studies search for skin derived biomarkers in adult psoriasis patients,[2,3,5,7,11-13,87,88] skin proteins that could serve as an accurate biomarker to predict a more severe disease course have not yet been identified. Furthermore, several genomic biomarker studies investigated *HLA-C*06:02,* a major genetic determinant of disease susceptibility, and found associations with disease severity.[87,89,91] *HLA-C*06:02* also showed a positive correlation with ustekinumab response compared to Tumor necrosis factor (TNF)-alpha inhibitors.[92] Additionally genes encoding members of the IL-23-mediated signaling pathway, a key pathway in psoriasis pathogenesis, have been identified as candidate genomic biomarkers for disease severity (*IL23A, IL23R*) and psoriatic arthritis (*IL23R*).[87] However, none of these biomarkers have sufficient evidence for clinical use at this moment.[92] Various consortia, such as 'BIOMarker in Atopic dermatitis and Psoriasis' (BIOMAP) and 'Next Generation Immunodermatology' (NGID), have been established to investigate biomarkers in skin and blood in adult psoriasis patients.[14,93] Prospective large-scale studies such as these are essential to further investigate and validate potential predictors, leading to a comprehensive understanding of (pediatric) psoriasis and ultimately facilitate in patient-centered treatment. In the future, combining several types of possible predictors - including genetic, immunological and clinical markers - through the application of algorithms and/or risk prediction models, might aid in stratifying certain phenotypes and in that way may predict psoriasis disease course or treatment success.

In the second part of this thesis, we have shed light on the treatment landscape in pediatric psoriasis, revealing that there is potential for earlier initiation of systemic therapy in these patients, especially in terms of quality of life and limiting life course impairment. Furthermore, extending our perspective, earlier initiation of systemic treatments might theoretically prove beneficial in modifying the risk of

comorbidities or even altering the disease course. Previous studies in rheumatoid arthritis, Crohn's disease and multiple sclerosis have linked early intervention with improved long-term disease outcomes.[94-97] In psoriasis, few retrospective observational studies have reported a decreased risk in developing psoriatic arthritis with the use of biologics in adult patients.[98-100] Notably, the PAMPA study, a multicenter randomized double-blind placebo-controlled trial, has been launched to compare the development of psoriatic arthritis in psoriasis patients treated with guselkumab versus non-biologic standard of care.[101] Furthermore, first steps are made to investigate the potential of early intervention with biologic treatment to modify the disease course of psoriasis in adult psoriasis patients.[102,103] Initial findings from the GUIDE study have shown that early treatment with guselkumab in adult psoriasis patients with a short disease duration (≤2 years) significantly increases the likelihood of achieving complete skin clearance.[104] Although we are many steps removed from investigating this in children, the concept of early intervention to alter the clinical disease course holds particular promise in the pediatric population. This vulnerable group may benefit most from early disease control and potential disease course modification so that psychological and emotional development is not impaired, and psoriasis does not or only minimally influence life course of young people.[86,105,106]

In the future, real-world studies will be increasingly important to provide evidence for clinical decision making in psoriasis care, in complement to evidence from randomized controlled trials. Preferably multicenter, longitudinal studies with a large number of patients are needed to further elucidate the prediction of psoriasis disease course, identify patients who are more likely to benefit from systemic treatment, and to evaluate if earlier initiation of systemic treatments can modify the risk of comorbidities or even disease course. In essence, these studies are important to determine the most fitting treatment at the right time for the right patient. Although there is much more to learn, the results of this thesis provide a steppingstone towards personalized care for children with psoriasis. Moving forward, better identification of children that are at risk for a more severe psoriasis disease course, prediction of treatment success for the individual patient as well as increasing real-world evidence on long-term effectiveness and safety of treatments are important for our aim to optimize the daily clinical care of pediatric psoriasis patients.

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Chapter 5

Nederlandse samenvatting

Nederlandse samenvatting

Psoriasis is een veelvoorkomende inflammatoire huidziekte met een chronisch en onvoorspelbaar ziekteverloop, die bij ongeveer een derde van alle patiënten tijdens de kindertijd ontstaat. De impact van psoriasis op het kind gaat verder dan alleen de huid, vanwege het risico op het ontwikkelen van comorbiditeiten en een aanzienlijke negatieve invloed op zowel de kwaliteit van leven als de latere levensloop. In recente jaren is het aantal behandelmogelijkheden voor kinderen met psoriasis toegenomen met de komst van nieuwe en effectievere biologics. Dit roept de vraag op of vroegtijdige interventie met deze effectievere therapieën zinvol zou zijn om de (cumulatieve) invloed van psoriasis op de kwaliteit van leven en de mogelijke ontwikkeling van comorbiditeiten tegen te gaan. Hoewel deze belangrijke vraag op dit moment nog niet definitief beantwoord kan worden, is er steeds meer aandacht voor het feit dat de behandeling van psoriasis afgestemd moet worden op de individuele behoeften van het kind. Hierbij dienen de ernst en lokalisatie van de psoriasis, alsook de invloed op de kwaliteit van leven, comorbiditeiten en de voorkeuren van ouders en kind mee te worden genomen. Idealiter zouden behandelkeuzes ondersteund moeten worden door (klinische) voorspellers van het te verwachten ziektebeloop en/of behandelsucces, met als uiteindelijk doel gepersonaliseerde zorg te bieden: de juiste behandeling, op het juiste moment, voor de juiste patiënt.

In dit proefschrift hebben we daarom getracht een stap dichter bij het doel van gepersonaliseerde zorg te komen. Enerzijds hebben we geprobeerd inzicht te verkrijgen in (klinische) biomarkers die mogelijk een ernstiger ziektebeloop kunnen voorspellen. Anderzijds hebben we de kennis over systemische behandelingen in de dagelijkse klinische zorg voor kinderen met psoriasis vergroot. In het eerste deel hebben we de toepassing van de Transdermale Analyse Patches (TAP) onderzocht voor het detecteren van mogelijke biomarkers (eiwitten) aan het huidoppervlak bij kinderen met psoriasis (**doelstelling 1a en 1b**). Tevens hebben we nagelpsoriasis bestudeerd als mogelijke (klinische) voorspeller van het ziektebeloop van psoriasis (**doelstelling 2**). Het tweede deel van het proefschrift richtte zich op het verbeteren van de behandeling van kinderen met psoriasis in de dagelijkse praktijk. We hebben de huidige behandelpatronen bestudeerd, en onderzocht welke factoren geassocieerd zijn met de overstap naar systemische behandeling (**doelstelling 3**). Verder hebben we onderzocht in welke mate een afname van psoriasis-ernst ook daadwerkelijk resulteert in een verdere verbetering in de kwaliteit van leven van kinderen met psoriasis (**doelstelling 4**). Daarnaast bekeken we of het type behandeling (topicaal versus systemische therapie) invloed heeft op de kwaliteit

van leven. Tot slot hebben we de effectiviteit en veiligheid van behandeling met methotrexaat bij kinderen met psoriasis in de dagelijkse praktijk onderzocht (**doelstelling 5**).

Niet-invasieve biomarkers bij kinderen met psoriasis

Doelstelling 1a. Het gebruik van het Transdermaal Analyse Patch (TAP) verkennen voor het meten van eiwitten op het huidoppervlak in de dagelijkse klinische praktijk.

In **hoofdstuk 2.1** en **hoofdstuk 2.2** hebben we de Transdermale Analyse Patch (TAP), een non-invasieve methode om (oplosbare) eiwitten aan het huidoppervlak te meten, onderzocht bij kinderen met psoriasis in de dagelijkse praktijk. De resultaten in **hoofdstuk 2.1** lieten zien dat er significante verschillen waren in eiwitconcentratie tussen de aangedane psoriasis huid en de niet-aangedane huid, met hogere concentraties van IL-1RA, hBD-2, IL-8, CXCL-1/2 en VEGF, en juist een lagere concentratie IL-1α in de aangedane huid. Ondanks dat IL-17A bekend staat als een belangrijke pro-inflammatoire cytokine bij psoriasis, werd dit tegen de verwachting in alleen in lage concentraties of zelfs helemaal niet gemeten in de aangedane huid. Er werden geen opvallende verschillen waargenomen tussen meetlocaties op het lichaam, en patiënten ervaarden de TAP als patiëntvriendelijk.

Doelstelling 1b Het onderzoeken van de correlatie tussen de door TAP gemeten eiwitten op het huidoppervlak en de ernst van de ziekte.

In **hoofdstuk 2.2** werd het gebruik van de TAP gedurende één jaar follow-up onderzocht, in de hoop een eiwit te vinden dat als biomarker zou kunnen fungeren. De resultaten van deze studie bevestigden de eerder gevonden verschillen in eiwitconcentraties tussen de aangedane en normale huid. Echter fluctueerden de eiwitconcentraties in de loop van de tijd en werd er geen robuuste correlatie gevonden tussen de eiwitniveaus en de ernst van de psoriasis. Om de detectiecapaciteit van de TAP te beoordelen, hebben we een aanvullend pilotonderzoek uitgevoerd waarin we de TAP vergeleken met tape-stripping, een veelgebruikte methode voor het detecteren van huideiwitten waarbij het stratum corneum wordt verwijderd. Tape-stripping resulteerde in een hogere detectie van eiwitten in de huid in vergelijking met de TAP. Op basis hiervan vermoedden we dat de aanzienlijke schilfering bij psoriasis mogelijk de detectiecapaciteit van de TAP belemmerde. Concluderend lijkt, op basis van **hoofdstuk 2.1 en 2.2**, het gebruik van de TAP in de dagelijkse praktijk voor het detecteren van huideiwitten die potentieel als biomarkers kunnen dienen, nog niet haalbaar.

Doelstelling 2. Onderzoeken of nagelpsoriasis als een mogelijke voorspeller kan dienen voor een ernstiger verloop van psoriasis bij kinderen.

In **hoofdstuk 2.3** werd onderzocht of nagelpsoriasis geassocieerd is met een ernstiger ziektebeloop op de lange termijn bij kinderen met psoriasis. Nagelpsoriasis kwam voor bij 19.0% van de 343 onderzochte kinderen en was vaker aanwezig bij jongens. Bij patiënten met nagelpsoriasis werden hogere pijnscores waargenomen. De aanwezigheid van nagelpsoriasis bij kinderen bleek verder geassocieerd te zijn met een ernstiger beloop van psoriasis gedurende een follow-up van 2 jaar. Het hebben van nagelpsoriasis kan daarom, los van fysieke (pijn)klachten en zichtbaarheid, een reden zijn om deze kinderen intensiever te behandelen.

Optimaliseren van de behandeling voor kinderen met psoriasis

Doelstelling 3. Het verkrijgen van inzicht in de huidige behandelingspatronen en therapiepersistentie bij kinderen met psoriasis in de klinische praktijk.

In **hoofdstuk 3.1** hebben we de huidige behandelpatronen en therapiepersistentie geëvalueerd in een prospectief, longitudinaal, observationeel cohort (2008 – 2018) van kinderen met psoriasis. Van de 448 patiënten bleef 62.3% tijdens follow-up op topicale therapie, startte 14.3% met lichttherapie (maar niet met systemische behandeling) en stapte 23.4% uiteindelijk over op systemische behandeling. De totale mediane tijd tot aan de start van een systemische behandeling was 10.8 jaar. Patiëntkenmerken die correleerden met het overstappen op systemische therapie waren een hogere ziekte-ernst en een grotere invloed op de kwaliteit van leven. Samenvattend is vastgesteld dat de tijd tot aan de start van systemische behandeling aanzienlijk is, wat suggereert dat er ruimte is voor een snellere overstap naar systemische therapie. Uiteraard zal in de klinische praktijk de beslissing om te starten met systemische therapie altijd afgestemd worden op het individuele kind en is afhankelijk van diverse factoren, waaronder de ernst van psoriasis, de invloed op de kwaliteit van leven en de voorkeuren van het kind en de ouders/verzorgers. Opmerkelijk is dat sinds de voltooiing van deze studie in de praktijk steeds sneller wordt overgegaan tot systemische behandeling, mede vanwege het toenemende bewijs (ook uit dit proefschrift) van de gunstige langetermijneffecten van systemische behandeling.

Doelstelling 4. Onderzoeken in welke mate een vermindering van psoriasis-ernst resulteert in een verbetering van de kwaliteit van leven bij kinderen met psoriasis, en of het type behandeling (topicaal versus systemisch) invloed heeft op de kwaliteit van leven.

Hoofdstuk 3.2 beschrijft een onderzoek onder 319 kinderen, waarbij werd onderzocht of een afname in de ernst van psoriasis ook leidde tot een (significante) verbetering van de kwaliteit van leven. Kwaliteit van leven werd gemeten middels de 'Children's Dermatology Life Quality Index' (CDLQI) en werd vergeleken met een afname in ziekteactiviteit, gemeten aan de hand van de 'Psoriasis Area and Severity Index' (PASI) en het lichaamsoppervlak (BSA). De resultaten lieten zien dat de meest duidelijke verbetering in kwaliteit van leven optrad bij een afname van 90% of meer in zowel de PASI- als de BSA-score. Ongeveer 65% van de patiënten met een afname van de ziekte-ernst van 90% of meer (gemeten met PASI of BSA), behaalde een CDLQI-score van 0 of 1, wat aangaf dat de kwaliteit van leven niet (meer) significant beïnvloed werd. Verder bleek uit de analyse dat systemische behandelingen een grotere verbetering in kwaliteit van leven gaven ten opzichte van topicale middelen, ongeacht de verbetering in ziekte-ernst. Op basis van deze bevindingen wordt aanbevolen te streven naar een PASI en/of BSA verbetering van 90% of meer. Hoewel topicale therapie de primaire behandelkeuze blijft voor kinderen met psoriasis en adequate ziektebeheersing kan bieden, kunnen clinici overwegen eerder over te schakelen naar systemische behandeling als de psoriasis actief blijft en/of aanzienlijke invloed heeft op de kwaliteit van leven.

Doelstelling 5. Bestuderen van de effectiviteit en bijwerkingen van methotrexaat bij kinderen met psoriasis in de dagelijkse praktijk.

In **hoofdstuk 3.3** hebben we de effectiviteit en bijwerkingen van methotrexaat in de dagelijkse praktijk geëvalueerd bij 105 kinderen met psoriasis. De effectiviteit van methotrexaat nam toe tot week 24, waarbij 29.4% van de patiënten een PASI75-respons (75% verbetering in PASI-score) bereikte en 44.1% een absolute PASI ≤3.0 behaalde. Ongeveer 46% van alle patiënten behield deze respons gedurende 2 jaar. Helaas bleken bijwerkingen, waaronder gastro-intestinale klachten, vermoeidheid, verhoogde transaminasespiegels en griepachtige symptomen, vaak voor te komen. Bijna een kwart van de patiënten stopte de behandeling vanwege bijwerkingen. We voerden een subanalyse uit om de frequentie van gastro-intestinale bijwerkingen te vergelijken tussen twee foliumzuurregimes (5 mg eenmaal per week versus 1 mg zes keer per week). Hoewel niet statistisch significant, suggereerde de analyse een mogelijke trend richting minder gastro-intestinale bijwerkingen bij het gebruik van foliumzuur zes keer per week ten opzichte van eenmaal per week (respectievelijk

31.8% vs. 41.7% na 1 jaar), waarbij vergelijkbare effectiviteit van methotrexaat werd waargenomen bij beide regimes.

Wanneer we de effectiviteit van methotrexaat stratificeerden tussen patiënten met en zonder bijwerkingen, bereikten nog altijd respectievelijk 39.2% en 33.3% een absolute PASI ≤3.0 zonder (aanhoudende) bijwerkingen na 1 en 2 jaar behandeling. Op basis van deze resultaten blijft methotrexaat op dit moment behoren tot de eerste optie voor systemische behandeling voor kinderen met psoriasis, mede vanwege de mogelijkheid van orale toediening en de kosteneffectiviteit. Niettemin kan voor patiënten die bijwerkingen ervaren, of voor wie een relatief langzame respons (24 weken) klinisch onaanvaardbaar is, een snellere of directe overstap naar een biologic worden overwogen, zeker gezien het toenemend aantal onderzoeken dat een gunstig veiligheidsprofiel van biologics aantoont. Deze overwegingen moeten natuurlijk zorgvuldig worden afgewogen in samenspraak met patiënten en hun ouders/verzorgers.

Chapter 6

Appendices

List of abbreviations

AE	Adverse event
BMI	Body mass index
BSA	Body Surface Area
CAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry
CCL	CC chemokine ligand
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CXCL	CXC chemokine ligand
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMM	Estimated marginal means
FA	Folic acid
FDA	Food and Drug administration
FU	Follow-up
hBD	Human beta-defensin
HLA	Human leukocyte antigen
HR	Hazard ratio
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IOTF	International Obesity Task Force
IQR	Interquartile range
KLK	Kallikrein-related peptidase
LDH	Low high-density lipoprotein
LMM	Linear mixed models
LOCF	Last observation carried forward
MHC	Major histocompatibility complex
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NB-UVB	Narrow band UVB
NL	Non-lesional
NS	Not significant
PASI	Psoriasis Area and Severity Index
PASI75	75% improvement in PASI
PASI90	90% improvement in PASI
PGA	Physician's global assessment

PML	Progressive multifocal leukoencephalopathy
PsA	Psoriatic arthritis
PSOR	Psoriasis susceptibility regions
QOL	Quality of life
RNA	Ribonucleic acid
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUM score	Severity score for a single psoriasis lesion (sum of erythema, induration and desquamation severity)
TAP	Transdermal analysis patch
TNF	Tumor necrosis factor
UV	Ultraviolet
UVB	Ultraviolet B
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WBC	White blood cell

List of publications

Publications related to this thesis

Schaap MJ, Bruins FM, van den Brink NJM, Orro K, Groenewoud HMM, de Jong EMGJ, van den Bogaard EH, Seyger MMB. Challenges in Noninvasive Skin Biomarker Measurements in Daily Practice: A Longitudinal Study on Skin Surface Protein Detection by the Transdermal Analysis Patch in Pediatric Psoriasis. Skin Pharmacol Physiol. 2022;35(6):319-327.

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Bruins FM, Bronckers IMGJ, Cai R, Groenewoud JMM, Krol M, de Jong EMGJ, Seyger MMB. Treatment persistence in paediatric and adolescent patients with psoriasis followed into young adulthood. From topical to systemic treatment: a prospective, longitudinal, observational cohort study of 448 patients. Br J Dermatol. 2021 Mar;184(3):464-472.

Bruins FM, Bronckers IMGJ, Groenewoud HMM, van de Kerkhof PCM, de Jong EMGJ, Seyger MMB. Association Between Quality of Life and Improvement in Psoriasis Severity and Extent in Pediatric Patients. JAMA Dermatol. 2020 Jan 1;156(1):72-78.

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Thomas SE, van Reek JMPA, Bruins FM, Groenewoud HMM, de Jong EMGJ, Seyger MMB. Unveiling the impact of itch, pain, fatigue and disease severity in paediatric patients with psoriasis and the influence of methotrexate and biologics. J Eur Acad Dermatol Venereol. 2024 Mar 7.

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PhD Portfolio

Name PhD candidate: F.M. Bruins
Department: Dermatology
PhD period: 01-01-2018 – 31-12-2023
PhD Supervisor(s): Prof. dr. E.M.G.J. de Jong
PhD Co-supervisor(s): Dr. M.M.B. Seyger

Training activities	**Hours**
Courses	
Radboudumc - Introduction day (2018)	6
RIHS - Introduction course for PhD candidates (2018)	15
Radboudumc - eBROK course (2018)	42
RU - Statistics for PhD's by using SPSS (2018)	60
RU - Scientific Writing for PhD candidates (2019)	84
Radboudumc - Scientific integrity (2020)	20
Seminars	
Radboud Research Rounds (poster) (2020)	1
Conferences	
Annual meeting NVED (Nederlandse Vereniging Experimentele Dermatologie) (poster presentation) (2018)	16
Annual meeting NVED (Nederlandse Vereniging Experimentele Dermatologie) (poster presentation) (2019)	16
European Academy of Dermatology and Venereology (poster presentation) (2019)	16
Annual meeting NVED (Nederlandse Vereniging Experimentele Dermatologie) 2020 (oral presentation) (2020)	24
European Academy of Dermatology and Venereology (poster presentation) (2020)	16
European Academy of Dermatology and Venereology (2023)	16
Other	
Department of Dermatology - Journal Club and Research Updates (2018 – 2020)	10
Teaching activities	
Supervision of internships / other	
Supervision of medical research intern (2018)	25
Supervision of medical research intern (2019)	50
Supervision of medical research intern (2020)	50
Total	**467**

Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. The study described in chapter 2.1 and 2.2 were subject to the Medical Research Involving Human Subjects Act (WMO) and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical ethical review committee 'METC Oost-Nederland' has given approval to conduct these studies (file number: NL60952.091.17). Informed consent was obtained from research participants. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage). Data for chapters 2.3, 3.1, 3.2, and 3.3 were sourced from the Dutch Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use) registry. Studies from this registry were exempted from formal ethical approval by the medical ethical review committee 'METC Oost-Nederland' (registration number: 2012/383). Still, written informed consent was obtained from all patients (and/or their guardians) that were enrolled in the Child-CAPTURE registry.

Data collection and storage

For chapter 2 and chapter 3, data was collected through electronic Case Report Forms (eCRF) using Castor EDC. From Castor EDC data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA) or SAS (SAS Institute Inc). Pseudonymized data were stored and analyzed in the Azure DRE, on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc. Paper (hardcopy) data is stored in cabinets on the department.

Availability of data

All studies are published open access. The data will be archived for 15 years after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

Dankwoord

Eindelijk is het zover: mijn proefschrift is af! Het was een jarenlange reis vol uitdagingen, maar ook overwinningen. Deze weg had ik nooit alleen kunnen bewandelen. Daarom wil ik graag de mensen bedanken die mij onderweg hebben gesteund, geïnspireerd en gemotiveerd.

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Curriculum Vitae

Finola Bruins werd geboren op 19 november 1990 in Uden, waar zij opgroeide. Na het cum laude behalen van haar gymnasiumdiploma aan het Udens College begon zij in 2009 aan de studie Geneeskunde aan de Universiteit Utrecht. Tijdens haar studie ontwikkelde zij een brede interesse in medisch-wetenschappelijk onderzoek en extracurriculaire activiteiten. In haar derde jaar liep zij een onderzoeksstage bij de afdeling Immuno-Rheumatologie van het Hôpital Saint-Eloi in Montpellier, Frankrijk. Gedurende de masterfase deed zij internationale ervaring op met een coschap Oogheelkunde aan het Himalaya Eye Hospital in Pokhara, Nepal, en een extracurriculaire onderzoeksstage bij de afdeling Dermatologie van de Feinberg School of Medicine, Northwestern University, in Chicago, VS. Daarnaast was zij actief als studentlid van de Opleidingscommissie Geneeskunde. Finola sloot haar studie af met een senior coschap Reumatologie in het UMC Utrecht en verdiepte zich verder in de dermatologie met een keuzecoschap in het Zuwe Hofpoort Ziekenhuis (nu onderdeel van het Antonius Ziekenhuis) en een onderzoeksstage bij de afdeling Dermatologie van het UMC Utrecht. In de zomer van 2016 behaalde zij haar artsexamen en begon zij later dat jaar als arts-niet-in-opleiding-tot-specialist (ANIOS) bij de afdeling Dermatologie van het Radboudumc. In 2018 startte zij haar promotieonderzoek aan dezelfde afdeling, onder begeleiding van prof. dr. Elke M.G.J. de Jong en dr. Marieke M.B. Seyger. Haar onderzoek richtte zich op psoriasis bij kinderen, wat zij combineerde met haar werkzaamheden als arts op het specialistische kindersporiasisspreekuur. In januari 2020 ontving zij de prijs voor de beste presentatie op het jaarlijkse congres van de Nederlandse Vereniging voor Experimentele Dermatologie (*Treatment persistence in pediatric and adolescent patients with psoriasis followed into young adulthood*). De resultaten van haar onderzoek verschenen in diverse wetenschappelijke tijdschriften en zijn gebundeld in dit proefschrift. Finola startte in januari 2021 met de opleiding tot dermatoloog in het Radboudumc.

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