

## Treatment Options for Pediatric Psoriasis

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**ABSTRACT** Psoriasis is a multifactorial inflammatory papulosquamous disease affecting 0.5% to 2% of the pediatric population. Pediatric psoriasis, presenting similar to adult psoriasis, significantly reduces patient quality of life, often requiring an individualized treatment approach for each patient. Combination and rotational therapy are helpful in reducing toxicity and maximizing efficacy. Patients with mild and limited disease severity respond well to topical treatment with steroids or vitamin D analogues, unlike moderate and severe psoriasis where sufficient remission is rarely achieved. Therefore phototherapy, systemic immunomodulators, or biologic agents are the next line of treatment to be considered. There is limited data available on the use and long-term safety of biologics in the pediatric population. Biologic agents must be administered by experienced dermatologists, only in patients with moderate-to-severe plaque psoriasis who are intolerant or refractory to other systemic conventional disease-modifying treatment or phototherapy, or if those treatments are contraindicated.

**KEY WORDS:** pediatric psoriasis; topical treatment; systemic treatment; biologic agents

### INTRODUCTION

Psoriasis is a chronic and relapsing papulosquamous inflammatory skin disease characterized by significantly reduced quality of life and impaired psychosocial functioning. Therefore, the main goal of treatment is to achieve long-term remission of the disease (1,2). Approximately one-third of patients with psoriasis develop clinical features in the first two decades of life. The congenital form of the disease present at birth or in the early neonatal period is extremely rare (3). Onset is usually after puberty, with no clear gender predilection (4). Family history is positive in 71% of affected children (5). Due to the chronic nature of psoriasis, the child and its family must learn to cope with the demanding treatment that involves frequent applications of topical agents as well as blood tests if systemic therapy has been started. The disease has a great impact on a child's well-being and development of self-confidence, as psoriasis mostly involves the

exposed skin. Patients suffer from feelings of shame, embarrassment, stigmatization, and social rejection (6). In this article, the use of different treatment options for childhood psoriasis has been reviewed.

### CLINICAL PRESENTATION

Plaque psoriasis is the most common form of pediatric psoriasis. The presentation in children resembles psoriasis in adults. However, initial lesions are less prominent, with mild scaling and induration, and can cause diagnostic difficulties (7). It is especially important to differentiate psoriasis from atopic dermatitis, which is significantly more frequent in the pediatric population. In later stages, the clinical presentation is dominated by scaly plaques accompanied by itching. Psoriasis frequently affects the scalp (Figure 1) in approximately 58% of patients, extensor surfaces of the extremities (Figure 2), trunk (Figure 3), face, and ears.



**Figure 1.** Psoriasis of the scalp

Considering the frequency of different clinical types of psoriasis, plaque psoriasis dominates throughout the childhood, while napkin or diaper psoriasis, occurs mostly during the first two years of life (8). Analysis of phenotypic variation in comparison with age of onset and family history showed that severity of skin and nail disease correlates with early onset of the disease and positive family history (9). Apart from the chronic plaque form, several other patterns of psoriasis occur in childhood. Guttate psoriasis is characterized by the acute onset of small drop-like papules, usually covered with a fine scale. Group A streptococcal pharyngitis often precedes the eruption by 1-2 weeks. Streptococcal perianal dermatitis has also been linked with the appearance of guttate psoriasis (9,10). The disease is usually self-limiting and spontaneously resolves within 3-4 months, although relapse can occur after 3 to 5 years (4). Intertriginous or inverse psoriasis is a relatively rare form of pediatric psoriasis affecting body folds, the genitals, and the periumbilical region. Psoriatic nail disease occurs in 7-40% of all children with psoriasis, and may be the only presenting manifestation of the disease, preceding skin involvement. Signs of nail psoriasis include onycholysis, resembling oil drops in the nail bed and pitting (Figure 4) (12). Rare forms of pediatric psoriasis include localized and generalized pustular psoriasis, psoriatic erythroderma, and linear psoriasis. Linear psoriasis is an uncommon clinical variant of the disease with a linear distribution of erythematous lesions along the lines of Blaschko, caused by genetic alterations in early embryogenesis (13).

### MANAGEMENT OF PEDIATRIC PSORIASIS

Treatment of psoriasis in pediatric patients is challenging because of the lack of clinical trials in the pediatric population as well as the lack of guidelines.



**Figure 2.** Psoriatic lesions on the extremities

Treatment success depends largely on parental involvement and education. Therefore, it is extremely important to have a positive approach to the treatment of this chronic disease (14,15). A better understanding of the pathogenesis of psoriasis is crucial for the effective treatment. Psoriasis is not solely a hyperproliferative disease of keratinocytes, but a chronic, inflammatory, multisystem disease associated with a number of co-morbidities such as cardiovascular diseases and metabolic syndrome with hyperlipidemia, obesity, hypertension, and diabetes mellitus (16). Atherogenic risk, resulting from oxidative stress and reduced antioxidant capacity of cells may significantly shorten life expectancy (17). Due to its



**Figure 3.** Psoriatic lesions on the back of the patient



**Figure 4.** Nail psoriasis

complex pathogenesis, psoriasis treatment depends on disease severity, while the patients' age should be considered at the same time. Treatment should be tailored to the individual patient.

### TOPICAL THERAPIES

Limited or mild disease can be managed effectively with topical therapies alone, such as corticosteroids, vitamin D analogues, or immunomodulators.

Calcineurin inhibitors, tacrolimus, and pimecrolimus are effective in the treatment of facial and genital psoriasis (18). Mild to moderate psoriasis of the limbs and torso is intermittently treated with topical corticosteroids and vitamin D analogues. Topical corticosteroids have an important role in treatment due to antiproliferative, anti-inflammatory, immunosuppressive, and vasoconstrictive properties. Lower-potency corticosteroids are especially recommended for use on the face, axillary areas, and groin in infants and children, whereas mid or higher potency corticosteroids can be used on thick psoriatic plaques (19). Side effects are not common when topical steroids are used sparingly and intermittently. In children, the risk of systemic adverse reactions, like hypothalamic-pituitary-adrenal axis suppression, is higher compared with adult patients due to increased surface area-to-body mass ratio. In order to reduce the side effects, it is crucial that appropriate corticosteroid formulation is used intermittently on affected skin with mandatory supervision during the treatment (20).

### PHOTOTHERAPY

Phototherapy is one of the treatment options for pediatric patients with moderate to severe psoriasis.

The most frequently used form is narrow band UVB (311 nm) in the treatment of plaque and guttate psoriasis. Long-term side effects depend on cumulative dosing of UV treatment and include increased risk of skin cancer and premature skin aging (21). Phototherapy is time consuming, interferes with school attendance and is not the treatment of choice for patients with phototoxic reactions.

### SYSTEMIC AGENTS

Systemic drug therapy in pediatric patients is mostly used for severe disease unresponsive to other treatment. Oral medications used for psoriasis treatment include retinoids, methotrexate, and cyclosporine.

Retinoids (e.g. acitretin) are effective treatment for erythrodermic and the pustular form of psoriasis. However, retinoids bear a high teratogenic risk and should be generally avoided or used with concomitant oral contraception during and two years after stopping the treatment in adolescent girls of childbearing potential. Common adverse effects include dose-dependent cheilitis, pruritus, epistaxis, conjunctivitis, and hair loss. Long-term use carries a risk of potential growth retardation due to premature closure of epiphyses (22,23).

Methotrexate, a folic acid antagonist, is used in the treatment of moderate to severe psoriasis and psoriatic arthritis in children. It provides a safe and effective treatment with regular screening of full blood count, liver function tests, and renal function. Folic acid supplements reduce side effects such as headache, nausea, and gastrointestinal discomfort (24,25).

Cyclosporine, an immunosuppressant and calcineurin inhibitor, can be used in pediatric patients with severe plaque psoriasis or as a short-term intervention therapy in relapse of psoriasis (26). The risk of nephrotoxicity, immunosuppression, hypertension, and mucocutaneous side effects such as hypertrichosis and gingival hyperplasia limit its use (27,28).

Use of standard systemic treatment and phototherapy, although generally effective, carries the risk of cumulative dose side effects, low compliance, and even gonadal toxicity, and the satisfactory therapeutic response is not achieved in some patients (29).

### BIOLOGICS

Development of biologics is based on the understanding of the complex etiopathogenesis of psoriasis. As a response to an unknown trigger, injury, or infection, naive immune cells such as macrophages,

NK cells, and plasmacytoid dendritic cells produce cytokines that stimulate the activation of dendritic cells and production of regulatory cytokines such as interleukin (IL) 12 and IL-23. IL-12 causes the differentiation of Th1 cells that produce tumor necrosis factor (TNF)  $\alpha$  and interferon- $\gamma$ . IL-23 stimulates the expansion of Th17 cells secreting IL17 A/F and Th22 cells secreting IL-22. Interleukins 17 A/F and IL-22 are effector cytokines, responsible for the activation and proliferation of keratinocytes. Keratinocytes attract inflammatory cells via cytokines and chemokines and start the inflammatory cycle characteristic for psoriasis (30-32). Biologic agents target specific parts of the immune system, inhibit T cell activation or migration in the skin, and block cytokines important for the development of psoriatic lesions. They represent a new therapeutic option for treating moderate-to-severe plaque psoriasis unresponsive to systemic therapy (33).

Tumor necrosis factor alpha inhibitors that have been used in the treatment of pediatric psoriasis include infliximab, etanercept, and adalimumab.

Infliximab is a chimeric monoclonal antibody against TNF-alpha that has been FDA-approved for the treatment of pediatric Crohn's disease (children  $\geq 6$  years) since 2006. There are sporadic case reports on the treatment of pediatric psoriasis. Due to its rapid onset of action and its high efficacy, infliximab can be used for generalized pustular or erythrodermic psoriasis (34,35).

Etanercept, a TNF receptor fusion protein, was long considered the drug of choice for the treatment of juvenile psoriasis due to good efficiency and excellent tolerability and safety profile (36). The European Medicines Agency (EMA) approved etanercept in 2009 for the treatment of chronic severe plaque psoriasis in pediatric patients (children  $\geq 6$  years) who are poorly controlled by or are intolerant to other systemic therapies or phototherapy (37,38).

Adalimumab is a recombinant human monoclonal antibody specific to TNF-alpha. It is approved for the treatment of chronic severe plaque psoriasis in children  $\geq 4$  years and adolescents with inadequate treatment response to other local therapies or phototherapy. Following the results of a multicentre, double-blind, phase 3 clinical trial evaluating the safety and efficacy of adalimumab 0.8 mg/kg and 0.4 mg/kg every other week compared with methotrexate in 114 patients, aged 4-18 years, adalimumab was approved for treatment of severe chronic plaque psoriasis in children (39).

Biologics are generally safe and well tolerated. The most common adverse effect seen with the use

of anti-TNF agents are injection-site reactions. Long-term use of anti-TNF agents may increase the risk of malignancy, especially lymphomas (40). TNF inhibitors are associated with an increased risk of all types of infections, including tuberculosis and invasive fungal and opportunistic infections. Adverse events in children and teenagers are generally similar in frequency and type as those seen in adult patients (41). Patients receiving TNF-alpha inhibitor treatment should be monitored for infections and should be educated about how to recognize signs of infection early and avoid fatal complications. Treatment with anti-TNF-alpha agents must not be initiated in patients with active infection, malignancies, demyelinating diseases of the central or peripheral nervous system, and congestive heart failure of NYHA classification grade III and IV (42).

## CONCLUSION

Treatment of childhood psoriasis is a challenge to dermatologists due to the lack of clinical trials and published data as well as insufficient guidelines to facilitate decision-making. Many medications are not registered for the use in the pediatric population or are used off-label. In recent years, development of biologic agents has led to a new era in psoriasis treatment. Considering the great impact of psoriasis on the quality of life of our young patients and their families, treatment is often a challenge and must be individualized, taking into consideration the efficacy and safety of the medication. Patient education and supportive care should be an important part of the treatment.

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