

Challenges in the treatment of psoriasis in childhood

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Abstract

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that affects up to 1.2% of children and adolescents. The treatment possibilities for pediatric psoriasis are usually based on the same principles as in adults. Most information on safety and efficacy has been derived from adult studies, but only some of the frequently used treatments have approval for use in children. Treatment options for psoriasis in children and adolescents are mostly off-label, with little available data on efficacy and safety, and so the treatment of pediatric psoriasis remains a challenge. In the future, new pediatric clinical trials should be undertaken to expand the therapeutic spectrum for psoriasis in children and adolescents.

Keywords: pediatric psoriasis, topical therapy, systemic therapy, unapproved treatment, childhood, adolescence

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Introduction

Psoriasis is a chronic inflammatory skin disease that affects 1 to 3% of the world population, with an equal distribution between men and women (1). Although it occurs less frequently in children than in adults, psoriasis affects approximately 0.5 to 1.2% of children and adolescents, and the prevalence linearly increases from 0.1% at age 1 to 1.2% at age 18 (2–4). Furthermore, a few prevalence surveys have demonstrated that about one-third of psoriasis patients develop their symptoms at least once during childhood, although psoriasis may not be diagnosed until adulthood (5).

Treatment

Treating pediatric psoriasis is in many ways based on the same principles as in adults. However, only a few of the current treatment options are approved for use in children and adolescents. Treatment is limited by a lack of randomized clinical trials assessing the treatment outcome, and so clinicians' treatment decisions are usually based on guidelines for psoriasis in adults, case series, expert opinions, or experience with drug safety and efficacy acquired in clinical trials investigating other pediatric disorders. Off-label treatments are therefore widely used, and the treatment of psoriasis in children and adolescents remains a challenge. When compared with the expanding treatment options for adults, the relatively limited number of medications with an indication for pediatric psoriasis that have approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is one of the most important reasons for off-label use of older and generally less effective treatment options. Emerging data suggest that biologic agents are safer and more effective than nonspecific immunosuppressants (e.g., methotrexate and cyclosporine) for pediatric psoriasis (6). Common initial therapies in childhood are etanercept, adalimumab, and ustekinumab.

When selecting a treatment for a child or adolescent with psoriasis, several factors need to be taken into account: age, severity of psoriasis, location of psoriasis, type of psoriasis, quality of life, tolerability, safety, cost, availability, and patient preferences (7–9).

Challenges when treating pediatric patients with psoriasis include the following (10): 1) the limited number of local and systemic medications approved by the FDA and EMA; 2) discomfort due to application of topical medications; 3) poor taste of oral medications; 4) resistance to and fear of injections; 5) emphasis on the necessary reduction of adverse effects due to the longer duration of treatment often required when psoriasis begins in childhood; and 6) hesitancy of therapists of pediatric psoriasis to change between biologic regimens or combine regimens involving biologics. All these challenges may lead to non-adherence to the treatment and consequent flare-ups of psoriasis and worsening of cardiovascular, metabolic, and psychological comorbidities, which ultimately increase costs for the healthcare system and families (10–12).

Topical treatment

In the majority of children, psoriasis can be managed with topical treatment, which is considered a first-line therapy, especially for mild psoriasis. However, most of the available topical treatment options are not approved for pediatric use, requiring off-label prescribing (9). The vehicle of the drug is very important, and its choice depends on the location of psoriasis, lesion characteristics, and patient preference (13). Available vehicles include creams, foams, ointments, gels, and lotions.

Topical treatments are widely considered for localized disease and play a key role in the treatment of psoriasis in children and adolescents (10, 14). Among these, topical steroids alone or in combination with vitamin D analogs are considered first-line therapy (15). Combined products for topical use in pediatric patients include calcipotriol 0.005% / betamethasone 0.064% foam and suspension. Such combination therapy is approved by the FDA, but it is not approved by the EMA (10, 14). Combination therapy is approved by the FDA for adolescents over age 12 for use on the body and scalp. Recently, calcipotriol foam 0.005% was approved by the FDA for patients ≥ 4 years old for use on the scalp and body (14). Despite lacking approval by the EMA, there are data showing a good effect and safety profile of a fixed combination of vitamin D analogs and betamethasone dipropionate in adult populations (16).

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Many off-label topical treatments have been used in pediatric psoriasis, including topical calcineurin inhibitors, tar-based therapies, and tazarotene, with variable effectiveness and safety profiles (17). Topical calcineurin inhibitors (tacrolimus 0.03% or pimecrolimus 1%) are an additional first-line treatment option for psoriasis in children. They are primarily used as an alternative to topical corticosteroid therapy for psoriasis on sites with the greatest risk for corticosteroid-induced skin atrophy, including the face and intertriginous areas (13).

Phototherapy and coal tar have traditionally been used for psoriasis, but there is only limited supporting evidence concerning their safety and efficacy in children (11).

Phototherapy

Controlled administration of artificial ultraviolet (UV) light, specifically narrowband UVB, can be an appropriate therapy in childhood psoriasis in some cases. Phototherapy options include narrowband UVB and targeted phototherapy with an excimer laser, but narrowband UVB is more commonly used (8).

Phototherapy is usually administered at an outpatient clinic two to three times per week. Once satisfactory improvement is achieved, the frequency of treatments is tapered as tolerated. The child must be able to follow instructions and should be comfortable with standing still in an enclosed space alone. School-age children are mostly able to manage such phototherapy, but some younger children can be candidates as well (8, 18).

In many young patients, the use of phototherapy for moderate to severe plaque psoriasis is based on the absence of the risk of serious systemic side effects that may occur with systemic therapies, and so phototherapy can be a useful option for children and families that wish to avoid systemic therapy. However, phototherapy requires frequent office visits (unless home phototherapy is implemented), which can be difficult for some families, and it is not recommended for very young children. In addition, there is some uncertainty regarding the long-term risk for skin cancer in children treated with narrowband UVB phototherapy (18). Ideal candidates for narrowband UVB phototherapy are children that can come to outpatient clinics frequently and are old enough to follow instructions to remain safely in a light booth alone. We typically consider phototherapy in children over 6 years old, but most commonly in preadolescents and adolescents.

Systemic treatment

In children with moderate to severe psoriasis recalcitrant to topical treatment, systemic treatments are indicated (19). However, the choice of agent remains a challenge because of the limited number of clinical trials and lack of guidelines in this age group (20). Most systemic treatments are not approved for use in children and are therefore used off-label. Regarding conventional systemic psoriasis therapy, the EMA and the FDA have not approved any such therapy for children and adolescents.

Methotrexate and cyclosporine are the most commonly used off-label systemic nonbiological medications for pediatric psoriasis (17, 18, 21). Advantages of methotrexate include a long history of use for children with psoriasis, availability of both oral and injectable formulations, and low cost compared with other systemic psoriasis therapies (21). However, methotrexate has a relatively slow onset of action and may lead to hepatotoxicity (21). In addition, methotrexate appears to be less effective than some biologic

agents (6, 21, 22).

Acitretin has also been used in a more limited number of pediatric patients with a good outcome (23). The advantages of oral retinoids include oral administration and lack of immunosuppression. Teratogenicity of oral retinoids is a concern for female adolescent and teenage patients.

Apremilast, an oral PDE4 inhibitor approved for adult psoriasis, is a new, safe, and quite effective therapy for psoriasis in adults. It is an attractive option for the treatment of childhood psoriasis because it is not an antineoplastic, has limited side effects, has no recommended laboratory monitoring, and is administered orally (24).

Although conventional systemic therapy for children is not approved by the FDA and the EMA, the guidelines generally provide that a biologic can only be initiated if a response to non-biologic systemic therapy is absent, contraindicated, or not tolerated (10).

The use of certain biologics for early intervention in the first severe outbreak of psoriasis in a child or adult patient has been investigated for several years. The results suggest that early treatment of psoriasis with systemic drugs could alter the course of psoriasis and completely silence it in some patients despite discontinuation of treatment (25). However, so far not enough is known about such possible management of psoriasis, and so there are no approved biologicals for interventional treatment at first outbreak of the disease.

So far, for pediatric psoriasis the EMA has approved five biological therapies, whereas the FDA has approved only four (Table 1). Etanercept (a tumor necrosis factor [TNF] alpha antagonist) was approved as a treatment option for psoriasis for children ≥ 6 years old by the EMA in 2008 and by the FDA in 2016 for children ≥ 4 years old. Because extensive data are available on its safety and efficacy, including randomized clinical trials, it has often been considered the first choice for biologic therapy in moderate to severe pediatric psoriasis (26, 27). Challenges include weekly injections, and monitoring all patients for active tuberculosis during treatment is recommended, even if the initial latent tuberculosis test was negative (28). A recent retrospective clinical record review has reported both a greater reduction in severity scores and higher drug survival rates when etanercept was compared with methotrexate in a real-world setting (29). Ustekinumab (an interleukin [IL]-12/23 inhibitor) was first approved for treatment of childhood psoriasis by the EMA in 2015 for children ≥ 12 years old and by the FDA in 2017, also for children ≥ 12 years old. The safety, efficacy, and pharmacokinetics of ustekinumab have recently been studied in young patients with moderate to severe psoriasis ≥ 6 years old, and so use was expanded to 6- to 11-year-old patients by the EMA and FDA in 2020 (30, 31). Ixekizumab was approved by the EMA and FDA in 2020 for children ≥ 6 years old with moderate to severe psoriasis. Secukinumab (a selective IL-17A monoclonal antibody) was approved by the EMA in 2020 and by the FDA in 2021 for patients ≥ 6 years old with moderate to severe psoriasis (32). Adalimumab (a recombinant monoclonal TNF alpha antibody) was approved only by the EMA in 2015 for patients ≥ 4 years old with moderate to severe psoriasis (33).

Data from adult clinical trials and case reports and series from pediatric patients also suggest that other biologics and small molecules are effective for pediatric psoriasis. These medications include infliximab (a TNF alpha inhibitor) (34), guselkumab (a selective IL-23 monoclonal antibody) (35), and tofacitinib (a JAK 1/3 inhibitor) (36).

Children and adolescents with psoriasis have a long median

switching time from topical to systemic treatment (37). It is very important to start with systemic treatment when the topical treatment effect is absent, even though there is a lack of data on systemic treatments in children and adolescents. In addition to prescribing treatment, it is very important to educate the patient and family about the chronicity of psoriasis, triggering factors, and treatment modalities (38). Another important component of therapy for children with psoriasis is psychosocial support (39). Our most frequent initial therapies for pediatric plaque psoriasis that cannot be managed with topical therapy are methotrexate, narrowband UVB, adalimumab, etanercept, and ustekinumab.

Psoriasis is a major criterion for diagnosing pediatric psoriatic arthritis (PsA), which affects up to 1.4% of children globally (40). When there are signs or suspicion of PsA, we always send a child with psoriasis to a pediatric rheumatologist, who establishes a diagnosis and then discusses the treatment possibilities with us. Rheumatologists mostly prescribe methotrexate or methotrexate in combination with TNF inhibitors, which is also a good treatment option for the psoriasis. Studies in adults have indicated that TNF inhibitors and methotrexate may also carry the potential to inhibit the possible development of cardiovascular comorbidities (41, 42). Whether early intensive treatment in new-onset psoriasis can modify the long-term natural course of the disease and lower the risk for comorbidities is still debated (43).

Another group of children with psoriasis of concern are those under 4 years of age. These children are likely to respond to the general approach described above, but usually at least some modifications are needed. In general, topical therapy should be

optimized as much as possible; in this age group we avoid phototherapy and systemic therapy, which are only considered in refractory cases.

When speaking of modification of topical therapy, the general approach is that less potent topical corticosteroids are preferred over higher-potency agents. Topical corticosteroid treatment of the diaper area (one of the preferable places where psoriasis in toddlers starts) in a child in diapers should be monitored closely because the occlusive effect of the diaper may increase the risk of cutaneous side effects. For the treatment of facial and intertriginous psoriasis, topical calcineurin inhibitors and low-potency topical corticosteroids are options. On those parts of the body, topical calcineurin inhibitors are preferred particularly when continuous therapy is required. Because of well-known side effect of local skin irritation, topical vitamin D analogs and topical retinoids are very rarely used in the treatment of infants.

Conclusions

Psoriasis begins in childhood in almost one-third of cases, and it is increasing in incidence and prevalence. The evidence for treatment safety and efficacy is still limited, and long-term data in pediatric patients are lacking. There is a need for future studies to investigate the efficacy and safety of unapproved treatments because they represent the foundation of current treatment options, and it is necessary to establish widely accepted guidelines for the treatment of psoriasis in children and adolescents.

Table 1 | Treatment approval status for psoriasis in children and adolescents by medical agency.

Treatment	EMA approval	FDA approval
Topical treatments		
Topical corticosteroids	Group I-II 3 months. Group III traditional use	Traditional use
Topical calcineurin inhibitor	Not approved	Not approved
Topical retinoids	Not approved	Not approved
Vitamin D analogs	Not approved	Not approved
Vitamin D analogs + betamethasone dipropionate	Not approved	> 12 years
Anthralin	Traditional use	Traditional use
Coal tar / Goeckerman therapy	Traditional use	Traditional use
Phototherapy	Traditional use	Traditional use
Systemic treatments		
Methotrexate	Not approved	Not approved
Retinoids	Not approved	Not approved
Cyclosporin	Not approved	Not approved
Fumaric acid esters	Not approved	Not approved
Apremilast	Not approved	Not approved
Biological treatment		
Adalimumab	> 6 years	Not approved
Sucukinumab	> 6 years	> 6 years
Ixekizumab	> 6 years	> 6 years
Etanercept	> 6 years	> 6 years
Ustekinumab	> 6 years	> 6 years

EMA = European Medicines Agency, FDA = Food and Drug Administration.

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