

# Management of psoriasis in adolescence

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**Abstract:** Psoriasis is a chronic inflammatory cutaneous disorder affecting 2%–4% of the world's population. The prevalence of the disease in childhood and adolescence ranges between 0.5% and 2%. The management of psoriasis in adolescence is an intriguing and complicated task. Given the paucity of officially approved therapies, the very limited evidence-based data from randomized controlled trials, and the absence of standardized guidelines, physicians must rely on published experience from case reports both from the field of dermatology as well as from the application of these drugs for other pediatric conditions coming from the disciplines of rheumatology, gastroenterology, and oncology. Psoriatic adolescents deal with a potentially disfiguring and lifelong disease that could permanently impair their psychological development. It must be clarified to them that psoriasis does not have a permanent cure, and therefore the main goal of treatments is to establish disease control and prolonged periods between flares. The majority of adolescents suffer from mild psoriasis, and thus they are treated basically with topical treatment modalities. Phototherapy is reserved for adolescents with mild-to-moderate plaque disease and/or guttate psoriasis when routine visits to specialized centers do not create practical problems. Systemic agents and biologics are administered to patients with moderate-to-severe plaque psoriasis, pustular psoriasis, or erythrodermic psoriasis.

**Keywords:** adolescent psoriasis, pediatric psoriasis, treatment, systemic treatment, biologic agents

## Introduction

Psoriasis is a chronic life-altering skin disorder with possible systemic comorbidities. Although it influences a considerable proportion of patients in childhood and adolescence, its management in this category of patients poses some challenge due to the lack of officially approved therapies and standardized methodology. For this paper, the existing literature was searched for randomized controlled trials (RCTs), open trials, case series and reports, and expert opinion consensus, as well as for existing psoriasis guidelines for adults with reference to juveniles. All the evidence was evaluated by the authors, who then combined this with clinical experience of everyday practice in an effort to provide a complete review on the management of psoriasis in adolescence.

## Epidemiology

Psoriasis is a chronic inflammatory cutaneous disorder affecting 2%–4% of the world's population.<sup>1,2</sup> According to a recently published review of all population-based studies, the prevalence of the disease in childhood and adolescence ranges between 0.5% and 2%, while its estimated incidence was reported to be 40.8 pediatric cases/100,000

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person-years.<sup>3,4</sup> Moreover, it has been shown that the prevalence of the disease exhibits a linear increase from the age of 1 year (0.12%) to the age of 18 years (1.2%).<sup>5</sup> Most studies agree that the mean patient age at disease onset for juvenile psoriasis is 7–11 years.<sup>4,6–8</sup> There seems to be no male or female predominance among children and adolescents suffering from psoriasis.<sup>4,6–10</sup>

## Pathogenesis

Psoriasis is a chronic T-cell-mediated inflammatory disease characterized by keratinocyte hyperproliferation, vascular endothelial proliferation, and inflammatory cell infiltration of the dermis and the epidermis.<sup>11,12</sup> Its pathogenesis, although not fully clarified yet, is based on a complicated interplay of genetic and environmental factors. There are several levels of evidence to support the role of the genetic background in psoriasis: 4.5%–91% of pediatric cases showed a positive family history of psoriasis, while in a study by Morris et al, 71% of children suffering from psoriasis had a first-degree relative with the disease.<sup>6–9,13</sup> At the same time, psoriasis is far more common in identical twins compared with fraternal ones.<sup>14</sup> This disparity in family history, between several studies, underlines the significant role of the genetic background of each population in the manifestation of this condition.<sup>13</sup> The early onset of the disease has been genetically linked with the human leukocyte antigen Cw6 disease allele at the psoriasis susceptibility 1 locus.<sup>15</sup> Intrinsic and extrinsic environmental influences seem to play a pivotal role in the precipitation and/or the exacerbation of psoriasis in the juvenile population to a greater extent than in adults.<sup>10</sup> For instance, upper respiratory infections, emotional stress, skin injury, and drugs are factors that have been implicated with the manifestation or the aggravation of the disease. Streptococcal infections from group A  $\beta$ -hemolytic streptococcus (pharyngitis or perianal dermatitis) frequently trigger the appearance of guttate psoriasis in children, while stressful events induce new psoriatic lesions more commonly in juveniles than in adults, possibly due to adolescents' emotional immaturity.<sup>9–11</sup>

## Clinical characteristics and comorbidities

Juvenile psoriasis clinically exhibits both similar and different characteristics compared with adult psoriasis. Plaque-type psoriasis is the most common form of the disease.<sup>11</sup> However, the lesions are usually smaller, thinner, and less scaly than those seen in adults.<sup>12</sup> The scalp and face are the most affected areas, followed by the extensor surfaces of knees and elbows, the trunk, and the groin.<sup>5,9–13</sup> In a recent

epidemiological study by Tollefson et al, the extremities were the most frequently involved anatomic sites, followed by the scalp.<sup>4</sup> Guttate disease generally more often presents during childhood and adolescence than in adulthood.<sup>11,12</sup> It is characterized by small nummular scaly lesions located on the trunk, abdomen, and back. Prior to the onset of this condition in children, a preceding streptococcal pharyngitis or perianal infection has been documented in several studies.<sup>7,8,16</sup> Erythrodermic, pustular, and inverse psoriasis may also occur in adolescents, but less frequently.<sup>11,12</sup> Nail psoriasis can be presented either in the background of plaque psoriasis or psoriatic arthritis or as isolated nail disease.<sup>11</sup>

A recent study by Augustin et al suggests that juvenile psoriasis may be associated with significant comorbidity (hyperlipidemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis, and Crohn's disease), as is the case with adults. It is possible that aspects of the metabolic syndrome may develop independently of the patient age and psoriasis duration as an underlying inflammatory process.<sup>5</sup>

## Management of psoriasis in adolescence

### General considerations

The management of psoriasis in adolescence is an intriguing and complicated task. Standardized guidelines for the treatment of children and adolescents with psoriasis are lacking, although certain published psoriasis guidelines for adults address several issues that concern younger populations.<sup>17–19</sup> Given the paucity of officially approved therapies and the very limited evidence-based data from RCTs, physicians must rely on published experience from case reports from the field of dermatology as well as from the application of these drugs for other pediatric conditions coming from the disciplines of rheumatology, gastroenterology, and oncology.

There are several issues that must be considered before one opts for the most appropriate treatment for each case of juvenile psoriasis: patient age, clinical severity of the disease, the psychological burden of the condition in the quality of life of the adolescent, the presence of comorbidities such as psoriatic arthritis and others, and last but not least the patient's previous treatments and preferences.

The clinical severity of juvenile psoriasis is measured using the standard methods that are applied for adults also. The Psoriasis Area and Severity Index (PASI)- which evaluates lesions by their characteristics of erythema, induration and scaling as well as by the surface area involved - is the most commonly used parameter. Body surface area (BSA) which determines the area involved in relation to the whole body surface and physician's global assessment (PGA) which

is an overall evaluation of lesion severity are implemented too. At this point, it must be noted that in children and in a lesser extent in adolescents, the BSA-to-mass ratio is different from the adult population, as well as the relative proportion of the head and body.<sup>20</sup> Generally, with a PASI and/or a BSA score higher than 10, psoriasis is considered severe. However, in everyday practice, the calculation of these indexes is not routinely performed, and at the same time their utility in a psoriatic population with mild disease is controversial.

Psoriatic adolescents deal with a potentially disfiguring and lifelong disease that could permanently impair their psychological development.<sup>21</sup> Even relatively mild forms of the disease could have a major impact in the quality of life of children and adolescents. During school years, patients and their families may need social and psychological support along with appropriate education about the nature of the disease, in order to be compliant with the treatment modalities and to have realistic expectations.<sup>12</sup> It must be clarified that psoriasis does not have a permanent cure, and therefore the main goal of treatments is to establish disease control and prolonged periods between flares.<sup>12</sup> Most of the time, the quality of life of children and adolescents is measured with the Children's Dermatology Life Quality Index, which according to several studies is only moderately correlated with the PASI score, and for this reason it should be taken into consideration when deciding on a treatment approach.<sup>22</sup>

## Topical therapies

### Corticosteroids

Topical corticosteroids remain the first-line treatment agents for psoriasis among adolescents as well as among all other age groups.<sup>23</sup> The role of corticosteroids is based on their anti-inflammatory and antiproliferative properties, which ultimately reduce erythema, scaling, and pruritus.<sup>12,24</sup> They are a relatively popular treatment among patients, because they can be easily applied to the skin, do not possess any special odor or staining capacity, and the onset of action is fast. In some cases, a burning sensation at the site of application has been described.<sup>25</sup> Corticosteroids are divided into seven classes (I–VII), according to their potency. Class I includes the most potent topical corticosteroids, while class VII the weakest ones. The potent corticosteroids must be avoided in such anatomical sites as the face, genital, and flexural areas, where the skin is thinner. Possible topical adverse events, if these agents are used for a prolonged period of time include skin atrophy, striae, telangiectasias, acneiform eruption, and tachyphylaxis, while suppression of the hypothalamic–pituitary–adrenal axis has not been observed.<sup>24</sup> Tachyphylaxis is defined as the loss of efficacy with continued use of topical

steroids, and although it has not been described in any study yet (probably due to the short duration of the studies), it must be taken into account when prescribing these agents. Moreover, it remains controversial whether the loss of efficacy with time must be attributed to tachyphylaxis or if it reflects the loss of compliance and adherence that usually characterizes adolescent patients treated with topical regimens. Despite steroids' frequent use in everyday clinical practice, only one RCT has been published concerning the use of clobetasol 0.05% (class I) in a small number of children with psoriasis for a short period of time (2 weeks).<sup>25</sup> Topical corticosteroids are usually combined with other topical agents, such as keratolytics (salicylic acid), vitamin D analogs in free or fixed combinations, or they may be prescribed in conjunction with systemic treatment.

### Vitamin D analogs

The topical vitamin D analogs calcipotriene and calcitriol contribute to the treatment of psoriasis by their capacity to stimulate keratinocyte differentiation and to inhibit their proliferation.<sup>12</sup> According to a recent study from the US, calcipotriene has been the second-most prescribed medication for childhood psoriasis for almost 30 years (1979–2007).<sup>23</sup> Furthermore, a systematic review of all treatments for childhood plaque psoriasis recommends calcipotriene and calcitriol as effective and well-tolerated treatments (level of evidence A and B, respectively).<sup>26</sup> Indeed, although not officially approved for their use in juvenile psoriasis, their efficacy is documented and evidence-based.<sup>27–29</sup>

Application on the face, genitalia, and intertriginous areas could be problematic, with mild local irritant reactions and itching being the most common side effects. Systemic absorption of vitamin D has not been observed, but it is better to use these agents when less than 30% of the BSA is involved.<sup>12</sup> Finally, an expert European consensus for the treatment of juvenile psoriasis suggests that we use this agent intermittently and in combination with steroids.<sup>20</sup>

### Topical calcineurin inhibitors

Topical tacrolimus 0.03% and 0.1% (for children 2–15 years and  $\geq 15$  years, respectively) as well as pimecrolimus 1% inhibit the enzyme calcineurin, which in turn blockades the production and release of interleukin (IL)-2, a cytokine that is implicated in psoriasis pathogenesis.<sup>24</sup> These agents are officially approved for the intermittent treatment of atopic dermatitis, but not for the treatment of childhood psoriasis.<sup>23</sup> In everyday practice, they are used most of the time for the treatment of psoriasis in areas with a high risk of skin atrophy,

such as the face, genitalia, and flexures.<sup>12</sup> In two non-RCTs, tacrolimus 0.1% exhibited clearance of facial and flexural childhood psoriasis lesions in a timeframe of 2–30 days.<sup>30,31</sup> The only side effect was pruritus. Generally, it is advised to avoid combining calcineurin inhibitors with phototherapy or extreme sun exposure due to a possibly increased risk of ultraviolet (UV) light-related skin tumors.<sup>20</sup>

### Anthralin

Anthralin 1% or dithranol has both anti-inflammatory and antiproliferative properties.<sup>12</sup> Although it is considered a relatively safe treatment option with almost no systemic absorption, its use is limited, due to the staining of the skin and the local irritation it provokes. It is not recommended for facial, flexural, erythrodermic, or pustular psoriasis, and it must be applied strictly to localized lesions.<sup>11,12</sup> In two published non-RCTs describing dithranol use in psoriatic children, 47 of 58 showed total remission, while 35 of 42 marked improvement.<sup>32,33</sup> Several authors consider dithranol a first-line treatment of juvenile psoriasis, although this opinion is not universal.<sup>23</sup>

### Other topical agents

Coal-tar compounds have antiproliferative and antipruritic properties, and some authors consider them a good solution for such areas as the face and flexures.<sup>12</sup> However, due to their strong odor and staining capacity, their use is very limited nowadays.<sup>11,12</sup> The application of tar, especially in the context of the Goeckerman regimen, has caused some controversy because of its possible genotoxic risk.<sup>34</sup>

The retinoid tazarotene 0.05% is used relatively rarely due to its local irritating properties.<sup>23</sup> It has been described in cases of childhood nail psoriasis.<sup>35</sup> Salicylic acid is a keratolytic agent suitable for localized hyperkeratotic plaques.<sup>12</sup> It may be used in adolescents but not in children smaller than 6 years of age, due to increased risk of systemic absorption and intoxication.<sup>24</sup>

## Phototherapy

General indications for phototherapy in adolescence are the presence of disseminated guttate lesions or thin plaques, lesions refractory to combination topical therapy, and difficult-to-treat palmoplantar psoriasis.<sup>36</sup> Phototherapy includes three types of UV light: narrow-band (NB) UVB (311–313 nm), broadband UVB (290–320 nm), and UVA (320–400 nm). Phototherapy is characterized by two phases: the clearing (the dose is increased based on response and absence of adverse effects) and the maintenance phase (the

same dose as in the clearing phase, but less frequent visits).<sup>36</sup> The UV phototherapy is more suitable for patients with a Fitzpatrick type II–IV.<sup>20</sup> Phototherapy can be a time-consuming procedure for adolescents that attend school, and despite the fact that it can be effectively administered at home, many authors believe that it is better performed in specialized centers that possess personnel experienced in treating children and adolescents.<sup>36</sup> Moreover, when one is treating adolescents and young people in general with phototherapy, one should be aware of the cumulative dosing of UV treatments, which has been linked in some cases with the possible long-term risk of carcinogenesis.<sup>17</sup>

NB UVB is considered the most efficacious and safe type of phototherapy for children.<sup>12,24,36</sup> It has been proved to be effective for moderate-to-severe psoriasis in juveniles, irrespective of skin type.<sup>36,37</sup> Acute, short-term adverse events of NB UVB include erythema, burning, pruritus, pigmentation, and transient lesional blistering, while long-term effects may include premature photoaging and cutaneous carcinogenesis.<sup>36</sup> For the long-term potential risk of carcinogenesis, there are no exact rates in the literature.<sup>38</sup> It is advised that NB UVB should be combined with topical therapies (calcipotriene, tazarotene, anthralin) in order to enhance efficacy and decrease carcinogenic risk.<sup>12,24,36</sup>

UVA plus psoralen must be prescribed only to children older than 12 years.<sup>36</sup> Topical psoralens are preferred instead of oral, in order to avoid gastrointestinal side effects and wearing of sunglasses for 24 hours after the administration of the drug.<sup>12</sup> Long-term adverse events include premature aging, cutaneous malignancy, and cataracts, while short-term ones are nausea, vomiting, headache, keratitis, hepatotoxicity, and generalized photosensitivity.<sup>36</sup>

## Systemic agents

### Retinoids

Retinoids are vitamin A analogs that affect cellular metabolism, epidermal differentiation, and apoptosis.<sup>36</sup> Acitretin is the most commonly used retinoid in everyday clinical practice, although no RCT exists supporting its use in pediatric psoriasis.<sup>26</sup> Indications for retinoid use in juvenile psoriasis include severe plaque, pustular (palmoplantar or generalized), and erythrodermic psoriasis.<sup>24</sup> However, retinoids are very rarely prescribed in children <10 years of age.<sup>20</sup> Doses range between  $\leq 0.5$  to 1.0 mg/kg.<sup>11,12,36</sup> Acitretin acts synergistically when it is combined with topical agents and NB UVB.<sup>12,39</sup> Short-term mucocutaneous side effects (cheilitis, xerosis, epistaxis, hair thinning, skin fragility, ocular toxicities) are

dose-dependent and reversible when the dose is tapered off.<sup>40</sup> During treatment, it is prudent to monitor patients for elevated triglycerides and liver enzymes, although these abnormalities are also transient and reversible.<sup>20,36</sup> Acitretin, as with all retinoids, bears a high teratogenic risk, and thus when administered to adolescent girls of childbearing potential, it must be combined with oral contraceptive therapy as well as counseling to avoid pregnancy during treatment and 3 years after.<sup>12,36</sup> This serious limitation makes acitretin a very unattractive and unreasonable treatment option for teenage girls. In the rare instance that oral retinoids cannot be avoided in this setting, isotretinoin, a less lipophilic analog of vitamin A, could be used instead of acitretin. Long-term side effects, such as premature epiphyseal closure and bone hyperostosis, have been described in children receiving retinoids for other indications in high doses and for prolonged periods of time. Nevertheless, it is advisable to perform a radiologic evaluation of the long bones and spine once a year when adolescents are on retinoid therapy for over a year.<sup>36</sup>

### Methotrexate

Methotrexate is a folic acid analog that reversibly inhibits dihydrofolate reductase, thus interfering with deoxyribonucleic acid synthesis and repair and replication of T and B lymphocytes.<sup>41</sup> It has been used in the treatment of psoriasis since the 1950s.<sup>36</sup> According to a systematic review of the existing literature on the treatment of childhood psoriasis (1980–2008) by de Jager et al, methotrexate is the systemic treatment of choice for children with moderate-to-severe plaque psoriasis.<sup>26</sup> However, according to published case series and reports, as well as expert consensus, methotrexate can be used successfully for the treatment of recalcitrant plaque, erythrodermic and pustular psoriasis, or even psoriatic arthritis.<sup>42–45</sup> Doses of methotrexate for adolescents range between 0.2 and 0.7 mg/kg.<sup>36,41</sup> An initial dose of 1.25–5 mg/week should be administered, ideally at the beginning of treatment, with 1-week laboratory follow-up to monitor for toxicity.<sup>36,41</sup> If it is well tolerated, then methotrexate dosage can be increased until therapeutic control is achieved. The tapering of the dose to the minimum effective 2 or 3 months after disease stabilization is advised in order to minimize possible side effects. Also, folic acid supplementation in parallel with methotrexate seems to improve the tolerability of the drug and to reduce the risk of several side effects.<sup>20</sup> Some authors prescribe folic acid 2 days after every methotrexate dose, while others daily except on the day of methotrexate therapy.<sup>20</sup> Safety issues with methotrexate in children are basically addressed in the rheumatologic

literature. The most common side effects are nausea, lost appetite, vomiting, and diarrhea.<sup>36</sup> The division of the weekly dose into three doses given 12 hours apart seems to be helpful, as is intramuscular administration of the drug.<sup>36</sup> However, the most severe adverse events with methotrexate are bone marrow toxicity, pulmonary toxicity, and hepatotoxicity.<sup>36,42</sup> Pulmonary toxicity is extremely rare in children. Bone marrow toxicity is potentially life-threatening, and may occur early in the course of treatment (4–6 weeks). Hepatotoxicity and liver fibrosis are much rarer in children than in adults, possibly due to lower cumulative doses of the drug.<sup>36,42</sup> In the absence of specific monitoring guidelines for liver fibrosis in pediatric patients, expert opinion suggests that biopsy is not required unless there is clinical and/or laboratory evidence of significant abnormality or cumulative doses exceeding 1.5 g.<sup>20</sup> Medications such as trimethoprim–sulfamethoxazole and nonsteroidal anti-inflammatory drugs must be avoided during treatment with methotrexate.<sup>42</sup>

### Cyclosporine

Cyclosporine is an immunosuppressant agent that reversibly inhibits T lymphocytes and suppresses IL-2 and interferon- $\gamma$ .<sup>36,42</sup> Despite the fact that it is officially approved by the US Food and Drug Administration (FDA) for the treatment of severe plaque psoriasis in immunocompetent adults, this is not the case for pediatric psoriasis. However, cyclosporine administration to children  $\geq 6$  months of age is approved for transplantations.<sup>42</sup> In the literature, there is evidence in the form of case series and reports that support the use of cyclosporine in the treatment of recalcitrant plaque and pustular juvenile psoriasis at doses of 1.5–5 mg/kg/day for 6 weeks to 2 years.<sup>46–50</sup> In most instances, cyclosporine is considered an ideal drug for the control of unstable disease, because it has a rapid onset of action (clinical improvement even in 2 weeks). In severe cases, an initial dose of 5 mg/kg/day is frequently required. It must be noted that children have higher BSA-to-weight ratios and thus present different pharmacokinetics for cyclosporine.<sup>50</sup> In that sense, children and adolescents may need higher doses compared with adults. Once the disease is controlled and stable, the dose may be tapered gradually according to clinical response or to the presence of elevated serum creatinine and blood pressure. Rebounds or relapses after the tapering of the dose are occasionally seen. Cyclosporine can be combined with several topical or systemic agents, such as acitretin, in order to reduce the total dose and duration of the two combined agents.<sup>36,42</sup> The combination with NB UVB is usually avoided in everyday practice, due to the potential long-term risk of

developing nonmelanoma skin cancer.<sup>20</sup> The most significant side effects of cyclosporine in adults are nephrotoxicity and arterial hypertension, which are dose-dependent and reversible with modification of the dose or discontinuation of the drug.<sup>36,42</sup> These adverse events could also emerge in the pediatric population, and for this reason patients should be regularly monitored during treatment with blood tests and blood pressure measurement. Elevation of serum creatinine >30% must be followed by dose decrease or treatment cessation. Other adverse events include nausea, diarrhea, myalgias, headache, hypertrichosis, and gingival hyperplasia. The last two adverse events are extremely annoying among adolescents. The potential long-term risk of developing malignancies, nonmelanoma skin cancers, or lymphomas is of some concern for children, but this risk is minimal if the dose is  $\leq 5$  mg/kg and the total duration of treatment with cyclosporine  $\leq 5$  years.

## Antibiotics

The use of oral antibiotics in childhood psoriasis is controversial and not substantiated by controlled trials.<sup>51</sup> It is generally accepted that pharyngeal and perianal streptococcal infections may precipitate or exacerbate guttate psoriasis and/or other variants of the disease. Given that background, some dermatologists prescribe empiric antibiotics (penicillin V or erythromycin) at the first sign of pediatric psoriasis or during recurrences and flares of guttate psoriasis.<sup>11,12,20</sup> Tonsillectomy is recommended by some experts in patients with recalcitrant psoriasis and recurrent tonsillitis.<sup>51</sup>

## Biologics

Biologic agents are a relatively new category of drugs that has enriched our armamentarium for the treatment of psoriasis. These agents target specific portions of the immune system and the inflammatory cascade, and thus they are considered less immunosuppressive than previous conventional treatments. In that sense, they represent a promising therapeutic alternative for juvenile psoriasis too. Despite the fact that several RCTs are in progress or have already been completed in the field of childhood psoriasis and biologics, certain issues regarding long-term safety still need to be addressed.<sup>52–54</sup> It must be noted that the majority of evidence regarding long-term safety issues comes from the field of rheumatology (juvenile idiopathic arthritis and biologics) and gastroenterology (Crohn's disease). The biologic agents that have been used in the treatment of childhood and adolescent psoriasis belong in two categories: the tumor necrosis factor (TNF)- $\alpha$  inhibitors, which include etanercept, infliximab and

adalimumab and the antagonist of human IL-12/23, which is called ustekinumab. It must be noted at this point that all biologics have a considerable financial cost for the insurance covering the patient's treatment, and this is an issue that must be taken into account when one prescribes these drugs. In the absence of official guidelines for the laboratory monitoring of children on therapy with biologics for psoriasis, they should undergo the baseline screening along with the treatment monitoring that is applied to adult patients.<sup>55</sup> Baseline screening includes the Mantoux test or interferon- $\gamma$ -release assays for tuberculosis, a chest X-ray, immunization updates, tests for hepatitis B and C and human immunodeficiency virus, and hematology and biochemical examinations that also include liver-function tests. The basic laboratory examinations are repeated routinely every 2–3 months, along with clinical surveillance. Of course, these suggestions may be individualized when appropriate.

## Etanercept

Etanercept is a soluble TNF-receptor fusion protein that competitively inhibits the binding of endogenous TNF $\alpha$  to its receptor. It was approved by the European Medicines Agency (EMA) in 2009 for the treatment of children  $\geq 6$  years who are suffering from severe, chronic plaque psoriasis refractory to or intolerant of other systemic agents or phototherapy.<sup>56</sup> The FDA, however, has not yet approved etanercept for the treatment of moderate-to-severe plaque psoriasis in patients <18 years, although it has done so for the treatment of juvenile idiopathic arthritis (JIA) in patients  $\geq 2$  years.

The drug is administered subcutaneously, and in most cases its dosing regimen is 0.8 mg/kg to a maximum of 50 mg once weekly and 0.4 mg/kg twice weekly.<sup>52,57–60</sup> In the pediatric and adolescent population, etanercept, compared with the other biologic agents, possesses the majority of available efficacy and safety data derived from one RCT with an open-label extension and several case series and reports.<sup>52,57–60</sup> The best efficacy data comes from a Phase III, double-blind RCT that compared etanercept 0.8 mg/kg once weekly to placebo in 211 patients aged 4–16 years suffering from moderate-to-severe plaque psoriasis.<sup>52</sup> At week 12, 57% of etanercept-treated patients and 11% of the placebo group reached PASI 75, while at week 36, after 24 weeks of open-label etanercept, rates of PASI 75 were 68% and 65% for patients initially assigned to etanercept and placebo, respectively.<sup>52</sup> This rate (57% at week 12) is higher than the 12-week PASI 75 response reported for adult patients with psoriasis who were treated with 25 mg of etanercept twice weekly (response rates 30%–34%), but

is consistent with rates reported in trials involving adults who received 50 mg of etanercept twice weekly (response rates, 47% to 49%).<sup>52</sup> During the withdrawal period from week 36 to week 48, response was lost by 42% of patients assigned to placebo at the second randomization. Four adverse effects were observed, three of which were infections (two cases of gastroenteritis and one case of pneumonia).<sup>52</sup> Data at the ongoing 264-week open-label extension of this study showed continued efficacy, tolerability, and safety of etanercept in 140 patients.<sup>54</sup> No serious adverse events, such as deaths, cancers, opportunistic infections, tuberculosis, or demyelinating disorders, were reported.<sup>57</sup> In two large studies of JIA, one with a duration up to 8 years, the safety profile of etanercept was almost the same as in pediatric psoriasis, although conclusions based on different disease populations could be biased.<sup>61,62</sup> According to several case reports and expert opinion, etanercept has also a favorable therapeutic profile in the treatment of severe erythrodermic and pustular pediatric psoriasis.<sup>20,58–60,63</sup> It is interesting to note that 70% of participants in a European expert group consensus consider etanercept as first-line treatment of juvenile chronic plaque psoriasis due to its strong efficacy, excellent tolerability, and good safety profile.<sup>20</sup>

### Infliximab

Infliximab is a chimeric monoclonal antibody with strong activity against TNF $\alpha$ . Published evidence of infliximab use in pediatric psoriasis is limited in sporadic case reports.<sup>64–66</sup> Experience from its administration in the pediatric population is derived from the field of gastroenterology, because it has been an FDA-approved for the treatment of pediatric Crohn's disease (children  $\geq 6$  years) since 2006. It is administered intravenously at doses of 3.3–5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter.<sup>64–66</sup> It has a very rapid onset of action, ranging from hours to days. Based on experience gathered from adult psoriasis patients, infliximab is associated with a relatively higher risk of tuberculosis reactivation, infections, congestive heart failure, and infusion reactions compared with other TNF $\alpha$  inhibitors.<sup>36,55</sup> In rare cases, it has been reported that children or young adults who received infliximab along with 6-mercaptopurine or azathioprine therapy for Crohn's disease developed hepatosplenic T-cell lymphoma, which is a serious and potentially fatal form of lymphoma.<sup>67,68</sup> This fact augments the need for close monitoring of children or adults who are under treatment with infliximab. According to expert opinion, infliximab can be useful for cases of recalcitrant, unstable, generalized pustular or

erythrodermic psoriasis due to its rapid onset of action and its high efficacy.<sup>20,36,55</sup>

### Adalimumab

Adalimumab is a fully human monoclonal antibody against TNF $\alpha$ . It is not officially approved for pediatric plaque psoriasis by either the FDA or the EMA. There has been certain experience with the drug in pediatric populations since it was approved by the FDA for JIA treatment (2008), where it is administered subcutaneously at 24 mg/m<sup>2</sup> (max 40 mg) every 2 weeks. Regarding juvenile psoriasis, there are only two published case reports in which adalimumab was prescribed to two adolescent patients with recalcitrant pustular psoriasis at a dose of 40 mg subcutaneously every 2 weeks, after the failure of etanercept and of other conventional systemic agents.<sup>69,70</sup> In both cases, there was a favorable outcome.<sup>69,70</sup> The only long-term safety data we have from the administration of adalimumab to children and adolescents comes from JIA trials, which show its safety profile to be similar to the other anti-TNF $\alpha$  agents.<sup>71</sup> Infections and injection-site reactions were the commonest adverse events.<sup>71</sup> A multicenter double-blind RCT evaluating the efficacy and safety of adalimumab versus methotrexate in pediatric patients aged 4–17 years with chronic plaque psoriasis is ongoing.<sup>54</sup> It is possible that in the near future, adalimumab will be another attractive therapeutic alternative for adolescent psoriasis, although there are still several important issues to be determined.

### Ustekinumab

Ustekinumab is a human monoclonal antibody directed against IL-12 and IL-23. It was recently approved for the treatment of adult chronic plaque psoriasis, and even more recently for the treatment of psoriatic arthritis. It is administered subcutaneously, one injection (45 mg) at weeks 0 and 4 and then every 12 weeks.<sup>72</sup> There is a paucity of data regarding its efficacy and safety in children and adolescents, with only one published case reporting the successful administration of ustekinumab in a 14-year-old male patient with plaque psoriasis who failed to respond to conventional systemic agents as well as etanercept.<sup>73</sup> However, there is an ongoing Phase III multicenter RCT evaluating the efficacy and safety of ustekinumab in the treatment of adolescent patients with chronic plaque psoriasis (CADMUS [A Study of the Safety and Efficacy of Ustekinumab in Adolescent Patients with Psoriasis]).<sup>53</sup> Ustekinumab's rapid onset of action as well as its convenient dosing schedule make it a promising treatment option, although it is very early to

recommend its universal adoption for the treatment of adolescent psoriasis.

## Discussion

The majority of adolescents suffer from mild psoriasis, and thus they are treated basically with topical treatment modalities. In many cases, combination treatments with two or more topical agents are prescribed. In everyday practice, the compliance of the adolescents remains the most important drawback of this category of drugs.

Phototherapy is reserved for adolescents with mild-to-moderate plaque disease and/or guttate psoriasis. The major consideration with this kind of treatment is the cumulative dosing of UV light, which has been shown to be linked to long-term risks of carcinogenesis. Phototherapy can be administered quite safely at home, but it is better performed in specialized centers with personnel experienced in treating children and adolescents.

Systemic agents, such as methotrexate, cyclosporine, and acitretin, are administered to patients with moderate-to-severe psoriasis plaque psoriasis, pustular psoriasis, or erythrodermic psoriasis, following appropriate monitoring for each drug. Methotrexate is also beneficial in adolescents with the arthritic form of the disease. Cyclosporine is especially helpful in the control of unstable disease, as it has a relatively rapid onset of action. Acitretin must be avoided in teenage girls of childbearing potential, because it is a teratogenic drug.

Biologic agents target specific portions of the immune system, and they have emerged as a new therapeutic option for the treatment of moderate-to-severe psoriasis that has failed to respond to systemic agents. Etanercept is the only biologic agent officially approved by the EMA for the treatment of childhood plaque psoriasis. Until now, biologic agents have been considered second- or even third-line agents for recalcitrant juvenile psoriasis, mainly because of possible unknown long-term safety issues (the FDA has issued a black-box warning concerning TNF $\alpha$  inhibitors and an increased risk of lymphoma in the pediatric population). Moreover, one should take into account their considerable cost, which in many cases is difficult to cover with insurance.

Preventive measures, such as early detection and management of bacterial infections – especially of group A  $\beta$ -hemolytic streptococcus – with antibiotics, have a role in the treatment of specific forms of the disease, such as guttate psoriasis.

Last but not least, adolescents and their families need to be sociopsychologically supported in order to better

understand the nature of their chronic and possibly disfiguring disease and to contribute to its satisfactory management.

## Disclosure

The authors report no conflicts of interest in this work.

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