

# Management Strategies for Pediatric Moderate-to-Severe Plaque Psoriasis: Spotlight on Biologics

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**Abstract:** Although psoriasis onset has been reported at any ages, in up to one-third of cases, it begins during childhood, with an estimated prevalence of about 2% in pediatric population. The management of moderate-to-severe forms of childhood psoriasis may represent a challenge for dermatologists, especially for parents' concerns about the need of systemic treatments. However, a prompt safe and effective treatment is mandatory in these patients, due to the significant impact that psoriasis may have on their quality of life, with well-known consequences on psychological health of both patients and caregivers. Due to the relatively frequent parents' refusal of systemic treatments, probably due to the fear of eventual adverse events, difficulties of oral or injective route, the management of moderate-to-severe forms still represents a challenge. Herein, we report a narrative review, aiming to resume the systemic treatments for pediatric psoriasis, focusing on the use of biologics and small molecules in the pediatric ages. The most widely used therapeutic strategies today for the pediatric population with moderate-severe psoriasis are traditional systemic therapies, while more innovative drugs such as biologics and small molecules now represent a somewhat unexplored but certainly promising field for unresponsive patients.

**Keywords:** psoriasis, biologics, childhood, pediatric, small molecules, treatment

## Introduction

Psoriasis is a chronic inflammatory disease, which may have a significant impact on patients' quality of life.<sup>1</sup> Although psoriasis onset has been reported at any ages, in up to one-third of cases, it begins during childhood, with an estimated prevalence of about 2% in pediatric population.<sup>2,3</sup> Pediatric psoriasis can be associated with several comorbidities including psoriatic arthritis (PsA), obesity, dyslipidemia, hypertension, insulin-resistant diabetes, and inflammatory bowel disease. For this reason, proper therapeutic management is essential to prevent pediatric patients with psoriasis from being adults with joint, metabolic, and cardiovascular comorbidities.<sup>1</sup> Psoriasis of the pediatric age may present with the same clinical manifestations; however, specific, and different morphology and distributions have been described.<sup>4</sup> As for adults, the plaque type represents the most frequent form, being scalp psoriasis the most described.<sup>5</sup> The management of moderate-to-severe forms of childhood psoriasis may represent a challenge for dermatologists, especially for parents' concerns about the need of systemic treatments. However, a prompt safe and effective treatment is mandatory in these patients, due to the significant impact that psoriasis may have on their quality of life, with well-known consequences on the psychological health of both patients and caregivers.<sup>6</sup> Due to the relatively frequent parents' refusal of systemic treatments, probably due to the fear of eventual adverse events, difficulties of oral or injective route (for example, due to difficulties in pills swallowing and needle-phobia), the management of moderate-to-severe forms still represents a challenge.

Moreover, studies reporting the efficacy and safety of systemic treatments of pediatric psoriatic patients are still poor, with most of the available clinical trials including young adults. Hence, most of the available literature data come from case reports or series, expert opinions and guidelines for the management of adult psoriatic patients.<sup>7,8</sup> Regarding available treatments, conventional systemic drugs, including cyclosporine, acitretin, and methotrexate, are frequently

used in moderate-to-severe forms, even if not labelled for pediatric ages. Particularly, most of the available safety data come from the use of the same drugs for other indications, such as the use of cyclosporin after organ transplantation or the use of methotrexate in rheumatoid arthritis.<sup>9,10</sup> The introduction of biologics and small molecules represents the greatest innovation in the management of patients with moderate and severe psoriasis. These therapies are widely used in the adult population, while their use in the pediatric population is still limited. Indeed, to date, only few agents have been approved for the treatment of moderate-to-severe plaque psoriasis of childhood, while data about efficacy and safety of newer classes come from case reports and real-life studies.<sup>11,12</sup> Herein, we report a narrative review, aiming to resume the systemic treatments for pediatric psoriasis, focusing on the use of biologics and small molecules in the pediatric ages.

## Traditional Systemic Therapy

### Phototherapy

Phototherapy represents a well-known treatment for the management of psoriasis, which is still effective and widely used. It is considered among the first-line therapies. The rationale behind this treatment is the evidence of clinical improvement of psoriatic lesions during the summer months related to sun exposure. The mechanism of action of phototherapy is based on ultraviolet (UV) rays, both UV-A (315–400nm) and UV-B (280–315nm) types, which explicate an immunosuppressive effect on the site of application through induction of apoptosis of T lymphocytes inside psoriatic skin lesions, direct action on Langerhans dendritic cells, downregulation of pro-inflammatory cytokines released by keratinocytes, and inhibition of keratinocyte hyperproliferation and angiogenesis, probably through damage of cell membranes and nucleic acids of these cells.<sup>13,14</sup> Phototherapy has comparable efficacy and safety to other traditional systemic therapies. In addition, it can be combined with topical or systemic drugs, particularly retinoids, which can reduce the radiation dose and increase efficacy. The recommended dosage for psoriasis therapy is 2–3 sessions weekly for several months.<sup>13–15</sup> In the pediatric population, there are several clinical trials showing the benefit of nb-UVB (wavelength of 311–313 nm) phototherapy practiced twice a week at increasing dosages for patients with guttate and plaque psoriasis. Reported data show significant clinical improvements in up to 96% of patients, reaching a complete skin clearance in about 50%, a percentage that increases if topical emollients are used in combination.<sup>1,16</sup> PUVA photochemotherapy could likewise be effective for the treatment of pediatric psoriasis, remembering, however, that both topical and systemic psoralen cannot be used before the age of 12 years and as of today there are only limited supporting evidence showing efficacy and safety in the pediatric population.<sup>1</sup> The commonly accepted idea for phototherapy in pediatric patients is that nb-UVB phototherapy is safer, more easily managed, and equally effective to PUVA photochemotherapy. There are several contraindications to phototherapy in pediatric patients with psoriasis: i) the inability to use psoralen in patients younger than 12 years old; ii) it is contraindicated in patients with generalized erythroderma or cutaneous cancer syndromes iii) it is not recommended in patients with photo-dermatosis specifically if it is given with the same wavelengths responsible for the pathology. Moreover, given the increased risk of cutaneous carcinogenesis, it should be used with extreme caution and close dermatologic follow-up in pediatric patients with numerous atypical nevi.<sup>1</sup> Furthermore, one of the main limitations in the use of phototherapy, shared with adult patients, is represented by the logistic difficulties that patients may have for long-term treatments, resulting in the reduction of patients' compliance and, hence, reduced clinical improvements.

### Methotrexate

Methotrexate is the most used conventional systemic drug for moderate to severe<sup>17</sup> pediatric psoriasis because of several factors, including the relatively low cost, good and well-proven efficacy, and long-term safety. Methotrexate is administered weekly, orally or by subcutaneous injection, and is effective in all subtypes of psoriasis.<sup>1</sup> It is an antimetabolite analogue of folic acid, the most relevant mechanism of which is the inhibition of dihydrofolate reductase (DHFR) activity, resulting in the inhibition of purine synthesis and thus of DNA and RNA nucleic acids. This effect is mainly manifested on cells with high proliferation capacity including lymphoid cells and epidermal cells, thus explaining the anti-proliferative and immunosuppressive effects of MTX.<sup>13,14</sup> It can be used as monotherapy or in combination; particularly it may be combined with biologics, providing increased prevention for anti-drug antibody formation that

would force the switch of the biologic drug, and improving biologic efficacy in case of partial responses on both psoriasis and PsA. Indeed, although it is not a fast-acting drug, it has significant long-term efficacy not only for skin lesions but also for PsA, which makes it particularly useful in the long-term therapeutic management of pediatric patients with PsA.<sup>1,18</sup> The suggested dose in patients <13 years of age is within an initial range of 0.2–0.7mg/kg/week up to maximum dose of 25mg/week to be reached by gradual increases while in patients older than 13 years of age the dosage is similar to the adult population following the same pattern of gradual increase in dosage up to a maximum of 25mg/week. As in adults, folic acid supplementation is essential during treatment with MTX in the pediatric population; this allows for a considerable reduction of gastrointestinal, hematological, and hepatic adverse effects.<sup>1,17</sup> The best administration, because of the lower gastro-toxicity and greater bioavailability, is subcutaneous injection; however, oral route may be sometimes preferred by patients. There are several clinical trials showing that MTX, although not a fast-acting drug, is very effective treatment for different types of psoriasis and on PsA; specifically, many patients show clinical benefit as early as 5–12 weeks, but at least another 3–4 months of continuous therapy is needed to achieve clearance. There are no univocal opinions on the length of therapy, conventionally accepted is a treatment period in which clinical clearance is maintained for at least 2–3 months.<sup>1,19,20</sup> Kaur et al retrospectively reviewed 24 pediatric patients with severe refractory psoriasis treated with methotrexate. Seventeen had plaque disease, 3 were erythrodermic, 3 had pustular disease, and 1 had palmoplantar psoriasis. The dosage of methotrexate ranged from 7.5 to 20 mg per week. The results were remarkable, 22 patients (91.7%) achieved PASI 75, thus a 75% improvement of skin lesions with significant improvement in quality of life, over a treatment period of 1.5 months to 3 years.<sup>21</sup> Methotrexate is not a drug free of side effects, but its wide use in both adult and pediatric populations has allowed for improved management of the drug by ensuring a lower occurrence of side effects than in the past. Elevation of transaminases is one of the most common adverse drug reactions that normally occurs a few days following drug administration. Other common adverse drug reactions are Nausea, vomiting, diarrhea and anorexia, and hair loss. More serious side effects are rare in the pediatric population including hepatotoxicity, pulmonary toxicity and bone marrow suppression. Hepatic fibrosis is a none reported in pediatric population using methotrexate. Bone marrow suppression occur after 4–6 weeks of treatment, but it is considerably reduced in patients who take regular folic acid supplement therapy. Immunosuppression is an adverse drug reaction linked to the action of the methotrexate and it is dose related. For this reason, pediatric patients treated with methotrexate must be monitored regularly by assessing the complete blood count, transaminases, and creatinine.<sup>1,22</sup> To date, methotrexate represents a drug with numerous evidences regarding its efficacy and safety, widely used in the pediatric population. Despite being relatively slow in therapeutic onset, it is effective against different forms of psoriasis. The side effects of the drug impose adequate monitoring and precautions (folic acid substitution therapy) but with proper management of dosage and laboratory parameters it represents a valuable therapeutic alternative for pediatric patients with moderate-to-severe psoriasis.

## Cyclosporine

Cyclosporine is an immunosuppressive drug that acts by binding to cyclophilin A, which is a receptor located within T lymphocytes, leading to the inhibition of calcineurin, and resulting in the block of the transcription of several pro-inflammatory cytokines, among which the most important are IL-2, IL-3 and INF gamma.<sup>13</sup> Advantages of cyclosporine treatment include good efficacy against different forms of psoriasis (plaque, pustular and erythrodermic), rapidity of action and good tolerability, at least as far as it concerns the pediatric population.<sup>1,23</sup> The recommended dosage for cyclosporine is in the range of 2–5mg/kg/day divided into two administrations. Any progressive increase in dosage should be considered at least after the first 1 to 2 weeks of treatment, which is important for pediatric patients because the child has minimal absorption and greater clearance than the adult population, although normally cyclosporine is used for a short period of time to achieve remission and cannot be considered long-term therapy. The length of treatment is between 3 and 6 months considering that the dosage should be gradually decreased before stopping the treatment, more specifically, it is considered good therapeutic management to gradually decrease the dosage after 2 months of disease clearance and by considering the use of another drug as a long-term therapy since cyclosporine has significant toxicity if used for a too long period. Several clinical studies show that the efficacy of cyclosporine in the treatment of childhood psoriasis in its plaque, pustular and erythrodermic variants is remarkable,

about 70–80% of patients treated for several months show clinical improvement of 75% of skin lesions and thus a PASI75.<sup>24–26</sup> The major limitation of cyclosporine is its toxicity in the case of long-term therapy, which is manifested by renal toxicity, hypertension, increased cardiovascular risk, hypertrichosis, headaches, paresthesia, arthralgias, gingival hyperplasia, and finally, an increased risk of lymphoproliferative malignancy has been observed in the pediatric population treated with cyclosporine. For this reason, cyclosporine can be used for up to 6–12 months, and throughout the treatment period, monitoring of complete blood count, creatinine, urea, cholesterol, triglycerides, serum electrolytes and blood pressure is required.<sup>1</sup> Cyclosporine represents an excellent bridge therapy to achieve adequate control of various forms of psoriasis that do not respond to other therapies, and a proper treatment schedule allows PASI75 or PASI100 to be achieved in a high percentage of treated patients with good safety and tolerability. Obviously, the limitation of this drug is the short length of treatment which will necessarily have to be followed by a different therapeutic strategy.

## Acitretin

Acitretin is a systemic retinoid derivative of vitamin A. Its action in the treatment of psoriasis is through regulation of keratinocyte maturation and turnover, reduction of inflammation, and inhibition of neutrophil chemotaxis. Acitretin resulted more effective for certain subtypes of psoriasis in which the role of neutrophils is most involved including psoriasis guttata, pustular psoriasis and palmoplantar psoriasis.<sup>13</sup> Another advantage of acitretin is that it represents a non-immunosuppressive drug; consequently, it can be used effectively in patients at major risk of infection including transplant patients, infants older than 6 weeks, and HIV-positive children.<sup>1</sup> Another advantage of acitretin is that it can be combined with different therapies including phototherapy, cyclosporine, methotrexate, biologic, and topical therapy. The recommended dosage in the pediatric patient is 0.1–1mg/kg/day with clinical benefit being observed, for plaque psoriasis, after 2–3 months of continuous therapy, while, for pustular psoriasis, improvement of lesions may be observed as early as 3 weeks of therapy.<sup>1,27</sup> Numerous studies highlight the efficacy of acitretin in pediatric patients with psoriasis, particularly when combined with other therapies.<sup>28–31</sup> Approximately 80% of patients with pustular psoriasis achieve skin clearance on monotherapy, which reaches 100% when in combination with other systemic therapies such as cyclosporine or methotrexate.<sup>28</sup> In pediatric forms of palmoplantar psoriasis treated with acitretin, clearance of skin lesions is observed in approximately 90% of patients.<sup>29</sup> Several studies reported that the association of acitretin and nb-UVB phototherapy is particularly effective in forms of pustular psoriasis, ensuring high rates of skin clearance.<sup>30,31</sup> Side effects of acitretin may include mucocutaneous reactions, hyperlipidemia, teratogenicity, and bone changes (epiphyseal closure, hyperostosis, calcification, decreased bone mineral density). The side effects described are most frequently associated with prolonged and high-dose therapies. During acitretin therapy, monitoring of liver function and serum lipids is necessary, while pregnancy prevention is required for women in childbearing age.<sup>1,32</sup>

## Dimethyl fumarate

Dimethyl fumarate (DMF) is the methyl ester of fumaric acid that acts by reducing the action of T lymphocytes, specifically by up-regulating cytokines that promote switching to T-helper 2 cells over T-helper 1 cells, thus acting as immunomodulators.<sup>13</sup> The use of DMF is limited by the occurrence of several side effects, such as diarrhea, flushing, leukopenia, and lymphopenia with an incidence of about 50%; renal and hepatic toxicities are relatively less common, which, however, pose a contraindication to the use of DMF for patients with hepatic and renal comorbidities, in addition to gastrointestinal ones.<sup>1,33</sup> There are few studies regarding its use in the pediatric population with psoriasis.<sup>34</sup> A retrospective multicenter study reports that of 390 pediatric psoriasis patients treated with dimethyl fumarate for a minimum of 3 months, 68% developed common side effects, such as diarrhea, headache, and flushing, which compromised treatment compliance. Ten percent percent of patients interrupted therapy due to the onset of serious side effects, such as pericarditis and bone marrow suppression.<sup>34</sup>

## Biologics

The numerous knowledge acquired over the years concerning the pathogenesis of psoriasis and thus of the immune process at the origin of cutaneous and systemic manifestations have led to the development of target therapies directed against key cytokines, thus enabling targeted therapy. Biologics represent to date a revolution in the treatment of psoriasis in terms of both efficacy and safety. Biologics are target immunomodulators that inhibit a specific cell signaling pathway, lymphocyte recruitment, cell apoptosis, pro-inflammatory cytokine formation, and lymphoid cell development. To date, only few biologic drugs are approved to date for the therapeutic management of severe moderate psoriasis in the pediatric population; specifically, the FDA and EMA approved biologics are as follows: Etanercept (anti-TNF) starting from the age of 4 years, Ustekinumab (anti-IL12 and IL23) starting from the age of 6 years, and Adalimumab (anti-TNF) starting at age 4 years, Secukinumab from the age of 6 years (anti-IL17) and Ixekizumab from the age of 6 years (anti-IL17). Although only 5 drugs are approved to date, data on the high safety and efficacy of biologics have led to off-label use of these drugs. Data in the literature show the efficacy of biologics for all the different forms of psoriasis, including for forms less responsive to traditional therapies (palmoplantar, pustular psoriasis and erythrodermic psoriasis) and psoriasis involving difficult sites while ensuring efficacy in the prevention and therapy of PsA, which we recall is the most frequent psoriasis-related comorbidity of pediatric age.<sup>1</sup>

## Anti-TNF

### Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that acts by binding soluble and transmembrane TNF $\alpha$ , preventing its action. The first dose of this drug, injected subcutaneously, is 80 mg, followed by a second dose of 40 mg one week apart, then 40mg every two weeks. Adalimumab received the EMA and FDA approval for the management of moderate-to-severe forms of childhood psoriasis, showing promising efficacy and safety profiles.<sup>35–37</sup> The efficacy of adalimumab stands at 75% in patients, achieving PASI75 at week 16, compared with 7% in placebo controls.<sup>35</sup> Interestingly, adalimumab showed even a long-term efficacy, with PASI75 maintained in up to 83% of patients after 100 weeks of follow-up and up to 76% after 160 weeks.<sup>35,36</sup> Adalimumab is considered one of the first-line biologic agents in the treatment of moderate-to-severe psoriasis. The most commonly reported adverse events include: injection site reactions, 14% of patients, and mild infections, especially of the upper respiratory tract. Rarely reported AEs include leukopenia, thrombocytopenia, and autoantibody formation. Very rare is the occurrence of malignancies, of which the most frequent are lymphomas.<sup>33,34</sup> Several clinical trials report that the efficacy and safety of adalimumab in pediatric patients is comparable to adult patients. Two clinical trials evaluated the efficacy and safety of adalimumab in pediatric ages, comparing it to MTX.

A sample of 114 pediatric patients with severe plaque psoriasis was randomized into 3 groups, treated with adalimumab 0.4mg/kg/day, adalimumab 0.8mg/kg/day, and MTX 0.1–0.4mg/kg/week, respectively. Moreover, 108 patients received a long-term extension treatment and the majority received adalimumab. Adalimumab treated patients reported the highest QOL score at weeks 52. The most frequently reported AEs during treatment were nasopharyngitis and headache, reported in more than 20% of patients, while injection site reaction was observed in only 3.7%. Particularly, at week 52, side effects were reported in 77% of patients treated with Adalimumab 0.8mg/kg/day, 76% of patients treated with Adalimumab 0.4mg/kg/day, and 76% of patients treated with MTX; however, from the results we can state that more serious adverse reactions occurred, with greater frequency, in the group of patients treated with MTX, as they were observed in 5.4% of patients treated with MTX versus only 2.4% of patients treated with Adalimumab. This trial highlighted the safety of adalimumab, regardless of the dosage, and it is not inferior to MTX; moreover, the safety data are similar to those observed in the adult population.<sup>37–39</sup> Another clinical trial compared the efficacy and safety of adalimumab versus MTX and placebo. Particularly, a total of 271 patients were included in the study and randomized to receive Adalimumab (108 patients), Methotrexate (110 patients) or placebo (53 patients). At week 16, approximately 80% of patients treated with adalimumab achieved PASI75 versus 35.5% of the MTX-treated group and only 18.9% of placebo-treated patients. At the last follow-up practiced, the data confirmed the clinical response at week 16 (79.6% ADA group, 36.4 MTX group and 18.9% in placebo group), and this evidence that Adalimumab has a fast drug action



and can maintain the clinical response achieved over time. Safety data showed the occurrence of minor side effects including non-serious infections, itching, headache, and nausea.<sup>37,40</sup>

## Etanercept

Etanercept is a recombinant fusion protein formed by the TNF $\alpha$  receptor conjugated to the Fc portion of a human IgG1. It acts by blocking the interaction of TNF $\alpha$  with its surface receptor thereby implementing its immunomodulatory action. It is administered subcutaneously at a dosage of 50 mg twice a week for the first 12 weeks of treatment, and then switches to a 50 mg once-weekly regimen. One advantage is that, unlike other TNF, Etanercept does not induce the formation of neutralizing antibodies, which ensures persistence of clinical response over the long term. Etanercept's efficacy and safety in the management of pediatric psoriasis was evaluated by a double-blind trial compared to placebo, administered in 211 pediatric patients with moderate-to-severe psoriasis given 0.8mg/kg/week, with a max dose of 50mg/week for 12 weeks.<sup>41</sup> About 57% of patients treated with Etanercept reached PASI75 response, versus 11% of those receiving placebo. The study demonstrated an improved CDLQI in 52.3% after 12 weeks of therapy, showing a significant improvement in quality of life.<sup>42</sup> The safety of Etanercept has been evaluated in different clinical trials in pediatric patients demonstrating great data. The long-term safety of etanercept was studied in 181 pediatric patients showing that at 96 weeks only 8% of patients had side effects, while at 264 weeks of treatment 89% of patients had at least one side effect, of which 8 had serious adverse reactions, although none of these were proven to be related to the drug itself.<sup>43,44</sup> The most frequent side effects are infections and injection site reactions; more rarely, heart failure and demyelinating diseases have been found, so the use of this drug in psoriatic patients with multiple sclerosis is not recommended.<sup>14,33,45</sup> Hence, etanercept should be considered as a safe and effective treatment option in pediatric patients suffering from moderate-to-severe forms of plaque psoriasis.

## Infliximab

Infliximab is a chimeric monoclonal antibody consisting of a constant region of human IgG1 and a murine variable region that binds soluble and transmembrane TNF $\alpha$ , preventing its action. Infliximab is indicated in patients with moderate-severe psoriasis unresponsive to conventional topical and systemic therapies and for psoriatic arthritis. Advantages of infliximab include a high speed of action, superior to other anti-TNF, with onset of action occurring after 3.5 weeks.<sup>46</sup> Efficacy trials of infliximab have found PASI75 to be achieved in 80% after ten weeks of continuous therapy.<sup>35,46,47</sup> The only disadvantage of infliximab is the mode of administration, ie, intravenous, which is unwieldy as it causes infusion reactions in 18% of patients, the primary cause of lower compliance, manifesting as flushing, headache, hypertension, itching, allergic reactions, and even anaphylactic shock.<sup>33,35,46</sup> Other adverse events include infections and the occurrence of ANA (50% of patient cases), with the possibility of lupus-like symptoms, especially skin symptoms.<sup>33,46</sup> Rarely, heart failure and demyelinating diseases have been found, so the use of this drug in psoriatic patients with multiple sclerosis is not recommended.<sup>14,33,45</sup> There are currently no studies and clinical trials related to the safety and efficacy of Infliximab in the therapeutic management of pediatric psoriasis.

## Certolizumab

Certolizumab is a monoclonal antibody with a monovalent Fab fragment of a humanized antibody containing a specific antigenic site that binds TNF, inhibiting its action. The Fc fragment is conjugated to two polyethylene glycol (PEG) molecules for the purpose of increasing the half-life of the drug itself.<sup>48,49</sup> Certolizumab is approved for moderate-severe psoriasis unresponsive to topical and systemic therapies and for psoriatic arthritis. Administration is subcutaneous with an induction dose of 400mg at weeks 0, 2, 4 followed by a 200mg dose every 2 weeks. Among the advantages of Certolizumab, we can include that the latter is the only biologic indicated in patients with moderate-severe psoriasis who are pregnant or breastfeeding as its composition prevents its passage through the placenta and into breast milk.<sup>48,50,51</sup> Evidence concerning efficacy shows that after about 16 weeks, PASI75 is observed in about 80% of treated patients. Side effects are roughly like other anti-TNF biologics with a higher incidence of upper respiratory tract infections.<sup>33,52</sup> There are currently no studies and clinical trials related to the safety and efficacy of Certolizumab in the therapeutic management of pediatric psoriasis.

## Anti IL-12/23

### Ustekinumab

Ustekinumab is a monoclonal antibody specifically binding the p40 subunit of IL-12 and IL-23, inhibiting the action of these interleukins, and resulting in the reduction of the inflammatory process underlying psoriasis.<sup>35,48</sup> Ustekinumab is approved for the management of adult, adolescent and pediatric patients (from 6 years old) with psoriasis. Moreover, it is also approved for the treatment of PsA, which is the leading comorbidity, in terms of incidence, of pediatric psoriatic patients. In addition, compared with anti-TNF, ustekinumab has a faster rate of action and is characterized by significantly greater safety.<sup>53</sup> In trials, it has been shown not to differ from patients who received placebo in the incidence of malignancies and infections.<sup>35,48,54</sup> Another advantage is subcutaneous administration, ensuring better patient compliance. The dosage is variable based on patient weight, for adults. Particularly, if body weight is less than 100 kg, the dose is 45 mg, while if it is more or equal to 100 kg, the dose increases to 90 mg to be taken at weeks 0 and 4, then every 12 weeks, while in pediatric patients, if body weight is less than 60 kg the dose is 0.75 mg/kg, while for body weight over 60 kg the dosage is the same as practiced in adults.<sup>48</sup> Clinical trials on the efficacy of Ustekinumab show that at week 12 about 66% of patients achieve PASI75 regardless of dose compared with about 3% observed for the group of patients who received placebo. Efficacy improves considerably at week 24 where PASI75 is achieved for 76.1% of patients given at the 45mg dosage and 85% of patients given at the 90mg dosage.<sup>54</sup> Efficacy and safety in pediatric patients reflect the data obtained in adult patients. The randomized trial CADMUS showed interesting data about the efficacy of ustekinumab in patients aged 12–17 years. Particularly, a total of 110 patients were divided into 3 groups: the first group was treated with ustekinumab full dose, the second group with half-dose, and the third group with placebo. The study showed, at week 12, PASI75 achievement in 80.6% of the first group, 78.4% of patients in the second group, and only 10.8% in the group that received placebo, while PASI90 was achieved in 61.1%, 54.1%, and 5.4%, respectively. Safety data showed a non-significant difference between the groups about the incidence of side effects proved to be greater if not equally in patients taking placebo than ustekinumab, with an incidence of at least one side effect, at week 12, of about 50%. Beyond week 60, in about 81% of patients, at least one side effect was reported.<sup>55</sup> A recent trial evaluated the efficacy and safety of ustekinumab in a sample of 44 patients aged 6–12 years. At week 12, 77% of patients achieved PASI75 and 64% achieved PASI90. This study, although it has a small reference population, confirms the efficacy and safety of the data demonstrated in the CADMUS adult trial.<sup>56</sup>

## Anti-IL17

Another class of biologics that represent an exceptional therapeutic option for pediatric patients with moderate-to-severe psoriasis unresponsive to traditional therapies is anti-IL-17, which inhibits this pro-inflammatory cytokine implicated in the inflammatory process underlying psoriasis. The greatest advantage of these drugs is that they are, among biologics, the fastest in inducing regression of the disease.<sup>35,57</sup> Another advantage to be counted is that anti-IL17 are safer drugs in patients with viral hepatitis and latent tuberculosis, as they have lower reactivation rates. In contrast, disadvantages of these drugs include exacerbation of IBD, so they are contraindicated for psoriasis in patients with inflammatory bowel disease.<sup>33,58</sup> Candida skin and mucocutaneous infections are another side effect of anti-IL17 with a higher incidence in patients treated with brodalumab and Ixekizumab.<sup>33,59</sup> Finally, a side effect that is rare but evidenced more frequently in patients treated with Ixekizumab is neutropenia, which is an adverse drug reaction that forces interruption of therapy.<sup>33</sup>

## Secukinumab

Secukinumab is a fully human IgG1 directed against IL-17 inhibiting its action and consequently the inflammatory process triggered by it, to date it is indicated as a 1st-line biologic for the therapy of moderate-severe psoriasis unresponsive to traditional therapies and for patients with psoriatic arthritis. Recommended dose includes subcutaneous administration of 300 mg at weeks 0, 1, 2, 3 and 4, then 300mg every four weeks, with the opportunity to half the dose in cases of minimal psoriasis severity or low body weight.<sup>48</sup> It represents in the modern panorama of biologics one of the most effective drugs with high safety. Another important advantage is the efficacy of Secukinumab in treating psoriasis in difficult-to-treat areas such as scalp and for palmoplantar psoriasis.<sup>48,57</sup> The only disadvantage is the contraindication of

treating for IBD patients, as for all other anti-IL17.<sup>33,58</sup> Several clinical trials showing achievement of PASI75 after 12 weeks in about 79% of patients versus the group taking placebo in which only 4.5% of patients achieved this result.<sup>57</sup> A comparative study highlights the superiority in terms of efficacy of Secukinumab versus Ustekinumab. At week 16 of therapy PASI90 is achieved in 79% of patients treated with Secukinumab versus 57.6% of patients treated with Ustekinumab.<sup>35,57</sup> Safety data are relevant because the incidence of side effects is rare and most ADRs are infections, specifically upper respiratory tract infections, and these infections are rarely responsible for discontinuation of therapy.<sup>33,35,48,57</sup> For the treatment of pediatric patients with severe plaque psoriasis, the efficacy and safety data do not differ from adults. A trial of patients with severe plaque psoriasis aged 6–18 years were randomized into 4 groups: group receiving low-dose Secukinumab (75mg for patients with body weight <50kg or 150mg in patients with body weight >50kg), group receiving high-dose Secukinumab (75mg for patients with body weight <25kg, 150mg for patients with body weight between 25–50kg or 300mg for patients with body weight >50kg), group receiving Etanercept 0.8mg/kg with maximum dose of 50mg and finally Placebo group. The efficacy of Secukinumab in terms of clinical benefit of lesions became evident as early as week 3–4 of treatment. The results obtained at week 12 were maintained for a long time until 52 weeks for the first group and until week 104 for the second group. At week 52, PASI75 was achieved in 87.5% of both groups taking Secukinumab versus 68.3% in patients taking Etanercept, PASI 90 was achieved in 75% of the first group and 80% of the second group taking Secukinumab versus 51.2% of the third group treated with Etanercept, and finally PASI100 achieved in 40% of the first group and 47.5% of patients in the second group versus 22% of patients treated with Etanercept. Comparable results were shown regarding the IGA score, IGA 0/1 was achieved in 72.5% of the first group, 75% of the second group and only 56.1% of the third group at week 52 of treatment.<sup>60,61</sup> We can conclude that both low-dose and high-dose Secukinumab is superior in terms of efficacy to both Etanercept and Placebo, and that high-dose has a more rapid onset of action and better results in terms of PASI and IGA in the long term. To demonstrate the greater efficacy of high-dose administration, a clinical trial randomized pediatric patients with moderate-severe psoriasis aged 6–18 years into a group given low-dose secukinumab (75mg for patients with body weight <50kg or 150mg in patients with body weight >50kg) and a group given high-dose secukinumab (75mg for patients with body weight <25kg, 150mg for patients with body weight between 25–50kg or 300mg for patients with body weight >50kg). At week 24, PASI75 and IGA 0/1 were achieved in 95.2% and 88.1% of patients in the first group versus 90.5% and 83.3% of patients in the second group, respectively. Significantly, PASI90/100 achievement at week 52 occurred in 76.2% and 52.4% of patients in the first group versus 83.3% and 69% of patients in the second group, respectively, demonstrating significantly higher efficacy in patients treated with a higher dosage.<sup>62,63</sup> In contrast, a Phase III trial highlighted the safety and tolerability of low- and high-dose secukinumab versus etanercept in a population of 198 pediatric patients with severe plaque psoriasis. The data reported that 74.5% of patients treated with low-dose secukinumab had at least one side effect vs 74% of patients treated with high-dose secukinumab vs 82.9% of patients treated with etanercept. Of these adverse reactions, most were infections, especially upper respiratory tract infections, and only 3% of Secukinumab-treated patients and 2% of etanercept-treated patients were forced to discontinue therapy due to adverse effects.<sup>64</sup> We can conclude by stating that secukinumab represents in today's environment an interesting drug for the therapeutic management of moderate-to-severe psoriasis in pediatric patients both because of its rapid onset of action and sustained efficacy over time but especially because of its high safety.

## Ixekizumab

Ixekizumab is a humanized IgG4 with an indication for the treatment of psoriasis and psoriatic arthritis. Its action is achieved through binding to IL-17A by inhibiting its action in the inflammatory process underlying psoriasis. Advantages of ixekizumab include its efficacy in the management of genital psoriasis; to date, it represents the only biologic with that indication, in adults, approved by the FDA.<sup>48</sup> The recommended dosage is 160 mg subcutaneously in week 0 followed by 80 mg administered every two weeks until week 12, finally the injection should be repeated every 4 weeks. Several clinical trials demonstrate good efficacy of ixekizumab, in fact we can state that at week 12 PASI75, PASI90 and PASI100 are achieved in 89%, 71% and 35% respectively<sup>65</sup> with a further increase at week 24 where they are achieved in 90%, 72%, 57%.<sup>66</sup> The safety data are equally good in that side effects are rare and the most frequent is the reaction at the injection site, with pain and erythema, which does not result in discontinuation of therapy.<sup>33,35,48</sup> Some side effects,



although very rare, are more severe, especially neutropenia, which is observed in about 3% of patients treated with Ixekizumab and may be a plausible reason for therapeutic discontinuation. Finally, a very rare side effect that is observed only in patients treated with ixekizumab and no other anti-IL-17 is thrombocytopenia, which although unlikely to be severe, may occasionally be responsible for treatment discontinuation.<sup>33</sup> Ixekizumab has indication as first-line therapy for pediatric patients with severe moderate psoriasis unresponsive to traditional therapies in patients >6 years old. The IXORA-PEDS trial includes 171 patients aged 6–18 years with psoriasis who were randomized into two groups: first group, patients taking ixekizumab (n=115) and second group, patients taking placebo (n=56), of these patients only 139 completed the study until week 108. The trial shows the superiority in terms of efficacy of Ixekizumab over placebo. At week 60, 90% of patients achieved PASI75 and 80.3% of patients achieved PASI90. At week 108, PASI75, PASI90 and PASI100 were achieved in 91.7%, 79% and 55.1%, respectively. At baseline, 78.5% of patients had an itch NRS score of 4 or greater who had an improvement of 4 or more points in that score at week 108. CDLQI of 0 or 1 was achieved in 60.6% of patients at week 108. At baseline, 26.9% of patients had NAPSI higher than 0 which gradually approached zero, indeed, at week 12 NAPSI=0 was achieved by 22.8% of patients while at week 108 it was achieved in 68.1%. This study also shows the high efficacy of Ixekizumab in treating psoriasis of difficult sites. Among patients with palmoplantar psoriasis, 46.2% achieved PPASI100 at week 12 and 90% at week 108. About 88.9% of patients of patients with scalp psoriasis had PSSI greater than 0 with achievement of PSSI=0 in 70.7% after 12 weeks and 76.2% after 108 weeks of Ixekizumab therapy. In the study, 32.2% of patients had genital psoriasis with clearance of lesions in 83.3% of patients after 12 weeks and 87.5% of patients after 108 weeks of Ixekizumab treatment. Safety data overall show good safety for Ixekizumab and are reported as treatment-emergent AEs (TEAEs), serious AEs (SAEs) and AEs of special interest. In the trial, safety was evaluated in all patients treated with Ixekizumab, including patients initially randomized to placebo, and, at week 108, overall TEAEs were reported in 87.7% of patients, of these, 41.3% had mild TEAEs, 40.3% had moderate TEAEs, and only 6.1% of patients had serious TEAEs. The largest percentage of TEAEs highlighted were minor infections. The most severe adverse reactions were the occurrence of astrocytoma, pityriasis rubra pilaris, and paradoxical psoriasis; in addition, 2 cases of Crohn's disease that arose during treatment were reported, SAEs that were responsible for discontinuation of ongoing therapy. No cases of anaphylaxis were reported, while 10.2% of patients presented with allergic or hypersensitivity reactions, 1.5% of patients presented with cytopenia, 2% presented with hepatopathy, 0.5% of patients presented with the occurrence of a neoplasm during therapy (astrocytoma), and in 4.1% of patients the occurrence of depression was reported.<sup>67</sup> Ixekizumab represents in the modern setting an effective and viable opportunity in the treatment of moderate-severe forms of psoriasis in pediatric patients, even for forms that are resistant to the most common therapies and for forms affecting difficult areas such as palmoplantar, scalp, and genital. Efficacy data show that the drug is able to provide clinical benefit in a large percentage of treated patients and in a short time while providing good safety and manageability.

## Brodalumab

Brodalumab is a newly approved (2017) monoclonal antibody for the therapeutic management of moderate-to-severe psoriasis unresponsive to traditional systemic therapies and PsA. It acts by inhibiting interleukin IL-17 (A-F) through binding to the A subunit of the IL-17R receptor. Advantages of brodalumab include its high speed of therapeutic onset with PASI75 being achieved in approximately 25% of patients after only 2 weeks of therapy.<sup>68</sup> Disadvantages of brodalumab include a recommendation in the therapeutic management of patients with a history of depression or other psychiatric disorders, as 3 suicides and 10 suicidal attempts or behavior emerged in 4464 patients during Phase 3 trials. Although brodalumab has not been proven to date to increase the risk of suicide, patients with a history of psychiatric disorders must be properly evaluated by a psychiatrist before starting therapy and during the therapy, and treatment must be discontinued if suicidal behavior or depression worsens.<sup>33,35,48,68</sup> The dosing schedule involves subcutaneous administration of 210mg at weeks 0, 1 and 2 followed by administration of the same dose every two weeks. Efficacy data for brodalumab show that PASI75 was achieved at week 12 in 83% of patients, PASI90 in 70% of patients and PASI100 in 42% of patients.<sup>35,68</sup> The results improve further in the continuation of therapy, in fact, at week 52 PASI90 is reached in 78% of patients and PASI 100 in 68% of patients, demonstrating the high efficacy and maintenance of the therapeutic response of the therapy over time.<sup>68</sup> Regarding efficacy and safety, a study was conducted with a sample of

181 patients with moderate-to-severe psoriasis treated with brodalumab for 264 weeks. Efficacy data show that PASI75 was achieved at week 8 in 94.9% of patients with therapeutic response maintained in more than 80% of patients for 4–264 weeks, while PASI100 was achieved in 64% of patients at week 8 maintaining therapeutic response in more than 50% of patients until week 240 demonstrating very good long-term maintenance of therapeutic response.<sup>69</sup> Safety results, assessed at week 264, showed the occurrence of AEs in 177 patients (97.8%), the most common being upper respiratory tract infections (53%) and arthralgia (20%). More severe AEs were identified in 41 patients (22.7%) although no direct correlation with the drug was identified. Only myocardial infarction was identified in 3 patients (1.7%). At week 264, no suicides were identified, and only one suicidal ideation was reported (0.55%).<sup>69</sup> Efficacy and safety data in the pediatric population with moderate-to-severe psoriasis are not yet available, but brodalumab, based on data obtained in the adult population, could be an excellent therapeutic opportunity in the future as it is characterized by a rapid therapeutic onset, high skin clearance rate and maintenance of therapeutic response in long-term therapy due to good safety and patient compliance data.

## Bimekizumab

Bimekizumab is a humanized IgG1 monoclonal antibody approved for the therapeutic management of moderate-severe plaque psoriasis unresponsive to traditional systemic therapies.<sup>70</sup> It acts by inhibiting interleukin IL-17 (A and F). The advantages of bimekizumab include a rapid therapeutic onset, which can be seen as early as week 4, and excellent long-term efficacy data (52 weeks) with a good safety profile.<sup>71</sup> A phase III study (BE READY) randomized 435 patients to receive bimekizumab 320mg every 4 weeks.<sup>72</sup> Efficacy at week 16 showed that PASI90 was achieved in 91% of patients and PASI100 in 68% versus only 1% of patients taking placebo. At week 16, IGA scores of 0/1 were achieved in 93% of bimekizumab-treated patients versus 1% of placebo-treated patients. Patients who had reached PASI90 were re-randomized into 3 groups: 1. Bimekizumab 320mg every 4 weeks. 2. Bimekizumab 330mg every 8 weeks. 3. Placebo every 4 weeks. At week 56, most re-randomized patients in groups 1 and 2 had PASI90 compared to patients taking placebo (group 3).<sup>72</sup> Safety data showed, at week 16, the occurrence of AEs in 61% of patients treated with bimekizumab, while at week 56 AEs were reported in 74% of patients in group 1 and 77% in group 2. Overall, only 3 (1%) cases required therapeutic discontinuation due to AEs.<sup>72</sup> To date, there are no data supporting its efficacy and safety in the pediatric population with moderate-to-severe psoriasis. The data obtained in trials in which the population is made up of adult patients show high efficacy from the first weeks of therapy and a long-lasting maintenance of the therapeutic response with acceptable safety, bimekizumab, although further studies are needed, could represent a drug with high speed of action and good tolerability in the panorama of therapeutic strategies for pediatric psoriasis that is not responsive to traditional therapies.

## Anti IL-23

IL-23 is a pro-inflammatory interleukin consisting of two main subunits IL-23p19 and IL-12p40<sup>73,74</sup> that is closely implicated in the pathogenesis of psoriasis. Specifically, IL-23 is produced by plasmacytoid dendritic cells and through binding to its receptor (IL-23R) triggers an inflammatory cascade responsible for the differentiation of naïve T lymphocytes into TH17 lymphocytes responsible for the secretion of other cytokines that play a fundamental role in the inflammatory process responsible for the clinical manifestations of psoriasis and its complications, such as IL-17. In turn, the cytokine IL17 is responsible for the proliferation of keratinocytes that induce the release of IFN-alpha, IFN-beta and cathelicidin, which mediate the release of the interleukin IL-23, triggering a vicious circle that self-fuels the inflammatory process.<sup>74–76</sup> The upstream role of the inflammatory process allows the manifestations of psoriasis to be inhibited extremely effectively and may also represent the rationale for which these drugs have excellent long-term efficacy that is perpetuated even after therapeutic discontinuation.<sup>77</sup> Improved knowledge of the role of IL-23 in the pathogenesis of psoriasis has enabled the development of biologic drugs directed against this interleukin, allowing target therapy, including guselkumab, tildrakizumab and risankizumab. All of the above-mentioned drugs are directed against the IL-23p19 subunit of IL-23. Advantages of anti-IL23 include the subcutaneous administration, which is generally better accepted by patients than intravenous administration, and the lower frequency of administration compared to other biologics. Another major advantage is the maintenance of the therapeutic response over time with improved results

during maintenance therapy.<sup>77</sup> In addition, anti-IL23, like anti-IL-17, have a lower risk of reactivation of latent tuberculous infections and viral hepatitis, although screening for latent tuberculosis and chronic viral hepatitis is still recommended at the preliminary visit.<sup>74,77-79</sup> In contrast to anti-IL-17, anti-IL-23 is not associated with de novo onset or worsening of IBD in treated patients.<sup>80</sup> Among the side effects, no particularly serious reactions are noteworthy, and most adverse drug reactions are upper airway infections and headache, demonstrating good safety data ensuring high patient compliance.<sup>77</sup>

## Guselkumab

Guselkumab is a fully human monoclonal antibody directed against interleukin IL-23 via binding to the IL-23p19 subunit, approved for the treatment of moderate-to-severe psoriasis unresponsive to conventional therapies and approved for PsA. The dosage regimen involves subcutaneous administration of 100mg at weeks 0 and 4 followed by administrations of the same dosage every 8 weeks.<sup>48</sup> The VOYAGE 1 trial evaluated the efficacy of guselkumab by randomizing adult patients with moderate-to-severe psoriasis into 3 groups: 1. patients randomized to guselkumab; 2. patients randomized to placebo; 3. patients randomized to adalimumab. At week 16, patients taking guselkumab achieved PASI75 in 91.2% and PASI90 in 73.3% of patients versus 62.6% and 47.9% of patients in group 3 versus 5.7% and 2.9%, respectively, for patients in group 2. After week 16, group 2 patients were randomized to guselkumab and at week 48 achieved PASI75 87.8% and PASI90 76.3% of group 1 patients versus 62.6% and 47.9%, respectively, for patients taking adalimumab.<sup>81-83</sup> Safety data show that the most common side effects of patients randomized to guselkumab are upper respiratory tract infections and nasopharyngitis, while, at week 48, the incidence of serious infections was overlapping for group 1 and group 3. Other serious AEs over 48 weeks were one major cardiovascular event in both group 1 and group 3, two basal cell carcinomas in group 1 versus one basal cell carcinoma in group 3 and two malignancies in group 1. Overall, guselkumab demonstrated acceptable safety as most of the adverse reactions were upper respiratory tract infections, nasopharyngitis, cafelea, diarrhea, and increased transaminases, while the correlation of guselkumab with serious AEs is still unproven and the risk of such reactions is similar to the general population. Another noteworthy study is the ECLIPSE trial that randomized adult patients with moderate-severe psoriasis into two groups: 1. randomized patients taking guselkumab; 2. randomized patients taking secukinumab. The study evaluated the efficacy of the two biologics up to week 44. At week 12, secukinumab had better efficacy, while, at the end of the study, PASI90 was achieved in 84.5% of patients receiving guselkumab and 70% of those receiving secukinumab. These data show that secukinumab has a higher speed of action than guselkumab, but over the long-term guselkumab has greater efficacy.<sup>81,82,84</sup> To date, there are no clinical trials concerning the efficacy and safety of guselkumab in pediatric patients, and the only scientific evidence is represented by a few case reports in pediatric patients with plaque psoriasis unresponsive to conventional therapies and at least one biologic; in these clinical cases, guselkumab proved to be extremely effective, guaranteeing almost complete skin clearance of the lesions without the development of any AEs.<sup>85,86</sup> Although data are insufficient, guselkumab could represent an effective and safe drug for pediatric patients with moderate-to-severe psoriasis.

## Tildrakizumab

Tildrakizumab is a humanized monoclonal antibody directed against IL-23 by binding to the IL-23p19 subunit, through its inhibition it acts on the inflammatory process implicated in the pathogenesis of psoriasis. The dosage schedule involves subcutaneous administration of 100mg at weeks 0 and 4 followed by administration of the same dosage every 12 weeks, and the frequency of administration that characterizes tildrakizumab ensures better compliance than other biologics.<sup>48,87</sup> Efficacy and safety were evaluated in the phase 3 reSURFACE 1 trial randomizing adult patients with moderate-to-severe psoriasis into 3 main groups: 1. Patients randomized to tildrakizumab 200mg; 2. At week 12, PASI75 was achieved in 62.3% of patients in group 1 versus 63.8% of patients in group 2 versus 5.8% of patients in group 3. After week 12, the placebo group was re-randomized into groups 1 and 2. At week 28, PASI75 was achieved in 81.9% of patients in group 1 versus 80.4% of patients in group 2, demonstrating that both dosage regimens had overlapping efficacy. After week 28, patients with a PASI greater than or equal to 75 were re-randomized to either tildrakizumab at the same dose or placebo, while group 2 patients with a 50<PASI>75 were re-randomized to tildrakizumab at the same

dosage or tildrakizumab at the 200mg dose. The final phase of the study, at week 64, demonstrates the maintenance of the therapeutic response in the long term.<sup>87–91</sup> The safety studied in this study shows that the most common AEs are nasopharyngitis and upper respiratory tract infections, headache, diarrhea and injection site reactions, while the incidence of serious AEs is no different from the general population.<sup>87–90</sup> There are no clinical trials or even case reports in the literature that provide data on the efficacy and safety of tildrakizumab for the therapeutic management of moderate-to-severe psoriasis in pediatric patients. Clinical trials will be needed to show that the efficacy and safety demonstrated in the adult population is similar for pediatric patients, thus representing a promising prospect in forms of moderate-to-severe psoriasis not responsive to traditional therapies.

## Risankizumab

Risankizumab is a humanized monoclonal antibody directed against interleukin IL-23 that acts by binding the IL-23p19 subunit, thus inhibiting its role in the pathogenesis of psoriasis. The dosage regimen is 150mg at weeks 0 and 4 followed by administration at the same dosage every 12 weeks, achieving good patient compliance.<sup>48,92</sup> Efficacy and safety were evaluated in the UltIMMa-1 trial randomizing adult patients with moderate-severe psoriasis unresponsive to traditional therapies into three groups: 1. patients randomized to Risankizumab; 2. patients randomized to Ustekinumab; 3. patients randomized to placebo. At week 16, PASI90 had been achieved in 75.3% of patients in group 1 versus 42% of patients in group 2 versus 4.9% in group 3. After week 15, patients in the placebo group were re-randomized to risankizumab until week 52. At week 52, PASI90 was achieved in 81.9% and sPGA 0/1 in 86.2% of group 1 patients versus 44% and 54% in group 2 patients, respectively.<sup>48,92–95</sup> These data show high efficacy of risankizumab compared to both placebo and ustekinumab with adequate maintenance of response over time. The study also evaluated the safety of risankizumab, and the data show that AEs occurred in 49.7% of patients versus 50% of patients taking ustekinumab and 51% of patients taking placebo; thus, both biologics used in this study had a comparable incidence of AEs to placebo. The most frequent AEs included upper airway infections and injection site reactions, but, in most cases, they were minor and did not require discontinuation of therapy.<sup>92,94</sup> It also seems to be associated with a higher incidence of mycosis.<sup>92</sup> AEs are very rare, with major cardiovascular events occur in 0.5%, serious infections in 1.5% and neoplasms in 0.7% of patients treated with risankizumab.<sup>95</sup> Overall, risankizumab represents a well-tolerated drug, another factor guaranteeing the excellent compliance that characterizes this biologic. To date, there are no clinical trials demonstrating efficacy and safety in the pediatric population. Potentially, risankizumab, for its high compliance and efficacy with acceptable safety, could represent a very useful drug for psoriasis in the pediatric population.

## Small Molecule

### Apremilast

Apremilast is a small molecule that acts by inhibiting PDE4, thereby promoting cell maturation and anti-inflammatory processes, thereby acting on both processes underlying the clinical manifestations of psoriasis. Inhibition of PDE4, specifically, induces an intracellular increase in cyclic adenosine monophosphate (cAMP) which in turn induces increased activation of PKA, which phosphorylates and activates numerous transcription factors implicated in the modulation of inflammatory and cell maturation processes.<sup>96,97</sup> Dosage is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no restrictions on food intake.<sup>98</sup> Advantages of apremilast include the oral mode of administration, which is well accepted by patients and allows for good compliance. The most important advantage is its efficacy in the therapeutic management of palmoplantar psoriasis as demonstrated in the ESTEEM 1, ESTEM 2<sup>99,100</sup> and in the management of psoriasis of difficult areas such as nails and scalp as demonstrated in the ESTEEM 1, ESTEM 2 and UNVEIL studies.<sup>99–102</sup> In the UNVEIL study, patients with moderate-severe plaque psoriasis were randomized into two groups: 1. Patients randomized to apremilast 30mg BID; 2. Patients randomized to placebo. Efficacy was assessed at week 16 by PGAXBSA score with results for apremilast of –48.1% versus –10.2% for placebo group patients and PASI75 achieved in 21.6% of group 1 patients versus only 8.2% of group 2 patients. After week 16, patients taking placebo were re-randomized to apremilast 30mg BID and evaluated until week 52. The results at the end of the study showed a PGAXBSA of –55.5% and PASI75 in 26.4% for patients who had been taking apremilast since the beginning of the study versus the PGAXBSA of –42.2% and PASI75 in 37.5% of patients who started taking apremilast after week 16.<sup>101</sup> Efficacy evaluation was studied in the ESTEEM 1 and 2 trials showing that most AEs were mild and were

represented by diarrhea (17.3%), nausea (15.7%), upper respiratory tract infections (15.5%), nasopharyngitis (14.4%) and headaches (6.3%); all AEs that did not involve discontinuation of ongoing therapy.<sup>99,100,103</sup> Three deaths were reported during the two studies from heart attack, stroke, and severe mitral stenosis, but no correlations between the occurrence of these events and apremilast therapy were demonstrated.<sup>103</sup> apremilast was also associated with an increased incidence of depression. The ESTEEM study shows that there is no increased incidence of depression in patients with psoriasis, whereas, for patients with psoriasis, anxiety disorder, depression and suicidal ideation are often identified among the comorbidities compared with the general population regardless of the therapy practiced.<sup>104–107</sup> Overall, apremilast is an innovative drug with good efficacy and excellent compliance with acceptable safety. In the pediatric population, there are few data regarding the efficacy and safety of apremilast. A clinical trial randomized pediatric patients (adolescents and children) into 3 main groups: 1. Adolescents randomized to apremilast 30mg BID; 2. Adolescents randomized to apremilast 20mg BID; 3. Children randomized to apremilast 20mg BID. Efficacy data show, at week 16, the percentage change in PASI score of –69.6 for group 1, –66.5 for group 2 and –79.3 for group 3. The safety data do not differ from the data for the adult population, in that the most common AEs are like those demonstrated in the adult population and are all reactions that do not induce discontinuation of ongoing therapy. A very common AE in the pediatric population is abdominal pain.<sup>108</sup> Although more studies and clinical trials related to both efficacy and safety of apremilast in the pediatric population are needed, this always represents a well-tolerated drug with good efficacy for the management of psoriasis in such patients.

## Conclusion

The management of moderate-to-severe forms of pediatric psoriasis still represents a challenge for dermatologists, due to the need of systemic treatments, which may raise several concerns among both patients and parents/caregivers. In this scenario, although systemic conventional treatments may still represent a useful management strategy, in unresponsive patients, as well as in those presenting contraindications, biological therapies may have a key role in the management of psoriasis in childhood ages. To date, only few biologics received the approval for these ages. However, increasing literature data have been reported, showing newer biological classes (anti IL-17 and anti-IL-23) as a safe and effective treatment in childhood psoriasis. Although no safety concerns have been raised during trials, further studies are needed to better evaluate the efficacy and safety of newer agents in pediatric ages, with trials and studies involving a higher number of patients, and even real-life studies, enrolling patients from the daily dermatological practice.

## Disclosure

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## References

1. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020;82(1):161–201. doi:10.1016/j.jaad.2019.08.049
2. Megna M, Camela E, Battista T, et al. Efficacy and safety of biologics and small molecules for psoriasis in pediatric and geriatric populations. Part I: focus on pediatric patients. *Expert Opin Drug Saf.* 2023;22(1):25–41. PMID: 36718762. doi:10.1080/14740338.2023.2173170
3. Megna M, Camela E, Battista T, et al. Efficacy and safety of biologics and small molecules for psoriasis in pediatric and geriatric populations. Part II: focus on elderly patients. *Expert Opin Drug Saf.* 2023;22(1):43–58. PMID: 36718748. doi:10.1080/14740338.2023.2173171
4. Ruggiero A, Fabbrocini G, Cacciapuoti S, Cinelli E, Gallo L, Megna M. Ocular manifestations in psoriasis screening (OcMaPS) questionnaire: a useful tool to reveal misdiagnosed ocular involvement in psoriasis. *J Clin Med.* 2021;10(5):1031. doi:10.3390/jcm10051031
5. Kwon HH, Na SJ, Jo SJ, et al. Epidemiology and clinical features of pediatric psoriasis in tertiary referral psoriasis clinic. *J Dermatol.* 2012;39(3):260–264. doi:10.1111/j.1346-8138.2011.01452.x
6. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol.* 2017;76(3):377–390. doi:10.1016/j.jaad.2016.07.064
7. Ruggiero A, Fabbrocini G, Cinelli E, Megna M. Real world practice indirect comparison between guselkumab and risankizumab: results from an Italian retrospective study. *Dermatol Ther.* 2022;35(1):e15214. PMID: 34800070; PMCID: PMC9285826. doi:10.1111/dth.15214
8. Megna M, Potestio L, Ruggiero A, Camela E, Fabbrocini G. Risankizumab treatment in psoriasis patients who failed anti-IL17: a 52-week real-life study. *Dermatol Ther.* 2022;35(7):e15524. PMID: 35439341; PMCID: PMC9539505. doi:10.1111/dth.15524
9. Napolitano M, Megna M, Balato A, et al. Systemic treatment of pediatric psoriasis: a review. *Dermatol Ther.* 2016;6(2):125–142.
10. Ruggiero A, Picone V, Martora F, Fabbrocini G, Megna M. Guselkumab, risankizumab, and tildrakizumab in the management of psoriasis: a review of the real-world evidence. *Clin CosmetInvestig Dermatol.* 2022;15:1649–1658. PMID: 35996400; PMCID: PMC9392468. doi:10.2147/CCID.S364640



11. Ruggiero A, Martora F, Picone V, et al. The impact of COVID-19 infection on patients with psoriasis treated with biologics: an Italian experience. *Clin Exp Dermatol*. 2022;47(12):2280–2282. PMID: 35867020; PMCID: PMC9349949. doi:10.1111/ced.15336
12. Ruggiero A, Martora F, Picone V, Marano L, Fabbrocini G, Marasca C. Paradoxical hidradenitis suppurativa during biologic therapy, an emerging challenge: a systematic review. *Biomedicines*. 2022;10(2):455. PMID: 35203664; PMCID: PMC8962303. doi:10.3390/biomedicines10020455
13. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J Am Acad Dermatol*. 2010;62(1):114–135. doi:10.1016/j.jaad.2009.08.026
14. Marasca C, Ruggiero A, Annunziata MC, Fabbrocini G, Megna M. Face the COVID-19 emergency: measures applied in an Italian Dermatologic Clinic. *J Eur Acad Dermatol Venereol*. 2020;34(6):e249. PMID: 32294282; PMCID: PMC7262301. doi:10.1111/jdv.16476
15. Martora F, Marasca C, Fabbrocini G, Ruggiero A. Strategies adopted in a southern Italian referral centre to reduce Adalimumab discontinuation: comment on ‘Can we increase the drug survival time of biologic therapies in hidradenitis suppurativa?’. *Clin Exp Dermatol*. 2022;47(10):1864–1865. doi:10.1111/ced.15291
16. Ersoy-Evans S, Altaykan A, Sahin S, Kölemen F. Phototherapy in childhood. *Pediatr Dermatol*. 2008;25(6):599–605. PMID: 19067863. doi:10.1111/j.1525-1470.2008.00773.x
17. Bronckers IM, Seyger MMB, West DP, et al. Psoriasis Investigator Group (PsIG) of the Pediatric Dermatology Research Alliance and the European Working Group on Pediatric Psoriasis (EWGPP). Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol*. 2017;153(11):1147–1157. PMID: 28903160; PMCID: PMC5710436. doi:10.1001/jamadermatol.2017.3029
18. Boffa MJ, Chalmers RJ. Methotrexate for psoriasis. *Clin Exp Dermatol*. 1996;21(6):399–408. PMID: 9167333. doi:10.1111/j.1365-2230.1996.tb00142.x
19. van Geel MJ, Mul K, de Jager ME, van de Kerkhof PC, de Jong EM, Seyger MM. Systemic treatments in paediatric psoriasis: a systematic evidence-based update. *J Eur Acad Dermatol Venereol*. 2015;29(3):425–437. PMID: 25346019. doi:10.1111/jdv.12749
20. Collin B, Vani A, Ogboli M, Moss C. Methotrexate treatment in 13 children with severe plaque psoriasis. *Clin Exp Dermatol*. 2009;34(3):295–298. PMID: 19175782. doi:10.1111/j.1365-2230.2008.02907.x
21. Kaur I, Dogra S, De D, Kanwar AJ. Systemic methotrexate treatment in childhood psoriasis: further experience in 24 children from India. *Pediatr Dermatol*. 2008;25(2):184–188. PMID: 18429775. doi:10.1111/j.1525-1470.2008.00629.x
22. Bedoui Y, Guillot X, Sélambarom J, et al. Methotrexate an old drug with new tricks. *Int J Mol Sci*. 2019;20(20):5023. PMID: 31658782; PMCID: PMC6834162. doi:10.3390/ijms20205023
23. Fradin MS, Ellis CN, Voorhees JJ. Efficacy of cyclosporin A in psoriasis: a summary of the United States’ experience. *Br J Dermatol*. 1990;122:21–25. PMID: 2196080. doi:10.1111/j.1365-2133.1990.tb02878.x
24. Bulbul Baskan E, Yazici S, Tunali S, Saricaoglu H. Clinical experience with systemic cyclosporine A treatment in severe childhood psoriasis. *J Dermatolog Treat*. 2016;27(4):328–331. PMID: 26651208. doi:10.3109/09546634.2015.1115813
25. Dogra S, Mahajan R, Narang T, Handa S. Systemic cyclosporine treatment in severe childhood psoriasis: a retrospective chart review. *J Dermatolog Treat*. 2017;28(1):18–20. PMID: 27771982. doi:10.3109/09546634.2015.1034072
26. Kiliç SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim I. Low dose cyclosporin A treatment in generalized pustular psoriasis. *Pediatr Dermatol*. 2001;18(3):246–248. PMID: 11438009. doi:10.1046/j.1525-1470.2001.018003246.x
27. Chao PH, Cheng YW, Chung MY. Generalized pustular psoriasis in a 6-week-old infant. *Pediatr Dermatol*. 2009;26(3):352–354. PMID: 19706107. doi:10.1111/j.1525-1470.2009.00918.x
28. Popadic S, Nikolic M. Pustular psoriasis in childhood and adolescence: a 20-year single-center experience. *Pediatr Dermatol*. 2014;31:575–579.
29. Chen P, Li C, Xue R, et al. Efficacy and safety of Acitretin monotherapy in children with pustular psoriasis: results from 15 cases and a literature review. *J Dermatolog Treat*. 2018;29:353–363. doi:10.1080/09546634.2017.1395798
30. Camela E, Potestio L, Fabbrocini G, Ruggiero A, Megna M. New frontiers in personalized medicine in psoriasis. *Expert Opin Biol Ther*. 2022;22(12):1431–1433. PMID: 35968665. doi:10.1080/14712598.2022.2113872
31. Ruggiero A, Fabbrocini G, Cacciapuoti S, Potestio L, Gallo L, Megna M. Tildrakizumab for the treatment of moderate-to-severe psoriasis: results from 52 weeks real-life retrospective study. *Clin Cosmet Invest Dermatol*. 2023;16:529–536. doi:10.2147/CCID.S402183
32. Dunn LK, Gaar LR, Yentzer BA, O’Neill JL, Feldman SR. Acitretin in dermatology: a review. *J Drugs Dermatol*. 2011;10(7):772–782. PMID: 21720660.
33. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris. *J Eur Acad Dermatol Venereol*. 2020;34:2461–2498. doi:10.1111/jdv.16915
34. Bronckers I, Seyger MMB, West DP, et al. Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol*. 2017;153:1147–1157. doi:10.1001/jamadermatol.2017.3029
35. Rønholdt K, Iversen L. Old and new biological therapies for psoriasis. *Int J Mol Sci*. 2017;18(11):2297. doi:10.3390/ijms18112297
36. Gordon K, Papp K, Poulin Y, et al. Long-term efficacy and safety of Adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. *J Am Acad Dermatol*. 2012;66(2):241–251. doi:10.1016/j.jaad.2010.12.005
37. Zangrilli A, Bavetta M, Bianchi L. Adalimumab in children and adolescents with severe plaque psoriasis: a safety evaluation. *Expert Opin Drug Saf*. 2020;19(4):433–438. doi:10.1080/14740338.2020.1752659
38. Papp K, Thaci D, Marcoux D, et al. Efficacy and safety of Adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. *Lancet*. 2017;390(10089):40–49. doi:10.1016/S0140-6736(17)31189-3
39. Thaci D, Papp K, Marcoux D, et al. Sustained long-term efficacy and safety of Adalimumab in paediatric patients with severe chronic plaque psoriasis from a randomized, double-blind, phase III study. *Br J Dermatol*. 2019;181(6):1177–1189. doi:10.1111/bjd.18029
40. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of Adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158(3):558–566. doi:10.1111/j.1365-2133.2007.08315.x
41. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241–251. doi:10.1056/NEJMoa066886

42. Langley RG, Paller AS, Hebert AA, et al. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. *J Am Acad Dermatol.* 2011;64:64–70. doi:10.1016/j.jaad.2010.02.060
43. Paller AS, Siegfried EC, Eichenfield LF, et al. Long-term etanercept in pediatric patients with plaque psoriasis. *J Am Acad Dermatol.* 2010;63:762–768. doi:10.1016/j.jaad.2010.04.004
44. Paller AS, Siegfried EC, Pariser DM, et al. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. *J Am Acad Dermatol.* 2016;74:280–287. doi:10.1016/j.jaad.2015.09.056
45. Kivelevitch D, Mansouri B, Menter A. Long term efficacy and safety of etanercept in the treatment of psoriasis and psoriatic arthritis. *Biologics.* 2014;8:169–182. doi:10.2147/BTT.S41481
46. Subedi S, Gong Y, Chen Y, Shi Y. Infliximab and biosimilar infliximab in psoriasis: efficacy, loss of efficacy, and adverse events. *Drug Des Devel Ther.* 2019;13:2491–2502. doi:10.2147/DDDT.S200147
47. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826–850. doi:10.1016/j.jaad.2008.02.039
48. Brownstone ND, Hong J, Mosca M, et al. Biologic treatments of psoriasis: an update for the clinician. *Biologics.* 2021;15:39–51.
49. Megna M, Ocampo-Garza SS, Potestio L, et al. New-onset psoriatic arthritis under biologics in psoriasis patients: an increasing challenge? *Biomedicines.* 2021;9(10):1482. doi:10.3390/biomedicines9101482
50. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis.* 2018;77(2):228–233. doi:10.1136/annrheumdis-2017-212196
51. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann Rheum Dis.* 2017;76(11):1890–1896. doi:10.1136/annrheumdis-2017-211384
52. Gottlieb AB, Blauvelt A, Thaçi D, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebocontrolled studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol.* 2018;79(2):302–314.e6. doi:10.1016/j.jaad.2018.04.012
53. Macaluso FS, Orlando A, Cottone M. Anti-interleukin-12 and anti-interleukin-23 agents in Crohn's disease. *Expert Opin Biol Ther.* 2019;19(2):89–98. doi:10.1080/14712598.2019.1561850
54. Savage LJ, Wittmann M, McGonagle D, Helliwell PS. Ustekinumab in the treatment of psoriasis and psoriatic arthritis. *Rheumatol Ther.* 2015;2(1):1–16. doi:10.1007/s40744-015-0010-2
55. Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol.* 2015;73(4):594–603. doi:10.1016/j.jaad.2015.07.002
56. Philipp S, Menter A, Nikkels AF, et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients ( $\geq 6$  to  $< 12$  years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study. *Br J Dermatol.* 2020;183(4):664–672. doi:10.1111/bjd.19018
57. Yang JE, Beck KM, Liao W. Secukinumab in the treatment of psoriasis: patient selection and perspectives. *Psoriasis.* 2018;8:75–82. doi:10.2147/PTT.S146004
58. Fauny M, Moulin D, D'Amico F, et al. Paradoxical gastrointestinal effects of interleukin-17 blockers. *Ann Rheum Dis.* 2020;79:1132–1138. doi:10.1136/annrheumdis-2020-217927
59. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol.* 2017;177(1):47–62. doi:10.1111/bjd.15015
60. Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a phase 3 double-blind randomized, controlled trial. *J Eur Acad Dermatol Venereol.* 2020;35(4):938–947. doi:10.1111/jdv.17002
61. Marasca C, Ruggiero A, Megna M, Annunziata MC, Fabbrocini G. Biologics for patients affected by hidradenitis suppurativa in the COVID-19 era: data from a referral center of Southern Italy. *J Dermatolog Treat.* 2022;33(1):592. doi:10.1080/09546634.2020.1769828
62. Magnolo N, Kingo K, Laquer V, et al. A phase III open-label, randomized multicenter study to evaluate efficacy and safety of secukinumab in pediatric patients with moderate to severe plaque psoriasis: 24-week results. *J Am Acad Dermatol.* 2021;85:AB119. doi:10.1016/j.jaad.2021.06.493
63. Reich A, Magnolo N, Kingo K, et al. Secukinumab treatment demonstrated high efficacy and safety in paediatric patients with moderate-to-severe plaque psoriasis: 52-week results from a randomised trial. *Pediatr Dermatol.* 2021;38(Suppl. 1):57–58.
64. Zagaria O, Villani A, Ruggiero A, Potestio L, Fabbrocini G, Gallo L. New-onset lichen planus arising after COVID-19 vaccination. *Dermatol Ther.* 2022;35(5):e15374. doi:10.1111/dth.15374
65. Azevedo A, Torres T. Clinical efficacy and safety of ixekizumab for treatment of psoriasis. *Actas Dermosifiliogr.* 2017;108(4):305–314.
66. Chiricozzi A, Burlando M, Caldarola G, et al. Ixekizumab effectiveness and safety in the treatment of moderate-to-severe plaque psoriasis: a multicenter, retrospective observational study. *Am J Clin Dermatol.* 2020;21(3):441–447. doi:10.1007/s40257-019-00490-2
67. Paller AS, Seyger MMB, Magariños GA, et al. IXORA-PEDS investigators. long-term efficacy and safety of up to 108 weeks of ixekizumab in pediatric patients with moderate to severe plaque psoriasis: the IXORA-PEDS randomized clinical trial. *JAMA Dermatol.* 2022;158(5):533–541. doi:10.1001/jamadermatol.2022.0655
68. Foulkes AC, Warren RB. Brodalumab in psoriasis: evidence to date and clinical potential. *Drugs Context.* 2019;8(212570):1–11. doi:10.7573/dic.212570
69. Lebwohl MG, Blauvelt A, Menter A, et al. Efficacy, safety, and patient-reported outcomes in patients with moderate-to-severe plaque psoriasis treated with brodalumab for 5 years in a long-term, open-label, phase II study. *Am J Clin Dermatol.* 2019;20(6):863–871. doi:10.1007/s40257-019-00466-2
70. Ruggiero A, Camela E, Potestio L, Fabbrocini G, Megna M. Drug safety evaluation of tildrakizumab for psoriasis: a review of the current knowledge. *Expert Opin Drug Saf.* 2022;21(12):1445–1451. doi:10.1080/14740338.2022.2160447
71. Oliver R, Krueger JG, Glatt S, et al. Bimekizumab for the treatment of moderate-to-severe plaque psoriasis: efficacy, safety, pharmacokinetics, pharmacodynamics and transcriptomics from a phase IIa, randomized, double-blind multicentre study. *Br J Dermatol.* 2022;186(4):652–663. doi:10.1111/bjd.20827

72. Gordon KB, Foley P, Krueger JG, et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. *Lancet*. 2021;397(10273):475–486. doi:10.1016/S0140-6736(21)00126-4
73. Megna M, Caiazzo G, Parisi M, et al. Eczematous drug eruption in patients with psoriasis under anti-interleukin-17A: does interleukin-22 play a key role? *Clin Exp Dermatol*. 2022;47(5):918–925. doi:10.1111/ced.15052
74. Gooderham MJ, Papp KA, Lynde CW. Shifting the focus – the primary role of IL-23 in psoriasis and other inflammatory disorders. *J Eur Acad Dermatol Venereol*. 2018;32(7):1111–1119. doi:10.1111/jdv.14868
75. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J Immunol*. 2018;201(6):1605–1613. doi:10.4049/jimmunol.1800013
76. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. *Ther Adv Chronic Dis*. 2018;9(5):111–119. doi:10.1177/2040622318759282
77. Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: a comprehensive review. *Am J Clin Dermatol*. 2020;21:1–20. doi:10.1007/s40257-019-00475-1
78. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Targeting IL-23 in psoriasis: current perspectives. *Psoriasis*. 2018;8:1–5. doi:10.2147/PTT.S98893
79. Potestio L, Genco L, Villani A, et al. Reply to ‘Cutaneous adverse effects of the available COVID-19 vaccines in India: a questionnaire-based study’ by Bawane J et al. *J Eur Acad Dermatol Venereol*. 2022;36(11):e863–e864. doi:10.1111/jdv.18341
80. Schmitt H, Neurath MF, Atreya R. Role of the IL23/IL17 Pathway in Crohn’s Disease. *Front Immunol*. 2021;12:622934. PMID: 33859636; PMCID: PMC8042267. doi:10.3389/fimmu.2021.622934
81. European Medicines Agency. Guselkumab (tremfya)\_Summary of Product Characteristics\_EMA; 2017. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/tremfya>. Accessed November 02, 2023.
82. Light JG, Su JJ, Feldman SR. Clinical utility of guselkumab in the treatment of moderate-to-severe plaque psoriasis. *Clin Cosmetol Invest Dermatol*. 2021;14:55–63.
83. Nakamura M, Lee K, Jeon C, et al. Guselkumab for the treatment of psoriasis: a review of phase III trials. *Dermatol Ther*. 2017;7(3):281–292. doi:10.1007/s13555-017-0187-0
84. Nogueira M, Torres T. Guselkumab for the treatment of psoriasis – evidence to date. *Drugs Context*. 2019;8:212594. doi:10.7573/dic.212594
85. Kim SR, Kibbi N, Craiglow BG. Guselkumab for the treatment of severe refractory psoriasis in a pediatric patient. *JAAD Case Rep*. 2019;5(6):552–554. PMID: 31245518; PMCID: PMC6581971. doi:10.1016/j.jcdr.2019.04.014
86. Song EJ, Whitman P, Samsel J. The use of ustekinumab and guselkumab in a pediatric psoriasis patient with active hepatitis B infection. *JAAD Case Rep*. 2020;8:37–39. PMID: 33490344; PMCID: PMC7806953. doi:10.1016/j.jcdr.2020.12.006
87. European Medicines Agency. Tildrakizumab (ilumetri)\_Summary of Product Characteristics\_EMA; 2018. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/ilumetri>. Accessed November 02, 2023.
88. Igarashi A, Nakagawa H, Morita A, et al. Efficacy and safety of tildrakizumab in Japanese patients with moderate to severe plaquepsoriasis: results from a 64-week phase 3 study (reSURFACE 1). *J Dermatol*. 2021;48(6):853–863. doi:10.1111/1346-8138.15789
89. Näslund-Koch C, Zachariae C, Skov L. Tildrakizumab: an evidence- based review of its use in the treatment of moderate-to-severe chronic plaque psoriasis. *Ther Clin Risk Manag*. 2020;16:903–916. doi:10.2147/TCRM.S227880
90. Ruggiero A, Potestio L, Cacciapuoti S, et al. Tildrakizumab for the treatment of moderate to severe psoriasis: results from a single center preliminary real-life study. *Dermatol Ther*. 2022;35(12):e15941. doi:10.1111/dth.15941
91. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *Br J Dermatol*. 2020;182(3):605–617. doi:10.1111/bjd.18232
92. European Medicines Agency. Risankizumab (skyrizi)\_Summary of Product Characteristics\_EMA; 2019. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi>. Accessed November 02, 2023.
93. Haugh IM, Preston AK, Kivelevitch DN, Menter AM. Risankizumab: an anti-IL-23 antibody for the treatment of psoriasis. *Drug Des Devel Ther*. 2018;12:3879–3883. doi:10.2147/DDDT.S167149
94. Ruggiero A, Potestio L, Martora F, Villani A, Comune R, Megna M. Bimekizumab treatment in patients with moderate to severe plaque psoriasis: a drug safety evaluation. *Expert Opin Drug Saf*. 2023;22(5):355–362. doi:10.1080/14740338.2023.2218086
95. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650–661. doi:10.1016/S0140-6736(18)31713-6
96. Carrascosa JM, Del-Alcazar E. Apremilast for psoriasis treatment. *G Ital Dermatol Venereol*. 2020;155(4):421–433. PMID: 32545946. doi:10.23736/S0392-0488.20.06684-5
97. Raker VK, Becker C, Steinbrink K. The cAMP pathway as therapeutic target in autoimmune and inflammatory diseases. *Front Immunol*. 2016;7:123. doi:10.3389/fimmu.2016.00123
98. Summary of product characteristics. Available from: [https://www.ema.europa.eu/en/documents/product-information/otezla-epar-product-information\\_it.pdf](https://www.ema.europa.eu/en/documents/product-information/otezla-epar-product-information_it.pdf). Accessed January 07, 2023.
99. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a Phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73:37–49. doi:10.1016/j.jaad.2015.03.049
100. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173:1387–1399. doi:10.1111/bjd.14164
101. Stein Gold L, Bagel J, Lebwohl M, et al. Efficacy and safety of apremilast in systemic- And biologic-naive patients with moderate plaque psoriasis: 52-week results of UnVEIL. *J Drugs Dermatol*. 2018;17:221–228.
102. Strober B, Bagel J, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate plaque psoriasis with lower BSA: week 16 results from the unveil study. *J Drugs Dermatol*. 2017;16:801–808.

103. Crowley J, Thaçi D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: pooled safety analysis for  $\geq 156$  weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol.* 2017;77:310–317.e1. doi:10.1016/j.jaad.2017.01.052
104. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol.* 2010;146:891–895. doi:10.1001/archdermatol.2010.186
105. Ruggiero A, Martora F, Fabbrocini G, et al. The role of teledermatology during the COVID-19 pandemic: a narrative review. *Clin Cosmet Investig Dermatol.* 2022;15:2785–2793. doi:10.2147/CCID.S377029
106. Lamb RC, Matcham F, Turner MA, et al. Screening for anxiety and depression in people with psoriasis: a cross-sectional study in a tertiary referral setting. *Br J Dermatol.* 2017;176:1028–1034. doi:10.1111/bjd.14833
107. Lakshmy S, Balasundaram S, Sarkar S, Audhya M, Subramaniam E. A cross-sectional study of prevalence and implications of depression and anxiety in psoriasis. *Indian J Psychol Med.* 2015;37:434–440. doi:10.4103/0253-7176.168587
108. Paller AS, Hong Y, Becker EM, et al. Pharmacokinetics and safety of apremilast in pediatric patients with moderate to severe plaque psoriasis: results from a Phase 2 open-label study. *J Am Acad Dermatol.* 2020;82(2):389–397. doi:10.1016/j.jaad.2019.08.019

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