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AN EVIDENCE-BASED REVIEW OF SYSTEMIC THERAPIES FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS IN THE PEDIATRIC POPULATION

Introduction

Psoriasis is a chronic immune-mediated inflammatory condition of the skin that affects 2-3% of the general population.¹ Onset during childhood and adolescence occurs in up to one-third of cases.² The plaque subtype is most common.³

Moderate-to-severe plaque psoriasis can have a significant impact on quality of life for affected pediatric patients and their adult caregivers.^{4,5} As a result, systemic therapy is often required. However, selecting the right treatment in this special population can be a challenge, given the paucity of data, standardized international guidelines, and approved options.

The aim of this article is to review the available evidence for systemic therapies used to treat moderate-to-severe plaque psoriasis in pediatric patients. In-depth discussion will be limited to the most rigorous studies only.

	Non-Biologic			Biologic			
	Conventional Immunosuppressants	PDE4 Inhibitors	Retinoids	TNF- α Inhibitors	IL-12/23 Inhibitors	IL-17 Inhibitors	IL-23 Inhibitors
On-Label (Health Canada-Approved) / Placebo-Controlled or Active Comparator Studies Completed & Published Data Available				Etanercept (4-17 Years of Age)	Ustekinumab (6-17 Years of Age)		
Off-Label (Not Health Canada-Approved) / Placebo-Controlled or Active Comparator Studies Completed & Published Data Available	Methotrexate			Adalimumab		Ixekizumab	
Off-Label (Not Health Canada-Approved) / Placebo-Controlled or Active Comparator Studies Underway or Planned		Apremilast		Certolizumab		Brodalumab Secukinumab	Guselkumab Risankizumab
Off-Label (Not Health Canada-Approved) / No Placebo-Controlled or Active Comparator Studies	Cyclosporine		Acitretin	Infliximab			

Figure 1. Systemic Therapies for Moderate-to-Severe Plaque Psoriasis in the Pediatric Population; developed by Prajapati, VH.

Overview

Systemic therapies for moderate-to-severe plaque psoriasis in pediatric patients can be classified into non-biologics and biologics. These are displayed in **Figure 1**. Despite an expanding therapeutic armamentarium, only etanercept and ustekinumab are approved by Health Canada for use in children and adolescents (etanercept: 4-17 years of age; ustekinumab: 6-17 years of age).⁶

In a multicentre, retrospective review of 390 pediatric patients with moderate-to-severe plaque psoriasis (mean age at diagnosis, 8.4 years; mean interval between diagnosis and initiation of systemic therapy, 3.0 years; 20 sites from several North American and European countries), the most frequently used treatment was methotrexate (69%), followed by etanercept (21%), acitretin (15%), and cyclosporine (8%).⁷ Compared with methotrexate, more adverse events (AEs) occurred with cyclosporine and acitretin, while fewer AEs occurred with TNF- α inhibitors (only adalimumab, etanercept, and infliximab were included). Having one or more

associated AEs (OR, 1.76; 95% CI, 1.06-2.92; $p=0.03$), gastrointestinal AEs (OR, 11.49; 95% CI, 3.31-39.88; $p<0.001$), AEs leading to discontinuation (OR, 5.69; 95% CI, 1.31-24.82, $p=0.02$), or abnormal laboratory test results (OR, 5.87; 95% CI, 1.81-18.99; $p=0.003$) was more likely with methotrexate than TNF- α inhibitors, but having one or more associated infections was less likely with methotrexate than TNF- α inhibitors. In addition, for those subjects who received methotrexate, the use of folic acid six days per week (OR, 0.16; 95% CI, 0.06-0.41; $p<0.001$) or seven days per week (OR, 0.21; 95% CI, 0.08-0.58; $p=0.003$) protected against gastrointestinal AEs more than folic acid one day per week, regardless of the total weekly dosage.

In a multicentre, retrospective review of 289 pediatric patients with moderate-to-severe plaque psoriasis (mean age, 11 years; four sites from a single European country), the most frequently used treatment was methotrexate (31%), followed by cyclosporine (29%) and acitretin (22%).⁸ One-year drug survival rates for acitretin,

methotrexate and cyclosporin were 36%, 21% and 15%, respectively. The most significant determinant of drug survival, which diminished over time, was treatment response. The *American Academy of Dermatology* and *National Psoriasis Foundation* recently published guidelines of care for psoriasis in pediatric patients.⁹ Methotrexate, cyclosporine, acitretin, etanercept, adalimumab, infliximab, and ustekinumab were all considered effective systemic therapies for plaque psoriasis in children and/or adolescents; of these, only three (etanercept, adalimumab, and ustekinumab) had the highest level of evidence (I) and only two (etanercept and ustekinumab) received the strongest recommendation (A).

Non-Biologics

Methotrexate

Methotrexate is a conventional immunosuppressant. Use in children and adolescents for plaque psoriasis has not been approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage is 0.2-0.7 mg/kg (up to a maximum of 25 mg) once weekly.⁹

It is available as an oral tablet or subcutaneous injection. Laboratory investigations are recommended before and during treatment.⁹

In a phase 3, multicentre, randomized, double-blind, active comparator study (n=114), methotrexate (0.1-0.4 mg/kg, up to a maximum dosage of 25 mg/week) was compared to adalimumab (0.4 mg/kg and 0.8 mg/kg, up to a maximum dosage of 40 mg/week) in pediatric patients with severe plaque psoriasis (≥ 4 to <18 years of age).¹⁰ At week 16, the proportion of subjects achieving PASI 75 with methotrexate was significantly lower compared to 0.8 mg/kg adalimumab (32% versus 58%, $p=0.027$). In addition, methotrexate provided PASI 90, PASI 100, and PGA 0/1 responses in 22%, 3%, and 41% of subjects, respectively—these were numerically, but not significantly, lower compared to 0.8 mg/kg adalimumab ($p=0.466$, $p=0.056$, and $p=0.083$, respectively). The change in CDLQI score from baseline was -5.0 for methotrexate and -6.6 for 0.8 mg/kg adalimumab ($p=0.304$), while the change in PedsQL score from baseline was 1.9 for methotrexate and 10.8 for 0.8 mg/kg adalimumab ($p=0.005$). The most common AE associated with methotrexate was infection (57%), and none were deemed serious.

Apremilast

Apremilast is a phosphodiesterase-4 inhibitor. Use in children and adolescents for plaque psoriasis is not approved by Health Canada, and, therefore, is considered off-label. While a standard pediatric dosage has yet to be determined, both 20 mg twice daily and 30 mg twice daily were investigated in clinical trials.¹¹⁻¹³

It is available as an oral tablet and laboratory investigations are not required as in adults.

In a phase 2, multicentre, open-label study, 42 patients with moderate-to-severe plaque psoriasis received weight-based dosing of apremilast (12-17 years and ≥ 35 kg: 20 or 30 mg twice daily; 6-11 years and ≥ 15 kg: 20 mg twice daily).¹¹ At week 16, improvements in mean PASI score were 70% (adolescents: 20 mg dosage), 67% (adolescents: 30 mg dosage), and 79% (children: 20 mg dosage). The most commonly reported AEs included nausea (52%), headache (45%), abdominal pain (43%), nasopharyngitis (38%), diarrhea (36%), and vomiting (31%). Nausea, nasopharyngitis, and diarrhea occurred more frequently in adolescents than children, while headache, abdominal pain, and vomiting occurred more frequently in children than adolescents. Nausea, headache, and diarrhea usually appeared during the first month of treatment and these generally resolved within three days of onset. Moderate weight loss developed in two adolescents, but this was transient and subsequently resolved. While the overall safety of apremilast in children and adolescents was generally similar to that observed in adults, this clinical trial did show a higher occurrence of the most commonly reported AEs. Dose titration was not part of the design and may have contributed to this finding. A phase 3, multicentre, randomized, placebo-controlled study with open-label long-term extension is underway.^{12,13}

Other Non-Biologics

Cyclosporine is a conventional immunosuppressant, while acitretin is a retinoid. Although frequently used to treat plaque psoriasis

in the pediatric population, neither has the Health Canada-approved indication for children and adolescents. The standard pediatric dosage is 1-5 mg/kg/day for cyclosporine and 0.1-1 mg/kg/day for acitretin.⁹ Both cyclosporine and acitretin are available as oral capsules. Laboratory investigations are recommended before and during treatment.⁹ At this time, there are no published data from rigorous placebo-controlled or active comparator studies to support the use of cyclosporine and acitretin for moderate-to-severe plaque psoriasis in pediatric patients; only case reports and case series exist.⁹

Biologics

Etanercept

Etanercept is a biologic that inhibits TNF- α . Use in children and adolescents for plaque psoriasis has been approved by Health Canada, and, therefore, is considered on-label (4-17 years of age). The standard pediatric dosage is 0.8 mg/kg (up to a maximum of 50 mg) once weekly, but 0.4 mg/kg twice weekly has also been investigated in clinical trials. It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.⁹

In a phase 3, multicentre, randomized, placebo-controlled study (n=211), etanercept (0.8 mg/kg once weekly, up to a maximum dosage of 50 mg/week) was compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (4-17 years of age).¹⁴ At week 12, etanercept was superior to placebo ($p<0.001$) for PASI 50 (75% versus 23%), PASI 75 (57% versus 11%), PASI 90 (27% versus 7%), and PGA 0/1 (53% versus 13%).

Additionally, the mean improvement in CDLQI from baseline was greater with etanercept than placebo (52% versus 18%, $p<0.001$). In a subanalysis, significant differences ($p<0.001$) in CDLQI change from baseline were noted as early as week 2 when comparing etanercept to placebo (27% versus 8%).¹⁵ At week 36, after 24 weeks of open-label treatment, PASI 75 was achieved in 68% and 65% with mean improvements in CDLQI of 63% and 59% in subjects initially assigned to etanercept and placebo, respectively.¹⁴ During the final withdrawal-retreatment phase, intermittent treatment was also found to be effective, with 80% of subjects on etanercept maintaining or regaining PASI 75 at the end of the 12-week period.^{14,16} The most common AEs were upper respiratory tract infection, headache, and nasopharyngitis.¹⁴ Four serious AEs occurred in three subjects being treated with etanercept during the open-label period. This included three infections. All resolved without sequelae.

A long-term extension of the aforementioned clinical trial was conducted.^{17,18} Of 182 enrolled subjects, 181 received treatment with 140 (77%) and 69 (38%) completing week 96 and week 264 of the study, respectively. At week 96, etanercept provided sustained responses for PASI 50 (89%), PASI 75 (61%), PASI 90 (30%), and PGA 0/1 (47%).¹⁷ For this interim analysis, 80% reported at least one AE; five serious AEs occurred in three patients, none of which were treatment-related. At week 264, etanercept provided PASI 75, PASI 90, and sPGA 0/1 responses in ~60-70%, ~30-40%, and ~40-50% of subjects, respectively.¹⁸ For this final analysis, 89% reported at least one AE. Upper

respiratory tract infection (38%), nasopharyngitis (26%), and headache (22%) were most common. Eight serious AEs occurred in seven subjects; only one (cellulitis) was considered related to treatment. There were no cases of opportunistic infections or malignancy.

Adalimumab

Adalimumab is a biologic that inhibits TNF- α . Use in children and adolescents for plaque psoriasis has not been approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage is 0.8 mg/kg (up to a maximum of 40 mg) at weeks 0, 1, and 2, then every 2 weeks thereafter.⁹ It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.⁹

In a phase 3, multicentre, randomized, double-blind, active comparator study ($n=114$), adalimumab (0.4 mg/kg and 0.8 mg/kg, up to a maximum dosage of 40 mg/week) was compared to methotrexate (0.1-0.4 mg/kg, up to a maximum dosage of 25 mg/week) in pediatric patients with severe plaque psoriasis (≥ 4 to <18 years of age).⁹ The proportion of subjects with PASI 75 at week 16 was significantly higher with 0.8 mg/kg adalimumab compared to methotrexate (58% versus 32%, $p=0.027$), a difference being noted as early as week 4 (24% versus 0%, $p=0.002$); in comparison to methotrexate, 0.8 mg/kg adalimumab also provided numerically, but not significantly, greater rates of PASI 90 (29% versus 22%, $p=0.466$), PASI 100 (18% versus 3%, $p=0.056$), and PGA 0/1 (61% versus 41%, $p=0.083$).

Additionally, the change in CDLQI score from baseline was -6.6 for 0.8 mg/kg adalimumab and -5.0 for methotrexate ($p=0.304$), while the change in PedsQL score from baseline was 10.8 for 0.8 mg/kg adalimumab and 1.9 for methotrexate ($p=0.005$). The proportion of subjects achieving PASI 75, PASI 90, PASI 100, and PGA 0/1 with 0.4 mg/kg adalimumab at week 16 was 44%, 31%, 10%, and 41%, respectively. The most common AE of adalimumab was infection, reported in 45% (0.8 mg/kg adalimumab) and 56% (0.4 mg/kg adalimumab) of subjects; only one (food poisoning coded as gastrointestinal infection) was deemed serious. A total of three serious AEs were recorded and not judged to be related to treatment.

A long-term extension of the aforementioned clinical trial was conducted.¹⁹ Of the 114 subjects randomized in the initial treatment period, 108 entered the long-term extension ($n=36$ in each group) with 90 (83%) completing the study through week 52. A total of 93 subjects received 0.8 mg/kg adalimumab. Efficacy in terms of PASI 75 was maintained or improved from entry to end of the long-term extension. At week 52, the overall proportion of subjects achieving PASI 75, PASI 90, PASI 100, and PGA 0/1 with adalimumab was 69%, 48%, 30%, and 60%, respectively. CDLQI and PedsQL also improved through week 52. For the final analysis, 79% reported at least one AE. Nasopharyngitis (26%), headache (21%), and nasopharyngitis (12%) were most common; five serious AEs occurred in five subjects with only one (eye nevus) being considered possibly related to treatment. There were no cases of malignancy, but two subjects (1.9%) did have latent (but not active) tuberculosis.

Ustekinumab

Ustekinumab is a biologic that inhibits IL-12 and IL-23. Its use in children and adolescents for plaque psoriasis has been approved by Health Canada, and, therefore, is considered on-label (6-17 years of age). The standard pediatric dosage is 0.75 mg/kg (≤ 60 kg), 45 mg (>60 kg but ≤ 100 kg), and 90 mg (>100 kg) at weeks 0 and 4, then every 12 weeks thereafter.⁹ It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.⁹

In a phase 3, multicentre, randomized, double-blind, placebo-controlled study (n=110), weight-based dosing of ustekinumab, both standard (≤ 60 kg: 0.75 mg/kg; >60 kg and ≤ 100 kg: 45 mg; >100 kg: 90 mg) and half-standard (≤ 60 kg: 0.375 mg/kg; >60 kg but ≤ 100 kg: 22.5 mg; >100 kg: 45 mg), were compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (12-17 years of age).²⁰ At week 12, both ustekinumab standard and half-standard dosage were superior to placebo ($p<0.001$) for PGA 0/1 (69.4% and 67.6% versus 5.4%), PGA 0 (47.2% and 32.4% versus 2.7%), PASI 75 (80.6% and 78.4% versus 10.8%), and PASI 90 (61.1% and 54.1% versus 5.4%). These responses were maintained from week 12 to week 52 in subjects receiving ustekinumab at baseline. Through week 12, 44% and 51% of subjects in the ustekinumab standard and half-standard dosage groups, respectively, had at least one AE. Nasopharyngitis (3% and 14% for ustekinumab standard and half-standard dosages, respectively) and headache (8% and 11% for ustekinumab standard and half-

standard dosages, respectively) were most common. Through week 60, 82% of subjects receiving ustekinumab reported at least one AE. Nasopharyngitis (35%) and upper respiratory tract infection (13%) were most common. Infections occurred in 67% of subjects receiving ustekinumab; only two (pyelonephritis and ear infection) were deemed serious. There were no cases of opportunistic infections or malignancy.

In a phase 3, multicentre, open-label study (n=44), pediatric patients (6-11 years of age) with moderate-to-severe plaque psoriasis received weight-based dosing of ustekinumab (<60 kg: 0.75 mg/kg; ≥ 60 kg and ≤ 100 kg: 45 mg; >100 kg: 90 mg).²¹ At week 12, ustekinumab achieved PGA 0/1, PGA 0, PASI 75, PASI 90, PASI 100, and CDLQI 0/1 in 77%, 39%, 84%, 64%, 34%, and 62% of subjects, respectively, with a mean change in CDLQI of -6.3. These responses were maintained from week 12 to week 52. Through week 56, 77% of subjects had at least one AE, with nasopharyngitis (25%), pharyngitis (14%), and upper respiratory tract infection (14%) being most common. Infections occurred in 66% of subjects receiving ustekinumab. Three serious AEs occurred and were not judged to be related to treatment.

Ixekizumab

Ixekizumab is a biologic that inhibits IL-17, specifically IL-17A. Its use in children and adolescents for plaque psoriasis is not approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage involves loading doses of 160 mg (>50 kg), 80 mg (≥ 25 kg and ≤ 50 kg), or 40 mg (<25 kg) followed by maintenance doses of

80 mg (>50 kg), 40 mg (≥ 25 kg and ≤ 50 kg), or 20 mg (<25 kg) every 4 weeks thereafter.²² It is available as a subcutaneous injection and laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.⁹

In a phase 3, multicentre, randomized, double-blind, placebo-controlled study (n=171), ixekizumab (<25 kg: 40 mg loading dose/20 mg maintenance dose; ≥ 25 kg and ≤ 50 kg: 80 mg loading dose/40 mg maintenance dose; >50 kg: 160 mg loading dose/80 mg maintenance dose) was compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (6-17 years of age).²² At week 12, ixekizumab was superior to placebo ($p<0.001$) for PASI 50 (92% versus 38%), PASI 75 (89% versus 25%), PASI 90 (78% versus 5%), PASI 100 (50% versus 2%), sPGA 0/1 (81% versus 11%), sPGA 0 (52% versus 2%), Itch NRS ≥ 4 (71% versus 20%), CDLQI/DLQI 0/1 (64% versus 23%), and PatGA 0/1 (79% versus 16%). In addition, significant differences between ixekizumab and placebo were noted as early as week 1 for PASI 50 ($p<0.001$), PASI 75 ($p=0.032$) and Itch NRS ≥ 4 ($p=0.008$) and as early as week 4 ($p<0.001$) for PASI 90, PASI 100, sPGA 0/1, and sPGA 0. A higher proportion of subjects achieved clearance of scalp and genital psoriasis by week 12 with ixekizumab than placebo ($p<0.001$). Additionally, in comparison to placebo, ixekizumab resulted in significantly greater mean change from baseline at week 12 for Itch NRS ($p<0.001$), NAPS (p=0.005), PSSI (p<0.001), and PPASI (p=0.006). Responses at week 12 with ixekizumab were sustained or further improved through week 48 for PASI 50 (92%),

PASI 75 (90%), PASI 90 (83%), PASI 100 (55%), sPGA 0/1 (81%), sPGA 0 (57%), Itch NRS $\geq$ 4 (87%), CDLQI/DLQI 0/1 (76%), and PatGA 0/1 (86%), with complete clearance of special sites also noted, including nail (50%), scalp (74%), palmoplantar (76%), and genital (90%). Through week 12, 56% of subjects receiving ixekizumab reported at least one AE, with only one deemed serious. Infections occurred in 32%; none of these were serious. Through week 48, 82% of subjects receiving ixekizumab had at least one AE, with 13 deemed serious; infections occurred in 66% (two serious: acute otitis media and tonsillitis). A total of four subjects (2%) developed probable Crohn's disease (one during the double-blind treatment period and three during the maintenance period). There were no cases of opportunistic infections or malignancy.

In the aforementioned clinical trial, ixekizumab was also compared to etanercept in countries where etanercept had received approval for severe plaque psoriasis in pediatric patients.²² At week 12, responses with ixekizumab were significantly greater than etanercept for PASI 90 (76% versus 40%, $p=0.003$), PASI 100 (61% versus 17%, $p<0.001$), and sPGA 0 (63% versus 17%, $p<0.001$). In addition, responses with ixekizumab were numerically, but not significantly, greater than etanercept for PASI 75 (84% versus 63%, $p=0.089$) and sPGA 0/1 (76% versus 53%, $p=0.070$).

Other Biologics

Despite their indication for plaque psoriasis in adults, other biologics that inhibit TNF- α (infliximab; certolizumab), IL-17 (brodalumab; secukinumab), and IL-23 (guselkumab; risankizumab) are not approved by Health Canada for use in children and adolescents. A phase 3 study has been completed for secukinumab, with the long-term extension

ongoing.^{23,24} Brodalumab, certolizumab, guselkumab, and risankizumab are also being investigated.²⁵⁻²⁸

Conclusion

Well-designed, randomized, placebo-controlled or active comparator studies have documented the efficacy and safety of methotrexate, adalimumab, etanercept, ixekizumab, and ustekinumab in pediatric plaque psoriasis with only methotrexate and adalimumab as well as ixekizumab and etanercept being compared head-to-head. Clinical trials investigating the use of secukinumab have been completed, while those for apremilast, brodalumab, certolizumab, guselkumab, and risankizumab are either underway or planned. As the therapeutic landscape continues to evolve and additional robust short- and long-term data become available, this will help fulfill the unmet need for more targeted Health Canada-approved systemic therapies to treat moderate-to-severe plaque psoriasis in the pediatric population.

References:

1. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: a systemic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-385.
2. de Jager ME, de Jong EM, Meeuwis KA, et al. No evidence found that childhood onset of psoriasis influences disease severity, future body mass index or type of treatments used. *J Eur Acad Dermatol Venereol*. 2010;24(11):1333-1339.
3. Tollefson MM, Crowson CS, McEvoy MT, Kremers HM. Incidence of psoriasis in children: a population-based study. *J Am Acad Dermatol*. 2010;62(6):979-987.
4. Randa H, Todberg T, Skov L, Larsen LS, Zachariae R. Health-related quality of life in children and adolescents with psoriasis: a systematic review and meta-analysis. *Acta Derm Venereol*. 2017;97(5):555-563.
5. Remrod C, Sjöström K, Svensson A. Psychological differences between early- and late-onset psoriasis: a study of personality traits, anxiety and depression in psoriasis. *Br J Dermatol*. 2013;169(2):344-350.
6. Lansang P, Bergman JN, Fiorillo L, et al. Management of pediatric plaque psoriasis using biologics. *J Am Acad Dermatol*. 2020;82(1):213-221.
7. Bronckers IMGJ, Seyger MMB, West DP, et al. Safety of systemic agents for the treatment of pediatric psoriasis. *JAMA Dermatol*. 2017;153(11):1147-1157.
8. Ergun T, Seckin Gencosmanoglu D, Alpsoy E, et al. Efficacy, safety and drug survival of conventional agents in pediatric psoriasis: a multicenter, cohort study. *J Dermatol*. 2017;44(6):630-634.
9. Menter A, Cordoro KM, Davis DRM, 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.
10. Papp KA, 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.
11. 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.
12. Efficacy and Safety Study of Apremilast (CC-10004) in Pediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis; ClinicalTrials.gov Identifier: NCT03701763; Accessed June 15, 2020.
13. A Long-term Extension Study of Apremilast (CC-10004) in Pediatric Subjects From 6 Through 17 Years of Age With Moderate to Severe Plaque Psoriasis; ClinicalTrials.gov Identifier: NCT04175613; Accessed June 15, 2020.
14. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *New Engl J Med*. 2008; 358(3):241-251.
15. 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(1):64-70.
16. Siegfried EC, Eichenfield LF, Paller AS, Pariser D, Creamer K, Kricorian G. Intermittent etanercept therapy in pediatric patients with psoriasis. *J Am Acad Dermatol*. 2010;63(5):769-774.
17. Paller AS, Siegfried EC, Eichenfield

LF, et al. Long-term etanercept in pediatric patients with plaque psoriasis. *J Am Acad Dermatol*. 2010;63(5):762-768.

18. 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(2):280-287.

19. Thaci D, Papp KA, 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.

20. 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.

21. Philipp S, Menter A, Nikkels AF, et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study. *Br J Dermatol*. 2020 Mar 16; doi: 10.1111/bjd.19018. Online ahead of print.

22. Paller AS, Seyger MMP, Alejandro Magarinos G, et al. Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study, in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS). *Br J Dermatol*. 2020 Apr 21; doi: 10.1111/bjd.19147. Online ahead of print.

23. Pediatric Study in Children and Adolescents With Severe Plaque Psoriasis; ClinicalTrials.gov Identifier: NCT02471144; Accessed June 15, 2020.

24. Study to Assess the Long-term Safety, Tolerability, Efficacy of Secukinumab in Pediatric Patients of Age 6 to < 18 Years, With Moderate to Severe Plaque Psoriasis; ClinicalTrials.gov Identifier: NCT03668613; Accessed June 15, 2020.

25. An Open-label, Single-dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Brodalumab in Pediatric Subjects; ClinicalTrials.gov Identifier: NCT03240809; Accessed June 15, 2020.

26. A Study to Evaluate the Efficacy, Safety, and Drug Concentration of Certolizumab Pegol (CZP) in Children and Adolescent Study Participants With Moderate to Severe Chronic Plaque Psoriasis (PSO) (CIMcare); ClinicalTrials.gov Identifier: NCT04123795; Accessed June 15, 2020.

27. A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Pediatric Participants (PROTOSTAR); ClinicalTrials.gov Identifier: NCT03451851; Accessed June 15, 2020.

28. A Study of Subcutaneous Risankizumab Injection for Pediatric Participants With Moderate to Severe Plaque Psoriasis to Assess Change in Disease Symptoms; ClinicalTrials.gov Identifier: NCT04435600; Accessed June 15, 2020.