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WHAT'S NEW AND OLD IN TREATMENTS FOR PEDIATRIC DERMATOLOGY

The past year has seen many new, exciting, approved treatments in pediatric dermatology become commercially available as well as the release of new evidence about existing therapeutic agents. This article will provide the reader with an overview of these treatments and their evidence.

PSORIASIS

Several biologics for the treatment of psoriasis in children have received expanded indications from Health Canada in the past year. Ustekinumab, an IL12/23 inhibitor, was approved in June 2020 for the treatment of chronic, moderate-to-severe plaque psoriasis in patients 6 to 17 years of age who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapy.

The approved dosing is weight- based (**Table 1**) with injections at 0, 4 and then every 12 weeks thereafter. The expanded indication is based on CADMUS Junior, a phase III open-label single arm study of 44 children aged 6 to <12 years with moderate-to-severe psoriasis for at least 6 months and a PASI score of ≥12. At week 12, 77% of patients achieved PGA 0/1, 84% achieved PASI75 and 64% achieved PASI90 response. Ustekinumab's onset of action resulted in approximately 25% of patients achieving PASI75 by week 4, and almost 60% of patients by week 8. The most common adverse effects reported were nasopharyngitis (25%) and infections requiring treatment (27%). Overall, 34 patients (77%) had at least one adverse event.[1]

Agent	Indication	Dose	Frequency	Efficacy	Adverse effects
Etanercept	**4 years and older:** chronic severe PsO who are candidates for systemic therapy or phototherapy	0.8 mg/kg	Once weekly	12 weeks: PASI75 ~60-70% PASI90 ~30-40%	URTI (37.6%) Nasopharyngitis (26%) Headache (21.5%)
Ustekinumab	**6 years and older:** For moderate-to-severe plaque psoriasis, who are candidates for phototherapy or systemic therapy	<60 kg: 0.75 mg/kg 60-100 kg: 45 mg >100 kg: 90 mg	0, 4, then every 12 weeks	12 weeks: PASI75 84% PASI90 64%	Nasopharyngitis (25%) URTI (14%) Infections requiring treatment (27%) ISR (14%)
Secukinumab	**12 years and older:** For severe plaque psoriasis, who are candidates for phototherapy or systemic therapy Must weigh > 50 kg	150 mg	0,1,2,3,4 weeks then monthly	12 weeks: PASI75 77.5-80% PASI90 67.5-72.5%	Neutropenia (2.6%), Candida infections (1.8%) ISR (6.1%)
Ixekizumab	**6 years and older:** For moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy	<25 kg: 40 mg then 20 mg 25-50 kg: 80 mg then 40 mg >150 kg: 160 mg then 80 mg	Every 4 weeks	12 weeks: PASI75 89% PASI90 78%	Infections (32%) Serious infections (0%) Crohn's disease (1%) ISR (12%)

Table 1. Currently Approved Biologics for Pediatric Psoriasis in Canada

The infrequent dosing of ustekinumab coupled with the absence of routine bloodwork enhances its appeal as a treatment option in the pediatric population. However, its efficacy in children with psoriatic arthritis or inflammatory bowel disease has not been studied in trials to date.

In January 2021, secukinumab, an IL-17A inhibitor, was approved by Health Canada for its use in adolescents 12 years and older with severe plaque psoriasis who are > 50 kg. The recommended dose is 150 mg subcutaneously at weekly intervals for the first 5 doses and then monthly thereafter. This dose can be doubled to optimize response. Support for this indication was demonstrated in a phase III multicentre double-blind study of 162 patients with severe psoriasis defined by a minimum PASI of 20, and PGA of 4. Patients were randomized to receive secukinumab (either 150 mg or 300 mg), placebo or etanercept. At week 12, PASI75 response was achieved in 80% of patients receiving high dose, and 77.5% of those receiving low dose. Secukinumab's onset of action resulted in 30-50% of patients achieving PASI75 response by week 4, and roughly 60% of patients by week 8. Among the 114 subjects receiving either dose of secukinumab, adverse reactions within the first year of treatment included neutropenia (2.6%), candida infections (1.8%) and injection site reactions (6.1%).[2]

A trial of children aged 2-17 years with enthesitis-related arthritis or juvenile psoriatic arthritis was completed in 2020, and results may help elucidate the effectiveness of secukinumab in pediatric arthritis (NCT03031782).

The most recent biologic approved in the pediatric population for psoriasis is ixekizumab, approved in March 2021 for children aged 6 to less than 18 years of age with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This approval was based on a phase III multicentre double-blind placebo-controlled trial of pediatric patients with moderate-to-severe plaque psoriasis, defined as a minimum PASI of 12, and sPGA of 3. Patients were randomized to receive ixekizumab every 4 weeks at weight tiered dosing (**Table 1**) or placebo. An etanercept reference arm was added. At week 12, PASI75 response and an IGA of 0/1 were achieved in 89% and 81% of patients receiving ixekizumab respectively. Approximately 35% of patients achieved PASI75 by week 4, and almost 65% by week 8. Adverse events at week 12 included injection site reactions in 12%, and infections in 32% of patients of which none were categorized as serious. Among the 196 patients who received at least one dose of ixekizumab, 1 patient had Crohn's disease at 12 weeks, with another 3 patients during the maintenance period.[3]

There were no cases of inflammatory bowel disease (IBD) in the adolescent psoriasis trial of secukinumab as compared to ixekizumab. However, the study populations for both trials were quite small. A claims-based retrospective case-control study of 7,686 children with psoriasis and 30,744 children without psoriasis revealed an incidence rate per 1000 person years of

0.97 (0.53-1.62) for Crohn's disease and 0.62 (0.28-1.17) for ulcerative colitis. This translated to an incidence rate ratio of 3.34 (1.60-6.86) for Crohn's and 2.70 (1.11-6.27) for ulcerative colitis, $p<0.05$ for both. More data is clearly needed before any conclusions can be drawn about whether these biologics have a true risk of uncovering IBD in a population at risk, and if any factors could help in screening those at increased risk.[4]

ATOPIC DERMATITIS

Dupilumab, a human monoclonal antibody targeting IL-4 and IL-13, is now approved for children with atopic dermatitis starting from the age of 6 years. The dosing is weight-based (**Table 2**). The adolescent phase III trial included 251 patients with moderate-to-severe disease, defined by a minimum IGA of 3, and EASI of 16 at baseline. Of note, patients were not allowed concurrent topical steroids in the trial. By week 16, EASI75 response was achieved in 38-42% of patients, and an IGA of 0/1 in 18-24% of patients. The majority of these participants responded by week 8.[5]

Conversely, the trial in children aged 6-11 years included 367 participants over 16 weeks and required slightly worse dermatitis at baseline, with a minimum IGA of 4 and EASI of 21. Subjects were allowed to use concurrent topical steroids with dupilumab therapy during the study period.[6]

At week 16, 67-69% of participants achieved EASI75 response, and 30-33% of subjects achieved an IGA of 0 or 1. The onset of action was similar to that seen in adolescents, with many participants achieving response 8 weeks after randomization.

The transition of patients from other systemic treatments to dupilumab have been proposed, with suggestions centering on longer tapers of cyclosporine to avoid a rebound. One published treatment algorithm suggests overlapping therapeutic agents for 8 weeks before tapering by 25% bi-weekly for cyclosporine, and by 50% every 4 weeks for other immunosuppressants.[7]

The guidance for the evaluation of risk and for the management of conjunctivitis and head and neck dermatitis are available for adult patients, and these could be used to inform the approach in pediatric patients. In the adolescent trial, most cases of conjunctivitis occurred in the first 2-3 months after treatment, and none led to the discontinuation of therapy. Interestingly, the rates of conjunctivitis in adolescents being treated with dupilumab for asthma are much lower than the rates of conjunctivitis seen in adolescents being treated with dupilumab for AD, and more research is required to determine possible explanatory factors for this phenomenon.[8] Recommendations for the screening and management of conjunctivitis include baseline assessment of risk factors including high IgE and pre-existing ocular signs or symptoms, use of lubricating drops, and involvement of ophthalmologists when symptoms develop.[9-11]

Head and neck dermatitis may be more common in the younger population, and a diagnostic challenge owing to its broad differential diagnoses. Morphologic distribution can be helpful; with isolated eyelid or periocular involvement more suggestive of allergic contact dermatitis, while involvement of both periocular and perioral regions being more consistent with periorificial dermatitis.[12] Malassezia-associated dermatitis may be more common in the pediatric population, and it is most prominent on the central face, forehead, chin and neck. Successful treatment of post-pubertal adolescents receiving dupilumab with head and neck dermatitis has been reported with systemic fluconazole for a week in a recently-published case series involving five adolescent patients.[13]

Dupilumab is also approved for the treatment of asthma in adolescents and is being studied in many eosinophil-mediated conditions. With JAK inhibitors on the horizon having potential for faster onset of action, concurrent treatment of atopic comorbidities will likely play a role in selecting optimal systemic treatments for children with atopic dermatitis.

Indication	Dose	Efficacy	Adverse effects
6 years and older: For moderate-to-severe atopic dermatitis, not adequately controlled with topical prescription therapies or when those therapies are not advisable	15-< 30 kg: 600 mg then 300 mg every 4 weeks 30-< 60 kg: 400 mg then 200 mg every 2 weeks 60 kg+: 600 mg then 300 mg ever 2 weeks	Age 6-12 years (Week 16) EASI75 ~75%, IGA 0/1 ~30-40% Age 12-17 years (Week 16) EASI75: 42% IGA 0/1: 24%	Age 6-12 years Conjunctivitis ~ 7-15% ISR ~10% Age 12-17 years Conjunctivitis ~ 10-11% ISR 6 - 8.5%

Table 2. Dupilumab indication, dose, efficacy and adverse event profile

Crisaborole 2% ointment remains a non-steroidal topical alternative for atopic dermatitis in children aged 2 years and older. The use of concurrent moisturizers to minimize any burning or irritation with application has been suggested by some clinicians. A small study examined the absorption of crisaborole in an ex vivo abdominal skin model.[14] When applied within 15 minutes after a moisturizer (in a cream or ointment), there was decreased absorption in both the epidermis and dermis. Additionally, there was decreased epidermal absorption of crisaborole when an ointment vehicle was applied immediately after. This small study suggests that waiting at least 15 minutes before applying moisturizers may optimize absorption of crisaborole.

ACNE

Trifarotene, a selective RAR-γ agonist, was recently approved as a 0.005% cream in Canada for treatment of facial and truncal acne in adolescents aged 12 years and older. The approval was supported by two phase III double-blind, randomized, vehicle-controlled, 12-week studies (PERFECT 1 and PERFECT 2) in 2420 patients aged 9 years and older.[15] For the 1214 patients treated with trifarotene and 1206 treated with vehicle, the week 12 facial success rates according to the IGA were 29.4% in PERFECT 1 and 42.3% in PERFECT 2 (vs 19.5% and 25.7% for vehicle [$P < .001$]); trifarotene had statistically significant superior success rates at week 4 (PERFECT 1) and week 8 (PERFECT 2). At week 12, the rates of success with trifarotene according to the truncal PGA were 35.7% in PERFECT 1 and 42.6% in PERFECT 2 (vs 25.0% and 29.9%, respectively for vehicle [each $P < .001$]). An open-label extension demonstrated ongoing improvement past 12 weeks, with an IGA of 0/1 being achieved in almost 70% of patients by 52 weeks.[16] The cream was well-tolerated in the majority of patients, with the main side effect of local irritation peaking in the first week on the face and at 2-4 weeks on the trunk with subsequent improvement over time.

Trifarotene has also been shown to increase expression of transglutaminase 1, which promotes keratinocyte cohesion.[17] Based on this observed effect, it is also being studied in clinical trials at higher concentrations (0.015% and 0.02%) in adolescents aged 12 years and older for lamellar ichthyosis (NCT03738800), but no interim results have been released and recruitment is ongoing.

Spironolactone has been used to treat acne in adults successfully for many years, but there has been limited data in pediatric patients. A recent retrospective review of 80 female patients including the pediatric population (median age 19 years; range 14-20) from a single clinic (Mayo Clinic, Rochester, Minnesota) reported complete response in 22.5% of patients, and a complete or a partial response greater than 50% in 58.8% of subjects.[18] The median dose was 100 mg, and median time to initial and maximal responses were 3 and 5 months respectively. Responders were more likely to have jawline distribution of acne (70.3% vs 56.3%) and cyclic flares (75% vs 56.3%), although this was not statistically significant. Only 3 patients experienced side effects (rash, breast tenderness, diarrhea, and headache) and required discontinuation of treatment. Investigators did not report symptoms of hypotension, although blood pressure and potassium were not routinely checked in the cohort due to a low risk of hyperkalemia in younger patients.

MORPHEA

There is now increasing evidence to support the efficacy and safety of mycophenolate mofetil (MMF) for pediatric morphea. To date, the combination of methotrexate (MTX) with pulse corticosteroids has been a first-line treatment approach for children with morphea requiring systemic treatment to prevent irreversible joint contractures or permanent deformities. However, up to 30% of patients do not respond to this combination treatment. Studies in adult populations suggest MMF may be an effective alternative.[19] In a retrospective study, outcomes of 47 patients treated with MTX were compared to 22 patients treated with MMF because of MTX-refractory disease or intolerance to MTX.[20] After a mean follow-up period of 9.4 years, 90.9% of patients on MMF and 100% of those on MTX had inactive disease.
Full doses of MTX and MMF were 15–17 mg/m2/week and 700-1000mg/m2/day respectively. Side effects of MMF included headache (22.7%), mild increase in transaminases (18.2%), nausea/vomiting (9.1%) and fatigue (9.1%), with none of the reported adverse events leading to drug discontinuation. Given the impressive performance of MMF, its efficacy in treatment-naïve patients compared to a traditional MTX and steroid combination may help secure its place in our treatment algorithm for pediatric morphea.

ALOPECIA AREATA

With the current lack of approval of JAK inhibitors for children with alopecia areata (AA), and challenges with availability and the cost of off-label preparations and compounds, this population remains in need of therapies for this condition. A recent review of five studies reported good or complete response in 34 of 68 children treated with methotrexate.[21] An additional retrospective review from Sunnybrook Health Sciences Centre in Toronto reported partial response in 4 of 7 children treated with MTX.[22] More data would help characterize responders and clarify optimal duration and dose of treatment.

There is also excitement about the potential of dupilumab for the treatment of AA, based on cases of regrowth of AA in patients with atopic dermatitis. A recent case series of 16 children with both atopic dermatitis and AA who were treated with dupilumab reported good regrowth in 4 of 8 children who had follow-up at 4 months.[23] One possible but unproven explanation for the divergent responses to dupilumab involves considering AA in four classifications as described by Ikeda.[24] In patients with severe atopic dermatitis and AA that is being perpetuated by massive interferon release, control of the dermatitis may be enough to allow for resolution of the alopecia. Conversely, in patients without pre-existing AA, treatment with dupilumab may lead to a shift in the immune system, triggering alopecia areata mediated by autoreactive CD8+ T cells.

HIDRADENITIS SUPPURATIVA (HS)

Adalimumab has been approved for the treatment of adolescent HS for several years, but the indication was not based on clinical trial data, thereby limiting our knowledge of its efficacy and onset of action in this patient population. A recent retrospective chart review of adolescents treated with biologics included seven patients aged 8-13 with Hurley Stage 2-3 disease treated with adalimumab.[25] Four patients responded with a minimum of 50% reduction in total abscess and inflammatory nodule count at 4 months, while the other 3 were switched to other biologics due to a failure in achieving Hidradenitis Suppurativa Clinical Response (HiSCR) on their original biologic therapy. No patients reported adverse events.

It is clearly an exciting time for pediatric dermatology, and the momentum is likely to continue with many new therapeutic options in the pipeline and new evidence emerging to optimize our treatment of dermatoses in this patient population.

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