The use of systemic medications in pediatric dermatoses: A review

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Abstract

Research has begun to illustrate a favorable efficacy and side-effect profile for many systemic agents used in pediatric dermatological conditions (i.e. atopic dermatitis, psoriasis, scleroderma, alopecia areata, chronic spontaneous urticaria, autoimmune blistering disorders, and hidradenitis suppurativa) despite not having extensive randomized clinical trials. The purpose of this article is to summarize the available data on the treatment regiments, safety, and efficacy of systemic immunosuppressants, including the newer biologics, focusing on the most up-to-date systematic reviews or randomized clinical trials. The review demonstrates that many of the present studies lack data on long-term efficacy and consist of small patient populations. Further research into the long-term safety of these systemic medications is of vital importance especially due to the chronic nature of most pediatric dermatological conditions that require the use of systemic agents.

Keywords: systemics, immunosuppressant medications, biologics, pediatric dermatology conditions

Introduction

Since their discovery in the 1940s1, glucocorticoids have become a main stay of treatment for many autoimmune and inflammatory conditions in both the adult and pediatric populations. However, despite their widespread use, chronic glucocorticoid treatment has significant side effects in the pediatric population including growth suppression, cataract formation, diabetes, adrenal insufficiency, and behavioral disturbances.2-13 Other oral and parenteral immunosuppressants have since been developed for use in the adult population with a side effect profile that can be monitored and managed, especially in dermatological conditions. Many of these systemic agents are not yet approved for use in the pediatric population, and there is a paucity of pharmacokinetic data. In addition, many pediatric dermatological conditions do not have standardized guidelines for the use of immunosuppressants. Few studies have examined the short- and long-term side effects of systemic agents. The purpose of this article is to provide a consolidated review of the data available involving the use of systemic agents in pediatric dermatological conditions. Online article databases (e.g. PubMed) were searched for pediatric dermatological conditions that mentioned the use of systemic agents for treatment. The primary focus was to include the most up-to-date systematic reviews or randomized clinical trials. However, in the instance that these were not available, case reports and case series were included to present a full summary of potential treatment options that could be explored.

Severe Atopic Dermatitis

Within pediatric dermatological conditions, the most comprehensive data on the use of newer immunosuppressants is for atopic dermatitis (AD)
and psoriasis. In 2014, the Pediatric Dermatology Research Alliance (PeDRA) surveyed 133 U.S. and Canadian members of the Society for Pediatric Dermatology to assess clinical practice regarding the use of systemic agents in the management of severe AD. Responders who did not prescribe systemic immunosuppressants were directed to the end of the survey, while those who did were presented with a clinical scenario of an adolescent patient who had failed treatment with potent topical corticosteroids, antihistamines, and phototherapy. Participating clinicians were asked to record their first-, second-, and third-line systemic drugs of choice. First-line drugs of choice were cyclosporine (45.2%), methotrexate (29.6%), and mycophenolate mofetil (13.0%). The most commonly used second line agents were methotrexate (31.3%) and mycophenolate mofetil (30.4%). Finally, azathioprine was the most commonly cited third-line agent. The initial and maximum dosages, length of treatment, and discontinuation regimens obtained from the survey results are included in Table 1, along with the percentage of respondents who prescribed each regimen. However, the clinical nature of the disease at the time of termination was not reported in the study, and the sequence of prescribing systemic medications or concomitant use of combination systemic therapy was not assessed. In addition, since the information was obtained from the respondents and chart review was not performed, recall bias could be another potential limitation. Of note, this study was performed before the approval of dupilumab for pediatric AD.

A 2014 retrospective chart review of 55 pediatric patients seen at Children’s Hospital of Philadelphia was performed to evaluate the efficacy of methotrexate (mean starting dose, mg/kg: 0.37 (0.12-0.73); mean highest dose reached, oral, mg/kg: 0.45 (0.12-1.00); mean highest dose reached, subcutaneous, mg/kg: 0.50 (0.22-0.77)) in children with severe AD. The strength of the study included measured improvement using the Investigator’s Global Assessment (IGA), a scale that rates AD symptoms from 0 to 5. The results demonstrated a significant change in the IGA score after at least 6-9 months of treatment with further improvement after 12-15 months. Forty-two patients (76.4%) showed improvement with methotrexate and 13 patients (23.6%) showed no significant improvement per provider documentation. The most common adverse side effect experienced was gastrointestinal discomfort and nausea. However, seven patients had either transiently elevated transaminases or a low hemoglobin and hematocrit necessitating in lowering the dose or discontinuation, and about half of the patients experienced skin infection while on methotrexate. Cyclosporine is a rapid-acting medication but is associated with quick relapse upon cessation; it has the risk of hypertension and renal damage with long term use. Azathioprine has a black box warning for malignancy. Therefore, the authors concluded that, methotrexate may be a safe reliable option for long-term symptom control in patients with severe AD. Similar results were seen in a study with 47 children by Dvorakova et. al with a mean methotrexate dose of 0.34 mg/kg (0.2-0.5 mg/kg) taken weekly. Finally, a 12-week multicenter randomized control trial with 40 children in Egypt demonstrated a similar efficacy between methotrexate (7.5 mg/week) and cyclosporine (2.5 mg/kg/day) in children with severe atopic dermatitis.

In the afore-mentioned studies, guidelines for monitoring while on systemic agents were not discussed, and official guidelines for monitoring while on systemic treatment for pediatric AD do not exist. However, in 2015, a review on the systemic therapy of childhood atopic dermatitis was performed which included collating available evidence on dosing and monitoring in children. These results are shown in Table 2.

In 2014, dupilumab, an IL-4/13 inhibitor previously approved for the use of adult moderate to severe atopic dermatitis, was also approved for use in adolescents ages 12-17 years for moderate to severe AD. Results from a phase III clinical trial of dupilumab in adolescents demonstrated that 38.1% of patients achieved a 75% or greater improvement in their Eczema Area and Severity Index (EASI) scores at 16 weeks on a monthly dosing, while 41.5% with dupilumab every two weeks versus only 8.2% of placebo achieved a 75% or greater improvement. The trial included weight-based dosing of either 200 mg or 300 mg injections every two weeks following a loading dose. Adverse events in the dupilumab versus placebo groups included injection site reactions (6.8-17.5 vs 3.5%) and conjunctivitis (10%-11% vs 5%). Conversely, skin infections were less common in the dupilumab treated patients (11%-13% vs 20%). Currently, other trials are being conducted to examine the effects and dosing of dupilumab in children ages 6-12 years (NCT03345914), 6 months to 18 years (NCT02612454), and PK studies in 2-6-year olds and 6 months-2-year olds (NCT03346434). It remains to be seen how prescribing practices and first line therapies may change with the Food and Drug Administration (FDA) approval of dupilumab.
Table 1. Dosing Schedules of Systemic Agents Prescribed by Respondents in the PeDRA survey (Totri et al.)\textsuperscript{14}

<table>
<thead>
<tr>
<th>Systemic Agent</th>
<th>Initial dose (%</th>
<th>Maximum dose (%)</th>
<th>Average duration of treatment (%)</th>
<th>Maximum duration of treatment (%)</th>
<th>Discontinuation Regimen (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>2 mg/kg/day (55.1)</td>
<td>3 mg/kg/day (70.0)</td>
<td>4-12 months (60.9)</td>
<td>&gt; 12 months (73.9)</td>
<td>Taper dose over 1 month (52.2)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3-5 mg/kg/day (53.8)</td>
<td>3-5 mg/kg/day (71.0)</td>
<td>4-12 months (65.6)</td>
<td>4-12 months (62.4)</td>
<td>Taper dose over 1 month (48.4)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>300 mcg/kg/week (26.1)</td>
<td>&gt; 400 mcg/kg/week (47.8)</td>
<td>4-12 months (70.7)</td>
<td>&gt; 12 months (78.3)</td>
<td>Taper dose over 1 month (34.8)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>10 mg/kg/day (39.7)</td>
<td>&gt; 20 mg/kg/day (41.0)</td>
<td>4-12 months (66.7)</td>
<td>&gt; 12 months (64.1)</td>
<td>Taper dose over 1 month (51.3)</td>
</tr>
</tbody>
</table>


Table 2. Dosing and Monitoring Guidelines for Pediatric AD Systemic Agents (Slater and Morrell)\textsuperscript{19}

<table>
<thead>
<tr>
<th>Systemic Agent</th>
<th>Starting dose</th>
<th>Dose adjustment</th>
<th>Recommended baseline testing</th>
<th>Monitoring</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>2.5-5 mg/kg, divided twice daily; 5 mg/kg usually considered max. Start with initial high dose (5mg) and taper, OR 2. Start with lower dose (2.5-3.5 mg) and gradually increase.</td>
<td>1. After response, decrease by 1 mg/kg every 2 weeks until minimum effective dosage for patient is reached. Treatment can be continued up to a year. 2. Increase in Increments of 0.5-1 mg/kg every 2 weeks until good response (5 mg/kg max).</td>
<td>Measure blood pressure; CMP with creatinine, CBC; consider LFTs and fasting lipids.</td>
<td>Repeat CBC, CMP every 2 weeks for first 1-2 months, then every 4-6 weeks. Check blood pressure at each visit. Discontinue or reduce dose when Creatinine &gt; 30% above baseline.</td>
<td>Most Common: GI disturbances, neurologic effects (headaches, paresthesias). Also watch for: mucocutaneous lesions, arthralgias renal dysfunction/increased creatinine, other laboratory abnormalities, hypertension.</td>
</tr>
</tbody>
</table>

Continued
### Table 2. Cont’d

<table>
<thead>
<tr>
<th>Systemic Agent</th>
<th>Starting dose</th>
<th>Dose adjustment</th>
<th>Recommended baseline testing</th>
<th>Monitoring</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azathioprine</strong></td>
<td>1. If TPMT 15.1-26.4 U/ml, start with 2.5 (range 2–3.5) mg/kg daily.</td>
<td>Consider dose adjustment or repeat TPMT measurement if response changes. Treatment often continued for more than 1 year, then gradually tapered after stable remission.</td>
<td>TPMT assay, CBC, CMP; consider pregnancy test.</td>
<td>CBC with differential, CMP, and LFTs every other week for 2 months, then every 2–3 months.</td>
<td>Most Common: GI disturbances, increased LFTs. Also watch for: severe myelosuppression (rare), malignancy (rare), cutaneous infections, hypersensitivity, teratogenicity.</td>
</tr>
<tr>
<td><strong>Mycophenolate mofetil</strong></td>
<td>2-3 g divided BID (adults); 20–50 mg/kg/day (younger patients).</td>
<td>Increase daily total dose in 500 mg increments every 2–4 weeks. Can be used for more than 1 year.</td>
<td>CBC, CMP, LFTs; consider tuberculosis test, pregnancy test.</td>
<td>CBC with differential, CMP, LFTs every 2–4 weeks following dose increase, and every 2–3 months on stable dose.</td>
<td>Most common: GI disturbances. Also watch for: increased predisposition to infections, malignancy (rare), myelosuppression, neurologic effects (headache, fatigue), teratogenicity.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Initiate with test dose of 5–10 mg (or 10–15 mg/m² in children). Typically given once weekly; alternative schedule (4 consecutive days) may be preferred in AD.</td>
<td>Escalate by 2.5-5 mg each week to effective dose. Taper by 2.5mg each week to lowest effective dose. Folic acid typically given on nontreatment days.</td>
<td>CBC with platelets, LFTs, Hepatitis B, C; CMP with creatinine; consider pregnancy test.</td>
<td>CBC, LFTs every 1–2 weeks for 2–4 weeks and after dose escalations; decrease to every 3–4 months.</td>
<td>Most common: GI disturbances, hepatotoxicity. Also watch for: neurologic effects (headache, fatigue), stomatitis, pneumonitis (rare), pancytopenia, abortifacient.</td>
</tr>
</tbody>
</table>

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Other biologic agents and small molecule inhibitors (ustekinumab, omalizumab, Lebrikizumab, traloknumab, fezakinumab, apremilast, mepolizumab, rituximab, infliximab, etanercept, adalimumab) have been studied in adults with AD with varying success; however,
none has been studied in children and therefore, will not be discussed further.

**Psoriasis**

Evidence on the efficacy and safety of systemic treatment for psoriasis in children is limited. Current treatment is based on guidelines for adult psoriasis, case series, expert opinion, or experience with systemic drug administration in other pediatric disorders. Most systemic treatments are not approved for psoriasis in children and are used off-label.21

**Plaque Psoriasis**

In 2017, a retrospective chart review was conducted at 20 centers in North America and Europe to assess patterns of use and relative risks of systemic agent use in 390 children with moderate to severe psoriasis. It was shown that methotrexate and tumor necrosis factor inhibitors were the most frequently used agents. In children, it is only approved for juvenile idiopathic arthritis (JIA), inflammatory bowel disease, and malignancies.21 Of the traditional systemic agents, more medication related adverse events occurred with cyclosporine, acitretin and fumaric acid esters, with methotrexate having the least side effects. A systematic review on efficacy and safety of systemic treatments in pediatric psoriasis by van Geel et al. recommended methotrexate as the first treatment of choice before use of other systemic treatment for plaque psoriasis in children who need to be treated with systemic agents.24 In comparison, tumor necrosis factor inhibitors were associated with fewer adverse events than methotrexate. Folic acid (a mean dose of 7.5 ± 5.8 mg/wk) administration 6-7 times per week protected more against methotrexate induced gastrointestinal side effects than did once weekly dosing. Methotrexate was administered both orally and subcutaneously with a mean treatment duration of 18.7 ± 16.8 months with a mean initial dose of 0.27 ± 0.13 mg/kg/wk and a maximal dose of 0.36 ± 0.16 mg/kg/wk.25 In general, for psoriasis in children, the dose of methotrexate varies from 0.3-0.7 mg/kg/week.21,23 If therapeutic effect is achieved, the dose can be tapered to maintenance dose.21 The most frequently reported adverse events from methotrexate use were GI related (nausea [46 of 270 (17.0%)], dyspepsia [19 of 270 (7.0%)], and elevated transaminases [36 of 270 (13.3%)]).

Systemic retinoids are not widely used for psoriasis in children because of a lack of clinical trials. Only case reports, case series, and retrospective analyses are available. Systemic retinoids can be used for plaque, guttate, palstular psoriasis and erythroderma.26 According to the German expert consensus, the dosage of acitretin is based on age and weight, with initial dose ≤ 0.5-1 mg/kg/day. The use of retinoids is known to cause several side effects such as teratogenicity especially in adolescent girls, elevated liver enzymes and elevated lipid profiles. Long-term use of high doses of retinoids has been linked with diffuse idiopathic skeletal hyperostosis, premature epiphyseal closure, and loss of bone mineral density.21

Another systemic agent used for psoriasis is cyclosporine. This agent can be used to treat plaque or pustular type psoriasis with dosage 1.5-5 mg/kg/day for 6 months to 2 years. The dose can be tapered after the disease has improved for 2-3 months to the lowest dose possible and for the shortest treatment period. It is important to monitor blood pressure and renal function during treatment with cyclosporine.21,26

Biologic agents have a more convenient schedule of administration and require less frequent laboratory monitoring; most of them have been approved for treatment in pediatric patients. They are used as second- and third-line therapy for severe and/or refractory cases of plaque, pustular and erythrodermic psoriasis. As targeted therapy, biologic agents have less toxicity potential. However, there have been some complications reported in children treated for JIA, including opportunistic infections, tuberculosis reactivation, malignancies, autoimmune and demyelinating diseases.27 Biologic agents may be considered in pediatric patients with PASI ≥ 10 or BSA ≥ 10% and DLQI > 10, who have failed phototherapy or other systemic therapy and who have contraindications to other traditional systemic therapies.28

In a retrospective chart review, etanercept was found to be the most frequently used biologic in both North America and Europe, with the most frequent adverse effects being injection site reactions and infections.25 Etanercept was the first biologic to be investigated for the treatment of psoriasis in the pediatric population; in 2016, it received approval for pediatric psoriasis in patients ages 4-17 years (United States and Canada) and ages 6-17 years (Europe). A phase III double blind, placebo-controlled study had been conducted in children ages 4-17 with moderate-to-severe plaque psoriasis testing etanercept. Fifty seven percent of patients achieved a 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 75) at week 12, while 27% achieved a 90% improvement in PASI score (PASI 90) by week 12 (p<0.001) on
etanercept 0.8 mg/kg weekly (maximum 50 mg per dose). The most commonly reported adverse events were upper respiratory tract infection, nasopharyngitis, and headache. In addition, effectiveness of etanercept was studied in 23 pediatric patients across multiple centers belonging to the ‘Pediatric Dermatology Group’ of the Italian Society of Dermatology (SiDeMaST). At week 12, 56.5% of the patients achieved PASI 75, 86.9% achieved PASI 50. Their observations further demonstrated that etanercept was well-tolerated and effective in a real-life pediatric cohort.

The next biologic that has received a significant amount of attention in pediatric patients with psoriasis is adalimumab. Adalimumab (ADA) is approved for use by the European Medicines Agency (EMA) for use in children ≥ 4 years for moderate-to-severe plaque psoriasis. A randomized double-blind phase III study was conducted in Europe to evaluate the long-term safety and efficacy of adalimumab in children with psoriasis. Patients were randomized 1:1:1 to adalimumab 0.8 mg/kg (40 mg maximum) or 0.4 mg/kg (20 mg maximum) every-other-week or to methotrexate (MTX) 0.1–0.4 mg/kg (25 mg maximum) weekly. The 16-week Initial Treatment (IT) period was followed by a 36-week withdrawal period and a 16-week retreatment period. Patients could enter the long-term expansion at pre-specified time points to receive ADA 0.8 mg/kg (blinded or open label), ADA 0.4 mg/kg (blinded), or remain off treatment. The study showed that children demonstrated reduced and maintained disease severity and no new safety risks were identified. It should be noted that at the time of this writing, adalimumab has not been approved by the US FDA for the treatment of pediatric plaque psoriasis in the United States.

Another biologic, ustekinumab, an IL12/23 inhibitor, is approved for adolescent psoriasis in patients 12–17 years of age in the United States, Canada, and Europe. The CADMUS study, a randomized phase III trial to evaluate ustekinumab in adolescents ages 12–17 with moderate-to-severe plaque psoriasis, showed that at week 12, 69.4% of patients achieved PGA 0/1 with ustekinumab standard weight-based dosing (0.75 mg/kg for ≤60 kg, 45 mg for if >60 to ≤100 kg, and 90 mg for >100 kg) compared to 5.4% in the placebo group. A greater proportion of patients achieved PASI 75 and PASI 90 compared to placebo (80.6% and 61.1% for ustekinumab versus 10.8% and 5.4% for placebo, p < 0.001). The most common adverse event was nasopharyngitis (2.5% for ustekinumab and 27% for placebo). The proportions of patients who achieved PGA 0/1, PASI 75, or PASI 90 responses were maintained from week 12 through week 52. Only one ustekinumab injection was associated with a mild injection-site reaction. There were no cases of serious or opportunistic infections, or malignancies over 60 weeks’ follow-ups. Additional studies to monitor the long-term safety and side effects of ustekinumab in adolescents are currently underway. In addition, a study is going on to evaluate the efficacy and safety in younger children ages 6–11 years (NCT02698475).

In 2006, infliximab was approved by the FDA as treatment for Crohn’s disease in children ≥ 6 years old, but it has not been approved for treatment in pediatric psoriasis patients. Evidence regarding the use of infliximab in pediatric patients only comes from case reports. Infliximab can be used for plaque and generalized pustular psoriasis with dose range of 3.3–5 mg/kg administered in weeks 0, 2, 6, and every 7–8 weeks thereafter.

A comprehensive review of current data on biologics for the treatment of pediatric psoriasis was most recently accepted for publication. A Canadian panel composed of experts in psoriasis, pediatric dermatology, and/or experience with the consensus recommendation process was selected to review the current landscape of pediatric psoriasis and clinical data on biologics plus identify special considerations for baseline work-up and monitoring. Their recommendations were as follows. Prior to initiating biologics, patients should be screened for infections such as tuberculosis (TB), hepatitis, and varicella along with obtaining renal studies and a complete CBC with differential. A chest radiograph should be performed if the initial screen for TB is positive. However, no routine ongoing monitoring was recommended during the use of biologics and any repeat testing could be considered on a case by case basis. Children should be up to date on all immunizations as per the national and/or Center for Disease Control and Prevention (CDC) guidelines prior to initiating a biologic, and treatment should not be initiated in children whose parents choose not to vaccinate their children. Live vaccines are contraindicated in patients on biologics. If live vaccines are required, the Canadian authors recommend discontinuation of the biologic for at least three months prior to vaccine administration, while British guidelines recommend at least six months prior to vaccine administration, and the reintroduction of the biologic can be done at least four weeks after vaccine administration. In addition, inactivated vaccines may be given while on biologics but for optimal immune response, can be given two weeks prior to initiation of
Further, monitoring antibody titer levels may be a reasonable approach if vaccines are administered while on treatment. Future directions in the treatment of pediatric psoriasis include testing the use of secukinumab, ixekizumab, and brodalumab in children (NCT02471144, NCT03073200, NCT03240809). Finally, a phase III pediatric psoriasis trial is currently underway to test guselkumab (NCT03451851) and a phase II study on the use of apremilast is being conducted (NCT02576678). Current biologics used in pediatric dermatology are listed in Table 3.

**Table 3. Biologics Used in Pediatric Psoriasis (Lansang et al)**

<table>
<thead>
<tr>
<th>Systemic Agent</th>
<th>Approval for psoriasis</th>
<th>Dosage and frequency</th>
<th>Prior to Initiation</th>
<th>Contraindications</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Ages 4-17 (United States and Canada) and ages 6-17 (Europe).</td>
<td>0.8mg/kg once weekly (maximum 50mg per dose)</td>
<td>Tuberculosis, hepatitis, varicella screening, renal studies, complete blood count with differential, up to date on all immunization</td>
<td>Live vaccines are contraindicated while on biologics</td>
<td>Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNFα-blockers. Demyelination disease. Caution during pregnancy.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Ages 4-17 (Europe)</td>
<td>0.8 mg/kg (maximum 40mg per dose)</td>
<td>Frequency: Week 0 and 1, followed by every other week</td>
<td>Active TB or other severe infections such as sepsis or opportunistic infections</td>
<td>Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNFα-blockers. Demyelination disease. Caution during pregnancy.</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Ages: 12-17 (United States, Canada, Europe)</td>
<td>&lt; 60kg: 0.75 mg/kg, ≥ 60kg to ≤ 100kg: 45 mg, &gt; 100 kg: 90mg</td>
<td>Frequency: Week 0 and 4, followed by every 12 weeks</td>
<td>Reversible posterior leukoencephalopathy syndrome</td>
<td>Caution during pregnancy.</td>
</tr>
</tbody>
</table>

Pustular Psoriasis
Despite the growing evidence for use of biologics in pediatric plaque psoriasis, there remains little data involving randomized clinical trials or guidelines on the treatment of generalized pustular psoriasis (GPP). Previously, oral retinoids, methotrexate, and cyclosporine were described as first line systemic agents for generalized pustular psoriasis in a systematic review by Posso-De Los Rios et al.\(^{36}\) Mean treatment doses included the following: acitretin (0.8 mg/kg ± 0.2 mg per day) for a duration of 20 ± 26 months, cyclosporine A (3.3 ± 3.1mg/kg per day) for a duration of 6 ± 4 months, and methotrexate (0.3mg/kg ± 0.1 mg per week) for a duration of 5 ± 8 months. However, despite acitretin, methotrexate, and cyclosporine appearing to control GPP within three months of therapy initiation in these studies, information on long term efficacy and safety was not available.\(^{36}\) On a rare occurrence, pseudotumors cerebi was reported in a 12-year-old boy with GPP using oral acitretin 25-35 mg/day for one and half months.\(^{37}\)

A systematic review was published in 2016 that encompassed twelve case reports which met the inclusion criteria. The objective of the study was to summarize and compare the efficacy and safety of biologic agents such as etanercept, adalimumab, and infliximab in the treatment of pediatric GPP. The case reports documented the successful use of biologic agents in refractory cases following the use of traditional systemics such as methotrexate, acitretin, and corticosteroids. After reviewing the efficacy of these drugs in pediatric pustular psoriasis and examining their adverse effects from the other uses in pediatric populations, it was concluded that etanercept could be a possible first line biologic agent for pustular psoriasis, followed by infliximab and adalimumab.\(^{38}\)

Dosages used for etanercept in the above case reports included 0.4 mg/kg twice weekly, and side effects noted included candidiasis and MRSA infection.\(^{39}\) Similarly, another case report of a 3-year-old child with GPP after failing treatment with cyclosporine A and acitretin, initially responded dramatically to infliximab (5 mg/kg at weeks 0, 2, and six and then every seven weeks thereafter) with complete resolution of the lesions in two weeks. However, after one year, exacerbation of the disease reoccurred, and the child was switched to subcutaneous etanercept at a dose of 0.4 mg/kg/day twice weekly for two months, then 0.4 mg/kg weekly.\(^{40}\) Other dosages of successful etanercept use included 25 mg twice weekly for thirteen months, 0.4 mg/kg twice weekly for sixty months, and 0.4 mg/kg twice weekly for eighty-six weeks.\(^{41-43}\)

In case reports included in the systematic review, infliximab was administered as an infusion (5 mg/kg) with either a repeat dose at two weeks or repeat doses at week 2 and 6, and every seven weeks thereafter, or repeat doses at week 0, 2, 6, and every eight weeks thereafter.\(^{44-46}\) Of note, one of the cases involved a patient who had the homozygous missense mutation in the IL36RN gene resulting in deficiency of the interleukin-36 receptor antagonist (DITRA) which presents as severe generalized pustular psoriasis very early in childhood. Treatment with anakinra, an IL-1 receptor antagonist, (4 mg/kg/day) had a markedly positive effect but did not result in total remission. Consequently, methotrexate was increased to 15 mg/m\(^2\)/week given subcutaneously. After eight weeks and optimized doses of 8 mg/kg/day of anakinra without sufficient remission, the treatment was shifted to infliximab 6.5 mg/kg/dose on day 0, 14, 28, and thereafter every four weeks with excellent effect within few days on the skin.\(^{47}\)

Overall, maintenance therapy after achieving remission with infliximab was with methotrexate, infliximab, or a combination of the two.

Finally, adalimumab was successful in three of the twelve cases. All three cases involved patients who were started on adalimumab after failing other systemic agents.\(^{48}\) The dosages of two cases were specified at 40 mg at week 0, 1, and then every two weeks and 40 mg every two weeks.\(^{49,50}\) Despite the growing number of case reports, formal randomized clinical trials are needed to gain a better understanding of the efficacy and side effects of these medications for pediatric pustular psoriasis.

Scleroderma
Localized Scleroderma
A good amount of literature is present on the treatment of moderate-to-severe juvenile localized scleroderma (jLS). A randomized double-blind controlled trial was performed in 2011 to assess the safety and efficacy of methotrexate in the treatment of jLS. Patients were randomized either to receive oral methotrexate (15 mg/m\(^2\), maximum 20 mg/m\(^2\)) or placebo once weekly for twelve months. The proportion of patients whose disease responded to treatment was consistently higher in the methotrexate group than in the placebo group. As commonly reported, the most frequent side effect to methotrexate administration were GI effects.\(^{51}\) In 2010, a survey administered to 195 members of the pediatric rheumatology alliance CARRA (Childhood Arthritis and Rheumatology

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Research Alliance) to assess how they treated pediatric localized scleroderma showed that once the disease was considered to be inactive, most pediatric rheumatologists in North America continued treatment with methotrexate for an additional six to twelve months.\textsuperscript{52}

In 2012, the same Childhood Arthritis and Rheumatology Research Alliance (CARRA) came up with guidelines for the treatment of high severity JLS and determined that this level of severity should be treated with systemic immunosuppressive agents.\textsuperscript{53} Since severity levels for JLS had not been previously determined, high severity was defined as presentation with generalized or pansclerotic morphea, craniofacial linear scleroderma (en coup de sabre), or other subtype with evidence of high morbidity (e.g., CNS involvement, limb shortening, joint contracture). Three different treatment regimens using a combination of methotrexate alone, methotrexate + IV steroids, or methotrexate + PO steroids were presented based on best available evidence and consensus agreement amongst members. The most commonly specified dose of methotrexate was 1 mg/kg/week with the majority favoring subcutaneous administration and a maximum dose of 25 mg weekly and supplementation with folic acid (0.4-1 mg per day or folic acid (5 mg weekly)).\textsuperscript{54}

Mycophenolate mofetil (MMF) has been presented as another potential option for the treatment of JLS. A retrospective chart review performed on ten patients who had failed the combination treatment of methotrexate and IV and/or oral corticosteroids were treated with mycophenolate mofetil. The MMF dose used ranged from 600 to 1200 mg/m\(^2\)/day twice daily. When MMF was initiated, the mean disease duration was 18 (range 8–62) months. In six patients, both immunosuppressants (methotrexate and MMF) were administered, whereas in two patients, methotrexate was discontinued at the introduction of MMF. The mean duration of treatment with MMF, at last follow-up evaluation, was 20 (range 6–40) months. All the patients tolerated MMF well and no side effects were noted with good clinical improvement.\textsuperscript{54} Despite not having extensive literature, in the interest of developing standardized guidelines amongst practitioners, CARRA recommended the following dosages of MMF to be used with or without corticosteroids: <1.25 m\(^2\): 600 mg/m\(^2\) twice a day, 40–50 kg or 1.25–1.5 m\(^2\) = 750 mg twice a day, or >50 kg or >1.5 m\(^2\) = 1,000 mg twice a day.\textsuperscript{53}

Systemic Sclerosis

Treatment of systemic sclerosis is organ based and the current treatments used are based on adult studies due to the lack of juvenile systemic sclerosis studies. In 2017, the European League Against Rheumatism (EULAR) updated their 2009 recommendations for the treatment of adult systemic sclerosis (SSc) with sufficient supporting data. EULAR recommended several agents including nifedipine (dihydropyridine-type calcium antagonist), phosphodiesterase type 5 inhibitors (PDE-5), iloprost (prostanoids) and fluoxetine to treat Raynaud’s syndrome in patients with SSc; PDE-5 and bosentan (endothelin receptor antagonist) to treat digital ulcers in patients with SSc; epoprostenol and prostacyclin analogues (iloprost, treprostinil) for SSc–pulmonary arterial hypertension; methotrexate, cyclophosphamide, and hematopoietic cell transplantation for SSc patients with skin and lung disease involvement; angiotensin-converting enzyme inhibitors in scleroderma renal crisis patients, and experts recommended proton pump inhibitors and intermittent or rotating antibiotics to treat SSc-related gastrointestinal disease.\textsuperscript{55}

Methotrexate was recommended for skin disease and mycophenolate was also thought to be beneficial.\textsuperscript{55} In pediatric patients, methotrexate dose of 25 mg/m\(^2\)/week orally or subcutaneously is well tolerated.\textsuperscript{57} Juvenile systemic scleroderma (JSS) with symptoms of vasculopathy (Raynaud’s phenomenon and digital ulceration) were treated with nifedipine (30 mg/day or 0.25–0.5 mg/day/kg orally) and/or bosentan (2 mg/kg/day).\textsuperscript{56} Iloprost, given intravenously (0.5-3 ng/kg/min for 3–5 consecutive days sequentially) or orally (50-150 μg twice a day), based on adult dose, is also effective in reducing the frequency and severity of Raynaud’s phenomenon-SSc and digital ulcer-SSc.\textsuperscript{55}

Musculoskeletal symptoms are present in about one-third of JSS patients. The treatment of musculoskeletal involvement is based on low-dose oral prednisone (0.3–0.5 mg/kg/day). In case of severe arthritis or myositis, there is an indication for the use immunomodulators (methotrexate) and, in refractory cases, biologic agents.\textsuperscript{56} Cyclophosphamide was recommended for interstitial lung disease but demonstrated limited efficacy with serious potential side effects.\textsuperscript{55} A high dose of cyclophosphamide (1 g/m\(^2\) intravenously/month) has been added to therapy during the first consecutive six months.\textsuperscript{57} Limited studies were available for use of MMF or rituximab for interstitial lung disease.\textsuperscript{58} A dose of rituximab.
Alopecia Areata

Methotrexate has been used as both a monotherapy and as an adjunct to topical, intralesional or oral corticosteroids in cases of severe alopecia areata; however, no set guidelines exist. A recent systematic review and meta-analysis was conducted to examine the efficacy and associated risks of MTX use in adults and children with alopecia areata (AA). Sixteen studies were selected for analysis, of which five were pediatric AA studies. Dosages used in the studies included starting at 2.5-5 mg methotrexate weekly in most cases, then advancing to 7.5-15 mg/wk, in combination with oral prednisolone either before or during therapy. Three consecutive months, followed by methotrexate 0.2 mg/kg/d. Maximum methotrexate 0.38 mg/kg/wk. Methotrexate 15-25 mg/wk in combination with corticosteroids. There was a significantly better complete (100%) and/or good/complete (50-100%) response to methotrexate in adults vs the pediatric population [44.7% vs 11.6% p = .001, 6.93% vs 46.5% p = .001]. In pooled analyses, patients treated with methotrexate and corticosteroids combination had a significantly higher odds of good or complete response when compared to methotrexate monotherapy. Finally, a large proportion of recurrences were noted upon tapering of treatment, highlighting the chronic nature of alopecia areata.

Recent studies have demonstrated that the JAK/STAT pathway may play an important role in the pathogenesis of alopecia areata, suggesting a role for JAK inhibitors in the treatment of AA. There are currently three available JAK inhibitors: tofacitinib, ruxolitinib, and baricitinib, but they are not approved by FDA for AA. Tofacitinib is an inhibitor for JAK1, JAK2, and most potently inhibits JAK3. It was FDA approved drug for rheumatoid arthritis. Baricitinib and ruxolitinib are JAK1 and JAK2 inhibitors. Ruxolitinib was FDA approved drug for myelodysplastic disorders. In 2017, Craiglow et al reviewed the records of 13 adolescent patients with AA treated with oral tofacitinib, 5 mg b.i.d. for 2-6 months, and in one patient, 10 mg in the morning and 5 mg in the evening, with good clinical response. Adverse events were mild, that included upper respiratory infections in four patients and a mild increase in liver transaminase levels in four patients. In another case report, a 14-year-old boy was given leflunomide with anthralin after failing treatments such as minoxidil, intralesional steroids, oral steroids, and azathioprine with anthralin. Initially, leflunomide was started at a dose of 10 mg/day with hair regrowth appearing after four weeks of initiation. The dose was then increased to 20 mg/day and complete regrowth was seen 3 months after initiation of leflunomide. Anthralin was then discontinued, and patient was given leflunomide 20 mg/day for an additional month. Ten months after stopping treatment, there had been no relapse. It was proposed that the clinical improvement was due to the action of leflunomide on the JAK-STAT pathway. The use of JAK inhibitors for AA needs to be evaluated further in prospective randomized trials. Long-term safety data on the potential side effects of prolonged treatment with JAK inhibitors are still limited. Due to their potent immunosuppressant properties, increased risk of infection and cancer is the major concern, even though no increased risk was reported so far.

Chronic Spontaneous Urticaria

Urticaria is characterized by the presence of itchy wheals, angioedema, or both. Chronic urticaria is defined as daily or almost daily activity for at least six weeks and then is further classified into spontaneous or inducible. Although there are guidelines for the management of chronic urticaria in adults, there is little data on the management of chronic spontaneous urticaria (CSU) in the pediatric population. In 2008, a systematic review was conducted to assess the published evidence on the management of pediatric CSU. Their initial search yielded 104 results of which 15 articles were included in the final analysis and the authors defined three major management strategies for CSU in children: H1 antihistamines, omalizumab (anti-IgE), and cyclosporine. Only one study has been published with enough research subjects which reported efficacy of H1-antihistamines in treating children < 12 years old with CSU. Second generation non-sedating antihistamines (cetirizine, levocetirizine, desloratadine, fexofenadine, or rupatadine) are the mainstay of pediatric CSU treatment. There is currently no RCT performed in children that compares the efficacy of increasing anti-histamine dose up to fourfold to switching to other treatment in patients with no improvement with the standard dose. H-1 antihistamines were
well tolerated in the previous studies, but those studies, due to lack of power, can not exclude the detection of rare adverse events such as QT prolongation which has been detected in adults taking fexofenadine and ebastine. Four RCTs demonstrated high efficacy and safety for the use of omalizumab involving adults and teenagers in doses of 150 mg to 300 mg subcutaneously once a month for six months. However, only a minority of the study population were teenagers and no children younger than 12 years were included. In severe cases of CSU in teenagers and children, there were case reports that supported the efficacy and safety of omalizumab and cyclosporine (3-4 mg/kg/d).

Another systematic review was published in 2018 to assess the efficacy and safety of treatment in children < 12 years old with CSU. Cyclosporine was effective and had no adverse effects in eighteen children. Omalizumab was reported in a very small series of five patients. In these studies, cyclosporine was used at a dose of 3 mg/kg/d and 4 mg/kg/d for two months and then 0.3 mg/kg/d every two months for one year. Omalizumab was used at dosages of 150 mg or 300 mg administered monthly.

Autoimmune Blistering Disorders

Autoimmune blistering disorders such as bullous pemphigoid and pemphigus vulgaris are common in the adult population and guidelines for treatment exist. However, autoimmune blistering disorders are very rare in childhood, and for those who fail topical and oral corticosteroids, few therapeutic alternatives have been researched. A retrospective study was conducted in 2015 examining twelve pediatric patients with either linear IgA disease, pemphigus vulgaris, bullous pemphigoid, bullous systemic lupus erythematosus, or pemphigus foliaceus. Oral corticosteroids and immunosuppressants were the mainstay of the treatment. Successful adjuvant therapies to oral steroids included azathioprine, mycophenolate mofetil, and cyclosporine. Biologic agents such as rituximab have been emerging as effective therapy for recalcitrant pemphigus vulgaris in children. One patient with recalcitrant PV improved after two cycles of intravenous rituximab administered two weeks apart at 750 mg/m²/dose, but clearly larger studies are needed.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition mainly affecting adults with an infrequent onset during childhood or adolescence. Guidelines regarding the treatment of childhood HS are lacking. However, in 2018, the FDA expanded the use of adalimumab to adolescents age twelve years and older with hidradenitis suppurativa. The effectiveness in the adolescent patients was extrapolated from two phase 3 studies performed in adults. The dosages approved for adolescent use include 30 kg - < 60 kg: initial dose (day 1) 80 mg, second (day 8) and subsequent doses: 40mg every other week; ≥ 60kg: initial dose (day 1) 160 mg, second dose two weeks later (day 15) 80 mg, third dose (day 29) and subsequent doses 40 mg every week. However, long term studies examining the safety and efficacy of adalimumab in adolescents for this indication are limited.

Conclusion

Despite not having extensive randomized clinical trials, data is emerging to illustrate a favorable efficacy and side effect profile for many of the systemic agents, including the newer biologics used in pediatric dermatological conditions. However, in 2009, the FDA issued a warning related to the development of malignancies in patients with juvenile idiopathic arthritis who had used anti-TNF medications for > 2.5 years. Other concerns with anti-TNF agents included the risk of serious infections, the development of autoimmune phenomena such as demyelinating diseases, autoantibodies, uveitis, a lupus-like syndrome, inflammatory bowel disease, and psoriasis.

Most of the studies discussed in this article lack data on long-term efficacy and were limited by the small patient populations. Because no treatments have long-term safety and efficacy data in children, no conclusive recommendations for a particular treatment can be made for each pediatric dermatological condition since none of the studies could conclude definitive superiority, and rarely gold standards exist. In addition, few studies examine a medication for the entire range of ages in the pediatric population. Further research into the long-term safety of these systemic medications is of vital importance especially due to the chronic nature of the previously discussed conditions.

References

2. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of


