Psoriasis is a chronic inflammatory disease that is not uncommon in children and adolescents. While exact prevalence rates of pediatric psoriasis have not been determined, 30% to 40% of adults with psoriasis report onset of their signs and symptoms before age 16. Although the diagnosis of pediatric psoriasis remains predominantly clinical, its presentation varies in clinical course, distribution, and morphology. The management of psoriasis in children ranges from topical medications for mild and moderate disease to the use of systemic immunomodulatory agents for more severe disease. None of the systemic medications, including methotrexate, cyclosporine, and biological agents, such as etanercept, infliximab, adalimumab, and ustekinumab have specific indication by the United States Food and Drug Administration (FDA) for pediatric psoriasis. The pediatric dermatologic literature has limited studies in which investigators examine the use of these therapies, unlike the corresponding adult literature. Subsequently, experts rely on unpublished clinical experience and studies of these systemic medications for other pediatric conditions, such as published in the rheumatologic, transplant, oncological, and gastroenterologic literature. In this article, we discuss the systemic treatment options for pediatric psoriasis, including drug mechanism of action and associated risks and benefits of treatment, to aid dermatologists in treating psoriasis in this special population.

Approach to Management

An interdisciplinary team approach is helpful in the management of pediatric psoriasis. Pediatricians, dermatologists, rheumatologists, and other subspecialists should work together to manage the diagnosis, treatment, and associated comorbidities of psoriasis. Early recognition and treatment is useful to minimize its psychosocial effects on the patient. Providing education and social support for both the patient and family members contributes to the successful control of the disease and treatment compliance. Education must reinforce the chronic nature of psoriasis; complete clearance is difficult to achieve, and disease control, rather than cure, is the goal.

Treatment choices are influenced by age, level of disability attributable to disease, morphology, distribution, severity, persistent course, and the presence of comorbidities, such as psoriatic arthritis. The practicality of the regimen must also be decided upon the basis of the impact of disease on the family. Additionally, the costs, associated risks and benefits, and accessibility of the different medications should be considered. Further considerations should be the possibility of adverse events, most commonly infectious, as well as undetermined long-term health risks of medication, or of inadequate treatment.

Methotrexate

Methotrexate (MTX) is a folic acid analog that reversibly inhibits dihydrofolate reductase, disrupting DNA synthesis, repair, and replication of T and B lymphocytes. MTX has been used successfully in the treatment of severe psoriasis in adults for decades. It is approved by the FDA for use in children for the treatment of juvenile idiopathic arthritis (JIA), historically known as juvenile rheumatoid arthritis, and certain malignancies. However, it has also been used off-label in children for many other rheumatologic and dermatologic conditions, including psoriasis.

Studies in which investigators evaluate the use of MTX for the treatment of psoriasis in children are limited in scope and exist primarily in the form of case reports and case series. Given the paucity of clinical evidence on the safety, efficacy, and indications for MTX use in the treatment of pediatric psoriasis, clinicians generally reserve it for cases of moderate-to-severe, refractory, disabling, erythrodermic, or pustular psoriasis. Kumar et al published a report of 7 children as young as 3 years of age, including cases of psoriatic erythroderma, generalized pustular psoriasis, and psoriatic arthropitis, treated with MTX (0.2-0.4 mg/kg/wk) for a mean of 38.8 weeks. Disease control was achieved in approximately 2
months, and all but one of the patients tolerated discontinuation of the drug. Side effects included nausea and vomiting, both relieved by folic acid supplementation. Case reports of pustular psoriasis treated with MTX have demonstrated treatment success at doses from 0.2 to 0.3 mg/kg/wk. A study of 24 severe psoriasics from 2.5 to 14 years of age, of which 17 had recalcitrant plaque-type psoriasis, showed excellent therapeutic response with 7.5 to 20 mg/wk of MTX. Mean duration to control was 5.1 weeks, and mean duration of use was 4.97 months, with a range of follow up from 1.5 to 3 years. Side effects of mild nausea, vomiting, and loss of appetite were observed in 37.5% and were effectively controlled with the administration of antiemetics. No significant alteration in standard laboratory parameters was detected. A similar study by Collin et al showed comparable success in disease control but did report 2 patients with elevated liver function tests.

A dosage range for MTX in children of 0.2 to 0.7 mg/kg/wk is recommended. A test dose of 1.25 to 5 mg should be administered ideally before initiation of therapy, with 1-week laboratory follow-up testing to monitor for toxicity. If tolerated, MTX dosage can be titrated to greater strengths of 1.25 to 5 mg/wk until therapeutic control is attained. Tapering the dose to an effective but lower maintenance dose to minimize side effects should be considered.

The side effect profile of MTX in children has been documented primarily in the rheumatologic literature (Table 1). The most common effects are abnormalities in liver function tests, stomatitis, nausea, and vomiting, all of which are usually reversible upon drug discontinuation. Rare pulmonary, renal, dermatologic, developmental, or cardiac side effects have been reported. The most severe adverse effects are hepatotoxicity, interstitial pneumonitis, bone marrow suppression, photosensitivity, lymphoma, and fetal death or malformation attributable to maternal MTX use during pregnancy. Interstitial pneumonitis is extremely rare and either presents in patients with risk factors for hepatotoxicity is recommended in children, but liver biopsy is not routinely performed unless laboratory or physical examination findings warrant further exploration.

Folic acid supplementation increases tolerability of MTX and reduces the risk of pancytopenia, nausea, macrocytic anemia, and liver enzyme elevations without altering efficacy. However, its use does not preclude the need for continued vigilant clinical and laboratory monitoring with MTX use (Table 2). In addition, there is an extensive list of drugs with pharmacologic interactions with MTX, potentially leading to increased risk of MTX toxicity. Physicians need to be aware of this before initiation of therapy; nonsteroidal anti-inflammatory drugs and trimethoprim sulfamethoxazole are of particular concern because these medications are commonly used in pediatric patients.

Cyclosporine

Cyclosporine is a noncytotoxic immunosuppressant that reversibly inhibits T lymphocytes and suppresses interferon-γ. It has been approved by the FDA for severe, recalcitrant psoriasis in nonimmunocompromised adults and for the prevention and treatment of transplant rejection in children older than 6 months of age. Even though medical literature supports the use of cyclosporine in children with atopic dermatitis and psoriasis, it remains unapproved by the FDA for these diagnoses. Dosages are generally restricted to a maximum of 4 mg/kg/d in the United States (5 mg/kg/d in Europe) and usually given for no longer than 1 to 2 years. In carefully selected and closely monitored patients, cyclosporine can produce relatively rapid clinical effects and can be effectively combined with topical and systemic therapies to increase efficacy and reduce drug toxicity.

Some studies have shown differences in the pharmacokinetics of cyclosporine between children and adults. In children, oral absorption may be lower, clearance more rapid, and volume distribution at steady state greater. Children may also require greater doses given their greater body surface area to body weight ratio. For atopic dermatitis, despite the pharmacokinetic differences between adults and children, reports suggest that the same dosage of 2.5 to 5 mg/kg/d is equally effective for both populations. In general, dose adjustments should be made on the basis of clinical response, blood pressure, and serum creatinine levels.

Most reports of cyclosporine efficacy in pediatric psoriatrics involve treatment of patients with plaque and pustular psoriasis, in whom it was well-tolerated. Review of the cyclosporine literature indicates its success in children as young as 11 months, with dosages ranging from 0.5 to 5 mg/kg/d. Clinical response has been reported between 2 and 8 weeks of treatment. Concurrent treatment with topical steroids, calcipotriene, coal tar, retinoids, and/or anthralin is recom-
mended by some experts. Mahé et al detailed the treatment of 4 patients with drug resistant psoriasis, including neonatal erythrodermic psoriasis, acral pustular psoriasis, generalized pustular psoriasis, and severe erythrodermic psoriasis. In the article by Mahé et al, cyclosporine dosages ranging from 2.5 mg/kg to an accidental 10 mg/kg were administered to 4 pediatric patients. Results were reported to be unsatisfactory, except for the patient receiving the accidental 10 mg/kg, which resulted in clearance within 1 month.

Cyclosporine may be well tolerated in children, although significant side effects have been reported primarily in adults, including nephrotoxicity and hypertension, may be observed. The most commonly reported side effects in both populations include nausea, vomiting, and diarrhea. In Dodolani’s review of pediatric dermatologic and rheumatologic literature, notable side effects included nausea, vomiting, hypertrichosis, mild hypertension, and moderate, but within normal, changes in renal function. Changes in creatinine usually range from 1- to 2-fold and are typically reversible by lowering the dose. Regardless, the use of cyclosporine in pediatric psoriasis remains limited given the rare reports of nephrotoxicity, hypertension, and immunosuppression (Table 1).

It is recommended that the lowest possible dose and shortest treatment period possible be administered. Laboratory and

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Side Effects and Contraindications</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>Folic acid analog analog dihydrofolate reductase inhibitor that disrupts DNA synthesis, repair, and replication of T and B lymphocytes.</td>
<td>Adverse events (AEs): nausea, vomiting, diarrhea, headache, hepatotoxicity, interstitial pneumonitis, bone marrow suppression, fetal death/malformation, photosensitivity, lymphoma. Contraindications (CIs): pregnancy, breastfeeding, liver disease, blood dyscrasias, alcoholism, renal dysfunction, immunodeficiency syndromes.</td>
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<tr>
<td>Cyclosporine</td>
<td>Noncytotoxic immunosuppressant that reversibly inhibits T lymphocytes and suppresses IL-2 and interferon-γ</td>
<td>AEs: nausea, hypertension, hyperlipidemia, nephrotoxicity, gingival hyperplasia, hyperkalemia, hypomagnesemia. CIs: hypertension, renal dysfunction, active infection, active malignancy, phototherapy.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Chimeric monoclonal antibody TNF-α antagonist.</td>
<td>AEs: reactivation of latent tuberculosis (TB) and HBV, invasive fungal infections, opportunistic bacterial and viral infections, lymphoma, hypersensitivity reactions, hepatotoxicity, hematologic abnormalities, demyelinating disorders, lupus-like syndrome. CIs: moderate-to-severe congestive heart failures (CHF), live vaccinations during treatment use with caution in patients with preexisting blood dyscrasias, liver disease, myelosuppression, or chronic infection.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Human monoclonal antibody TNF-α antagonist.</td>
<td>AEs: reactivation of latent TB and hepatitis B virus (HBV), invasive fungal infections, opportunistic bacterial and viral infections, lymphoma, nonmelanoma skin cancer, hypersensitivity, pancytopenia, demyelinating disorders, lupus-like syndrome. CIs: moderate-to-severe CHF, live vaccinations during treatment use with caution in patients with preexisting blood dyscrasias, liver disease, myelosuppression, or chronic infection.</td>
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<tr>
<td>Etanercept</td>
<td>Soluble TNF-α fusion protein that competitively inhibits The binding of endogenous TNF-α</td>
<td>AE: nausea, vomiting, headache, reactivation of latent TB and HBV, invasive fungal infections, opportunistic bacterial and viral infections, lymphoma, hypersensitivity, pancytopenia, demyelinating disorders, lupus-like syndrome. CI: moderate to severe CHF, live vaccinations during treatment use with caution in patients with preexisting blood dyscrasias, liver disease, myelosuppression, or chronic infection.</td>
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<tr>
<td>Alefacept</td>
<td>Human dimeric fusion protein that interferes with Lymphocyte activation by specifically binding to the CD2 lymphocyte antigen</td>
<td>AE: nausea, vomiting, headache, lymphopenia, hepatic injury, hypersensitivity. CI: HIV.</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Human interleukin-12 and -3 antagonist</td>
<td>AE: literature unpublished. CI: none.</td>
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blood pressure monitoring are mandatory, and it should be recognized that side effects are often related to dose; cyclosporine-induced nephropathy can be reduced by avoiding doses greater than 5 mg/kg/d and avoiding doses that elevate serum creatinine greater than 30% above baseline. Prevention or reversal of side-effects may be achieved by discontinuing therapy after the induction of clearing. Other side effects of cyclosporine include arthralgia, myalgia, tremors, headache, paresthesias, and gingival hyperplasia. An increased risk of malignancy, including skin cancer and lymphoproliferative disorders, has been documented in transplant populations; the risks may be less in patients using less than 5 mg/kg/d and in those who are not on concurrent immunosuppressants. Adjuvant phototherapy is not recommended while a patient is receiving cyclosporine, given the increased risk of developing skin cancer.

**Etanercept**

Etanercept is a soluble tumor necrosis factor fusion protein that competitively inhibits the binding of endogenous tumor necrosis factor (TNF)-α to its receptor. It is approved by the FDA for the treatment of adults 18 years and older for moderate-to-severe rheumatoid arthritis, chronic, moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. It is also approved by the FDA for use in moderate-to-severe polyarticular JIA in children 2 years and older. Etanercept is administered by subcutaneous injection 1 or 2 times per week.

In 2008, a double-blind, multicenter, phase 3, randomized controlled trial was conducted to evaluate the safety and efficacy of etanercept in pediatric patients ages 4 to 17 years with moderate-to-severe plaque psoriasis. Two hundred eleven patients were randomly assigned to weekly injections of 0.8 mg/kg of either etanercept or placebo for 12 weeks, followed by 24 weeks of once-weekly open-label etanercept. At week 36, a second randomization was conducted on 138 patients to investigate the effects of withdrawal and retreatment. The primary endpoint was improvement of 75% or greater from baseline in the Psoriasis Area-and-Severity Index (PASI 75) at week 12. At week 12, 57% of patients receiving etanercept achieved PASI 75, compared with 11% receiving placebo. During the withdrawal period, therapeutic response...
was lost by 42% of patients initially treated with etanercept who were assigned to placebo in the second randomization. Four serious adverse events occurred during treatment with open-label etanercept, including severe gastroenteritis and basilar pneumonia, all of which resolved without sequelae. Three patients had a transiently elevated hemoglobin concentration. No deaths, cancers, severe opportunistic infections, or demyelinating events were reported. It was concluded that etanercept is well tolerated and significantly reduces disease severity in pediatric patients with moderate-to-severe plaque psoriasis compared with placebo. The drug is not FDA indicated for pediatric use in the United States at this time.

The investigators of 3 case reports have detailed etanercept use in pediatric psoriasis. Kress described its use in 10 children ages 8 to 18 years with moderate-to-severe plaque psoriasis, of whom 5 had concurrent psoriatic arthritis. Therapy was initiated at 0.4 mg/kg twice weekly in patients weighing less than 50 kg and 25 mg twice weekly in patients weighing more than 50 kg. All 10 patients were rated as clear or almost clear by the Investigators Global Assessment after initiation. Of the 5 patients with psoriatic arthritis, 2 noted improvement, and 3 reported clearance, of arthritis symptoms. The average time to response was 2 to 3 months for skin improvement, and 3 reported clearance, of arthritis symptoms. Of the 5 patients with psoriatic arthritis, 2 noted improvement, and 3 reported clearance, of arthritis symptoms. The average time to response was 2 to 3 months for skin improvement, and 3 reported clearance, of arthritis symptoms. Of the 5 patients with psoriatic arthritis, 2 noted improvement, and 3 reported clearance, of arthritis symptoms. The average time to response was 2 to 3 months for skin improvement, and 3 reported clearance, of arthritis symptoms. Of the 5 patients with psoriatic arthritis, 2 noted improvement, and 3 reported clearance, of arthritis symptoms. The average time to response was 2 to 3 months for skin improvement, and 3 reported clearance, of arthritis symptoms. Of the 5 patients with psoriatic arthritis, 2 noted improvement, and 3 reported clearance, of arthritis symptoms.

Adalimumab

Adalimumab is a human monoclonal antibody that acts as a TNF-α antagonist. It is approved by the FDA for the treatment of adult psoriasis, psoriatic arthritis, rheumatoid arthritis, JIA, Crohn’s disease, and ankylosing spondylitis. Adalimumab is also used off-label for the treatment of pediatric inflammatory bowel disease and uveitis. It is administered as a subcutaneous injection every 2 weeks. In reviewing the pediatric dermatology, rheumatology, and gastroenterology literature, there is scarce information published regarding its use in children. No literature for use in pediatric psoriasis has been published to date.

A double blind 48-week phase III study, followed by an open-label extension study, has evaluated the safety and efficacy of adalimumab, with or without MTX, in children with JIA. A weight-based dose of adalimumab was administered every other week for 16 weeks. Ninety-four percent of those receiving adalimumab and MTX achieved a positive response with an improvement in JIA symptoms of 30% or greater. Seventy-four percent of patients on adalimumab alone achieved a positive response. The most common adverse effects were infection and injection site reactions. Serious adverse events were all of infectious etiology, including bronchopneumonia, herpes simplex virus infection, pharyngitis, and herpes zoster. No deaths, malignancies, opportunistic infections, demyelinating diseases, or lupus-like reactions were reported. In a 12-month retrospective study of 115 pediatric Crohn’s disease patients on adalumimab, the most common adverse effects were also infectious. No malignancies or opportunistic infections were reported. It is likely that studies evaluating the efficacy and safety of adalimumab in the treatment of pediatric psoriasis will follow, given its success in JIA patients and adult psoriatics. Adalimumab was included by the FDA in the list of medications receiving a "boxed warning" to alert health professionals of increased malignancy risks with TNF blockers, though the strength of the association was limited by a variety of factors. (See below) Given the positive results from the pediatric etanercept trial and from rheumatologic literature, etanercept may provide a promising systemic treatment option for pediatric psoriasis patients. It is recommended that patients and families be counseled about possible increased cancer risks in children and adolescents, assessing clinical utility and risks and benefits of these and other immunosuppressive therapies, and risks of untreated disease.

Infliximab

Infliximab is a chimeric monoclonal antibody, composed of human and murine proteins, which targets TNF-α and func-
tions as a TNF-α antagonist. It is approved by the FDA for adult psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, and adult and pediatric Crohn’s disease. Infliximab can only be administered as an intravenous infusion. A randomized, multicenter, phase 3 open-label study of pediatric patients with moderate-to-severe Crohn’s disease revealed that 88.4% of patients treated with 5 mg/kg at 0, 2, and 6 weeks had a decrease of greater than or equal to 15 in the Pediatric Crohn’s disease Activity Index. The primary side effect was an increased risk of infection.

The use of infliximab infusions have been reported in the treatment of pediatric psoriasis in 3 case reports. Mentzer and Cush used infliximab in a 8-year-old girl with severe, disabling plaque-type psoriasis that had failed phototherapy, MTX, cyclosporine, acitretin, and mycophenolate mofetil. She was given a dose of 200 mg, 3.3 mg kg⁻¹ at weeks 0, 2, 6, and then maintenance doses every 8 weeks thereafter. After 6 infusions, the trunk and limb plaques had cleared, there remained significant palmoplantar improvement, and no side-effects were reported. Pereira et al treated a 3-year-old girl with generalized pustular psoriasis recalcitrant to other systemic treatments, including cyclosporine. Infliximab was instituted at a dose of 75 mg, 5 mg kg⁻¹ at weeks 0, 2, 6, and thereafter every 7 weeks for maintenance. Two weeks after the first infusion, the patient was clear. The child remained in remission until 10 months, when she developed thick scalp plaques and scattered pustules, at which time MTX was added to the treatment regimen. Two months later, she developed acute erythematous and exudative plaques, widespread pustules, and subsequent exfoliative erythroderma. Laboratory tests showed anemia, leukocytosis, and severe liver enzyme elevations. Infliximab and MTX were discontinued, and hepatic enzymes normalized. Cyclosporine, prednisone, and acitretin were used during this acute flare, and she later achieved clearance on etanercept.

In 2005, Farnsworth et al reported a case of a 14-year-old boy with severe flare, and she later achieved clearance on etanercept. In sporine, prednisone, and acitretin were used during this period. Infliximab and MTX were discontinued, and hepatic enzymes normalized. Cyclosporine and MTX were used to decrease the rate of antibody formation to infliximab. The authors of a multicenter cohort study of 729 pediatric patients with Crohn’s disease, of whom 202 received infliximab, studied the efficacy and safety of long-term infliximab. One patient had conversion of a purified protein derivative (PPD) skin test, with a normal chest x-ray finding. Another developed a varicella infection severe enough to require hospitalization and antiviral therapy; the patient recovered without sequelae. One patient developed Hodgkin’s lymphoma while on both infliximab and 5-aminosalicylate, prednisone, and 6-mercaptopurine. There was 1 death, attributable to cardiac arrest, in a patient with a known history of arrhythmias. In the FDA safety analysis, it was concluded that U.S. reporting rates for cases of malignancy with infliximab were higher compared to expected background rates for lymphomas and all malignancies, though conclusions are limited by concurrent use of other immunosuppressive agents in the pediatric cases. Given the paucity of data on infliximab in the treatment of psoriasis in children, future clinical trials investigating its safety and efficacy in the treatment of this specific patient population are needed.

**Other Biologics**

**Lacking Specific Pediatric Data**

Alefacept is an immunosuppressive fully human dimeric fusion protein that interferes with lymphocyte activation by specifically binding to the CD2 lymphocyte antigen. This inhibits the interaction between CD2 and human leukocyte function antigen-3. It is indicated for the treatment of adult patients 18 years and older with moderate-to-severe chronic plaque psoriasis. Alefacept is given as a once weekly intramuscular injection for 12 weeks, followed by a minimum 12-week break from treatment. Retreatment with an additional 12-week course may be initiated if CD4⁺ T lymphocytes counts are within the normal range, and a minimum of a 12-week interval has passed since the previous treatment course.

Ustekinumab is a new human interleukin-12 and -3 antagonist that is approved by the FDA for the treatment of adult patients 18 years and older with moderate-to-severe chronic plaque psoriasis. It is administered as a subcutaneous injection once a month for 2 months, and subsequently every 12 weeks. No literature detailing the safety and efficacy of the aforementioned medications for the treatment of the pediatric population has been published as of this paper’s submission.

**Safety and Malignancy Risk**

It appears that all systemic immunosuppressive and biologic agents used for psoriasis may be associated with an undefined but increased risk of malignancy. However, it is difficult to assess this, given the limited, small number of studies of these medications in this population, and little long-term safety data. The FDA analysis concluding that there is an increased risk of lymphoma and other malignancies in children and adolescent treated with TNF blockers. Forty-eight cases of malignancy were identified, approximately half of which were lymphomas. Malignancy rates were higher than expected background rates for lymphomas and all malignancies with infliximab, while malignancy reporting rates for etanercept were similar to background rates for all malignancies, although higher than background rates for lymphomas. Adalimumab was not included in the analysis due to its minimal use in pediatric patients. However, eighty-eight percent of the patients were also using other immunosuppressive medications such as methotrexate and azathioprine, and the
contribution of underlying disease states on risk of malignancy could not be assessed. The FDA concluded that it is "unable at this time to fully characterize the strength of the association between the use of TNF blockers and developing a malignancy," and that additional data from ongoing long term studies are to be expected. At this time, it appears reasonable to counsel patients and families concerning these issues and to consider risks and benefits of all therapies, as well as the risks of untreated disease, prior to starting these biologic medications.

Conclusions

Pediatric dermatologic, rheumatologic, and gastroenterologic literature, albeit limited, supports the efficacy and safety of TNF-α antagonists, MTX, and cyclosporine in the treatment of severe pediatric immune-mediated disease processes. It is recommended that dermatologists be aware of the utility of these agents in the treatment of difficult cases of pediatric psoriasis. However, physicians must carefully balance the risk and benefits of these agents before their use in children. Regardless, with such promising short-term data, the use of the biologics opens up an exciting new frontier in the treatment of moderate-to-severe pediatric psoriasis.

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