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Atopic Dermatitis: Systemic Immunosuppressive Therapy

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Atopic dermatitis (AD) is a pruritic, relapsing skin disorder that negatively impacts the quality of life of those affected and that of their families. Treatment options for AD encompass a variety of emollients, topical corticosteroids, topical immunomodulators, phototherapy, and systemic agents. Such agents as systemic corticosteroids, cyclosporine, azathioprine, interferon-γ, methotrexate, and mycophenolate mofetil have been shown to be efficacious in the treatment of moderate-to-severe AD but are not officially approved for this purpose. In this article, we review some of the data supporting efficacy of these medications and discuss some of the adverse events associated with their use.
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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition in which a combination of genetic tendency, environmental stimuli, epidermal barrier abnormalities, and immune dysregulation lead to eczematous changes, severe pruritus, and lichenification. Theories regarding pathogenesis have centered around alterations in cutaneous immune response involving hyperstimulatory T cells, dendritic cells expressing the high affinity IgE receptor, humoral factors, and Th1-Th2 perturbations.[1]

The great negative impact of disease on the quality of life of patients with chronic moderate-to-severe AD is well established, affecting them socially, economically, and psychologically.[2] The clinician's armamentarium against AD comprises a wide variety of treatment modalities. Topical management typically includes treatment with emollients, corticosteroid preparations, topical antibiotics, and calcineurin inhibitors. Phototherapy and systemic treatment with antibiotics, antihistamines, and leukotriene antagonists, as well as systemic corticosteroids and other immunomodulatory agents, can complement topical therapy in more severe disease or in AD that is found to be refractory to topical therapy.

Systemic corticosteroids remain an effective immunosuppressive treatment for severe AD, although side effects limit their long-term use. Alternative immunomodulatory agents that have been used with success in the treatment of AD include the calcineurin inhibitor, cyclosporine (Neoral®, Novartis, East Hanover, NJ), azathioprine (Imuran®, Prometheus Laboratories, Greenville, NC), interferon-gamma therapy, methotrexate, mycophenolate mofetil (Cellcept®, Roche, Nutley, NJ), and to a limited extent a few of the newer biologic immunomodulators. This article reviews some of the systemic immunomodulatory agents that are used in the treatment of AD, including some of the antipsoriatic biologicals. It cannot be overemphasized that treatment with any of these agents is considered an "off-label" use, and it is incumbent on the physician to provide full disclosure to the patient or parent. It is strongly suggested that written informed consent be obtained before the use of any of these drugs.

Systemic Corticosteroids

Systemic corticosteroids have a limited role in the treatment of severe or recalcitrant AD. Their use is most often confined to short courses for the treatment of acute flares or as a temporary measure to control disease while transitioning to slower acting systemic therapies or phototherapy.[3] Although chronic therapy with oral corticosteroids has occasionally been advocated as an effective and beneficial treatment option, it carries a significant risk for a number of important side-effects.[4] This risk increases with duration of use and includes growth retardation in children, Cushing's syndrome, hypertension, glucose intolerance, myopathy, osteonecrosis, glaucoma, and cataracts. Although-long term therapy with systemic corticosteroids is best avoided, should it be necessary, alternate-day treatment regimens may be preferable to decrease the risk of some, although not all, of these side effects. Another potential problem, even with short-term cor-

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ticosteroid use is a rebound phenomenon, wherein skin lesions may worsen significantly in some patients following cessation of therapy. These patients typically resemble those suffering from an acute exacerbation of AD, both clinically and in their immunological profile, with a predominantly Th2 pattern of immunity.[5]

Cyclosporine and Other Calcineurin Inhibitors

During the last 2 decades, cyclosporine, an oral calcineurin inhibitor, has been perhaps the most commonly used systemic immunosuppressive therapy in the treatment of AD. Cyclosporine binds to the intracellular receptor cyclophilin, inhibiting activation of nuclear factor of activated T cells, ultimately decreasing T-lymphocyte activation and transcription of IL-2 and other cytokines involved in AD.

The efficacy of cyclosporine in the treatment of both pediatric and adult AD is well established, having been confirmed in numerous placebo-controlled randomized trials.[6] Most studies have confirmed the efficacy of cyclosporine and have supported its use as a systemic agent in refractory AD.[7-10] Doses of oral cyclosporine used in studies typically range from 2.5 to 5 mg/kg/d.

As with systemic corticosteroids, the long-term use of cyclosporine is limited because of the risk of side effects, and treatment should be restricted to less than 1 year. Potential complications of cyclosporine therapy include nephrotoxicity, hyperlipidemia, hypertension, hypertrichosis, gingival hyperplasia, adverse drug interactions, and occasional rebound flare after discontinuation of treatment.[11] Changes in renal function are typically reversible with cessation of therapy or reduction in dose.[12] Studies have also shown cyclosporine to induce bone loss, with one study reporting that pediatric patients on a combination of systemic cyclosporine and topical corticosteroids have decreased lumbar spine bone mass compared with pediatric AD patients using topical corticosteroids alone.[13] Rare-but-serious side effects of cyclosporine include increased formation of malignancies, including lymphomas and skin cancers, as well as serious infections.

Cyclosporine may be started at a higher initial dose (4-5 mg/kg/d) for a rapid initial response and then tapered to a lower-maintenance dose. Alternatively, a lower dose (2.5 mg/kg/d) may be initiated and gradually increased if clinical response is inadequate. Short courses of cyclosporine (up to 3 months) with periods of rest can be administered to limit total exposure to the drug. Cyclosporine interacts with a significant number of other medications, so it is essential that patients be forewarned about potential drug interactions.

Oral pimecrolimus and tacrolimus, 2 other calcineurin inhibitors, have also been studied in the treatment of AD, although clinical use of these medications is typically limited to their topical formulations. In a double-blind, randomized, placebo-controlled trial of more than 100 patients with moderate-to-severe AD, oral pimecrolimus was effective and well tolerated.[14] There was no evidence of renal toxicity or hypertension during the 12-week treatment phase or 12-week follow-up phase of the study.

Azathioprine

Azathioprine is a purine antagonist that has been used as an effective systemic immunosuppressive for nearly 50 years. In vivo, azathioprine is cleaved to 6-mercaptopurine, which exerts the agent's immunosuppressive effects by altering the synthesis and function of RNA and DNA in lymphocytes.

Several studies support the efficacy of azathioprine in the treatment of severe AD. In one retrospective study of 35 patients with AD who were treated with an average of 100 mg/d of azathioprine for a median of 7 months, 69% of patients reported subjective improvement in their symptoms.[15] In another retrospective study of 38 patients with severe AD, azathioprine showed some efficacy in nearly 80% of patients and this was accompanied by decreased serum IgE levels.[16] In a randomized double-blind placebo-controlled trial, a 27% improvement in disease was observed at 12 weeks in patients treated with 2.5 mg/kg/d of azathioprine.[17]

One of the main limitations to the use of azathioprine is its slow onset of action, typically at least 4 weeks. Major concerns with azathioprine use include risk of bone marrow suppression, hepatotoxicity, and increased risk of malignancy, including non-Hodgkin's lymphoma and squamous cell skin cancer.[18] It is now well established that certain patients with deficient activity of the enzyme thiopurine S-methyltransferase (TPMT) are at increased risk for myelosuppression from treatment with azathioprine. TPMT catalyzes the S-methylation of azathioprine, and a deficiency of the enzyme can lead to toxic accumulation of the drug.[19] Approximately 1 in 300 individuals are homozygotes for the autosomal-recessive deficiency of TPMT, and 1 in 10 are heterozygotes with intermediate deficiency. Molecular diagnosis of TPMT deficiency before initiating therapy can potentially decrease risk of adverse events to patients. Both anecdotally and in published reports, AD patients with partial TPMT have been successfully and safely treated with reduced doses of azathioprine.[20] A rare azathioprine-induced hypersensitivity reaction can occur usually with fever and gastrointestinal symptoms on initial presentation.[21] A maculopapular rash, urticaria, vasculitis, erythema multiforme or erythema nodosum, hepatotoxicity and nephritis may be associated with this complication.

Mycophenolate Mofetil

Mycophenolate mofetil is an inhibitor of the de novo purine synthesis pathway and acts by blocking the activity of the enzyme inosine monophosphate dehydrogenase. Inhibition of this enzyme ultimately decreases guanine nucleotides needed for RNA-primed DNA synthesis in T and B lymphocytes that rely on the de novo purine biosynthesis pathway.

There are 2 uncontrolled studies supporting the use of mycophenolate mofetil in the treatment of AD. In one 12-week pilot study of 10 patients ranging in age from 29 to 47 years with severe AD, there was a median improvement of

68% in disease severity with concomitant decrease in serum IgE levels.[22] During the 12-week study period, patients' white blood counts didn't change significantly. Nausea occurred in 2 patients, and one patient developed thrombocytopenia. In another study of 10 patients with severe AD, treated for a total of 8 weeks with mycophenolate mofetil, the SCORAD (SCORing Atopic Dermatitis) index of disease severity was reduced by a median of slightly more than 55%.[23] Of note, one patient in this study developed herpes retinitis and had to discontinue therapy after 4 weeks.

A retrospective chart review of 20 patients ages 54 to 79 with longstanding AD showed improvement in 17 within 4 weeks of starting mycophenolate mofetil.[24] Ten patients had remission of disease and were able to discontinue the drug. Notably, herpes zoster occurred in 4 patients, herpes simplex in 1, and staphylococcal skin infections in 2. Another retrospective chart review, this one of 14 children ages 2 to 16 years (mean 10 years) with severe AD reported complete clearance in 4 patients (29%), ≥90% improvement (almost complete) in 4 patients (29%), 60 to 90% improvement in 5 patients (35%), and treatment failure in one.[25]

The most commonly reported side effect with mycophenolate mofetil is gastrointestinal disturbance with nausea, diarrhea, and vomiting. Gastrointestinal symptoms can usually be reduced by dividing the total daily dose into 2 or 3 equal doses per day. As with other systemic immunosuppressive drugs, there is an increased risk of infection with the use of mycophenolate mofetil, but it has been suggested that this drug may have less potential for tumor genesis than other immunosuppressive agents. However, there have been cases of central nervous system lymphoma in patients treated with mycophenolate for lupus and myasthenia gravis.[26,27] A recent alert from the FDA has suggested a possible link between immunosuppression with mycophenolate and the development of progressive multifocal leukoencephalopathy.[28]

Methotrexate

Methotrexate is a competitive inhibitor of dihydrofolate reductase that also has immunosuppressive function through its effect on T cells. Although much more commonly used in dermatology in the treatment of psoriasis, there are a few case reports and one open-label prospective study supporting the use of methotrexate in the treatment of pompholyx, eczema in the elderly and AD.[29-31] In the open label study of 12 patients average disease activity improved by 52%, 24 weeks after starting therapy. Therapy was well tolerated, with only one patient withdrawing due to minor adverse effects. An additional case report suggests that successful treatment of atopic dermatitis with methotrexate is accompanied by a selective loss of activated allergen-specific T cells.[32] Earlier anecdotal reports suggested that the drug be given at a dose of 2.5 mg/d for 4 days out of the week but more recent studies used a once-weekly regimen as in psoriasis. Serious adverse events associated with methotrexate use include hepatotoxicity, bone marrow suppression, and pneumonitis.

Interferon-γ (INF-γ)

INF-γ is a Th1 cytokine, and an in vitro inhibitor of IL-4-induced IgE synthesis. However, its mechanism of action in AD is unclear, as studies have shown INF-γ therapy can produce significant improvement in patients with AD without decreasing serum IgE levels.[33] In a randomized placebo-controlled trial of 83 pediatric and adult patients, INF-γ given by daily subcutaneous injection during a 12-week period was effective and well tolerated.[34] In another randomized control trial comparing 2 doses of INF-γ and placebo, clinical improvement was significant in both high- and low-dose INF groups, with the high dose group achieving faster benefit in the first 6 weeks.[35] Flu-like symptoms such as fever, muscle ache, headache, and chills, are common adverse events with INF-γ therapy and can limit acceptance of therapy. These symptoms can persist during therapy despite treatment with analgesics.[34]

Other Immunobiologics

The use of immunobiologics, now popular treatment options for psoriasis, has been limited in AD. An uncontrolled study of 9 patients with refractory AD treated with the chimeric monoclonal antibody to TNF-α, infliximab, produced disappointing results, with only 2 patients achieving greater than 50% improvement at week 10.[36] More encouraging results were found in a prospective open-labeled pilot study of efalizumab in 10 patients with AD.[37] Efalizumab, a humanized monoclonal antibody that binds to human CD11a, produced 52% improvement in disease at week 12 in this study. In another report, efalizumab was evaluated by Takiguchi and coworkers in 10 patients with severe AD.[38] After an initial dose of 0.7 mg/kg, patients received 11 additional weekly injections of 1 mg/kg. A 50% or greater improvement was achieved in 6 of 10 patients by week 12; however, several side effects, including thrombocytopenia, viral gastroenteritis, rebound of dermatitis, and staphylococcal infection, complicated the treatment.

Blockage of T-cell extravasation into tissue was shown to be the major mechanism by which efalizumab reduced cutaneous inflammation.[39] In a case report of a single patient with chronic refractory severe AD, a positive response was noted to treatment with omalizumab (Xolair®, Genentech/Novartis, East Hanover, NJ), a humanized monoclonal anti-IgE antibody.[40] Another small series of 11 patients with generalized AD and high IgE levels (>1000 IU/mL) were treated with low-dose omalizumab (10 cycles of 150 mg given subcutaneously in 2 week intervals).[41] Of the 11 patients, 2 had a very good response with a SCORAD reduction of more than 50%. Another 4 patients achieved a reduction in SCORAD of between 25 and 50%. In a recent open-label pilot study, 6 patients with severe atopic dermatitis were treated with the chimeric monoclonal anti-CD20 antibody, rituximab (Rituxan®, Genentech/Biogen IDEC, Cambridge, MA) given as 2 intravenous injections each 1000 mg, 2 weeks apart.[42] All patients showed an improvement in their skin disease within 4 to 8 weeks. In another report, 2 patients with severe atopic

dermatitis were treated with rituximab, 2 infusions of 500 mg during a 2-week period with no significant improvement.[43]

Discussion

Atopic dermatitis can be a vexing therapeutic challenge for even the most experienced clinician. Treatment is based on an individualized approach utilizing topical corticosteroids and immunomodulators, emollients, antibiotics, phototherapy and immunosuppressive agents.[44] Despite this broad array of therapies, many patients are left inadequately treated, refractory to traditional therapies and unable to tolerate the adverse events associated with systemic immunosuppressive drugs. Although there have been many exciting advancements in the development and use of immunobiologics in the treatment of psoriasis, these have not as yet been a "slam dunk" in the treatment of AD. For now, clinicians must rely on systemic immunosuppressive agents for the treatment of severe and refractory disease. We remain hopeful that new biologicals and systemic agents with greater efficacy and improved side effect profiles will be developed to treat this sometimes recalcitrant and frustrating disease.

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