Advances in Management of Atopic Dermatitis: New Therapies and Novel Uses of Existing Treatments
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Atopic dermatitis (AD) is a chronic inflammatory skin condition marked by intensely pruritic, eczematous changes that occur chronically with periods of remissions and flares. The traditional treatment of AD encompasses combating flares when they arise with topical anti-inflammatory agents applied only to affected areas and then tapering the medications once visible resolution is achieved. Current medications are topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), and emollients. When topical treatment proves ineffective or moderate-to-severe AD is present, phototherapy or systemic therapy with antibiotics, immunosuppressives, or immunomodulatory agents can be incorporated.

Occasionally traditional treatment options are insufficient or are associated with undesirable side effects; thus, developing novel agents is crucial. This article will encompass emerging AD treatments and discuss potential new uses for established therapies. We have focused our efforts on describing the spectrum of novel drugs and their targets that have been further developed since the 2008 atopic dermatitis issue of Seminars in Cutaneous Medicine and Surgery. We will discuss advancements made in the areas of barrier therapy, antistaphylococcal regimens, and immunomodulatory treatments, including both topical and systemic agents. Additionally, we will cover novel antipruritic modalities and discuss the use of diet and probiotics for treatment of AD. We will conclude with a discussion of novel uses of traditional AD medications. Although promising, many of the treatment regimens or therapies described in this article remain investigational or unproven at this point.

New Therapies for AD
Innovative Class of Barrier Therapy for the Treatment of AD
The rationale underlying barrier therapy is that mending the abnormal epidermal barrier present in AD patients prevents environmental triggers from penetrating through epidermal defects. Several topical agents approved as medical devices purportedly assist in restoring barrier function. MAS063DP (Atopiclair® Sinclair IS Pharma, plc, Godalming, Surrey, UK) includes hyaluronic acid and glycyrrhetinic acid, which along with other components impart antioxidant, antiprotease, moisturizing, and anti-inflammatory properties. Epiceral® (Ceragenix Pharmaceuticals, Inc, Denver, CO) was developed to improve barrier function by giving a par-
ticular ratio of ceramides, cholesterol, and fatty acids to the skin’s surface, which augments the skin’s structural defense. In addition to lipids, which moisturize the skin and mimic the stratum corneum framework, MimyX® (Stiefel Laboratories, Inc, Coral Gables, FL) is composed of N-palmitoylethanolamine, which activates cannabinoid receptors, leading to a dampened inflammatory response. Another barrier cream includes 5% urea (Canoderm® cream, ACO HUD NORDIC AB, Upplands Vasby, Sweden). Results from a recent prospective, randomized controlled trial suggest that using a moisturizing cream containing urea may reduce the risk of AD relapse and prolong its remission.

Although several randomized, vehicle-controlled trials have supported the efficacy of Atopiclair® for treating adults and children with mild-to-moderate AD, a recent study found that no statistically significant difference exists in efficacy measures among Atopiclair®, Epiceram®, and an over-the-counter, petroleum-based moisturizer with thrice-daily administration for 3 weeks. Additionally, the authors concluded that over-the-counter petroleum moisturizer is 47 times more cost-effective than the 2 prescription barrier creams. A randomized, investigator-blinded trial that evaluated Epiceram® and a moderate-potency TCS in pediatric patients with moderate-to-severe AD found no statistically significant difference in reduction of AD severity after 28 days, although Epiceram® demonstrated a slower onset of efficacy.

Although TCSSs may be associated with adverse side effects with long-term use, few adverse effects resulting from prescription barrier creams have been reported. However, because the FDA granted them approval as medical devices, these creams have withstood less scientific scrutiny than substances approved as drugs. Therefore, additional studies are necessary to support the safety and efficacy of their long-term use in AD.

 Novel Antistaphylococcal Therapy for the Treatment of AD

Because patients with AD are more likely to become infected or colonized by Staphylococcus aureus, antistaphylococcal treatments have been used as adjunct treatments in AD with varying success. Currently, the literature regarding this practice is conflicting. A recent Cochrane review failed to find any evidence that current antistaphylococcal interventions, such as oral antibiotics or topical antibiotics, are beneficial in the clinical course of patients with eczema who are not clinically infected. However, novel antistaphylococcal interventions may become part of the dermatologist’s armamentarium for AD. A study by Huang et al examined efficacy of dilute bleach baths in a randomized, investigator-blinded, placebo-controlled study of children with AD. Twice-weekly bleach baths combined with intranasal mupirocin administered 5 times per month resulted in a significant decrease in the Eczema Area and Severity Index (EASI) scores when compared with placebo. The severity scores from those areas not submerged in bleach water (the head and neck region) were not reduced. No patients withdrew from the study because of intolerance to bleach water, and no adverse events were reported. Applications of these agents may be most useful for those patients with recurrent methicillin-resistant Staphylococcus aureus (MRSA) or in weepy-type AD.

Topical antiseptic therapy offers the advantage of reducing colonization of S. aureus while not inducing bacterial resistance as readily as a topical antibiotic. In a recent study, treatment with 1% triclosan in emollient was compared with emollient alone in patients with mild-to-moderate AD. Although the AD severity scores had significantly improved in the triclosan group when compared with the emollient-alone group at day 14, this difference was no longer statistically significant by day 27. However, patients using triclosan required less topical steroids than those with emollient alone.

The skin of AD patients exhibits increased colonization of pathogenic species of bacteria, such as S. aureus, yet nonpathogenic or commensal bacteria normally present on the skin’s surface may play a protective role. Recent research has found that commensal species, like Staphylococcus epidermidis, may act as anti-inflammatory agents in skin epithelium. Therefore, antimicrobial therapy should target pathogenic species. Several studies have reported antimicrobial fabrics as novel therapy for AD, with silver-coated fabrics holding the most promise. A recent study compared cotton-based textiles with silver-loaded seaweed fiber textiles on the arms of 37 AD patients with mild-to-moderate eczema. The silver-based treatment significantly reduced S. aureus colonization and did not alter the numbers of nonpathogenic skin surface bacteria. The fabric’s discernment between the 2 may prove vital, given the anti-inflammatory properties of commensal species. Moreover, the silver-loaded seaweed fabric therapy reduced transepidermal water loss in those areas of mild eczema.

 Anti-inflammatory and Immunomodulation Therapies for the Treatment of AD

 New Topical Anti-inflammatory and Immunomodulation Therapies

Mainstream topical pharmacologic agents for AD are limited to TCSSs and TCSSs; however, additional targeted approaches are on the horizon. Transcription factors (TFs) are critical in regulating gene expression. By blocking TFs responsible for promoting the inflammatory pathway, topical decoy oligodeoxynucleotides (ODNs) may offer a targeted treatment for AD. Phase I and II clinical trials were completed for one such decoy, which would block NF-κB, a crucial TF in inflammation, and the results are pending. Another decoy ODN works by blocking STAT6, a TF vital in the process of allergic inflammation. In an open-label pilot study, this topical decoy ODN was applied to one side of 10 adults with mild-to-moderate AD, whereas an emollient was applied to a paired eczematous lesion on the contralateral side. The topical ODN ointment produced significantly reduced AD severity scores and pruritic measures at both the 2- and 4-week visits.

A recent meta-analysis examined the use of topical sulteplast tosilate, a Th2 cytokine inhibitor, in combination with
topical tacrolimus. Comparing combination therapy with topical tacrolimus alone, the meta-analysis found that the combination therapy produced more improvement in skin symptom scores and significantly reduced the necessary dosage of topical tacrolimus in patients with refractory facial erythema resultant from AD.25

Increased phosphodiesterase-4 (PDE4) action escalates the production of proinflammatory prostaglandins as well as IL-4.20 Patients with AD exhibit increased activity of PDE4 within their leukocytes.21 Exogenous PDE4 inhibitors, such as CP80,633 and cipamfylline, represent a novel therapeutic approach for AD. Although one study found that the efficacy of cipamfylline is less than that of hydrocortisone 17-butyrate,28 cipamfylline and CP80,633 significantly reduced the severity of AD when compared with cream vehicle alone and petrolatum-based vehicle alone, respectively, in 2 double-blind, placebo-controlled studies.28,29 Phase I and II clinical trials for the treatment of AD using a new PDE4 inhibitor were completed in 2011, and the results are pending.30

Vitamin B12 inhibits T cell production of inflammatory cytokines and thus represents a potential new AD therapy.31 In a randomized, placebo-controlled phase III multicenter clinical trial, topical vitamin B12 was tested and proven efficacious for reducing the extent and severity of AD without adverse effects.32 The topical B12 was applied twice daily for 8 weeks to affected areas on one side of the body, with the placebo applied to opposite-sided lesions.32 A phase II clinical trial examining the use of topical vitamin B12 in pediatric AD patients began in 2007 and has not yet been completed.33

A compound under investigation composed of extract from *Vitreoscilla filiformis* (VF), a nonphotosynthetic bacterium, may provide a new treatment option in AD. A randomized, double-blind study comparing 5% VF cream with vehicle found that treatment with VF cream for 4 weeks reduced eczema severity significantly in areas of mild-to-moderate AD compared with treatment with vehicle alone.34 Likewise, in another randomized, double-blind, vehicle-controlled study, treatment for 30 days with 5% VF cream resulted in a significant reduction in SCORAD (SCORing Atopic Dermatitis) scores, pruritus, loss of sleep, and *S. aureus* colonization.35

**New Systemic Anti-inflammatory and Immunomodulation Therapies**

Systemic medications traditionally used in AD do not consistently provide sufficient therapeutic response and are associated with potential severe toxicities. However, agents designed for specific molecular targets offer the prospect of a more precise, and therefore theoretically less harmful, tactic for systemic AD therapy; such is the promise of biologics for the treatment of AD.36 Table 1 includes a summary of recent prospective trials evaluating the use of recombinant monoclonal antibody or fusion protein biologics in the treatment of AD (see Table 1).

Tumor necrosis factor alpha (TNF-α) is increased in AD lesions.26 In a prospective study of 9 patients, infliximab (Remicade®, Centocor Ortho Biotech, Inc, Horsham, PA), a TNF-α inhibitor, was given at 0, 2, and 6 weeks and then every 8 weeks for 4 additional infusions. Although the results demonstrated statistically significant improvement at week 2, 6 of the 9 participants discontinued the medication by week 10 because of a lack of substantial clinical improvement.37

Omalizumab (Xolair®, East Hanover, NJ; Genentech, South San Francisco, CA) is a monoclonal antibody that prevents the proinflammatory effects of IgE by blocking it from binding to its receptors on mast cells. Studies concerning the efficacy of omalizumab in treating AD show conflicting results. Several case reports and 1 pilot study support its use in AD, principally in patients who also suffer from asthma or in subjects with recalcitrant AD.38,47-50 However, a recent placebo-controlled, double-blind pilot study of 20 AD patients randomized to receive 16 weeks of subcutaneous omalizumab or placebo did not reveal a significant difference in the clinical disease parameters of the 2 groups. The treatment group demonstrated a reduction in serum IgE levels, an improvement in atopy patch test, and an increase in the threshold allergen concentration necessary to produce a type 1 hypersensitivity reaction in the titrated skin test. These results may suggest that the benefit of omalizumab in AD, if actual, is more apparent in patients with an acute form of the disease.39

Efalizumab (Raptiva®, Genentech, South San Francisco, CA) and alefacept (Amevive®, Biogen, Inc, Cambridge, MA) both interfere with T cell-mediated inflammation. Acting as an antibody against CD11a, efalizumab disrupts recruitment of T cells, whereas alefacept impairs T cell activation.33-35 The literature regarding their use in AD is conflicting. Several case reports and 1 open-label trial of 10 patients support efalizumab’s efficacy in reducing AD severity as well as pruritus measures in patients with severe AD, but a recent retrospective study of 11 severe cases treated with efalizumab found improvement in only 2 patients.40,52-55 Moreover, serious side effects have been reported, and the drug is being withdrawn from the market.56,57 Likewise, the few published reports evaluating alefacept for AD have conflicting results.40,41

Only 2 studies, both in the same patient population, have been completed examining the use of mepolizumab (Bosatria®, GlaxoSmithKline, London, England), a humanized monoclonal antibody targeted against IL-5, in treating AD.43,44 In one study of 43 individuals, 2 single doses of 750 mg of mepolizumab resulted in modest improvement in Physician’s Global Assessment in 72% of the treatment group compared with 41% treated with placebo. However, only 22.2% of the treated and 4.6% of the placebo group achieved substantial improvement.43 More encouraging results were found in an open-label trial evaluating the monoclonal anti-CD20 antibody rituximab (Rituxan®, Biogen Idec, Weston, MA), which eliminates B cells by inducing antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, or apoptosis. Six patients received 2 rituximab infusions of 1000 mg, spaced 2 weeks apart. All 6 patients demonstrated significant improvement in severity of their disease, and that improvement was maintained for 24 weeks.45

A systematic review in 2007 suggested that intravenous immune globulin (IVIG) treatment for AD could not be recommended.38 However, a recent study of 40 children with
moderate-to-severe AD, who were randomized to receive placebo or 3 injections of 2.0 g kg\(^{-1}\) IVIG at 1-month intervals over a 12-week period, showed a significant decrease in AD severity at visit 5 compared with visit 1 in the IVIG-treated group. After 3 months of therapy, IVIG may improve AD in children, but the beneficial effects diminish by 6 months after treatment.\(^5\)  

Two randomized, placebo-controlled studies have demonstrated that recombinant interferon\(^\gamma\) can effect 50% improvement in AD severity in a substantial proportion of patients.\(^6\) In an additional study, researchers determined that AD patients with a peripheral eosinophil count of <9% and a serum baseline IgE <1500 IU/mL are the individuals most likely to achieve a beneficial outcome if treated with interferon\(^\gamma\).\(^7\)  

AER003 (Aeroderm®, Aerovance, Berkeley, CA) interferes with the IL-4\(\alpha\) receptor to block the action of IL-4 and IL-13. A phase IIa trial evaluated AER003 for use in moderate-to-severe AD adult patients. Although therapy with twice-daily 30-mg subcutaneous injections of AER003 did not demonstrate a statistically significant difference in AD severity at 28 days, the treatment group evidenced a significant reduction in their eczema exacerbations compared with the placebo group.\(^8\) Thus, AER003 might play a role in preventing acute exacerbations of AD in the future.

Rosiglitazone (Avandia®, GlaxoSmithKline, London, England) is a peroxisome proliferator-activated receptor agonist thought to stimulate anti-inflammatory and epidermal repair activity in cells of the immune system and keratinocytes. In a retrospective review of 6 patients with severe AD, rosiglitazone dosed 2-4 mg daily was steroid sparing and improved AD severity when used with oral corticosteroid or wet-wrap therapy.\(^9\)  

Likewise, a novel therapy using vitamin D or heliotherapy for the treatment of AD is also on the horizon. This treatment is based on a study in which 23 Finnish adults with AD received heliotherapy during January and March, and subsequently they experienced a significant reduction in their AD severity scores. The consequential increase in the circulating form of vitamin D was positively correlated with the improved SCORAD severity index in the March group.\(^10\) Given the serious long-term risks of developing skin cancer, clinicians must cautiously weigh the benefits of heliotherapy. To achieve an improvement in AD without placing participants

### Table 1 Recent Prospective Studies Examining Recombinant Monoclonal Antibodies or Fusion Proteins in the Treatment of AD

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Rationale</th>
<th>Study</th>
<th>Study Design</th>
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<tr>
<td>Infliximab</td>
<td>Antibody against TNF-(\alpha)</td>
<td>TNF-(\alpha) is increased in AD lesions</td>
<td>Jacobi et al(^3)</td>
<td>Open-label</td>
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<tr>
<td>Omalizumab</td>
<td>Antibody against IgE</td>
<td>Blocks IgE from binding to receptor on mast cells</td>
<td>Sheinkopf et al(^3)</td>
<td>Open-label</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Antibody against CD11a</td>
<td>Disrupts recruitment of T cells</td>
<td>Takiguchi et al(^3)</td>
<td>Open-label</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Fusion protein, which interferes with LFA-3/CD2 interaction</td>
<td>Impairs T cell activation</td>
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<tr>
<td>Mepolizumab</td>
<td>Antibody against IL-5</td>
<td>IL-5 stimulates eosinophil differentiation, growth, and release from bone marrow</td>
<td>Oldhoff et al(^3)</td>
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<tr>
<td>Rituximab</td>
<td>Antibody against CD20 on B cells acts to destroy the B cells</td>
<td>Loss of the antigen-presenting and immunomodulatory functions of B cells</td>
<td>Simon et al(^3)</td>
<td>Open-label</td>
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AD, atopic dermatitis; TNF-\(\alpha\), tumor necrosis factor alpha; EASI, Eczema Area and Severity Index; IgE, immunoglobulin E; IGA, investigator’s global assessment; SCORAD, SCORing Atopic Dermatitis; CD11a, cluster of differentiation 11a; LFA3/CD2, lymphocyte function-associated antigen 3/cluster of differentiation 2; IM, intramuscular; IL-5, interleukin 5; PGA, Physician’s Global Assessment; CD20, cluster of differentiation 20.
at risk, researchers devised a randomized, double-blind, placebo-controlled pilot study that distributed oral vitamin D supplementation to pediatric AD patients in Boston from February to March. In the small study, which included 11 mostly mild AD patients, 80% of the patients taking vitamin D demonstrated an improved Investigator’s Global Assessment (IGA) score compared with 20% of the placebo group.66

Allergen immunotherapy, another possible AD treatment, has not been evaluated in randomized, controlled, double-blinded trials until recently, and results have varied. In one such multicenter trial, immunotherapy treatment with subcutaneous house dust mite (HDM) allergen produced a dose-response improvement in adult subjects with chronic AD. More importantly, the therapy was TCS sparing in those individuals who received larger doses of HDM allergens, and no AD flare resulted from use of the treatment.67 Because AD affects as many as 10%-20% of children and only 2% of adults worldwide, sublingual immunotherapy has the potential to provide a more appropriate administration route compared with injection. Unfortunately, in another trial, sublingual immunotherapy with HDM allergen extract did not significantly reduce AD severity in severe AD patients after 18 months of treatment.68 Additional studies are necessary to determine whether the inconsistency in these results is due to different routes of administration.

Because AD is characterized by a preponderance of Th2 cytokine effects, shifting the response from Th2 to Th1 represents one novel strategy in treatment. Mycobacterial infections are known to stimulate a Th1 response. Therefore, studies examining the efficacy of heat-killed *Mycobacterium vaccae* vaccination in the treatment of AD offer a novel therapy for AD. Unfortunately, studies have demonstrated conflicting results.69,70

**Novel Antipruritic Therapy for the Treatment of AD**

A molecularly targeted approach to AD is no longer limited to those agents, which fight inflammation; the discovery of specific sites believed to be associated with the pathology of pruritus, such as IL-31 or Sema3A, offers the possibility of a targeted anti-itch therapy for AD.71-73 Currently, the most promising mechanism for achieving relief from pruritus in AD lies in opioid receptor antagonism through naltrexone cream 1%, oral naltrexone, and selective serotonin reuptake
inhibitors (SSRIs). Applied topically, naltrexone, a μ-opioid receptor antagonist, achieved better itch relief and delivered that relief faster when compared with placebo in a controlled, double-blind trial of AD adult patients. Alternatively, the administration of 25-mg naltrexone capsules twice daily liberated adult AD patients from pruritus, as evidenced by their significantly reduced visual analogue scale (VAS) scores compared with placebo at the end of weeks 1 and 2 in a 2-week study. Additionally, an open-label study of 72 patients with chronic pruritus evaluated 2 SSRIs as long-term antipruritic agents. Although only 3 patients within the study had AD, collectively they represented one of the best responses to the anti-itch therapy of SSRIs among the various subsets of patients.

Use of Diet and Probiotics in the Treatment of AD

A Cochrane review reported that there is little evidence to support the use of exclusionary diets to treat unselected patients with AD. Although the review revealed that there may be some benefit in removing eggs from the diets of those infants who have positive specific IgE to eggs and are suspected to be egg allergic, further studies evaluating patients with proven food allergy are necessary before diet exclusion can be recommended as a treatment for AD.

Likewise, clinical trials and 2 meta-analyses examining pre- and postnatal supplementation with probiotics have demonstrated conflicting results. Although one meta-analysis could not support probiotics as a viable treatment of established AD, it concluded that their use in preventing AD holds more promise. Alternatively, a slightly larger meta-analysis determined that a statistically significant difference in reduction in SCORAD is associated with probiotic treatment when compared with placebo. Although it remains worthwhile to pursue investigations aiming to identify a subset of AD patients in which probiotic use would prove effective, probiotics cannot be recommended for the treatment of AD until studies reveal further data.

Novel Uses of Existing AD Therapies

Because patients with AD wait for further clinical data to be gathered on the emerging therapy options, novel approaches using existing AD treatments are worthy of consideration. Traditionally, in cases of eczema, dermatologists have recommended maintaining skin hydration with consistent emollient use and applying topical anti-inflammatory agents, including tacrolimus (Protopic®, Astellas Pharma, Inc, Japan) and pimecrolimus (Elidel®, Galderma, Switzerland), only to affected areas as they arise. Thus, treatment has been responsive in strategy. However, recent evidence suggests that a paradigm shift may be appropriate. A novel tactic has been described, which does not wait for skin to clinically demonstrate manifestations of AD. Instead, this “proactive” approach assumes, based on the histopathological evidence, that the epidermal barrier dysfunction, inflammatory infiltrate, and immunological disturbances at the root of AD are ever-present, even if subclinical. Thus, after active areas have resolved, in this novel strategy, patients apply topical anti-inflammatory agents intermittently during remission periods to areas previously affected, along with emollients to unaffected skin.

Of the 9 articles describing 8 randomized controlled trials reporting on the efficacy of such long-term anti-inflammatory treatments in flare prevention, roughly equal numbers of them examine topical tacrolimus and topical fluticasone propionate, and 1 investigates methylprednisolone aceponate. A recent systematic review determined that the various agents appraised in these trials performed more effectively in preventing flares than vehicle. According to a meta-analysis, topical fluticasone propionate may be more efficacious than topical tacrolimus in preventing disease flares.

In addition to preventing the recurrence of AD flares, thwarting their progression with topical medication represents a novel strategy. In a 26-week randomized controlled trial of 543 adult patients with a history of mild or moderate AD, pimecrolimus cream 1% given at the first signs or symptoms of relapse significantly reduced the number of flares requiring TCS use and decreased the number of unscheduled office visits by 30% when compared with vehicle. This study highlights the possibility of a future shift in the long-term management of AD in which TCS are used only as rescue medication if flares persist despite early TCI administration.

Conclusions

Management of AD can be challenging even for the most proficient clinician. Although current treatment options are able to control most mild-to-moderate cases, severe cases can be difficult to treat. Innovative therapies, which rebuild barrier defects, protect against microbial attack, and restore immunological balance, are on the horizon. While sufficient data on new therapies accumulate, some experts have applied creativity in their approach to treatment by using traditional medications in a novel manner. We excitedly await the future in AD as these novel approaches and new therapies coalesce to improve patient quality of life.

References

Advances in management of atopic dermatitis

25. Available at: http://clinicaltrials.gov/ct2/show/NCT00465699