New therapies for atopic dermatitis: Additional treatment classes

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Background: A wide array of miscellaneous agents is being studied for the treatment of atopic dermatitis (AD), including targeted topical, oral systemic, and biologic agents.

Objective: To review the known efficacy and safety to date for such agents being studied for the treatment of AD.

Methods: A nonsystematic review of the literature was performed. PubMed and ClinicalTrials.gov were searched for studies assessing agents not described previously for the treatment of AD. Randomized controlled trials were primarily sought, but other study types were also included if they contained pertinent data. Agents are presented by mechanism of action, with analysis of mechanism of action and data regarding efficacy and safety in patients with AD.

Results: Data regarding the following agents are presented: omiganan (an antimicrobial peptide), tapinarof (a nonsteroidal anti-inflammatory agent), PR022 (hypochlorous acid), asimadoline (a κ-opioid agonist), DS107 (dihomo-γ-linolenic acid), ZPL-389 (a histamine H4 receptor antagonist), secukinumab (an interleukin 17A inhibitor), and fezakinumab (interleukin 22 inhibitor).

Limitations: Limited clinical data exist for many of the described agents.

Conclusions: As recent research has improved our understanding of AD pathogenesis, various agents with unique mechanisms of action have been studied for the treatment of AD. Many of these hold great therapeutic promise for AD, and continued research and development is warranted. (J Am Acad Dermatol 2018;78:S76-83.)

Key words: asimadoline; atopic dermatitis; emerging agents; fezakinumab; hypocholrous acid; omiganan; secukinumab; tapinarof.

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting as many as 15% to 20% of children and 1% to 10% of adults worldwide.[1-4] AD is associated with a heterogeneous constellation of signs and symptoms, including pruritus, xerosis, and a chronic or chronically relapsing course, with oozing/weeping acute lesions and lichenification in chronic lesions.[5] It is believed that AD pathogenesis is highly influenced by a combination of genetic, environmental, and immunologic factors.[6-8] Moderate-to-severe AD often requires systemic immunosuppression; however, these agents have variable efficacy and numerous safety concerns. Currently, there is a need for additional agents that are effective and safe for the treatment of AD. As knowledge about the pathogenesis of AD increases,

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agents directed toward a wide variety of pathogenic targets have been or are being developed. These include recently discussed agents targeting Interleukin 13 (IL-13) and IL-31 (IL-31), phosphodiesterase-4, Janus kinase, neurokinin, and thymic stromal lymphopoietin. Of interest in this article, is the development of agents affecting lesser-known miscellaneous targets in AD pathogenesis. The objective of this article is to review the mechanism of some of these agents (Table I), existing data regarding the efficacy and safety of their use, and how these agents fit into the landscape of future AD therapeutic decision making.

CAPSULE SUMMARY

- Numerous miscellaneous targeted topical, oral systemic, and biologic agents atopic dermatitis (AD) are being studied.
- This review presents efficacy and safety data regarding antimicrobial peptide, hypochlorous acid, κ-opioid receptor, essential fatty acid, histamine H4 receptor, interleukin 17A, and interleukin 22 involved agents.
- Several miscellaneous agents hold great therapeutic promise for AD; continued research will help delineate their future roles in AD pharmacotherapy.

TOPICAL AGENTS

AMP: omiganan

Antimicrobial peptides (AMPs) are short peptides within the innate immune system and are often potent antimicrobial agents. Although most AMPs have direct antimicrobial activity, others may modulate the host's innate immune system to promote pathogen clearance.[9,10] Patients with AD have decreased AMP production, resulting in microbial colonization, bacterial and viral infections, and possibly increased disease severity as measured via severity assessments (eg, SCORing Atopic Dermatitis [SCORAD]).[11] Patients with AD have elevated risk for development of serious cutaneous, multiorgan, and systemic infections.[12,13] Thus, AMP therapies might improve the innate immune system and eventually lead to decreased cutaneous inflammation and epidermal barrier repair. Omiganan is an AMP that is currently being studied as a topical gel for various infectious and inflammatory disorders, including acne vulgaris, condylomata acuminate, vulvar intraepithelial neoplasia, and rosacea.[14-17] A phase 2, double-blind, placebo-controlled randomized controlled trial (RCT) assessing the pharmacodynamics, efficacy, and safety of omiganan in adults with moderate-to-severe AD has recently been completed (NCT02456480), with another currently in recruitment (NCT03091426).[18,19] Omiganan topical gel has previously been reported to be well tolerated overall without systemic absorption.[20] Although the efficacy of AMP therapy in AD has yet to be determined, it may have a role in AD, particularly in those with frequent or debilitating superimposed infections.

Nonsteroidal anti-inflammatory agent: tapinarof

Tapinarof (GSK2894512 [previously WBI-1001]) is a bacteria-derived polyphenol that acts on the aryl hydrocarbon receptor (AhR) (a ligand-dependent transcription factor) and nuclear factor erythroid 2—related factor 2 (a basic leucine zipper protein) and also has free radical scavenging ability.[21] AhR has recently been shown to have a role in the innate immune system, whereas nuclear factor erythroid 2—related factor 2 is involved in protection against inflammatory-induced oxidative damage.[22] Keratinocytes with limited AhR activity have been shown to be hyperresponsive to inflammatory cytokines.[23] Interestingly, AhR-dependent anti-inflammatory activity has been proposed as a mechanism contributing to coal tar therapy efficacy for psoriasis.[24] Tapinarof treatment in animal models has also shown to decrease skin inflammation and inflammatory cytokines.[21,25]

A phase 2, double-blind, placebo-controlled RCT studying tapinarof in adults with plaque psoriasis (NCT02564042)[26] found that 65% and 56% of patients in the groups receiving tapinarof 1% cream twice daily and once daily, respectively, achieved both a Physician's Global Assessment score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline and at least a 75% improvement in Psoriasis and Severity Index (PASI 75) score. Ten percent of patients in the tapinarof groups discontinued the study because of adverse events (AEs), with contact dermatitis being the most common reason.[27]

A phase 2, double-blind, placebo-controlled RCT assessing the efficacy and safety of 4 weeks of topical tapinarof 0.5% and 1% cream in patients with AD was conducted in 2010.[28] Tapinarof demonstrated significant reductions in EASI (59.3% and 54.9%, respectively, vs 7.1% for placebo [$P = .03$]), SCORAD (56.2% and 50.1%, respectively, vs 18.4% for placebo [$P = .04$]), Investigator's Global Assessment (IGA) (38.9% and 45.8%, respectively, versus 5.6% for