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Title: New Therapies for Atopic Dermatitis: Additional Treatment Classes

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Abstract

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 non-systematic review of the literature was performed. PubMed and ClinicalTrials.gov were searched for studies assessing agents not described in previous chapters for the treatment of AD. Randomized controlled trials (RCTs) 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 AD patients.

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

Limitations: Limited clinical data exists 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.

Capsule Summary

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

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting up to 15-20% of children and 1-10% 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, agents directed towards a wide variety of pathogenic targets have been or are being developed. These include recently discussed agents targeting Interleukins 13 (IL-13) and 31 (IL-31), phosphodiesterase-4 (PDE-4), janus kinase (JAK), neurokinin and thymic stromal lymphopoietin (TSLP). Of interest in this manuscript, 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, existing data regarding the efficacy and safety of their use, and how these agents fit into the landscape of future AD therapeutic decision-making.

Topical agents

Antimicrobial peptide: Omiganan

Antimicrobial peptides (AMPs) are short peptides within the innate immune system and are often potent antimicrobial agents. While 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 (i.e. SCORAD).¹¹ AD patients have elevated risk of

developing 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 currently being studied as a topical gel for various infectious and inflammatory disorders, including acne vulgaris, condylomata acuminata, vulvar intraepithelial neoplasia, and rosacea.¹⁴⁻¹⁷ A phase 2, double-blind, placebo-controlled 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 overall well-tolerated without systemic absorption.²⁰ While the efficacy of AMP therapy in AD has yet to be determined, there may be a role in AD, particularly in those with frequent or debilitating superimposed infections.

Non-steroidal 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 (NFE2)-related factor 2 (Nrf2), a basic leucine zipper protein, and that also has free radical scavenging ability.²¹ AhR has recently been shown to have a role in the innate immune system, while Nrf2 is involved in the protection against inflammatory-induced oxidative damage.²² Keratinocytes with limited AhR activity have been shown to be hyper-responsive 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 BID and daily tapinarof 1% groups respectively achieved both a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline, as well as at least 75% improvement in Psoriasis and Severity Index (PASI 75) score. Ten percent of patients in the tapinarof groups discontinued the study due to adverse events (AEs), with contact dermatitis being the most common reason.²⁷

A phase 2, double-blind, placebo-controlled RCT was conducted in 2010 assessing the efficacy and safety of 4 weeks of topical tapinarof 0.5% and 1% cream in AD patients.²⁸

Tapinarof demonstrated significant reductions in EASI [59.3% and 54.9%, respectively, vs. 7.1% (placebo); $p=0.03$], SCORAD [56.2% and 50.1%, respectively, vs 18.4% (placebo); $p=0.04$], IGA [38.9% and 45.8%, respectively, vs 5.6% (placebo); $p=0.003$], pruritus scores [74.0% and 56.0%, respectively, vs 30.2% (placebo); $p=0.04$], and affected BSA [64.4% and 57.7%, respectively, vs 10.8% (placebo); $p=0.03$]. A similar 2012 phase 2, double-blind, placebo-controlled RCT assessing the efficacy and safety of 6 weeks of topical tapinarof 0.5% and 1% cream in mild-to-severe AD patients demonstrated significant reductions in IGA [-1.3 and -1.8, respectively, vs. -0.5 (placebo); $p<0.001$] with a few cases of contact dermatitis AEs.²⁹

Additionally, a 12-week, phase 2, double-blind, placebo-controlled RCT studying tapinarof 0.5% and 1% cream daily and BID in moderate-to-severe AD patients was recently completed (NCT02564055).³⁰ A greater number of patients receiving tapinarof

achieved an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction [0.5% cream daily (34%) and BID (37%), 1% cream daily (46%) and BID (53%) vs. placebo daily (28%) and BID (24%)], as well as achieved EASI-75 [0.5% cream daily (39%) and BID (51%), 1% cream daily (51%) and BID (60%) vs. placebo daily (25%) and BID (26%)]. Tapinarof also reduced pruritus scores greater than placebo, and was overall well tolerated.³¹

Hypochlorous acid: PR022

Sodium hypochlorite (NaOCl or bleach) has been used as a treatment to reduce AD severity and bacterial colonization of skin in AD patients. A recent meta-analysis found that bleach baths were effective at improving AD severity after 4 weeks of treatment; however, they were not significantly more effective than water baths alone.³² These results suggest that most of the benefit of bleach baths is derived from the water baths and not the bleach per se.

Hypochlorous acid (HOCl) is more reactive than NaOCl, with a potentially greater irritant effect on the skin.³³ HOCl has been shown to decrease numerous inflammatory cytokines, including TNF- α , IFN- γ , IL-2, and histamine, and NF- κ B-mediated pathways in experimental models.³³⁻³⁶ Topical HOCl was studied as a potential treatment for pruritus and found to significantly reduce scratching behavior in AD mouse models.³⁷ In a recent case series, seven days of treatment in AD patients with topical hydrogel containing 0.008% HOCl and 0.002% NaOCl significantly reduced pruritus.³⁸

PR022 is a topical formulation of HOCl being studied for the treatment of mild-to-moderate AD, with preclinical studies demonstrating lesional improvement with topical application. A phase 2 vehicle controlled RCT of PR022 hydrogel is underway in adults

with mild-moderate AD.

Oral systemic agents

Kappa opioid agonists: Asimadoline

Opioid receptors are hypothesized to be involved in cutaneous itch.³⁹ It is believed that greater mu-opioid receptor activity compared to kappa-opioid receptor activity results in pruritus.⁴⁰ Preliminary data regarding the use of kappa-opioid receptor agonists for pruritus indicates potential benefit. Nalfurafine, a kappa-opioid receptor agonist, has been shown to significantly reduce refractory pruritus associated with end-stage renal disease,^{41,42} and its use was approved for this indication in Japan in 2009. Other kappa-opioid receptor agonists have also shown to inhibit induced-pruritus in animal models.^{43,44} Asimadoline is a primarily peripherally-acting, orally active, kappa-opioid receptor agonist initially developed for the treatment of irritable bowel syndrome.⁴⁵ However, it has also been found to inhibit induced pruritus and scratching behavior in preclinical studies.⁴⁶⁻⁴⁹ A phase 2, double-blind, RCT evaluating the efficacy of asimadoline in AD patients with pruritus is currently in recruitment (NCT02475447).⁵⁰ With low permeability across the blood-brain barrier, asimadoline use is likely to have minimal central opioid agonist AE.⁵¹

Dihomo-gamma-linolenic acid: DS107

Disorders of the metabolism of essential fatty acids (EFA) are potentially related to AD. Previous research has shown that the EFA linoleic acid is often elevated in AD patients, while its metabolites, including dihomogamma-linolenic acid (DGLA) are decreased, likely due to a defect in a vital converting enzyme, delta-6-desaturase.⁵²⁻⁵⁴ DGLA is a bioactive EFA and component of cellular plasma membranes, and is a precursor of

184 numerous anti-inflammatory metabolites. DGLA was shown to be lower in AD patients
185 compared to healthy individuals,⁵⁵ and levels correlated with AD treatment efficacy.⁵⁶ It
186 has been postulated that in a certain subset of AD patients, enzymatic dysfunction
187 leading to low DGLA levels may play a pathogenic role in AD via decreased anti-
188 inflammatory action.⁵² The concept of simply administering an oral, safe, bioactive fatty
189 acid that could lead to measurable clinical improvement in patients with moderate-to-
190 severe AD is intriguing.

191 Two studies demonstrated that DGLA administration prevented the development of AD
192 in mouse models.^{57,58} These studies contributed to the development of DS107, an oral
193 agent containing DGLA as its active ingredient. A phase 2, double-blind, placebo-
194 controlled RCT assessing the efficacy and safety of DS107 in moderate-to-severe AD
195 patients (NCT02211417) demonstrated that a numerically higher proportion of patients
196 receiving DS107 achieved a two-point decrease in IGA to a score of 0 (clear) or 1
197 (almost clear) compared to placebo at 8 weeks, but this result was not statistically
198 significant.^{59,60} DS107 use led to significant improvement in pruritus and POEM scores
199 compared to placebo. DS107 was overall well-tolerated, with the most common AE
200 being transient gastrointestinal-related events. Although the role of DGLA in AD is
201 controversial,⁶¹ DS107 showed initial promise in improving some AD outcomes. An
202 additional phase 2, double-blind, placebo-controlled RCT assessing the efficacy and
203 safety of DS107 in moderate-to-severe AD patients is currently in recruitment
204 (NCT02864498).⁶²

205 Histamine H4 receptor antagonist: ZPL-389

Histamine is a well-known pruritogen, and is also known to be elevated in patients with AD.⁶³ However, there is poor evidence regarding the efficacy of histamine antagonists, particularly histamine type 1 (H1) and type 2 (H2) receptor antagonists, in reducing AD-associated pruritus, and their use is often unreliable. Recently, research has also shed light on the role of histamine type 3 (H3) and type 4 (H4) receptors in pruritus.^{64,65} Activity of the H4 receptor, found on keratinocytes and Th2 cells, has been shown to be involved in allergic inflammation.⁶⁶⁻⁶⁸ H4 receptor agonists have demonstrated in mice the induction of pruritus likely via action on peripheral nerves.⁶⁹ An H4 receptor antagonist, JNJ-7777120, has been shown to decrease pruritus and scratching behavior in animal models with allergic disease.^{70,71} Additionally, the H4 receptor antagonist JNJ-39758979 was found to significantly reduce pruritus in AD, but was discontinued due to neutropenia.⁷² Interestingly, H4 receptor antagonism has also shown to inhibit pruritus resistant to H1 receptor antagonists.^{73,74} ZPL-389, a H4 receptor antagonist, recently completed phase 2 clinical trials in AD patients, and demonstrated significant improvement in EASI scores, but did not demonstrate significantly different reduction in pruritus.⁷⁵ Although ZPL-389 significantly improved AD severity outcomes, it is interesting that pruritus was not comparably improved. If further research is able to show that H4 receptor antagonists can significantly decrease pruritus as hoped, then these agents may hold therapeutic promise in AD. As many clinicians can attest to, the current pruritus-specific therapies are often inadequate at controlling symptoms, and thus H4 receptor antagonists may replace the current antihistamines used in AD, particularly if improved severity is also seen.

Biologic agents

Interleukin 17A inhibitor: Secukinumab

Interleukin 17A (IL-17A), produced by Th17 cells, has been shown to be elevated in peripheral blood and lesions in AD patients.⁷⁶⁻⁷⁸ IL-17A has also been found to stimulate Th2 responses in the acute phase of AD.⁷⁹ However, the role of IL-17A in AD pathogenesis is unknown, but might contribute to inflammatory responses in a subset of AD patients.⁷⁶ Secukinumab is a fully human monoclonal antibody directed against IL-17A that is currently FDA approved for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis.⁷⁹ A phase 2, placebo-controlled RCT assessing the efficacy and safety of secukinumab for adults with moderate-to-severe AD is currently in recruitment (NCT02594098).⁸⁰ The efficacy and safety of IL-17A inhibitors in AD, and whether a subset of AD patients may particularly benefit from them remains to be determined.

Interleukin 22 inhibitor: Fezakinumab

Interleukin 22 (IL-22) is produced primarily by Th22 cells and has been found to be elevated in both acute and chronic AD lesions and correlated with AD severity.^{80,81} IL-22 may increase epidermal barrier dysfunction, induce epidermal hyperplasia, and inhibit key proteins involved in epidermal differentiation (i.e. filaggrin, loricrin).⁸⁰⁻⁸² However, whether IL-22 is pathogenic or merely an elevated bystander in AD patients remains unknown. Fezakinumab (formerly ILV 094) is a fully human monoclonal antibody directed against IL-22. A 12 week, phase 2, placebo-controlled RCT of fezakinumab in adults with moderate-to-severe AD was recently completed (NCT01941537).⁸³ Recently presented results showed that SCORAD improvement was significantly greater with

fezakinumab vs. placebo in patients with severe AD at 12 weeks (36.4% vs. 22.3%; $p < 0.05$) and at 20 weeks (46.2% vs. 22.6%; $p < 0.01$), but less of a response was seen in patients with moderate AD.⁸⁴ Fezakinumab was overall well-tolerated. These results suggest a potential role of IL-22 in AD pathogenesis.

Conclusion

As recent research and clinical trials have improved our understanding of AD pathogenesis, the landscape of AD pharmacotherapy is broadening and evolving at an unprecedented rate. A wide array of miscellaneous agents are in development for AD, including targeted topical, oral systemic and biologic agents. Many of these agents hold great therapeutic promise, and continued research and development is necessary to continue to help shape AD pharmacotherapy.

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Table 1. Summary table of other therapeutic agents in development for atopic dermatitis				
Drug	Drug class or target	Efficacy	Safety	Comments
Topical agents				
Omiganan	Antimicrobial peptide	N/A	N/A	Potential role in AD, particularly in infection-prone patients.
Tapinarof	Non-steroidal anti-inflammatory agent; ligand at AhR	Significant improvements in EASI, SCORAD, IGA, and pruritus scores	Well tolerated; Contact dermatitis	Demonstrated relatively consistent efficacy, and has therapeutic potential in AD, where need exists for long-term, non-steroidal topical options.
PR022	Hypochlorous acid	Preclinical studies suggest reduced pruritus	N/A	TBD
Oral systemic agents				
Asimadoline	Kappa opioid agonist	Preliminary data consistent with other kappa opioid agonists, suggesting benefit for improving pruritus.	N/A	Potential role as anti-pruritic agent.
DS107 (dihomo-gamma-linolenic acid)	Fatty acid	Non-significant improvement in IGA; significant improvement in POEM and pruritus scores	Transient gastro-intestinal-related AEs	Demonstrated initial promise in improving some AD outcomes, further trials are warranted.
ZPL-389	Histamine H4 receptor antagonist	Significant improvement in EASI but not pruritus	N/A	If significantly decreased pruritus is eventually demonstrated, then H4 receptor antagonists may replace current anti-histamines, particularly if improved

				severity is also demonstrated.
Biologic agents				
Secukinumab	IL-17A	N/A	N/A	TBD
Fezakinumab	IL-22	Significant improvement in SCORAD in severe AD; less of a response seen in moderate AD	Well tolerated	Suggests potential role of IL-22 in AD pathogenesis

AD=atopic dermatitis, AE=adverse event, EASI=Eczema Area and Severity Index,

IGA=Investigator Global Assessment, IL=interleukin, N/A=not available, POEM=Patient

Oriented Eczema Measure, SCORAD=SCORing AD, TBD=to be determined.

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