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New Era of Biological Therapeutics in Atopic Dermatitis

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Abstract

Introduction—Atopic Dermatitis (AD) is a common inflammatory skin disease regulated by genetic and environmental factors. Both skin barrier defects and aberrant immune responses are believed to drive cutaneous inflammation in AD. Existing therapies rely largely on allergen avoidance, emollients and topical and systemic immune-suppressants, some with significant toxicity and transient efficacy; no specific targeted therapies are in clinical use today. As our specific understanding of the immune and molecular pathways that cause different subsets of AD increases, a variety of experimental agents, particularly biologic agents that target pathogenic molecules bring the promise of safe, and effective therapeutics for long-term use.

Areas covered—This paper discusses the molecular pathways characterizing AD, the contributions of barrier and immune abnormalities to its pathogenesis, and development of new treatments that target key molecules in these pathways. In this review, we will discuss a variety of biologic therapies that are in development or in clinical trials for AD, perhaps revolutionizing treatment of this disease.

Expert opinion—Biologic agents in moderate to severe AD offer promise for controlling a disease that currently lacks good and safe therapeutics posing a large unmet need. Unfortunately, existing treatments for AD aim to decrease cutaneous inflammation, but are not specific for the pathways driving this disease. An increasing understanding of the immune mechanisms underlying AD, brings the promise of narrow targeted therapies as has occurred for psoriasis, another inflammatory skin disease, for which specific biologic agents have been demonstrated to both control the disease and prevent occurrence of new skin lesions. Although no biologic is yet approved for AD, these are exciting times for active therapeutic development in AD that might lead to revolutionary therapeutics for this disease.

Keywords

Atopic Dermatitis; Eczema; Therapeutics; Biologics

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Declaration of interest

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1. Overview

Atopic dermatitis (AD) is the most common inflammatory skin disease, affecting up to 25% of children and up to 3% of the adult population[1,2,3]. Together with asthma and allergic rhinitis, it constitutes the “atopic triad.”[4] AD is multifaceted and regulated by a complex array of genetic and environmental factors. Approximately 80% of patients have a personal or family history of atopy, associated with a high serum immunoglobulin E level and/or elevated eosinophil count. This AD subset are often referred to as the extrinsic AD population, in contrast to intrinsic AD that lacks these characteristics[5]. The prevalence of AD has increased 2–3 fold during the last century, particularly in industrialized countries.[1, 2, 6] Despite its increasing prevalence worldwide, and the burden on society, specific therapies for AD are still limited, and most commonly used therapies are not based on a scientific mechanistic understanding. Although patients with mild disease can be effectively treated by topical emollients and anti-inflammatory agents, no available treatments can provide long-term remission for patients with moderate to severe AD, creating a large unmet need for effective systemic treatment.[7, 8, 9]

In recent years, new insights into the pathogenesis of AD have reshaped the historical role offormulated novel concepts such as the Th1/Th2 paradigm in disease processes. The identification of new T-cell subsets, particularly Th17, and Th22, and an understanding of the relative role of these T cell subsets in the pathogenesis of the disease, introduce the possibility of individualized rational-based therapeutic approaches for different immunologic subsets of this disease.[7, 10]

Psoriasis, another inflammatory skin disease, which like AD involves both abnormalities of innate and adaptive immune responses, serves as a good model to follow in this endeavor of successfully targeting specific cytokines/molecules as a therapeutic strategy. Both AD and psoriasis are characterized by activation of distinct T-cell subsets, dense T-cell and DC infiltrates, as well as epidermal hyperplasia in their chronic phases.[6, 7] Although previously characterizedrecognized as Th1 vs. Th2 T-cell polarized diseases, these conditionsthey have recently also been demonstratedshown to exhibit distinctthave differential expression of the newly described Th17 and Th22 T-cell subsets.[10, 11] Psoriasis has a strong Th17 activation, while AD has smaller Th17 component and, with a marked Th22 activation. The importance of these differences in T-cell subsets is that disease activity may be driven only by one key T-cell subset and cytokine, e.g., Th17 T-cells and their major cytokine, IL-17 for psoriasis.[10–16] In psoriasis, multiple clinical trials recently showed that targeting a single cytokine (such as IL-17 or IL-23 or its subunit p40) can successfully reverse the disease clinically as well as molecularly, in a relatively short time frame.[12, 16–19] Treatments for psoriasis were developed based on known cytokine-signaling pathways, and the fact that these treatments achieve complete clearance in majority of patients, advocate for upstream effects of reduced gene expression of induced genes along with other cytokines, suggesting a feed forward inflammatory loop that amplifies drug effects.[20] In psoriasis, neutralization of IL-17 by antibodies to IL-17A cytokine or to its receptor can lead to clinical disease reversal in 80% or more of treated subjects. Antagonism of this polarized T-cell pathway seems to produce few adverse effects related to immune antagonism, unlike the multiple adverse effects with broad T-cell suppression.[16, 20]

Moreover, in psoriasis, the epidermal hyperplasia has been shown to be driven by underlying immune activation[21–23], Reversal of the clinical phenotype with therapeutic agents having broad actions (i.e CsA, CTLA4Ig, efalizumab, and alefacept), and selective immune antagonists (anti IL-17, anti IL17R, IL23p40, or anti TNF antibodies) associated with reversal of the epidermal hyperplasia, and immune phenotype of lesional skin (Figure 1).[16–20, 24–27] Since the epidermal reaction in psoriasis is largely restored to normal with

selective immune suppression[28–30], one might hypothesize that similar epidermal responses could occur in AD with specific immune antagonism. This hypothesis is supported by recent findings that link immune and epidermal barrier defects in AD, suggesting that disease-driving cytokines involved in AD, such as IL-4, IL-13 and IL-22 inhibit production of barrier proteins (i.e FLG and LOR) and antimicrobial peptides (Figure 1). Thus, inhibition of specific adaptive immune responses or cytokine pathways would be expected to lead to skin barrier repair. A recent study of AD patients that were treated with narrow band (NB) UVB therapy, also showed that reversal of clinical disease activity was associated with reversal of the epidermal pathology including reduction in epidermal thickness, and expression of proliferation markers (K16 and Ki67).[31] However, since NB-UVB therapy has direct effects on keratinocytes, future studies with specific immune antagonists are still needed to confirm that reversal of the epidermal pathology in AD results from inhibition of immune activation.

1.1 Broad Epidermal Barrier Abnormalities characterize lesional and non-lesional AD

Multiple studies emphasize that lesional and even normal appearing skin of AD patients are deficient in various lipids[32], and many keratinocyte differentiation proteins that play important functions in barrier formation and hydration. These molecules include ceramides, cholesterol, free fatty acids, as well as filaggrin, loricrin, involucrin and other barrier proteins.[32–38] The role of the epidermal barrier defects in the pathogenesis of AD gained its strongest support by recent genetic research that AD was associated withtwo loss of function mutations in the FLG gene. Loss of filaggrin has been linked to enhanced allergen penetration into the skin resulting in systemic allergen sensitization, as well as increased *S. aureus*, R501X and viral growth in the skin and susceptibility to the cytotoxic effects of staphylococcal toxins, e.g. alpha toxin.[39–40] Between 10–50% (depending on population) of the AD patients have been reported to have *FLG* mutations.[41–42]2282del4 with AD. Significant linkage was also found between AD and chromosome 1q21, which contains genes in the epidermal differentiation complex, such as filaggrin, loricrin, involucrin, etc.[43] Moreover, both lesional and non-lesional AD skin show large abnormalities in many of these barrier proteins.[32] We are not aware at present of clinical trials that target restoration of these proteins. [39]

1.2 Novel T-cell subsets and their role in the pathogenesis of Atopic dermatitis

The original hypothesis that AD is mediated primarily by activation of the Th2 T-cell subset was recently modified with the recent discovery of the new T-cell subsets, Th17 and also Th22.[7,10] Th17 T-cells produce IL-17, and some IL-22.[7,4440] Th17 T-cells regulate production of antimicrobial peptides in keratinocytes, and neutrophil chemotaxis, and were shown to have a pathogenic role in psoriasis.[7,44–4540–41] In AD, Th17 T-cells were found to be increased in AD skin lesions, although in a comparative study with psoriasis, IL17 mRNA levels were significantly less in AD. The relatively reduced level of IL-17 production in AD, in comparison with psoriasis, might contribute to the decreased production of antimicrobial peptides (AMPs) observed in atopic as compared to psoriasis patients (Figure 1). Although similar colonization with bacteria has been shown in psoriasis and AD, in psoriasis, there is a decreased rate of infections in contrast with an increased rate of infection in AD. This may be due to differences in IL-17 and the antimicrobial axis.[10, 45–4741–43] The reduced expression of IL-17 in AD has also been postulated to result from the inhibition of IL-17 production by the Th2 cytokines (IL-4/IL-13).[4642]

Although Th17 produce small amounts of IL-22, the newly described subset of Th22 T-cells are responsible for the majority ofmost IL-22 production in AD skin lesions.[10] The immune infiltrates in chronic AD skin lesions has been shown to be primarily composed of Th2 and Th22 T-cells, although Th1 and Th17 T-cells are also present.[10] Furthermore,

numbers of both Th22 and Tc22 were increased in AD as compared with psoriasis, and they were correlated with the AD disease activity as defined by the Scoring of AD (SCORAD) index.[10] IL-22 is considered to have a major role in induction of epidermal hyperplasia and hypogranularity, and might contribute to the significant epidermal acanthosis seen in chronic stages of AD (Figure 1).[10].

1.3 The link between Immune and Skin Barrier defects

Two competing hypotheses are still debated regarding primary disease pathogenesis: 1) the "inside-out" hypothesis: AD is a disease of reactive epidermal hyperplasia, primarily driven by an immune stimulus (primarily the underlying activation of Th2, and Th22); and 2) The "outside-in" hypothesis: genetically-transmitted defects in epidermal barrier products lead to an abnormal growth/differentiation of keratinocytes, with a reactive (secondary) immune activation.[6] The first hypothesis is supported by the broad down-regulation of terminal differentiation products, extending far beyond the filaggrin protein, in lesional and also non-lesional AD skin, supporting a potential epidermal reaction to a primary immune stimulus. The second hypothesis predicts a relatively fixed epidermal growth defect that would still exist even if underlying immune activation would be suppressed. The second view is supported by the recent discovery of the loss of function mutations in filaggrin[35, 39, 4244]. However, patients that harbor these mutations can outgrow the disease[4345], and topical calcineurin inhibitors, and gentamycin were demonstrated to restore expression of barrier proteins, including filaggrin.[4846] These data suggest that in the majority of patients inflammation or immune activation can inhibit filaggrin expression.

Several observations suggest the cross talk between the immune system and barrier defects in AD.[36–38,47–49–51] A large bulk of evidence suggests that the Th2 cytokines, IL-4[50–52–54], IL-13[53] and recently also IL-31[56–6154–59] regulate important functions of the epidermal barrier, including epidermal cornification and production of AMPs.[7, 60–62–64] Th2 cytokines also inhibit major terminal differentiation proteins, such as filaggrin, loricrin, and involucrin.[62, 6360, 61] The IL-13 cytokine has also been shown to induce proliferation of airway epithelium.[6563] Thus it can be postulated that in AD, Th2 cytokines might initiate a feedback mechanism that induces regenerative hyperplasia through the inhibition of terminal differentiation. However, activation of Th2 cytokines in AD cannot solely account for the epidermal hyperplasia that characterizes chronic AD. The hyperplasia of epidermal keratinocytes might primarily relate to overproduction of IL-22 in chronic AD skin lesions.

1.4 Paving the Path for Future Therapeutic Development in AD

Several clinical trials with broad T-cell targeting therapeutics such as cyclosporine (CsA)[64–66–68], Alefacept[6866], and efalizumab[6967], found clinical benefit in patients with moderate to severe AD. However, due to their toxicity, these agents are not suitable for long-term administration. Another issue impeding the development of therapeutics for AD is that the vast majority of AD clinical trials lack biomarker correlations, partially due to an evolving understanding of pathogenic mechanisms underlying the disease and lack of markers for tissue reversal. However, last year our group recently identified a set of molecular biomarkers for disease response that may be used to track therapeutic responses.[31, 32,3664, 68] This will enable us to pursue drug discovery strategies similar to those done with psoriasis, where clinical studies with an evolving series of immune antagonists had the ability to relate clinical outcomes with histological and molecular correlates (biomarkers) of disease.[66,7064, 68]

2. Emerging therapeutics (Table 1)

2.1 Barrier repair

The innate immune system is linked to skin barrier function. Thus, therapeutic strategies which improve innate immunity might ultimately lead to repair of the epidermal barrier. In preliminary studies, vitamin D3 supplements upregulated production of AMPs[7169]; these findings should be validated in larger populations of patients with AD. Probiotics (cultures of commensal bacteria) might restore a healthy microbial balance to patients with AD and other inflammatory disorders. The hygiene hypothesis prompted studies of these bacteria and found that they had immunomodulatory properties.[7270] However, a meta-analysis of trials of probiotics did not show that they benefitted patients with AD.[7371] Because an imbalance of proteases has been proposed to contribute to AD, topical protease inhibitors are also being tested for treatment of AD, although there is no evidence for their benefit.[7472] Another approach that is under development aims to restore and increase the expression of epidermal differentiation proteins, such as filaggrin and loricrin in order to repair the barrier.[7,75,7673,74]

2.2 Allergen Specific Immunotherapy

Allergen immunotherapy is a well-established treatment forused (perhaps the first “biological”?) against sensitization in allergen induced asthma or allergic rhinitis. Patients with AD are often produce IgE against specificsensitized to inhalant and food allergens.[77] based on immediate or prick skin testing or blood IgE results.[75] In patients who have an exacerbation of their underlying allergic disease (asthma, food allergy or AD), there may be a role for immunotherapy to the allergens which trigger their illness.[7876] Double-blinded, multi-center, randomized trials with house dust mites have been reported to significant improve the eczema in patients with AD who are sensitized to house dust mite allergen.[79–8077–78] Oral immunotherapy protocols are also being optimized for patients with a history of AD and food allergy.[81–8279–80] The immune mechanisms by which immunotherapy acts are complex and include the induction of regulatory T cells and the suppression of basophil activation as well as Th2 cells.[83–85.[81–82]

2.3 Targeted Immunomodulating therapies

Most traditional therapies are intended foraim at clinical improvement and symptomatic relief without targeting the specific pathways that initiate and promote AD. Biologic agents hold the promise for a more targeted, effective and less toxic approach to systemic therapy, as is evidenced by the revolution in psoriasis therapeutics during the last decade,[89–8983–86] in which biologic therapies were approved for psoriasis and psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease.[90–9687–93] In this section, we will discuss the various biologic treatments that have been used for AD, though although currently there are currently no biologic therapies officially approved for the diseaseAD. With only few exceptions, most biologics used for AD were initially developed and / approved for other diseases, such as psoriasis.[7,9794] Recently, there has an effort to develop biologics that will be specific for AD and or other atopic diseases, such as asthma.

Biologics that target adaptive immune responses have been tested in patients with AD that does not respond to other therapies.[98, 9995, 96] These include inhibitors of IgE, B cells, T cells, and Th2 cytokines or cytokine receptors, as well as Th1 agonists, and antagonists of pro-inflammatory cytokines.[74, 10072, 97]

2.3.1 Anti-IgE therapy—Although the role of IgE in the pathogenesis of AD is not clear, omalizumab, a humanized IgG1 monoclonal antibody against IgE, has been tested in AD mainly in patients refractory to conventional therapy. In contrast to patients with severe

asthma and chronic idiopathic urticaria (CIU) that showed significant improvement in their disease, omalizumab has not been observed to have consistent significant clinical effects in most patients with AD, despite its ability to downregulate FceRI on DCs.[101–10498–100] This may be in part due to the very high serum IgE levels which may be difficult to neutralize in AD as compared to asthmatics who have lower serum IgE. Alternatively, IgE might only play a secondary role to the primary cellular mechanisms in atopic dermatitis, in which case the therapeutic efficacy of omalizumab would be limited Overall, this highlights the heterogeneity and complexity of allergic diseases suggesting that more work is needed to characterize AD patients into defined immunologic profiles and phenotypes which may benefit from specific biological therapies.

2.3.2 Anti CD20—Small studies of rituximab, an antibody against CD20 that depletes B cells, which was developed for hematologic disorders, have had contradictory results in patients with AD.[105–106101,102] One study showed that treatment with rituximab resulted in a rapid and sustained decrease of skin inflammation in patients with AD, suggesting a possible role for B-cells in its pathogenesis, although IgE levels remained unchanged during treatment.[106103] Further studies are required to determine whether reagents that inhibit or deplete B cells might be used to treat AD.

2.3.3 Inhibition of T-cell responses—Biologics that target T cells, such as efalizumab and alefacept, have been approved by the FDA for treatment of psoriasis and have also been found to have some efficacy in patients with AD. Efalizumab and alefacept were effective in patients with psoriasis because they interfered with receptor–ligand interactions that activate T cells (such as LFA1–ICAM1 and LFA3–CD2, respectively). Although shown in few small clinical trials to possibly have a benefit in AD patients, these studies lacked mechanistic information; These agents are thought to non-specifically deplete T cells in the skin, potentially reducing inflammation.[107–110101, 104–106] Both of these agents were recently withdrawn from the market, and are unavailable. Efalizumab has been removed from the market because cases of progressive multifocal leukoencephalopathy (PML) were observed in psoriasis patients treated continuously for more than 3 years, and Alefacept was also removed recently due to insufficient market.

2.3.4 Th2-inhibition strategies

Anti IL-4 therapies: Cytokines produced by Th2 cells inhibit production of anti microbial peptides (AMPs) and terminal differentiation proteins.[60–62–64] IL-4 promotes differentiation of Th2 cells and IgE class switching by B cells; mutations in IL-4 and its receptor have been associated with AD.[111–112107, 108] Therapeutic strategies that inhibit cytokines produced by Th2 cells, particularly IL-4, might therefore have therapeutic effects in patients with AD (Table 1). Since IL-4 and IL-13 signal through a common receptor, IL4RA, targeting this receptor might reduce the response to both cytokines.

Few inhibitors of the IL-4 R are currently available. An inhibitor of IL-4 receptor signaling (pitrakinra/pascolizumab) that competitively binds to IL-4RA to inhibit binding of IL-4 and IL-13 has shown efficacy in trials of patients with asthma,[113–114109, 110] but has not been tested for patients with AD.[7472] Of great interest is REGN668, an anti IL-4R antibody currently evaluated in clinical trials for AD and eosinophilic asthma (phase 2 in eosinophilic asthma and completing phase 1 in AD). We are not aware of reports of the efficacy of IL-13 antagonists in AD patients.

Anti IL-5 strategies: IL-5, another important cytokine produced by Th2 cells, induces eosinophil differentiation, activation, mobilization, and survival.[115–116111, 112] Eosinophils are important mediators of the inflammatory process in AD, so agents that block IL-5 might

be developed as therapeutics.[117113] However, mepolizumab, a fully humanized, monoclonal antibody against IL-5, reduced blood and tissue eosinophilia but did not show clinical efficacy in patients with moderate to severe AD.[118–120114–116] Mepolizumab reduced the numbers of eosinophils in patients with asthma, but had no effects on T-cell responses,[121–122117, 118] arguing against its role in treatment of AD.

Anti IL-31: IL-31 is a cytokine produced by Th2 cells that is believed to promote itching in AD. We have recently shown that IL-31 is one of the markers that are most significantly increased in acute AD, possibly correlating with the greatly increased pruritus at this stage[57–59, 123119], and this treatment might hold promise for the treatment of eczema as well as other itch-related dermatoses. Therapeutics that target IL-31 are under development or in phase I clinical trials (clinicaltrials.gov).

Targeting TSLP: TSLP mediates signaling by DCs that promotes Th2-cell responses, and are highly upregulated in atopic skin.[124–126120–122] Investigational agents that block the action of these molecules are of great interest due to the role of TSLP in promoting the inflammatory Th2 pathway. Antagonists of the TSLP pathway are under investigation for patients with AD or Asthma or in phase I clinical trials (clinicaltrials.gov).

2.3.5 Targeting Th22—The Th22 T-cell, is a novel T-cell subset, which was recently described by us as a distinct T-cell[10], and its role in AD was suggested by the correlation between these cells and disease activity. Numbers of Th22 cells, which produce IL-22, are increased in patients with chronic AD, and mRNA expression of the IL-22 cytokine and its induced factors are also increased in acute AD[127, 128123, 124], indicating that that IL-22 might be a therapeutic target for patients with AD.

2.3.6 Targeting Th17/IL12/IL-23 pathway—Since we and others found levels of IL-17 and its related factors to be increased in patients with acute AD[10, 11, 14, 15, 128124], agents directed against IL-17 cytokine or its receptor (such as Ixekinumab, Brodalumab, or AIN457) and/or IL23, such as MK-3222 might be effective for patients with acute exacerbations of AD. Anti-p40 (ustekinumab/Stelara) might also be effective by targeting multiple pathways involved in AD, including the Th17 and Th22 pathways.[129125]

2.3.7 Recombinant Interferon Gamma—IFNγ is the premier cytokine produced by Th1. Peripheral blood mononuclear cells of AD patients have been shown to produce lower levels of IFNγ.[130–132126–128] The rationale for its use in AD patients is that administration of recombinant IFNγ to patients with AD might restore the balance of Th1- and Th2-cell responses, and lower IgE production. However, trials showed effectiveness of this treatment in only a subset of patients, and did not reduce levels of IgE.[133, 134129, 130] Nevertheless, this treatment might still have a potential role in patients with concomitant skin infections, such as herpes simplex, and molluscum contagiosum.[8]

2.4 Anti IL-6R

Tocilizumab is an IL-6 receptor antagonist, FDA approved in 2008 for the treatment of rheumatoid arthritis.[135,136131,132] Recent reports on off label usage, included other systemic inflammatory disorders, such as lupus erythematousus, systemic sclerosis, and polymyositis. Recently, this antagonist was used to treat 3 AD patients, refractory to other treatments, including cyclosporine A.[137133] All patient showed significant clinical improvement, with more than 50% reduction in the Eczema Area and Severity (EASI) score. However, bacterial infections were observed in two of the three patients. Further studies are needed to evaluate the potential efficacy and the safety of tocilizumab in patients with severe AD.

2.5 Anti TNF agents

Anti-TNF agents have been successful in treating psoriasis;[138–140134–136] probably because TNF and its synergistic interaction with IL-17 mediate the pathogenesis of psoriasis.[121117] Furthermore, TNF antagonists inhibit the pathogenic Th1- and Th17-cell responses that contribute to psoriasis.[141,142137, 138] However, a pilot study of the effects of the TNF antagonist, infliximab, in patients with moderate-to-severe AD, and another study on etanercept in two children, demonstrated had disappointing results,[143, 144139] possibly because TNF-induced inflammatory responses have only a minor role in AD.[47,12143, 117] Although clinical improvement was obtained, the patients did not show sustained responses.[144139]

2.6 Phosphodiesterase Inhibitors

Increased levels of phosphodiesterase-4 (PDE4) activity has been described in mononuclear cells from AD patients.[145,146140,141] Inhibitors of PDE have shown clinical benefit when used topically in AD patients.[148143] An open label study with Apremilast, a novel oral PDE4 inhibitor that is currently in phase 2 clinical trials for psoriasis, was given to 16 adult patients with moderate to severe AD, in two cohorts of 6 patients receiving a lower dose of 20 mg twice daily and 10 on the higher dose of 30 mg twice daily.[149144] The clinical responses seen at 6 months showed a reduction of approx 50% in the EASI score in the cohort obtaining the highest dosing. Further larger, controlled studies are needed to evaluate this potentially promising treatment modality for AD.

2.7. Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists (Thiazolidinediones)

Thiazolidinediones activate the nuclear receptor, PPAR-γ, which is expressed on adipocytes and immune cells.[150–154145–149] Activation of PPAR-γ decreases production of pro-inflammatory cytokines (i.e TNF-α and IL-6) and also increases responses to insulin. These agents were first approved for treatment of diabetes mellitus and recently also explored for inflammatory skin diseases, such as psoriasis and AD. Few clinical studies with systemic PPAR-γ agonist, Rosiglitazone led to clinical improvement and reduced number of flares in few patients with recalcitrant AD[155150], and topical PPAR-α agonist showed beneficial clinical effects in pediatric AD.[156151] Both PPAR-γ and PPAR-α are thought to have anti-inflammatory and barrier-normalizing properties, and might be useful for treatment of established AD skin lesions and also possibly for prevention of new lesions.

2.8 Chymase Inhibitor

Chymase is an inflammatory molecule, which is produced by mast cells, and might be involved in the inflammation and itching associated with AD. After testing a chymase inhibitor (SUN-C8257) in mice with AD-like skin lesions and showing significant improvement in the dermatitis and itch of these mice, clinical trials were issued in humans, and currently an oral chymase inhibitor. SUN 13834 is in Phase II in AD patients.[157, 158152, 153]

3. Possible Future Developments

- Inhibitors of JAK-kinase to block γ_c signaling (IL-4 signal transduction). Oral JAK inhibitors, such as Tofacitinib and Ruxolitinib showed rapid and good clinical efficacy in psoriasis, and are in advanced stages of development.[159154]
- Targeting cytokines that promote T-cell differentiation and survival

- Targeting chemokines that are increased in skin and blood of AD patients, such as CCL17/TARC and CCL22/monocyte-derived chemokine (MDC) that are both ligands of CCR4, which is expressed on Th2 T-cells.

4. Expert Opinion

Traditional systemic therapies used for the treatment of patients with moderate to severe AD are associated with significant toxicity, that limit their applications and the time frame they are used. There is a very large unmet need for new development of novel specific therapeutics for this large group of patients, in adults as well as in children. Biologic agents maypotentially could hold great promise for the treatment of AD if they can offer the following advantages: 1. Low toxicity,. 2. Good efficacy,. 3. Improved patient compliance viaGiven weekly/biweekly/ and even monthly administration,, greatly increasing patient compliance. 4. Reduction ofControl disease activity,. 5. Relapse prevention.Prevent relapses.

AD is a complex disease, with activation of both Th2 and Th22. Thus, successful treatment of the disease might necessitate targeting Th2 or Th22 (with a possible synergy between these axes), or perhaps a more complex strategy that aims at targeting both axes simultaneously or sequentially might be needed to maximize effectiveness. Perhaps, by analogy to psoriasis that is a Th1 and Th17 disease, where targeting a single cytokine, IL-17, results in clearance of disease in most patients, in AD, we could obtain disease resolution by targeting a single pathway or cytokine, such as the Th2 pathway with blockade of the IL-4R, or targeting the IL-22 cytokine. Importantly, we now have validated biomarkers for disease improvement, that as in psoriasis will provide an appropriate way to determine whether clinical resolution of disease is also accompanied with molecular and tissue resolution, as well as determine unique characteristics of responders versus non-responders.[31–32,36]. Finally, a biologic agent that targets a specific pathway or molecule in the disease with high efficacy will also be able to provide the final proof for primary immune pathogenesis if epidermal pathology is reversed with successful treatment. Since there is a very close relationship between elucidation of molecular disease pathways and development of targeted therapeutics, academic institutions and researchers will need to work closely with the industry to assure rapid drug development to benefit AD patients. Furthermore, regulatory and funding agents will need to acknowledge the large unmet need and current lack of safe, adequate treatments for such a common disease in adults, and not only in children as was believed in the past, and support the effort for translational and drug development for this disease.

5. Conclusions

The recent advances in our understanding of the pathogenic mechanisms implicated in AD provides an opportunity for development of biologic therapies directed at pathways driving AD. We believe that this is the beginning of a new, exciting era in AD therapeutics, with impending availability of narrow-targeted drugs with low toxicity and increased patients compliance. These specific drugs are predicted, to not only treat existing disease, but also prevent onset of new skin lesions.

Acknowledgments

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Abbreviations

AD	Atopic Dermatitis
Th1	Type 1 Helper T Cell
Th2	Type 2 Helper T Cell
Th17	Type 17 Helper T Cell
Th22	Type 22 Helper T cell
IL	Interleukin
IL4RA	Interleukin 4 Receptor α
IL23p40	Interleukin 23 Subunit p40
TNF	Tumor Necrosis Factor
LOR	Loricrin
AMPs	antimicrobial peptides
CsA	Cyclosporine A
FceRI	Fc Epsilon Receptor 1
DCs	Dendritic Cells
CD20	Cluster Differentiation 20 (B-cell marker)
LFA1-ICAMI	Lymphocyte function-associated antigen 1 (Intercellular Adhesion Molecule 1)
LFA3-CD2	Lymphocyte function-associated antigen 3 (Cluster of Differentiation 2)
FLG	Gene encoding the skin barrier protein filaggrin
IgE	Immunglobulin E
REGN668	IL4 Receptor Antibody
TSLP	Thymic stromal lymphopoietin
IFNy	Interferon gamma
mRNA	Messenger Ribonucleic Acid
AIN457	IL-17A Antibody
MK-3222	IL-23 Antibody
EASI	Eczema area and severity index
PDE4	Phosphodiesterase 4
PPAR-y	Peroxisome proliferator-activated receptor gamma
PPAR-a	Peroxisome proliferator-activated receptor alpha
SUN-C8257	Chymase inhibitor
SUN13834	Chymase inhibitor
JAK	Janus kinase
CCL17	Chemokine ligand 17
TARC	Thymus and activation-regulated chemokine (CCL17)
CCL22	Chemokine ligand 22

CCR4	Chemokine receptor 4

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Article highlights

- Atopic dermatitis is the most common inflammatory skin disease, with a substantial health-economic impact and a large unmet therapeutic need
- Current management of atopic dermatitis include allergen avoidance, skin emollients, topical and systemic immune-supressants, and phototherapy. Some of these treatments cannot be used widely due to associated toxicities (e.g. cyclosporin A) or time-consuming requirements (i.e phototherapy).
- With an increasing understanding of pathogenic mechanisms, biologic therapies represent promising therapeutic strategies for atopic dermatitis.
- Although no biologic therapy is yet to be approved for AD, there are many molecules that are currently under development.

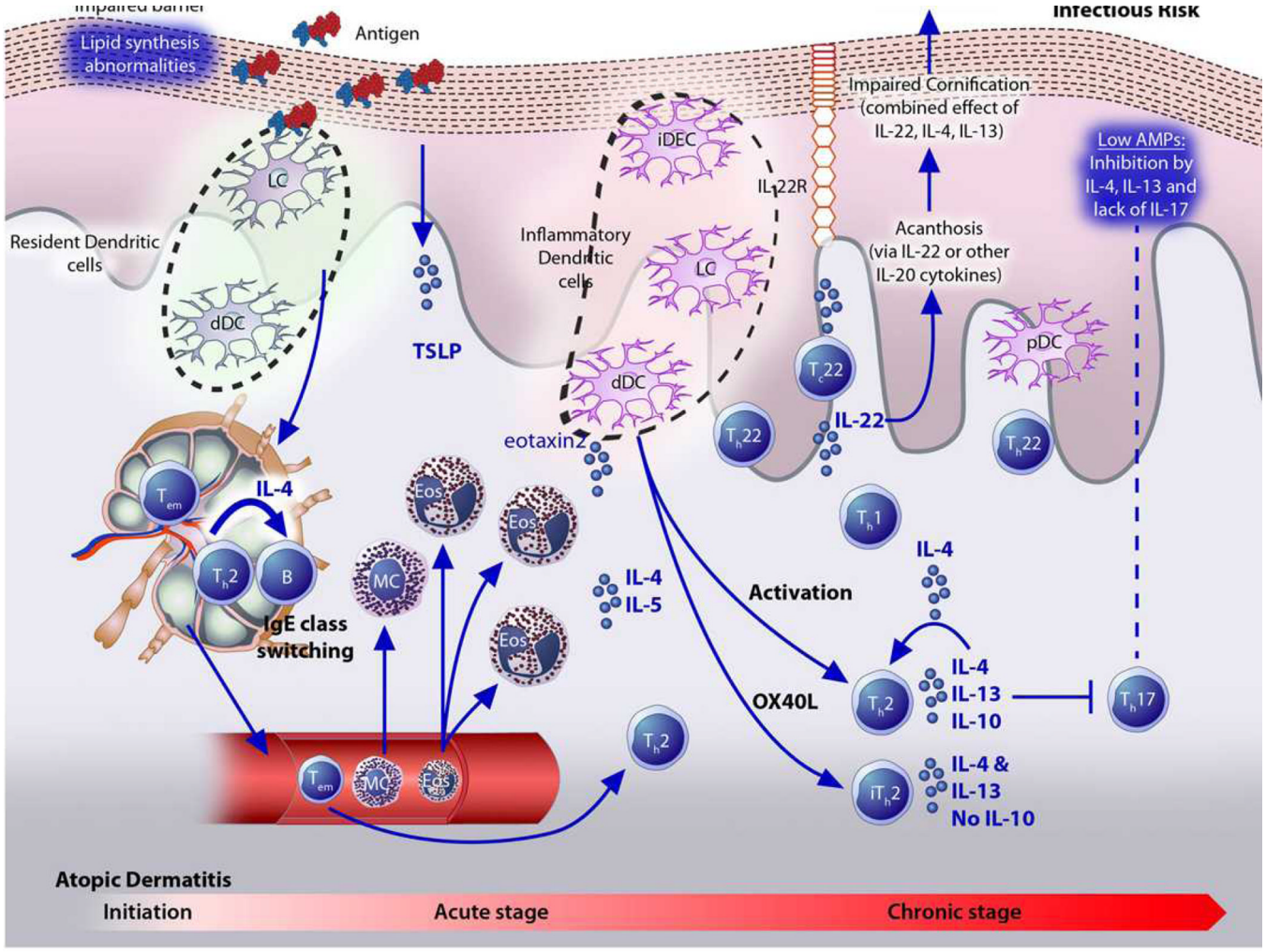

Fig. 1. The pathogenesis of atopic dermatitis (AD)

The disease has three main phases, including initiation, acute and chronic stages. Defects in the epidermal barrier lead to the penetration of the skin by epicutaneous antigens, which in turn encounter Langerhans and dermal Dendritic cells that activate Th2 cells and IL-4 and IL-13 production. These cytokines result in two major effects: IgE class switching and increased Th2 cell survival. Additionally, these cytokines gradually increase from nonlesional through chronic disease, and have several direct effects on the epidermis. These include increased TSLP production by keratinocytes, inhibition of anti-microbial peptide (AMP) production, and impaired epidermal differentiation. The resulting disrupted epithelial barrier further increases AD-associated infections. In addition, the inflammatory mediators of Th2 T-cells and DCs induce peripheral eosinophils and mast cells. Also of significance is an increase in Th22 cells in AD skin; this subset produces IL-22, which is most significantly increased in chronic AD skin. IL-22 inhibits terminal differentiation and induces epidermal hyperplasia, which is an important characteristic of chronic disease. Thus, the barrier defect in AD most likely results from a combined effect of Th2 and Th22 cytokines. Similarly to T-cells, there is a progressive increase in dendritic cells and langerhans cells from non-lesional through chronic AD. The role of Th17 T-cells and their cytokine, IL-17 in AD is less significant to the pathogenesis of AD compared with psoriasis, and more modest increases in this cytokine were found in acute and chronic AD, as compared to psoriasis. This might

explain the decreased production of AMPs in AD patients as compared with psoriasis, secondary to both Th2 cytokine inhibition and relatively lower levels of IL-17.
Adapted from: Guttman-Yassky E, Nograles K, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--Part II: Immune cell subsets and therapeutic concepts. J Allergy Clin Immunol 2011;127:1420–1432.

Table 1

Experimental Therapeutics in AD

Adaptive immunotherapy
Allergen-specific immunotherapy (targeting allergen-specific T- and B-cells)
Experimental innate immune system & barrier therapeutics
• Oral Vitamin D supplementation (increase AMP production) • Probiotics (restore microbial balance) • Topical protease inhibitors
Biologics targeting the adaptive immune system
• Anti-IgE therapies (Omalizumab) • B-cell targeting (Rituximab) • T-cell targeting (Alefacept*, Efalizumab*) • Th2 cytokine product targets: – IL-4 receptor inhibition (Pitrakinra, Pascolizumab, REGN668) – IL-13 inhibition – Anti-IL5 (Mepolizumab) – Anti-IL-31 • Th2 recruitment/activation inhibitors: – Targets include TSLP and OX40 signaling • Target Th22 or Tc22 cells (Anti-IL-22) • Inhibition of Th17/IL-12/IL-23 pathway: – IL-17 cytokine and receptor antagonists (Ixekinumab, Brodalumab, AIN457) – IL-23 inhibitors (MK-3222) – p40 inhibitors (Ustekinumab) • Restoration of balance between Th1- and Th2 response (IFNγ administration) • IL-6 receptor inhibitors (Tocilizumab) • Anti-TNF reagents (Etanercept, Infliximab, Adalimumab
Non-biologic therapies targeting the adaptive immune system
• PDE4 inhibitors (Apremilast) • PPARγ agonists (Thiazolidinediones) • Chymase inhibitors (SUN-C8257)
Potential future biologic therapies and targets
• JAK kinase inhibitors to block γ_c signaling involved in IL-4 signal transduction (Tofacitinib, Ruxolitinib) • Cytokines that promote T-cell differentiation and survival • Chemokines that are increased in the skin and blood of AD patients (including CCL17/TARC and CCL22/MDC)