

# Monoclonal Antibodies for Atopic Dermatitis: Progress and Potential

Paras P. Vakharia<sup>1</sup> · Jonathan I. Silverberg<sup>2,3</sup>

© Springer International Publishing AG 2017

**Abstract:** Atopic dermatitis (AD) is a complex and heterogeneous inflammatory skin disorder with a profound symptom and lesional burden. Moderate-to-severe AD is particularly challenging to manage, as topical treatments are often inadequate and the systemic immunosuppressants are limited by concerns of toxicity and tolerability. Recent AD research has elucidated the mechanisms and immunologic factors involved in AD pathogenesis. These breakthroughs have led to the development of multiple therapeutic monoclonal antibodies that are directed against specific immunologic targets. This review provides an overview on the pathogenesis of AD as well as the rationale for the targets of various monoclonal antibodies. Additionally, this review explores the efficacy and safety of use for various monoclonal antibodies in the management of AD, as well as the potential role of these agents in the treatment of AD.

## Key Points

There are major unmet needs for the treatment of patients with moderate-to-severe atopic dermatitis (AD), where topical therapies are often inadequate and systemic immunosuppressive therapies are often associated with systemic adverse effects.

As the pathogenesis and immunologic pathways of AD are elucidated, opportunities for development of targeted agents in AD are expanding, particularly monoclonal antibodies. Various monoclonal antibodies have recently been approved or are in development for the treatment of moderate-to-severe AD.

The use of monoclonal antibodies for the treatment of AD holds great promise and potential. Continued research and surveillance are required to understand the role of the various agents.

✉ Jonathan I. Silverberg  
JonathanISilverberg@Gmail.com

<sup>1</sup> Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

<sup>2</sup> Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

<sup>3</sup> Northwestern Medicine Multidisciplinary Eczema Center, Chicago, IL, USA

## 1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects up to 15–20% of children and 1–10% of adults worldwide, including 13% of US children and 7.2% of US adults [1–4]. AD is associated with a heterogeneous constellation of signs and symptoms, including pruritus, xerosis, oozing/weeping in acute lesions, lichenification and prurigo nodules in chronic lesions, a chronic or chronically relapsing course, and an age-related distribution of cutaneous lesions [5].

A combination of genetic, environmental, and immunologic factors contributes to AD pathogenesis [6–8].

Genetic mutations, most notably in the *Filaggrin* gene, can contribute toward a compromised skin barrier in certain population subsets, although mutations may be absent in certain ethnic groups. The *Filaggrin* gene encodes for the epidermal protein filaggrin, which is a component of natural moisturizing factor and is involved in normal epidermal skin differentiation. This skin barrier dysfunction leads to increased transepidermal water loss (TEWL) and resultant dry skin, as well as the introduction of allergens, irritants, and bacteria into the skin, leading to immune activation and inflammation [9–13]. Additionally, adaptive T helper cell type 1 (Th1)- and T helper cell type 2 (Th2)-mediated immune dysregulation also contribute to AD pathogenesis. An imbalance of T helper cells, most notably Th1, Th2, T helper cell type 17 (Th17), and T helper cell type 22 (Th22), is found to occur in AD skin. Elevation of Th2 cells occurs during both the acute and chronic phases of AD, whereas Th1 cells are increased during the chronic phase of disease [14]. Skewed Th2 responses occurring in AD lead to increased production of interleukin (IL)-4, IL-5, IL-13, and IL-31, which have a number of downstream effects in AD (Fig. 1) [13–20]. Moreover, recent studies found that inflammation occurring in AD is sufficient to downregulate the expression of epidermal filaggrin even in the absence of *Filaggrin* gene mutations [14, 21]. Thus, cutaneous inflammation alone may be sufficient to lead to impaired skin barrier function. It appears that a combination of both epidermal barrier defects and immunologic dysregulation contribute to the pathogenesis of AD.

Mild-to-moderate cases of AD may be adequately treated with moisturizers and emollient agents, topical corticosteroids (TCS), and/or topical calcineurin inhibitors. Moderate-to-severe cases of AD often require systemic immunosuppressants in order to achieve adequate disease control, including cyclosporine (ciclosporin), methotrexate, mycophenolate mofetil, and azathioprine. However, these systemic agents have variable efficacy and numerous safety and tolerability concerns that limit their use [22, 23]. Thus, there are major unmet needs for systemic agents that are both effective and safe for the treatment of AD. Several targeted agents, such as monoclonal antibodies, directed toward immune pathways and cytokine mediators have either been approved and/or are in development for the treatment of patients with moderate-to-severe AD. Monoclonal antibodies, in comparison to other systemic treatments, offer various advantages. By having high therapeutic target specificity, they have greater precision with fewer indirect toxicity results. Additionally, monoclonal antibodies generally have longer half-lives, permitting less frequent dosing. Lastly, fewer drug–drug interactions are seen as these agents interact less, if at all, with cytochrome P450 enzymes [24–26]. The objective of this article is to review the mechanism and available data

related to the safety and efficacy of various monoclonal antibodies in AD, and to provide insight into their potential role in the treatment of AD.

## 2 Methods

A non-systematic review of the literature was performed. PubMed and ClinicalTrials.gov were searched for studies describing the use of monoclonal antibodies in AD patients. Articles or trials discussing the use of monoclonal antibody therapy for AD were selected for in-depth review, with a focus on articles published within the last 10 years. Randomized controlled trials (RCTs) were primarily sought, but other study types were also reviewed and included if they were found to include pertinent data. Monoclonal antibodies are presented by mechanism of action, with analysis of the target's role in AD along with clinically relevant and available results regarding efficacy and safety in AD patients described.

## 3 Discussion

### 3.1 Interleukin (IL)-4/IL-13

Dupilumab is a fully human monoclonal antibody directed against the IL-4 receptor  $\alpha$  subunit (IL-4R $\alpha$ ). IL-4R $\alpha$  is part of the receptor complex for both IL-4 and IL-13, and thus inhibition of the IL-4R $\alpha$  inhibits both IL-4 and IL-13 signaling. As mentioned earlier, AD is associated with elevated and skewed Th2 responses, including the production of IL-4 and IL-13 [13, 14, 27]. These cytokines stimulate immunoglobulin E (IgE) production, and promote further Th2 differentiation and epidermal barrier disruption in AD via multiple mechanisms, most notably inhibiting keratinocyte differentiation [13, 14]. The significance of these interleukins was shown by Hamilton et al. [28] when dupilumab use dramatically reversed the AD transcriptome (pattern of gene expression) and led to concomitant clinical AD improvement.

Multiple phase I and II double-blinded, placebo-controlled RCTs were performed in adults with moderate-to-severe AD assessing dupilumab either as monotherapy (two 4-week trials, one 12-week trial) or in combination with TCS (one 4-week trial) [29]. All trials showed improvement in clinical indexes with generally favorable adverse event (AE) profiles. At 12 weeks, a significantly higher proportion of patients treated with dupilumab achieved a 50% improvement of the Eczema Area and Severity Index (EASI) from baseline (EASI-50) compared with placebo (85 vs. 35%;  $p < 0.001$ ), whereas at 4 weeks, more dupilumab and TCS combination therapy patients

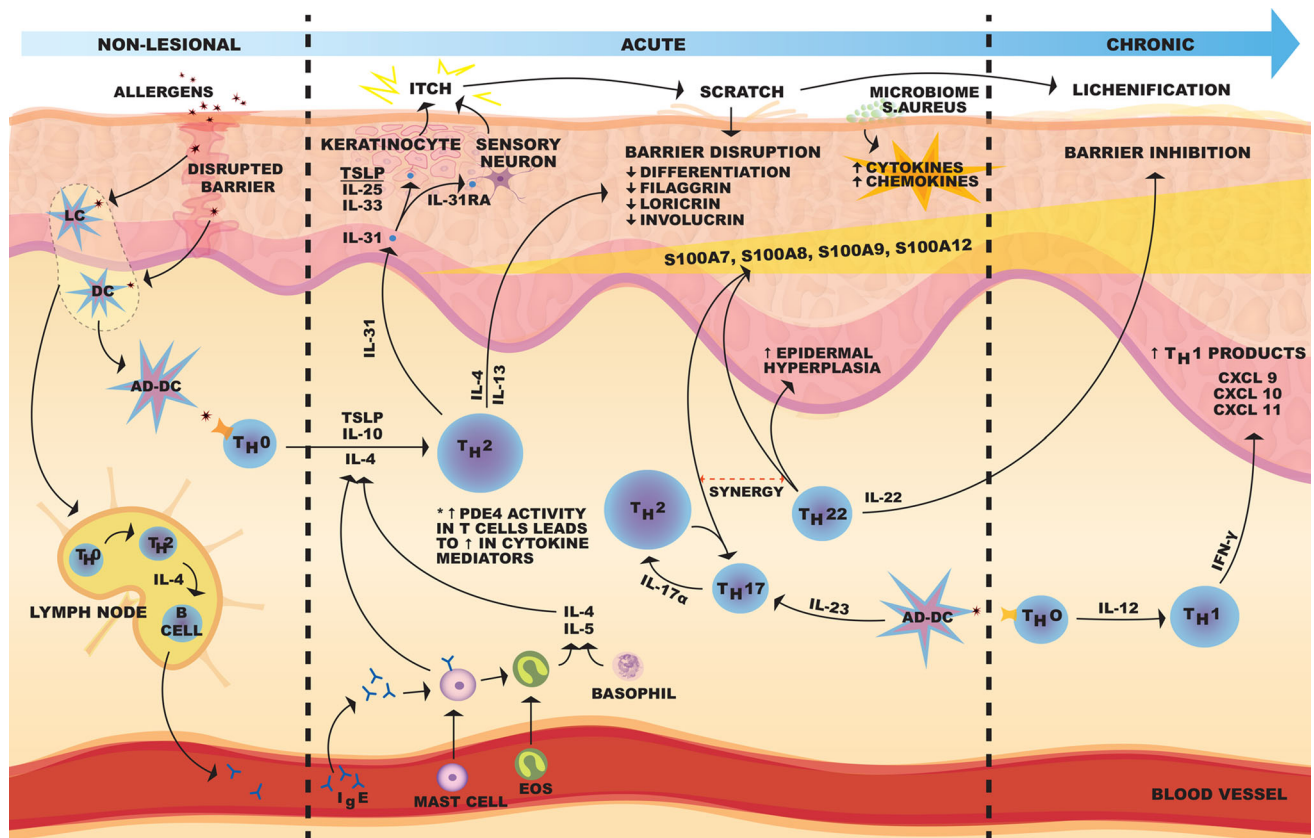


**Fig. 1** Immunologic pathways involved in the pathogenesis of acute AD and progression to chronic AD. Barrier defects in non-lesional AD skin leads to penetration of allergens that encounter the antigen-presenting Langerhans cells and dendritic cells in the epidermis and dermis, respectively. This leads to immune activation and inflammatory cell recruitment, inducing a skewed Th2 response in the acute state. Elevated Th2 levels lead to increased secretion of IL-4, IL-5, IL-13, and IL-31. Prominently, IL-4 and IL-13 disrupt the skin barrier by decreasing expression of barrier proteins (i.e., filaggrin, loricrin, involucrin). Additionally, these Th2 cytokines recruit eosinophils and basophils to lesional inflammatory sites, and increase B cell IgE production. Eosinophils, basophils, and activated IgE-bound mast cells lead to the release of pro-inflammatory mediators, further potentiating AD pathogenesis. Th17 and Th22 cells, which release IL-17 and IL-22, respectively, are also elevated in the acute phase of AD. IL-22 induces epidermal hyperplasia, and also acts in synergy with IL-17 to alter terminal differentiation proteins such as S100A7, S100A8, S100A9, and S100A12. IL-31, recently shown to be a

mediator of itch, is also elevated in acute disease, and acts directly on neurons and keratinocytes to trigger itch. Th2 cytokines also impair AMP responses to pathogens. This, in combination with barrier disruption, allows for greater risk of colonization and barrier penetration by allergens and pathogens (i.e., *Staphylococcus aureus*). Epithelial damage and inflammation leads to the release of TSLP, IL-25, and IL-33, and these, along with IL-10, also further drive Th2 differentiation. AD inflammation is associated with a skewed Th2 response (Th2, Th17, Th22) in acute AD lesions, but IL-12 production in chronic AD results in skewed Th1 response, with increased IFN- $\gamma$  expression. The resulting Th1-induced chemokine production (including CXCL9, CXCL10, and CXCL11) in the chronic state leads to further inflammation and immune activation. AD atopic dermatitis, AMP antimicrobial peptide, CXCL chemokine (C-X-C motif) ligand, DC dendritic cell, EOS eosinophil, IFN- $\gamma$  interferon- $\gamma$ , IgE human immunoglobulin E, IL interleukin, LC Langerhans cell, PDE4 phosphodiesterase 4, Th T helper cell type, TSLP thymic stromal lymphopoietin

achieved EASI-50 (100%) compared with placebo (50%) [29]. A phase II, double-blind, placebo-controlled, dose-ranging RCT in adults with moderate-to-severe AD showed that multiple dosing regimens of dupilumab significantly improved EASI scores compared with placebo ( $p < 0.0001$ ). The most efficacious groups were dupilumab 300 mg weekly and every 2 weeks, which led to the use of these dosing regimens in future trials [30].

In two identical phase III, randomized, placebo-controlled RCTs (SOLO-1 and SOLO-2), the efficacy and safety of dupilumab (300 mg weekly or 300 mg every

other week) at 16 weeks were assessed in adults with moderate-to-severe AD with an inadequate response or contraindication to topical therapy. The two trials showed similar significant results, with 38%/37% and 36%/36% of patients treated with dupilumab 300 mg weekly/300 mg every other week achieving an Investigator Global Assessment (IGA) score of clear or almost clear (with at least a 2-point reduction) compared with 10 and 8% in the placebo group ( $p < 0.001$  for all comparisons). In addition, patients treated with dupilumab had significantly higher rates of 75% improvement of EASI (EASI-75) responses

(SOLO-1: 52%/51% vs. 15%; SOLO-2: 48%/44% vs. 12%;  $p < 0.001$  for all comparisons), decreased pruritus (designated as  $\geq 4$ -point decrease from baseline) (SOLO-1: 40%/41% vs. 12%; SOLO-2: 39%/36% vs. 10%;  $p < 0.001$  for all comparisons), and reduced Dermatology Life Quality Index (DLQI) scores (SOLO-1:  $-9/-9.3$  vs.  $-5.3$ ; SOLO-2:  $-9.5/-9.3$  vs.  $-3.6$ ;  $p < 0.001$  for all comparisons) and Hospital Anxiety and Depression Scale scores (SOLO-1:  $-5.2/-5.2$  vs.  $-3$ ; SOLO-2:  $-5.8/-5.1$  vs.  $-0.8$ ;  $p < 0.001$  for all comparisons) compared with placebo [31].

Additionally, CHRONOS, a phase III, placebo-controlled RCT of dupilumab (300 mg weekly or every 2 weeks) in combination with TCS in patients with moderate-to-severe AD showed similar results after 16 and 52 weeks. Patients treated with dupilumab 300 mg weekly/every 2 weeks versus placebo were significantly more likely to achieve an IGA score of clear or almost clear (16 weeks: 39%/39% vs. 12%; 52 weeks: 40%/36% vs. 13%;  $p < 0.0001$  for all comparisons), EASI-50 (16 weeks: 78%/80% vs. 37%; 52 weeks: 70%/79% vs. 30%;  $p < 0.0001$  for all comparisons), EASI-75 (16 weeks: 64%/69% vs. 23%; 52 weeks: 64%/65% vs. 22%;  $p < 0.0001$  for all comparisons), and 90% improvement of EASI (EASI-90) (16 weeks: 43%/40% vs. 11%; 52 weeks: 51%/51% vs. 16%;  $p < 0.0001$  for all comparisons). Additionally, dupilumab significantly reduced pruritus (designated as  $\geq 4$ -point decrease from baseline) (16 weeks: 51%/59% vs. 20%; 52 weeks: 39%/51% vs. 13%;  $p < 0.0001$  for all comparisons), Patient-Oriented Eczema Measure (POEM) (16 weeks:  $-12.5/-12.4$  vs.  $-4.7$ ; 52 weeks:  $-12.7/-13.7$  vs.  $-5/3$ ;  $p < 0.0001$  for all comparisons), and DLQI (16 weeks:  $-10.5/-9.7$  vs.  $-5.3$ ; 52 weeks:  $-10.7/-10.9$  vs.  $-5.6$ ;  $p < 0.0001$  for all comparisons) scores compared with placebo [32].

An open-label extension study for AD patients who participated in previous dupilumab clinical trials is also ongoing (NCT01949311) [33]. Preliminary results from the 52-week analysis were recently presented and showed that approximately 75 and 50% of dupilumab-treated patients achieved an EASI-75 and IGA score of clear or almost clear, respectively [34]. Dupilumab was well-tolerated overall, with the most common AE being injection-site reaction, nasopharyngitis, and conjunctivitis [34]. Dupilumab was approved by the US Food and Drug Administration (FDA) in March 2017 for the treatment of adults with moderate-to-severe AD and inadequate response or contraindication to topical therapy, and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended approval of dupilumab for AD in adults in the European Union in July 2017 (Table 1).

A phase II open-label, ascending-dose trial exploring the pharmacokinetics, efficacy, and safety of dupilumab in

pediatric patients (aged 6–17 years) with moderate-to-severe AD was recently conducted (NCT02407756) [35]. The results of this study were presented in 2017 and showed that patients achieved reductions in EASI and pruritus scores ranging from 63 to 76 and 30 to 42%, respectively. The most common AEs were any infection and nasopharyngitis [36].

Dupilumab is the first targeted systemic agent and monoclonal antibody to demonstrate the level of safety and efficacy in moderate-to-severe AD. Given that dupilumab blocks signaling of both IL-4 and IL-13, it remains unclear how much of the demonstrated efficacy is due to IL-4, IL-13, or both. There has been some controversy as to which of these cytokines is most important in AD. It may be that similar efficacy can be achieved with even more focused targeting of IL-4 alone or IL-13 alone. Alternatively, it may be that blockade of both IL-4 and IL-13 signaling is necessary to achieve clinical efficacy. In Sect. 3.2, data are reviewed for studies of targeted therapies aimed at IL-13 signaling.

### 3.2 IL-13

IL-13 has been shown to be elevated in the skin of AD patients and has been proposed to be a key player in the pathogenesis of AD [13, 14, 27]. IL-13 promotes elevated and skewed Th2 inflammatory responses in the skin and inhibits epidermal differentiation, leading to skin barrier dysfunction [7, 13]. IL-13 also upregulates cutaneous colonization with *Staphylococcus aureus* and inhibits antimicrobial peptides (AMPs), thereby predisposing patients to infections and worsening inflammation [37]. Lebrikizumab and tralokinumab are two monoclonal antibodies directed against IL-13, thereby preventing it from binding to its receptors and downstream signaling.

A phase II double-blind, placebo-controlled RCT assessing the efficacy and safety of 12 weeks of tralokinumab in combination with TCS in adults age 18 years or older with moderate-to-severe AD was recently completed (NCT02347176) [38]. The results were recently presented and showed that tralokinumab 150 mg and 300 mg versus placebo significantly reduced EASI [adjusted mean difference:  $-4.4$  ( $p = 0.027$ ) and  $-4.9$  ( $p = 0.011$ ), respectively] and Scoring Atopic Dermatitis (SCORAD) ( $p = 0.003$  and  $p = 0.002$ , respectively) scores [39]. Patients treated with tralokinumab 300 mg versus placebo had significantly decreased DLQI scores ( $p = 0.006$ ) and *S. aureus* colonization ( $p < 0.001$ ), and higher EASI-50 response rates (73.4 vs. 21.5%;  $p = 0.025$ ). Serum dipeptidyl peptidase-4 (DPP-4), a marker of IL-13 activity, was previously reported to be a predictive biomarker for tralokinumab efficacy in patients with severe asthma [40]. Similarly, DPP-4 was found to be a predictor of efficacy in

**Table 1** Summary table of monoclonal antibodies for atopic dermatitis

| Drug                     | Target         | Efficacy                                                                                                                                                 | Safety                                                                  | Comments                                                                                                                                                                                                                                                                                           |
|--------------------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dupilumab<br>[29–36]     | IL-4R $\alpha$ | Highly significant reductions in EASI, IGA, pruritus, POEM, DLQI scores with maintenance of efficacy. EASI and pruritus reductions seen in pediatric RCT | Injection-site reaction, conjunctivitis, herpes simplex virus infection | Novel drug that showed significant and sustained efficacy across numerous domains with an acceptable safety profile. Will likely soon be gold-standard treatment in moderate-to-severe AD as post-marketing outcomes are reported. Preliminary data also show promising role in pediatric patients |
| Mepolizumab<br>[49]      | IL-5           | Modest improvement in PGA and SCORAD scores; decreased eosinophil levels                                                                                 | Well-tolerated                                                          | Equivocal results may indicate eosinophils play only a partial role in AD pathogenesis                                                                                                                                                                                                             |
| Tocilizumab<br>[53]      | IL-6 receptor  | Improved pruritus and EASI scores (case series)                                                                                                          | Infection                                                               | Promising efficacy; more data needed. Infection risk may limit use                                                                                                                                                                                                                                 |
| Tralokinumab<br>[38, 39] | IL-13          | Significantly reduced <i>Staphylococcus aureus</i> colonization and EASI, SCORAD, and pruritus scores                                                    | Nasopharyngitis, injection-site reaction                                | IL-13 inhibitors shown to be safe and efficacious for AD treatment. Will likely be a mainstay in future AD pharmacotherapy                                                                                                                                                                         |
| Lebrikizumab<br>[43, 44] | IL-13          | Significant improvements in EASI and SCORAD scores                                                                                                       | Conjunctivitis, injection-site reaction                                 |                                                                                                                                                                                                                                                                                                    |
| Secukinumab              | IL-17A         | N/A                                                                                                                                                      | N/A                                                                     | TBD                                                                                                                                                                                                                                                                                                |
| Fezakinumab              | IL-22          | N/A                                                                                                                                                      | N/A                                                                     | TBD                                                                                                                                                                                                                                                                                                |
| Ustekinumab<br>[69, 70]  | IL-12/IL-23    | 2 RCTs showed non-significant severity improvements                                                                                                      | Well-tolerated. Known ADR: URI                                          | Non-significant RCT tempered expectations from promising case reports/series; likely less role in AD of IL-12/IL-23. Select patient cohort may benefit                                                                                                                                             |
| Nemolizumab<br>[79–83]   | IL-31 receptor | Highly significant pruritus reductions; non-significant EASI score reductions                                                                            | Exacerbation of AD, peripheral edema, nasopharyngitis                   | May be emerging option for patients with severe, disabling itch. However, efficacy in reducing AD severity is still TBD                                                                                                                                                                            |
| Efalizumab<br>[90, 91]   | LFA-1          | Variable efficacy                                                                                                                                        | Infection, PML                                                          | Drug withdrawn due to safety concerns                                                                                                                                                                                                                                                              |
| Omalizumab<br>[95, 96]   | IgE            | One SR found some beneficial effect; another SR found no evidence of efficacy                                                                            | Well-tolerated                                                          | Inconsistent efficacy evidence in AD patients with normal or elevated IgE levels; likely limited role of IgE in AD.                                                                                                                                                                                |
| Ligelizumab<br>[98, 99]  | IgE            | No significant EASI score improvement                                                                                                                    | Unknown                                                                 | Further studies needed to determine patient subsets that may benefit from anti-IgE therapy                                                                                                                                                                                                         |
| Infliximab<br>[103]      | TNF- $\alpha$  | Initial but limited maintenance of clinical improvement                                                                                                  | AD worsening. Known ADRs: infection, infusion reactions, malignancy     | Due to limited efficacy in maintenance of improvement, the risk of worsening AD, and safety profile, TNF- $\alpha$ inhibitors are not recommended for AD treatment                                                                                                                                 |
| Tezepelumab              | TSLP           | N/A                                                                                                                                                      | N/A                                                                     | TBD                                                                                                                                                                                                                                                                                                |
| Rituximab<br>[121–123]   | CD20           | Mostly lack of significant change in EASI or SCORAD scores (case series)                                                                                 | URI, nausea. Known ADRs: infection, fever, lymphopenia                  | Due to lack of consistent efficacy, potential ADRs, and availability of other options, rituximab is not recommended for AD treatment                                                                                                                                                               |

AD atopic dermatitis, ADR adverse drug reaction, CD20 B lymphocyte surface antigen CD20, DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, IGA Investigator Global Assessment, IgE immunoglobulin E, IL interleukin, IL-4R $\alpha$  IL-4 receptor  $\alpha$  subunit, LFA-1 lymphocyte function-associated antigen 1, N/A not available, PGA Physician Global Assessment, PML progressive multifocal leukoencephalopathy, POEM Patient Oriented Eczema Measure, RCT randomized controlled trial, SCORAD SCORing AD, SR systematic review, TBD to be determined, TNF- $\alpha$  tumor necrosis factor- $\alpha$ , TSLP thymic stromal lymphopoietin, URI upper respiratory infection

AD patients, with significantly higher IGA response rates (IGA score of 0–1) in patients with DPP-4 levels above the median level treated with tralokinumab 300 mg versus

placebo (34.5 vs. 8.3%;  $p < 0.05$ ). Tralokinumab was well-tolerated overall with an AE profile consisting of nasopharyngitis and injection-site reaction. Two phase II

double-blinded, placebo-controlled RCTs evaluating the safety and efficacy of tralokinumab in patients with moderate-to-severe AD will begin in the second half of 2017 (NCT03131648, NCT03160885) [41, 42].

A phase II RCT was performed to evaluate the safety and efficacy at 12 weeks of lebrikizumab, a monoclonal antibody that binds to IL-13, in adults aged 18 years or older with persistent, moderate-to-severe AD inadequately controlled by TCS (NCT02340234) [43]. The results were recently presented and showed that lebrikizumab 125 mg injections every 4 weeks combined with twice-daily mid-potency TCS significantly improved the proportion of patients achieving an EASI-50 at 12 weeks (primary efficacy endpoint) compared with placebo and TCS (82.4 vs. 62.3%;  $p < 0.05$ ), as well as EASI-75 and EASI-90, but did not significantly improve the IGA [44]. An additional phase II randomized, open-label clinical trial comparing lebrikizumab to TCS was conducted in patients with moderate-to-severe AD (NCT02465606) [45]. This study has been completed, but no results have been published yet. Phase III studies are awaited. The abovementioned data demonstrating efficacy of tralokinumab and lebrikizumab suggests that blockade of IL-13 alone is a viable strategy in AD.

### 3.3 IL-5

IL-5 has been suggested to play a role in the immune response of AD primarily by promoting eosinophil differentiation and activation. Elevated blood eosinophils levels are known to occur in patients with AD [46]. Although the role of eosinophils in AD pathogenesis is not fully elucidated, eosinophils likely are involved in the release of pro-inflammatory mediators and resulting tissue damage [46–48]. Mepolizumab is a humanized monoclonal antibody directed against free IL-5, thus inhibiting IL-5 binding to its eosinophil-surface receptor and downstream signaling. Mepolizumab has been studied for the treatment of other eosinophil-mediated diseases, including asthma, AD, and eosinophilic gastrointestinal disease. A randomized, double-blinded, placebo-controlled trial assessing the effects of mepolizumab 750 mg intravenously was conducted in patients with moderate-to-severe AD [49]. No significant difference was found between the percentage of patients achieving marked improvement ( $>50\%$  improvement) in the Physician's Global Assessment (PGA) [50] and SCORAD severity scores at day 14. Notwithstanding, mepolizumab did significantly lead to modest improvement ( $<50\%$  improvement) in PGA scores ( $p < 0.05$ ). Mepolizumab was also found to significantly decrease blood eosinophil levels ( $p < 0.05$ ), correlating with its mechanism of action. The equivocal results of this trial may be due to the short duration for effect measurement (14 days),

but may also indicate that eosinophils play only a partial role in AD pathogenesis. Only mild AEs were reported with the use of mepolizumab, as the drug was well-tolerated overall. Currently, a phase II randomized, double-blinded, placebo-controlled trial assessing the efficacy and safety of mepolizumab in moderate-to-severe AD is in the recruitment phase (NCT03055195) [51].

### 3.4 IL-6

IL-6 levels have been shown to be elevated in both peripheral blood and skin lesions of AD patients, but the exact role of IL-6 in AD pathogenesis is not completely understood [52]. Tocilizumab is a humanized monoclonal antibody directed against the IL-6 receptor, and is currently approved by the FDA for treatment of rheumatoid arthritis. In a case series of three adult patients with severe, refractory AD, tocilizumab 8 mg/kg dosed every 4 weeks was found to resolve pruritus within 6 weeks. Additionally, all patients achieved an EASI-50 response [53]. Of note, two patients reported bacterial infections that resolved with discontinuation. Tocilizumab is known to be associated with higher rates of infections in rheumatoid arthritis patients [54]. While additional efficacy data are needed to determine the role of IL-6 antagonists in severe AD, the safety concerns regarding a higher risk of infection due to IL-6 blockade may limit the use of tocilizumab.

### 3.5 IL-17A

IL-17A levels were found to be elevated in peripheral blood and lesions in some studies of AD patients [9, 18, 55]. IL-17A may stimulate Th2 responses in the acute phase of AD [56]. Some authors have suggested a mixed Th1/Th2/Th17 inflammatory response in AD [9], particularly in more psoriasiform lesions present in Asian patients [57]. However, it is unclear if IL-17A plays a pathogenic role in all AD patients, specific subsets of AD patients, or is merely secondarily upregulated in AD without playing a pathogenic role per se. Secukinumab is a fully human monoclonal antibody directed against IL-17A that is FDA approved for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. A phase II randomized, placebo-controlled clinical trial assessing the efficacy and safety of secukinumab for adults with moderate-to-severe AD is currently in recruitment (NCT02594098) [58].

### 3.6 IL-22

IL-22 is primarily produced by Th22 cells, which have been found to be elevated in AD lesions. IL-22 has been shown to increase epidermal barrier dysfunction, induce

epidermal hyperplasia, and inhibit key proteins, such as filaggrin and loricrin, involved in epidermal differentiation [14, 15, 19]. IL-22 expression has been found to correlate with AD severity and to be elevated in both acute and chronic AD lesions compared to normal skin [14, 19]. It is unclear, though, if IL-22 plays a major pathogenic role in all AD patients, specific subsets of AD patients, or is merely secondarily upregulated in AD without playing a pathogenic role per se. Fezakinumab (formerly ILV 094) is a fully human monoclonal antibody directed against IL-22. A 12-week phase II, randomized, placebo-controlled clinical trial studying the effects of fezakinumab in adult patients with refractory moderate-to-severe AD is currently ongoing (NCT01941537) [59].

### 3.7 IL-12/IL-23

IL-12 leads to differentiation and clonal expansion of Th1 cells, while IL-23 leads to Th17 and Th22 cell production. IL-23 has been shown to be elevated in serum and skin lesions of persons with versus without AD. The possible roles of IL-17A and IL-22 in AD were mentioned in Sects. 3.5 and 3.6. Thus, agents that target the IL-12/IL-23 pathways might be effective in AD [18, 55, 60, 61].

Ustekinumab is a fully human monoclonal antibody directed against the p40 subunit of IL-12 and IL-23, preventing them from binding to T cell-surface receptors and causing differentiation and clonal expansion of naïve T cells into specific T helper subtypes. Ustekinumab is EMA and FDA approved for the treatment of moderate-to-severe plaque psoriasis. Several case reports have been published regarding the effects of ustekinumab in AD patients. An adolescent with severe, refractory AD was completely cleared after 5 months of ustekinumab therapy and remained clear at 14 months [62]. An adult with moderate-to-severe, refractory AD also demonstrated complete clearance after 19 weeks of ustekinumab therapy [63]. An adult with severe, refractory AD demonstrated complete clearance and resolution of pruritus at 1 month that was maintained for at least 12 months [64]. A case series of four males with severe, refractory AD treated with ustekinumab found that all demonstrated a significant (>50%) improvement in SCORAD and pruritus at week 16 [65]. A 13-year-old with severe, refractory AD demonstrated improvement in SCORAD and DLQI scores after ustekinumab treatment, with the best results at week 24, but experienced flares after this point [66].

Despite that, other case series have shown lack of effectiveness. A case series of ten patients treated with ustekinumab resulted in only four patients achieving complete or almost complete improvement, with six non-responders [67]. Additionally, two adults with severe, refractory AD failed to respond to ustekinumab, with

waning efficacy noted [68]. In one of the authors' (JIS) anecdotal experience, six adults with moderate-to-severe AD were treated with ustekinumab for at least 6 months and showed no improvement of EASI, SCORAD, pruritus, POEM, or DLQI. A phase II randomized, crossover, double-blinded, placebo-controlled trial of ustekinumab with concomitant TCS was conducted in 33 adults with moderate-to-severe AD. The ustekinumab group demonstrated no significant improvement in SCORAD-50 response rates at weeks 12, 16, or 20; only three patients had clinical improvements [69]. The authors postulated the lack of a significant effect might have been due to use of concomitant TCS, small sample size, and insufficient dosing. An additional phase II randomized, double-blinded, placebo-controlled trial also assessed the effects ustekinumab in 79 Japanese adults with severe to very severe AD. No significant improvements of EASI scores, EASI-50, EASI-75, or IGA response rates, or DLQI were noted at week 12 [70]. Overall, ustekinumab was well-tolerated in both trials.

Data regarding the use of ustekinumab in moderate-to-severe AD from original case reports and series were promising; however, the multiple non-significant clinical trial results have tempered expectations. Given the lack of efficacy in clinical trials, ustekinumab is not currently recommended for the treatment of AD. This is particularly true given the recent FDA (and pending European) approval of dupilumab, which showed highly efficacious and consistent results across numerous trials. Further, the lack of efficacy for ustekinumab in clinical trials suggests that IL-12 and IL-23 have a lesser contribution than IL-4 and IL-13 in AD pathogenesis. It remains to be seen whether there is a yet-to-be identified subset of AD patients that may have clinical benefit from ustekinumab.

### 3.8 IL-31

IL-31, which is secreted primarily by Th2 cells, affects terminal epidermal differentiation and has been proposed as the main cytokine contributing to pruritus [71, 72]. IL-31 can bind to receptors on sensory neurons, upregulate cellular pruritogens, and directly induce pruritus [72]. IL-31 has been found to be elevated in acute and chronic skin lesions of AD patients compared with normal skin [71–74], and has been found to correlate with AD severity [71, 75]. Anti-IL-31 agents have been shown in numerous studies to reduce pruritus in AD animal models, with equivocal effects on AD lesions [73, 76–78].

Nemolizumab is a humanized monoclonal antibody directed against IL-31 receptor A. In a double-blind, placebo-controlled phase I/Ib RCT, a single subcutaneous dose of nemolizumab in AD patients reduced visual analogue scale (VAS) itch scores by ~50% at week 4

compared with ~20% for placebo, as well as increased sleep efficiency and decreased the use of hydrocortisone butyrate [79]. There were no serious AEs, but increased creatine phosphokinase was more common in the nemolizumab groups.

In a double-blind, placebo-controlled phase II dose-escalating RCT (NCT01986933) [80–82] of 264 adults with moderate-to-severe AD (age 18–65 years), subcutaneous injections of nemolizumab 0.1, 0.5, and 2.0 mg/kg every 4 weeks patients reduced VAS itch scores at 12 weeks by 43.7, 59.8, and 63.1%, respectively, compared with a 20.9% reduction in the placebo group ( $p < 0.01$  for all comparisons) [81]. Patients treated with the 0.5 mg/kg dose showed the greatest reduction of EASI scores from baseline at week 12 (42.3%) compared with placebo (26.6%) [81]. Results from the 64-week extension of the phase II study were recently presented and showed that significant reductions in pruritus at 12 weeks were maintained at 64 weeks, with an even greater proportion of patients achieving improvement [83]. The most common reported AEs were AD exacerbation, nasopharyngitis, and peripheral edema. An additional phase II randomized, double-blinded, placebo-controlled clinical trial assessing the effects of nemolizumab in patients with moderate-to-severe AD is underway (NCT03100344) [84]. Nemolizumab therapy appears to be highly effective at reducing pruritus in patients with moderate-to-severe AD, and is a promising therapeutic option for itch in AD and perhaps other inflammatory disorders.

### 3.9 Lymphocyte Function-Associated Antigen 1

Lymphocytes require lymphocyte function-associated antigen 1 (LFA-1) to bind to intracellular adhesion molecule 1 (ICAM-1) on endothelial cells to migrate into skin, as well as antigen presenting cell (APC) surfaces in order to improve adhesion between these cells and transmit signals that promote T cell activation and differentiation. Efalizumab is a monoclonal antibody directed against the CD11a subunit of LFA-1, which prevents its binding to ICAM-1. This leads to numerous anti-inflammatory effects, particularly the inhibition of leukocyte extravasation and T cell activation at inflammatory sites [85, 86]. Efalizumab was initially approved for the treatment of adult moderate-to-severe plaque psoriasis. Potential efficacy in AD was reported shortly thereafter. In a murine model of AD, administration of intraperitoneal prophylactic anti-LFA-1 antibodies successfully improved skin severity scores, indicating a potential role of LFA-1 blockade as a treatment for AD [87]. Subsequently, several cases were reported in 2006 of severe refractory AD successfully treated with efalizumab [88, 89]. A prospective study in 2007 evaluating efalizumab treatment in ten adults with

severe AD showed a significant improvement in EASI ( $p < 0.0001$ ) and pruritus scores ( $p < 0.015$ ) from baseline at 12 weeks, with six patients reaching EASI-50. The trial showed AE of thrombocytopenia, viral gastroenteritis, and AD exacerbation after drug discontinuation [90]. A study published in 2010 by Ibler et al. [91] reported 11 cases of severe AD treated with standard dosed efalizumab, with only two patients having clinical improvement (though specific endpoints were not specified). Known AEs of efalizumab include bacterial sepsis, secondary bacterial infections, viral meningitis, and progressive multifocal leukoencephalopathy (PML) [92]. After being made aware of concerns of PML and other infections, the EMA and the FDA withdrew support of efalizumab, and the drug was withdrawn from the US market in 2009.

### 3.10 Human Immunoglobulin E

The role of IgE in AD pathogenesis remains controversial. A large proportion of AD patients have elevated IgE levels and are prone to atopic disorders [93]. Given that targeting IgE is efficacious in other atopic diseases, such as allergic asthma, several studies have assessed the efficacy of IgE blockade in AD.

Omalizumab is a humanized monoclonal antibody directed against free human IgE and membrane-bound IgE on the surface of B cells. Inhibition of IgE from binding to its high-affinity receptor (FcεRI) on basophils and mast cells prevents degranulation and the release of pro-inflammatory mediators [25, 93]. Low-affinity Fcε receptors are also present on the surface of dendritic cells and may play a role in antigen presentation [93, 94]. Some studies have shown increased levels of low-affinity Fcε receptors on dendritic cells in the skin of some AD patients. Omalizumab can also inhibit these receptors, thereby potentially inhibiting downstream antigen presentation to T cells [94].

A recent systematic review of 26 studies (five case reports, 18 case series and only two RCTs), consisting of 174 patients, was performed assessing the efficacy and safety of omalizumab for treating AD [95]. This review found that 129 patients (74.1%) experienced some beneficial effect (ranging from little to complete response). The study also found omalizumab to be well-tolerated overall, albeit expensive. The authors concluded that omalizumab was a safe treatment with some clinical benefit for severe, refractory AD, although future trials are needed to confirm this. The results of this review need to be interpreted cautiously given the disparate disease severity definitions, outcome measures and lack of controls in 24 of the 26 included ‘studies’. Another recent systematic review and meta-analysis analyzing 13 studies (two RCTs and 11 case series with at least three patients), consisting of 103 patients, found no evidence to support the effectiveness of

omalizumab for the treatment of AD [96]. In this study, only 43% of included AD patients achieved excellent clinical response after omalizumab treatment, with 30.1% showing irrelevant clinical change or even deterioration. Additionally, some studies showed that AD patients with *Filaggrin* gene mutations or with higher serum IgE levels were often non-responders to omalizumab treatment. This systematic review is also limited by the disparate disease severity definitions, outcome measures, and lack of controls in 11 of the 13 included ‘studies’. Notably, with the mere exclusion of anecdotal case reports with only one or two patients, the demonstrated efficacy for omalizumab was poor. Currently, a phase IV randomized, double-blinded, placebo-controlled clinical trial assessing the use of omalizumab in pediatric patients with severe AD is underway (NCT02300701) [97].

Ligelizumab (formerly QGE031) is another humanized monoclonal antibody directed against IgE. The efficacy and safety of ligelizumab was assessed in a phase II double-blinded, placebo and active comparator (cyclosporine) controlled RCT in patients with moderate-to-severe AD (NCT01552629) [98]. The data were recently presented and showed no significant improvement of EASI scores with ligelizumab compared with placebo at 12 weeks [99].

To summarize, there is inconsistent evidence to support the use of anti-IgE agents in AD patients with either normal or elevated IgE levels. This could partly be due to variability in dosing and treatment duration, as well as differences in IgE levels between AD and allergic asthma. In regards to this latter point, this may indicate the need for a higher dosage. However, the risk of increasing adverse drug event frequencies should be considered. Nonetheless, studies that failed to show clinical improvement did demonstrate decreasing serum IgE levels. This indicates that the drugs ‘met their mark’. Rather, these studies suggest a limited or lack of a pathogenic role of IgE in AD. This emphasizes the complexity of AD pathogenesis and the existence of various pathogenic factors, of which IgE may be only a minor player. Further investigation and clinical trials are warranted to determine which patient subsets may benefit from anti-IgE therapy.

### 3.11 Tumor Necrosis Factor- $\alpha$

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine that enhances the Th1 and Th17/IL-23 pathways [60, 61], as is known to be involved in the pathogenesis of multiple chronic inflammatory diseases [25]. TNF- $\alpha$  has been shown to be involved in the pathogenesis of multiple chronic inflammatory diseases with a skewed Th1 response, including psoriasis and rheumatoid arthritis [100, 101]. TNF- $\alpha$  has also been shown to be produced by dendritic cells in the acute phase of AD, despite AD being a predominantly

Th2-skewed disease state [102]. A prospective case series assessing the use of infliximab 5 mg/kg in nine patients with moderate-to-severe AD was associated with an initial clinical improvement in EASI and pruritus scores, yet only two patients maintained improvement by the end of the study [103]. Additionally, one case report described an adult with severe AD who obtained significant improvement with maintenance after treatment with infliximab [104].

A case series of etanercept use in two adults with chronic AD showed complete resolution and long-term maintenance of resolution. On the other hand, a case report of two children with AD treated with etanercept showed minimal clinical efficacy with no significant improvement in EASI scores [105]. Anecdotally, one of the authors (JIS) has seen minimal or no efficacy in more than 20 adults with moderate-to-severe AD after 4–12 months of therapy. Moreover, there are also reports of induction or worsening of AD secondary to TNF- $\alpha$  inhibitor use [106–108], possibly due to the Th1 inhibition leading to a skewed Th2 response [17, 109]. Overall, considering the limited efficacy in maintaining improvement in AD, the risk of worsening AD, as well as the side effect profiles (infection, infusion reactions, malignancy, and others) [100, 101], TNF- $\alpha$  inhibitors are not recommended for the treatment of AD.

### 3.12 Thymic Stromal Lymphopoietin

Thymic stromal lymphopoietin (TSLP) is produced by damaged keratinocytes (and other epithelial cells) in pro-inflammatory states and has recently been postulated to play a key pathogenic role in AD, by bridging barrier disruption and cutaneous inflammation. TSLP acts on myeloid dendritic cells and Langerhans cells, leading to a Th2-skewed inflammatory response with the release of IL-4, IL-5, and IL-13 [110–112]. TSLP has been shown to be significantly elevated in both acute and chronic AD lesions, as well as in peripheral blood of AD subjects compared to healthy subjects [112–114]. Tezepelumab (formerly AMG 157) is a fully human monoclonal antibody directed against TSLP, thereby preventing the interaction of TSLP with its receptor. A phase I double-blinded, placebo-controlled RCT of tezepelumab in healthy and moderate-to-severe AD subjects (NCT00757042) [115] and a phase II double-blinded, placebo-controlled RCT of tezepelumab in moderate-to-severe AD subjects (NCT02525094) [116] recently finished. No study results have been published at the time of this publication.

### 3.13 B Lymphocyte Antigen CD20

It has been postulated that B cells may play some role in AD immune dysregulation by undergoing class-switching

to produce IgE [117], and has been shown to be elevated in the skin and blood of patients with AD [118].

Rituximab is a chimeric monoclonal antibody directed against B lymphocyte surface antigen CD20, leading to lysis and depletion of B cells, and has shown efficacy in the treatment of various autoimmune diseases [119, 120]. A case series of six patients with severe AD treated with two doses of rituximab 1 g showed significant improvement in pruritus and EASI scores within 4–8 weeks ( $p < 0.001$ ), which was maintained for 24 weeks in five patients. Peripheral blood CD20+ B lymphocyte levels were undetectable by day 3, skin B cell levels decreased by approximately 50%, and peripheral blood IgE levels decreased only slightly [121]. However, another study assessing the benefit of two doses of rituximab 500 mg in two patients with severe AD did not lead to a significant improvement in SCORAD scores. Additionally, IgE levels did not significantly change after treatment in these patients [122]. A case series of rituximab therapy in three patients with severe AD refractory to standard therapy found low to absent peripheral blood counts of CD19+ B cells, but no significant change in EASI scores [123]. Overall, rituximab was well-tolerated in these series of patients, with common adverse drug reactions of upper respiratory infections and mild nausea.

The efficacy seen in these studies is likely due to B cell depletion and a resulting decrease in T cell activation. Nevertheless, rituximab was also shown to have little to no effect on IgE levels, likely because IgE-producing plasma cells do not express CD20 antigen and are not targeted by rituximab. Based on its lack of consistent efficacy in controlling AD or reducing IgE levels, its potential AEs, and the availability of safer and more effective treatment options, rituximab is not recommended for the treatment of AD.

## 4 Conclusion

The burdensome signs and symptoms and chronic nature of AD can have a profound impact on quality of life and function in affected patients. Moderate-to-severe AD is a noteworthy treatment challenge, as topical therapies are often insufficient, and a majority of the current systemic therapies have variable efficacy, as well as dose- and duration-limiting toxicities. There are tremendous unmet therapeutic needs in patients with chronic, refractory, moderate-to-severe AD. Recent research has helped us gain a better understanding of the multifactorial nature of AD, particularly pathogenic immunologic pathways. These insights have led to the testing and development of a number of targeted therapies, specifically monoclonal

antibodies that can directly target specific pathways involved in disease pathogenesis.

The development and clinical success of dupilumab has helped usher in a new era of biologics in AD. Numerous clinical trials showed consistent efficacy of dupilumab (targets both IL-4 and IL-13 signaling) in adults with moderate-to-severe AD refractory to TCS, which led to its swift approval by the FDA. Based on clinical trial results and the need for therapeutic growth, dupilumab offers the potential for long-term disease control. Additionally, the potential for future use in pediatric patients leads to even greater promise for dupilumab [124]. Tralokinumab and lebrikizumab (target IL-13 signaling) showed success in early-phase studies of adults with moderate-to-severe AD with overall well-tolerated AE profiles. Future trials may also help delineate the roles and differences between individual IL-13 blockade compared to combined IL-4 and IL-13 blockade. Nemolizumab (targets IL-31RA) represents a potential therapeutic paradigm shift by treating severe pruritus in AD. Future research will be needed to determine the ideal patient population for this therapeutic approach. Ongoing and future clinical trials will help shed light on the role of a variety of monoclonal antibodies targeting IL-5, IL-6, IL-22, IL-17, and TSLP. Monoclonal antibodies targeting other factors in the disease process (i.e., IL-12/IL-23, IgE, TNF- $\alpha$ , CD20) have limited evidence to support their efficacy in AD. At this point, these pathways appear to be less promising, and the currently available antibodies targeting these pathways are not recommended for the treatment of AD. Future research and clinical reporting may provide more insight on which subsets of AD patients may benefit from these therapies. As numerous monoclonal antibodies are being studied for the treatment of AD, safety concerns may emerge that restrict their use. Agents targeting IL-6 and LFA-1 have been associated with higher rates of serious infections, and these agents are either not recommended for the treatment of AD or are no longer available in the USA, respectively.

The landscape of AD pharmacotherapy is rapidly evolving. Monoclonal antibodies targeting specific immunologic and other pathways hold great therapeutic promise. As more is learned about the different phenotypes of AD, we may reach a pivotal stage where certain types of AD may be found to be more amenable to certain monoclonal antibody treatments over others. Sustained research, focus, and pharmacovigilance are warranted to help discern the role of the various monoclonal antibodies and targeted agents in AD pharmacotherapy.

## Compliance with Ethical Standards

**Disclosures** Paras Vakharia has no relevant disclosures or conflict of interests. Jonathan Silverberg has been an investigator for Abbvie, Celgene, Chugai, Eli Lilly, Galderma, GlaxoSmithKline, Realm,

Regeneron-Sanofi; consultant for Abbvie, Anacor, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Menlo, Pfizer, Realm, Regeneron-Sanofi; and speaker for Regeneron-Sanofi.

**Funding** This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), Grant number K12 HS023011, and the Dermatology Foundation.

## References

- Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, ISAAC Phase III Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol*. 2009;124(6):1251e1223–58e1223.
- Garg N, Silverberg JI. Epidemiology of childhood atopic dermatitis. *Clin Dermatol*. 2015;33(3):281–8.
- Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135(1):56–66.
- Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. 2013;132(5):1132–8.
- Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy*. 2012;67(12):1475–82.
- Guttman-Yassky E, Nogales KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part II: immune cell subsets and therapeutic concepts. *J Allergy Clin Immunol*. 2011;127(6):1420–32.
- Proksch E, Brasch J. Abnormal epidermal barrier in the pathogenesis of contact dermatitis. *Clin Dermatol*. 2012;30(3):335–44.
- Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004;113(5):651–7.
- Batista DI, Perez L, Orfali RL, et al. Profile of skin barrier proteins (filaggrin, claudins 1 and 4) and Th1/Th2/Th17 cytokines in adults with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2015;29(6):1091–5.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338–51.
- Kawasaki H, Nagao K, Kubo A, et al. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J Allergy Clin Immunol*. 2012;129(6):1538.e1536–46.e1536.
- Miajlovic H, Fallon PG, Irvine AD, Foster TJ. Effect of filaggrin breakdown products on growth of and protein expression by *Staphylococcus aureus*. *J Allergy Clin Immunol*. 2010;126(6):1184.e1183–90.e1183.
- Suarez-Farinas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *J Allergy Clin Immunol*. 2013;132(2):361–70.
- Gittler JK, Shemer A, Suarez-Farinas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344–54.
- Auriemma M, Vianale G, Amerio P, Reale M. Cytokines and T cells in atopic dermatitis. *Eur Cytokine Netw*. 2013;24(1):37–44.
- Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. *J Clin Cell Immunol*. 2011;2(3):110.
- Chan JL, Davis-Reed L, Kimball AB. Counter-regulatory balance: atopic dermatitis in patients undergoing infliximab infusion therapy. *J Drugs Dermatol*. 2004;3(3):315–8.
- Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. *J Invest Dermatol*. 2008;128(11):2625–30.
- Nogales KE, Zaba LC, Shemer A, et al. IL-22-producing “T22” T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol*. 2009;123(6):1244e1242–52e1242.
- Souwer Y, Szegedi K, Kapsenberg ML, de Jong EC. IL-17 and IL-22 in atopic allergic disease. *Curr Opin Immunol*. 2010;22(6):821–6.
- McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol*. 2013;131(2):280–91.
- Walling HW, Swick BL. Update on the management of chronic eczema: new approaches and emerging treatment options. *Clin Cosmet Investig Dermatol*. 2010;3:99–117.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116–32.
- Montes-Torres A, Llamas-Velasco M, Perez-Plaza A, Solano-Lopez G, Sanchez-Perez J. Biological treatments in atopic dermatitis. *J Clin Med*. 2015;4(4):593–613.
- Harskamp CT, Armstrong AW. Immunology of atopic dermatitis: novel insights into mechanisms and immunomodulatory therapies. *Semin Cutan Med Surg*. 2013;32(3):132–9.
- Ibler KS, Jemec GB. Novel investigational therapies for atopic dermatitis. *Expert Opin Investig Drugs*. 2015;24(1):61–8.
- Kagami S, Saeki H, Komine M, et al. Interleukin-4 and interleukin-13 enhance CCL26 production in a human keratinocyte cell line, HaCaT cells. *Clin Exp Immunol*. 2005;141(3):459–66.
- Hamilton JD, Suarez-Farinas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(6):1293–300.
- Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med*. 2014;371(2):130–9.
- Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387(10013):40–52.
- Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–48.
- Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287–303.
- Clinicaltrials.gov. Open-label study of dupilumab (REGN668/SAR231893) in patients with atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT01949311>. Accessed 10 May 2017.
- Deleuran M, Thaci D, Beck L, et al. Long-term safety and efficacy of open-label dupilumab in patients with moderate-to-severe atopic dermatitis. 2017 annual meeting of the American academy of allergy, asthma & immunology (AAAAI); 3–6 Mar 2017; Atlanta.

35. Clinicaltrials.gov. A study to determine the safety and tolerability of dupilumab (REGN668/SAR231893) in patients aged  $\geq 6$  to  $< 18$  years with atopic dermatitis (eczema). <https://www.clinicaltrials.gov/ct2/show/NCT02407756>. Accessed 10 May 2017.
36. Cork M, Thaci D, DiCioccio T, et al. Pharmacokinetics, safety, and efficacy of dupilumab in a pediatric population with moderate-to-severe atopic dermatitis: results from an open-label phase 2a trial. American academy of dermatology 75th annual meeting; 3–7 Mar 2017; Orlando.
37. Renert-Yuval Y, Guttman-Yassky E. Systemic therapies in atopic dermatitis: the pipeline. *Clin Dermatol*. 2017;35(4):387–97.
38. Clinicaltrials.gov. Phase 2 study to evaluate the efficacy and safety of tralokinumab in adults with atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT02347176>. Accessed 10 May 2017.
39. Wollenberg A, Howell MD, Guttman-Yassky E, et al. A phase 2b dose-ranging efficacy and safety study of tralokinumab in adult patients with moderate to severe atopic dermatitis. American Academy of Dermatology 75th Annual Meeting; 3–7 Mar 2017; Orlando.
40. Brightling CE, Chanez P, Leigh R, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med*. 2015;3(9):692–701.
41. Clinicaltrials.gov. Tralokinumab monotherapy for moderate to severe atopic dermatitis (ECZema TRAlokinumab Trial no. 2) (ECZTRA 2). <https://www.clinicaltrials.gov/ct2/show/NCT03160885>. Accessed 10 May 2017.
42. Clinicaltrials.gov. Tralokinumab monotherapy for moderate to severe atopic dermatitis - ECZTRA 1 (ECZema TRAlokinumab Trial no. 1) (ECZTRA 1). <https://www.clinicaltrials.gov/ct2/show/NCT03131648>. Accessed 10 May 2017.
43. Clinicaltrials.gov. A study of lebrikizumab in participants with persistent moderate to severe atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT02340234>. Accessed 10 May 2017.
44. Simpson E, Flohr C, Eichenfield L, et al. Efficacy and safety of lebrikizumab in patients with atopic dermatitis: a phase II randomized, controlled trial (TREBLE). 25th EADV Congress; 28 Sep–2 Oct 2016; Vienna.
45. Clinicaltrials.gov. A study to evaluate the safety of lebrikizumab compared to topical corticosteroids in adult patients with atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT02465606>. Accessed 10 May 2017.
46. Corren J. Inhibition of interleukin-5 for the treatment of eosinophilic diseases. *Discov Med*. 2012;13(71):305–12.
47. Molino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. *Clin Exp Allergy*. 2012;42(5):712–37.
48. Smith DA, Minthorn EA, Beerah M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. *Clin Pharmacokinet*. 2011;50(4):215–27.
49. Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy*. 2005;60(5):693–6.
50. Freedman JD, Gottlieb AB, Lizzul PF. Physician performance measurement: tiered networks and dermatology (an opportunity and a challenge). *J Am Acad Dermatol*. 2011;64(6):1164–9.
51. Clinicaltrials.gov. Efficacy and safety study of mepolizumab in subjects with moderate to severe atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT03055195>. Accessed 10 May 2017.
52. Toshitani A, Ansel JC, Chan SC, Li SH, Hanifin JM. Increased interleukin 6 production by T cells derived from patients with atopic dermatitis. *J Invest Dermatol*. 1993;100(3):299–304.
53. Navarini AA, French LE, Hofbauer GF. Interrupting IL-6-receptor signaling improves atopic dermatitis but associates with bacterial superinfection. *J Allergy Clin Immunol*. 2011;128(5):1128–30.
54. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum*. 2006;54(9):2817–29.
55. Toda M, Leung DY, Molet S, et al. Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol*. 2003;111(4):875–81.
56. Dhingra N, Guttman-Yassky E. A possible role for IL-17A in establishing Th2 inflammation in murine models of atopic dermatitis. *J Invest Dermatol*. 2014;134(8):2071–4.
57. Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136(5):1254–64.
58. Clinicaltrials.gov. Secukinumab for Treatment of Atopic Dermatitis. <https://clinicaltrials.gov/ct2/show/NCT02594098>. Accessed 10 May 2017.
59. Clinicaltrials.gov. Randomized placebo controlled study to determine safety, pharmacodynamics and efficacy of ILV-094 in atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT01941537>. Accessed 10 May 2017.
60. Noda S, Krueger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J Allergy Clin Immunol*. 2015;135(2):324–36.
61. Zaba LC, Suarez-Farinas M, Fuentes-Duculan J, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol*. 2009;124(5):1022–10.e1–395.
62. Agusti-Mejias A, Messeguer F, Garcia R, Febrer I. Severe refractory atopic dermatitis in an adolescent patient successfully treated with ustekinumab. *Ann Dermatol*. 2013;25(3):368–70.
63. Shroff A, Guttman-Yassky E. Successful use of ustekinumab therapy in refractory severe atopic dermatitis. *JAAD Case Rep*. 2015;1(1):25–6.
64. Puya R, Alvarez-Lopez M, Velez A, Casas Asuncion E, Moreno JC. Treatment of severe refractory adult atopic dermatitis with ustekinumab. *Int J Dermatol*. 2012;51(1):115–6.
65. Fernandez-Anton Martinez MC, Alfageme Roldan F, Ciudad Blanco C, Suarez Fernandez R. Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients. *Actas Dermosifiliogr*. 2014;105(3):312–3.
66. Wlodek C, Hewitt H, Kennedy CT. Use of ustekinumab for severe refractory atopic dermatitis in a young teenager. *Clin Exp Dermatol*. 2016;41(6):625–7.
67. Nic Dhonncha E, Clowry J, Dunphy M, Buckley C, Field S, Paul L. Treatment of severe atopic dermatitis with ustekinumab: a case series of 10 patients. *Br J Dermatol*. 2016. doi:10.1111/bjd.15262.
68. Samorano LP, Hanifin JM, Simpson EL, Leshem YA. Inadequate response to ustekinumab in atopic dermatitis—a report of two patients. *J Eur Acad Dermatol Venereol*. 2016;30(3):522–3.
69. Khattri S, Brunner PM, Garcet S, et al. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol*. 2017;26(1):28–35.
70. Saeki H, Kabashima K, Tokura Y, et al. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 2 study. *Br J Dermatol*. 2017. doi:10.1111/bjd.15493.
71. Dillon SR, Sprecher C, Hammond A, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004;5(7):752–60.

72. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol*. 2006;117(2):411–7.
73. Grimstad O, Sawanobori Y, Vestergaard C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol*. 2009;18(1):35–43.
74. Nobbe S, Dziunycz P, Muhleisen B, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. *Acta Derm Venereol*. 2012;92(1):24–8.
75. Szegedi K, Kremer AE, Kezic S, et al. Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. *Exp Dermatol*. 2012;21(6):431–6.
76. Kasutani K, Fujii E, Ohyama S, et al. Anti-IL-31 receptor antibody is shown to be a potential therapeutic option for treating itch and dermatitis in mice. *Br J Pharmacol*. 2014;171(22):5049–58.
77. Lewis KE, Holdren MS, Maurer MF, et al. Interleukin (IL) 31 induces in cynomolgus monkeys a rapid and intense itch response that can be inhibited by an IL-31 neutralizing antibody. *J Eur Acad Dermatol Venereol*. 2017;31(1):142–50.
78. Oyama S, Kitamura H, Kuramochi T, et al. Cynomolgus monkey model of interleukin-31-induced scratching depicts blockade of human interleukin-31 receptor A by a humanized monoclonal antibody. *Exp Dermatol*. 2016. doi:10.1111/exd.13236.
79. Nemoto O, Furue M, Nakagawa H, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol*. 2016;174(2):296–304.
80. Clinicaltrials.gov. A phase 2 study of CIM331 for atopic dermatitis patients. <https://www.clinicaltrials.gov/ct2/show/NCT01986933>. Accessed 10 May 2017.
81. Ruzicka T, Hanifin JM, Furue M, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med*. 2017;376(9):826–35.
82. Hanifin J, Ruzicka T, Masutaka F, et al. Randomized, double-blind, placebo-controlled, multicenter, multidose phase II study of anti-interleukin-31 receptor A monoclonal antibody CIM331 (nemolizumab) in patients with moderate to severe atopic dermatitis. American academy of dermatology 74th annual meeting; 4–8 Mar 2016; Washington, DC.
83. Kabashima K. Efficacy and safety of nemolizumab over 64 weeks in patients with moderate-to-severe atopic dermatitis: results from the long-term extension of the phase 2 study. American academy of dermatology 75th annual meeting; 3–7 Mar 2017; Orlando.
84. Clinicaltrials.gov. Dose-ranging study of nemolizumab in atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT03100344>. Accessed 10 May 2017.
85. Chacko M, Weinberg JM. Efalizumab. *Dermatol Ther*. 2007;20(4):265–9.
86. Weinberg JM, Siegfried EC. Successful treatment of severe atopic dermatitis in a child and an adult with the T-cell modulator efalizumab. *Arch Dermatol*. 2006;142(5):555–8.
87. Ohmura T, Konomi A, Satoh Y, et al. Suppression of atopic-like dermatitis by treatment with antibody to lymphocyte function-associated antigen-1 in NC/Nga mouse. *Eur J Pharmacol*. 2004;504(1–2):113–7.
88. Farshidi A, Sadeghi P. Successful treatment of severe refractory atopic dermatitis with efalizumab. *J Drugs Dermatol*. 2006;5(10):994–8.
89. Hassan AS, Kaelin U, Braathen LR, Yawalkar N. Clinical and immunopathologic findings during treatment of recalcitrant atopic eczema with efalizumab. *J Am Acad Dermatol*. 2007;56(2):217–21.
90. Takiguchi R, Tofte S, Simpson B, et al. Efalizumab for severe atopic dermatitis: a pilot study in adults. *J Am Acad Dermatol*. 2007;56(2):222–7.
91. Ibler K, Dam TN, Gniadecki R, Kragballe K, Jemec GB, Agner T. Efalizumab for severe refractory atopic eczema: retrospective study on 11 cases. *J Eur Acad Dermatol Venereol*. 2010;24(7):837–9.
92. Baniandres O, Pulido A, Silvente C, Suarez R, Lazaro P. Clinical outcomes in patients with psoriasis following discontinuation of efalizumab due to suspension of marketing authorization. *Actas Dermosifiliogr*. 2010;101(5):421–7.
93. Liu FT, Goodarzi H, Chen HY. IgE, mast cells, and eosinophils in atopic dermatitis. *Clin Rev Allergy Immunol*. 2011;41(3):298–310.
94. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcεpsilonRI expression. *J Allergy Clin Immunol*. 2003;112(6):1147–54.
95. Holm JG, Agner T, Sand C, Thomsen SF. Omalizumab for atopic dermatitis: case series and a systematic review of the literature. *Int J Dermatol*. 2017;56(1):18–26.
96. Wang HH, Li YC, Huang YC. Efficacy of omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2016;138(6):1719.e1711–22.e1711.
97. Clinicaltrials.gov. Role of anti-IgE in severe childhood eczema (ADAPT). <https://www.clinicaltrials.gov/ct2/show/NCT02300701>. Accessed 10 May 2017.
98. Clinicaltrials.gov. Study evaluating the safety and efficacy of QGE031 in atopic dermatitis patients. <https://www.clinicaltrials.gov/ct2/show/NCT01552629>. Accessed 10 May 2017.
99. Bangert C. Efficacy, safety and pharmacodynamics of a high-affinity anti-IgE antibody in patients with moderate to severe atopic dermatitis: a randomized, double-blind, placebo-controlled, proof of concept study. 25th EADV congress; 28 Sep–2 Oct 2016; Vienna.
100. Lin J, Ziring D, Desai S, et al. TNFα blockade in human diseases: an overview of efficacy and safety. *Clin Immunol*. 2008;126(1):13–30.
101. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008;117(2):244–79.
102. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008;358(14):1483–94.
103. Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. *J Am Acad Dermatol*. 2005;52(3 Pt 1):522–6.
104. Cassano N, Loconsole F, Coviello C, Vena GA. Infliximab in recalcitrant severe atopic eczema associated with contact allergy. *Int J Immunopathol Pharmacol*. 2006;19(1):237–40.
105. Buka RL, Resh B, Roberts B, Cunningham BB, Friedlander S. Etanercept is minimally effective in 2 children with atopic dermatitis. *J Am Acad Dermatol*. 2005;53(2):358–9.
106. Lebas D, Staumont-Salle D, Solau-Gervais E, Flipo RM, Delaporte E. Cutaneous manifestations during treatment with TNF-α blockers: 11 cases [in French]. *Ann Dermatol Venereol*. 2007;134(4 Pt 1):337–42.
107. Mangge H, Gindl S, Kenzian H, Schauenstein K. Atopic dermatitis as a side effect of anti-tumor necrosis factor-α therapy. *J Rheumatol*. 2003;30(11):2506–7.
108. Ruiz-Villaverde R, Galan-Gutierrez M. Exacerbation of atopic dermatitis in a patient treated with infliximab. *Actas Dermosifiliogr*. 2012;103(8):743–6.
109. Wright RC. Atopic dermatitis-like eruption precipitated by infliximab. *J Am Acad Dermatol*. 2003;49(1):160–1.

110. Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med*. 2005;202(9):1213–23.
111. Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med*. 2006;203(2):269–73.
112. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002;3(7):673–80.
113. Han NR, Moon PD, Kim HM, Jeong HJ. Tryptanthrin ameliorates atopic dermatitis through down-regulation of TSLP. *Arch Biochem Biophys*. 2014;542:14–20.
114. Lee EB, Kim KW, Hong JY, Jee HM, Sohn MH, Kim KE. Increased serum thymic stromal lymphopoietin in children with atopic dermatitis. *Pediatr Allergy Immunol*. 2010;21(2 Pt 2):e457–60.
115. Clinicaltrials.gov. Safety study of AMG 157 in healthy subjects and subjects with atopic dermatitis. <https://www.clinicaltrials.gov/ct2/show/NCT00757042>. Accessed 10 May 2017.
116. Clinicaltrials.gov. Phase 2a study to evaluate the efficacy and safety of MEDI9929 in adults with atopic dermatitis (ALLEVIAD). <https://clinicaltrials.gov/ct2/show/NCT02525094>. Accessed 10 May 2017.
117. Bremmer MS, Bremmer SF, Baig-Lewis S, Simpson EL. Are biologics safe in the treatment of atopic dermatitis? A review with a focus on immediate hypersensitivity reactions. *J Am Acad Dermatol*. 2009;61(4):666–76.
118. Czarnowicki T, Gonzalez J, Bonifacio KM, et al. Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. *J Allergy Clin Immunol*. 2016;137(1):118.e115–29.e115.
119. Bennett DD, Ohanian M, Cable CT. Rituximab in severe skin diseases: target, disease, and dose. *Clin Pharmacol*. 2010;2:135–41.
120. Nagel A, Hertl M, Eming R. B-cell-directed therapy for inflammatory skin diseases. *J Invest Dermatol*. 2009;129(2):289–301.
121. Simon D, Hosli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol*. 2008;121(1):122–8.
122. Sediva A, Kayserova J, Vernerova E, et al. Anti-CD20 (rituximab) treatment for atopic eczema [letter]. *J Allergy Clin Immunol*. 2008;121(6):1515–6 (**author reply 1516–1517**).
123. McDonald BS, Jones J, Rustin M. Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients. *Clin Exp Dermatol*. 2016;41(1):45–7.
124. D'Erme AM, Romanelli M, Chiricozzi A. Spotlight on dupilumab in the treatment of atopic dermatitis: design, development, and potential place in therapy. *Drug Des Devel Ther*. 2017;11:1473–80.