

BIOLOGICS FOR THE MANAGEMENT OF ATOPIC DERMATITIS

Rannakoe J Lehloenya^{1,2}

Thuraya Isaacs¹

Carol Hlela³

¹ Division of Dermatology, Department of Medicine, Groote Schuur Hospital and University of Cape Town

² Combined Drug Allergy Clinic, Groote Schuur Hospital, Cape Town

³ Division of Dermatology, Department of Medicine, Red Cross War Memorial Children's Hospital and University of Cape Town

Email | carol.hlela@uct.ac.za

WHAT IS ATOPIC DERMATITIS?

Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disease that clusters in families with atopic diseases. Atopic, or the allergic march, refers to a phenomenon in which AD in children is often followed by asthma and rhinitis, in sequence with an IgE antibody response to environmental antigens.^{1,2} The diagnosis of AD is still based mainly on clinical features, because to date there have been no reliable biomarkers to define the disease stage, severity or therapeutic response.

NATURAL HISTORY AND EPIDEMIOLOGY OF AD

The natural history of AD in an individual cannot be predicted. Symptoms can start at any stage, with 60% of cases manifesting in the first year of life.³ Although still primarily considered a disease of childhood, recent studies indicate that it can be a lifelong disease. AD is becoming increasingly prevalent (15–20% in children and 2–10% in adults) globally and much of this burden has been reported from industrialised countries.^{4,5} Although developing countries reportedly have a lower prevalence of AD, time trends data from 1995 and 2002 (ISAAC phase 1 and 3 respectively) show an increasing prevalence of AD along with other atopic disorders.^{3,6} In South Africa, the one-year prevalence rate among 13–14-year-old schoolchildren in Cape Town was 8.3%–13.3%, with 2.3% having the disease severely.^{7,8} Among 3–11-year-old Xhosa children, the one-year prevalence rate was 1%–2.5% – the prevalence being higher among those who live in urban areas.⁹

The increasing prevalence is attributed to environmental factors, smaller families, increased income, higher levels of education, migration from rural to urban areas, reduced exposure to potential antigens in early life and the increased use of antibiotics.⁸ AD persists in >5% of 20-year-olds who had the disease as children. However, a predisposition to contact dermatitis and skin susceptibility to irritants persists lifelong.¹⁰ An estimated 2%–3% of patients with AD have a disease severe enough to require systemic therapy.¹¹

PERSONAL AND SOCIETAL IMPACT OF AD

AD can have a profound impact on the patients' and their families' quality of life (QoL). The relentless pruritus gravely disturbs

sleep for both the patients and their caregivers, affecting their functionality at school, work and in the social environment.¹² An analysis of the 2013 Global Burden of Disease attributed dermatitis as a skin disease with the highest global burden as measured by the disability adjusted life years.^{3,13,14} More studies point to the systemic nature of AD.¹⁵ German National Health Insurance data of beneficiaries <40 years of age ($n = 655\,815$) show an increased risk of incident rheumatoid arthritis and inflammatory bowel disease (IBD) in AD.¹⁶ Other non-atopic comorbidities that have been reported to have a higher prevalence in AD include neuropsychiatric disorders, atherosclerosis, cardiovascular disease and cerebrovascular accidents.^{17–19}

PATHOGENESIS OF AD

AD is a complex multifactorial disease influenced by genetic predisposition, skin-barrier abnormalities, immune dysregulation and environmental factors such as allergens, irritants, microbes, diet, stress and air quality.^{20,21} Concordance rates among monozygotic twins with AD is as high as 86 per cent, which supports a strong heritability pattern.²² Numerous genes have been associated with AD, most notably filaggrin (FLG), claudin-1 (CLDN1) and serine protease inhibitor Kazal-Type 5 (SPINK5) genes. Mutations of these genes are associated with abnormalities of barrier function via abnormalities in cutaneous pH, hydration, tight junction formation, skin-barrier homeostasis, desquamation, lipid-barrier construction and the formation of cornified cell envelopes.^{22,23} The expression of CLDN1 on keratinocytes is regulated by interleukin-4 (IL-4) and IL-13, two of the most critical cytokines in AD. Patients with AD have reduced Toll-like receptor (TLR) function. TLR stimulation by microbes or trauma leads to the release of antimicrobial peptides and the strengthening of tight junction to limit penetration of allergens and microbes, functions that are impaired in AD.²²

Dysregulated immune responses are central to the pathogenesis of AD. The skin in AD has a higher infiltration of T-cells, pro-inflammatory phenotypes of dendritic cells, type-2 innate lymphoid cells, eosinophils, mast cells and pro-inflammatory cytokines.^{22,24,25} Immune responses in AD are globally attenuated and differentially polarised, that is, they are indicated by a decrease in T_H1 and an increase in T_H2/T_H17 responses and products.²⁶ Even non-lesional skin in individuals with AD has

TABLE I: A SUMMARY OF TARGET MOLECULES, ROLE OF THESE MOLECULES IN AD, CURRENT BIOLOGICS AGAINST THESE TARGETS, ROUTE OF ADMINISTRATION AND CURRENT STATUS OF THE BIOLOGIC IN AD.

MAIN TARGET	ROLE IN AD	TARGET MOLECULE	MECHANISM	BIOLOGIC	ROUTE	CURRENT STATUS IN AD	REFS
B cells	Produce IgE under influence of IL-4 and IL-13	CD20 receptor on cell surface	Chimeric mAb that is cytolytic on receptor binding	Rituximab	IVI	Unclear benefits: may work better in combination with omalizumab.	27, 28
IgE	Unclear role in AD but high levels in majority of AD cases	IgE receptor	Humanised mAb against Fc receptor of IgE	Omalizumab	SC	May be effective in a subset of AD cases	29
IL-4	Induction and perpetuation of the TH2 response	IL-4 receptor	Human mAb, competitively blocks IL-4/ α and binding of IL-4 and IL-13 preventing activation of the JAK1/STAT6 signalling cascade	Dupilumab	SC	Approved for AD	30
IL-4	Induction and perpetuation of the TH2 response	IL-4 α receptor	Mutant recombinant human IL-4 protein that blocked the alpha sub-unit of the IL-4 receptor	Pitrakinra	SC	Terminated	31
IL-1	Initiation and maintenance of Th2 responses	IL-1 receptor	Recombinant IL-1 receptor antagonist	Anakinra	SC	Terminated	75
IL-13	Induces B-cell maturation and differentiation, IgE secretion and eosinophil chemotaxis	IL-13 molecule	Human mAb against Fab fragment of IL-13 preventing docking in IL-13 receptor	Tralokinumab	SC	Phase III	32
IL-13	Induces B-cell maturation and differentiation, IgE secretion and eosinophil chemotaxis	IL-13 molecule	Human mAb against soluble IL-13 preventing IL-13R α 1/IL-4R α heterodimerisation and subsequent signalling	Lebrikizumab	SC	Phase IIb	33
IL-5	Drives for eosinophil growth, differentiation and migration	IL-5 receptor	Human mAb against IL-5 receptor alpha subunits on eosinophils	Mepolizumab	SC	Not effective	34
IL-31	Produced by Th2 cells and mast cells, sustains inflammation by inducing cytokines that recruit T cells to inflamed site. Major driver of itch in dorsal-root ganglia	IL-31 receptor	Human mAb against IL-31 receptor A, especially in neurons	Nemolizumab	SC	Phase III	35
IL-12 / IL-23	Activation of Th17 responses especially IL-17	IL-12 and IL-23 molecules	Human mAb against p40 sub-unit of IL-12 and IL-23	Ustekinumab	SC	Not effective	36, 37
IL-17	Produced mainly by Th17 cells under influence of IL-23. High expression in sites of acute AD	IL-17A	Human mAb against IL-17A	Secukinumab	SC	Phase II	38, 39
IL-22	Promotes epidermal hyperplasia and inhibits keratinocyte differentiation, impairing barrier function	IL-22 molecule	Human mAb against IL-22	Fezakinumab	IVI	Phase IIa	40
JAK-STAT	Signalling pathway that activates STAT3. STAT3 is a transcription factor, and also mediates mast-cell degranulation, Th17 differentiation, drives abnormal keratinocyte differentiation and epidermal barrier dysfunction in AD. STAT3 mutations cause hyper-IgE syndrome, which has AD features	JAK-STAT	Variable	Ruxolitinib, Baricitinib, Upadacitinib, Tofacitinib, JTE-052, F-04965842	Oral or topical	Different stages of development	41-44

Abbreviations: AD – atopic dermatitis; SC – subcutaneous; IVI – intravenous

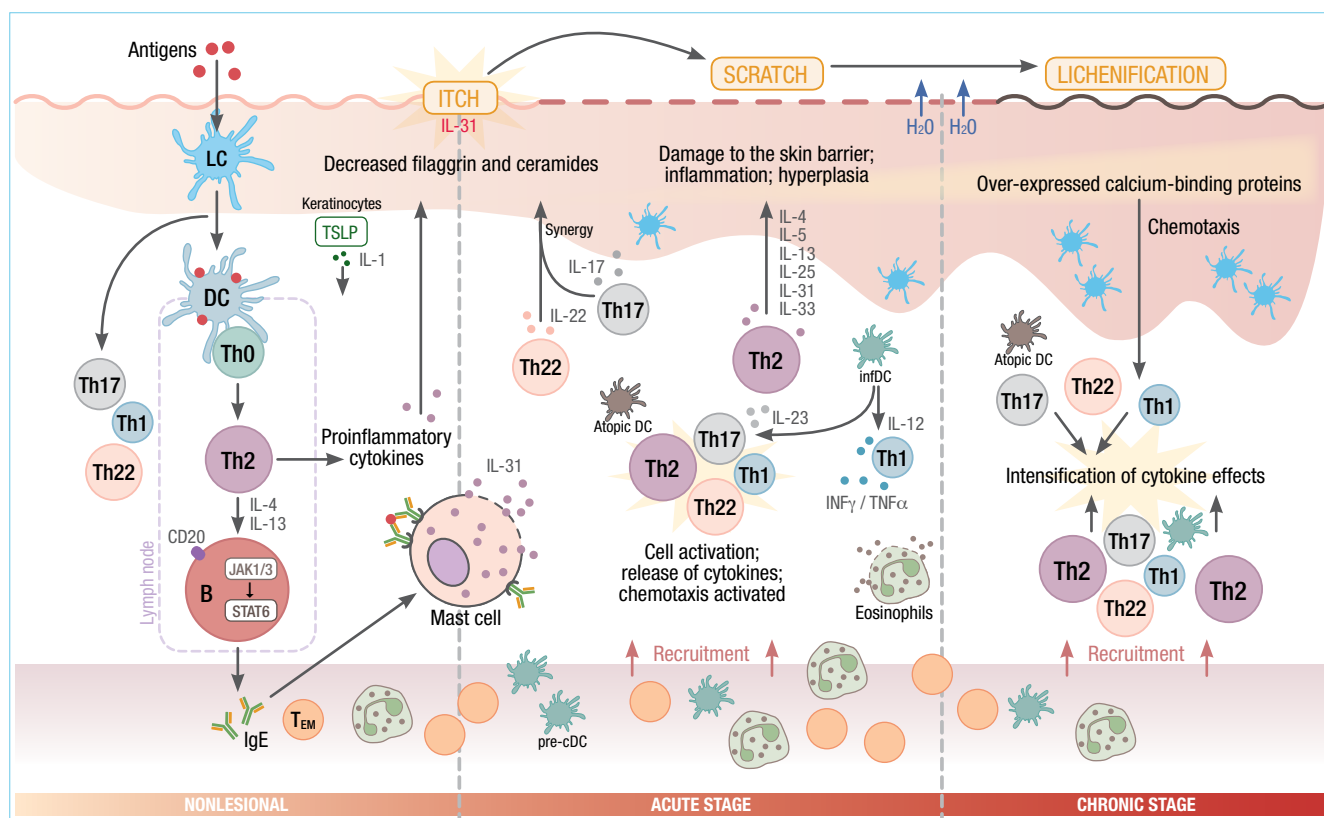


Figure 1: Immunopathologic mechanisms underlying AD

Abbreviations: LC – Langerhans cells; DC – dendritic cells; Th – T-helper cell type; IL – interleukin; JAK – Janus kinase; STAT – signal transducer and activator of transcription; TSLP – thymic stromal lymphopoietin; pre-cDC – precursor dendritic cells; Tem – effector memory T-cell

heightened systemic immune activation.²² The centrality of T_H2 cytokines (thymic stromal lymphopoietin, IL-4, IL-5, IL-13, IL-25 and IL-33) in both acute and chronic AD, and the roles of T_H22 and T_H17 cytokines (IL-22 and IL-17) are well described.^{3,45-50} Other cytokines thought to play a role in AD include IL-23, interferon- γ (IFN- γ) and tumour necrosis factor- α (TNF- α).⁵⁰ Any of these cells or cytokines can be a potential therapeutic target. The cytokines thought to play a role in AD are summarised in Table I and Figure 1.

CURRENT MANAGEMENT STRATEGIES FOR AD

Therapy is usually individualised according to the patients' age, severity and extent of AD, as well as the distribution. Treatment is categorised into basic general measures, standard medical treatment and adjuvant treatment, summarised in Table II.^{5,51}

The standard medical treatment is either topical or systemic:

- Topical corticosteroids (TCS) are the mainstay of treatment and effective in controlling symptoms and signs of AD. The selection of appropriate TCS depends on the patient's age, disease extent and severity, as well as anatomical distribution. Superpotent TCS are most effective for acute flares followed by a weaning regimen to weaker TCS on improvement. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) offer an alternative to TCS. Their potency is equivalent to that of medium-potency TCS. Their main role is that of steroid

sparing agents in sensitive areas such as the face and the eyelids, when prolonged therapy is required or as a preventive therapy in patients with frequent flares.⁵² However, they are contra-indicated for patients under the age of two.

- Histamine is not the only mediator of AD-associated pruritus; the efficacy of antihistamines in AD is limited. However, sedating older-generation oral antihistamines are useful in preventing scratching at night and in improving sleep. Systemic treatment is reserved for severe recalcitrant cases that fail to respond to either topical or adjuvant therapy. For best results, these are usually combined with topical therapy.⁵³
- Systemic corticosteroids are not recommended for treatment of AD; however, in acute cases they may be used for control followed by rapid weaning and replacement with topical treatment or other systemic agents.⁴ Systemic corticosteroids can also be used as co-treatment during the initiation and optimisation of phototherapy, and with other systemic immunosuppressants.
- Cyclosporine, an immunomodulator that inhibits cytokine transcription, is an effective AD treatment for recalcitrant and severe AD in both adults and children. However, hypertension and renal toxicity limit its long-term use and alternatives should be found on discontinuing the drug.⁴
- Azathioprine, alitretinoin (not registered in South Africa), methotrexate and mycophenolate mofetil are other immunosuppressants with established, but limited, efficacy in

TABLE II: STEP-CARE MANAGEMENT OF AD BASED ON SEVERITY (ADAPTED FROM BOGUNIEWICZ ET AL, 2018)⁵⁴

NON-LESIONAL SKIN	MILD	MODERATE	SEVERE
Basic management Skin care - Moisturise liberally and frequently - Avoid excessively long and hot baths or showers - Use non-soap cleansers. Avoid washing > once a day - Moisturise after each wash, including normal skin Trigger avoidance - Avoid known allergens triggers and common irritants such as soaps, wool and temperature extremes Consider comorbidities	Basic management + Antiseptic measures - Dilute bleach baths <2 × a week, especially with recurrent infections - Systemic antibiotics, if indicated Specific management - Apply low- to medium-potency TCS 2 × a day to inflamed skin for 3–7 days beyond clearance - Consider TCI and crisaborole	Basic management, antiseptic measures + Specific management - Apply medium- to high-potency TCS to inflamed skin 2 × daily for 3–7 days beyond clearance - If not resolved within seven days consider: non-adherence infection, misdiagnosis, contact allergy to medications, and referral Maintenance TCS - Apply moderate to potent TCS on inflamed areas of previous or potential symptoms - Low-potency TCS 1–2 × daily (including face) - Medium potency 1–2 × weekly (except face) OR Maintenance TCI 1–2 × daily 2–3 × weekly OR Crisaborole 2% 2 × daily	Basic management, antiseptic measures, topical anti-inflammatories + Referral to AD specialist Phototherapy Wet-wrap therapy Systemic immunosuppressants - Cyclosporine A - Methotrexate - Mycophenolate mofetil - Azathioprine - Corticosteroids for some acute cases to gain control Short-term hospitalisation Dupilumab

Abbreviations: TCS – topical corticosteroids; TCI – topical calcineurin inhibitors

the treatment AD. They are also limited by their side-effect profiles, which range from hepatotoxicity, bone-marrow suppression to infections.⁴

Apart from systemic corticosteroids, none of the systemic immunosuppressants have been approved for the treatment of AD by the FDA.⁵⁵ Adjuvant therapies for AD include phototherapy and allergen immunotherapy. The currently recommended step-care management of atopic eczema is summarised in Table II.

Most of the current therapies for AD have been in use for decades and during this period they have all shown limited efficacy. Current therapeutic trends are geared towards understanding AD endophenotypes, personalised treatment approaches and targeting cytokines that mediate AD.²⁰ These approaches have spawned a new group of drugs commonly referred to as 'biologics'.

INDICATIONS FOR USE OF BIOLOGICS IN AD

There are currently no universally accepted guidelines for who should receive biologics. Indeed, their use and indication depend on the cost of the drug, the disease being treated, the country and the influence of healthcare funders. Limited data specific to AD are available, owing to the relative infancy of biologic use in AD exist, with one drug only currently approved by the US Food and Drug Administration (FDA). In general, biologics are indicated for moderate-to-severe disease that has failed

to respond adequately to standard therapy. However, severity-based scoring systems alone should not determine the need for biologics – a holistic assessment is needed. Other points to consider before prescribing biologics include the certainty of diagnosis, co-morbidities and side-effects.

BIOLOGICS APPROVED FOR USE IN AD

Dupilumab is a fully human monoclonal antibody directed against the alpha sub-unit of the IL-4 receptor. The drug inhibits both IL-4 and IL-13 pathways as this sub-unit is shared between both receptors. A systemic review and meta-analysis found four double-blind, randomised-controlled trials (RCT) of dupilumab alone or associated with topical corticosteroids were assessing dupilumab for efficacy and safety. In this trial, dupilumab was found to induce rapid and dose-dependent improvements in the Eczema Area and Severity Index (EASI) score, the investigator's global assessment score, and in pruritus. At a dose of 300 mg there was an incremental improvement after 12 weeks of continuous treatment. At least 50% improvement of the scores was achieved in the 85% of patients. A significant reduction was seen in the pruritus scores. When dupilumab was used in combination with topical steroids for four weeks, 100% of patients reached these targets.⁵⁶ Adverse events associated with dupilumab include injection-site reactions, conjunctivitis, headache, nasopharyngitis, alopecia areata and erythrodermic psoriasis. Conjunctivitis that was severe enough to warrant the interruption of dupilumab has been reported.^{43,57,58}

BIOLOGICS WITH PROMISING UTILITY IN AD BUT NOT APPROVED

Nemolizumab is a humanised antibody against IL-31 receptor A. IL-31 is a cytokine that is produced mainly by Th2 cells and it has an increased expression in acute and chronic lesions of AD.^{59,60} It has been shown to play a role in the pathogenesis of AD, particularly pruritus.^{61,62} In a phase 2, double-blind, placebo-controlled 12-week RCT, 264 adults with moderate to severe AD were assigned 1 : 1 : 1 : 1 to three different, four-weekly dosing schedules of nemolizumab, one eight-weekly dose and a placebo. The primary efficacy endpoint was the percentage improvement between baseline and week 12 in the score on the pruritus visual-analogue scale. In total, 216 completed the study and a significant reduction in pruritus occurred in all those who were on the four-weekly dosing schedule. There was also an improvement in the dermatitis and sleep measures versus the placebo.³⁵

In a 52-week, double-blind extension of the same study, 191/216 continued with their original randomisation schedule and 131 completed the entire 64 weeks. The improvement was maintained or progressively increased with long-term treatment for the 64 weeks. During the extension, the use of topical corticosteroids was permitted and there was a trend towards a lower duration and cumulative dose of concomitant TCS in those receiving higher doses of nemolizumab.

Overall, nemolizumab was well tolerated over the 64 weeks.⁶³ The exacerbation of AD, nasopharyngitis, upper respiratory-tract infection, peripheral oedema and increased creatine kinase levels were the most common adverse events associated with nemolizumab.³⁵

Tralokinumab is a fully human monoclonal antibody against IL-13. IL-13 levels are not only increased in the lesional and non-lesional skin of AD patients, they are proportional to disease severity and response to treatment. In a phase 2, double-blind, placebo-controlled 12-week RCT, 204 adults with moderate to severe AD were assigned 1 : 1 : 1 : 1 to receive 45, 150 or 300 mg of subcutaneous tralokinumab or a placebo every two weeks for 12 weeks with concomitant topical glucocorticoids. Co-primary efficacy endpoints were the change in EASI score from baseline to week 12 and the percentage of participants achieving an Investigator's Global Assessment response of 0 (clear) or 1 (almost clear), with a reduction of two grades or more from baseline to week 12. An exploratory analysis for biomarkers of IL-13 activity was performed on the responders. An early (week 4) and sustained response was seen with a 300 mg dose and patients with higher IL-13 activity were the best responders. Tralokinumab had an acceptable safety and tolerability profile similar to those of the previous studies.³² The most frequent are injection-site reactions, exacerbation of asthma, headache, nasopharyngitis, diarrhoea and urinary tract infections (UTIs).⁶⁴

Lebrikizumab is an anti-IL-13 monoclonal antibody. Recently, a proof-of-concept phase 2 RCT that enrolled 209 patients

with moderate to severe AD was published. The patients were randomised 1 : 1 : 1 : 1 to receive lebrikizumab 125 mg single dose, lebrikizumab 250 mg single dose, lebrikizumab 125 mg every four weeks for 12 weeks, or a placebo every four weeks for 12 weeks, after a protocol-mandated, two-week, medium-potency topical corticosteroid run-in. A statistically significant greater proportion of patients in the lebrikizumab 125 mg every four weeks group achieved the primary endpoint of an EASI-50 response compared to the placebo grade. The lower doses of lebrikizumab showed a trend towards an improvement, suggesting a dose-response relationship. The limitations of the study were the protocol-mandated use of topical steroids twice a day for two weeks and the short duration.³³ The only adverse events associated with lebrikizumab not seen in the placebo group are musculoskeletal. These include arthralgia, body pain, myalgia and arthritis.⁶⁴

Fezakinumab is a human monoclonal antibody against IL-22. IL-22 plays a role in the epidermal barrier dysfunction associated with AD, and also seems to be responsible for the characteristic epidermal hyperplasia of AD.⁴³ A phase 2a RCT of 60 cases with moderate to severe AD, 40 of whom received intravenous fezakinumab as monotherapy every two weeks for ten weeks and 20 of whom received a placebo, has recently been reported. There was a significantly higher improvement in the fezakinumab group that was progressive beyond the last dosing (ten weeks) until end of the study at 20 weeks and was well tolerated.⁴⁰ The only reported adverse events with fezakinumab that vary significantly from those in placebo groups are upper respiratory-tract infections.⁴⁰

Rituximab is a monoclonal antibody against CD20, a protein found primarily on the surface of B-lymphocytes and inducing their lysis and subsequent B-depletion. This has an inhibitory effect on antibody production, T-cell-dependent B-cell activation and antigen presentation.⁴³ A small open-label study of six patients using two doses of 1 000 mg by intravenous infusion for two weeks showed significant improvement. This was associated with a reduction in the number of B-lymphocytes in both lesional and non-lesional skin as well as IL-5, IL-1 and total serum IgE levels.²⁷ However, two other patients treated with a 500 mg intravenous infusion over two weeks actually worsened on rituximab.²⁸ Another, more recent, series of treatment of three consecutive patients with AD who were treated with rituximab failed to show an improvement.⁶⁵ Promising results have been seen when combining rituximab with omalizumab, a monoclonal antibody against IgE, in six patients with AD.⁶⁶ Current data are insufficient to reach definite conclusions and larger studies are therefore necessary to determine the efficacy and optimal dosing of rituximab in AD. Adverse events with the use of rituximab include infusion reactions, progressive hypogammaglobulinemia, thrombocytopenia, non-infectious interstitial lung disease, psoriasis, cutaneous vasculitis, Stevens-Johnson syndrome and liver failure in patients with hepatitis-B virus infection.⁶⁴

Omalizumab is a recombinant, humanised monoclonal antibody against the high-affinity Fc receptor of human IgE. The drug is

FDA approved for chronic spontaneous urticaria and has proved to be very effective.⁶⁷ The use of omalizumab in AD has yielded mixed results. A recent systematic review found that fewer than half of the patients treated with omalizumab achieved significant clinical improvement.⁶⁸ However, there seems to be a subset of AD cases that is responsive to the drug, including those with the wild-type FLG gene and low serum IgE levels.^{55,68-70} If this proves to be true on further investigation, it would improve patient selection and the overall efficacy of the drug. Omalizumab is safe and well tolerated. Adverse events are usually mild and include injection-site reaction, headache and pharyngitis. Anaphylaxis is a rare association.⁶⁴

Janus kinase (JAK) inhibitors block IL-4 signalling through the JAK 1/3-STAT6 pathway. The pathway moderates inflammation and the activation of STAT3, which is responsible for the abnormal keratinocyte differentiation and epidermal-barrier dysfunction seen in AD. Baricitinib, upadacitinib and F-04965842 are systemic JAK inhibitors that have shown promising results in treating AD and they are currently in phase 2 clinical trials. Another JAK inhibitor, itacitinib, is on trial for pruritus.^{43,44}

Tezepelumab is a novel human monoclonal antibody that prevents the interaction of thymic stromal lymphopoietin (TSLP) with its receptor. TSLP is a cytokine that is secreted by keratinocytes and is thought to play an important role in the pathogenesis of AD. It is highly expressed in acute and chronic lesions of AD and promotes the activation of myeloid dendritic cells; it favours lymphocyte activation and a Th2-polarised response with the consequent release of pro-inflammatory cytokines. The results from a phase 1 trial of tezepelumab in patients are pending.⁴³

BIOLOGICS TRIALLED FOR AD FOUND NOT BE EFFICACIOUS

TNF- α blockers, *infliximab*, a chimeric monoclonal TNF- α antibody, and *etanercept*, a human-recombinant fusion protein that blocks the TNF- α receptor, have been evaluated for treatment of AD in both children and adults have shown limited efficacy. Their use is also associated with an increased frequency of infections and a rapid loss of efficacy.⁷¹⁻⁷³ Another deterrent to the use of TNF- α blockers is the development of AD in patients with psoriasis who are treated with the drugs.⁷⁴⁻⁷⁶

Mepolizumab is a monoclonal antibody against IL-5, a cytokine that drives eosinophil growth, differentiation and migration. Considering the frequently elevated eosinophil levels in AD and its significant glucocorticoid-sparing effect in patients with severe eosinophilic asthma, mepolizumab has been trialled in the management of AD.^{77,78} Despite effecting a reduction in blood and tissue eosinophils, the clinical improvement of AD was not achieved in small randomised-controlled trials of short duration.³⁴

Ustekinumab is a fully human monoclonal antibody that binds to the shared p40 sub-unit of IL-12 and IL-23 to inhibit the differentiation and clonal expansion of naive cells into Th1 or Th17 responses respectively. IL-17, a Th17 cytokine, is highly

expressed in both the lesional skin and the circulation of patients with AD and it is thought to play a role in the pathogenesis of the disease.⁷⁹ Two well-designed randomised-controlled trials have shown the drug to be ineffective in treating AD.^{36,37,80}

Anakinra is a recombinant human-receptor antagonist against interleukin IL-1, a pro-inflammatory cytokine that plays a role in the initiation and maintenance of Th2 response. A study evaluating the efficacy of anakinra in AD was terminated for unknown reasons.⁸¹

BIOLOGICS TRIALLED FOR AD BUT SINCE WITHDRAWN FROM THE MARKET

Efalizumab was a humanised monoclonal antibody that prevented lymphocyte function-associated antigen 1 from binding to ICAM-1 on endothelial and antigen-presenting cells. This reduced T-lymphocyte recruitment and activation at sites of inflammation. Its use in AD produced conflicting results before the drug was withdrawn after being associated with progressive multifocal leukoencephalopathy.⁴³

Alefacept was a human-dimeric fusion protein that blocked the interaction of lymphocyte function-associated antigen 3 and CD2, expressed on antigen-presenting cells and T-lymphocytes respectively. This interaction provided co-stimulatory signals for the activation of T-lymphocytes. The drug showed promising results before it was withdrawn owing to a lack of demand.^{43,64}

Pitrakinra was a recombinant human IL-4 protein that blocked the alpha sub-unit of the IL-4 receptor, inhibiting the downstream signalling pathways of IL-4 and IL-13. The trial to assess its efficacy in AD was not published after clinical development of the drug was terminated.^{31,82}

USE OF BIOLOGICS IN COMBINATION WITH OTHER BIOLOGICS OR TRADITIONAL THERAPIES

Limited data exist on the use of a combination of two or more biologics in general, not only in AD. Biologics are highly selective and as used in other diseases they seem to demonstrate the required efficacy to be administered as monotherapy. In other diseases, the rationale for combination therapy with other drugs includes:

- the prevention of antibody formation to the biologic;
- an inadequate response to the biologic;
- efficacy synergies for a more complete response;
- a quicker response, and
- a broader response to treatment including extra-cutaneous complications such as cardiovascular disease that may not be targeted by the highly selective biologic.^{83,84}

USE OF BIOLOGICS IN PREGNANCY AND LACTATION

The largest repository on the use of biologics in pregnancy and lactation involves TNF- α blockers. There are no controlled studies and the total number of pregnant or lactating women exposed to biologics is still too small to make definitive conclusions on their safety profile in these situations. This is further complicated by use of multiple drugs in most patients included in current reports

of biologics in pregnancy and breastfeeding. Currently, it seems that the benefits of TNF- α blockers to the foetus and to breastfed children outweigh the risks. This cannot be generalised to other biologics, however.^{85,86}

USE OF BIOLOGICS IN CHILDREN

The safety and efficacy of biologics in children with AD, the most commonly affected population, is not clear, since almost all the published studies excluded patients under the age of 18. Currently, no biologics are approved for use in children with AD. Following the success of dupilumab in adult patients with severe AD, a number of clinical trials on children with AD are in progress. These include an open-label study (R668-AD-1434); a double-blind, placebo-controlled RCT investigating the efficacy and safety of dupilumab administered concomitantly with TCS in patients over six years but younger than 12 years of age with severe AD (R668-AD-1652), and phase 2 and 3 studies. These last two studies are investigating the pharmacokinetics, safety and efficacy of dupilumab in patients aged between six months and six years with severe AD (R668-AD-1539 and 0456-0107, respectively). Preliminary data from these studies suggest outcomes that are even better than those observed in adults (personal communication).

Omalizumab has been approved for asthma in children <12 years of age. There is an ongoing trial of omalizumab for severe childhood eczema.⁸⁷ Etanercept, adalimumab, abatacept and tocilizumab all have no significant role in AD but have been approved for use in juvenile arthritis. Concerns over their use in children are controversial, reported adverse events including malignancies, infections and autoimmune diseases.⁸⁸ The available data are mainly derived from case reports.

NEUTRALISING ANTIBODIES AGAINST BIOLOGICS

The formation of antibodies against monoclonal antibodies has a significant impact on their efficacy. This has been linked to a reduction in serum levels of the drug and an increase in antibody clearance correlating to a reduced clinical response.⁸⁹ Infliximab and adalimumab are known to be associated with anti-drug-neutralising antibodies that decrease their efficacy.⁹⁰ Non-neutralising antibodies against nemolizumab have been

reported.³⁵

LIMITATIONS OF THE USE OF BIOLOGICS IN AD

The use of biologics in AD is still in its infancy and data on their efficacy, patient selection, interchangeability with biosimilars and other molecules with similar targets, and unknown long-term risk are limited at this stage. Most data are derived from rheumatology. A major challenge is the cost of the drugs, being out of reach of most people, particularly those in developing countries.⁹¹

FUTURE DIRECTIONS

It is becoming increasingly clear that AD is just one disease of many for which biologics may be an appropriate intervention. The differing responses to biologics point towards differences in disease pathogenesis. Current and future studies need to focus on delineating AD phenotypes based on variables such as age of onset, ethnicity, severity, biomarkers and genetics. Pharmacogenomics will further determine response to specific drugs.¹¹⁻⁷⁵

The next generation of biologicals is small proteins that may either:

- have an antibody or novel binding domains;
- have diverse specificity;
- be able to be engineered to bind more than one target;
- be able to be produced in bacteria at a lower cost;
- be relatively stable, or
- because of their small size, be able to penetrate diseased tissues more effectively than antibodies.⁹²

Oral JAK kinase inhibitors fall into this category.

CONCLUSIONS

The use of biologics in the treatment of AD is still in its infancy, but promising new and repurposed drugs are in the pipeline.

DECLARATION OF CONFLICT OF INTEREST

The authors declare not conflict of interest.

ACKNOWLEDGEMENTS

Thanks to Karen Adamson for the illustrations.

This article has been peer reviewed.

REFERENCES

1. Cheng JF, Ott NL, Peterson EA, George TJ, et al. Dermal eosinophils in atopic dermatitis undergo cytolytic degeneration. *J Allergy Clin Immunol* 1997;99(5):683–692.
2. Frisch S, Siegfried EC. The clinical spectrum and therapeutic challenge of eczema herpeticum. *Pediatr Dermatol* 2011;28(1):46–52.
3. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016;387(10023):1109–1122.
4. Megna M, Napolitano M, Patruno C, Villani A, et al. Systemic treatment of adult atopic dermatitis: A review. *Dermatol Ther (Heidelb)* 2017;7(1):1–23.
5. Lee JH, Son SW, Cho SH. A comprehensive review of the treatment of atopic eczema. *Allergy Asthma Immunol Res* 2016;8(3):181–190.
6. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007;18(7):560–565.
7. Williams H, Robertson C, Stewart A, Ait-Khaled N, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103(1 Pt 1):125–138.
8. Asher MI, Montefort S, Björkstén B, Lai CK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368(9537):733–743.
9. Chalmers DA, Todd G, Saxe N, Milne JT, et al. Validation of the U.K. Working Party diagnostic criteria for atopic eczema in a Xhosa-speaking African population. *Br J Dermatol* 2007;156(1):111–116.
10. Ahn C, Huang W. Clinical presentation of atopic dermatitis. *Adv Exp Med Biol* 2017;1027:39–46.

11. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? *J Allergy Clin Immunol* 2017;139(4S):S58–S64.
12. Schmitt J, Apfelbacher C, Chen CM, Romanos M, et al. Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (German Infant Nutrition Intervention plus). *J Allergy Clin Immunol* 2010;125(2):404–410.
13. Hay RJ, Johns NE, Williams HC, Bolliger IW, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014;134(6):1527–1534.
14. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, et al. Global skin disease morbidity and mortality: An update from the Global Burden of Disease Study 2013. *JAMA Dermatol* 2017;153(5):406–412.
15. Brunner PM, Silverberg JL, Guttman-Yassky E, Paller AS, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol* 2017;137(1):18–25.
16. Schmitt J, Schwarz K, Baurecht H, Hotze M, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol* 2016;137(1):130–136.
17. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. *Allergy* 2014;69(1):37–45.
18. Silverberg JL. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. *Allergy* 2015;70(10):1300–1308.
19. Silverberg JL, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. *J Allergy Clin Immunol* 2015;135(3):721–728 e6.
20. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. *J Dermatol Sci* 2010;58(1):1–7.
21. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242(1):233–246.
22. Al-Shobaili HA, Ahmed AA, Alnomair N, Alobead ZA, Rasheed Z. Molecular genetic of atopic dermatitis: An update. *Int J Health Sci (Qassim)* 2016;10(1):96–120.
23. Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci*. 2009;122(Pt 9):1285–94.
24. Biedermann T, Skabytska Y, Kaesler S, Volz T. Regulation of T cell immunity in atopic dermatitis by microbes: The yin and yang of cutaneous inflammation. *Front Immunol* 2015;6:353.
25. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of Type 2 immunity. *Immunity* 2015;43(1):29–40.
26. Correa da Rosa J, Malajian D, Shemer A, Rozenblit M, et al. Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. *J Allergy Clin Immunol* 2015;135(3):712–20.
27. Simon D, Hosli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol* 2008;121(1):122–128.
28. Sediva A, Kayserova J, Vernerova E, Polouckova A, et al. Anti-CD20 (rituximab) treatment for atopic eczema. *J Allergy Clin Immunol* 2008;121(6):1515–1516; author reply 6–7.
29. Liu FT, Goodarzi H, Chen HY. IgE, mast cells, and eosinophils in atopic dermatitis. *Clin Rev Allergy Immunol* 2011;41(3):298–310.
30. Awosika O, Kim L, Mazhar M, Rengifo-Pardo M, Ehrlich A. Profile of dupilumab and its potential in the treatment of inadequately controlled moderate-to-severe atopic dermatitis. *Clin Cosmet Investig Dermatol* 2018;11:41–49.
31. Durham AL, Caramori G, Chung KF, Adcock IM. Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. *Transl Res* 2016;167(1):192–203.
32. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JL, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol* 2018.
33. Simpson EL, Flohr C, Eichenfield LF, Bieber T, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol* 2018;78(5):863–871 e11.
34. Oldhoff JM, Darsow U, Werfel T, Katzer K, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy*. 2005;60(5):693–696.
35. Ruzicka T, Hanifin JM, Furue M, Pulka G, et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. *N Engl J Med* 2017;376(9):826–835.
36. Khattri S, Brunner PM, Garcet S, Finney R, et al. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol* 2017;26(1):28–35.
37. Saeki H, Kabashima K, Tokura Y, Murata Y, et al. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br J Dermatol* 2017;177(2):419–427.
38. Hofmann MA, Kiecker F, Zuberbier T. A systematic review of the role of interleukin-17 and the interleukin-20 family in inflammatory allergic skin diseases. *Curr Opin Allergy Clin Immunol* 2016;16(5):451–457.
39. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: End of the drought? *J Allergy Clin Immunol* 2017;140(3):633–643.
40. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: A randomized, double-blind, phase 2a trial. *J Am Acad Dermatol* 2018;78(5):872–881 e6.
41. Siegel AM, Stone KD, Cruse G, Lawrence MG, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. *J Allergy Clin Immunol* 2013;132(6):1388–1396.
42. Forbes LR, Milner J, Haddad E. Signal transducer and activator of transcription 3: a year in review. *Curr Opin Hematol* 2016;23(1):23–27.
43. 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.
44. Cinats A, Heck E, Robertson L. Janus kinase inhibitors: A review of their emerging applications in dermatology. *Skin Therapy Lett* 2018;23(3):5–9.
45. Brunner PM, Israel A, Zhang N, Leonard A, et al. Early-onset pediatric atopic dermatitis is characterized by TH2/TH17/TH22-centered inflammation and lipid alterations. *J Allergy Clin Immunol* 2018;141(6):2094–2106.
46. Wistok-Wulfing A, Schmidt P, Darsow U, Ring J, et al. Atopy patch test reactions are associated with T lymphocyte-mediated allergen-specific immune responses in atopic dermatitis. *Clin Exp Allergy* 1999;29(4):513–521.
47. Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J Dermatol Sci* 2013;70(1):3–11.
48. Wawrzyniak P, Akdis CA, Finkelman FD, Rothenberg ME. Advances and highlights in mechanisms of allergic disease in 2015. *J Allergy Clin Immunol* 2016;137(6):1681–1696.
49. Werfel T, Allam JP, Biedermann T, Eyerich K, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016;138(2):336–349.
50. Kim J, Kim BE, Lee J, Han Y, et al. Epidermal thymic stromal lymphopoietin predicts the development of atopic dermatitis during infancy. *J Allergy Clin Immunol* 2016;137(4):1282–1285 e4.
51. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics* 2008;122(4):812–824.
52. Paller AS, Eichenfield LF, Kirsner RS, Shull T, et al. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. *Pediatrics* 2008;122(6):e1210–1218.
53. Deleuran MS, Vestergaard C. Therapy of severe atopic dermatitis in adults. *J Dtsch Dermatol Ges* 2012;10(6):399–406.
54. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, et al. Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol* 2018;120(1):10–22 e2.
55. Boguniewicz M. Biologic therapy for atopic dermatitis: moving beyond the practice parameter and guidelines. *J Allergy Clin Immunol Pract* 2017;5(6):1477–1487.
56. Wang FP, Tang XJ, Wei CQ, Xu LR, et al. Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis. *J Dermatol Sci* 2018;90(2):190–198.
57. Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. *JAMA Dermatol* 2018.
58. Mitchell K, Levitt J. Alopecia areata after dupilumab for atopic dermatitis. *JAAD Case Rep* 2018;4(2):143–144.

59. Nobbe S, Dziunycz P, Muhleisen B, Bilsborough J, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. *Acta Derm Venereol*. 2012;92(1):24–28.
60. Szegedi K, Kremer AE, Kezic S, Teunissen MB, et al. Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. *Exp Dermatol*. 2012;21(6):431–436.
61. Bilsborough J, Leung DY, Maurer M, Howell M, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006;117(2):418–425.
62. Cevikbas F, Wang X, Akiyama T, Kempkes C, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol* 2014;133(2):448–460.
63. Kabashima K, Furue M, Hanifin JM, Pulka G, et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study. *J Allergy Clin Immunol* 2018.
64. Boyman O, Kaegi C, Akdis M, Bavbek S, et al. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders. *Allergy* 2015;70(7):727–754.
65. 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):45–47.
66. Sanchez-Ramon S, Eguluz-Gracia I, Rodriguez-Mazariego ME, Paravisini A, et al. Sequential combined therapy with omalizumab and rituximab: a new approach to severe atopic dermatitis. *J Investig Allergol Clin Immunol*. 2013;23(3):190–196.
67. Wu KCP, Jabbar-Lopez ZK. Omalizumab, an Anti-IgE mAb, receives approval for the treatment of chronic idiopathic/spontaneous urticaria. *J Invest Dermatol* 2015;135(1):13–15.
68. 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):1719–1722 e1.
69. Hotze M, Baurecht H, Rodriguez E, Chapman-Rothe N, et al. Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines. *Allergy* 2014;69(1):132–135.
70. Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. *J Am Acad Dermatol* 2005;53(2):338–340.
71. 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):358–359.
72. 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):522–526.
73. Farnsworth NN, George SJ, Hsu S. Successful use of infliximab following a failed course of etanercept in a pediatric patient. *Dermatol Online J* 2005;11(3):11.
74. 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):2506–2507.
75. Ruiz-Villaverde R, Galan-Gutierrez M. Exacerbation of atopic dermatitis in a patient treated with infliximab. *Actas Dermosifiliogr* 2012;103(8):743–746.
76. Lebas D, Staumont-Salle D, Solau-Gervais E, Flipo RM, Delaporte E. [Cutaneous manifestations during treatment with TNF- α blockers: 11 cases]. *Ann Dermatol Venereol* 2007;134(4 Pt 1):337–342.
77. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371(13):1189–1197.
78. Keating GM. Mepolizumab: first global approval. *Drugs* 2015;75(18):2163–2169.
79. 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):2625–2630.
80. Batista DI, Perez L, Orfali RL, Zaniboni MC, 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):1091–1095.
81. A Pilot Study Using Anakinra/Kineret for the Treatment of Patients with Severe Atopic Dermatitis. [Internet]. [cited 20 August 2018]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01122914>
82. A Phase 2a Study to Investigate the Effects of Repeated Administration of AeroDerm in Subjects with Atopic Eczema. [Internet]. [cited 20 August 2018]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT00676884>
83. Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. *Am J Clin Dermatol* 2014;15(6):467–478.
84. Blauvelt A, De Bruin-Weller M, Gooderham M, Cather JC, 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):2287–2303.
85. Bogas M, Leandro MJ. Biologic therapy and pregnancy. A systematic literature review. *Acta Reumatol Port* 2011;36(3):219–232.
86. Brown SM, Aljefri KA, Waas R, Hampton PJ. Systemic medications used in treatment of common dermatological conditions: Safety profile with respect to pregnancy, breast feeding and content in seminal fluid. *J Dermatolog Treat* 2017:1–53.
87. Chan S, Cornelius V, Chen T, Radulovic S, et al. Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT): the role of anti-IgE in severe paediatric eczema: study protocol for a randomised controlled trial. *Trials* 2017;18(1):136.
88. In: Field MJ, Boat TF, editors. *Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act*. Washington (DC)2012.
89. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet* 2010;49(8):493–507.
90. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: a systematic review. *Br J Dermatol* 2014;170(2):261–273.
91. Gu T, Shah N, Deshpande G, Tang DH, Eisenberg DF. Comparing biologic cost per treated patient across indications among adult US managed care patients: A retrospective cohort study. *Drugs Real World Outcomes* 2016;3(4):369–381.
92. Nilvebrant J, Tessier PM, Sidhu SS. Engineered autonomous human variable domains. *Curr Pharm Des* 2016;22(43):6527–6537.