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Through an understanding of the pathophysiology of atopic dermatitis and the role of Type 2 cytokines, new targeted systemic therapies are emerging which have the potential to greatly impact a patient’s quality of life. This review is a summary of a Sanofi Genzyme-sponsored breakfast Symposium presented by Dr Mark Boguniewicz (Denver, United States) during the 2018 Annual Scientific Meeting for the Australasian College of Dermatologists, held on May 21 at the Gold Coast Convention and Exhibition Centre. During the Symposium Dr Boguniewicz provided an overview of the pathophysiology of atopic dermatitis, the systemic therapies that have been used to treat the disease, new and emerging targeted biologic therapies such as dupilumab and nemolizumab and practical guidance for treating patients in a rapidly evolving landscape.

The evolving management of severe atopic dermatitis

Presentation by Professor Mark Boguniewicz

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The burden of atopic dermatitis

Atopic dermatitis is a disease with a global scope. It can affect patients of all ages in developed and developing countries. It is often a persistent, lifelong disease with major implications for global health issues. The prevalence of atopic dermatitis in adults is similar in Australia and the US, with 1-year prevalence rates of 6.9% and 7.2%, respectively. Severe atopic dermatitis is a burdensome disease which impacts the quality of life of patients and carers. Patients can be socially isolated, functionally unable to participate in school and workplace activities and can suffer from secondary bacterial and viral infections.

A recent analysis of patient-reported outcomes from 380 moderate-to-severe atopic dermatitis patients helped to define the burden of the disease: 41% of patients had atopic dermatitis for less than 5 years and 37% were diagnosed 20 or more years ago. 40% of patients also had asthma and 61% had other allergic conditions. Despite almost half (48%) of the patients using systemic therapies in the past year, many patients still reported problems with itching frequency (65% of patients), itch duration (42% reported itching for 18 hours or more each day), and itch severity (55% of patients reporting sleep disturbances for 5 or more days per week). 22% of patients may have been suffering from anxiety or depression.

Recent insights into atopic dermatitis

The involvement of cytokines in atopic dermatitis was first demonstrated in 1994 using gene expression analyses. Since then the role of cytokines and the innate and adaptive immune systems in atopic dermatitis has become clearer, with Type 2 cytokines driving immune dysregulation.

Atopic dermatitis is unique among inflammatory skin diseases, where active colonisation with microbial organisms occurs. Many patients are methicillin resistant Staphylococcus aureus (MRSA)-positive and there is an epidemic of community associated-MRSA in the US. The increased susceptibility of atopic dermatitis patients to infection or colonisation with microbial organisms such as S. aureus and Herpes simplex virus has implications for the management of infectious complications.

Research into understanding the interaction of microbes with the skin has led to the classification of the skin microbiome as well as the identification of phenotypes and endotypes for atopic dermatitis patients who are colonised by S. aureus. Compared to S. aureus negative atopic dermatitis patients, S. aureus positive patients had more severe disease (except itch), greater type 2 immune deviation, allergen sensitisation, lactate dehydrogenase (LDH) elevation and barrier disruption. S. aureus colonization in atopic dermatitis has also been associated with an altered composition of epidermal lipids, which appears to be driven by Type 2 cytokines.

Atopic dermatitis as a systemic disorder

Atopic dermatitis is a result of altered skin barrier and immune dysregulation. A growing body of evidence suggests it is a systemic disorder where immune activation occurs beyond the skin, including in circulating T cells, B cells/IgE and cytokines. Further support for the systemic nature of the disease is the association of atopic dermatitis with cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease, neuropsychiatric disorders and potentially cancer.

Systemic treatments for atopic dermatitis

Systemic therapies have been used for decades to treat atopic dermatitis and there are a number of algorithms that help the clinician to evaluate if a patient requires systemic therapy. For example, the International Eczema Council have developed a framework for evaluating atopic dermatitis patients and created recommendations to guide the use of systemic therapy in these patients. The treatment algorithm takes into consideration the disease severity and impact on quality of life, patient education, prior topical therapy, whether alternative diagnoses have been ruled out and the availability and/or results of phototherapy.
Prior to the approval of dupilumab (Dupixent®, Product Information)®, cyclosporin A was the only approved systemic treatment of atopic dermatitis in Australia.17 A systematic review evaluating the safety and efficacy of 12 different systemic treatments in 1653 moderate-to-severe atopic dermatitis patients found that cyclosporin A improved the clinical signs of the disease and as such it was recommended as first-line treatment for short-term use in chronic and refractory atopic dermatitis patients.18

Targeted systemic treatment for atopic dermatitis

Type 2 immunity refers to a specialized immune response involving the innate and adaptive components of the immune system in order to promote barrier immunity on mucosal surfaces and eliminate parasitic pathogens. It is associated with several cytokine mediators including IL-4, IL-5, IL-9 and IL-13.19 Epithelial-derived cytokines, thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 also propagate or initiate type 2 responses, but their functions are not limited to type 2 immune responses.19 This inflammatory response can also be initiated in response to allergens, leading to allergic diseases.20

Specific targets for skin barrier and immune system abnormalities include:20

- Microbial-directed therapies
- Pruritus-directed therapies
- Skin barrier-directed therapies
- Immunologic therapies.

Rather than reducing inflammation with broad-acting immunosuppressants or narrowly targeting downstream products such as IgE, efforts to target the key proximal type 2 cytokines IL-4, IL-5 and IL-13 are promising targets with the potential for therapeutic benefit across multiple diseases.19

Dupilumab

Dupilumab is a fully monoclonal antibody against the IL-4 receptor alpha and inhibits IL-4 and IL-13-mediated signalling.19 Transcriptome studies demonstrate dupilumab treatment can correct the abnormal gene expression observed in atopic dermatitis patients.21 A number of Phase 3 trials have been completed including two monotherapy studies (SOLO 1 and SOLO 2) and two studies that allowed concomitant use of topical corticosteroids (LIBERTY AD CHRONOS and LIBERTY CAFE).

SOLO 1 and SOLO 2 Studies

Two randomised, placebo-controlled, phase 3 trials of identical design (SOLO 1, N=671 and SOLO 2, N=708) were conducted in adults with moderate-to-severe atopic dermatitis who were inadequately controlled by topical treatment.22 Patients were randomised 1:1:1 to receive 300 mg subcutaneous dupilumab or placebo weekly, or 300 mg dupilumab every two weeks alternating with placebo for 16 weeks.23 Patients also received a 600 mg loading dose of dupilumab (or placebo).23 Approximately half of the patients had moderate atopic dermatitis and half had severe atopic dermatitis classified by the Investigator’s Global Assessment (IGA) score with a median of 50% of the body-surface area affected.23 The median disease duration was 24 to 28 years, almost one third of patients had previously received systemic immunosuppressant agents.23

The primary endpoint was the proportion of patients with an IGA score of 0 or 1 (clear or almost clear) and a reduction of ≥2 points in that score from baseline to Week 16.23 Dr Boguniewicz noted this is a difficult endpoint to achieve in moderate to severe atopic dermatitis patients and reflects the stringency of the trial design. There was a significant difference between both dupilumab arms and placebo for the IGA primary endpoint as well as for Eczema Area and Severity Index (EASI) 75 (P<0.001 for all dupilumab vs placebo; Figure 1).23 Improvements in EASI score and pruritus were significant and rapid (P<0.001 for all dupilumab vs placebo; Figure 2).23 The overall rate of adverse events was comparable between the dupilumab and placebo groups (65-73% dupilumab vs 65-72% placebo).23 The rate of serious adverse events was 1-3% for dupilumab and 5-6% for placebo.23 Serious and severe infections were numerically higher in placebo groups in both studies (0.5-1% dupilumab and 2-3% placebo).23 Adverse events that were more common in the dupilumab groups included injection site reactions (8-19% dupilumab vs 6% placebo) and conjunctivitis (7% dupilumab vs 2% placebo).23 There were no discontinuations due to injection site reactions and there was 1 discontinuation due to conjunctivitis.23

LIBERTY AD CHRONOS Study

Long-term (1 year) use of dupilumab was studied in patients with moderate-to-severe atopic dermatitis in a randomised, double-blind, placebo-controlled, phase 3 study.24 Patients were administered 300 mg subcutaneous dupilumab or placebo weekly, or 300 mg dupilumab every two weeks alternating with placebo for 52 weeks in addition to concomitant topical corticosteroids.24 Compared to placebo, more dupilumab-treated patients achieved the primary endpoint of IGA of 0 or 1 and ≥2 points improvement from baseline (P<0.0001) and the key secondary endpoint of EASI 75 (P<0.0001) at Weeks 16 and 52 (Figure 3).24 There was also a significant improvement in pruritus as early as Week 2 which was sustained to Week 52.24 The proportion of patients with 1 or more adverse events or serious adverse events was similar between the treatment arms, and numerically more placebo-treated patients discontinued treatment (2-3% dupilumab vs 8% placebo).24 Adverse events that were more common in the dupilumab groups included injection site reactions (15-19% dupilumab and 8% placebo) and conjunctivitis (14-19% dupilumab and 8% placebo) while non-herpetic skin infections were less common in the dupilumab group (8-11% dupilumab and 18% placebo).24

LIBERTY AD CAFE Study

The efficacy and safety of dupilumab with concomitant topical corticosteroids was evaluated in 325 adults with atopic dermatitis who had an inadequate response or intolerance to cyclosporin A, or for whom cyclosporin A was medically inadvisable.25 Patients were randomised to 300 mg subcutaneous dupilumab or placebo weekly, or 300 mg dupilumab every two weeks alternating with placebo for 16 weeks in addition to concomitant medium potency topical corticosteroids.25 Significantly more patients in the dupilumab plus topical corticosteroid treatment groups achieved ≥75% improvement from baseline in EASI at Week 16 compared to the placebo plus topical corticosteroid group (59-63% vs 30%; P<0.0001 for both doses).25 There was also a significant improvement in pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life in both dupilumab treatment groups.25 The overall rate of adverse events was comparable between the dupilumab and placebo groups (69-72% dupilumab and 69% placebo).25 The rate of serious adverse events was 2% for all three treatment groups.25 Conjunctivitis was more common in dupilumab-treated patients while skin infections were less common compared to placebo.25
Post-hoc analysis of the LIBERTY AD CHRONOS and SOLO studies

The primary endpoint in the LIBERTY AD CHRONOS and SOLO studies was based on the proportion of patients with an IGA score of 0 or 1 (clear or almost clear) and a reduction of ≥2 points in that score from baseline to Week 16. This is a very stringent endpoint but is not the only measure of patient improvement. A post-hoc analysis of the EASI score changes in patients from the LIBERTY AD CHRONOS and SOLO studies who did not get an IGA score of 0 or 1 at Week 16 was conducted in 370 patients treated with placebo and 262 patients treated with 300 mg dupilumab every two weeks. The change from baseline was statistically significantly (P<0.0001) greater in dupilumab-treated patients compared to placebo-treated patients and the improvement from baseline was clinically significant (Figure 4).

Photographs taken before and after dupilumab treatment demonstrate the improvement that was achieved in two patients from the phase II and III trials (Figure 5).

Dupilumab is not approved for use in patients under 18 years of age. There are currently 3 studies underway that will examine the safety and efficacy of dupilumab in children and adolescents.

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**Figure 2.** Mean change from baseline for EASI-75 and pruritus from SOLO 1 and SOLO 2.

**Figure 3.** Primary endpoint (qualifying IGA score) and key secondary endpoint (EASI-75) from the LIBERTY AD CHRONOS study.

**Figure 4.** Mean change from baseline in EASI score in placebo and dupilumab-treated patients from the LIBERTY AD CHRONOS and SOLO studies.
Emerging targets and therapies for atopic dermatitis

The pathophysiology of atopic dermatitis is complex and there are several targets for new biologic therapies including IL-31, histamine receptors, substance P receptors and TRPV channels. Nemolizumab is an anti-IL-31 receptor A antibody that is currently being studied for the treatment of atopic dermatitis. A randomized phase 2, double-blind, placebo-controlled study of 264 adults with moderate-to-severe atopic dermatitis who were inadequately controlled with topical therapy examined placebo or 0.1 mg, 0.5 mg or 2.0 mg/kg nemolizumab every 4 weeks or 2 mg/kg nemolizumab every 8 weeks. Compared to placebo, all doses of nemolizumab resulted in significantly greater changes from baseline in pruritus score at 12 weeks (Figure 6). Changes in EASI ranged from -23% to -43% for nemolizumab compared to -27% for placebo.

There were a similar number of patients who experienced an adverse event among the 5 treatment arms (67-77% nemolizumab and 68% placebo). The incidence of serious adverse events was uncommon (0-6% nemolizumab and 2% placebo). Exacerbation of atopic dermatitis (17-21% nemolizumab and 13% placebo) and peripheral oedema (4-10% nemolizumab and 0% placebo) were more common in the nemolizumab groups than in the placebo group. A recent systematic review and meta-analyses analysed clinical trial and observational study data for 9 biologic therapies and included high quality evidence for dupilumab, nemolizumab, ustekinumab. All medications had a comparable safety profile to placebo and the authors concluded that dupilumab is currently the only biologic with robust evidence of efficacy in atopic dermatitis.

Guidelines and expert recommendations

The US expert perspectives on the management of moderate-to-severe atopic dermatitis have been updated to reflect the latest clinical trial data. An Australian consensus algorithm is being developed and was presented by Dr. Saxon Smith at ACC. The US expert panel recommendations include:

- Atopic dermatitis is most likely a systemic disease, suggesting that systemic treatment could be an important strategy for disease control
- Moderate-to-severe atopic dermatitis may be considered when there is a minimum involvement of 10% body surface area, or if the patient has lesions with moderate-to-severe features or the lesions are in highly visible areas or areas important for function, or if the patient has a significantly impaired quality of life
- Treatment failure may be defined as failure to achieve stable long-term disease control, inadequate clinical improvement, presence of ongoing impairment while on treatment, or unacceptable adverse events. There is no typical time to treatment failure for topical treatments and if failure is suspected, patient adherence should be assessed
- Dupilumab is recommended as a first-line systemic treatment option for adults with moderate-to-severe atopic dermatitis whose disease is not controlled by topical therapies
- When choosing a therapy for moderate-to-severe atopic dermatitis patients, it is important to include the patient in the decision-making process.

In a therapeutic landscape that is rapidly evolving, new practical recommendations may help clinicians determine the most appropriate acute and maintenance treatment strategies for their atopic dermatitis patients.

Conclusion/Take home messages

- Atopic dermatitis is a chronic disease with a global scope affecting patients of all ages.
- The increased susceptibility of atopic dermatitis patients to infection or colonisation with microbial organisms such as Staphylococcus aureus and Herpes simplex virus has implications for the management of the disease.
- Atopic dermatitis is a systemic disease which is a result of altered skin barrier and immune dysregulation.
- Of the 9 biologic therapies for which there is clinical trial or observational data in atopic dermatitis patients, only dupilumab has robust evidence of efficacy.
- Biologic agents, including dupilumab and nemolizumab have safety profiles similar to placebo.
- Guidelines and expert recommendations have been created and updated to help clinicians determine the appropriate treatment for their atopic dermatitis patients in a rapidly evolving landscape.
References


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