Consensus statement

CONSENSUS STATEMENT OF THE MANAGEMENT OF SEVERE, DIFFICULT-TO-TREAT ATOPIC DERMATITIS IN ADULTS AND ADOLESCENTS IN SOUTH AFRICA AND THE ROLE OF BIOLOGICS

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ABSTRACT

The first biological agent for treatment of moderate-to-severe atopic dermatitis (AD), dupilumab, has recently been introduced to South Africa and guidance is required as to its place in therapy. Consequently, an expert panel was convened to reach consensus on 14 statements relevant to contemporary management of AD and the use of dupilumab. In summary, the objectives of therapy are to reduce skin inflammation and pruritus, restore skin-barrier function, avoid flares, and improve quality of life. Useful comprehensive scoring tools to assess severity of AD and guide decisions to step up from topical to systemic therapy (including to a biologic agent), include SCORing Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI). In addition, a photographic record of pre-treatment and follow-up assessments is helpful. When systemic therapy is required, options include cyclosporin, which should be limited to short-term use, and off-label use of methotrexate. Systemic corticosteroids should be considered only in short courses for rescue therapy in the event of flares. New classes of medication for the treatment of moderate-to-severe AD are in various stages of development. The two most prominent classes of new therapies are biologics and small molecules. Dupilumab is the first fully humanised monoclonal antibody (MAB) biologic approved for the treatment of moderate-to-severe AD. It is an effective and well-tolerated, long-term treatment and has a favourable safety profile.

Keywords: atopic dermatitis, severe, biologics, adults, dupilumab

BACKGROUND

A detailed South African guideline for the management of atopic dermatitis (AD) was published in 2008.[1] It was revisited in 2014, and this later document was complemented by a series of detailed continuing medical education review articles relating to aetiology, diagnosis and management of AD.[2–8] Recently, a new biological treatment, dupilumab, has been introduced for management of moderate-to-severe AD and guidance is required on its place in therapy in South Africa. Because this does not warrant a full review of the previous AD guidelines, an expert panel was convened to reach consensus on statements relevant to contemporary management of AD and the use of dupilumab. A summary of the statements and the results are provided in Table I.

METHODS

An expert panel of South African allergists and dermatologists was convened early in 2020 to generate statements relevant to the use of dupilumab for the treatment of AD. Statements were generated based on a recent Canadian consensus document on the assessment and management of adult patients with moderate-to-severe AD[9] and during discussions among the group. Thereafter, the panel voted on the validity of each statement according to a 5-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree). The prespecified cut-off for consensus was set at 75% 'strongly agree' or 'agree' responses.

I. PATIENT-REPORTED OUTCOMES

Consensus statement 1: Patient-reported outcomes are helpful in assessing patient well-being, and in evaluating disease severity and treatment efficacy. Moderate-to-severe disease can be defined by:

i. POEM score ≥ 8

Consensus: 90% (Voting results: 3, 4, 4, 4, 5, 5, 5, 5, 5, 4)

ii. DLQI score ≥ 10

Consensus: 100% (Voting results: 4, 4, 4, 4, 5, 5, 5, 5, 5, 5)

iii. Pruritus NRS ≥ 4

Consensus: 90% (Voting results: 3, 4, 4, 4, 5, 5, 5, 5, 5, 5)

The panel reached consensus on these recommendations.

Rationale

AD is a chronic, relapsing, non-contagious, pruritic inflammatory skin disease.[10] In addition to pruritus, most patients also present with generalised skin dryness.[11] Because there is no specific test to define AD, clinical assessment and scoring systems are used to determine disease severity and monitor response to treatment. Except where the disease has continued from childhood and has typical characteristics of AD, the clinical presentation in adolescents and adults is variable, such that diagnosis is not always straightforward. Although the usual flexural dermatitis seen in children may be present, uncharacteristic morphological features (eg nummular, prurigo-like and follicular patterns) and localisation are common. Revised criteria for diagnosis of AD in adolescents and adults are presence of pruritus plus at least 3 of i. history of, or visible flexural dermatitis or involvement of cheeks and/or extensor surfaces; ii. history of dry skin in the past year; iii. history of asthma or hay fever; and iv. onset < 2 years.[2]

AD can have a significant impact on QoL (eg sleep disturbances, absenteeism, visible scratch marks, social withdrawal) and the panel agreed that subjective patient reported outcomes (PRO) are an important consideration when assessing disease, choosing treatment and assessing outcomes.[2,12,13] Although no single PRO tool provides a comprehensive assessment of all elements of AD, adding a PRO to objective assessment improves the ability to assess the overall impact of disease and treatment.[13] The Patient-Oriented Eczema Measure (POEM) is a simple, validated, repeatable tool to monitor disease severity and is the preferred scoring system to measure PROs. It evaluates seven symptoms experienced during the preceding week (itch, sleep, bleeding, weeping/oozing, cracking, flaking and dryness/roughness). Each symptom is rated on a 5-point scale (no days: 0 points; 1–2 days: 1 point; 3–4 days: 2 points; 5–6 days: 3 points; every day: 4 points) to give a score out of a maximum total of 28. Higher scores are associated with both more severe disease and worse QoL.[14]

The Dermatology Life Quality Index (DLQI) is a dermatology-specific (but not AD-specific) tool designed to assess the impact of skin disease on QoL (symptoms and feelings, daily activities, leisure, work and school, personal relationships and the impact of treatment). It comprises ten questions, each rated 0 to 3, depending on the impact of AD during the previous week. The maximum total score is 30. DLQI is reliable, responsive to change and has been extensively validated with respect to its psychometric properties and use in clinical research. Validated score banding (eg 0–1 indicates no effect on a patient's life, whereas 11–20 indicates a large effect) helps to inform clinical decision-making.[15]

A numeric rating scale (NRS) is a simple, commonly used method to quantify pruritus. Itch is rated from 0 to 10, where 0 represents 'no itch' and 10 represents 'worse itch imaginable'.[13]

Consensus was reached for cut-off scores indicating moderate-to-severe AD, namely, a score of ≥ 8 for POEM, ≥ 10 for DLQI and ≥ 4 on NRS.[13]

II. COMORBIDITIES

Consensus statement 2: Atopic comorbidities include asthma, AR, food allergy and ocular disorders. Depression and anxiety are also more prevalent in patients with AD. Healthcare-providers should be aware of these comorbidities and refer appropriately.

Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 5)

The panel reached consensus on this recommendation.

Rationale

AD is increasingly being recognised as a systemic disease, with signs of systemic inflammation, including systemic T-cell activation, dysregulation and activation of inflammatory cytokines, chronically activated memory B cells and higher levels of IgE antibodies.[10,16] The pathophysiology involves complex reciprocal interactions between a dysfunctional epidermal barrier, skin microbiome abnormalities and local, predominantly (but not exclusively) Type-2 inflammatory response. The Type-2 cytokines, including interleukin (IL)-4,

TABLE I: CONSENSUS STATEMENTS AND VOTING RESULTS

SECTION	CONSENSUS STATEMENT *Voting result: 1 = Strongly disagree; 2 = Disagree; 3 = Neither agree nor disagree; 4 = Agree; 5 = Strongly agree*
I. Patient-reported outcomes	1. Patient-reported outcomes are helpful in assessing patient well-being, and in evaluating disease severity and treatment efficacy moderate-to-severe disease can be defined by: i. POEM score ≥ 8 *Consensus: 90% (Voting results: 3, 4, 4, 4, 5, 5, 5, 5, 5, 5)* ii. DLQI score ≥ 10 *Consensus: 100% (Voting results: 4, 4, 4, 4, 5, 5, 5, 5, 5, 4)* iii. Pruritus NRS ≥ 4 *Consensus: 90% (Voting results: 3, 4, 4, 4, 5, 5, 5, 5, 5, 5)*
II. Comorbidities	2. Atopic comorbidities include asthma, allergic rhinitis (AR), food allergy and ocular disorders. Depression and anxiety are also more prevalent in patients with AD. Healthcare-providers should be aware of these comorbidities and refer appropriately. *Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 4)*
III. Aims of treatment and treatment response	3. The objectives of therapy are to reduce skin inflammation and pruritus, restore skin-barrier function, and improve quality of life (QoL). *Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)* 4. Response to treatment includes a reduction in the number of flares, an improvement in the patient's QoL and an ability to maintain remission or a low disease activity state. *Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)* 5. Uncontrolled disease is a failure to achieve stable long-term disease control. This includes the occurrence of flares (of any severity) or treatment with rescue oral corticosteroids. *Consensus 100% (Voting results: 4, 4, 4, 4, 5, 5, 5, 5, 5, 5)* 6. An adequate response is defined as: i. 50% reduction from baseline in the EASI score (EASI50), indicating clinical improvement. *Consensus 90% (Voting results: 3, 4, 4, 4, 4, 5, 5, 5, 5, 4)* ii. ≥ 4-point reduction in DLQI score, indicating decreased impairment and improved QoL. *Consensus 90% (Voting results: 3, 4, 4, 4, 4, 5, 5, 5, 5, 5)* iii. ≥ 1-point decrease in IGA score, indicating clinical improvement. *Consensus 80% (Voting results: 3, 3, 4, 4, 4, 4, 5, 5, 5, 5)*
IV. Systemic therapy	7. Consider systemic corticosteroids only in short courses as rescue therapy. *Consensus 90% (Voting results: 1, 4, 4, 5, 5, 5, 5, 5, 5, 5)* 8. According to clinical evidence and the registered indication, cyclosporin should not be used for long-term control of AD. Short-term use of cyclosporin, as recommended by the registered package insert, may be considered for rapid control in patients who experience acute flares or have unstable disease. *Consensus 100% (Voting results: 4, 4, 4, 5, 5, 5, 5, 5, 5, 5)* 9. Off-label use of methotrexate is an effective option for the treatment of moderate-to-severe AD. *Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 4)* 10. Discontinuation of a systemic therapy should be considered if there is no visible improvement in skin involvement or QoL, or in the event of severe adverse events. *Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 4)*
V. Dupilumab	11. Dupilumab is an effective and well tolerated long-term treatment option for patients with moderate-to-severe AD. *Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)* 12. The safety profile of dupilumab is reassuring from a clinician perspective, and it can be regarded as a safer option compared to other systemic therapies indicated for treatment of AD and currently being used in patients with severe AD. *Consensus 90% (Voting results: 3, 4, 4, 5, 5, 5, 5, 5, 5, 5)* 13. Dupilumab should be clinically positioned in patients with moderate-to-severe AD who are eligible for systemic therapy. *Consensus 100% (Voting results: 4, 4, 4, 5, 5, 5, 5, 5, 5, 5)*
VI. Scoring systems to support step-up in therapy	14. The following scoring systems are recommended for local use to support the decision to step-up therapy. i. SCORAD *Consensus 80% (Voting results: 3, 3, 4, 4, 5, 5, 5, 5, 5, 5)* ii. EASI *Consensus 90% (Voting results: 3, 4, 4, 4, 4, 5, 5, 5, 5, 5)* iii. POEM *Consensus 60% (Voting results: 1, 3, 3, 3, 4, 4, 4, 5, 5, 4)** iv. IGA *Consensus 60% (Voting results: 2, 2, 3, 3, 4, 4, 5, 5, 5, 4)** v. DLQI *Consensus 80% (Voting results: 3, 3, 4, 5, 5, 5, 5, 5, 5, 4)* *Consensus not reached

DLQI – Dermatology Life Quality Index; EASI – Eczema Area and Severity Index; IGA – Investigator Global Assessment; NRS – Numeric Rating Scale; POEM – Patient Oriented Eczema Measure; SCORAD – SCORing Atopic Dermatitis

-5, -13 and -31 produced by T-helper (Th) cells, keratinocytes and other inflammatory cells, play important roles in chemokine production, down-regulation of production of epidermal barrier proteins, suppression of antimicrobial peptides, pruritus and allergic inflammation. Furthermore, IL-31 induces sensory-nerve elongation and branching, which induces sensitivity to minimal stimuli and sustains chronic itch.[17,18]

AD usually begins in childhood and it is frequently associated with a number of other atopic diseases with overlapping pathophysiologies. These may manifest throughout life, and include food allergies, asthma, AR and allergic conjunctivitis. Especially during adulthood, patients with AD are also more likely to suffer from hand eczema and allergic contact dermatitis (ACD).[16,19] Approximately 30% of children with moderate-to severe AD have immediate-type (IgE-mediated) food allergy, but delayed-type hypersensitivity contributing to difficult-to-treat AD is rare. Those with moderate-to-severe AD have 50% risk of developing asthma and 75% risk of developing AR.[20] Although the historical concept of the 'atopic march' suggested a serial development of allergic conditions through childhood to adolescence and adulthood, this has not been proved in longitudinal studies. The progression is not uniform in all children and the association of AD with other allergic comorbidities is variable. Furthermore, each of the allergic diseases can first manifest at any point during life.[1,21]

In comparison to the general population, patients with AD are at higher risk for depression and anxiety.[22] Symptoms of depression tend to be more severe with increasing severity of AD and studies of adults and adolescents with AD show a positive association between AD severity and both suicidal ideation and completed suicide.[18] Treatment of AD reduces these risks. The presence of sleep disorders and/or mental health comorbidities may warrant more intensive systemic therapy to address the underlying inflammation and gain better long-term control of AD.[22]

Likewise, because management of comorbidities in patients with AD leads to improved overall clinical outcomes, clinicians should look actively for them and treat or refer as necessary.[18,23]

III. AIMS OF TREATMENT AND TREATMENT RESPONSE

Consensus statement 3: The objectives of therapy are to reduce skin inflammation and pruritus, restore skin-barrier function, and improve QoL.

Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)

Consensus statement 4: Response to treatment includes a reduction in the number of flares, an improvement in the patient's QoL and an ability to maintain remission or a low disease activity state.

Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)

Consensus statement 5: Uncontrolled disease is a failure to achieve stable long-term disease control. This includes the occurrence of flares (of any severity) or treatment with rescue oral corticosteroids.

Consensus 100% (Voting results: 4, 4, 4, 4, 5, 5, 5, 5, 5, 5)

Consensus statement 6: An adequate response is defined as:

i. 50% reduction from baseline in the EASI score (EASI50), indicating clinical improvement.

Consensus 90% (Voting results: 3, 4, 4, 4, 4, 5, 5, 5, 5, 4)

ii. ≥ 4-point reduction in DLQI score, indicating decreased impairment and improved QoL.

Consensus 90% (Voting results: 3, 4, 4, 4, 5, 5, 5, 5, 5, 4)

iii. ≥ 1-point decrease in IGA score, indicating clinical improvement.

Consensus 80% (Voting results: 3, 3, 4, 4, 4, 4, 5, 5, 5, 4)

The panel reached consensus on these recommendations.

Rationale

AD is a chronic disease characterised by recurrent flares and, at present, there is no curative treatment. Therefore, because symptoms significantly impact overall health and QoL, aims of management are to establish long-term disease control with sustained relief from symptoms and improved QoL.[10,11] Most patients present with dry skin. Emollients are the mainstay of treatment for AD. They may improve barrier function and, by increasing skin hydration, reduce xerosis, itch and flares. When used regularly, they may reduce the need for anti-inflammatory medication. Topical corticosteroids are the recommended first-line anti-inflammatory therapy, and they are commonly used as maintenance therapy to reduce the incidence of flares. Combined use of an emollient with a topical corticosteroid provides better symptom control than corticosteroid alone.[3,24,25] Topical calcineurin inhibitors may be used as alternatives to topical corticosteroids.[3,26]

Systemic therapies are indicated when control cannot be achieved with the appropriate use of topical treatments (ie potency/strength of formulation, frequency of application and duration of treatment). However, due to the safety profile of conventional systemic therapies, none are recommended for long-term use,[10] leaving some patients with suboptimal management and vulnerable to flares and recurrences.

There are no validated biomarkers to monitor treatment response in patients with AD. Therefore, assessment of treatment response relies on objective assessments of disease activity and patient-reported improvement in subjective symptoms and QoL.[13] The Investigator Global Assessment (IGA) is a frequently used outcome measure to evaluate global severity of skin signs (usually redness and induration). Signs are rated on a 5-point Likert scale from 0 to 4 (0 representing: 'clear'; 1: 'almost clear'; 2: 'mild'; 3: 'moderate' or 4: 'severe'). However, the IGA is not standardised or validated and, although achievement of IGA 0 or 1 has been the primary definition of treatment success in registration trials, in trials of dupilumab, significant improvement in signs, symptoms and QoL were observed regardless of IGA score (see Section V).[27,28] Therefore, the panel agreed that a reduction of IGA score ≥ 1 point may be clinically meaningful.

IV. SYSTEMIC THERAPY

Consensus statement 7: Consider systemic corticosteroids only in short courses as rescue therapy.

Consensus 90% (Voting results: 1, 4, 4, 5, 5, 5, 5, 5, 5, 4)

The panel reached consensus on this recommendation.

Rationale
In the event of a severe acute flare up, a short course of systemic corticosteroids may be considered, but another modality (systemic or phototherapy) should be initiated for longer term management of severe disease.[3,25,26] Adverse effects that limit long-term use of systemic corticosteroids include hypertension, glucose intolerance, gastritis, weight gain, decreased bone density, adrenal suppression and emotional lability. In addition, because discontinuation of oral or injectable corticosteroids frequently precipitates a rebound flare, repeated courses of systemic corticosteroids are not recommended.[10]

Consensus statement 8: According to clinical evidence and the registered indication, cyclosporin should not be used for long-term control of AD. Short-term use of cyclosporin, as recommended by the registered package insert, may be considered for rapid control in patients who experience acute flares or have unstable disease.
Consensus 100% (Voting results: 4, 4, 4, 5, 5, 5, 5, 5, 5, 4)

The panel reached consensus on this recommendation.

Rationale
Systemic cyclosporin is a non-selective immunosuppressive treatment that, especially with long-term use, may be associated with significant adverse effects. These include infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma.[10] However, it may be useful to gain control in patients with moderate-to-severe AD who are unresponsive to topical treatments. The panel were in agreement with current recommendations in the South African guideline that cyclosporin could be used short-term for severe, refractory AD.[1]

Consensus statement 9: Off-label use of methotrexate is an effective option for the treatment of moderate-to-severe AD.
Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 4)

The panel reached consensus on this recommendation.

Rationale
Methotrexate is not registered for use in patients with AD in South Africa. However, it has been used off-label for many years for moderate-to-severe AD, with good effect. A number of treatment guidelines recommend methotrexate for first- or second-line systemic treatment of moderate-to-severe disease and its use is supported by a limited number of randomised controlled trials, observational studies, and systematic reviews and meta-analyses.[9,10,25,26,29–39]

Consensus statement 10: Discontinuation of a systemic therapy should be considered if there is no visible improvement in skin involvement or QoL or in the event of severe adverse events.
Consensus 100% (Voting results: 4, 5, 5, 5, 5, 5, 5, 5, 5, 4)

The panel reached consensus on this recommendation.

Rationale
Inadequate clinical improvement, failure to achieve long-term stable disease control, presence of ongoing impairment (eg pruritus, pain, loss of sleep and poor QoL), unacceptable adverse events or poor tolerability experienced with treatment are signs of treatment failure.[10] Where it is conferring no clinical benefit or where risks of treatment outweigh benefits, systemic treatment for AD should be discontinued. If no response is noted (after three months of methotrexate or one month of cyclosporin) at adequate dosages an alternative systemic treatment should be offered.

V. DUPILUMAB

Consensus statement 11: Dupilumab is an effective and well-tolerated long-term treatment option for patients with moderate-to-severe AD.
Consensus 100% (Voting results: 4, 4, 5, 5, 5, 5, 5, 5, 5, 5)

Consensus statement 12: The safety profile of dupilumab is reassuring from a clinician perspective, and it can be regarded as a safer option compared to other systemic therapies indicated for treatment of AD and currently being used in patients with severe AD.
Consensus 90% (Voting results: 3, 4, 4, 5, 5, 5, 5, 5, 5, 5)

Consensus statement 13: Dupilumab should be clinically positioned in patients with moderate-to-severe AD who are eligible for systemic therapy.
Consensus 100% (Voting results: 4, 4, 4, 5, 5, 5, 5, 5, 5, 5)

The panel reached consensus on these recommendations.

Rationale
Dupilumab is a fully human monoclonal antibody that competitively binds to the shared α sub-unit of the interleukin (IL)-4 receptor and thereby inhibits IL-4 and IL-13 signal transduction. These cytokines are primarily produced by Th2 cells and, by blocking downstream signalling of IL-4 and IL-13, dupilumab alters the expression of genes and proteins that play a central role in the pathogenesis of AD.[40,41] Effects of dupilumab include down-regulation of inflammatory mediators and markers of epidermal proliferation, and upregulation of structural proteins, lipid metabolism proteins and epidermal barrier proteins, resulting in normalisation of skin.[40]

A series of phase 3 *(LIBERTY AD)* randomised placebo-controlled clinical trials (RCTs) demonstrated the clinical efficacy of dupilumab in moderate-to-severe AD inadequately controlled by topical medications (or where topical medications were contraindicated), either as monotherapy in adults *(SOLO 1* and *2*) and adolescents ≥ 12 to < 18 years of age (*ADOL*), or with concomitant administration of topical corticosteroids (*CHRONOS*) in adult patients.[42–46] A fourth study evaluated dupilumab plus topical corticosteroids in adult patients with inadequate response to, or intolerance of, cyclosporin A (*CAFÉ*).[47]

During 16 weeks of treatment, dupilumab was associated with meaningful improvements in objective signs of AD, subjective PROs (pruritus, pain and sleep disturbance), symptoms of anxiety and depression, and QoL. There were no significant differences in outcomes between weekly and biweekly (every two weeks) dosing schedules.

In the 16-week RCTs of adults with moderate-to-severe AD inadequately controlled by topical medications, in comparison

with placebo, significantly more patients treated with dupilumab monotherapy biweekly achieved ≥ 50% improvement in Eczema Area and Severity Index (EASI50) (67.0% vs 23.3%; $p < 0.0001$) and ≥ 4 point improvement in DLQI score (68.8% vs 29.0%; $p < 0.0001$).[42] Improvement in Investigator's Global Assessment (IGA) after treatment with dupilumab was associated with significant improvements in several outcome measures, including EASI, pruritus, affected body surface area, POEM and DLQI. This was not only true for patients with IGA < 1 at 16 weeks, but also for patients with IGA > 1 and across sub-groups of patients with IGA score 2, 3 or 4.[27,45]

The overall incidence of adverse events was similar in the dupilumab and placebo groups. The most frequent adverse events associated with dupilumab, and which occurred more frequently than with placebo, were conjunctivitis and injection site reactions. These were generally mild. Serious adverse events were more common (approximately two-fold) among patients receiving placebo, and fewer patients receiving dupilumab required rescue therapy for intolerable symptoms. Extension studies show that clinical responses are sustained with long-term treatment for up to 52 and 76 weeks, with no new safety signals.[20,46,48] In both the initial RCTs and extension studies, there were no clinically important changes in routine laboratory parameters that could be attributed to dupilumab.[46,49]

In contrast to alternative systemic treatments for AD, dupilumab is not an immunosuppressant. By specifically targeting overactive inflammatory pathways involved in the pathogenesis of AD, it improves skin-barrier integrity and changes the cutaneous microbiome.[50] In a 16-week study of patients with moderate-to-severe AD, treatment with dupilumab was associated with reduced density of *Staphylococcus aureus* and increased microbial diversity in both lesional and non-lesional skin.[51] Furthermore, dupilumab appears to improve immunologic protection against infection. In a population-based claims data study of adult patients with AD, the incidence of serious infections was 7.53 per 1 000 among patients treated with systemic non-biologics, 7.38 per 1 000 treated with phototherapy and 2.6 per 1 000 treated with dupilumab.[52] In clinical trials, in comparison to placebo, dupilumab was associated with a similar overall infection rate, but reduced risk of severe infections, skin infections and clinically important herpesviral infections (eczema herpeticum or herpes zoster).[53]

Immunogenicity is a concern with biological therapies. Approximately 7% of patients receiving dupilumab in the 16-week studies developed anti-drug antibodies (ADA), of which 30% were classified as neutralising.[40] In a 72-week open-label extension study, including 1 491 adults who had participated previously in phase 1 through 3 clinical trials, the incidence of treatment-emergent ADAs in the overall population was 2.8%. However, no patients had high titre levels and, in comparison with ADA-negative patients, there was no difference in functional dupilumab concentrations or treatment efficacy in those who were ADA-positive.[20]

Several real-world evidence studies from Spain, Italy, Austria, Canada and the United States, have reported on dupilumab use in routine clinical practice, with treatment durations of up to one year.[54–58] In adults with moderate-to-severe AD, dupilumab treatment was associated with rapid and significant improvement in objective and subjective clinical parameters, psychosocial impact and QoL. Response rates were similar or higher than those observed in clinical trials. Dupilumab was generally well tolerated, with high patient satisfaction and adherence to treatment. The most commonly reported adverse event was mild conjunctivitis. In a retrospective cohort study including data from 1 963 adults who initiated treatment with dupilumab, persistence at six and 12 months was 91.9% and 77.3%, respectively.[58] Among patients who discontinued dupilumab, the risk of reinitiation was 78.8% within an average of four months.

There are no head-to-head studies comparing dupilumab with other systemic therapies for AD. A large systematic review of the literature and meta-analysis including 39 trials with 6 360 subjects, showed that dupilumab and cyclosporin were similarly effective in comparison with placebo in clearing clinical signs of AD during the first four months of therapy, and may be superior to methotrexate and azathioprine.[29] An indirect comparison of results from patients treated with dupilumab in the CHRONOS study and patients treated with cyclosporin in clinical practice showed that dupilumab was associated with significantly more patients achieving 50% and 75% improvement on EASI score at weeks 12 to 16 and at weeks 24 to 30.[59]

Consensus-based European guidelines for treatment of AD recommend dupilumab as a disease-modifying drug for long-term maintenance in patients with moderate-to-severe AD, in whom topical treatment is not sufficient and other systemic treatment is not advisable. It is administered by subcutaneous injection as an initial dose of 600 mg, followed by 300 mg given every other week and should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed.[26,60]

VI. SCORING SYSTEMS TO SUPPORT STEP-UP IN THERAPY

Consensus statement 14: The following scoring systems are recommended for local use to support the decision to step-up therapy:

i. SCORAD

Consensus 80% (Voting results: 3, 3, 4, 4, 5, 5, 5, 5, 5, 5)

ii. EASI

Consensus 90% (Voting results: 3, 4, 4, 4, 4, 5, 5, 5, 5, 5)

iii. POEM

Consensus 60% (Voting results: 1, 3, 3, 3, 4, 4, 4, 5, 5, 5)

iv. IGA

Consensus 60% (Voting results: 2, 2, 3, 3, 4, 4, 5, 5, 5, 5)

v. DLQI

Consensus 80% (Voting results: 3, 3, 4, 5, 5, 5, 5, 5, 5, 5)

The panel reached consensus that the SCORing Atopic Dermatitis (SCORAD), EASI and DLQI were suitable AD scoring systems for local use. Photographs of the skin at the initial consultation and follow-up visits are helpful to complement AD scoring results, track progress with therapy and support application to funders for reimbursement of medication costs.

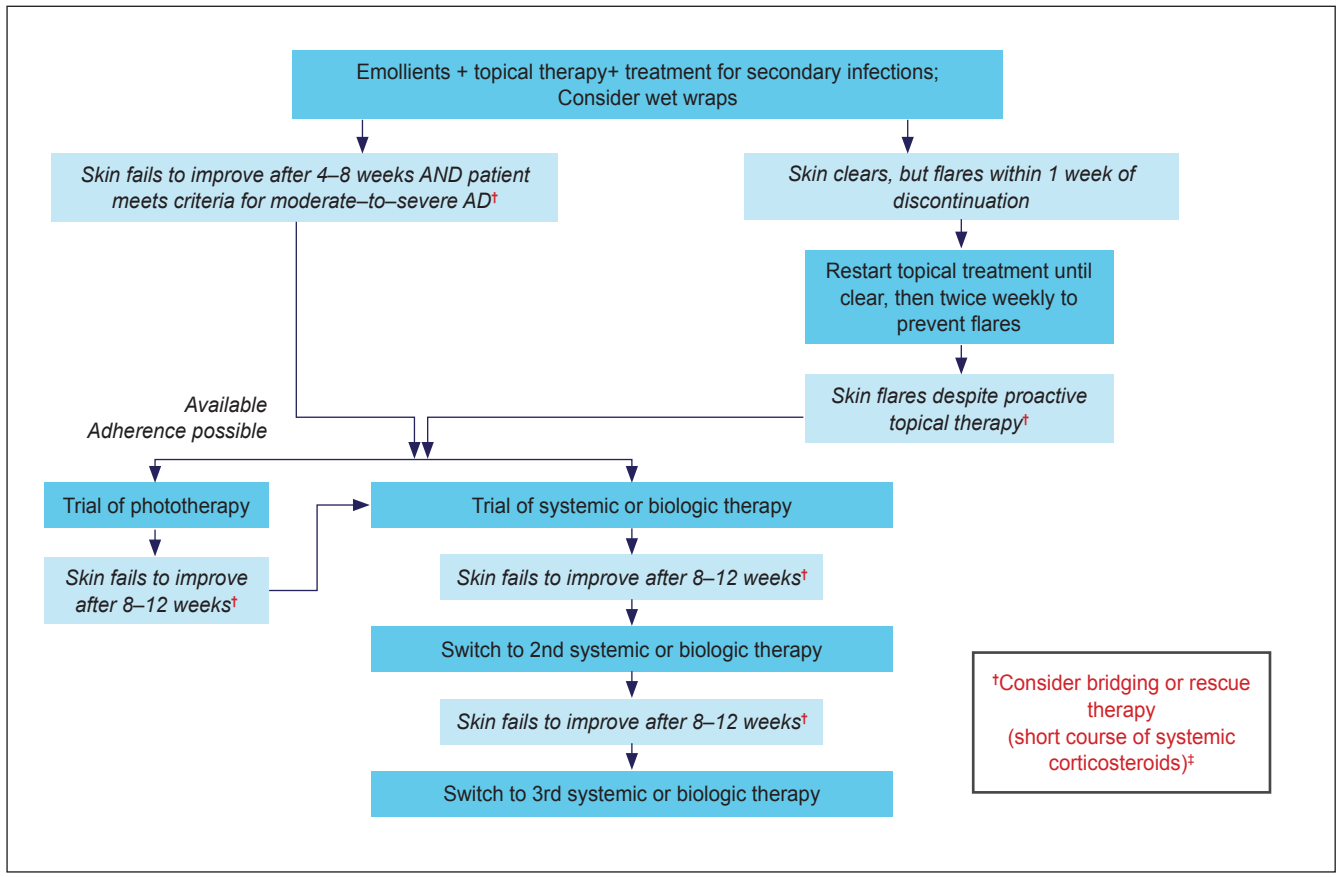

Figure 1: Step-wise approach to management of moderate-to-severe AD in adolescents and adults
**Wet wraps are cream or ointment applied to the skin, then covered by a double layer of cotton bandages, with a moist first layer and a dry second layer and kept in place for 24 hours.[1]*

‡Systemic corticosteroids are a last resort and should be considered only for short-term management of flares.
[Adapted from Lynde CW, Bourcier M, Gooderham M, et al. Review J Cutan Med Surg *2018;22(1):78–83.64 Copyright© 2017 (The authors). Adapted with permission of SAGE publications, Inc.]*

Rationale

There are a number of scoring systems for AD, none of which on their own captures the full extent and impact of AD. The EASI is one of the best validated scoring systems for assessing disease severity and it has been found to be feasible and acceptable in terms of ease of use in both clinical trials and everyday practice. It has a short administration time; and adequate validity, sensitivity to change, internal consistency, and intra-observer reliability.[61,62] However, it does not assess subjective symptoms, which are important for assessing patient morbidity and disease severity.[63]

SCORAD is the most widely validated disease-severity instrument. In addition to measuring disease severity, it also assesses two subjective symptoms, pruritus and sleep loss. It is valid and reliable and has shown excellent agreement with global assessments of disease severity.[63]

Clinical judgement is necessary to assess the overall impact of AD. In addition to scoring disease severity, it is important to make an ongoing assessment of disease recurrences, flares, involvement of functionally important or highly visible areas (eg face, hands, genitals), PROs and persistence with treatment.[9]

VII. MANAGEMENT ALGORITHM

A suggested step-wise approach for treatment of AD is presented in Figure 1.

Step-up to systemic therapy is appropriate for patients with moderate-to-severe AD with significant persistent symptoms despite optimal topical therapy (potency, frequency of application and duration of treatment). Quick and simple symptom measures that can be incorporated into everyday clinical practice and cut-off scores at which systemic therapy could be considered include: (1) pruritus NRS ≥ 4; (2) body surface area (BSA) ≥ 10%; (3) investigator/physician global assessment score (IGA/PGA) ≥ 3; and (4) DLQI score ≥ 10.[64]

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DECLARATION OF CONFLICT OF INTERESTS

Professor Levin is on advisory boards for Bayer and

Pharmadynamics and is principal investigator on a clinical trial for dupilumab (Sanofi); Dr Raboobee is a medical advisor to SkinTECH; Dr Visser has received honoraria from Meda Pharma. Dr Kannenberg*+§, Dr Karabus§, Prof Levin*+§, Dr Mabelane*+§, Dr Manjra+§, Dr Pillay*+§, Dr Raboobee*+§, Dr Singh*§, Dr Weiss*+§ and Dr Visser*+§ have received honoraria from Sanofi for participation in advisory boards*, speaker engagements+ and medical education activities§. The authors report no other conflicts of interest related to this work.

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