



Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy

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Abstract: Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases. The prevalence of AD is increasing and is currently estimated at 10–20% in adults worldwide. In the majority of patients, AD can be adequately controlled with topical treatment or ultraviolet light therapy, but there is a high unmet need for effective and safe therapeutics in patients with more severe or difficult to treat AD. During the past decade, new advances in the understanding of the underlying immune pathogenesis of AD have led to the development of new, more targeted therapies. Dupilumab, a fully human monoclonal antibody targeting the interleukin (IL)-4 receptor α , thereby blocking the IL-4 and IL-13 pathway, is one of the first biologics that has been developed for AD. Dupilumab has shown promising results in phase III trials and has recently been approved by the US Food and Drug Administration and the European Commission for the treatment of moderate to severe AD. With the approval of dupilumab, we are entering a new era of biological therapeutics in AD management. The place of dupilumab should be established in the current treatment standards. Based on current treatment guidelines and experts' opinions in the management of AD, we have built a proposal for a treatment algorithm for systemic treatment of AD in European countries.

Keywords: atopic dermatitis, dupilumab, biologics, interleukin-4, interleukin-13, systemic treatment

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Introduction

Atopic dermatitis (AD) is one of the most common chronic and relapsing inflammatory skin diseases worldwide. The lifetime prevalence of AD has increased in the past decades and is currently estimated at 10–20% in developed countries.¹ Cutaneous inflammation and intense pruritus are the clinical hallmarks of AD and the associated sleep deprivation and social stigmatization causes a significant effect on the psychosocial wellbeing of patients and their relatives. Additionally, AD is associated with a substantial economic burden derived from direct but also indirect costs caused by missed work and school, reduced work productivity and costs associated with medical visits.^{2,3}

In the majority of patients, AD can be adequately controlled with topical corticosteroids, topical immunomodulators, or ultraviolet (UV) light

therapy. However, in case of more severe or difficult to treat AD, treatment with systemic immunosuppressive drugs may be required.⁴ The last breakthrough in the systemic immunosuppressive treatment of AD was reported in 1991 for the use of cyclosporine A for the treatment of severe, refractory AD.

Until now, cyclosporine A was the only oral immunosuppressive drug officially approved for the treatment of AD in many European countries. However, in nearly half of the patients, treatment with cyclosporine A has to be discontinued due to ineffectiveness or both patient-reported and clinician-reported (nephrotoxicity and hypertension) side effects.⁵ In the US, the only approved systemic drugs for the treatment of AD are oral corticosteroids. However, there is international consensus that the use of oral corticosteroids

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should be limited to short-term use due to their side-effect profile and the risk of severe rebound flares after discontinuation.⁶ Several other drugs are used off-label for the treatment of moderate to severe AD in daily practice, including azathioprine, methotrexate, mycophenolate mofetil, and enteric-coated mycophenolate sodium. Most of these drugs are incorporated in international guidelines and are suggested for AD treatment when cyclosporine A is ineffective, leads to side effects, or in the case of contraindications. However, many patients treated with second-line oral immunosuppressive drugs have to discontinue treatment because of ineffectiveness or side effects.^{5,7} Moreover, long-term effectiveness and safety data of these off-label drugs are scarce.

During the past decade, the increased understanding of the underlying immune pathogenesis of AD has led to the development of new, more targeted therapies. Dupilumab, a fully human monoclonal antibody targeting the interleukin (IL)-4 receptor α , thereby blocking both the IL-4 and IL-13 pathway, is the first antibody-based treatment for AD. Dupilumab has shown promising results in phase III trials and has recently been approved by the US Food and Drug Administration (FDA) and the European Commission (EC) for the treatment of moderate to severe AD.^{8,9} The approval of dupilumab will lead to a new era of antibody-based therapeutics in AD management and may address the large unmet needs in the treatment of AD. Besides dupilumab, more targeted systemic therapies are being developed and are currently under investigation, including agents targeting IL-4 (pitrakinra), IL-5 (mepolizumab), IL-13 (tralokinumab and lebrikizumab), IL-31 (nemolizumab), thymic stromal lymphopoietin (TSLP) (tezepelumab) and janus kinase (JAK) pathways (upadacitinib and baricitinib).

In this review we will discuss the results of dupilumab treatment for AD, based on the results of recent clinical trials and we will discuss the future place of dupilumab in the treatment of AD.

Immunopathogenesis of AD and effects of dupilumab treatment

AD is a complex and heterogeneous chronic, inflammatory skin disease with a multifactorial pathogenesis. The two major factors contributing to this multifactorial pathogenesis are epidermal barrier disruption and abnormalities in the adaptive immune system. It remains an unresolved

issue whether the barrier disruption precedes immune alterations ('outside-in' hypothesis) or immune dysregulation precedes barrier disruption ('inside-out' hypothesis).¹⁰ However, it is also known that these two factors are closely related to each other. Epidermal barrier disruption leads to increased transepidermal water loss and increased permeation of exogenous stimuli such as allergens, irritants, and microbes, which induce activation of the immune system. Cytokines produced by an activated immune system, however, also lead to an affected epidermal barrier.¹¹⁻¹⁴

AD lesional skin reflects the hyperactive immune system: it is characterized by infiltration of a large number of inflammatory cells, including dendritic cells (DCs), eosinophils, mast cells, immunoglobulin E (IgE)-producing plasma cells, but especially numerous T cells.¹⁵⁻¹⁷ AD is considered a primarily T helper 2 (Th2) cell-driven disease, as Th2-related markers (IL-4, IL-5, and IL-13) are highly expressed in lesional AD skin compared with nonlesional skin.¹⁸ Although AD is thought to be a mainly Th2-driven disease, recent literature has shown that the Th22 and Th17 pathways have also been shown to contribute to the pathogenesis of AD.^{16,19}

Since the Th2-signature cytokines IL-4 and IL-13 are considered to play a central role in the pathogenesis of AD, they have been identified as targets for the development of new therapeutic agents. Dupilumab inhibits the signalling of IL-4 and IL-13 by blocking the shared α subunit of the IL-4 receptor. IL-4 and IL-13 act on various cells involved in the pathogenesis of AD: both cytokines promote IgE class switching, stimulate eosinophil recruitment, and induce Th2 cell survival and activation.^{20,21} Furthermore, IL-4 and IL-13 act on keratinocyte differentiation and downregulate the production of filaggrin (filament aggregating protein) and cell adhesion molecules, contributing to skin barrier defects.^{22,23}

Dupilumab has been shown to normalize the expression of Th2 inflammatory molecules and reverse barrier abnormalities. In a mechanistic study by Hamilton and colleagues gene expression of pre- and post-treatment lesional and nonlesional skin was analyzed.²⁴ Biopsies were obtained from 18 adult patients with moderate to severe AD who participated in two phase I clinical trials in which patients were treated with dupilumab 150 mg or 300 mg weekly or placebo for 4 weeks. Disease severity, assessed by the Eczema Area and Severity Index (EASI), significantly improved in patients

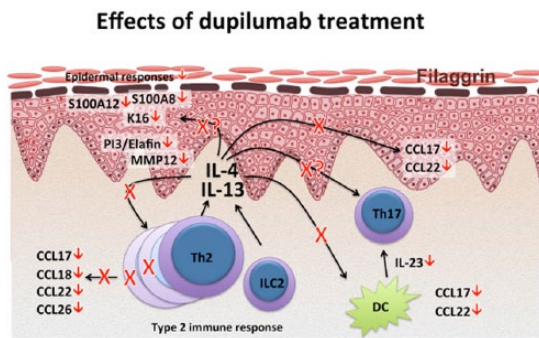


Figure 1. Schematic representation of pathways influenced by dupilumab treatment on lesional atopic dermatitis (AD) skin. This figure was reproduced with permission of the publisher from Brunner *et al.*²⁵ The ↓ represent a downregulation of specific inflammatory mediators, the X represents immunologic pathways blocked by dupilumab. The efficacy of dupilumab demonstrates the role of T helper 2 (Th2) cytokine pathways in the pathogenesis of AD. However, Th17 and Th22-associated mediators, such as S100 proteins and PI3/Elafin, are also strongly decreased by dupilumab treatment and might have a role in AD development. DC, dendritic cell; ILC2, group 2 innate lymphoid cells; K16, keratin 16; MMP12, matrix metalloproteinase 12; PI3, peptidase inhibitor 3.

treated with dupilumab compared with the placebo group. Dupilumab significantly downregulated genes encoding multiple inflammatory mediators (MMP12 and S100A12), Th2-associated molecules (CCL17, CCL18, and CCL26) and epidermal proliferation markers, such as K16 (Figure 1). Furthermore, significant increases in lipid product levels and the expression of epidermal differentiation genes were seen in dupilumab-treated AD skin. These molecular changes induced by dupilumab treatment were dose dependent and correlated with clinical improvement.²⁴

Clinical data from phase III randomized controlled trials

The efficacy and safety of dupilumab were evaluated in recent randomized, double-blind, placebo-controlled clinical trials (two phase I studies, two phase IIa studies, one phase IIb study and four phase III studies).^{8,9,26,27} Study characteristics and key study results are summarized in Table 1 (study characteristics) and Table 2 (clinical scores and patient-related outcomes).

The results of two identical randomized, placebo-controlled, phase III studies (SOLO I and SOLO

II) investigating the efficacy of dupilumab in 671 and 708 (SOLO I and SOLO II respectively) patients with moderate to severe AD with inadequate response to topical corticosteroid treatment were reported by Simpson and colleagues.⁹ Patients were treated with dupilumab monotherapy 300 mg once a week, 300 mg every 2 weeks, or placebo for 16 weeks. Dupilumab monotherapy significantly improved signs and symptoms of AD, including pruritus, sleep deprivation, and quality of life compared with placebo. The primary outcome of an Investigator's Global Assessment (IGA) 0 (clear) or 1 (almost clear) or reduction of at least two points was achieved in 36–37% of the patients treated with dupilumab 300 mg weekly and in 36–38% of the patients treated with dupilumab 300 mg every other week compared with 8–10% in the placebo arm ($p < 0.001$ for both comparisons with placebo). The least-squares mean percent change in the EASI from baseline to week 16 was 69–72% in the dupilumab 300 mg weekly groups and 67–72% in patients treated with dupilumab 300 mg every other week compared with 31–38% in the placebo arms ($p < 0.001$ for the comparison of each dupilumab group *versus* placebo). The key secondary endpoint of an improvement from baseline of at least 75% on the EASI (EASI-75) was reported in 44–52% of patients in the dupilumab arms compared with 12–15% in patients treated with placebo ($p < 0.001$ for the comparison of each dupilumab group *versus* placebo).

Blauvelt and colleagues reported the results of a 1-year, randomized, double-blind, placebo-controlled phase III trial investigating the long-term efficacy and safety of dupilumab combination therapy with topical corticosteroids in 740 patients with AD.⁸ Patients were assigned to receive dupilumab 300 mg weekly, 300 mg every other week, or placebo. All three groups were concomitantly treated with medium-potency or low-potency topical corticosteroids (TCS) or topical calcineurin inhibitors. At week 16, the primary endpoint of IGA 0/1 or a reduction from baseline of at least two points was achieved in 39% of patients who received dupilumab 300 mg weekly (+TCS) and in 39% of patients treated with dupilumab 300 mg every other week (+TCS) *versus* 12% of patients who received placebo (+TCS) ($p < 0.001$). Similar results were found at week 52 with 40% of patients achieving an IGA 0/1 in the dupilumab 300 mg weekly (+TCS) group and 36% in the dupilumab 300 mg every other week (+TCS) group, compared with 13%

Table 1. Characteristics of dupilumab studies in atopic dermatitis (AD).

Reference	Study	Study design	Phase	Population	Subjects (n)	Treatment duration	Study drug (dupilumab, dose)	Outcome measures
Beck <i>et al.</i> ²⁷	1: M4A 2: M4B 3: M12 4: C4	Randomized, double-blind, placebo-controlled trials (4 subtrials)	I-II	Moderate-severe AD (IGA ≥ 3)	1: 30 2: 37 3: 109 4: 31	1: 4 weeks 2: 4 weeks 3: 12 weeks 4: 4 weeks	1: 75 mg weekly, 150 mg weekly, 300 mg weekly or placebo 2: 150 mg weekly, 300 mg weekly or placebo 3: 300 mg weekly or placebo 4: 300 mg weekly + TCS or placebo + TCS	EASI, BSA, IGA, pruritus (VAS)
Thaçi <i>et al.</i> ²⁶	-	Randomized, double-blind, placebo-controlled trial	IIb	Moderate-severe AD (EASI ≥ 16 , IGA ≥ 3 , BSA $\geq 10\%$)	380	12 weeks	300 mg weekly, 300 mg every other week, 200 mg every other week, 300 mg every 4 weeks, 100 mg every 4 weeks or placebo	EASI, BSA, IGA, pruritus (VAS)
Simpson <i>et al.</i> ⁹	1: S0L01 2: S0L02	Randomized, double-blind, placebo-controlled trial (2 subtrials)	III	Moderate-severe AD (IGA ≥ 3)	1: 671 2: 708	16 weeks	300 mg weekly, 300 mg every other week, or placebo	EASI, BSA, IGA, pruritus (VAS)
Blauvelt <i>et al.</i> ⁸	LIBERTY AD CHRONOS	Randomized, double-blind, placebo-controlled trial	III	Moderate-severe AD (EASI ≥ 16 , IGA ≥ 3)	740	52 weeks	300 mg weekly + TCS, 300 mg every other week + TCS, or placebo + TCS	EASI, BSA, IGA, pruritus (VAS)
de Bruin-Weller <i>et al.</i> ²⁸	LIBERTY AD CAFÉ	Randomized, double-blind, placebo-controlled trial	III	Moderate-severe AD (EASI ≥ 20 , IGA ≥ 3), not adequately controlled with or intolerant to CsA or when this treatment is medically inadvisable	325	16 weeks	300 mg weekly + TCS, 300 mg every other week + TCS, or placebo + TCS	EASI, BSA, IGA, pruritus (VAS)
BSA, body surface area, CsA; cyclosporine A; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid; VAS, Visual Analog Scale.								

Table 2. Clinical scores and patient-related outcomes of dupilumab studies.

Study	Study	EASI outcome	IGA	BSA	Pruritus (VAS)
Beck <i>et al.</i> ²⁷	1: M4A 2: M4B 3: M12 4: C4	1 and 2: EASI-50 in 59% dupilumab <i>versus</i> 19% placebo, EASI-75 in 29% dupilumab <i>versus</i> 6% placebo 3: EASI-50 in 85% dupilumab <i>versus</i> 35% placebo, EASI-75 in 62% dupilumab <i>versus</i> 15% placebo 4: EASI-50 in 100% dupilumab <i>versus</i> 50% placebo, EASI-75 in 62% dupilumab <i>versus</i> 40% placebo	1 and 2: 0 [clear] or 1 [almost clear] in 12% dupilumab <i>versus</i> 6% in placebo group 3: 0 [clear] or 1 [almost clear] in 40% dupilumab <i>versus</i> 7% in placebo group 4: 0 [clear] or 1 [almost clear] in 52% dupilumab <i>versus</i> 30% in placebo group	1 and 2: -37% in dupilumab <i>versus</i> -15% in placebo group 3: -60% in dupilumab <i>versus</i> -18% in placebo group 4: -64% in dupilumab <i>versus</i> -37% in placebo group	1 and 2: -41 in dupilumab <i>versus</i> -19 in placebo group 3: -56 in dupilumab <i>versus</i> -15 in placebo group 4: -71 in dupilumab <i>versus</i> -25 in placebo group
Thaçi <i>et al.</i> ²⁶	-	EASI-50 in 83% dupilumab 300 mg weekly group <i>versus</i> 30% in placebo group, EASI-75 in 62% dupilumab 300 mg weekly <i>versus</i> 15% in placebo group	0 [clear] or 1 [almost clear] in 33% dupilumab 300 mg weekly, 30% in 300 mg every other week, 28% in 200 mg every other week, 22% in 300 mg every 4 weeks, 12% in 100 mg every 4 weeks <i>versus</i> 2% in placebo group	-66% in dupilumab 300 mg weekly, -52% in 300 mg every other week, -55% in 200 mg every other week, -49% in 300 mg every 4 weeks, -26% in 100 mg every 4 weeks <i>versus</i> -8 in placebo group	-47% in dupilumab 300 mg weekly, -40% in 300 mg every other week, -34% in 200 mg every other week, -33% in 300 mg every 4 weeks, -16% in 100 mg every 4 weeks <i>versus</i> 5% in placebo group
Simpson <i>et al.</i> ⁹	1: S0L01 2: S0L02	1: EASI-50 in 61% 300 mg weekly, 69% 300 mg every other week <i>versus</i> 25% in placebo, EASI-75 in 52% 300 mg weekly, 51% 300 mg q2w <i>versus</i> 15% in placebo 2: EASI-50 in 61% 300 mg weekly, 65% 300 mg every other week <i>versus</i> 22% in placebo, EASI-75 in 48% 300 mg weekly, 44% 300 mg every other week <i>versus</i> 12% in placebo	1: 0 [clear] or 1 [almost clear] or reduction of ≥ 2 points from baseline in 37% in dupilumab 300 mg weekly, 38% 300 mg every other week <i>versus</i> 10% in placebo 2: 0 [clear] or 1 [almost clear] or reduction of ≥ 2 points from baseline in 36% in dupilumab 300 mg weekly, 36% 300 mg every other week <i>versus</i> 8% in placebo	1: -34% in dupilumab 300 mg weekly, -33% in 300 mg every other week <i>versus</i> 15% in placebo group 2: -32% in dupilumab 300 mg weekly, -31% in 300 mg every other week <i>versus</i> 13% in placebo group	1: improvement ≥ 4 points from baseline in 40% dupilumab 300 mg weekly, 41% in 300 mg every other week <i>versus</i> 12% in placebo group 2: improvement ≥ 4 points from baseline in 39% dupilumab 300 mg weekly, 36% in 300 mg every other week <i>versus</i> 10% in placebo group

(Continued)

Table 2. (Continued)

Study	Study	EASI outcome	IGA	BSA	Pruritus (VAS)
Blauvelt <i>et al.</i> ⁸	LIBERTY AD CHRONOS	week 16: EASI-50 in 78% weekly + TCS, 80% every other week + TCS <i>versus</i> 37% in placebo + TCS; EASI-75 in 64% weekly + TCS, 69% every other week + TCS <i>versus</i> 23% in placebo + TCS week 52: EASI-50 in 70% weekly + TCS, 79% every other week + TCS <i>versus</i> 30% in placebo + TCS; EASI-75 in 64% weekly + TCS, 65% every other week + TCS <i>versus</i> 22% in placebo + TCS	week 16: 0 (clear) or 1 (almost clear) or reduction of ≥ 2 points from baseline in 39% dupilumab 300 mg weekly + TCS, 39% in 300 mg every other week + TCS <i>versus</i> 12% in placebo group week 52: 0 (clear) or 1 (almost clear) or reduction of ≥ 2 points from baseline in 40% dupilumab 300 mg weekly + TCS, 36% in 300 mg every other week + TCS <i>versus</i> 13% in placebo group	week 16: -37% in dupilumab 300 mg weekly + TCS, -39% in 300 mg every other week + TCS <i>versus</i> -19% in placebo group week 52: -40% dupilumab 300 mg weekly + TCS, -42% in 300 mg every other week + TCS <i>versus</i> -20% in placebo group	week 16: improvement ≥ 4 points from baseline in 51% dupilumab 300 mg weekly + TCS, 59% in 300 mg every other week + TCS <i>versus</i> 20% in placebo group week 52: improvement ≥ 4 points from baseline in 39% dupilumab 300 mg weekly + TCS, 51% in 300 mg every other week + TCS <i>versus</i> 13% in placebo group
de Bruin-Weller <i>et al.</i> ²⁸	LIBERTY AD CAFÉ	EASI-50 in 86% weekly + TCS, 85% every other week + TCS <i>versus</i> 44% in placebo + TCS; EASI-75 in 59% weekly + TCS, 63% every other week + TCS <i>versus</i> 30% in placebo + TCS	0 (clear) or 1 (almost clear) or reduction of ≥ 2 points from baseline in 39% dupilumab 300 mg weekly + TCS, 40% in 300 mg every other week + TCS <i>versus</i> 14% in placebo group	-38% in dupilumab 300 mg weekly + TCS, -39% in 300 mg every other week + TCS <i>versus</i> -20% in placebo group	improvement ≥ 4 points from baseline in 40% dupilumab 300 mg weekly + TCS, 46% in 300 mg every other week + TCS <i>versus</i> 14% in placebo group
BSA, body surface area; CsA, cyclosporine A; EASI, Eczema Area and Severity Index; TCS, topical corticosteroids; VAS, Visual Analog Scale.					

in the placebo (+TCS) arm [$p < 0.0001$ for the comparison of each dupilumab (+TCS) group *versus* placebo (+TCS)]. The coprimary endpoint of EASI-75 at week 16 was reached in 64% of patients who received dupilumab 300 mg weekly (+TCS) and in 69% who received dupilumab 300 mg every other week (+TCS) compared with 23% treated with placebo [$p < 0.0001$ for the comparison of each dupilumab (+TCS) group *versus* placebo (+TCS)]. At week 52, the EASI-75 endpoint was achieved in 64% of patients in the dupilumab 300 mg weekly (+TCS) and in 65% of patients in the 300 mg every other week (+TCS) groups *versus* 22% of patients in the placebo (+TCS) group [$p < 0.0001$ for the comparison of each dupilumab (+TCS) group *versus* placebo (+TCS)].

The most recent published study of de Bruin-Weller and colleagues reported the results of a 16-week, phase III, randomized, double-blind, placebo-controlled trial involving patients with AD and a history of failure on treatment with cyclosporine A (ineffectiveness or side effects) or with contraindications for cyclosporine A treatment.²⁸ Concomitant treatment with a medium potency TCS was allowed. Patients were randomized in a 1:1:1 ratio to receive dupilumab 300 mg weekly, every other week, or placebo, with respectively 110, 107, and 108 patients randomized to each group. Dupilumab (+TCS) significantly improved all measures of clinical efficacy *versus* placebo (+TCS). The primary endpoint of EASI-75 at week 16 was reached in 59% of the patients treated with dupilumab weekly (+TCS) and in 63% of the patients treated with dupilumab every other week +TCS, compared with 29.6% of patients who received placebo (+TCS) ($p < 0.0001$). Among the subgroup of patients with prior exposure to CsA, significantly more patients receiving dupilumab (+TCS) weekly or every other week achieved EASI-75 (57% and 58% respectively) compared with the placebo (+TCS) group (26%, $p < 0.001$). At week 16, the secondary outcome of IGA 0/1 or at least a two-point reduction from baseline was achieved in 40% of patients who received dupilumab (+TCS) weekly and in 39% of patients treated with dupilumab (+TCS) every other week *versus* 14% of patients in the placebo (+TCS) group ($p < 0.0001$).

Treatment with dupilumab resulted in improvement of pruritus symptoms as measured by the pruritus Numerical Rating Scale (NRS) in all four phase III randomized, double-blind,

placebo-controlled trials.^{8,28,29} During dupilumab treatment, other clinically relevant patient-reported outcomes including sleep and health-related quality of life significantly improved as well.

Overall, dupilumab was well tolerated in all trials and has shown a favourable safety profile with no dose-limiting toxicity.^{8,9,26–29} The dupilumab-treated groups had higher rates of injection-site reactions, mostly mild or moderate, and localized herpes simplex infections than patients treated with placebo. The incidence of conjunctivitis (including conjunctivitis of unknown cause, bacterial conjunctivitis, viral conjunctivitis, allergic conjunctivitis and atopic keratoconjunctivitis) was higher in the dupilumab-treated patients (5–28%) than in patients treated with placebo (1–11%).^{8,28,29} Conjunctivitis developed more often in patients with severe AD or coexisting allergic conjunctivitis.²⁹ Symptoms of conjunctivitis were mostly mild or moderate and resolved with topical eye treatment during the study. The pathogenesis of conjunctivitis occurring during dupilumab treatment remains unclear and needs further investigation. Higher rates of conjunctivitis were not reported in patients treated with dupilumab in trials involving patients with asthma or nasal polyposis, suggesting a unique AD-specific underlying mechanism.²⁹

Place of dupilumab in AD treatment

Before the approval of dupilumab, systemic corticosteroids were the only FDA-approved systemic treatment for AD in the US. As systemic corticosteroids are not recommended for long-term use, dupilumab was recently recommended as a first-line systemic treatment option for patients with moderate to severe AD by a steering committee of AD experts in the US.³⁰ Although cyclosporine A is registered for AD in most European countries, it is not always the first choice treatment in daily practice. The preferred treatment not only depends on licensing considerations, but also on individual patient factors, including disease severity, impact on the quality of life, prior therapies, financial factors, comorbidities, and the experience of the physician. As there is broad experience with systemic agents from clinical use in other inflammatory skin diseases, such as bullous diseases and psoriasis, the threshold to use these agents off-label in the treatment of AD might be lower than starting treatment with cyclosporine A. With the approval of dupilumab we are

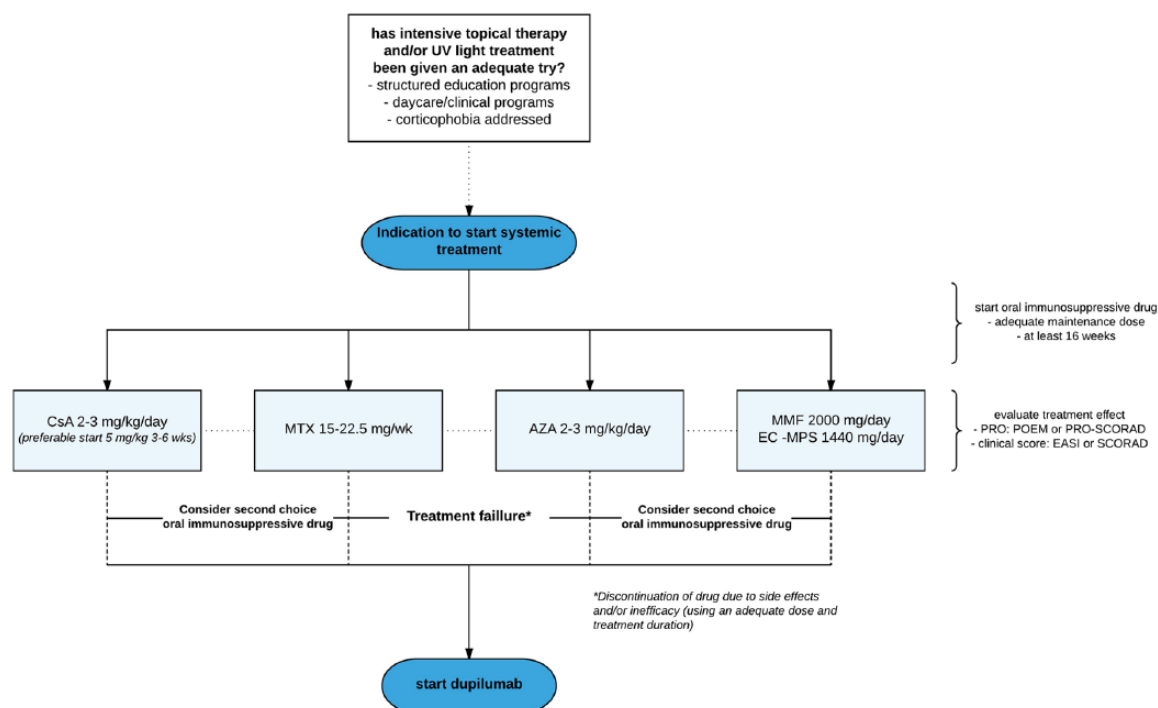


Figure 2. Proposed treatment algorithm for systemic treatment of atopic dermatitis (AD) in Europe.

AZA, azathioprine; CsA, cyclosporine A; EASI, Eczema Area and Severity Index; EC-MPS, Enteric-Coated Mycophenolate Sodium; MMF, mycophenolate mofetil; MTX, methotrexate; POEM, Patient-Oriented Eczema Measure; PRO, Patient-Reported Outcome; SCORAD, SCORing Atopic Dermatitis; UV, ultraviolet.

entering a new era of biological therapeutics in AD management, and its place should be established in the current treatment standards.

Proposed treatment algorithm for difficult to treat AD in Europe

Based on clinical evidence and experts' opinion in the management of AD, we proposed a treatment algorithm for difficult to treat AD in Europe (Figure 2). This algorithm provides guidance on making the decision of whether to start or switch oral immunosuppressive drugs or dupilumab.

In patients with moderate to severe AD whose condition failed to improve after an adequate try of topical therapy or UV light therapy (difficult to treat AD), systemic treatment is indicated. Adequate topical therapy consists of treatment with appropriate amounts of medium-to-high potency topical corticosteroids (TCS) combined with a structured patient education program and if needed daycare or clinical programs. In most European countries, CsA is the systemic treatment of first choice in the treatment of difficult to treat AD, although other, off-label oral immunosuppressive drugs

are frequently used as first choice systemic treatment.

The general approach for treatment with cyclosporine A is a high starting dose, tapering to a maintenance dose after 3–6 weeks. Most patients have an adequate response on a high dose, however for long-term treatment the effectiveness on a maintenance dose should be taken into account. Clinical effectiveness of slow-acting agents, such as methotrexate; azathioprine, mycophenolate mofetil and enteric-coated mycophenolate sodium (adequate doses are described in the algorithm; Figure 2) can only be evaluated properly after 3–4 months. An adequate induction phase should be followed by an assessment of treatment effect. This can be evaluated using clinical scores, such as the EASI or SCORing Atopic Dermatitis score (SCORAD), and Patient Reported Outcome (PRO) measures, such as the Patient-Oriented Eczema Measure (POEM) or Patient-Oriented SCORAD. In the case of treatment failure, which is defined as discontinuation due to side effects or ineffectiveness (using an adequate dose), treatment with a second choice oral immunosuppressive drug can be considered.

Dupilumab is very effective in AD and has a favourable safety profile in all clinical trials. The current efficacy/safety profile of dupilumab is based on 1-year data, which seems favourable compared with currently used oral immunosuppressive drugs. However, long-term safety data are limited and there are no head-to-head trials available comparing dupilumab with currently used oral immunosuppressive drugs. Besides there will be limitations in the use of dupilumab due to higher costs compared with oral immunosuppressive drugs. Given the lack of long-term safety data, lack of comparative head-to-head trials and financial implications of dupilumab, we suggest that treatment with dupilumab should be limited to severe recalcitrant cases.

Dupilumab treatment

Dupilumab is administered by a subcutaneous injection. The recommended dose of dupilumab for adult patients is a loading dose of 600 mg (two injections of 300 mg), followed by one injection of 300 mg every other week. The most common side effects are injection site reactions, herpes simplex virus infections, blepharitis, and conjunctivitis (including conjunctivitis of unknown cause, bacterial conjunctivitis, viral conjunctivitis, allergic conjunctivitis, and atopic keratoconjunctivitis). In the case of ophthalmic complaints it is recommended to refer patients to an ophthalmologist. Treatment with dupilumab may lead to fast and strong clinical disease improvement, resulting in rapid tapering or discontinuation of topical corticosteroid treatment. Therefore, physicians should be aware of the risk on tertiary adrenal insufficiency as a result of prolonged suppression of the hypothalamic–pituitary–adrenal axis by long-term use of (potent) topical corticosteroids. Testing for adrenal insufficiency should be considered, especially in patients with severe AD, using large amounts of potent topical corticosteroids or in patients presenting with symptoms of adrenal insufficiency, including flu-like symptoms, dizziness, pains in the joints and muscles, lack of appetite, or fatigue.

Drug interactions

The formation of cytochrome P450 (CYP450) enzymes can be influenced by the presence of increased cytokines during chronic inflammation. As dupilumab targets the IL-4 receptor α , thereby blocking both the IL-4 and IL-13 pathway, dupilumab may affect the formation of CYP450

enzymes. Therefore, the concomitant use of drugs which are CYP450 substrates during dupilumab treatment is not recommended. Temporary discontinuation of dupilumab, or monitoring of drug concentration should be considered in patients treated with CYP450 substrates, especially in those with a narrow therapeutic window. As dupilumab has not been studied with live attenuated vaccines, live vaccines should not be given concurrently with dupilumab. Possible travel plans and other vaccination indications should be discussed before the initiation of treatment with dupilumab. According to experience in the treatment with biologic agents in other inflammatory and rheumatic diseases, the optimal time for administering vaccines is prior to the start of biological treatment.³¹ We recommend vaccinating at least 14 days prior to the start of dupilumab treatment. In case of the need for vaccination with a live attenuated vaccine after initiation of treatment with dupilumab, treatment should be discontinued for at least 12 weeks.

Pregnancy

There are no data available concerning the use of dupilumab during pregnancy as none of the clinical trials included pregnant patients. Therefore, dupilumab should not be used in female patients who wish to become pregnant. In a pre/postnatal developmental animal study, there were no dupilumab-related effects (maternal, fetal, or infant) at doses of 0, 25, and 100 mg/kg/week. Dupilumab is not contraindicated in male patients with a wish for family planning.

Future perspectives

Dupilumab is a very interesting new therapeutic option for patients who have had severe AD for many years. However, no data on dupilumab in daily practice treatment are available. Real-life data from patients with AD treated with dupilumab in daily practice can provide important and essential information in addition to existing trial data. Patients participating in randomized controlled trials are often carefully screened based on predefined inclusion and exclusion criteria, and therefore have similar patient characteristics. However, patients treated in a real-life setting often differ in characteristics such as unstudied comorbidities and medication use. Therefore, information derived from clinical trials may not be generalizable to a population treated with dupilumab in a daily practice setting. In a real-life

situation, the balance between effectiveness and side effects determines whether treatment will be continued or not. Other factors that influence treatment success in daily practice include patients' adherence and the availability of alternative treatment options. Prospective registries will be useful to assess the long-term safety and effectiveness of dupilumab in daily practice and will allow comparisons between currently used systemic treatments and dupilumab in the treatment of AD. Considering the high price of dupilumab and the importance of efficient prescription nowadays, prospective registries will also offer new possibilities for further research on interval extension or treatment discontinuation. Since AD is a lifelong chronic disease, these studies will be very valuable.

Future implementation of data concerning the effectiveness and safety of dupilumab derived from a daily practice setting including an unselected group of patients will help to determine the position of dupilumab in the treatment of patients with AD. Besides, more insight is needed in the occurrence and cause of conjunctivitis appearing in patients treated with dupilumab for AD. As this clinically relevant complication might limit potential use of dupilumab, future studies on the underlying mechanism for the development of conjunctivitis in these patients are warranted. Furthermore, research on the underlying pathogenesis of AD may lead to early identification of patients in need of systemic treatment. Identification of patients who are the best candidates for specific systemic therapies will lead to a more personalized treatment approach and might prevent delay of adequate treatment and reduce costs. More insight in the pathogenesis of AD may also lead to the identification of specific endotypes. Recently, four AD patient clusters based on serum biomarker profiles were identified, implying that each of these clusters is driven by a distinct underlying pathway. Patients in two of those clusters, representing 48% of patients, showed particularly high Th2 cytokine levels and could represent those patients that would respond best to Th2 targeting drugs, including dupilumab.³²

Conclusion

Dupilumab has shown very promising results in the treatment of patients with moderate to severe AD in phase III trials. Treatment with dupilumab resulted in significant improvement in clinical and patient-reported outcomes and may address

the longstanding unmet need for safe and effective therapeutics in the management of difficult to treat AD. We would recommend using dupilumab in patients with uncontrolled AD despite adequate use of topical corticosteroids and treatment failure on one or more oral immunosuppressive drugs. Future, long-term data concerning the effectiveness and safety of dupilumab derived from a real-life setting will provide important information and will help to establish a more definitive place of dupilumab in the treatment of patients with moderate to severe AD.

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Conflict of interest statement

M.S. de Bruin-Weller is principal investigator, advisory board member, and consultant for Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme; and principal investigator and advisory board member for AbbVie. The other authors declare no conflict of interest.

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