



Dupilumab in Atopic Dermatitis

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Abstract

Purpose of review Atopic dermatitis (AD) is a common chronic inflammatory relapsing skin disease that greatly affects the quality of life of patients and their relatives. Topical treatment represents the initial therapeutic option in AD, although in patients with severe AD that do not respond to first-line topical therapies treatment with systemic immunosuppressive drugs is usually required. New advances in the understanding of the immune pathogenesis of AD have led to the development of targeted therapies.

Recent findings Dupilumab, the only biologic approved for AD treatment, is a fully human monoclonal antibody IgG4 directed to the α subunit of the interleukin-4 receptor (IL-4R α), blocking the IL-4 and IL-13, both crucial cytokines of the Th2 pathway. It has shown a significant clinical efficacy with good tolerance.

Summary In this review, we will discuss the results of recent clinical trials and real-life studies.

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory recurrent skin disease that affects up to two out of ten children [1]. In adults, AD may present as a

persistent or relapsing form of childhood AD or develop de novo (adult-onset AD) [2, 3]. It can affect over 2–8% of adults. The percentage is considerably lower in the

elderly [4]. In children, AD is considered the first step of the atopic march, associated with an increased risk of developing allergic rhinoconjunctivitis, asthma, or food allergy [5]. Frequently, patients with AD refer a personal or family history of atopic diseases.

AD has a chronic relapsing course that can lead to sleep disturbances and social stigmatization, which affect the quality of life of patients and their families. The disease associates a large socioeconomic burden [6, 7] in part due to the lack of effective treatments to control the more severe cases [8].

Interactions between epidermal barrier, immune dysregulation, skin microbiota, and genetic factors are proposed to explain the complicated nature of AD [9]. It is still not completely known whether skin inflammation arises initially from defects of the epidermal barrier or from immune dysregulation. Recent insight into immunological factors focuses on AD as a primarily T_H2 -dominated disease; in addition, T_H22 , T_H17 , and T_H1 cytokines have been implicated in some subtypes and phases of AD. Also, some AD lesions show infiltrates of type 2 innate lymphoid cells (IL-2) able to promote T_H2 response [10•].

Elevated serum concentrations of CCL17 (thymus and activation-regulated chemokine [TARC]), CCL18 (pulmonary and activation-regulated chemokine [PARC]), eosinophilic cationic protein (ECP), and periostin have been described in AD, showing correlation with the severity of the disease [11••]. Most of AD patients show elevated total and specific IgE levels [11••].

The diagnosis of AD is based on a clinical setting, since there are no objective diagnostic tests [12]. Pruritus and chronic or relapsing eczematous lesions with typical morphology and distribution in patients with a history of atopy are essential for diagnosis. The Hanifin and Rajka criteria [13] are often recommended for the diagnosis of AD; they are frequently used in clinical trials, but they are less suitable for clinical practice. Other criteria have been developed, such as the UK Working Party Diagnostic Criteria for AD (UK criteria) [14–16], the AAD consensus criteria [17], or the Millennium Criteria [18].

The classification of AD severity as mild, moderate, or severe is based on validated scoring systems, such as SCORAD (SCORing Atopic Dermatitis), ranging from 0 to 103, or EASI (Eczema Area and Severity Index), ranging from 0 to 72 [12, 19–21]. There is still debate about which scoring system is the easiest to use by physicians, particularly when facing decisions involving new and

expensive treatments such as biologics. They are useful for research studies, but they are not frequently used in clinical practice and they may not reflect the patient perception of severity. The Patient-Oriented Eczema Measure (POEM), a patient-derived and patient-assessed scale, has been proposed to complete the AD evaluation [22]. Also, the patient-oriented (PO) SCORAD allows patients or parents to measure the severity of AD [23, 24].

Although most patients with AD have mild-to-moderate disease [25]; others develop severe symptoms, with continuous itching, widespread skin lesions, and sleep disturbances that significantly compromise patients' quality of life. For patients with severe AD that do not respond to first-line topical therapies, treatment with systemic immunosuppressive drugs may be required; these patients are classified as having a severe, refractory disease. Based on a consensus report of the European Task Force on Atopic Dermatitis [26], AD is considered "severe" if the objective SCORAD is ≥ 40 . According to a recent US study [27], AD is considered to be severe if EASI is > 22 .

Several circumstances have been described as the cause of a poor response to treatment: incorrect use of medications or lack of adherence [28, 29], environmental triggers, infections, contact dermatitis to topical treatments [30], or hypersensitivity to food or aeroallergens. Clinicians should confirm that severe, refractory disease is not a result of an avoidable or treatable factor before prescribing second-line treatments.

Current topical treatments are used in patients with both mild and moderate-to-severe AD. The regular application of emollients reduces the number of exacerbations [31] and, if initiated early after birth, might avoid the atopic march [32–34]. An appropriate use of topical corticosteroids is considered the gold standard anti-inflammatory treatment of AD [35]. Particularly in children, and in face, eyelids, neck, and skin folds, topical calcineurin inhibitors can be useful. In a systematic review and meta-analysis of randomized clinical trials (RCTs) that compare topical calcineurin inhibitors with topical corticosteroids for AD, a similar efficacy was observed, although considering the higher cost and side effects for calcineurin inhibitors, topical corticosteroids should be the initial choice for AD treatment [36]. In 2016, the FDA approved the use of topical crisaborole, a phosphodiesterase-4 (PDE-4) inhibitor, for the treatment of mild-to-moderate AD in adults and in children ages > 2 years. Several other topical PDE-4 inhibitors are in phase I or II of development [37].

Second-line treatments could be required for severe AD. Several systemic immunosuppressants (cyclosporine A, azathioprine, methotrexate, and mycophenolate mofetil) have shown efficacy for the treatment of moderate-to-severe AD [38].

Recent clinical investigations on the effects of anti-IL-4, anti-IL-13, anti-IL-31 receptor, and anti-IL-22

monoclonal antibodies, as well as on small molecules targeting the histamine-4-receptor (ZPL389) and the Janus kinase inhibitor, have been published (results from phase II and phase III studies) in the last two years [39••]. Of them, we will focus on dupilumab, the only monoclonal antibody approved for the treatment of AD.

Mechanism of action

Dupilumab is a fully human IgG4 monoclonal antibody directed to the α subunit of the interleukin-4 receptor (IL-4R α) [40, 41]. There are two types of IL-4 receptors: the type I, a heterodimer of IL-4R α and the common γ chain (γ C), and the type II, a heterodimer of IL-4R α and the IL-13 alpha chain (IL-13R α 1) [42]. IL-4 binds with very high affinity to IL-4R α in a species-specific manner, leading to the recruitment of γ C or IL-13R α 1 [43]. IL-4R α and IL-13R α 1 chains are widely expressed at low levels on most cell types, whereas the γ C chain is primarily expressed on hematopoietic immune cells. IL-4 binding to type I receptor complex phosphorylates tyrosine kinases of the Janus family (JAK1/3), which in turn phosphorylate tyrosines within the IL-4R α cytoplasmic domain [44, 45]. These phosphotyrosine residues create docking sites for STAT6, a cytoplasmic transcription factor in the family of signal transducers of activation of transcription (STAT) family [46] or/and IRS-2 (insulin receptor substrate) [47] (Fig. 1). STAT6 and IRS-2 are the primary pathways involved in IL-4/IL-13 responsiveness [44, 47]. STAT6 tyrosine phosphorylation promotes phospho-STAT6 homodimerization, nuclear translocation, and gene transcription to modulate expression of target genes responsible for the biological effects of IL-4 and IL-13 [44, 47]. Tyrosine phosphorylation of IRS-2 leads to the activation of PI3-K, AKT, and NF- κ B-driven gene transcription, activation of the cell cycle, proliferation, and survival [44].

Blocking IL-4R α inhibits the downstream signaling of IL-4 and IL-13 [44] that are crucial cytokines of the Th2 pathway, which is involved in the differentiation of dendritic cells (DCs), B cell activation and IgE class-switching, and eosinophil recruitment [48–50].

The IL-4 and IL-13 cytokines have been suggested to have direct effects on the epidermis of patients with AD, inducing suppression of barrier protein expression (involucrin, loricrin, filaggrin) [51], keratinocyte hyperproliferation [52–55], spongiosis [56], inhibition of lipid synthesis [56], inhibition of the synthesis of antimicrobial peptides [57–60], and promotion of binding and colonization by *Staphylococcus aureus* [61].

Pharmacokinetics/pharmacodynamics

A subcutaneous injection of 600 mg of dupilumab takes one week to reach the maximum serum concentration (64% bioavailability) [62]. A pharmacokinetic study for functional dupilumab was performed [41]: Data of

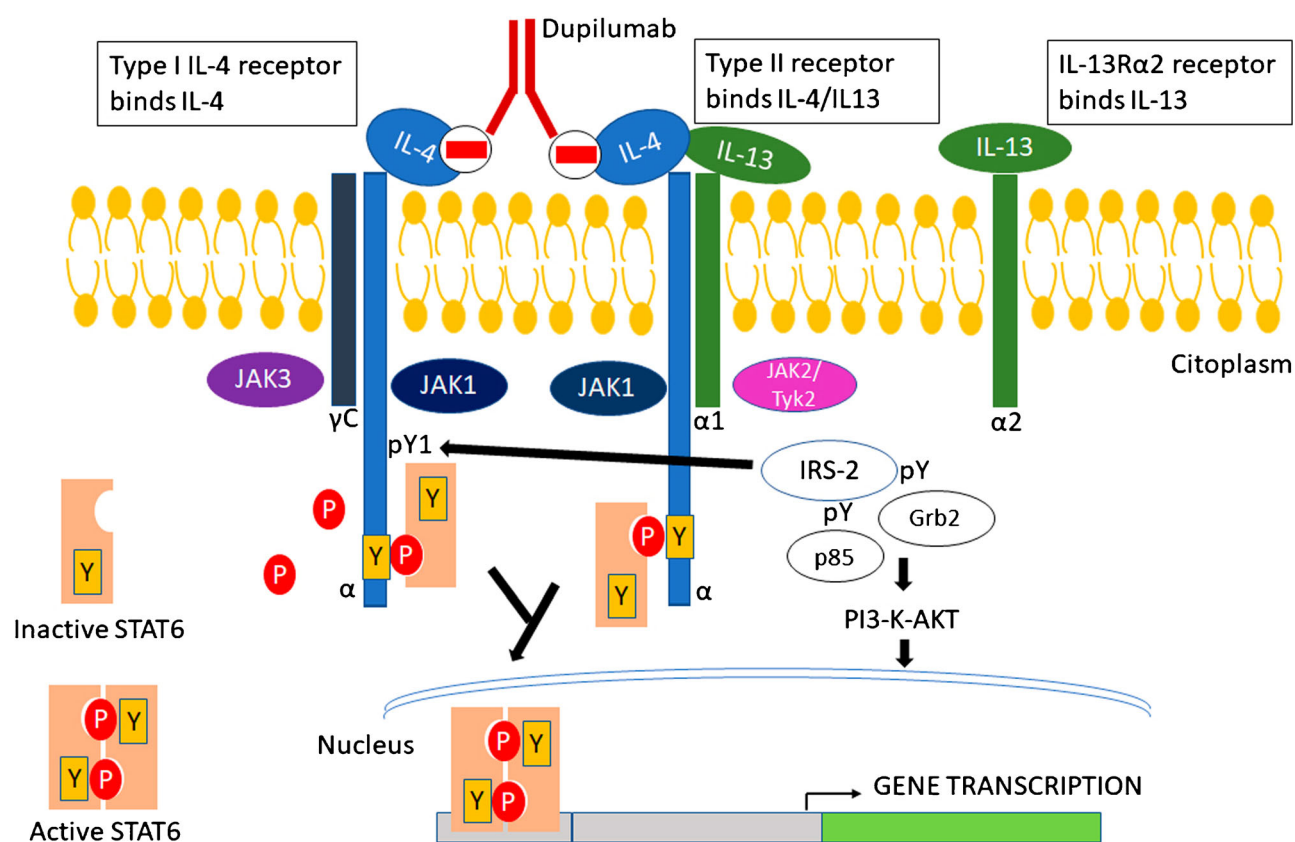


Fig. 1. Mechanism of action of dupilumab. Dupilumab is a monoclonal antibody against IL-4Rα that inhibits IL-4/IL-13 signaling. IL-4 can bind two possible receptors: type I and type II, both heterodimeric complexes. Type I is formed by IL-4Rα and γC chain and type II by IL-4Rα and IL-13Rα1. IL-4 binding to IL-4Rα triggers the signaling pathway. IL-13 binds to IL-13Rα1, which complexes with the IL-4Rα composing the receptor type II. The type I receptor activates the JAK-STAT-IRS-2 signaling pathways, whereas the type II receptor predominantly activates STAT6. IL-4 also activates PI3-K and AKT. IL-13 also binds to IL-13Rα2 with greater affinity than to IL-13Rα1, so IL-13Rα2 is a decoy receptor for IL-13.

197 participants from six phase I and phase II studies including healthy volunteers and patients with AD that received intravenous or subcutaneous (sc) doses were evaluated. There were no differences in the production rate of IL-4Rα between control and patients [41]. The elimination of dupilumab is expected to be degraded into small peptides via catabolic pathways as endogenous IgGs [62].

Patients with moderate-to-severe AD treated with dupilumab significantly reduced the expression of genes involved in type 2 inflammation (IL-13, IL-31, CCL17, CCL18, and CCL26), epidermal hyperplasia (keratin 16 [k16] and Mki67), T cells, dendritic cells (ICOS, CD11c, and CTLA4), and Th17/Th22 activity (IL-17A, IL-22, and S100As) and increased expression of lipid metabolism and barrier genes (ELOVL3, loricrin (LOR), claudins, filaggrin (FLG)) [11••]. Dupilumab also significantly reduced total and allergen-specific IgE levels [11••, 55]. A decrease of lactate

dehydrogenase (LDH), a biomarker associated to the activity and the severity of the AD, was also observed [63].

Dupilumab: clinical data from randomized controlled trials

The first safety and efficacy studies of dupilumab for the treatment of moderate-to-severe AD in adults were published in 2013. Results of phase II and III studies have shown efficacy for AD treatment; in addition to EASI, the assessed endpoints were the Investigator's Global Assessment score (IGA; range from 0 to 4) [64] and the score numerical-rating scale of itch (NRS; range from 0 to 10), as well as health-related quality of life (HRQoL) questionnaires.

Included patients had moderate-to-severe AD that had been present for at least three years, with an EASI score ≥ 16 and an IGA score of three (moderate) or four (severe) and an AD that was inadequately controlled by topical treatment or topical treatment was inadvisable. In adults, dupilumab was authorized by the FDA in March 2017 and by the EMA in September 2017 [65].

Phase I–IIa studies

The phase I–IIa studies (NCT01259323, NCT01385657, NCT01015027 trials) did not reveal safety issues related to dupilumab compared with placebo.

Dupilumab was evaluated as monotherapy (NCT01259323, NCT01385657, NCT01639040, and NCT01548404) in three trials (two of four weeks, one of 12 weeks), and in combination with topical corticosteroids (TSC) in another four-week study. In the studies that lasted four weeks, dupilumab showed dose-dependent improvements in all efficacy endpoints, such as the IGA and NRS scores. The results showed that dupilumab monotherapy for 12 weeks significantly improved the proportion of patients who achieved an EASI-50 (85% of patients in the dupilumab group, compared with 35% of those with placebo; $p < 0.001$), an IGA of 0–1 (40% of patients in the dupilumab group, compared with 7% in the placebo group; $p < 0.001$), or a decrease in the pruritus score (55.7% in the dupilumab group compared with 15.1% in the placebo group; $p < 0.001$). In addition, serum and tissue biomarkers indicated a normalization of the affected skin. All patients treated with dupilumab and topical steroids (versus 50% of those in the placebo group) ($p < 0.05$) met the EASI-50 criterium [40].

Phase IIb study

A phase IIb study (NCT01859988) included 380 adult patients with moderate-to-severe AD who were inadequately controlled with topical treatments [66]. Patients were randomly assigned to receive subcutaneous dupilumab 300 mg once a week (qw), 300 mg every two weeks (q2w), 200 mg q2w, 300 mg every four weeks (q4w), 100 mg q4w, or placebo qw for 16 weeks. The primary efficacy endpoint was the change in the EASI score from baseline. Reductions in the EASI score were significantly favorable for all dose regimens with dupilumab versus placebo ($p < 0.0001$), with up to a 74% reduction in the case of the 300-mg dose, compared with an 18% in the placebo group (Table 1). A total of

Table 1. Randomized controlled trials with dupilumab

References	Study	Phase and study design	Study drug (dupilumab dose)	Subjects (n)	Treatment duration	Outcomes measures (EASI)
Beck et al. [40]	M4A	Phase I Randomized, double-blind, placebo-controlled trials	Placebo or 75 mg qw,	30	4 weeks	22.8 (placebo)
	M4A		150 mg qw, 300 mg qw	37	4 weeks	30.0 (dupilumab group)
	M4B		Placebo or 150 mg qw, 300 mg qw			
Beck et al. [40]	M12	Phase IIa Randomized, double-blind, placebo-controlled trials	Placebo or 300 mg qw	109	12 weeks	30.8 (placebo) 28.4 (300 mg qw)
Beck et al. [40]	C4	Phase IIa Randomized, double-blind, placebo-controlled trials	Placebo + TCS or 300 mg qw + TCS	31	4 weeks	24.1 (placebo) 23.1 (300 mg qw)
Thaci et al. [66]	-	Phase IIb Randomized, double-blind, placebo-controlled trial	Placebo or 300 mg qw,	380	12 weeks	32.9 (placebo)
			300 mg q2w, 200 mg q2w,			33.8 (300 mg qw)
			300 mg q4w, 100 mg q4w			30.1 (300 mg q2w)
						32.9 (200 mg q2w)
						29.4 (300 mg q4w)
						32.2 (100 mg q4w)
Simpson et al. [67]	SOLO 1	Phase III Randomized, double-blind, placebo-controlled trial	Placebo or 300 mg qw, 300 mg q2w	671	16 weeks	31.8 (placebo) 30.4 (300 mg qw)
Simpson et al. [67]	SOLO 2	Phase III Randomized, double-blind, placebo-controlled trial	Placebo or 300 mg qw, 300 mg q2w	708	16 weeks	29.8 (300 mg q2w) 30.5 (placebo)
Blauvelt et al. [68]	LIBERTY AD CHRONOS	Phase III Randomized, double-blind, placebo-controlled trial	Placebo + TCS or 300 mg weekly + TCS, 300 mg every other week + TCS,	740	52 weeks	28.6 (300 mg qw)
						29.0 (300 mg q2w)
de Bruin-Weller et al. [69]	LIBERTY AD CAFÉ	Phase III Randomized, double-blind, placebo-controlled trial	Placebo + TCS or 300 mg weekly + TCS, 300 mg every other week + TCS	325	16 weeks	29.6 (placebo)
						30.9 (300 mg qw)
						29.0 (300 mg q2w)
						29.6 (placebo) 62.6 (300 mg q2w + TCS) 59.1 (300 mg qw + TCS)

qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids

82.5% of patients achieved EASI-50 and 60.3% of subjects achieved EASI-75 with significant differences compared with the placebo arm ($p < 0.0001$). Furthermore, dupilumab improved PROs of pruritus and HRQoL [67]. Compared with placebo, a greater proportion of subjects treated with 300 mg dupilumab qw and q2w showed improvement ≥ 3 of the pruritus NRS at 16 weeks (54 and 41%, respectively, vs 8%; $p < 0.0001$ for both doses). During the 16-week treatment period, dupilumab also resulted in significant improvements ($p < 0.0001$) in HRQoL at all doses except for the 100-mg q4w dose, as measured by the Dermatology Quality of Life Index (DLQI) [70].

Phase III studies

Phase III trials, SOLO 1 and SOLO 2 (NCT02277743 and NCT02277769), were prospective, double-blind, placebo-controlled trials of identical design, carried out to evaluate the efficacy and safety of dupilumab [71]. Adult patients with moderate-to-severe AD (671 in SOLO 1 and 708 in SOLO 2) were randomized to receive injections of 300 mg dupilumab qw or q2w after a 600-mg loading dose or placebo. The primary objective was to analyze the proportion of patients who achieved an IGA score of 0 or one and a reduction of two points or more from baseline in week 16. This goal was achieved by 38% and 36% in the groups that received biweekly injections and by 37% and 36% among the patients who received weekly injections in SOLO 1 and SOLO 2, respectively, compared with a 10% and 8% in the placebo group ($p < 0.001$ for all comparisons with placebo). Similarly, the percentage of patients who achieved an EASI-75 in week 16 was significantly higher in patients who received dupilumab than in those who received placebo (SOLO 1: 300 mg qw 52%, 300 mg q2w 51%, placebo 15%; SOLO 2: 300 mg qw 48%, 300 mg q2w 44%, placebo 12%; $p < 0.001$ for all comparisons). Significant improvement in pruritus and quality of life scores was also reported by patients who received dupilumab (Table 1).

More recently, a third phase III trial, LIBERTY AD CHRONOS (NCT02260986), compared the concomitant use of dupilumab qw and q2w and medium-potency TCS therapy (with or without topical calcineurin inhibitors) with placebo and TCS treatment in 740 patients over 52 weeks [68]. The co-primary endpoints were the IGA 0/1 response and EASI-75 at week 16. The results were maintained after one year of treatment, showing a marked improvement in the percentage of AD flares through week 52 in the groups treated with dupilumab plus TCS (13 and 14%, qw and q2w, respectively) compared with the control group (41%; $p < 0.0001$). Globally, 39% of the patients in the active group achieved an IGA 0/1, in comparison with 12% in those who received placebo ($p < 0.0001$). In addition, an EASI-75 was achieved in 64% of patients who received dupilumab plus TCS qw and 69% of those who received dupilumab q2w compared with 23% in the placebo arm ($p < 0.0001$) [19, 20]. Among patients with baseline NRS score $\geq$ four, the proportion of patients that experienced an improvement of $\geq$ four points at week 16 was significantly higher in the groups receiving dupilumab injections qw (51%) or q2w (59%) when compared with the control group (20%; $p < 0.0001$ for both comparisons). This improvement was maintained at week 52. These findings were also associated with improvement in HRQoL over 52 weeks; reduction from

baseline in DLQI score was significant with both dupilumab dosing regimens ($p < 0.0001$).

The LIBERTY AD CAFÉ trial (NCT02755649) was designed to evaluate the efficacy of dupilumab in patients diagnosed with AD that had an inadequate response to cyclosporine A, side effects, or contraindications [69]. In this 16-week, double-blind, randomized, placebo-controlled, phase III trial, 318 patients were randomized to receive dupilumab 300 mg (qw or q2w) or placebo, with associated medium-potency TCS. As a final objective, patients who achieved the primary endpoint (EASI-75) were 59.1% and 62.6%, respectively, in the active groups, compared with 29.6% in the placebo ($p < 0.0001$). At week 16, the secondary outcome of IGA 0/one or at least a two-point reduction from baseline was achieved by 40% of patients who received dupilumab qw and by 39% of patients who were treated with dupilumab q2w. This figure was 14% in the placebo group ($p < 0.0001$). In both dupilumab regimens, significant improvement in pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life was observed. The main characteristics of the trials are included in Table 1.

Studies in progress [72]

A phase IIa open-label study to determine the safety and tolerability of dupilumab in patients aged ≥ 6 to < 18 years with AD (NCT02407756) is ongoing to characterize the safety and pharmacokinetics of dupilumab in pediatric patients with moderate-to-severe AD (for adolescents ≥ 12 to < 18 years of age) or severe AD (for children ≥ 6 to < 12 years of age); the secondary objective is to explore the immunogenicity and efficacy of dupilumab in pediatric patients. Results have not been published yet.

A phase III open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials, LIBERTY AD SOLO MAINTAIN (NCT01949311), is in progress to evaluate the number of treatment emergent adverse events (TEAEs), with the incidence and rate (events per patient-year) of TEAEs through the last study visit as primary endpoint.

A phase III open-label study to assess the long-term safety of dupilumab administered in participants ≥ 6 months to < 18 years old with AD is also in progress (NCT02612454). The primary objective of the study is to assess the long-term safety of dupilumab in pediatric patients.

A SOLO-Continue study to confirm the efficacy and safety of different dupilumab dose regimens in adults with AD (NCT02395133) has been designed. This is a phase III, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of multiple dupilumab dose regimens administered as monotherapy for maintaining the treatment response in patients with AD. The primary outcome is to evaluate the difference between current study baseline and week 36 in percent change in EASI from parent study baseline (NCT02277743 and NCT02277769). The results have not been reported yet.

A phase III multicenter, randomized, double-blind, placebo-controlled trial in adults with chronic moderate-to-severe AD (NCT03389893) investigating the effect of six weeks of dupilumab treatment considering quantitative and qualitative measures of cutaneous microbial community structure, skin barrier

biology, and circulating T cell profiles has been initiated in July 2018 with an estimated study completion date in December 2019.

A phase IV (NCT03667014) single-center, open-label study will examine the effect of dupilumab in the quality of life in AD. The improvement in patients' quality of life after 52 weeks of treatment with dupilumab will be evaluated using validated dermatologic and non-dermatologic psychometric instruments. The primary endpoint is the improvement in quality of life measured by change in Psychological General Well-Being (PGWB) scale at week 16 from baseline. Patients have not been included yet.

Adult patients with a difficult-to-treat AD according to the Dutch AD guideline (failure of at least 1 oral immunosuppressive drug or a contraindication for oral immunosuppressive drugs) are being recruited for an observational prospective study (NCT03549416) in which they will receive dupilumab.

There is also a phase IV, immunogenetic profiling study of dupilumab for the treatment of AD (NCT03293030), with an estimated inclusion of 15 subjects with moderate-to-severe AD that will receive dupilumab during 52 weeks (i.e., last injection on week 50). All subjects will undergo skin biopsies for molecular profiling (the primary outcome is the percentage of change of CD4+ T effector cells that express IL-4).

Side effects

In general, the incidence of adverse effects (AEs) was similar in dupilumab-treated groups and in placebo groups in all clinical trials (phase I and IIa), and those that appeared well tolerated and manageable [40]. The most common side effects in phase IIb trial included nasopharyngitis, headache, exacerbation of AD, and upper respiratory tract infections; mild and moderate herpes viral infections were more frequent in patients receiving dupilumab than in the placebo group (8% vs 2%, respectively). Injection-site reactions were reported in 22 (7%) of 318 patients in the combined dupilumab doses group and two (3%) of 61 patients in the placebo group; conjunctival infections, irritations, and inflammation were reported by 7% of the patients in the combined dupilumab group vs 3% in the placebo group [66].

In phase III trials, SOLO 1 and SOLO 2, dupilumab-treated patients reported a higher incidence of injection-site reactions and conjunctivitis, compared with the placebo arms. Exacerbations of AD and skin infections were more common in the placebo groups [71].

LIBERTY AD CHRONOS phase III trial reported similar rates of AEs during the 52-week treatment period in the treated group in comparison with higher overall rates of serious AEs in the placebo plus topical corticosteroids group. The dupilumab plus topical corticosteroids groups reported higher rates of injection-site reactions. Also, the incidence of conjunctivitis (including conjunctivitis, bacterial, viral, allergic conjunctivitis, and atopic keratoconjunctivitis) was higher in the dupilumab plus topical corticosteroids groups (14% dupilumab qw plus topical corticosteroids group and 19% dupilumab q2w plus topical corticosteroids group) than that in the placebo plus corticosteroids group. Most cases were mild. Two patients (1%) who received dupilumab qw plus topical corticosteroids and one patient (< 1%) who received placebo plus topical corticosteroids had severe conjunctivitis: severe allergic conjunctivitis (one patient of each group) and severe bacterial conjunctivitis (one patient in

the dupilumab qw plus topical corticosteroids group). One patient in the dupilumab qw plus topical corticosteroids group discontinued due to conjunctivitis [68].

A meta-analysis including seven randomized, double-blinded, placebo-controlled clinical trials (2 phase I, 2 phase IIa, 1 phase IIb, and 2 phase III) reported that dupilumab was better tolerated and had a more favorable safety profile than most systemic agents. The most common reported AEs were nasopharyngitis, headache, and injection-site reaction with a similar rate among different trials. AEs occurred at a similar rate among different trials without statistical significance (RR 0.99; 95% CI, 0.95–1.04; $p = 0.827$) [73••].

Another meta-analysis of randomized clinical trials (from phase I to phase III) showed that patients treated with dupilumab had a decreased risk of all skin infections (RR 0.54; 95% CI 0.42–0.70) including eczema herpeticum (OR 0.34; 95% CI 0.14–0.84); there was no significant association between dupilumab and overall infection risk (RR 0.98; 95% CI 0.83–1.16) or between dupilumab and herpes infections (RR 1.16; 95% CI 0.78–1.74) [74].

The six trials, ranging from phase II to III, included in a systematic review and meta-analysis reported an overall incidence of adverse events similar in dupilumab-treated (42%) and placebo-treated (43%) patients (RR = 1.0; 95% CI 0.96–1.04; $p = 0.83$) [75].

It has been speculated that the increase of conjunctivitis could limit the use of dupilumab in the treatment of allergic diseases, especially in children. It is important to note that other trials of dupilumab in patients with asthma, chronic sinusitis, and nasal polypsis did not show an increase in conjunctivitis compared with placebo, suggesting a mechanism dependent on AD [76–78].

Real-life studies

There is still short experience with dupilumab in real-world practice. Nevertheless, some data have been published. A series of 13 patients treated with dupilumab 300 mg sc q2w following a 600-mg loading dose showed a 38.5% in the EASI-75 response [79]. A retrospective study of six children that received dupilumab at a regular dose if patients weight > 40 kg or half dose if < 40 kg has been published. Using biweekly doses of dupilumab (300 or 150, average treatment 8.5 months), all patients had a decrease in IGA of at least two points with a 50% patients achieving an IGA of 1 [80]. The administration of dupilumab 300 q2w showed an improvement in the visual analogical scale (VAS), quality of life (DLQI, EQ5D3L), anxiety and depression symptoms (HADS), or SCORAD in AD patients, similar to what has been described in other series. The most common AEs were local site-reaction or conjunctivitis; it is known that AD can associate with conjunctivitis [79, 81–84]. In a group of 15 patients that did not respond to previous systemic immunosuppressant treatments, dupilumab showed to be effective and safe in moderate-to-severe AD [83]. A retrospective multicentric study reviewed 27 patients with moderate-to-severe AD with at least 12 weeks of treatment (dupilumab 600 at week 0 and 300 q2w). A significant improvement of SCORAD and pruritus (measured by VAS) was observed from week four. The most frequent AEs were the same as mentioned above; there was no need of discontinuing the treatment [84]. Finally, there is a case report of a patient with a severe AD (patient SCORAD 88)

diagnosed with anaphylactic shock after eating canned corn that after starting treatment with dupilumab showed an AD improved and developed tolerance to canned corn and nuts, demonstrated by oral challenges [85].

Conclusions

With the recent approval of dupilumab, the revolution of biologics has finally reached the treatment of AD. Clinical trials and real-life studies indicate a consistent efficacy and a favorable safety profile of dupilumab alone or in combination with TCS. In patients with moderate-to-severe AD, it is recommended as a systemic treatment in adults with AD not adequately controlled with topical therapies. In addition, pediatric studies are ensuing and a future approval is expected. The use of dupilumab in clinical practice will permit a better selection of responding patients. In addition, the use of dupilumab will reveal new insights into the role of IL-4 and IL-13 in the etiopathogenesis of AD.

Compliance with Ethical Standards

Conflict of Interest

Milagros Lázaro-Sastre declares that she has no conflict of interest.

Aída Gómez-Cardenosa declares that she has no conflict of interest.

María Asunción García-Sánchez declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
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