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Review Article

Dupilumab in the treatment of moderate-to-severe atopic dermatitis: A focused review

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin condition causing significant decline in quality of life. Moderate-to-severe AD is refractory to first-line topical therapy, while systemic immunosuppressants can have significant adverse effects. Dupilumab is a fully human monoclonal antibody and the first food and drug administration approved biologic therapy for the treatment of adults with moderate-to-severe AD. It inhibits the actions of both interleukin (IL)-4 and IL-13, two T helper cell type 2 cytokines involved in the pathogenesis of AD. Dupilumab has been found to be an efficacious treatment option in AD with its main adverse reactions being conjunctivitis, injection site reaction, and facial redness. Dupilumab is known to improve the severity and extent of AD, as measured by the eczema area severity index and dermatology life quality index. A similar observation was made by the authors in 30 patients. Thus, dupilumab represents a valuable new treatment option for moderate-to-severe AD, however, high cost remains a major consideration.

Keywords: Atopic dermatitis, Dupilumab, Eczema area severity index, Dermatology life quality index

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease typified by pruritus and a dysfunctional skin barrier.[1] The pathophysiology of AD is complex and apart from the immune mechanism and defective skin barrier, genetic and environmental factors also play a role.[2] Current mainstay treatments include topical emollients, topical corticosteroids, calcineurin inhibitors, and phototherapy. In addition, systemic therapies such as oral corticosteroids and other immunosuppressants including cyclosporine, azathioprine, and methotrexate are often needed to manage more severe cases.[3]

Moderate-to-severe AD is often recalcitrant to first-line topical therapy, while systemic immunosuppressants, although usually successful, can have significant adverse effects.[4]

Dupilumab was approved by the U.S. food and drug administration (FDA) on March 28, 2017, for the treatment of moderate-to-severe AD in adults whose disease is not adequately controlled with topical therapies or when conventional systemic treatments are not advisable.[5] It was further approved by the U.S FDA on May 26, 2020 for children aged 6–11 years for similar indications.[6] Dupilumab is the first and the only biologic approved for patients with AD.

MECHANISM OF ACTION

In patients with AD, there are two main pathophysiological components: an increased skin inflammation and abnormal structure and function of skin barrier.[7] Due to the disturbed

epidermal barrier, there is increased permeation of various antigens which are recognized by Langerhans cells and innate lymphoid subtype 2 cells. These antigens are then presented to T cells in the skin and lymph nodes resulting in the initiation of a type 2 immune response. Consequently, T helper type 2 (Th2) associated, inflammatory and pruritogenic cytokines such as interleukin (IL)-4, IL-13, and IL-31 are released.[8]

Dupilumab is a human monoclonal antibody that binds specifically to the IL-4Rα subunit of the receptor complexes for IL-4 and IL-13. This suppresses IL-4 and IL-13 signaling leading to a decrease in IL-4 and IL-13 cytokine-induced responses. These include a suppression of the release of pro-inflammatory cytokines, chemokines, and immunoglobulin (Ig) E resulting in reduction in epidermal hyperplasia, inflammation, and pruritus.[9]

Bakker *et al*. after studying the effect of dupilumab treatment in moderate-to-severe AD patients, reported that the drug completely blocked IL-4Rα expression and STAT (signal transducers and activators of transcription) -6 phosphorylation in CD19+ B-cells and CD4+ T-cells. This was achieved within two hours of administration of the drug and the effect persisted through week 52. At week 4, a significant reduction was observed in the percentage of proliferating (Ki67+) T cells and skin homing CD4+ T-cells that produce Th2/Th22 cytokines. On long term, no effect was noted on overall Th-cell skewing.[10]

PHARMACOLOGY

Dupilumab is administrated by subcutaneous (SC) injection and is to be used under the guidance of a health-care provider. Patients can be trained to self-inject using either a pre-filled syringe or a pen. The recommended dose of dupilumab is 300 mg every 2 weeks after an initial loading dose of 600 mg (two 300 mg injections at different sites).[9]

Following an initial SC dose of 600 mg or 400 mg, dupilumab reached peak mean ± standard deviation concentrations by approximately 1-week post-dose. Steady-state concentrations were achieved by week 16. The bioavailability of dupilumab following a SC dose ranges between 61% and 64%.[11]

As dupilumab is a human monoclonal IgG4 antibody, it is expected to be broken down into small peptides and amino acids through the catabolic pathways similar to the degradation of endogenous IgG. The median time taken for dupilumab levels to fall to undetectable levels after the last steady-state dose of 300 mg every 2 weeks is 10–11 weeks.[11]

CLINICAL EFFICACY AND QUALITY OF LIFE

A variety of scoring systems that include subjective as well as objective measurements are used to assess the severity of atopic dermatitis, its impact on quality of life, and response to treatment.[12] Some of the most common scoring systems used by health-care professionals in the clinical assessment of AD patients are listed in Table 1.

EVIDENCE OF DUPILUMAB EFFICACY

FDA approval of dupilumab was based on efficacy and safety results from three phase 3 trials (SOLO 1 and 2 and CHRONOS) in the global LIBERTY AD program that included more than 2500 patients.[13,14] All three trials were phase 3 randomized, double-blind, placebo-controlled, parallel group studies to confirm the efficacy and safety of dupilumab therapy in adults with moderate-to-severe AD. SOLO 1 and SOLO 2 trials monitored the improvement with dupilumab as monotherapy till 16 weeks.[13] In contrast, the CHRONOS was a long-term trial till 52 weeks (1 year), and in this trial, all patients were simultaneously initiated daily treatment with a medium or low potency topical corticosteroid.[14] The primary outcome measured in the three trials was an investigator global assessment (IGA) score of "0" or "1" and a reduction from baseline of ≥2 points at week 16. In addition, the improvement as assessed by IGA scale, eczema area severity index (EASI), and numerical rating scale scores among others was also assessed at 52 weeks in the CHRONOS trial.[14] The data from the three trials are outlined in Table 2.[13,14]

Halling *et al*. in a systematic review and meta-analysis of 22 observational studies on the efficacy and safety of dupilumab in AD, reported that the pooled proportion of patients achieving EASI-50, EASI-75, and EASI-90 after 16 weeks of treatment was 85.1%, 59.8%, and 26.8%, respectively.[15]

SAFETY AND ADVERSE EFFECTS

There was no significant difference in adverse reactions recorded between the three groups in the CHRONOS trial (patients receiving dupilumab weekly, patients receiving dupilumab once every 2 weeks, and patients receiving placebo).[14] There were no noticeable laboratory anomalies caused by dupilumab. Injection site reactions and conjunctivitis were more common in patients treated with dupilumab and topical corticosteroids than in patients treated with placebo plus topical corticosteroids.[14] In the systematic review by Halling *et al*. also, conjunctivitis was noted as the most common adverse event and was documented in a pooled proportion of 26.1% of cases.[15]

Overall, injection site reactions, conjunctivitis, blepharitis, keratitis, eye pruritus, dry eye, and herpes simplex virus infection are the most prevalent adverse reactions in dupilumab treated adult patients with atopic dermatitis.[9] Nasopharyngitis, elevation of eosinophil count from baseline, rosacea like folliculitis, alopecia, and arthralgia are the other adverse events noted.[13-16]

Table 1: Scoring systems used in atopic dermatitis.

Scoring systems	EASI	SCORAD	IGA	POEM	Pruritus NRS	DLQI
Description	Grades the physical signs of AD (erythema, edema/papulation, excoriation, lichenification) on four anatomic regions of the body: Head, trunk, and upper and lower extremities	A clinical tool for assessing extent and intensity of eczema as well as subjective signs (insomnia, etc.)	Assessment of severity of AD and clinical response to treatment on a 5-point scale	Patient-reported questionnaire used to assess disease symptoms	Patient-reported tool to assess intensity of itch in AD using this scale from 0 (no itch) to 10 (worst itch)	Patient-reported questionnaire that used to assess different aspects that may affect quality of life over the past week
Factors assessed						
Erythema	Y	Y	Y			
Edema	Y	Y	Y			
Papulation	Y	Y	Y			
Lichenification	Y	Y				
Infiltration			Y			
Oozing/weeping			Y	Y		
Crusting			Y			
Dryness		Y		Y		
Pruritus		Y		Y	Y	Y
Sleep disturbance		Y		Y		
Excoriation		Y				
Flaking/cracking				Y		
Bleeding				Y		
Quality of life and self-consciousness						Y
Maximum score	72	103	5	28	10	30

EASI: Eczema area severity index, SCORAD: Severity scoring of atopic dermatitis, IGA: Investigator global assessment, POEM: Patient-oriented eczema measure, NRS: Numerical rating scale, DLQI: Dermatology life quality index, AD: Atopic dermatitis, Y: Yes

Table 2: Summary of three trials that were considered to assess dupilumab efficacy and safety for FDA approval.

Trial	Total number of patients	Number of patients on weekly 300 mg dupilumab (Group 1)	Number of patients on 300 mg dupilumab every other week (Group 2)	Number of patients on weekly placebo (Group 3)	Number of patients (%) achieving primary outcome measure (at week 16)		
					Group 1	Group 2	Group 3
SOLO 1 (2014–2016)	671	223	224	224	83 (37)	85 (38)	23 (10)
SOLO 2 (2014–2016)	708	239	223	236	87 (36)	84 (36)	20 (8)
CHRONOS (2014–2016)	740	319	106	315	125 (39)	41 (39)	39 (12)

FDA: Food and drug administration

Conjunctivitis is one of the most common side effects of dupilumab. It often occurs 2–6 weeks after initiation of dupilumab.[15] Previous history of allergic conjunctivitis is suggested as a risk factor.[15] It is still unknown whether dupilumab triggers a rise in conjunctivitis rates in patients with AD or if higher rates of conjunctivitis are seen in patients with AD because they are already at a higher risk of developing conjunctivitis.[17] Conjunctivitis should be considered, when a patient with AD receiving dupilumab, presents with bilateral hyperemic and pruritic eyes. Data are currently insufficient to recommend an eye examination by an ophthalmologist for each patient before starting dupilumab.[17] Dupilumab discontinuation and even dose frequency spacing have rarely been needed to manage dupilumab-induced conjunctivitis, which is attributed to the early and effective diagnosis and treatment.[18]

Mild conjunctivitis can typically be managed conservatively with warm compresses and artificial tears, sodium

hyaluronate, trehalose/hyaluronate tear substitute, or antihistamine eye drops, whereas moderate or severe conjunctivitis necessitates the use of anti-inflammatory eye drops or ointments containing corticosteroids, calcineurin inhibitors, or cyclosporine.[19]

Dupilumab-induced facial redness is a specific side effect that has been identified.[15] After a median duration of 65 days, exacerbation or new onset of head-and-neck dermatitis has been confirmed in approximately 4% of adult patients treated with dupilumab. The exact pathogenesis of this reaction is unknown. The hypotheses put forth to explain the head-and-neck dermatitis include exacerbation of AD due to withdrawal of topical steroid during treatment with dupilumab, unmasking of an allergic contact dermatitis by modulation of T helper cell signaling (induced by IL-4 receptor alpha blockade), and proliferation of Malassezia fungus by activation of Th17 pathway.[20]

De novo psoriasis is a rare side effect of dupilumab treatment, but one that the treating physician must be aware of.[21] Patients treated with dupilumab (n = 373) were screened for new onset psoriasis in a retrospective cohort study conducted over a 3-year period in six French centers. At a mean duration of 16 weeks after starting dupilumab therapy, seven patients developed either plaque, pustular or nail psoriasis. It is proposed that blocking of the Th2 pathway by dupilumab can cause the Th17/ IL23/ tumour necrosis factor pathways to become overactive. To better understand the prevalence, mechanisms, and possible risk factors of this adverse effect, further research is required.[21]

DUPILUMAB TREATMENT IN THE NATIONAL HEALTH SERVICE (NHS) ENGLAND SETTING

The European Medicines Agency granted regulatory approval for dupilumab in September 2017. It was then assessed by the National Institute for Health and Care Excellence (NICE), and in August 2018, NICE approved it for regular use on the NHS in England and Wales. Funding for dupilumab is approved for patients with moderate-to-severe atopic eczema (as assessed by EASI score) whose disease has not responded to at least one other systemic therapy, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, or when these are contraindicated or not tolerated. Their dermatology life quality index (DLQI) score should also be greater than or equal to 10. In 16 weeks, an adequate response is described as 50% reduction in the EASI and a 4-point reduction in the DLQI. If this is not reached, dupilumab therapy is discontinued.[22]

The recommended dose, given by SC injection, is initially 600 mg (2 × 300 mg injections), followed by 300 mg given every other week.[23] Patients are trained to self-inject dupilumab.

OUR EXPERIENCE

The authors' experience, in the 30 patients who received dupilumab for atopic eczema, is as followed.

The age of the patients ranged 20–80 years. Fifteen (50%) were men and 15 (50%) were women. All the patients also received topical steroids and emollients. Patients had AD for an average of 10 years. At initiation of treatment with dupilumab, AD involved an average of 60% of their body surface area. They had average scores of 30 on EASI and 15 on the DLQI. All have been on one or more immunosuppressive drugs for at least 1 year. All the 30 patients showed adequate response at 16 weeks and therefore continued to receive dupilumab. Mean percent change in EASI after 16 weeks was reduction by 70% and further decrease to 75% by week 52. EASI-75 was achieved by 60% at week 16 and 70% at week 52. By week 16, 4-point or more reduction in DLQI was achieved in all the 30 patients. The most reported side effect was conjunctivitis in 12 (40%) patients and red face was reported in 2 (6.7%) patients. These side effects were managed conservatively and did not require discontinuation of dupilumab treatment. Dupilumab had to be subsequently discontinued in two women as they became pregnant while on treatment.

CONCLUSION

Dupilumab is recommended for patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies and/or when immunosuppressive agents such as cyclosporine, methotrexate, mycophenolate mofetil, or azathioprine have failed or are not tolerated. Compared with conventional immunosuppressive agents, dupilumab has a favorable safety profile with injection site reactions and conjunctivitis being the main associated adverse events. High cost may be a major consideration with dupilumab.

Declaration of patient consent

Not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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