

Report

Real-world experience of dupilumab treatment for atopic dermatitis in adults: a retrospective analysis of patients' records

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Abstract

Background Clinical trial data for dupilumab, a monoclonal antibody against the interleukin-4 receptor (IL-4R α), have shown that it is safe and effective for the treatment of moderate to severe atopic dermatitis in patients whose disease is resistant to other therapies. However, little real-world experience with dupilumab use has been reported thus far. The aim of this retrospective study was to assess overall outcomes in adult patients with atopic dermatitis (AD) treated with dupilumab.

Methods A retrospective review of electronic medical records was conducted for patients treated with dupilumab in the Department of Dermatology at the University of California, Irvine.

Results We analyzed the medical records of 77 AD patients who received dupilumab according to standard dosing and had at least one documented follow-up visit. In 66 patients (86%), dupilumab improved clinical disease severity, with 23 patients (30%) experiencing complete clearance on dupilumab. Dupilumab was generally well-tolerated and caused no serious adverse events. The most common side effects included dry eyes, conjunctivitis, and keratitis. The most common reason for discontinuation of treatment was lack of substantial clinical improvement or progression of disease severity, followed by ophthalmologic side effects.

Conclusions Overall, dupilumab was well-tolerated and resulted in clinical improvement in our patient population. These results provide additional important information on the safety and utility of dupilumab treatment for moderate to severe atopic dermatitis in the real-world clinical setting.

Introduction

Atopic dermatitis (AD) is a common, chronic skin disorder characterized by inflammatory lesions and pruritus.¹ Prevalence of AD in the adult population in the United States is around 7%.^{2,3} There is a significant physical and psychological burden associated with AD. The disease is characterized by skin xerosis, erythema, exudative lesions, and lichenification. Pruritus is often the most difficult symptom to manage and contributes significantly to disease burden. AD has been shown to impact quality of life and increase the likelihood of anxiety and depression.^{3,4}

The pathophysiology of AD is complex and involves skin barrier dysfunction, immune dysregulation, genetic abnormalities, environmental triggers, and the microbiome. Increased expression of the T helper (Th) 2 cytokine axis occurs in AD, with interleukin (IL)-4 and IL-13 playing a major role in this disease.⁵ Single-nucleotide polymorphisms occur in the genes for IL-4, IL-13, and their receptors in AD patients, and both cytokines have

been implicated in inhibiting antimicrobial peptide production.^{5,6} Upregulation of Th17 and Th1 cytokines is also observed in AD.⁵

Dupilumab is an IL-4 receptor α antagonist that inhibits IL-4 and IL-13 cytokine-induced responses.⁷ It was FDA approved in March 2017 for the treatment of moderate to severe atopic dermatitis in adults.⁸ It is administered subcutaneously every other week at a dose of 300 mg (with an initial dose of 600 mg divided into two separate 300 mg doses given on the same day in two sites). The majority of data supporting the use of dupilumab is from clinical trials. The three randomized, double-blind, placebo-controlled phase III clinical trials assessing the safety and efficacy of dupilumab, SOLO1, SOLO2, and CHRONOS, evaluated 2,119 patients.^{9,10}

The first two trials examined dupilumab as monotherapy and found significant improvement in measures of skin clearing and overall severity of disease at 16 weeks of treatment. The third

trial, CHRONOS, examined dupilumab treatment in conjunction with topical corticosteroids and found significant improvement in overall disease severity at 16 and 52 weeks, as compared to placebo with topical corticosteroids.¹⁰

The objective of our study was to assess overall outcomes of dupilumab use in adults with AD in a real-world setting. To date, there have been reports on real-world experience with dupilumab, including two retrospective multicenter studies – one of 27 AD patients in Spain¹¹ and another on 241 AD patients in France.¹² Herein, we evaluate the utility and safety of dupilumab in a larger patient population at a single clinical center.

Materials and methods

This retrospective chart analysis was conducted in the Department of Dermatology at the University of California, Irvine (UCI), after receiving approval from the UCI Institutional Review Board. The electronic medical records were queried between the dates of May 1, 2017, to January 25, 2019, to identify patients who were prescribed dupilumab. A complete chart review was conducted on all patients prescribed dupilumab by two dermatologists in the Department of Dermatology.

Patients with moderate to severe AD, 18 years old and older who had had their disease for three or more years and failed previous therapies – including at least one systemic modality with corticosteroids and/or immunosuppressants, such as cyclosporine – were prescribed dupilumab (Dupixent; Sanofi and Regeneron Pharmaceuticals, Inc.) at an initial dose of 600 mg (two 300 mg injections at different sites), followed by a 300 mg subcutaneous injection administered every other week. A follow-up visit after initiating treatment was scheduled between 6–8 weeks, with subsequent visits to monitor progress approximately every 12 weeks. No routine laboratory monitoring was performed, as it is not indicated with the use of dupilumab.

Since these patients were evaluated during routine clinical visits, no numeric scoring of disease severity was implemented. Changes in physical exams described in the charts, however, allowed us to estimate response to dupilumab treatment qualitatively. Clinical response was measured as complete clearance (BSA = 0%), partial improvement, and lack of improvement.

Results

The patients that met inclusion criteria for this review consisted of 121 adult patients, among whom 77 had a documented follow-up visit within 16 weeks of starting the medication and received at least one dose of the medication (Table 1). Prior to starting dupilumab, all 77 patients (100%) had been treated with topical corticosteroids, 14 (18%) with crisaborole, and seven (9%) with calcineurin inhibitors. For systemic therapies, 73 patients (95%) had received systemic corticosteroids (orally or

intramuscularly), 25 (32%) cyclosporine, 12 (16%) phototherapy (either narrowband UVB or excimer), five (6%) mycophenolate mofetil, four (5%) azathioprine, four (5%) apremilast, four (5%) methotrexate, three (4%) omalizumab, one (1%) adalimumab, and three (4%) were previously treated with intravenous immunoglobulin.

Of the 77 patients on dupilumab, 23 (30%) achieved complete clinical remission, 43 (56%) demonstrated partial but stable improvement, and 11 (14%) had either no improvement or worsening of disease severity (Table 2). Of these 11 patients, 10 patients were on dupilumab for less than 18 weeks; the average duration of treatment for these 10 patients was 8 weeks. Fifty-eight patients are currently undergoing treatment with dupilumab. The average duration of therapy for these patients is 11.7 months. There were two patients who experienced complete clearance on dupilumab and were encouraged to begin tapering of the medication after 12 months of treatment by decreasing the frequency of injections to every 3–4 weeks. One patient who achieved complete clinical resolution discontinued the medication and is in stable remission for at least 6 weeks.

Among those receiving dupilumab, 73 patients also used topical or systemic medications at some point during their treatment duration (Table 3). Out of the 73 patients receiving a concomitant therapy, 59 (81%) used topical corticosteroids, 10 (14%) used crisaborole, 10 (14%) received intramuscular systemic corticosteroids, five (7%) had UV light therapy, and four (5%) used topical calcineurin inhibitors. One patient received hydroxychloroquine while on dupilumab.

Adverse events were reported by 20 patients (26%) at some point during treatment with dupilumab (Table 4). Most of these

Table 1 Baseline characteristics among patients who received dupilumab with at least one follow-up appointment

	<i>n</i> (%)
Characteristic	
Total patients	77 (100)
Age, mean ± SD	47 ± 18
Males	35 (45)
Females	42 (55)
Previous treatment method	
Topical corticosteroids	77 (100)
Systemic corticosteroids (intramuscular or oral)	73 (95)
Cyclosporine	25 (32)
Light therapy (NBUVB or excimer)	12 (16)
Crisaborole	14 (18)
Topical calcineurin inhibitors	7 (9)
Mycophenolate mofetil	5 (6)
Azathioprine	4 (5)
Apremilast	4 (5)
Methotrexate	4 (5)
Omalizumab	3 (4)
Intravenous immunoglobulin	3 (4)
Adalimumab	1 (1)

Table 2 Clinical response to dupilumab in patients with ongoing therapy ($n = 77$)

Clinical response	<i>n</i> (%)
Complete clearance	23 (30)
Partial clearance	43 (56)
No clearance	7 (9)
Worsening of disease severity	4 (5)

Table 3 Therapies used in combination with dupilumab ($n = 73$)

Therapy	<i>n</i> (%)
Topical corticosteroids	59 (81)
Crisaborole	10 (14)
Systemic corticosteroids (intramuscular or oral)	10 (14)
Topical calcineurin inhibitors	4 (5)
Light therapy (NB-UVB or excimer)	5 (7)
Hydroxychloroquine	1 (1)

Table 4 Most common adverse events reported by patients receiving dupilumab ($n = 20$)

Adverse event	<i>n</i> (%)
Dry eyes	8 (40)
Conjunctivitis	6 (30)
Keratitis	3 (15)
Blurry vision	2 (10)
Herpes simplex virus infection	2 (10)
Blepharitis	2 (10)
Foreign body sensation (ophthalmic)	1 (5)
Hypersensitivity	1 (5)

adverse events were dry eyes ($n = 8$), conjunctivitis ($n = 6$), or keratitis ($n = 3$) that resolved after treatment by an ophthalmologist with lubricating eye drops or with addition of ophthalmologist-initiated prednisolone acetate 1% ophthalmic suspension. Eighteen patients discontinued dupilumab for reasons other than complete clearance which include: adverse events ($n = 6$), no to minimal improvement in disease activity ($n = 9$), issues with insurance coverage ($n = 2$), and death due to an unrelated cause ($n = 1$) (Table 5).

Twenty-four patients are still pending follow-up assessment. The majority of patients who have not followed up are either in the process of attaining dupilumab approval or recently started the medication and are not yet due for a follow-up appointment. Among the patients prescribed dupilumab who did not initiate therapy, the most common reason for not starting dupilumab was related to insurance coverage. Some patients elected not to start dupilumab as they improved with current therapy or did not feel comfortable using an injectable medication.

Table 5 Reasons for discontinuation of dupilumab ($n = 19$)

Reason for discontinuation	<i>n</i>
Complete clearance of disease	1
Minimal to no improvement	6
Disease progression/flare	3
Blurry vision, self-discontinued	1
Ocular symptoms including any of the following: dry eyes, blepharitis, keratitis, conjunctivitis	4
Hypersensitivity reaction	1
Patient deceased	1
Insurance coverage	2

Discussion

In our patient population, dupilumab showed excellent therapeutic effectiveness and was fairly well-tolerated. Eighty-six percent of patients experienced partial to complete clearance, and only 11 patients (14%) were unresponsive to treatment. Out of the 11 patients who had no improvement or progression of disease while on therapy, 10 discontinued dupilumab prior to 16 weeks of treatment. In the phase III studies conducted, overall disease severity was assessed at 16 weeks of dupilumab treatment. Thus, these patients may have discontinued treatment too soon to adequately assess response. The remaining patient who did not respond to dupilumab was later diagnosed with psoriasis, which may explain his lack of response to dupilumab.

Dupilumab was approved by the FDA to be used either as a monotherapy or with topical corticosteroids. Accordingly, our patients were encouraged to use a combination therapy if required for adequate control of disease. The majority of patients used topical corticosteroids concomitantly.

Adverse events occurred in less than one-third of patients (26%) and were mostly represented by dry eyes, conjunctivitis, keratitis, and blepharitis, all of which are known common side effects of dupilumab.¹³ We observed two cases of herpes simplex virus outbreaks, another reported side effect of dupilumab.¹³ The majority of cases of ophthalmologic involvement as a reported side effect improved after initiation of appropriate therapy by ophthalmology. One patient reported a hypersensitivity reaction upon initiation of dupilumab treatment which recurred upon re-challenge, and thus the medication was immediately discontinued. None of the adverse events were life-threatening or resulted in discontinuation of medication in the majority of affected patients. The percentage of patients who prematurely discontinued therapy (prior to achieving a desirable therapeutic response), however, was higher in our patient population than in the SOLO1 and 2 trials, which ranged from 6.6 to 9.4% (due to adverse effects, lack of efficacy, or protocol violation). However, the higher rate of discontinuation in our population is likely a result of lower adherence to medical therapy in real life compared to clinical trials.

A real-world retrospective study was previously conducted in Spain and evaluated dupilumab treatment outcomes in 27 patients with at least 12 weeks follow-up.¹¹ The authors measured baseline AD activity score and pruritus intensity at baseline, 4, and 12 weeks and noted improvement in both measures in their patient population. They reported three cases of conjunctivitis and no severe adverse effects. A retrospective multicenter study including 241 patients in France also showed significant reductions in AD severity at 3 months follow-up with conjunctivitis reported in 38.2% of patients.¹² These findings are in agreement with our study.

Limitations of our study include its retrospective nature – which is inherently subject to threats to internal validity such as confounding and selection bias – as well as external validity. Another limitation is that our data were collected from a routine patient management environment rather than in a clinical research setting, and thus formal instruments to grade disease activity were not utilized. Also, because the data were retrieved from a single dermatology center, the results may not be generalized to other patient populations due to variations in the health plan coverage policies for dupilumab, providers' drug-prescribing patterns, and other subjective issues that may potentially influence treatment choice and outcome.

In summary, based on the clinical improvement seen in the majority of our patients and lack of serious adverse events, these data further support dupilumab as a promising option for the treatment of moderate to severe atopic dermatitis. Our results also suggest that patients may require at least 16 weeks of treatment before improvement is noted, as the majority of our nonresponders received dupilumab for less than 16 weeks. Additionally, we highlight the use of dupilumab as a monotherapy or in combination with other treatment modalities. This study provides additional information on the safety and utility of dupilumab in the real-world clinical setting, with the goal of informing clinicians of the value of this therapy in the treatment of moderate to severe atopic dermatitis.

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