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EXPERT OPINION

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Dupilumab for the treatment of atopic dermatitis: A clinical trial review

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Introduction: Current treatment options for moderate-to-severe atopic dermatitis (AD) are limited and have potentially dangerous side effects. Dupilumab is a novel monoclonal antibody that was recently studied in adult patients with moderate-to-severe AD. Dupilumab inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling and was previously found to be effective in asthma. Considering that both AD and asthma are Th2 cell-mediated inflammatory processes, it is reasonable to suspect that dupilumab would be beneficial in AD.'

Areas covered: This article is a review of the one major clinical trial that assessed the efficacy of dupilumab in patients with AD. Its goal is to provide a comparison to the current modalities for the treatment of AD and expert insight regarding future studies.

Expert opinion: The results of this study are a significant therapeutic advancement. Dupilumab was shown to provide a mean percent change in Eczema Area and Severity Index score of $-74\% \pm 3.6$, in addition to, statistically and clinically significant reductions the severity, symptomatology, and morbidity associated with AD. However, the small sample size makes it difficult to assess the magnitude of this effect. As a result, dupilumab will likely be reserved for cases of severe AD unresponsive to traditional modalities.

Keywords: eczema, interleukin-13, interleukin-4, itch, pruritus, quality of life, sleep

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1. Introduction

Dupilumab is a novel monoclonal antibody that was recently studied in adult patients with moderate-to-severe atopic dermatitis (AD) [ClinicalTrials.gov number NCT01259323, NCT01385657, NCT01548404, NCT01639040] [1]. Topical corticosteroids are presently the mainstay of therapy in patients with mild disease. However, questions regarding long-term efficacy, low compliance, and concerns over atrophy have led to the development of other modalities, though risk of skin atrophy is not as pronounced in patients with mild disease. As the disease progresses in severity, patients sometimes require treatment with systemic immunomodulatory agents that have potentially severe side effects, many of which preclude long-term use (Table 1) [2]. Additionally, biologic therapy with omalizumab has been previously attempted; however, no significant improvement was noted [3].

The pathophysiology of AD is complex and abnormal cellular immune-mediated responses are central to the underlying problem. Generally speaking, the currently available systemic medications inhibit the inflammatory effects of both B and T cells. However, abnormal Th2-mediated responses may direct the immune-driven process of acute AD, whereas Th1 lymphocytes play a role in chronic AD [4,5]. Th2 lymphocytes secrete interleukin-4 (IL-4) and interleukin-13 (IL-13) which promote IgE production, down regulation of cutaneous antimicrobial peptides,

Table 1. Comparison of currently available systemic treatments for severe atopic dermatitis [2].

Medication	Mechanism of action	Adverse effects
Cyclosporine	Inhibits calcineurin preventing the production of interleukin-2 (IL-2)	Nephrotoxicity Hyperkalemia Hypertension Hypertrichosis Gingival hyperplasia Tremor Infection/lymphoma
Azathioprine	Purine analog that inhibits DNA production in B and T cells	Nausea/vomiting Bloating Anorexia Headache Elevated LFTs Leukopenia*
Methotrexate	Folate antimetabolite that inhibits dihydrofolate reductase preventing DNA, RNA, and purine synthesis	Nausea/diarrhea/vomiting Stomatitis Elevated LFTs Bone marrow suppression Pulmonary fibrosis
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase preventing purine synthesis in B and T cells	Nausea/vomiting Headache Fatigue Anemia Leukopenia Thrombocytopenia
IFN- γ	Cytokine that activates natural killer cells and enhances macrophage oxidation	Fever Nausea/vomiting Fatigue Myalgia
Systemic corticosteroids	Generalized immunosuppression with multiple effects	Hypertension Glucose intolerance Gastritis Weight gain Osteoporosis Cushing's syndrome Cataracts
Narrowband Ultraviolet B	Downregulation of immune mediating cytokines	Burning Tenderness Erythema Stinging Photoaging Possibility of increased skin cancer risk

*Thiopurine Methyltransferase (TPMT) activity levels should be obtained prior to starting as mutations may lead to more hematologic adverse effects.
LFT: Liver function tests.

and eosinophil recruitment [4]. Dupilumab inhibits IL-4 and IL-13 signaling through its interaction with the α -subunit of the IL-4 receptor (IL-4R α) ultimately blocking the downstream effects of both cytokines [1,6]. Previously, dupilumab has been studied in patients with asthma, and significantly

reduced the number of exacerbations in comparison to placebo [7]. Considering that both AD and asthma are Th2 cell-mediated inflammatory processes, it is reasonable to suspect that inhibition of IL-4 and IL-13 would provide a beneficial response in both diseases. The goal of this paper is to review the efficacy and safety data from one clinical trial on the use of dupilumab in AD and to provide expert insight regarding future studies.

2. Study design

The M12 trial was conducted in five European countries (Czech Republic, France, Germany, Hungary, and Poland) and a total of 109 patients were randomized to either dupilumab 300 mg subcutaneously once weekly as monotherapy or placebo for a period of 12 weeks. Adult patients (≥ 18 years old) with poorly controlled, moderate-to-severe AD with an Eczema Area and Severity Index (EASI) score ≥ 16 , an Investigator's Global Assessment (IGA) score of ≥ 3 , $\geq 10\%$ of body surface area (BSA) affected, and a diagnosis of AD for ≥ 3 years were included in the study. Patients who used topical corticosteroids or calcineurin inhibitors within 1 week and systemic medications within 4 weeks of the trial starting were excluded. Both the investigators and patients were blinded to treatment allocation, and the primary end point of the study was the percent change in the EASI score.

Overall, the trial was designed appropriately. The diagnostic criteria for AD and outcomes assessed are in concordance with the current American Academy of Dermatology guidelines [2]. Concerning outcomes, the EASI is a validated measure of severity with scores ranging from 0 to 72 [1]. It takes into account both the degree of involvement, and objective clinician findings of erythema, induration, excoriation, and lichenification. Higher scores indicate worse disease, and an EASI score above 16 is consistent with moderate-to-severe AD. In comparison, SCORAD is also a validated measure of severity with more widespread clinical trial use. SCORAD scores range from 0 to 103 and higher scores indicate worse disease [1]. Additionally, SCORAD incorporates objective findings, pruritus, and loss of sleep, which provide a better assessment of quality of life. Whereas the use of validated severity indices adds to the strength of the study, the small sample size remains a limitation.

3. Key results

3.1 Percent change in the EASI score

The baseline EASI score in patients randomized to dupilumab was 28.4 ± 1.8 and the mean percent change in the EASI score at the end of 12 weeks was $-74\% \pm 3.6$, which was greater than placebo ($-23.3\% \pm 6.7$, $p < 0.0001$). In comparison, a patient with a moderate AD confined to 30 – 50% of their trunk, upper extremities, and lower extremities would have an EASI score of 21.6. A 75% reduction in the above patient's EASI score would be -16.2 and the minimum clinically

important difference in the EASI score is 6.6 [1]. Thus, these results represent a substantial reduction in disease severity that is comparable to both topical and systemic therapies [8,9]. However, the percent change in the SCORAD score was not reported and would have been valuable in analyzing the primary endpoint.

3.2 Investigator's global assessment (IGA)

The mean baseline IGA score in patients randomized to dupilumab was 3.9 ± 0.1 , and the percentage of patients who achieved a score of (0) clear or (1) almost clear was 40% in comparison to 4% with placebo ($p < 0.0001$). Whereas this is substantial, it should be noted that the EASI score is a validated and reliable method that looks at both the extent of disease and clinical findings to assess the severity of AD. Although widely used in clinical trials, IGA scores are more subjective and may not adequately characterize the true benefit.

3.3 Change in the pruritus numerical-rating scale

The mean baseline pruritus numerical-rating scale score in patients randomized to dupilumab was 6.1 ± 0.2 , and the mean percent change after 12 weeks was $-55.7\% \pm 3.8$ (SE) in comparison to $-15.1\% \pm 5.7$ with placebo ($p < 0.05$). These results represent a substantial reduction in morbidity, as pruritus is related to the severity of AD and ultimately leads to lichenification. However, it is difficult to interpret the magnitude of these results as no reliable measures of quality of life were reported.

3.4 Reduction in BSA affected

The mean baseline BSA affected in patients randomized to dupilumab was $46.8\% \pm 3.3$, and there was approximately a 60% reduction ($-59.9\% \pm 6.4$) in comparison to placebo ($-17.8\% \pm 7.2$). This represents a clinically significant difference in the degree of involvement, but whether a reduction from ~ 50 to 20% BSA affected leads to improved quality of life is uncertain.

3.5 Safety

The most commonly reported adverse events in patients treated with dupilumab were nasopharyngitis, headache, and injection site reactions. However, it was not mentioned whether these results were statistically significant in comparison to placebo. Additionally, a greater number of patients in the placebo group had cutaneous infections in comparison to dupilumab (24.1 vs 5.5%). This is likely due to improved barrier function associated with decreased AD disease severity in these patients. In comparison, dupilumab appears to have a side-effect profile that is substantially better than most systemic agents (Table 1). However, the risk of adverse reactions is yet to be determined, as additional long-term safety data are needed.

4. Expert opinion

Presently, AD is treated in a stepwise fashion based on the severity and degree of involvement with more severe and extensive disease warranting systemic treatments. The results of this study are a significant therapeutic advancement, as unlike the currently available systemic treatments, dupilumab offers a new targeted approach to therapy with minimal (short term) side effects, and may offer substantial benefit for patients with extensive involvement, as the topical application is cumbersome in this setting. However, given the relatively small sample size, it is difficult to assess the magnitude of this effect. In comparison, a study that compared tacrolimus 0.1% ointment twice daily to low-potency topical corticosteroid ointment twice daily in 972 adult patients with moderate-to-severe AD found that 72.6% of patients treated with tacrolimus and 52.3% patients treated with topical corticosteroid were able to achieve at least a 60% improvement in the modified EASI score [8]. Although not clearly evident of clinical success, 85% of patients in the dupilumab group were able to achieve at least a 50% reduction in the EASI score. However, it is important to note that Reitamo *et al.* [8] did not utilize EASI scores to determine baseline disease severity indices, making it difficult to compare the two studies. With regard to systemic treatment, a study that compared weight-based dosing of methotrexate and azathioprine in 42 adult patients with severe AD found a 42 and 39% reduction in SCORAD scores, respectively [9]. Whereas the percent change in the SCORAD score was not reported in the dupilumab study, the reductions observed in both EASI and pruritus numerical-rating scale scores appear to be comparable in efficacy to other systemic treatments.

Although the results of this study are intriguing, it is difficult to extrapolate the results of this trial to our most commonly affected population, children, since only patients over the age of 18 were included. Although AD may persist into the second decade of life, the majority of AD cases affect children and generally begin under the age of 2 years old [10,11]. Regardless, there were statistically and clinically significant reductions the severity, symptomatology, and morbidity associated with AD in this study. These results will likely be received with cautious intrigue as the biologic era unfolds and additional safety data accumulate. Furthermore, although we do not know what this medication will cost, using current biologic medications as a guide would suggest that dupilumab will likely cost tens of thousands of dollars per year, which is significantly higher than the currently available systemic medications for AD. If FDA approved, dupilumab will likely be reserved for cases of severe AD that is unresponsive to traditional modalities, even if able to achieve superiority in head-to-head trials.

Declaration of interest

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Dr. Feldman is the founder and holds stock in Causa Research and holds stock and is majority owner in Medical Quality Enhancement Corporation. He receives Royalties from UpToDate and Xlibris. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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