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PRODUCT REVIEW

A review of dupilumab in the treatment of atopic diseases

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ABSTRACT

Dupilumab is a fully human monoclonal IgG4 antibody directed against the alpha subunit of the IL-4 receptor and prevents the signaling of IL-4 and IL-13, two type 2 cytokines known to be important drivers of atopic diseases. In March of 2017, the United States Food and Drug Administration (FDA) approved dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults that is uncontrolled with topical medications, becoming the first biologic agent approved to treat this chronic skin condition. In October of 2018, Dupilumab received approval by the FDA as an add-on maintenance therapy in patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. This review summarizes the characteristics of dupilumab and the clinical research that has been published to date, including treatment efficacy and adverse events.

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Introduction

Dupilumab (Dupixent®) is a fully human monoclonal IgG4 antibody directed against the alpha subunit of the IL-4 receptor and blocks the signaling of IL-4 and IL-13.[1] IL-4 and IL-13 are key drivers of the type 2 inflammatory response and are integral to the pathogenesis of atopic diseases including atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis. IL-4 has been shown to induce the differentiation of naïve CD4 + T cells into Th2 effector cells, while IL-13 plays an important role in goblet cell metaplasia, mucus hypersecretion, and smooth muscle contractility.[2,3] Both cytokines also promote class switching to IgE and the chemotaxis of eosinophils.[4]

The drug was developed as a joint effort between Regeneron and Sanofi and is currently approved in the United States (U.S.) for the treatment of atopic dermatitis and asthma. In March of 2017, the FDA approved dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults uncontrolled with topical medications, and in October of 2018, dupilumab was approved as an add-on maintenance therapy in patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. Phase 3 clinical trials for the treatment of pediatric atopic dermatitis and chronic sinusitis with nasal polyposis as well as phase 2 trials for the treatment of eosinophilic esophagitis are currently ongoing.

Dupilumab is supplied as a single-dose pre-filled syringe with dosages of either 300 mg per 2 ml solution or 200 mg per 1.14 mL solution. The injections are administered subcutaneously. The recommended dose for atopic dermatitis is an initial dose of 600 mg (two 300 mg injections at different injection sites) followed by 300 mg injected every other week. There are two indicated doses for the treatment of asthma: either an initial dose of 400 mg (two 200 mg injections) followed by 200 mg every other week or an identical dosing regimen to atopic dermatitis.[1] Maintenance therapy with dupilumab is utilized for the chronic suppression of atopic conditions, with the goals of therapy being to decrease symptoms, reduce morbidity, and improve quality of life. At the time of this manuscript's publication, there were no limits as to duration of therapy and no recommendations regarding discontinuing therapy in stable disease. In similarity to other chronic inflammatory conditions treated with monoclonal antibodies, discontinuation of dupilumab therapy would likely lead to increased severity of the underlying disease state.

Pharmacodynamics of dupilumab

Dupilumab inhibits the signaling of IL-4 and IL-13 by blocking the IL-4 receptor subtypes (Type 1 and Type 2) that facilitate the downstream effects of both cytokines. Dupilumab blocks IL-13 signaling via blockage of the Type 2 receptor (a combination of two proteins: IL-13 receptor alpha 1 and IL-4 receptor alpha) and blocks IL-4 signaling via blockage of both Type 1 and Type 2 IL-4 receptors, both of which share the targeted alpha subunit. This action prevents the downstream release of proinflammatory cytokines, chemokines, and IgE, and leads to increased serum levels of IL-4 and IL-13.[1] The Type 2 IL-4 receptor is made up of two proteins: an IL-13 receptor alpha 1 chain to which IL-13 binds and an IL-4 receptor alpha chain which stabilizes the interaction. Blockage of the IL-4 receptor alpha chain by dupilumab prevents the downstream signaling of IL-13. A second IL-13 receptor, IL-13 receptor alpha 2 has also been identified, but is not targeted by dupilumab due to its lack of an IL-4 receptor alpha chain. This receptor was initially believed to be a "decoy" receptor due to its short tail and

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its lack of a secondary signaling domain; however, new research shows that it may be active in numerous signaling pathways and may be an important target for cancer immunotherapy.[5]

Completed clinical trials of dupilumab in patients with atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis have shown that patients treated with dupilumab experience a reduction in levels of circulating T-helper 2 (Th2)-associated biomarkers including IgE, thymus and activation-regulated chemokine (TARC/CCL17), plasma eotaxin-3, and periostin.[6-8] Reductions of fractional exhaled nitric oxide (FE_{NO}) were also seen in patients with asthma treated with dupilumab.[9] Transient elevations in peripheral eosinophil levels have been noted following the initiation of dupilumab.[10] In a study of patients with atopic dermatitis, dupilumab was found to significantly reduce the expression of genes associated with the Th2 inflammatory response (IL-13, IL-31, CCL17, CCL18, and CCL26) and epidermal hyperplasia (K16 and MKi67), leading to reduced thickness of lesional skin when compared to placebo.[11]

Despite its role in modifying the immune cascade, no reduction in IgG response was seen to either tetanus or meningococcal vaccination in patients with atopic dermatitis treated with dupilumab versus placebo.[12]

Pharmacokinetics of dupilumab

Subcutaneous dupilumab exhibits nonlinear target-mediated pharmacokinetics with systemic drug levels increasing at higher than proportional rates to the drug dose (i.e. systemic exposure increased 30-fold following an 8-fold increase in the dose). The bioavailability of dupilumab is estimated to be around 64% following subcutaneous injection. Although the metabolic pathway of dupilumab has not been fully elucidated, it is believed that the molecule is degraded into small peptides and amino acids similarly to endogenous IgG. There have not been any studies on the pharmacokinetics of the drug in patients with hepatic or renal impairment.[1] The pharmacokinetic properties of dupilumab follow a two-compartment model with parallel linear and Michaelis-Menten elimination from the central compartment.[13]

A peak mean ± SD concentration (C_{max}) of 70.1 ± 24.1 mcg/mL was reached approximately 1 week after the initial subcutaneous dose of 600 mg with steady-state concentrations being reached by week 16 for both the 300 mg weekly (QW) and every other week (Q2W) dosages. Within the clinical trials, the mean ± SD steady-state trough concentrations for the 300 mg weekly and every 2 weeks doses were 173 ± 75.9 mcg/mL to 193 ± 77.0 mcg/mL and 73.3 ± 40.0 to 79.9 ± 41.4, respectively. Trough concentrations were noted to be lower in patients with higher body weights and in those over 65 years of age, although no dose adjustments in these populations were recommended.[1] When controlling for body weight, no pharmacokinetic differences were noted between genders.[13] After reaching steady-state, the concentration of drug becomes non-detectable (<78 ng/mL) after 10 and 13 weeks for the 300 mg Q2 W and 300 mg QW doses, respectively.[1]

In a cohort of patients with moderate-to-severe atopic dermatitis, treatment with dupilumab was found to have no meaningful effect on the metabolism of midazolam, omeprazole, S-warfarin, caffeine, or metoprolol (CYP3A, CYP2C19, CYP2C9, CYP1A2, and CYP2D6 substrates, respectively).[14]

Atopic dermatitis

Disease description and pathogenesis (role of IL-4 and IL-13 in atopic dermatitis)

Atopic dermatitis is a chronic inflammatory skin disorder that affects up to 20% of the population worldwide.[15] The condition is characterized by erythematous, xerotic, and lichenified papules and plaques and is associated with intense pruritus and unpleasant sensations such as stinging and burning. These symptoms often result in difficulty sleeping, psychological distress, and loss of productivity that negatively impact patients' quality of life.[16] Before the approval of dupilumab, treatment options included three main categories: topical therapies (corticosteroids, calcineurin inhibitors, and PDE-4 inhibitors), systemic immunosuppressants (corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil), and phototherapy.

The pathogenesis of atopic dermatitis is complex and involves genetic predisposition, impaired skin barrier function, over-activation of the Type 2/Th2 immune response, and an altered skin microbiome. Type 2 inflammatory cytokines, including IL-4 and IL-13, are upregulated in atopic dermatitis and are believed to be important drivers of its pathology.[17] Dupilumab, with its ability to block IL-4 and IL-13 signaling, showed clinical efficacy in clinical trials and was FDA-approved for patients with moderate-to-severe atopic dermatitis uncontrolled with topical medications in March 2017.[1]

Phase 1 trials: M4A and M4B

Two phase 1 studies were completed in the United States and internationally that recruited patients with moderate-to-severe atopic dermatitis. The US study (M4A) recruited 30 patients and randomized them 1:4 to placebo or weekly doses of dupilumab (75 mg, 150 mg, or 300 mg) while the multinational study (M4B) recruited 37 patients and randomized them 1:3 to placebo or weekly dupilumab (150 mg or 300 mg). The primary endpoint in each study was the assessment of drug safety, but clinical endpoints such as Investigator's Global Assessment (IGA) of 0 or 1, Eczema Area and Severity Index (EASI) reduction from baseline, itch questionnaires, and levels of biomarkers (TARC and IgE) were also assessed. Both studies showed clinical improvement and reductions in TARC serum levels in all dupilumab-treated groups in a dose-dependent fashion. The higher doses (300 mg and 150 mg) reached statistical significance over placebo in percentage of patients reaching EASI-50 and change in average weekly pruritus scores.

Eighteen patient from the above phase 1 studies also participated in a sub-study that evaluated RNA-expression in lesional and non-lesional skin. After 4 weeks of therapy, dupilumab doses of 150 mg and 300 mg weekly were found to shift lesional transcriptomes by 24% and 49%, respectively, toward the profile of non-lesional skin. During this same time period, placebo patients experienced an average exacerbation of 21% in lesional transcriptomes ($P < 0.001$).

Phase 2a trials: M12 and C4

Two phase 2a studies were completed. Both were conducted in Europe and recruited patients with moderate-to-severe atopic dermatitis. Study M12 recruited 109 patients and randomized them 1:1 to placebo or dupilumab 300 mg weekly. The primary endpoint was percent change in EASI score, but changes in Body Surface Area (BSA), SCORing Atopic Dermatitis (SCORAD), IGA, and pruritus were also assessed. The second phase 2a study, C4, recruited 31 patients who were randomized 2:1 to dupilumab 300 mg weekly or placebo. Each group in Study C4 also received a standardized regimen of topical steroids to assess combination therapy. Adverse events (AEs) were the primary endpoint of this combination study, with clinical metrics such as EASI, SCORAD, and pruritus assessed as secondary endpoints.

Study M12 showed similar clinical efficacy by week 4 as the phase 1 studies and demonstrated continued clinical improvement through week 12. By day 85, dupilumab-treated patients experienced an average reduction in EASI score of 74.0 ± 3.6% versus 23.3 ± 6.7% for placebo. Sixty-two percent of dupilumab-treated patients achieved EASI-75 at day 85 as compared to 15% of placebo patients ($P < 0.001$).

Study C4, which evaluated combination therapy of dupilumab with topical steroids versus placebo with topical steroids, found that by week 4 all patients on dupilumab had achieved EASI-50 as compared to only 50% of the placebo group ($P = 0.002$). Significant reductions were also seen in the Pruritus Numerical Rating scale (NRS) ($P = 0.005$) despite the dupilumab group using 50% less topical steroids than the placebo group ($P = 0.16$).

Across all phase 1 and 2 studies, rates of AEs and serious adverse events (SAE) were similar between placebo and dupilumab groups. The most common AEs were headache and nasopharyngitis. Thirteen AEs occurred across all four studies, with nine of the 13 occurring in placebo groups. This difference was mainly driven by increased rates of skin infections between the placebo and treatment groups (0.20 infections per patient in the placebo group versus 0.05 infections per patient in the dupilumab groups). No opportunistic infections were reported in the dupilumab-treated groups, and there were no reported deaths in the phase 1 or 2 clinical trials.[18]

Phase 2b trial

Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomized, placebo-controlled, dose-ranging phase 2b trial (clinicaltrials.gov, number NCT01859988)

The phase 2b trial was a randomized, placebo-controlled, double-blind, parallel-group, dose ranging study, which recruited 380 adult patients with moderate-to-severe atopic dermatitis. To be eligible, patients had to have chronic disease (duration greater than or equal to three years), EASI score of at least 12 at screening, IGA score of 3 or more at screening, and BSA involvement of more than 10%. Patients were randomized 1:1:1:1:1:1 to receive dupilumab 300 mg weekly, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, or weekly placebo. Throughout the study, patients were not allowed to apply any medicated topicals – only non-medicated emollients were permitted. The primary efficacy endpoint was percent change in EASI score from baseline to week 16. Secondary assessments included IGA, SCORAD, BSA involvement, and Dermatology Quality of Life Index (DLQI) scores.

All dupilumab-treated groups experienced significant improvement in EASI scores as compared to placebo ($P < 0.001$) at the end of the 16-week treatment period. The change from baseline to week 16 for each group was −73.7% (standard error (SE) 5.2) for 300 mg weekly, −68.2% (SE 5.1) for 300 mg every 2 weeks, −65.4% (SE 5.2) for 200 mg every 2 weeks, −63.5% (SE 4.9) for 300 mg every 4 weeks, −44.8% (SE 5.0) for 100 mg every 4 weeks, and −18.1% (SE 5.2; $P < 0.001$) for placebo. Rates of EASI-50, EASI-75, and EASI-90 were significantly higher for all dupilumab groups with the exception of 100 mg every 4 weeks when compared to placebo. Similarly, all dosages of dupilumab other than 100 mg every 4 weeks resulted in significant reductions in SCORAD and pruritus NRS scores as well as improvement in DLQI scores.

SAEs occurred in 4% of dupilumab-treated patients in comparison to 7% of those who received placebo. The most commonly reported side effects were nasopharyngitis, worsening of atopic dermatitis, headache, and upper respiratory infections (URI). Herpes viral infections occurred at higher rates in the dupilumab groups (8%) vs placebo (2%) – all of these infections were of mild-to-moderate severity and consisted mainly of reactivation of perioral lesions.[8]

Phase 3 trials

SOLO 1 and SOLO 2

SOLO 1 and SOLO 2 were identical randomized, double-blind, placebo-controlled, parallel-group trials that recruited 671 and 708 patients, respectively, with moderate-to-severe atopic dermatitis inadequately controlled with topical therapies. Patients were randomized 1:1:1 to receive dupilumab 300 mg weekly, dupilumab 300 mg every other week, or

placebo for 16 weeks. Medicated topicals and other systemic therapies were prohibited during the trial. The primary efficacy endpoint was the proportion of patients with an IGA score of 0 or 1 and a two-point decrease from baseline. Other endpoints included rates of EASI-50, 75, and 90, improvements in quality of life assessed by DLQI scores, and reductions in pruritus, anxiety, and depression assessed by SCORAD and Hospital Anxiety and Depression Scale (HADS) scores.

All dupilumab-treated patients met the primary endpoint with statistical significance in both trials. In SOLO 1, 37% of patients dosing weekly and 38% dosing every other week achieved an IGA of 0 or 1 as compared to 10% of patients receiving placebo ($P < 0.001$). SOLO 2 had similar results, with 36% of patients in both weekly and every other week dosing regimens achieving IGA scores of 0 or 1 versus 8% of those receiving placebo ($P < 0.001$). Across all dupilumab-treated groups at week 16, rates of EASI-50, EASI-75, and EASI-90 were significantly higher and affected BSA was significantly lower when compared to the placebo groups. In SOLO 1, mean percent change in EASI score was −72.0% ± 2.6 among those dosed weekly, −72.3% ± 2.6 among those dosed every other week, and 37% ± 3.3 among those receiving placebo ($P < 0.001$). Similarly, the reductions seen in SOLO 2 were −69.1% ± 2.5, −67.1% ± 2.5, and −30.9% ± 3.0, respectively ($P < 0.001$). In all dupilumab-treated groups, significant improvements in scores assessing pruritus, quality of life, sleep, anxiety, and depression were seen.

Similar rates of AEs were seen across all groups with nasopharyngitis and atopic dermatitis exacerbations most commonly reported. Bacterial skin infections were reported in 6% of dupilumab-treated patients in SOLO 1 and SOLO2 and in 8% of the placebo group in SOLO 1 and 11% of the placebo group in SOLO 2. Herpes infections were seen in 4% (dupilumab weekly), 7% (dupilumab every other week), and 4% (placebo) of SOLO 1 patients and in 5%, 4%, and 3% of SOLO 2 patients, respectively. Patients receiving dupilumab experienced higher rates of injection site reactions, while patients receiving placebo experienced higher rates of skin infections and atopic dermatitis exacerbations. Conjunctivitis from any cause occurred more frequently in patients receiving dupilumab, with 60 combined cases from all dupilumab groups versus 7 total cases from the placebo groups. Multiple cases of transient peripheral eosinophilia were noted in the dupilumab groups upon drug initiation, but these trended toward baseline by week 16.[10]

Liberty AD chronos

LIBERTY AD CHRONOS is a randomized, placebo-controlled, double-blind, multinational, parallel-group phase 3 trial, which recruited 740 patients with moderate-to-severe atopic dermatitis that remained uncontrolled despite appropriate topical therapy or systemic treatment. Patients were randomized 3:1:3 to receive dupilumab 300 mg weekly (QW), dupilumab 300 mg every other week (Q2W), or placebo for a 52-week treatment period. In addition to dupilumab, all treatment groups were allowed to use topical steroids (once daily medium or low-potency) and topical calcineurin inhibitors. Patients requiring high-potency rescue topical steroids were allowed to continue the study drug, while patients requiring rescue phototherapy or other systemic medications were temporarily discontinued on the study drug but were allowed to restart once rescue therapy was complete. Co-primary endpoints were patients who attained an IGA score of 0 or 1 with at least a 2-point reduction from baseline to week 16 and the proportion of patients achieving EASI-75 by week 16. Secondary endpoints included changes in pruritus scores, SCORAD scores, Patient Oriented Eczema Measure (POEM) scores, HADS scores, DLQI scores, and changes in EASI score from baseline to week 52.

Patients receiving either dose of dupilumab with concomitant topicals were more likely to achieve the co-primary endpoints than patients receiving placebo with concomitant topicals. An IGA score of 0 or 1 with at least a 2-point reduction from baseline was achieved by 39% of both the QW and Q2W dupilumab plus topicals groups versus 12% of patients receiving placebo plus topicals ($P < 0.001$ for each). By week 16, 64% of the weekly dupilumab group and 69% of the Q2W dupilumab group achieved EASI-75 in comparison to 23% of the placebo group ($P < 0.001$ for each). Pruritus NRS improvement of 4 or higher was seen in 51% of patients treated weekly with dupilumab plus topicals, 59% of patients treated Q2W with dupilumab plus topicals, and 20% of patients treated with placebo plus topicals ($P < 0.001$ for each). Similarly, significant improvements were seen in SCORAD scores, POEM scores, DLQI scores, and HADS scores amongst patients receiving dupilumab plus topicals versus patient receiving placebo plus topicals despite the latter group requiring more frequent use of topical medications and topical/systemic rescue therapies. Overall, 52% of the placebo plus topicals group required some sort of rescue treatment in comparison to 17% of the dupilumab QW group and 16% of the dupilumab Q2W group.

Rates of AEs were similar amongst all groups. The placebo plus topicals group experienced higher rates of SAEs and discontinuations, driven mainly by atopic dermatitis flares. Injection-site reactions were more common in the dupilumab groups and were mild or moderate in severity. Two patients reported these reactions as their reason for early discontinuation. Conjunctivitis of any etiology was reported more frequently in patients who received dupilumab. Reactions were typically mild or moderate and occurred in 59 patients in the dupilumab QW group, 15 patients in the dupilumab Q2W group, and 25 patients in the placebo group. Three patients total had severe cases of conjunctivitis: one case of severe allergic conjunctivitis in both the dupilumab QW and placebo groups and one case of severe bacterial conjunctivitis in the dupilumab QW group. Only one study discontinuation occurred due to conjunctivitis, with most episodes resolving with topical eye treatments. Overall, rates of herpes infections were similar between groups, with localized herpes simplex infections more common in patients receiving dupilumab and herpes zoster and eczema herpeticum more common in placebo-treated patients. Non-viral skin infections were more

common in the placebo plus topicals group than the dupilumab QW or Q2W groups (18% vs 8% vs 11%, respectively).[19]

Liberty AD café

Liberty AD Café is a randomized, double-blind, placebo-controlled, parallel-group phase 3 study, which enrolled 325 adult patients with chronic moderate-to-severe atopic dermatitis not adequately controlled with topicals. To be eligible, patients must also have either failed treatment with cyclosporine due to lack of efficacy or intolerance or have a medical contraindication to treatment with cyclosporine. Patients were randomized 1:1:1 to receive dupilumab 300 mg weekly (QW), dupilumab 300 mg every other week (Q2W), or placebo for 16 weeks. Patients in all arms were also allowed to use medium or low-potency topical corticosteroids (TCS) daily to active lesions throughout the study. The primary endpoint was the proportion of patients in each arm achieving EASI-75 by week 16. Secondary endpoints at week 16 included assessments of SCORAD scores, average weekly pruritus NRS scores, BSA, DLQI scores, POEM scores, and HADS scores.

Treatment with dupilumab plus TCS significantly increased the rates of EASI-75 at week 16 when compared to placebo plus TCS, with 59.1% of the QW group, 62.6% of the Q2W group, and 29.6% of the placebo group reaching the primary endpoint ($P < 0.001$ for each vs placebo). The effect of dupilumab on EASI-75 proportions remained significant regardless of previous treatment with cyclosporine, which 65% of the total population had experienced. In addition to significant improvements in all efficacy endpoints, dupilumab therapy plus TCS also significantly improved itch and quality of life as measured by average pruritus NRS scores, DLQI scores, POEM scores, and HADS scores (significance not reached for HADS scores with the weekly dupilumab arm vs placebo). The improvements in clinical and self-reported outcomes occurred despite the dupilumab plus TCS groups using significantly less topical and rescue medications.

Similar rates of AEs were reported across all groups, with two SAEs reported in each arm – none of which were determined to be related to study treatment. The placebo group experienced more bacterial skin infections and atopic dermatitis exacerbations while the dupilumab plus TCS groups experienced more instances of conjunctivitis. Conjunctivitis of any etiology was reported in 16% of the dupilumab QW group, 28% of the dupilumab Q2W group, and 11% of the placebo group, with only one instance being considered severe. Herpes infections were seen in 7% (QW dosing), 5% (Q2W dosing), and 6% (placebo).[20]

AEs of special concern

The prescribing information for dupilumab lists eczema herpeticum, herpes zoster, and conjunctivitis as specific adverse reactions of the drug. Also listed are hypersensitivity reactions, eosinophilia, and cardiovascular events.[1]

A meta-analysis by Ou et. al. of eight trials of dupilumab in patients with atopic dermatitis found that treatment with dupilumab resulted in a lower risk of overall skin infections (risk ratio 0.54; 95% confidence interval (CI) 0.42–0.69), but an increase in injection site reactions, headache, and most strongly, conjunctivitis (RR 2.64; 95% CI 1.79–3.89).[21] A second meta-analysis by Fleming and Drucker further characterized the relationship between dupilumab therapy and infection. They replicated the reduced risk of overall skin infection (RR 0.54; 95% CI 0.42–0.70), but found that dupilumab also reduced the risk for eczema herpeticum (RR 0.34; 95% CI 0.14–0.84) while having no significant impact on overall herpes virus infections (RR 1.16; 95% CI 0.78–1.74).[22] Normalization of the skin barrier is thought to be the driver of this reduced risk of infection.

In the clinical trials for atopic dermatitis, dupilumab-treated patients reported significantly higher rates of conjunctivitis than placebo-treated patients. Importantly, this increased risk has not been seen in the trials for asthma and chronic sinusitis.[10] Episodes of conjunctivitis have generally been mild to moderate in severity and were rarely the cause of drug discontinuation. In one case series of 142 patients with atopic dermatitis treated with dupilumab, 12 patients developed signs and symptoms of conjunctivitis. Of those 12 patient who developed conjunctivitis, one patient discontinued dupilumab temporarily while two discontinued permanently.[23] The majority of cases reported during the clinical trials were resolved or resolving by the end of the treatment periods.[20] A case series of 13 patients with atopic dermatitis who developed conjunctivitis while taking dupilumab found that the condition could be successfully treated with topical tacrolimus or corticosteroids.[24] Severe atopic dermatitis, preexisting conjunctivitis, and an increased atopic phenotype have all been associated with higher risks of developing conjunctivitis in response to dupilumab therapy.[23,24] Throughout the various phase 3 trials of dupilumab for atopic dermatitis (CAFÉ, SOLO 1/2, and CRONOS), no significant differences were noted in the rates of adverse events between patients treated with dupilumab weekly versus those treated every other week.

Asthma

Disease description and pathogenesis

Asthma is a chronic, recurring, inflammatory lung disorder characterized by reversible airway obstruction due to bronchial hyperresponsiveness to various environmental triggers. Typical symptoms include dyspnea, cough, and wheezing with the severity of symptoms ranging from mild to immediately life-threatening. The condition is common globally, with up to 400 million individuals expected to be affected by 2025.[25] Treatment involves a stepwise approach that includes combinations of inhaled corticosteroids, inhaled long-acting beta 2 agonists (LABAs), leukotriene-receptor antagonists, oral LABAs, oral corticosteroids, anti-IgE therapies, and targeted biologics. Despite recent advances, many asthma patients remain incompletely controlled and experience significantly decreased quality of life.[26]

The current understanding of asthma pathogenesis recognizes distinct phenotypes and endotypes, with an upregulated Type 2/Th2 inflammatory response observed in up to 50% of patients.[27] Recent clinical trials of various other monoclonal antibodies targeting Th2 cytokines have shown increased efficacy in patients

with elevated markers of Th2 inflammation, such as increased levels of eosinophils, IgE, TARC, and FE_{NO}.[28,29] Two Th2 cytokines implicated in the pathogenesis of asthma are IL-4 and IL-13, which represent the therapeutic targets of dupilumab. Following the results of the trials detailed below, the FDA approved dupilumab in October of 2018 as an add-on maintenance therapy in patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.

Phase 2a trial

Dupilumab in persistent asthma with elevated eosinophil levels (clinicaltrials.gov number, NCT01312961)

This randomized, double-blind, placebo-controlled, parallel-group, phase 2A study recruited 104 patients with persistent, moderate-to-severe asthma not well controlled on medium to high-dose inhaled glucocorticoids plus long-active beta-agonists (LABAs). Patients must also have had elevated levels of eosinophils ($\geq$ 300 blood eosinophils per μL or $\geq$ 3% sputum eosinophils) to be eligible for the study. Patients were randomized 1:1 to receive either dupilumab 300 mg subcutaneously every two weeks or placebo. LABAs were discontinued at week 4 and inhaled glucocorticoids were tapered and discontinued between weeks 6 and 9. Study drug was administered for up to 12 weeks or until a subject experienced an asthma exacerbation requiring escalation of therapy. Patients were followed for 8 weeks following last injection.

The primary endpoint of asthma exacerbation occurred in 3 of 52 patients receiving dupilumab (6%) and 23 of 52 patients receiving placebo (44%) (odds ratio for dupilumab, 0.08; 95% CI 0.02 to 0.28; $P < 0.001$). Secondary endpoints included time to exacerbation, change from baseline forced expiratory volume in one second (FEV1), morning and evening symptoms and peak expiratory flows (PEF), nocturnal awakenings, Asthma Control Questionnaire-5 (ACQ-5) scores, and number of glucocorticoid inhalations per day. All secondary endpoints except evening PEF, nocturnal awakenings, and various survey items significantly favored the dupilumab group.

Markers of Th2 inflammation were also monitored throughout the study. In the dupilumab group, FE_{NO} levels decreased dramatically at week 4 and remained below baseline through week 12, in contrast to the placebo group, which saw an increase in FE_{NO} from week 8 to 12. Levels of TARC, eotaxin-3, and IgE all decreased from baseline in the dupilumab group and remained unchanged in the placebo group. No differences in levels of carcinoembryonic antigen (CEA) or the chitinase-like protein YKL-40 were noted between the groups or from baseline.

Similar rates of AEs were reported in the placebo (77%) and dupilumab (81%) groups. Most AEs in the dupilumab group were of mild-to-moderate intensity and included injection-site reactions, nasopharyngitis, nausea, and headache. Three patients in the dupilumab group discontinued the study due to an AE (angioedema, worsening of bipolar disorder, and worsening of asthma symptoms). Four patients in the dupilumab group experienced large increases in blood eosinophil levels, an event not seen in the placebo group.[30]

Phase 2b trial

Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta-2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial (clinicaltrials.gov, number NCT01854047)

This randomized, double-blind, placebo-controlled, parallel-group, phase 2B trial recruited 776 patients with asthma treated with medium-to-high dose inhaled corticosteroids plus LABAs. Recruitment continued until 300 subjects with a baseline blood eosinophil count of $\geq$ 300 were obtained. Patients were randomized 1:1:1:1:1 to receive dupilumab 200 mg every 4 weeks, 300 mg every 4 weeks, 200 mg every 2 weeks, 300 mg every 2 weeks, or placebo. Patients continued their baseline inhaled steroids and LABAs throughout the study and were followed for a 24-week treatment period and a 16-week follow-up period.

The primary endpoint was change in FEV_1 from baseline to week 12 in patients with blood eosinophil counts of at least 300. Across all dose regimens except 200 mg every 4 weeks, dupilumab significantly (300 mg every 4 weeks, $p = 0.0212$; 200 mg every 2 weeks, $p = 0.0008$; 300 mg every 2 weeks, $P = 0.0063$) increased FEV_1 versus placebo in this subpopulation with a range of 0.17 liters (L) (95% CI 0.03–0.32) to 0.26 L (0.11–0.40). Across the study, dupilumab increased the FEV_1 at week 24 by 16.6% to 17.3% in the overall population, 22.9% to 24.9% in the eosinophilic subgroup, and 12.6% to 13.4% in the non-eosinophilic subgroup. Dupilumab dosed every 2 weeks also reduced annualized rates of severe asthma exacerbations across both eosinophil-count groups by 33% to 81%. Every two-week dosing also showed significant improvements in ACQ-5 and Asthma Quality of Life Questionnaire (AQLQ) scores at week 24 from baseline.

Rates of AEs were similar across all study groups (75% with placebo vs 75–83% with dupilumab). The most common events included upper respiratory infections (14% vs 18% for placebo), headache (10% vs 13% for placebo), and injection site reactions (18% vs 13% for placebo). SAEs occurred in 45 (7%) of patients treated with dupilumab and 9 (6%) of patients receiving placebo. Two deaths occurred in the settings of acute cardiac failure and metastatic gastric cancer. Transient eosinophilia was noted in the higher eosinophil-count group and was present from weeks 4 to 16. One patient discontinued study treatment due to hypereosinophilic syndrome, which was quickly reversed with methylprednisolone.[31]

Phase 3 trials

Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma (LIBERTY ASTHMA VENTURE clinicaltrials.gov number, NCT02528214)

This international, randomized, double-blind, placebo-controlled, phase 3 trial enrolled 210 patients with glucocorticoid-dependent severe asthma and randomized them 1:1 to

receive either dupilumab 300 mg every 2 weeks or matched placebo as add-on therapy. Patients were allowed to continue high-dose inhaled glucocorticoid and up to two controller medications (LABA or leukotriene-receptor antagonists), but dosages of oral steroids were decreased every 4 weeks over the course of the 24-week intervention period. Oral steroid doses were reduced until patients experienced a severe exacerbation, required an increased dose of oral steroid, or had an increase of 0.5 in their ACQ-5 score. The primary endpoint was percent reduction in oral glucocorticoid dose from baseline to week 24 while maintaining asthma control.

At week 24, the least squares mean change in oral glucocorticoid dose was −70.1% ± 4.9 in the dupilumab group and −41.9% ± 4.6 in the placebo group ($P < 0.001$). Eighty percent of the dupilumab-treated group experienced at least a 50% reduction in oral steroid dose as compared with 50% in the placebo group ($P < 0.001$). Reductions of at least 75% and 90% were also significantly more common in the dupilumab group, and 69% of dupilumab-treated patients were able to decrease their oral steroid dose to less than 5 mg per day versus only 33% of placebo-treated patients ($P < 0.001$). While significant reductions were seen across all patients in the dupilumab group, its effect was largest in those patients with elevated baseline levels of blood eosinophils. In patients whose steroid dose decreased by at least 50%, the odds ratio for dupilumab versus placebo was 6.59 (95% CI, 2.13 to 20.42) in patients with elevated blood eosinophils ($\geq$ 300) and 2.91 (95% CI, 1.28 to 6.63) in patients with less than 300 eosinophils/microliter. By the end of the intervention period, 48% of the dupilumab-treated patients had discontinued oral steroids completely compared to 25% of placebo-treated patients ($P = 0.002$). Treatment with dupilumab also resulted in a severe exacerbation rate that was 59% (95% CI, 37 to 74) lower than the placebo group – these benefits were again more pronounced in the cohort with elevated levels of Th2 biomarkers. Increases in FEV_1, improvement in ACQ-5 scores, and decreases in FE_{NO} also all significantly favored the dupilumab group.

AEs were reported in 62% of the dupilumab group and in 64% of the placebo group. The most common events in each group were viral URIs (9% of dupilumab patients vs 18% of placebo patients), bronchitis (7% vs 6%), sinusitis (7% vs 4%), influenza (3% vs 6%), and asymptomatic eosinophilia (14% vs 1%). Injection site reactions were reported by 9% of dupilumab-treated patients and 4% of placebo-treated patients. There were nine (9%) SAEs in the dupilumab group and six (6%) in the placebo group with no deaths occurring in either. No episodes of conjunctivitis were seen throughout the study.[9]

Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma (LIBERTY ASTHMA QUEST clinicaltrials.gov number, NCT02414854)

This randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial recruited 1,902 patients with moderate-to-severe asthma uncontrolled on medium-to-high dose inhaled glucocorticoids and up to two additional controllers (LABA or leukotriene-receptor antagonist) and randomized them 2:2:1:1 to receive dupilumab 200 mg every 2 weeks, 300 mg every 2 weeks, or matched placebos as add-on therapy. The intervention period lasted 52 weeks, and patients were then followed for an additional 12 weeks. Primary endpoints were annualized rates of severe exacerbations and change in FEV_1 from baseline to week 12.

Annualized rates of severe exacerbations were 0.46 (95% CI, 0.39 to 0.54) in the dupilumab 200 mg group vs 0.87 (95% CI, 0.72 to 1.05) in matched placebo and 0.52 (95% CI, 0.45 to 0.61) in the dupilumab 300 mg group vs 0.97 (95% CI, 0.81 to 1.16) in matched placebo for an overall reduction in exacerbation rates of 47.7% ($P < 0.001$) and 46% ($P < 0.001$) respectively. Rates of severe exacerbations were significantly lower with both doses of dupilumab in patients with blood eosinophil counts of $\geq$ 150 per microliter, but in patients with less than 150 eosinophils per microliter, exacerbation rates between the dupilumab and placebo groups were similar (0.47 (95% CI, 0.36 to 0.62) for low-dose group vs 0.51 (95% CI, 0.35 to 0.76) for placebo and 0.74 (95% CI, 0.58 to 0.95) for high-dose vs 0.64 (95% CI, 0.44 to 0.93) for placebo).

Change in FEV_1 at week 12 from baseline was 0.32 L for the 200 mg dupilumab group vs 0.18 L for matched placebo (difference of 0.14 L, $P < 0.001$) and 0.34 L for the 300 mg dupilumab group vs 0.21 L for matched placebo (difference of 0.13 L, $P < 0.001$). As with exacerbation rates, larger changes in FEV_1 were seen in the cohort of patients with higher levels of blood eosinophils. Among patients with eosinophil counts $\geq$ 300 per microliter, change in FEV_1 at week 12 was 0.43 L for the 200 mg dupilumab group vs 0.21 L for placebo (difference of 0.21 L; 95% CI, 0.13 to 0.29) and 0.47 L for the 300 mg dupilumab group vs 0.22 L for placebo (difference of 0.24 L; 95% CI, 0.16 to 0.32; $P < 0.001$). Among patients with eosinophil counts < 150 per microliter, change in FEV_1 at week 12 was 0.19 L for the 200 mg dupilumab group vs 0.13 L for placebo (difference of 0.06 L; 95% CI, −0.04 to 0.15) and 0.20 L for the 300 mg dupilumab group vs 0.11 L for placebo (difference of 0.09 L; 95% CI, −0.01 to 0.18). Patients with baseline blood eosinophil counts between 150 and 300 per microliter experienced mixed results. Greater changes in FEV_1 were similarly seen in patients with higher baseline levels of FE_{NO}. Improvements in ACQ-5 scores, morning and evening asthma symptom scores, and peak expiratory flow were also seen in the dupilumab-treated group along with a 46.8% reduction in hospitalizations and ED visits. Greater reductions in IgE, periostin, eotaxin-3, and TARC were seen in the cohorts receiving either dose of dupilumab.

Similar rates of AEs were seen between the combined dupilumab groups (81.0%) and combined placebo groups (83.1%). Injection site reactions were the only common AE that occurred more frequently in the dupilumab groups (15.2% of 200 mg dose arm and 18.4% of 300 mg dose arm) than the matched placebo groups

(5.4% and 10.3%, respectively). Eosinophilia was seen in 52 (4.1%) of dupilumab-treated patients and 4 (0.6%) placebo-treated patients. Four patients with eosinophilia who received dupilumab experienced clinical symptoms, and two resulted in SAEs (worsening of hypereosinophilia and chronic eosinophilic pneumonia). Eosinophilia resulted in discontinuation of the intervention in eight patients (seven in the dupilumab groups and one in the placebo group). In total, 1.2% of dupilumab-treated patients experienced eosinophil counts of > 3,000 per microliter compared to 0.3% of placebo-treated patients. SAEs were seen in 8.2% (104 total) of patients who received dupilumab and 8.4% (53 total) of patients who received placebo. Pneumonia was the most common SAE and was seen in 0.3% of both cohorts. Eight deaths occurred during the study (5 in dupilumab groups and 3 in placebo group) – none of which were considered related to the intervention.[7]

Chronic rhinosinusitis and nasal polyposis

Disease description and pathogenesis (role of IL-4 and IL-13 in chronic sinusitis)

Chronic rhinosinusitis is an inflammatory disorder of the sinuses and nasal passages that has an estimated prevalence of 2.1% amongst U.S. adults.[32] The condition is characterized by nasal congestion, anterior and posterior nasal drainage, facial pain and pressure, decreased sense of smell, and headaches that often result in significantly decreased quality of life.[33] Chronic rhinosinusitis is divided into two distinct subtypes: chronic rhinosinusitis with nasal polyposis (CRSwNP) and chronic rhinosinusitis without nasal polyposis (CRSsNP). Nasal polyps are gelatinous masses that develop in the sinus cavities and nasal passages and contribute to airway obstruction. Treatment options for CRSwNP include nasal saline irrigation, intranasal glucocorticoids, oral antibiotics, oral glucocorticoids, antileukotriene agents, and, in refractory cases, surgical excision.[34]

While the etiology of inflammation in chronic rhinosinusitis has not been fully elucidated, bacterial superantigens have been identified as a crucial component in the pathogenesis of CRSwNP.[35] When compared to patients without polyposis, Caucasian patients with CRSwNP are more likely to have an eosinophilic inflammatory pattern of their nasal mucosa as well as a Th2-skewed local cytokine milieu with elevated levels of IL-4, IL-5, IL-9 and IL-13.[36] This Th2 predominance, in addition to elevated IgE levels to staphylococcal superantigens, has been implicated in the increased risk of comorbid asthma seen in North American and European patients with CRSwNP.[37] IL-4 and IL-13 play an important role in this Th2-driven inflammatory pathway. Due to their similar structures, both of these cytokines are able to bind to the IL-4 receptor, which induces the local production of IgE and upregulates VCAM-1, leading to increased infiltration of eosinophils.[38] Because of its ability to block both IL-4 and IL-13 from binding to the IL-4 receptor, dupilumab was hypothesized to reduce the Th2-predominant inflammation associated with CRSwNP, thus providing symptomatic relief to patients.

Phase 2 trial

An evaluation of dupilumab in patients with nasal polyposis and chronic symptoms of sinusitis (clinicaltrial.gov identifier: NCT01920893)

A phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group study enrolled 60 patients with bilateral nasal polyposis and chronic symptoms of sinusitis uncontrolled on corticosteroid treatment. Patients underwent a four-week run-in treatment period with 100 μg of mometasone furoate nasal spray BID in each nostril. Participants were then randomized to two treatment groups: dupilumab 600 mg loading dose followed by 15 weekly doses of 300 mg or matched placebo for 16 weeks. Patients were monitored for the 4 weeks of run-in therapy, 16 weeks of treatment, and 16 weeks of follow-up, during which they were allowed to continue mometasone furoate nasal spray therapy.

The primary endpoint of mean change in bilateral endoscopic nasal polyp score (score between 0 and 8 with higher numbers indicating worse disease) between baseline and week 16 was −0.3 (95% CI, −1.0 to 0.4) in the placebo group and −1.9 (95% CI, −2.5 to −1.2) in the dupilumab group with a least squares mean difference of −1.6 (95% CI −2.4 to −0.7, $P < 0.001$). Secondary endpoints included reduction in radiographic signs of disease via the Lund-Mackay CT score, increase in morning peak nasal inspiratory flow, improvement in quality of life measured via the 22-item SinoNasal Outcome Test (SNOT-22), and reduction in daily symptoms measured with the University of Pennsylvania Smell Identification Test (UPSIT). All of these secondary endpoints were met with statistical significance between the placebo and treatment groups. Within the subset of patients with comorbid asthma (n = 35), those treated with dupilumab experienced improved lung function (least squares mean difference in FEV_1 of 7.2 with a 95% CI of 0.4 to 13.9 and $P = 0.04$) and increased asthma control (least squares mean difference in the 5-question Asthma Control Questionnaire of −1.1 with a 95% CI of −1.5 to −0.6 and $P < 0.001$). Serum levels of total IgE, TARC, and plasma eotaxin-3 were all significantly reduced in the dupilumab treatment group when compared with placebo via lease squares mean percentages; however, mean blood eosinophil count was not significantly affected.[6]

AEs were reported frequently in both arms of the trial (25 of 30 in the placebo group and 30 of 30 in the dupilumab group). The most common events were nasopharyngitis (33% of placebo group vs 47% of dupilumab group), injection site reactions (7% vs 40%), and headache (17% vs 20%). Six SAEs were reported; these included uterine cancer, transient ischemia attack (TIA), asthma, and nasal polyp in the placebo group, and in the dupilumab group, herpes zoster and arrhythmia with upper extremity pain or numbness. No SAEs were considered related to dupilumab, and no deaths occurred during the active portion of the trial.[6]

Other atopic conditions currently under investigation

As of December 2018, phase 3 clinical trials were underway for pediatric and adolescent atopic dermatitis, pediatric asthma, nasal polyposis, and eosinophilic esophagitis. In addition, phase 2 trials evaluating dupilumab for the treatment of alopecia areata and eosinophilic gastritis were also ongoing. See Table 1 below for more information on current clinical trials.

Expert opinion: important future developments

In the last six years, dupilumab has gone from being a molecule of interest to treating thousands of patients suffering from atopic diseases across two indications. Over the next few years, our knowledge about this drug will continue to expand as further research is completed. It is of utmost importance that safety data continue to be collected and analyzed. While dupilumab's safety profile at this point appears relatively benign, data on adverse events should periodically be reviewed to ensure no harmful signals appear. For patients whose disease remains uncontrolled despite treatment with dupilumab, studies evaluating the safety and efficacy of various combination therapies will also need to be completed. Lastly, further investigation into the mechanism of action of dupilumab-associated conjunctivitis in patients with atopic dermatitis is warranted. If the mechanism of action is deduced, targeted and possibly novel treatment options could help to increase the drug's safety and tolerability.

Conclusions

Throughout the clinical trials of atopic dermatitis, the most common AEs were injection site reactions, headache, and conjunctivitis.[21] Patients should be screened frequently for eye irritation or redness and consultation with an ophthalmologist should be considered. The conjunctivitis experienced by these patients is typically mild-to-moderate in intensity and easily controlled with topical medications in most cases.[24]

Significant AEs in the clinical trials for asthma included injection site reactions and asymptomatic eosinophilia. Elevated levels of peripheral blood eosinophils were typically transient and were associated with initiation of the medication. Rarely, symptoms and sequelae of hypereosinophilia have occurred.[7] Practitioners should be aware of the clinical presentations of vasculitis and eosinophilic pneumonia in order to properly screen their patients. There are currently no recommendations for routine lab monitoring of patients on dupilumab.

In conclusion, dupilumab is a safe and effective treatment option for patients with moderate-to-severe atopic dermatitis and in specific subsets of patients with asthma. Further research is required to evaluate its effectiveness in other atopic conditions and in pediatric populations. Clinical trials for these indications are currently ongoing.

Disclosure of potential conflicts of interest

Dr. Liao has a research grant with Sanofi/Regeneron, which manufactures dupilumab. Dr. Bhutani has a pending research grant with Sanofi/Regeneron. The remaining authors have no conflicts of interest to report.

Table 1. Current clinical trials evaluating the efficacy and safety of dupilumab in various disease states.

Study Title	Phase	Condition	Intervention	Study Population	Status	Patient Number	Identifier
Study to Assess the Long-term Safety of Dupilumab Administered in Participants ≥6 Months to <18 Years of Age With Atopic Dermatitis (AD)	3	Atopic dermatitis	Dupilumab	Pediatrics (≥ 6 months to < 18 years)	Enrolling by invitation	765	NCT02612454
Efficacy and Safety of Dupilumab in Patients ≥12 to <18 Years of Age, With Moderate-to-Severe Atopic Dermatitis	3	Atopic dermatitis	Dupilumab Placebo	Adolescents (≥ 6 months to < 6 years)	Completed	251	NCT03054428
Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion)	3	Asthma	Dupilumab Asthma controllers	Pediatrics (7 to 12 years)	Recruiting	377	NCT03560466
Evaluation of Dupilumab in Children With Uncontrolled Asthma (VOYAGE)	3	Asthma	Dupilumab Placebo	Pediatrics (6 to 11 years)	Recruiting	471	NCT02948959
Study to Determine the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients With Eosinophilic Esophagitis (EoE)	3	Eosinophilic esophagitis	Dupilumab Placebo	Adults and adolescents (12 years and older)	Recruiting	425	NCT03633617
An Evaluation of Dupilumab in Patients With Nasal Polyposis And Chronic Symptoms Of Sinusitis	3	Nasal polyps	Dupilumab Placebo	Adults	Completed	60	NCT01920893
A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps (SINUS-24)	3	Nasal polyps	Dupilumab Placebo	Adults	Completed	276	NCT02912468
A Study to Determine the Safety and Tolerability of Dupilumab (REGN668/SAR231893) in Patients Aged ≥6 to <18 Years With Atopic Dermatitis (Eczema)	2	Atopic dermatitis	Dupilumab	Adolescents (≥ 6 to <18 years)	Completed	78	NCT02407756
Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Severe Atopic Dermatitis (Liberty AD PRESCHOOL)	2	Atopic dermatitis	Dupilumab Placebo	Pediatrics (≥ 6 months to < 6 years)	Recruiting	280	NCT03346434
DEGS – Dupilumab for Eosinophilic Gastritis Study	2	Eosinophilic gastritis	Dupilumab Placebo	Adults	Not yet recruiting	109	NCT01548404
Treatment of Alopecia Areata (AA) With Dupilumab in Patients With and Without Atopic Dermatitis (AD)	2	Alopecia areata	Dupilumab Placebo	Adults	Recruiting	54	NCT03359356
Dupilumab in Chronic Spontaneous Urticaria	2	Chronic urticaria/ Recurrent angioedema	Dupilumab Placebo	Adults	Recruiting	72	NCT03749135
Study of Dupilumab in Adult Patients With Active Eosinophilic Esophagitis (EoE)	2	Eosinophilic esophagitis	Dupilumab Placebo	Adult	Completed	47	NCT02379052

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