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Conflicts of Interest:

Dr. Tyring and Dr. Vangipuram have served as investigators for Regeneron Pharmaceuticals.

ABSTRACT

Atopic dermatitis (AD) is the most common chronic inflammatory disease affecting 2-10% of adults and up to 15-30% of children. Despite a rising prevalence, effective and safe therapeutics for patients with moderate-to-severe AD are limited due to toxicity and side effects. Dupilumab, an interleukin (IL)-4 and IL-13 antagonist that limits type 2 T helper (Th2) driven inflammatory activity, is a promising therapeutic option. In clinical trials, it has demonstrated efficacy by reducing clinical activity and symptoms, and showed improvement in the AD genomic phenotype, including a significant reduction in Th2 chemokines and reversal of key epidermal markers of AD. It also has a favorable safety profile. This review discusses the role of dupilumab in treating Th2 related inflammation, and its efficacy and safety, as demonstrated in clinical trials. Dupilumab (Dupixent®) recently gained US FDA approval for patients with moderate-to-severe AD, and is poised to revolutionize the management of this chronic, relapsing condition.

Key Words:

atopic dermatitis, biologics, dupilumab, eczema, Th2 related inflammation

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease with a prevalence of 2-10% among adults and up to 15-30% among children.[1,2] It is a chronic, relapsing inflammatory skin disorder characterized by intensely pruritic scaly and dry eczematous lesions. AD is often associated with other atopic disorders, such as allergic rhinitis and asthma. It causes substantial morbidity and greatly impacts the quality of life of affected individuals and their families.[3] While around 85% of patients first develop the disease in childhood, adult-onset AD has also been recognized.[4,5] The incidence of AD has been rising over the last decades, especially in industrialized nations.[1] One-third of all adults with AD are classified as having moderate-to-severe disease, representing a large and unmet need for safe, effective and reliable treatments.[6]

Pathogenesis of Atopic Dermatitis

The pathogenesis of AD is complex and includes immunological abnormalities, an impaired epidermal barrier, and altered skin microbiota.[7-10] An increased susceptibility to infections is also observed in patients with AD.[9,10] Immunologically, AD is characterized by excessive T-cell activation, with significant skin infiltration by T-cells and dendritic cells (DCs). There is increased expression of Th2 cytokines in the acute lesional skin of AD patients, with a corresponding decrease in the T helper type 1 (Th1) cytokines.[7,8] T helper type 2 (Th2) cells produce interleukin (IL)-4, IL-5 and IL-13; and activate eosinophils, basophils and mast cells, as well as immunoglobulin E (IgE)-producing B cells, which are all involved in allergic reactions.

In addition, the Th2 cytokines have specific effects on the epidermis, including suppression of keratinocyte differentiation and antimicrobial peptide (AMP) production, which contribute to the AD skin phenotype.[8] High levels of the Th2 cytokines IL-4 and IL-13 in AD skin have been shown to act as inhibitors of both epidermal differentiation and production of AMPs.[8]

Current Treatments

Despite the high prevalence of AD, treatment options for patients with moderate-to-severe disease are limited. Current therapies for AD provide symptomatic relief, in the form of topical emollients and topical anti-inflammatory agents, with limited, nonspecific options for moderate-to-severe disease. Immunosuppressive agents such as cyclosporine, methotrexate, and systemic corticosteroids can only be used as short-term options due to their side effect profile. Off label agents such as mycophenolate mofetil and azathioprine are used when all available options have been exhausted. Narrow band ultraviolet B (UVB) phototherapy is another option; however, it is time-consuming and inconvenient. There is a great unmet need for safe and efficacious longterm therapy for the management of moderate-to-severe AD. Dupilumab is a promising alternative.

Phase 1 and 2 Studies

Dupilumab is a fully human monoclonal antibody that binds to the shared alpha chain subunit of the IL-4 receptor, and blocks both IL-4 and IL-13 signaling. Early-phase studies showed the efficacy of dupilumab in patients with asthma[11,12] and chronic sinusitis with nasal polyposis[13], which are both driven by Th2 cytokines. It is administered subcutaneously. Beck et al. published the first trials involving dupilumab in AD patients in 2014.[14] They conducted four randomized, double-blind, placebo-controlled trials in patients with refractory moderate-to-severe AD. Two of the studies evaluated the safety of dupilumab monotherapy for 4 weeks. Efficacy measurements were obtained as the secondary endpoints of the study. The third study assessed the safety and efficacy of dupilumab monotherapy for 12 weeks, as primary and secondary endpoints, respectively. The fourth study evaluated the incidence and severity of adverse events associated with combination therapy with topical steroids for 4 weeks. Patients who were treated with dupilumab in all four trials experienced rapid improvement in AD disease activity. In the 4-week

monotherapy studies, 59% of patients on dupilumab achieved a 50% reduction in the Eczema Area and Severity Index (EASI-50) as compared to 19% of patients on placebo ($p<0.05$).[14] In the 12-week monotherapy trial, 85% of patients in the dupilumab arm reached EASI-50 as compared to 35% in the placebo arm ($p<0.001$).[14] When combined with topical glucocorticoids, all patients treated with dupilumab reached EASI-50, compared with only half of those receiving topical glucocorticoids plus placebo ($p=0.002$).14 Notably, patients receiving dupilumab used less than half the glucocorticoid therapy compared with those who were on placebo ($p=0.16$).[14]

Hamilton et al. studied the effects of IL-4/IL-13 blockade at the molecular level, via transcriptomic analyses of pre-treatment and post-treatment skin biopsies from 18 patients with moderate-to-severe AD.[15] All subjects received weekly treatment with 150 mg or 300 mg of dupilumab or placebo in the aforementioned 4-week monotherapy trials. Dupilumab improved the AD signature in a dose-dependent manner, with a measurable response after 4 weeks of treatment.[15] The molecular changes paralleled improvements in clinical scores. Dupilumab suppressed mRNA expression of genes related to activation of T cells, DCs, eosinophils, inflammatory pathways, and Th2-inducing chemokines in skin lesions.[15] Moreover, dupilumab reversed the epidermal phenotype of Th2 driven skin lesions of AD, without major effects on the Th1 axis.[15] On the other hand, exacerbation of the AD transcriptome was observed in placebo-treated patients.[15] Thaçi et al. studied the efficacy of dupilumab in 380 patients in a randomized, double-blind, placebo-controlled, dose-ranging phase 2b trial in adult patients with moderate-to-severe AD.[16] Patients were randomly assigned to receive 300 mg of dupilumab once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks, or a placebo. Patients were required to apply a topical emollient twice a day for the first few weeks of the study, and could continue using a topical emollient during the study.In the highest dosage group (300 mg once a week), 73.7% of patients achieved the primary endpoint of EASI-50. In addition, 68.2% of patients in the second highest dosage group (300 mg every 2 weeks), and 44.8% in the lowest dosage group (100 mg every 4 weeks) also achieved EASI-50, compared to 18.1% of placebo patients.[16] The strong placebo effect could be partly explained by the mandatory use of an emollient. Changes in clinical assessment and symptom reduction were noted during the first week of treatment, with the greatest improvement in symptoms achieved with 4 weeks of treatment. This study showed the clinical efficacy of dupilumab at five different dose regimens in moderate-to-severe AD patients, with the most consistent benefits recorded at the higher dose regimens (300 mg once a week and 300 mg every 2 weeks).

Phase 3 Studies

Simpson et al. reported the findings from two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2).[17] Dupilumab 300 mg or placebo was injected subcutaneously weekly or every other week for 16 weeks, in 671 patients in SOLO 1 and 708 patients in SOLO 2. Enrolled patients had moderate-to-severe AD that was inadequately controlled by topical treatment. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment (IGA) and a reduction of 2 points or more in that score from baseline at week 16. In SOLO 1, 37% patients who received dupilumab weekly and 38% of patients who received dupilumab every other week achieved an IGA of 0 or 1, as compared with 10% of patients who received placebo ($p<0.001$ for both comparisons with placebo).[17] Similar results were reported in SOLO 2, with 36% of patients who received dupilumab weekly and 36% of patients who received dupilumab every other week achieved an IGA of 0 or 1, compared to 8% of patients who received placebo ($p<0.001$ for both comparisons).[17] Additionally, in both trials, an improvement from baseline to week 16 of at least 75% on the EASI was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo ($p<0.001$ for all comparisons).[17]

Patient Reported Outcomes

Patients who received dupilumab in clinical trials consistently reported a rapid and substantial reduction in pruritus, as well as improvement in anxiety and depression symptoms and overall quality of life, which further solidifies

dupilumab's role in the management of moderate-to-severe AD. In the early phase trials conducted by Beck et al., patients treated with dupilumab also experienced a notable reduction in pruritus when compared to those on placebo, as measured by the pruritus Numerical Rating Scale (NRS) (56% vs. 15%, respectively; $p<0.05$).[14] Similar results were reported by Thaçi et al. in their phase 2 trial, in which treatment with dupilumab resulted in marked improvement in pruritus NRS scores at week 16, with significant reduction as early as week 1.[15] Improvement in pruritus symptoms was dosedependent. Additionally, dupilumab resulted in improvement of patients' assessment for quality of life: dupilumab improved Dermatology Life Quality Index (DLQI) scores from baseline to week 16 in a dose-dependent manner for all dose regimens ($p<0.0001$) except 100 mg every 4 weeks.[15]

Patient-reported outcomes obtained in Thaçi et al.'s phase 2b trial were further analyzed by Simpson et al.[18] Dupilumab led to rapid and persistent patient-reported and clinically relevant improvements in sleep, mental health, and health-related quality of life, which was most pronounced with the two 300 mg dose regimens. All dupilumab doses except 100 mg every 4 weeks also significantly improved other skin symptoms, such as itchy, bleeding, oozing, cracked, flaking, and dry/rough skin, at 16 weeks when compared to placebo ($p<0.0001$).[18] Among patients who reported moderate or severe pain/discomfort at baseline, 57.4% on the 300 mg weekly dose, 51.2% on the 300 mg every 2 weeks dose, and 53.8% on the 200 mg every 2 weeks dose reported no pain/discomfort at week 16, compared with 20.5% of patients on placebo ($p<0.005$ vs. placebo for all 3 doses).[18] Patients receiving dupilumab also reported significant improvement in sleep relative to placebo ($p<0.05$) starting at week 1, which was maintained over the treatment duration at all doses except 100 mg every 4 weeks.[18] Patients treated with dupilumab reported significant improvements in psychological symptoms at 16 weeks as indicated by reductions in Hospital Anxiety and Depression Scale (HADS) total score. In addition, all dupilumab doses except 100 mg every 4 weeks resulted in consistent and significant ($p<0.05$) improvements on each of the six DLQI domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment) relative to placebo at week 16.[18]

In the SOLO 1 and SOLO 2 phase 3 trials, dupilumab was associated with improvements in pruritus, symptoms of anxiety or depression, and quality of life. By week 2, patient-reported scores with respect to itching were markedly better among patients receiving dupilumab than among those receiving placebo.[17] In these trials, dupilumab significantly reduced patient-reported symptoms of AD and its effect on sleep, anxiety or depression, and quality of life.

Safety

In the phase 1 trials conducted by Beck et al., adverse events occurred with a similar frequency in the placebo and dupilumab groups. Most were graded as mild or moderate in severity and self-limited. However, nasopharyngitis and headache were observed more commonly in dupilumab patients than placebo.[14] These findings were also reported at a higher frequency in patients taking dupilumab for asthma and elevated eosinophil levels.[11] Injection-site reactions were observed more frequently in the dupilumab group. Severe adverse events were reported by 11.2% of placebo patients, compared to 1.5% of dupilumab patients.[14] The majority of these severe adverse events were related to a greater number of skin infections and exacerbations of AD in the placebo groups, which led the authors to speculate that dupilumab improves the skin-barrier function.[14]

In the trial reported by ThaÃ§i and colleagues, in which safety outcomes were monitored from baseline until week 32, the dupilumab and placebo treatment groups had similar rates of treatment-emergent adverse events.[15] Dupilumab was well tolerated in this study, with most adverse events classified as mild or moderate. These included nasopharyngitis, exacerbation of AD, headache and upper respiratory tract infection.[15] Injectionsite reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups; however, the rate of serious treatment-emergent adverse events was higher in the placebo group (7%) than in the dupilumab groups (4%).[15] Herpes viral infections were more frequent in patients given dupilumab vs. placebo (8% vs. 2%,

respectively);[15] this finding was not reported in the first four phase 1 and 2 studies. All herpes viral infections were mild to moderate, and most cases were confined to the perioral area.

Similarly, in the phase 3 trials, the overall incidence of adverse events was similar in the dupilumab and the placebo groups. The most common adverse events in the two trials were exacerbations of AD, injection-site reactions, and nasopharyngitis.[17] The incidence of nasopharyngitis was generally equal across the dupilumab and placebo groups.[17] Dupilumab was associated with a higher rate of injection-site reactions, most of which were mild or moderate. Exacerbations of AD and most types of skin infections were more common in the placebo groups. The rates of conjunctivitis with an unspecified cause and allergic conjunctivitis were higher in the dupilumab groups than in the placebo groups. Herpes infections were reported in 7% of patients receiving dupilumab every week, 4% of dupilumab every other week, and 4% of placebo in SOLO 1. In SOLO 2, herpes infections were reported in 4% of patients receiving dupilumab every week, 5% of dupilumab every other week, and 3% of placebo.[17]

In all reported trials, laboratory values, vital signs, and electrocardiographic assessments did not significantly differ among treatment groups.[14,16,17]

Long-term Efficacy and Safety

In a long-term open label study, dupilumab demonstrated sustained efficacy and safety through 52 weeks of treatment.[19] The percentage of dupilumab-naïve patients or those re-treated with dupilumab, who maintained an IGA of 0-1 at week 52 was approximately equal (49.1% and 50.7%, respectively).[19] Moreover, 73.3% and 80.6% of dupilumab-naïve and re-treated patients, respectively, sustained EASI-75.[19] The decrease in peak pruritus NRS and DLQI were also sustained over the treatment period.

Safety analyses through week 52, which included 459 subjects, did not identify any concerns associated with long-term treatment.[19] The rate of previously noted adverse events (nasopharyngitis, exacerbation of AD, conjunctivitis, and herpes labialis infections) did not increased with long-term treatment; moreover, there were no new side effects or adverse events identified through week 52.

Pediatric Patients and Future Trials

The results of a phase 2a, open-label, ascending-dose, sequentialcohort trial among AD pediatric patients who failed topical corticosteroid therapy recently became available.[20] Up to 20% of these patients previously failed non-steroidal systemic medications. There were four cohorts, which were stratified based on age (age 6 to 11 with an IGA of 4; age 12-17 with an IGA of 3-4) and dosage (2 mg/kg and 4 mg/kg). The study was divided into two parts: in part A, subjects were given one dose and followed for 8 weeks; in part B, subjects were given four weekly doses and followed for 8 weeks. The primary objective of the study was to characterize the pharmacokinetic (PK) profile of dupilumab in the pediatric AD population. Secondary endpoints included the rate of adverse events, percent change from baseline EASI, and percent change in baseline peak pruritus NRS score. Based on the analysis of 77 subjects, the PK profile of dupilumab in pediatric patients with AD was consistent with that observed in adults with moderate-to-severe AD; moreover, it correlated with improvements in EASI score and reduction in pruritus.[20] Both the 2 mg/kg and 4 mg/kg dose regimens showed comparable responses in clinical endpoints; however, the 4 mg/kg dosage was associated with a higher frequency of adverse events, including nasopharyngitis, exacerbation of AD, injection-site reaction, infections, and conjunctivitis.

Future trials for dupilumab include a long-term, open-label extension of the pediatric phase 2a study to assess safety[20], a phase 3 placebo-controlled trial to investigate the efficacy and safety of dupilumab monotherapy in pediatric patients >12 years of age[21], and a study comparing a dupilumab auto-injector device to a pre-filled syringe[22].

Conclusion

Dupilumab is a promising therapeutic option for patients with moderate-to-severe AD. The remarkable and rapid onset of efficacy has been clearly demonstrated in published trials. Moreover, dupilumab has produced significant and sustained improvements in the symptomatology of AD, and has improved the quality of life for patients suffering from this disease. Its approval by the US FDA was based on the efficacy and safety results of phase 3 trials. While investigations of longer duration are needed to further characterize the long-term effectiveness and safety of this drug, especially in the pediatric population, dupilumab is poised to revolutionize the management of moderate-to-severe AD.

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