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Dupilumab Use in Moderate-to-Severe Atopic Dermatitis

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On March 18, 2019, the Food and Drug Administration (FDA) extended the approval for dupilumab to include adolescents 12 to 17 years of age for the treatment of moderate to severe atopic dermatitis not adequately controlled by topical treatment.[1] It may be used alone or in conjunction with topical corticosteroids or topical calcineurin inhibitors applied in limited problem areas. Dupilumab was initially approved by the FDA on March 28, 2017 for use in adults with atopic dermatitis. On October 19, 2018, it was approved for adults and adolescents with moderate-to-severe asthma who have an eosinophilic phenotype or have oral corticosteroid-dependent asthma. This newest action by the FDA makes dupilumab the first biologic to be approved for atopic dermatitis in younger patients.[1-3]

Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that acts as an interleukin-4 (IL-4) receptor subunit alpha (IL-4Rα) antagonist.[1-3] This receptor is found on both IL-4 and interleukin-13 (IL-13). Binding at the IL-4Rα site inhibits IL-4 and IL-13 signaling through type II receptors. A number of cells involved in inflammatory response express IL4R, including mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, and goblet cells. Administration of dupilumab results in inhibition of proinflammatory cytokine release, as well as the production or release of chemokines, nitric oxide, and IgE.

Pharmacokinetics

The pharmacokinetic profile of dupilumab has been evaluated in studies of adults with atopic dermatitis and in those with asthma.[2] Dupilumab demonstrated nonlinear target-mediated pharmacokinetics. Following subcutaneous injection, mean (± SD) trough dupilumab concentrations ranged from 29.2 ± 18.7 mcg/mL to 36.5 ± 22.2 mcg/mL in those receiving 200 mg every other week and from 60.3 ± 35.1 mcg/mL to 79.9 ± 41.4 mcg/mL in patients receiving 300 mg every other week. Bioavailability following subcutaneous injection ranged from 61% to 64%, with a mean volume of distribution of 4.8 ± 1.3 L. Dupilumab is degraded to smaller peptides and amino acids similar to endogenous immunoglobulins. In clinical studies, the median time to non-detectable concentrations ranged from 9 to 13 weeks.

Trough serum concentrations were evaluated in adolescents 12 to 17 years of age receiving doses of 200 mg (in those weighing less than 60 kg) or 300 mg every other week. The mean steady state trough concentration was 54.5 ± 27.0 mcg/mL, similar to the values obtained in adults.[2] These results were replicated in the pharmacokinetic component of a phase 2a ascending-dose study. This study, also conducted by the manufacturer, evaluated dupilumab in 40 adolescents (12 to 17 years of age) with moderate-to-severe atopic dermatitis and 37 children (6 to 11 years of age) with severe disease. Patients received a single dose of 2 mg/kg or 4 mg/kg, followed by a 4-week treatment phase starting 8 weeks after the initial dose.[4,5]

Clinical Experience

Dupilumab has been shown in both clinical trials and post-marketing studies to be a safe and effective therapy for the treatment of atopic dermatitis unresponsive to traditional therapy with topical or systemic corticosteroids, topical calcineurin inhibitors, phototherapy, cyclosporine, or other immunosuppressive agents.[3,6] In their 2018 guideline for the treatment of atopic dermatitis, Boguniewicz and colleagues recommend dupilumab as an option for maintenance therapy in patients with moderate-to-severe disease.[6] They note that, in their opinion, its efficacy and adverse effect profile n children and adults is better than that of immunosuppressive agents or phototherapy. They note, however, that the cost of dupilumab may restrict its use.

Clinical trials in adults have demonstrated significant benefit from the addition of dupilumab in patients with moderate-to-severe atopic

dermatitis. The improvement in symptoms has been sustained with prolonged use, and many patients are able to taper their dose or discontinue oral corticosteroids after dupilumab was initiated. The LIBERTY AD CHRONOS study, a phase 3 randomized, double-blind, placebo-controlled study conducted at 161 centers in 14 countries, demonstrated the efficacy of dupilumab for up to 1 year.[7] A total of 740 adult patients were randomized in a 3:1:3 design to receive a dose of 300 mg once weekly, 300 mg every 2 weeks, or placebo. All patients received topical corticosteroids, or if not indicated or tolerated, a topical calcineurin inhibitor. Primary endpoints were the percentage of patients achieving an Investigator Global Assessment (IGA) score of 0 or 1 on a scale of 0 (clear skin) to 4 (severe disease), with at least a 2-point decrease from baseline, and an improvement in the Eczema Area and Severity Index score of 75% (ESAI-75) or more from baseline at weeks 16 and 52.

At week 16, 39% of the patients in the weekly treatment group and 39% of the patients in the group receiving treatment every other week achieved the IGA goal, compared to only 12% in the placebo group ($p < 0.0001$). Percentages achieving the ESAI-75 goal were 64%, 69%, and 23%, respectively ($p < 0.0001$). These results were maintained at week 52. Injection site reactions were the most commonly reported adverse effects, followed by conjunctivitis in the treatment groups.

The efficacy of dupilumab in adults with atopic dermatitis, as well as its approval for the treatment of moderate-to-severe asthma in adolescents, soon led to off-label use of the drug in refractory cases of atopic dermatitis in adolescents. Earlier this year, Treister and Lio published their experience with using dupilumab off-label for long-term therapy as a case series in *Pediatric Dermatology*.[8] They described six children ranging in age from 7 to 15 year (mean 10.8 years) who were treated between March 2017 and May 2018. All patients had an IGA of 4 at baseline despite treatment with topical corticosteroids, topical calcineurin inhibitors, and phototherapy. Five of the six were also receiving immunosuppression with cyclosporine, mycophenolate, and/or oral prednisone. Patients weighing less than 40 kg received a loading dose of 300 mg followed by a dose of 150 mg every other week. Patients weighing 40 kg or more received a loading dose of 600 mg followed by a dose of 300 mg every other week. Doses were administered by clinic staff to maintain the blind.

The mean initial dose for the six patients was 11.4 mg/kg, with a range of 8.6 to 15 mg/kg. The mean maintenance dose was 5.7 mg/kg, with a range of 5 to 7.5 mg/kg. The mean length of therapy at the time of the analysis was 8.5 months, with a range of 6 to 11 months. All patients had a reduction in IGA score of 2 points or more during treatment. Three patients (50%) improved to an IGA score of 1 with almost clear skin. The percentage of body surface area (BSA) involved decreased from 55% (range 35-70%) at baseline to 25% (range 6-11%) at last follow-up. The authors found that dupilumab produced similar improvement in atopic dermatitis symptoms in adolescents to those reported in adult trials, but acknowledged that further study was needed to optimize dosing.

In the phase 2a dose-ranging dupilumab study described earlier, 78 children from 6 to 18 years of age received a single 2 mg/kg or 4 mg/kg injection followed 8 weeks later by the same dose given weekly for 4 weeks.[4] In the patients between 12 and 17 years of age, the single dose of dupilumab produced an improvement in EASI scores 2 weeks post-dose of 34% in the 2 mg/kg group and 51% in the 4 mg/kg dose, At week 12 following 4 weekly doses, EASI scores improved by 66% in the 2 mg/kg group and 70% in the 4 mg/kg group. The results in the younger children were similar, with improvement in EASI scores of 33% in the 2 mg/kg group and 37% n the 4 mg/kg group at 2 weeks and 63% and 76% in the 2 mg/kg and 4 mg/kg groups, respectively, at week12. Injection site reactions were reported in 5% of the patients and conjunctivitis in 11%.

The FDA approval for use of dupilumab in adolescent atopic dermatitis was based on safety and efficacy data obtained from a multicenter randomized, double-blind, placebo-controlled phase 3 trial of 251 patients between 12 and 17 years of age (mean 14.5 years).[2] All patients had moderate-to-severe atopic dermatitis, defined as an IGA score of 3 or greater, an ESAI of 16 or greater (on a scale of 0 to 72), a minimum body surface area (BSA) involvement of 10%, and an inadequate response to topical corticosteroids. At enrollment, 54% of the patients had an IGA score of 4 and the mean EASI score was 36. Mean BSA involvement was 57%. Forty-two percent had previously received immunosuppressive therapy. Comorbidities were common, with allergic rhinitis in 66%, asthma in 54%, and food allergies in 61% of the patients enrolled in the study.

Patients randomized to receive dupilumab who weighed less than 60 kg received an initial dupilumab dose of 400 mg given subcutaneously followed by 200 mg every other week for 16 weeks. Patients in dupilumab group who weighed 60 kg or greater received the standard adult dose, with an initial dose of 600 mg followed by 300 mg every other week. The primary endpoint was the percentage of patients with an IGA of 0 or 1 with at least a 2-point decrease compared to baseline at week 16. Secondary endpoints included the percentage with improvement in their symptoms of at least 75% or 90% (EASI-75 or EASI-90) and a reduction in the Peak Pruritus Numeric Rating Scale (NRS) by 4 or more points.

Dupilumab produced significant improvement in each outcome measure. At week 16, 24% of the patients in the dupilumab group had an IGA score of 0 or 1, compared to only 2% of those in the placebo group. EASI-75 and EASI-90 scores were achieved in 42% and 23% of the treated patients, compared to 8% and 2% of the placebo group, respectively. Improvement in peak pruritus NRS scores was found in 37% of the dupilumab patients, but only 5% of the controls. The results of this study support the findings from the earlier clinical reports and confirm that dupilumab has a similar efficacy in adolescents to that demonstrated in adults. After 16 weeks of treatment, 42% of the adolescents had at least a 75% reduction in symptoms, similar to the results reported by Blauvelt and colleagues in the LIBERTY AD CHRONOS study where 43% of adults achieved a 75% reduction in symptoms at 16 weeks and 38.8% maintained that level of improvement after 1 year of treatment.[7]

An additional publication has described the successful use of dupilumab in a 14-year-old girl with eosinophilic annular erythema.[9] The patient had experienced 4 months of an annular rash that began on her lower extremities and spread to her trunk, arms, and face, along with severe pruritus. Biopsy results showed acute spongiotic dermatitis with intraepidermal vesicles and intravesicular eosinophils with focal epidermal ulceration. The patient's absolute eosinophil count was 0.70 K cells/μL (normal range 0.05-0.17 K cells/μL), with 11.3% eosinophils (normal range 1 to 3%). Traditional treatments for atopic dermatitis were initiated with minimal response. At 10 months post-diagnosis, a trial of dupilumab was initiated with a one-time dose of 600 mg given subcutaneously followed by 300 mg every 2 weeks. The authors describe dramatic improvement after two doses, with resolution of the lesions and pruritus. At follow-up, she had continued on dupilumab for 5 months without recurrence.

There are a number of active studies with dupilumab currently listed on www.clinicaltrials.gov, including use in infants and younger children from 6 months to 11 years of age with atopic dermatitis (NCT03346434), in children 7 to 12 years of age with asthma (NCT02948959 and NCT03560466), and as adjunctive therapy in children 6 to 17 years of age undergoing peanut allergy desensitization (NCT03793608 and NCT03682770). There are also ongoing studies of dupilumab in adults with eosinophilic esophagitis and chronic rhinosinusitis with nasal polyps.

Contraindications, Warnings, and Precautions

Dupilumab is contraindicated in patients with a history of hypersensitivity to the drug or the excipients used in preparation of the solution.[2] Hypersensitivity reactions to dupilumab appear to be rare, with an incidence < 1% in clinical trials. Symptoms range from pruritus and rash to anaphylaxis or serum sickness. A serum sickness-like reaction has also been reported, associated with the development of high levels of antibodies to dupilumab.

Conjunctivitis has been reported in approximately 10% of patients in dupilumab clinical trials.[2] In the cases reported to date, conjunctivitis has been treated successfully without the need to discontinue dupilumab. In the May 2019 issue of the *Journal of the European Academy of Dermatology and Venereology*, 46 members of the International Eczema Council published a consensus statement to call attention to this adverse effect and provide guidance on the identification and treatment of conjunctivitis in patients with atopic dermatitis with and without dupilumab.[10] The authors recommend that patients and their families be asked about signs and symptoms of eye discomfort, itching, or changes in vision prior to starting dupilumab and at every subsequent encounter. Patients who develop conjunctivitis should be referred to an ophthalmologist, with dupilumab continued whenever possible.

When used for the treatment of asthma, dupilumab has been associated with the development of systemic eosinophilic granulomatosis with polyangitis.[2] Patients and families should report any signs of a rash, pulmonary, or cardiac symptoms to their healthcare provider. While systemic or topical corticosteroids may often be successfully reduced or discontinued after treatment with dupilumab has been started, they should be tapered gradually.[2]

Adverse Effects

In pooled data from three premarketing clinical trials in adults, the most common adverse effects with dupilumab were injection site reactions (reported in 10% of patients receiving doses of either 200 mg or 300 mg), conjunctivitis (reported in 10% of patients receiving 300 mg and 9% in patients receiving 200 mg), blepharitis (< 1% and 5%), oral herpes (4% and 3%), keratitis (< 1% and 4%), eye pruritus (1% and 2%), other herpes simplex virus infections (2% and 1%), and dry eye (<1% and 2%).[2] Fewer than 2% of patients taking dupilumab discontinued therapy because of adverse effects. Data from a trial of 250 adolescents treated for 16 weeks produced similar results. Safety assessment during an open-label continuation study found no differences in the adverse effects reported at weeks 16 and 52.

As with other biologic proteins, dupilumab treatment may result in the formation of antibodies. In studies of patients treated for asthma, 9% developed antibodies to dupilumab, with 4% having neutralizing antibodies. Studies of adolescents being treated for atopic dermatitis have identified antibodies in 16% of patients after

16 weeks of therapy, with 5% having neutralizing antibodies. Dupilumab dose does not appear to be correlated with higher antibody titers.[2]

Drug Interactions

No drug interactions with dupilumab have been identified to date. Patients receiving dupilumab are considered immunosuppressed and should not receive live vaccines due to the risk for infection. Non-live (killed) vaccines may be administered and have been found to produce appropriate seroconversion rates.[2]

Availability and Cost

Dupilumab is available in 200 mg/1.14 mL and 300 mg/2 mL pre-filled syringes for self-administration.[2] The estimated cost for dupilumab is approximately $30,000 per year.[11] The manufacturer provides patient access support through their Dupixent® My Way program. Details of the program are available at https://www.dupixenthcp.com/. In their treatment guideline, Boguniewicz and colleagues provide readers with a table of recommendations for documentation to include when prescribing dupilumab in order to facilitate meeting the requirements for insurance coverage.[4] Additional suggestions for wording appeal letters to insurers is included in the commentary accompanying the article.[5]

Dosing Recommendations

The recommended dose of dupilumab in adults and adolescents weighing 60 kg or more is an initial dose of 600 mg (two 300 mg subcutaneous injections) followed by an injection of 300 mg every other week.[2] In adolescents weighing less than 60 kg, the initial dose of 400 mg (two 200 mg injections) should be followed by a dose of 200 mg every other week. The two injections used for the initial dose should be administered at two separate injection sites. Injections may be administered into the thigh or abdomen at least 2 inches away from the navel. The upper arm may be used for injection by a healthcare provider or trained family member. If a dose is missed, it should be administered within 7 days. If the missed dose was more than 7 days ago, the patients should wait until the next dose to resume their injection schedule.

Summary

Dupilumab offers a new option for the management of moderate-to-severe atopic dermatitis not responsive to traditional therapy. It has been shown to reduce atopic dermatitis symptoms by 75% in most patients for periods up to one year and is generally well tolerated. While dupilumab offers significant advantages over other therapies and may minimize reliance on long-term corticosteroid administration, its cost will likely limit its use.

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