Dupilumab: A review of its use in the treatment of atopic dermatitis

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Atopic dermatitis (AD) is a chronic, pruritic immune-mediated inflammatory dermatosis characterized by a T helper 2 (Th2) immune response phenotype and may be associated with systemic inflammation. Dupilumab is an interleukin 4 (IL-4) receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit. Blockade of IL-4/13 is effective in reducing Th2 response. Dupilumab has recently been approved in the United States and Europe for the treatment of adult patients with moderate-to-severe AD. Clinical trials have shown that adults with moderate-to-severe AD who receive weekly or biweekly dupilumab injections have significantly improved clinical and patient-reported outcomes, including Eczema Area Severity Index, SCORing Atopic Dermatitis, Dermatology Life Quality Index, and itch Numeric Rating Scale scores. Concomitant use of topical corticosteroids along with dupilumab results in a greater improvement in signs and symptoms of AD than with use of dupilumab alone. Biomarker analyses show that dupilumab modulates the AD molecular signature and other Th2-associated biomarkers. Common adverse events reported in the clinical trials were nasopharyngitis, upper respiratory tract infection, injection site reactions, skin infections, and conjunctivitis. These were mild-to-moderate in nature, and overall rates of adverse events occurred with similar frequency between the treatment and placebo groups. There were no significant serious safety concerns identified in phase III clinical trials. Dupilumab, as monotherapy or with concomitant use of topical corticosteroids, can significantly improve clinical outcomes and quality of life in patients suffering from moderate-to-severe AD. Ongoing studies of dupilumab will help determine the clinical efficacy and safety profile of its long-term use. (J Am Acad Dermatol 2018;78:S28-36.)

Key words: biologics; dupilumab; IL-4; IL-13; IL-4Rα; moderate-to-severe atopic dermatitis; systemic therapy.

Atopic dermatitis (AD) is a common, pruritic inflammatory dermatosis. The clinical features and traditional management have been covered elsewhere in this Supplement.

AD is immunologically characterized by the overexpression of T helper 2 (Th2) cytokines, (including interleukin 4 [IL-4], IL-5, and IL-13) and chemokines (C-C motif chemokine ligand 17 [CCL17], CCL18, and CCL22), and IL-22, a Th22 cytokine (Fig 1).[1] IL-4 and IL-13 are cytokines central to the pathogenesis of atopic disease and primarily produced by Th2 cells.[2-4] IL-13 is thought to function as a primary disease-inducing effector cytokine, whereas IL-4 functions as a key amplifier of type 2 immunity by

Publication of this article was supported by Leo Pharma, Bayer, and Sanofi/Regeneron.

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Funding sources: Supported by Bayer, LEO Pharma, and Sanofi.

Disclosure: Dr Gooderham has served as an investigator, speaker, consultant and advisory board member for AbbVie, Actelion, Akros, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GSK, Incyte, Janssen, Leo Pharma, Medimmune, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, UCB, and Valeant. Dr Hong has served as an investigator, speaker, consultant, and advisory board member for Abbvie, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Incyte, Leo Pharma, Medimmune, Novartis, Pfizer, Roche, Regeneron, Sanofi Genzyme, and Valeant. Dr Papp has served as an investigator, speaker, consultant, and advisory board member for AbbVie, Akros, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFile, Celgene, Dermavant, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GSK, Incyte, Janssen, Kyowa Hakko Kirin, LEO Pharma, Medimmune, Meiji Seika Pharma, Merck, Merck Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant. Ms Eshtiaghi disclosed no conflicts of interest.

Accepted for publication December 9, 2017.
Reprints not available from the authors.

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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2017.12.022

facilitating expansion of the $CD4^+$ Th2-cell population in secondary lymphoid organs.[5]

IL-4 and IL-13 can activate and promote survival of Th2 cells, induction of differentiation and activation of myeloid and atopic dendritic cells, activation of B cells, stimulation of IgE class switching, and eosinophil recruitment.[6] As well, type 2 cytokine effects modulate numerous skin changes. These include (1) suppression of terminal differentiation proteins, such as filaggrin, loricrin, and involucrin; (2) inhibition of antimicrobial peptides; (3) upregulation of S100As; (4) induction of epidermal hyperplasia; (5) suppression of lipid synthesis; and (6) induction of spongiosis.[1]

IL-4 and IL-13 levels have been correlated with AD disease activity.[5]

CAPSULE SUMMARY

- Atopic dermatitis is an immune-mediated disorder that is manifested and promulgated by disruption of epidermal barrier function and T helper 2 activation.
- Blockade of interleukin 4 and interleukin 13 is an effective and safe approach to suppressing T helper 2—mediated inflammation and normalization of barrier function.
- Dupilumab is the drug to which all future systemic therapies will be compared.

MECHANISM OF ACTION

Dupilumab, a fully human monoclonal IgG4 antibody, inhibits IL-4 and IL-13 signal transduction through competitively binding to the shared α subunit of the IL-4 receptor.[7] Blocking downstream signaling of IL-4 and -13 has been shown to alter the AD transcriptome in a dose-dependent fashion. Differences in gene expression following administration of dupilumab include (1) downregulation of markers of epidermal proliferation, (2) downregulation of inflammatory mediators, (3) upregulation of structural proteins, (4) upregulation of lipid metabolism proteins, and (5) upregulation of epidermal barrier proteins resulting in normalization of skin.[6]

Dupilumab has also been reported to significantly reduce serum levels of CCL17 (or thymus and activation-regulated chemokine), a key regulator of Th2-mediated immunity and a specific and objective biomarker of AD disease activity.[8]

PHARMACOKINETICS

With a bioavailability of 64%, a subcutaneous injection of dupilumab takes 1 week to reach maximum serum concentration following a loading dose of 600 mg.[9] Steady-state concentrations were achieved by week 16 in both dosing regimens in the phase III studies.[10]

Dupilumab decreases to a nondetectable concentration following the last steady-state dose of biweekly and weekly injections in median times of 10 and 13 weeks, respectively.[9] The total volume of distribution reflects that of serum and is approximately 4.8 plus or minus 1.3 L.

A population-based pharmacokinetic model has been published recently.[11] In this study, it was determined that a 2-compartment model with parallel linear and Michaelis-Mentin elimination from the central compartment properly described the dupilumab concentration-time data in normal volunteers and patients with AD in a larger population. Perhaps surprisingly, a dose adjustment for patient weight was not required.

Inflammatory cytokines can suppress the formation of cytochrome P450 (CYP450) enzymes including the CYP450 2C and CYP450 3A families.[12] Dupilumab inhibits IL-4 and IL-13 receptor signaling, which could normalize levels of these enzymes. Dose adjustment and drug effect monitoring is recommended for CYP450 substrates, particularly those with a narrow therapeutic index (such as cyclosporine and warfarin, for example) upon initiation or discontinuation of dupilumab.[9]

ADAs

Immunogenicity is a risk for any therapeutic protein. The detection of antidrug antibodies (ADAs) depends on the sensitivity and specificity of the assay and the assay's ability to detect an ADA in the presence of a drug. The observed incidence of ADAs, neutralizing antibodies included, is influenced by a number of factors, including assay methodology and platform, sample handling, timing of sample collection, concomitant medications, and underlying disease. As such, rates of antibody formation cannot be compared from one therapeutic protein to another.[9]

When a bridging electrochemiluminescence assay with a sensitivity of 9.9 ng/mL and drug tolerance of 74 ng/mL was used, approximately 7% of patients receiving dupilumab for 16 weeks developed ADAs at some time point.[13] Of the ADAs developed by patients, 30% were classified as neutralizing.[9] Patients who developed ADAs to dupilumab had lower serum concentrations of dupilumab.

A small number of patients in the placebo arms also developed ADAs.[9] ADA titers were generally