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Dupilumab

Updated: August 1, 2018.

OVERVIEW

Introduction

Dupilumab is a human monoclonal antibody to the interleukin-4 (IL-4) receptor which leads to a decrease in production inflammatory mediators of allergic symptoms and is used in the therapy of atopic dermatitis. Dupilumab therapy has not been associated with serum enzyme elevations or to instances of clinically apparent drug induced liver injury.

Background

Dupilumab (doo pil' ue mab) is a recombinant human IgG4 monoclonal antibody to the IL-4 receptor subunit alpha which blocks the activation of the IL-4 signaling pathway. IL-4 plays a critical role in Th-2 inflammatory reactions, important in mediation of allergic and atopic conditions. Therapy with dupilumab has been shown to alleviate signs and symptoms of atopic dermatitis and asthma. Dupilumab was approved for use in the United States in 2017 for therapy of moderate-to-severe atopic dermatitis that does not respond adequately to topical treatments. It is under investigation as therapy of other allergic conditions including asthma. Dupilumab is available in solution in single dose prefilled syringes of 300 mg in 2 mL under the brand name Dupixent. The recommended dose is an initial subcutaneous injection of 600 mg followed by 300 mg every other week. Side effects are not common and generally mild, but can include injection site reactions, conjunctivitis, keratitis and dry eyes. Rare but potentially severe adverse events include hypersensitivity reactions and herpes simplex infections.

Hepatotoxicity

In several large randomized, placebo controlled trials, serum enzyme and bilirubin levels did not change during dupilumab therapy and there were no reported liver related serious adverse events or causes for early discontinuation. There have been no published reports of clinically apparent acute liver injury attributed to dupilumab therapy, but it has had limited general clinical use. Thus, liver injury from dupilumab must be rare, if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Liver Injury

Dupilumab is a human monoclonal antibody and is unlikely to be inherently hepatotoxic. Recombinant proteins are often metabolized in the cells on which they act but are also metabolized in the liver, largely to small peptides and amino acids which may be reused to synthesize proteins and are unlikely to be toxic or immunogenic.

Inhibition of IL-4 signaling does not appear to have serious infectious consequences, although reactivation of herpes simplex infections may be an effect of the agent and its effects (or lack of effects) on hepatitis B virus or tuberculosis infections have not been clearly defined.

Drug Class: Dermatologic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dupilumab – Dupixent®

DRUG CLASS

Dermatologic Agents, Atopic Dermatitis

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Dupilumab	1190264-60-8	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 01 August 2018

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents; "the biological immuno-suppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; dupilumab is not specifically mentioned).

Barnes PJ. Pulmonary pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1031-65.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

Drugs for asthma and COPD. Treat Guidel Med Lett 2013; 11 (132): 75-86. PubMed PMID: 23896773.

(Concise summary of guidelines for therapy of asthma, discusses omalizumab [monoclonal anti-IgE] but not dupilumab).

Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013; 368: 2455-66. PubMed PMID: 23688323.

(Among 104 adults with moderate-to-severe asthma and eosinophilia who were treated with dupilumab or placebo weekly for 12 weeks, clinical exacerbations occurred in only 6% of dupilumab- vs 44% of placebo treated subjects while adverse event rates were similar, and "no clinically significant changes in… clinical laboratory testing… were reported in either group").

Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, et al.; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371: 1198-207. PubMed PMID: 25199059.

(Among 576 patients with severe eosinophilic asthma treated with mepolizumab [75 mg iv or 100 mg sc] or placebo every 4 weeks for 32 weeks, rates of exacerbation were less with mepolizumab [0.9 to 0.9 yearly] vs placebo [1.7 yearly] and side effects were similar; no mention of ALT elevations or hepatotoxicity).

Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371: 130-9. PubMed PMID: 25006719.

(Among 206 patients with moderate-to-severe atopic dermatitis treated in 3 controlled trials of 4 and 12 weeks of therapy, "clinically significant values for clinical laboratory tests…assessments were balanced between treatment groups;" no mention of ALT elevations or hepatotoxicity).

Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016; 375: 2335-48. PubMed PMID: 27690741.

(Among 1379 patients with refractory atopic dermatitis treated in 2 controlled trials, response rates were greater with dupilumab [36% to 38%] than placebo [8% to 10%], while adverse event rates were similar except for injection site reactions [8% to 19% vs 6%] and conjunctivitis [3% to 5% vs 1%], and there were no liver related serious adverse events or causes of early discontinuation).

Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016; 388: 31-44. PubMed PMID: 27130691.

(Among 769 adults with asthma refractory to standard therapies treated with dupilumab [200 or 300 mg every 2 or 4 weeks] or placebo for 24 weeks, lung function improved and exacerbations were reduced with dupilumab and adverse events were similar in all groups; no mention of ALT elevations or liver related severe adverse events).

Chung KF. Dupilumab: a potential new treatment for severe asthma. Lancet 2016; 388: 3-4. PubMed PMID: 27130690.

(Editorial in response to Wenzel [2016] on the potential role of dupilumab in management of severe asthma).

Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, et al. Effect of Subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016; 315: 469-79. PubMed PMID: 26836729.

(Among 60 patients with chronic sinusitis and nasal polyps treated with dupilumab or placebo for 16 weeks, adverse event rates were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, Soong W, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016; 387: 40-52. PubMed PMID: 26454361.

(Among 380 adults with moderate-to-severe atopic dermatitis treated with different regimens of dupilumab or placebo for 16 weeks, clinical responses were more frequent with dupilumab as were adverse events including injection site reactions [7% vs 3%], conjunctivitis [7% vs 3%], and herpes infections [8% vs 2%]; no mention of ALT elevations or liver related adverse events).

Tsianakas A, Ständer S. Dupilumab: a milestone in the treatment of atopic dermatitis. Lancet 2016; 387: 4-5. PubMed PMID: 26454359.

(Editorial in response to Thaçi [2016]).

Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, Simpson EL, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017; 389: 2287-303. PubMed PMID: 28478972.

(Among 740 adults with moderate-to-severe atopic dermatitis treated with topical corticosteroids and either dupilumab or placebo for 1 year, response rates were higher with dupilumab [39% vs 12%] and adverse events were similar in the two groups; there were no liver related serious adverse events and ALT elevations above 3 times ULN occurred in 2% on placebo and 1% on dupilumab).

Dupilumab (Dupixent) for moderate to severe atopic dermatitis. Med Lett Drugs Ther 2017; 59 (1519): 64-6. PubMed PMID: 28419072.

(Concise review of the mechanism of action, clinical efficacy, safety and cost of dupilumab shortly after its approval in the US as therapy of severe atopic dermatitis).

Chang HY, Nadeau KC. IL-4Rα Inhibitor for Atopic Disease. Cell 2017; 170: 222. PubMed PMID: 28708993.

(Brief review of the role of the IL-4 receptor in mediation of IL-4 effects in activating inflammatory pathways and the history of development of IL-4 receptor inhibitors as therapy of atopic dermatitis).

Shirley M. Dupilumab: first global approval. Drugs 2017; 77: 1115-21. PubMed PMID: 28547386.

(Review of the development of dupilumab, its clinical efficacy and safety; does not mention ALT elevations occurring on therapy or instances of hepatotoxicity).

de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, Zhang Q, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol 2018; 178: 1083-101. PubMed PMID: 29193016.

(Among 325 patients with refractory atopic dermatitis treated with dupilumab [weekly or every other week] or placebo for 16 weeks, rates of clinical improvement were greater with dupilumab while adverse event rates were similar; there were no treatment related serious adverse events and no "clinically meaningful differences in laboratory values").

Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378: 2475-85. PubMed PMID: 29782217.

(Among 1902 patients with uncontrolled asthma treated with dupilumab or placebo for 52 weeks, exacerbations of asthma were less with dupilumab and adverse event rates were similar; no mention of ALT elevations or serious hepatic adverse events).