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Emapalumab

Updated: April 12, 2019.

OVERVIEW

Introduction

Emapalumab is a human monoclonal antibody to interferon gamma which acts to block its binding to cell surface receptors and activation of inflammatory signals. Emapalumab is used to treat the severe inflammatory condition of hemophagocytic lymphohistiocytosis (HLH) in which serum gamma interferon levels are elevated. Emapalumab therapy is associated with mild and transient serum enzyme elevations during therapy, but has not been linked to instances of clinically apparent acute liver injury.

Background

Emapalumab (em" a pal' ue mab) is a recombinant, human IgG1 monoclonal antibody to gamma interferon, which inhibits its binding to cell surface interferon receptors and the subsequent activation of intracellular proinflammatory signaling pathways. Gamma interferon levels are known to be elevated in patients with hemophagocytic lymphohistiocytosis (HLH), a life-threatening inflammatory syndrome marked by fever, enlargement of liver and spleen, macrophage update of red blood cells (hemophagocytosis) in bone marrow, spleen and lymph nodes, low natural killer cell activity and high levels of serum ferritin, triglycerides and multiple cytokines. HLH has primary genetic causes but can also arise secondarily as a complication of viral infections, cancer, severe rheumatic diseases and immunosuppression after transplantation. In clinical trials, emapalumab was found to reduce hemolysis and the need for blood transfusions with subsequent improvement in symptoms and quality of life in children and adults with recurrent HLH. Emapalumab was approved for use in HLH in the United States in 2018. Emapalumab is available as a solution in single dose vials of 10 mg in 2 mL or 50 mg in 10 mL (5 mg/mL) under the commercial name Gamifant. The recommended starting dose is 1 mg/kg as an intravenous infusion twice per week. Doses can be modified based upon clinical and laboratory results and therapy continued until hematopoietic cell transplantation, or unacceptable toxicity or until it is no longer thought to be needed. Premedication with dexamethasone is recommended as is prophylaxis for herpes zoster, Pneumocystis jirovecii and fungal infections. Side effects can include infusion site reactions, infections, fever and hypertension. Uncommon severe complications include severe infusion reactions and severe infections, including reactivation of tuberculosis, herpes zoster, pneumocystis jirovecii and fungal infections. Generally, however, the symptoms and complications of the underlying HLH overshadow the adverse effects of inhibition of gamma interferon.

Hepatotoxicity

In clinical trials of emapalumab in patients with HLH, serum enzymes were usually elevated before therapy as a part of the underlying the hyperinflammatory condition. In the small number of patients treated, there was little

evidence of hepatotoxicity, serum enzyme elevations generally being transient and rising only slightly above baseline elevated levels. There have been no reports of clinically apparent liver injury with jaundice attributed to emapalumab therapy in patients with HLH. Because in blocks interferon gamma signaling, it may cause reactivation of microbial organisms that are ordinarily modulated by interferon gamma-induced cytokines or intracellular proteins. Reactivation of tuberculosis, pneumocystis jirovecii, herpes zoster and fungal infections but not hepatitis B or C are listed as potential complications of therapy. In preregistration clinical trials, there were no reports of reactivation of hepatitis B and none have been published since the introduction of emapalumab therapy into clinical practice.

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

Mechanism of Injury

The mechanism by which emapalumab might cause liver injury is unknown. Emapalumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity.

Outcome and Management

Emapalumab therapy has been linked to instances of mild, transient serum enzyme elevations during therapy, typically arising a few weeks after an initial or an early infusion of the monoclonal antibody. These elevations are typically mild and self-limiting and rarely require dose modification. Neverthelss, routine pre-screening as well as on-therapy monitoring of renal, electrolyte and hepatic function is recommended. In patients who develop persistent marked elevations of serum ALT or alkaline phosphatase or who develop jaundice and symptoms, therapy should be interrupted at least until levels return to or near baseline values. Restarting emapalumab should be done with caution and continued monitoring.

Drug Class: Hematologic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Emapalumab – Gamifant®

DRUG CLASS

Hematologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Emapalumab	1709815-23-5	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Abbreviations used: HLH, hemophagocytic lymphohistiocytosis.

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 monoclonal antibodies used as immunosuppressive agents; mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; emapalumab is not specifically mentioned).

Krensky AM, Azzi JR, Hafler DA. Immunosuppressants and toleragens. In, Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 637-54.

(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; mentions that liver enzyme elevations were present in almost all subjects who received emapalumab as therapy for primary HLH and levels increased in a proportion during treatment, but the elevations were usually minimally above baseline and none required early discontinuation of treatment; in studies in normal volunteers, emapalumab was associated with mild aminotransferase elevations during treatment that were rarely above twice normal and always resolved once the infusions were stopped).

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Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. Pediatr Int 2016; 58: 817-25. PubMed PMID: 27289085.

(Review of the clinical features, diagnosis, etiology, natural history and management of HLH before the availability of emapalumab).

Esteban YM, de Jong JLO, Tesher MS. An overview of hemophagocytic lymphohistiocytosis. Pediatr Ann 2017; 46: e309-e313. PubMed PMID: 28806468.

(Review of the causes, clinical features, diagnosis and management of HLH).

Lounder DT, Bin Q, de Min C, Jordan MB. Treatment of refractory hemophagocytic lymphohistiocytosis with emapalumab despite severe concurrent infections. Blood Adv 2019; 3: 47-50. PubMed PMID: 30617216.

(Case report of a child with primary HLH with severe complications and multiorgan failure who received emapalumab on a compassionate use basis [for 14 weeks] and had a dramatic response, beginning within days

of starting infusions and resulting in a complete remission that was maintained for several years after all therapy was stopped).

Al-Salama ZT. Emapalumab: first global approval. Drugs 2019; 79: 99-103. PubMed PMID: 30623346.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy, toxicity and current ongoing evaluation of emapalumab shortly after its approval in the US as therapy of primary HLH).