OVERVIEW
Tocilizumab

Introduction

Tocilizumab is a humanized monoclonal antibody to the interleukin-6 (IL-6) receptor which is used in the therapy of rheumatoid arthritis and other autoinflammatory conditions. Tocilizumab commonly causes mild serum aminotransferase elevations which are usually short lived and asymptomatic and has also been linked to rare instances of clinically apparent liver injury with jaundice.

Background

Tocilizumab (toe" si liz' ue mab) is humanized IgG1 monoclonal antibody to the IL-6 receptor that is used largely as therapy of refractory rheumatoid arthritis and other inflammatory arthridites. Tocilizumab blocks the action of IL-6, which is a key proinflammatory cytokine that mediates a wide spectrum of biologic activities including activation of T cells, differentiation of B cells, induction of acute phase reactants, proliferation of fibroblasts, and damage to cartilage and joints. IL-6 levels are elevated in patients with active rheumatoid arthritis. In controlled trials and open label studies, tocilizumab therapy led to improvements in symptoms and laboratory abnormalities associated with several forms of inflammatory arthritis. Tocilizumab was approved for use in the United States in 2010 and current indications include rheumatoid arthritis and both the polyarticular and systemic forms of juvenile idiopathic arthritis (formerly juvenile rheumatoid arthritis). Tocilizumab is considered a disease modifying antirheumatic drug (DMARD) and improves signs and symptoms of disease and decreases cartilage and tissue destruction. Tocilizumab is given by intravenous infusion every 4 weeks, in doses of 4-12 mg/kg depending upon indication and body weight. Tocilizumab is available in vials of 20 mg/mL under the brand name Actemra. The most frequent side effects are upper respiratory symptoms, headache, infusion reactions and hypertension.

Hepatotoxicity

In registration trials, serum aminotransferase elevations occurred in a high proportion (10% to 40%) of patients receiving tocilizumab. ALT elevations often rose to 1 to 3 times the ULN 2 weeks after each infusion, but decreased towards baseline by the time of the next 4-weekly administration and were usually normal within 8 weeks of stopping the infusions. In some instances (~1% to 2%), levels rose above 5 times the ULN which triggered discontinuation or temporary suspension of treatment. Interestingly, the ALT elevations were somewhat dose related and tended to recur, but did not worsen with repeated exposures. In preapproval registration trials, there were no reports of clinically apparent liver injury with jaundice, and most ALT elevations were without symptoms and

with minimal or no elevations in serum bilirubin or alkaline phosphatase levels. Since its licensure and availability, however, tocilizumab therapy has been linked to several instances of clinically apparent liver injury with jaundice. The injury arose after several months of therapy and was predominantly hepatocellular with no immunoallergic or autoimmune features. While the liver injury was severe, it was usually self-limited with complete recovery in 2 to 3 months. In at least one instance, however, the affected patient died with liver failure and hepatic atrophy that seemed to be initiated by tocilizumab therapy.

Tocilizumab is an immunosuppressive agent, but has not been implicated in causing reactivation of hepatitis B. In several cases reports, tocilizumab has been used safety and without worsening of disease in patients with concurrent chronic hepatitis C, but there has been at least one case report of mild and transient worsening of hepatitis C with its use.

Likelihood score: D (possible cause of clinically apparent liver injury).

Mechanism of Injury

Tocilizumab is a monoclonal antibody and has minimal hepatic metabolism. The mechanism by which it causes liver injury is unknown, but may be the result of its effects on the immune system or on the IL-6 pathway which is important in liver regeneration.

Outcome and Management

The mild liver injury caused by tocilizumab is generally short lived and resolves within 2 to 6 weeks. The majority of patients can continue the 4 weekly infusions, although dose reduction may be warranted. The more severe, clinically apparent liver injury caused by tocilizumab should trigger its permanent discontinuation. The effects of reexposure to tocilizumab after clinically apparent liver injury have not been reported, but rechallenge should probably be avoided. On the other hand, there is no reason to suspect that there may be cross sensitivity to hepatic injury between tocilizumab and other immune modulating biologic agents or anti-IL1 blockers such as anakinra, canakinumab and rilonacept.

Drug Class: Antirheumatic Agents

Other Drugs in the Subclass, Interleukin Receptor Antagonists: Anakinira, Canakinumab,Rilonacept

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PRODUCT INFORMATION
Tocilizumab

REPRESENTATIVE TRADE NAMES

Tocilizumab – Actemra®

DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

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CHEMICAL FORMULA AND STRUCTURE
Tocilizumab

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tocilizumab	375823-41-9	Monoclonal Antibody	Not Available