Formulary Review: Actemra®
Generic Name: Tocilizumab
Manufacturer: Genentech
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Executive Summary

Introduction

Tocilizumab is a monoclonal antibody labeled for the treatment of Rheumatoid Arthritis (RA). Tocilizumab is the first biologic agent to target the proinflammatory cytokine, interleukin 6 (IL-6). Tocilizumab is not labeled for first-line treatment of RA, but as a therapeutic option for adults who do not respond to treatment with anti-tumor necrosis factor (anti-TNF) agents. Tocilizumab alone or in combination with methotrexate or other disease modifying antirheumatic drugs (DMARDs) is more effective than methotrexate or other DMARDs alone.

Pharmacology/Pharmacokinetics

Tocilizumab is a humanized monoclonal antibody which competitively inhibits the actions mediated by IL-6 signaling by binding to both soluble and membrane-bound IL-6 receptors. Steady state mean maximum plasma concentration is 88.3mcg/mL following a 4mg/kg dose and 183mcg/mL following an 8mg/kg dose. Tocilizumab has a steady state volume of distribution of 6.4L. The route of tocilizumab metabolism is unknown. At steady-state, the half-life is approximately 11 to 13 days and is concentration dependent.

Clinical Efficacy

Eight published randomized controlled trials including meta-analysis of 4 trials and one descriptive long-term study evaluated the efficacy of tocilizumab in patients with active RA. No trials compared tocilizumab to TNF antagonists or other biologic DMARDs. Significantly more treatment-responsive patients treated with tocilizumab 8mg/kg monotherapy achieved an ACR20 response (70%) compared to patients treated with methotrexate monotherapy (52%). In patients with active RA despite conventional therapy, significantly more patients achieved an ACR20 response with tocilizumab 8mg/kg alone (63% to 80%) or in combination with DMARD therapy (50% to 74%) compared to those treated with placebo (11%) or DMARDs alone (10% to 41%).

A meta-analysis found similar results in addition to a significant difference in ACR20 response rate between tocilizumab 8mg/kg (56.6%) and tocilizumab 4mg/kg (43.1%). In a long term extension trial, 78% of patients treated with tocilizumab 8mg/kg maintained an ACR20 response after 5 years of treatment. In DMARD-refractory patients, radiographic joint damage in the hands and feet was significantly decreased in Japanese patients treated with tocilizumab for one year compared to those treated with conventional DMARD therapy. The proportion of patients with no radiographic progression was significantly higher in the tocilizumab group (56%) compared to the DMARD group (39%). A few published trials evaluated the efficacy of tocilizumab for off-label indications including Juvenile Idiopathic Arthritis, Castleman disease, and Crohn's disease. More data are needed before tocilizumab can be recommended for these indications.

Adverse Drug Reactions

The most common side effects occurring in patients treated with tocilizumab or tocilizumab in combination with other DMARDs include an increase in alanine aminotransferase concentrations (3-6%), hypertension (4-6%), nasopharyngitis (4-7%), headache (5-7%), and upper respiratory tract infection (6-8%). The most common serious adverse event associated with tocilizumab is serious infection. The overall rate of serious infection in clinical trials was 4.7 events per 100 patient-years. Tocilizumab carries a black box warning describing an increased risk of serious infection in treated patients, especially those taking concurrent immunosuppressants. Other less common serious side effects include gastrointestinal perforation, demyelinating disorders, and malignancy.

Drug Interactions

Do not administer tocilizumab in combination with biologic DMARDs such as TNF antagonists or rituximab. Tocilizumab may result in increased metabolism of CYP450 substrates. Do not administer live vaccines to patients receiving tocilizumab.

Dosage and Administration

Tocilizumab is administered as monotherapy or in combination with other non-biologic DMARDs. The initial recommended dose is 4mg/kg administered as a 60 minute IV infusion every 4 weeks. The dose may be increased to 8mg/kg every 4 weeks in patients not responding adequately to 4mg/kg. Doses greater than 800mg are not recommended. Tocilizumab dosing may require adjustment for neutropenia, thrombocytopenia, hepatic transaminase elevation, or serious infection. No dosage adjustments are recommended for elderly patients or patients with renal insufficiency. Tocilizumab is not recommended in patients with hepatic impairment.

Summary

Tocilizumab is a novel immunomodulator labeled for the treatment of RA refractory to treatment with one or more TNF antagonists. Tocilizumab alone or in combination with DMARDs is more effective than DMARDs alone in the treatment of patients with RA both responsive and unresponsive to conventional therapy. Current guidelines do not address the management of RA refractory to TNF antagonists. Tocilizumab offers another therapeutic option for these patients.

Cost

Drug	Available size	Cost/vial
Tocilizumab	80mg/4mL	$324.03
	200mg/10mL	$810.08
	400mg/20mL	$1620.16

Estimated cost (based on 70kg patient, 4-8mg/kg q 4 weeks): $1134-$2268/month

Look-alike/sound-alike potential

None at this time

Status

Formulary; restricted to use in the outpatient setting