



Tocilizumab for the Treatment of Rheumatoid Arthritis

Tocilizumab (Actemra) was approved by the FDA on January 8, 2010 for the treatment of rheumatoid arthritis. The U.S. approval was based on five pivotal trials and other experience (1-6). Tocilizumab has previously been approved for clinical use in Japan and Europe.

Tocilizumab is a humanized recombinant IgG_{1k} monoclonal antibody against the interleukin 6 receptor. It inhibits IL-6, a cytokine with diverse effects on many cells relevant to RA. Tocilizumab has been approved for use in adults with moderate to severely active RA who have not responded to one or more anti-TNF therapies. It may be used as monotherapy or concomitantly with methotrexate or other DMARDs. It has not been studied, and should not be used, in combination with other biologic DMARDs because of the possibility of increased toxicity.

Tocilizumab has been studied in 5 randomized, double-blind, 6 month trials in adult RA patients. In all trials, tocilizumab was given intravenously every 4 weeks, with no loading dose. In all studies, tocilizumab was superior to comparator at 24 weeks. In studies using different doses, responses to tocilizumab 8 mg/kg were generally higher than those seen with 4 mg/kg.

Table 1. Clinical Trial Response Rates at 24 Weeks

Population Studied	N	Dose	ACR20 (%)	ACR50 (%)	ACR70 (%)
MTX Naïve	570	TCZ 8 mg/kg	70	44	28
		MTX	53	34	15
MTX inadequate response (two trials)	1812	TCZ 4 mg/kg + MTX	48,51	25,32	11,12
		TCZ 8 mg/kg + MTX	56,59	32,44	13,22
		Placebo + MTX	27	11	2
DMARD IR	1216	TCZ 8 mg/kg + DMARD	61	38	21
		Placebo + DMARD	25	9	3
Anti-TNF IR	489	TCZ 4 mg/kg + MTX	30	17	5
		TCZ 8 mg/kg + MTX	50	29	12
		Placebo + MTX	10	4	1

Safety of Tocilizumab

- To date, virtually all human safety data has come from clinical trials, with limited post-marketing data from Europe and Japan. A risk evaluation and mitigation strategy, or REMS, program, designed to guide patient selection and monitoring, is described in the label.
- Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral and protozoal and other opportunistic pathogens have occurred in patients receiving tocilizumab, and a black box warning is included in the label. The rate of serious infections in the all-exposure drug treatment group was 4.7 per 100 patient-years, in the range of other biologic agents. Screening for latent tuberculosis prior to starting therapy is recommended.
- Gastrointestinal perforations have been reported in clinical trials, primarily as a complication of diverticulitis, however, the drug is not specifically contraindicated in patients with diverticular disease.
- Elevations of total, LDL, and HDL cholesterol as well as triglycerides have been seen with tocilizumab use. The package insert gives recommendations for monitoring. Hepatic transaminase elevations are frequently seen, often post-dosing; however clinical hepatitis or hepatic insufficiency was not reported.
- Neutropenia and thrombocytopenia have also been reported, though with no specific relationship with infection or bleeding.

- Other warnings, precautions and recommendations for monitoring and management are in the product insert.
- Live vaccinations should not be given concurrently with tocilizumab. The effectiveness of pneumococcal or influenza vaccinations has not been studied.

Supply, Administration, and Cost

Tocilizumab is supplied as 80mg/4ml, 200mg/10ml, and 400mg/20ml vials. It is given once every 4 weeks as a 60 minute single intravenous drip infusion. The recommended starting dose when used as monotherapy or in combination with DMARDs (including MTX) is 4 mg/kg, with the possibility to increase the dose to 8 mg/kg based on clinical response. There is no set time duration needed prior to advancing to the 8 mg/kg dose and no other specific guidance as to what the clinical response should be. There is no data on intermediate doses between 4 and 8 mg/kg and no guidance on adjusting the dose for lean body weight; there is no dose adjustment for mild renal impairment. Tocilizumab has not been studied in patients with renal failure or hepatic impairment (including HBV and HCV positive serology). A dose reduction from 8 to 4mg/kg is recommended in response to hepatic enzyme elevations, neutropenia, and/or thrombocytopenia. Doses exceeding 800 mg per infusion are not recommended. The cost of tocilizumab is estimated to be \$1,060 to \$2,125 per month, depending on the dose.

The Bottom Line

Tocilizumab is the first biologic agent specifically targeting IL-6. It has demonstrated clinical efficacy in a number of RA populations; In the USA, it is currently approved only for TNF inadequate responders. It has a safety profile similar to other biologic agents with respect to infections, including serious infections – i.e., a slight increased risk, including opportunistic infections. Other safety issues include neutropenia, thrombocytopenia, hepatic transaminase elevations, and lipid elevations, all of which need to be monitored according to guidance provided in the PI. Tocilizumab is given intravenously every 4 weeks at a dose of 4mg/kg, which can be increased to 8mg/kg depending on clinical response.

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References

1. [Ann Rheum Dis.](#) 2008 Nov;67(11):1516-23. Epub 2008 Jul 14. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. [Emery P](#), [Keystone E](#), [Tony HP](#), [Cantagrel A](#), [van Vollenhoven R](#), [Sanchez A](#), [Alecock E](#), [Lee J](#), [Kremer J](#).
2. [Arthritis Rheum.](#) 2008 Oct;58(10):2968-80. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. [Genovese MC](#), [McKay JD](#), [Nasonov EL](#), [Mysler EF](#), [da Silva NA](#), [Alecock E](#), [Woodworth T](#), [Gomez-Reino JJ](#).
3. [Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate.](#) Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröll J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D, Kishimoto T; CHARISMA Study Group. [Arthritis Rheum.](#) 2006 Sep;54(9):2817-29. Erratum in: [Arthritis Rheum.](#) 2008 Mar;58(3):887. PMID: 16947782 [PubMed - indexed for MEDLINE]
4. [Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis \(OPTION study\): a double-blind, placebo-controlled, randomised trial.](#) Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, Woodworth T, Alten R; OPTION Investigators. [Lancet.](#) 2008 Mar 22;371(9617):987-97. PMID: 18358926 [PubMed - indexed for MEDLINE]
5. [Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study.](#) Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, Siri DA, Tomsic M, Alecock E, Woodworth T, Genovese MC. [Ann Rheum Dis.](#) 2010 Jan;69(1):88-96. Epub . PMID: 19297346 [PubMed - in process]
6. [Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis \(the STREAM study\): evidence of safety and efficacy in a 5-year extension study.](#) Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. [Ann Rheum Dis.](#) 2009 Oct;68(10):1580-4. Epub 2008 Nov 19.