



# Monitoring tocilizumab therapy

Evidence Based Medicine

Official recommendations

Expert opinion

Clinical and laboratory parameters should be monitored to assess the effectiveness and safety of tocilizumab therapy.

Treatment monitoring is easy to perform during the monthly intravenous infusions (see the model information letters for the usual rheumatologist and primary-care physician). **European recommendations advise a dosage of 8 mg/kg every 4 weeks.**

In the short-term, patients should be monitored for infusion-related reactions (see the sheet on “Infusion-related reactions”).

● Clinical parameters are monitored to evaluate the treatment response, based on the number of joints with synovitis and the DAS 28. Given the mechanism of action of tocilizumab, markers for inflammation may improve in the absence of clinical improvements. In theory, the objective of tocilizumab therapy is to achieve a remission or, at least, a low level of disease activity (DAS28 <3.2).

- If the DAS 28 score has not fallen by at least 0.6 point after 12 weeks, further treatment with tocilizumab is not recommended.
- Subsequently, the treatment response should be monitored every 3 months by performing a basic evaluation of clinical disease activity and laboratory evidence of inflammation (ESR and/or CRP) (see the model letter for the usual rheumatologist in the appendices).
- Radiographs of the hands and feet should be obtained once a year to monitor progression of the structural damage.
- Safety should be monitored at each tocilizumab infusion and whenever an unexpected event occurs. As with all biotherapies, tocilizumab requires a high level of alertness to bacterial and viral infections and to symptoms that might indicate cancer or a haematological malignancy (see the fact sheets entitled “Bacterial and viral infections” and “Solid cancer or haematological malignancy”).

The data from the OPTION, TOWARD, LITHE, AMBITION, SAMURAI, and RADIATE trials have been used to assess the tocilizumab response profile over at least 6 months. In patients who had responded inadequately to TNF antagonists, tocilizumab therapy produced significant decreases in disease activity. A significant decrease of at least 1.2 in the DAS 28 score was found as early as the first treatment month.

The response occurred promptly (week 2) and increased in magnitude with continued treatment. The optimal time for assessing the effectiveness of tocilizumab therapy is 3 to 6 months after treatment initiation.

### ● **Laboratory tests for treatment monitoring**

Specific laboratory tests are required to monitor tocilizumab therapy, in addition to the inflammation marker assays needed to determine the DAS 28 score and to the laboratory tests required by concomitant treatments (e.g., methotrexate).

The following tests should be obtained before each tocilizumab infusion:

- **Serum transaminases (ALAT and ASAT):** During the clinical trials of tocilizumab, many patients had mild to moderate elevations in serum liver transaminase levels, which were either transient or intermittent, in the absence of clinical liver impairment. If the tests done during the first 3 treatment months show no evidence of liver toxicity, subsequent testing at 3-month intervals is appropriate. If they show transaminase elevation, in contrast, the methotrexate dosage should be adjusted if needed. The CRI expert panel developed two algorithms for managing patients with persistent transaminase elevation (see the sheet entitled “Management of patients with past or present hepatic abnormalities”, Figures 1 and 2).
- **Blood cell counts:** Decreases in neutrophil and platelet counts have been noted after tocilizumab therapy in a dosage of 8 mg/kg in combination with methotrexate. The risk of neutropenia may be increased in patients who have a history of TNF antagonist therapy. Table 2 describes the management strategy for patients in whom neutropenia or thrombocytopenia develops during follow-up.

A **serum lipid profile before** the third tocilizumab infusion, including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides: Increases in these lipid parameters have been reported in patients taking tocilizumab, with no increases in the atherogenicity indices. Total cholesterol elevation responded to statin therapy.

- In women of childbearing potential, contraception should be used throughout tocilizumab therapy and for the first 12 weeks following the last infusion. The tocilizumab elimination half-life suggests 3 months as a reasonable interval between the last infusion and conception (as 97.5% of the drug is eliminated in 3 months) (see the sheet entitled “Management of patients who are pregnant”). The potential effects of tocilizumab on spermatogenesis are unknown. Therefore, men should follow the same precautions as women (3-month wait between the last infusion and conception).

- **Monitoring potential drug-drug interactions:** Tocilizumab therapy may diminish the effectiveness of drugs that are metabolized by the CYP450 isoenzymes such as benzodiazepines, warfarin, atorvastatin, calcium channel inhibitors, and theophylline. Therefore, the dosages of these drugs should be adjusted upon tocilizumab initiation and discontinuation, while bearing in mind the possible persistence of tocilizumab-induced effects on CYP450 isoenzymes for several weeks after the drug is stopped. The most widely used medications that are metabolized by CYP450 are listed in Table 1.

A number of clinical situations (pregnancy, vaccination, travel, surgery, and drug-drug interactions) are discussed in specific fact sheets.