Management of Patients Who Require Surgery or Dental Care

Evidence Based Medicine | Official recommendations | Expert opinion

Surgery in patients receiving tocilizumab therapy may, in theory, lead to infectious complications and/or delayed healing [78, 79]. However, these risks have not been evaluated in detail in published studies (no clear recommendation in the Summary of Product Characteristics). Therefore, the advice given here is based on the opinions of experts, who considered, among other factors, the risk of infection associated with the surgical procedure.

Pharmacokinetic data [47]

The half-life of tocilizumab varies with the concentration of the drug. At the steady state, after a dose of 8 mg/kg every 4 weeks, the effective half-life decreases from 14 to 8 days as the concentrations decline over the interval between infusions.

Anti-IL-6 treatment: data from the literature

No specific data are available on the risk of postoperative infection in patients treated with tocilizumab. The only available study is a retrospective study designed to investigate changes in parameters suggesting infection (fever, CRP level, leukocyte count, neutrophil count, and lymphocyte count) for 2 weeks after surgery in 22 patients receiving tocilizumab (8 mg/kg every 4 weeks) and 22 patients receiving conventional maintenance treatment (including 10 on methotrexate and 17 on glucocorticoids) matched on age, sex, and type of surgical procedure [80].

Tocilizumab therapy was not stopped. The mean time from the last tocilizumab infusion to surgery was 16.0±9.5 days (3-27 days). Nevertheless, no cases of postoperative infection or delayed healing were recorded in the tocilizumab group. Tocilizumab therapy was associated with significantly less body temperature elevation (0.45° *vs* 0.78°C) and with complete absence of the CRP elevation usually seen after surgery: thus, of the 22 tocilizumab patients, 18 had normal CRP values and 4 had increases by 1 to 10 mg/L; whereas CRP levels were elevated in all the controls (55 mg/L on day 1, 29 mg/L after 1 week, and 22 mg/L after 2 weeks). Finally, the leukocyte counts did not change substantially in either group.

The only available recommendations are those found in the practical guide to tocilizumab use issued in 2009 by the Japan College of Rheumatology [43]. Given that tocilizumab may delay healing and can blunt signs of postoperative infection (no fever, normal CRP), the authors recommend that surgery be postponed until at least 14 days have elapsed since the last tocilizumab infusion.

Elective surgery

Given the half-life of tocilizumab and the persistence of active drug levels 4 weeks after the infusion, in this situation where postponing surgery is feasible, the experts recommend stopping tocilizumab therapy at least 4 weeks before the surgical procedure.

This washout period may be adjusted and modified on a case-by-case basis depending on the factors listed below.

- nature of the surgical procedure, as the risk of infection may vary across procedures: "sterile environment" (e.g., cataract surgery), septic environment (e.g., sigmoiditis), or environment at risk for sepsis (e.g., joint replacement surgery);
- co-morbidities and other patient-related factors: history of infection, joint prostheses, diabetes, concomitant corticosteroid therapy;
- severity of the joint disease and degree of control achieved by treatment (a longer wash-out period, which probably decreases the risk of postoperative infection, does not necessarily carry a risk of RA exacerbation).

In every case, tocilizumab therapy should be re-started only when healing is complete and provided there is no infection.

Emergent surgery

For patients who require immediate surgery, the experts suggest the following recommendations.

- Stop tocilizumab therapy.
- Consider prophylactic antimicrobial therapy if the procedure is associated with a high risk of infection (e.g., peritonitis) [81].
- Provide very close postoperative monitoring: special attention should be directed to the local operative site findings and to the presence of pain, as patients on tocilizumab therapy may have no fever or CRP elevation.
- Re-treat with tocilizumab only after complete healing is achieved (and any antibiotics are discontinued), in the absence of infection.

Dental care

Regular oral hygiene and visits to the dentist are recommended. Appropriate dental care should be provided before initiating tocilizumab therapy.

- **Routine dental care (cavities, scaling):**

Although there are no data suggesting a need to discontinue tocilizumab therapy, prophylactic antimicrobial therapy can be suggested.

- **Dental procedures associated with a risk of infection (e.g., extraction, apical granuloma, or abscess):**

Tocilizumab should be stopped at least 4 weeks before the procedure and prophylactic antimicrobial therapy should be suggested [82].

- **Implants :**

There is no definite indication to stop tocilizumab, although a high level of vigilance for potential infection is in order.