Management of Patients

Receiving Concomitant Medications

Evidence Based Medicine | Official recommendations | Expert opinion

The initiation of tocilizumab treatment in combination with conventional DMARDs or after other biological agents raises many questions about the potential of concomitant medications for maintaining or even increasing the effectiveness of tocilizumab and, more importantly, about potential drug-drug interactions that may lead to adverse events. The results of the therapeutic trials have led to the recommendation that tocilizumab be used in combination with methotrexate. However, tocilizumab may be used alone in patients who cannot tolerate methotrexate or in whom further methotrexate therapy would be inappropriate.

In practice, when considering tocilizumab therapy in combination with a DMARD other than methotrexate, the TOWARD study [35] is of interest: the results suggest that such combinations may raise no specific safety concerns and may produce a similar level of therapeutic efficacy.

Tocilizumab therapy can be considered in a patient already treated with another biological agent, provided this last agent is discontinued and a suitable wash-out period is allowed to elapse. The duration of the wash-out period depends on the nature and half-life of the agent. Finally, pharmacokinetic data indicate that methotrexate, NSAIDs, and glucocorticoids have no effect on the clearance of tocilizumab.

In contrast, medications that are metabolized by the cytochrome P450 enzymes require individual dosage adjustment to maintain effectiveness.

Tocilizumab combined with, or given after, another biologic agent

See table 9.

In the RADIATE study [36], treatment with tocilizumab or a placebo combined with methotrexate was offered to patients who had intolerance or an inadequate therapeutic response to TNF antagonists. The interval between TNF antagonist discontinuation and tocilizumab initiation was at least 5 times the half-life of the TNF antagonist. Tocilizumab was more effective than the placebo. The most common adverse events in the tocilizumab group were infections, gastrointestinal symptoms, and headaches.

Tocilizumab in combination with conventional disease-modifying antirheumatic drugs

The OPTION trial [32] established the efficacy and safety of tocilizumab in combination with methotrexate in a mean dosage of 15 mg/week. In patients with intolerance or contraindications to methotrexate, the efficacy and safety of using another DMARD are key concerns. In the TOWARD trial [35], patients received either tocilizumab or a placebo, and they continued their previous DMARDs. The analysis of subgroups based on the nature of the DMARD (methotrexate, antimalarials, sulfasalazine, leflunomide, gold, or azathioprine) showed that, overall, the tocilizumab/DMARD combination was more effective than the DMARD alone and that the various DMARDs used with tocilizumab were fairly well tolerated. In this trial, no noticeable differences in adverse event rates were found across the DMARDs used with tocilizumab.

The most common adverse events in the tocilizumab/DMARD group were headaches, hypertension, neutropenia, cytolysis, and hypercholesterolemia (Table 10). It is unclear whether the tocilizumab/DMARD combination is associated with a higher adverse event rate than tocilizumab alone, as there are no published studies comparing a group of patients given tocilizumab alone to another group given tocilizumab plus a DMARD. However, in 5 patients who experienced neutropenia, decreasing the DMARD dosage significantly improved the neutrophil count.

The ongoing Act-Ray trial is comparing the efficacy and safety of tocilizumab alone or with methotrexate.

Recommendations

Methotrexate is the recommended concomitant medication for patients on tocilizumab. However, in patients with intolerance or contraindications to methotrexate, another conventional DMARD may be used in combination with tocilizumab, and preference should then be given to DMARDs with proven structural effects.

In the event of neutropenia or cytolysis (<3 x ULN), refer to the sheets entitled “Monitoring tocilizumab therapy” and “Management of patients with past or present hepatic abnormalities”.

Tocilizumab monotherapy

In patients who cannot tolerate any of the conventional DMARDs or who are unwilling to continue DMARD therapy, tocilizumab monotherapy may be considered.

➢ In the AMBITION trial [37], patients with RA and no history of failing methotrexate or biological therapy received either methotrexate or tocilizumab monotherapy. Tocilizumab monotherapy was more effective than methotrexate, and safety was fairly similar except for higher rates in the tocilizumab group of grade 3 neutropenia (500-1,000/mm^3; 3.1% *vs*. 0.4%), dyslipidaemia (13.2% *vs*. 0.4%), and severe infection (1.4% *vs*. 0.7%).

➢ The efficacy and safety of tocilizumab were also assessed comparatively to methotrexate in two studies, the SATORI study [33] and the SAMURAI study 31).

- The SATORI study was a multicentre randomised controlled trial in which 125 patients who had failed low-dose methotrexate therapy were given either tocilizumab 8 mg/kg once monthly + placebo or continued low-dose methotrexate (8 mg/kg/week). The proportion of patients who had an ACR20 response after 24 weeks was 80.3% in the tocilizumab group and 25.0% in the methotrexate group ($p<0.001$). A DAS remission was achieved in 43.1% of the tocilizumab patients and in 1.6% of the controls [33]. Serious adverse events were reported in 6.6% of the patients on tocilizumab and 4.7% of those on methotrexate; these events had favourable outcomes with appropriate treatment [34].
- The SAMURAI trial was a multicentre, randomised, controlled, open-label trial in RA patients who had failed at least one DMARD. Tocilizumab 8 mg/kg once monthly (n=158) was compared to DMARDs (including methotrexate, in a mean dosage of 8 mg/week) (n=148). The change in the total Sharp score between baseline and week 52 (primary criterion) was significantly smaller in the tocilizumab group than in the DMARD group ($p<0.001$) and significant differences in favour of tocilizumab were also found for the ACR20, ACR50, and ACR70 response rates ($p<0.001$ for all comparisons). At week 52, a DAS remission was noted in 59.1% of the patients given tocilizumab compared to 3% of those given a DMARD ($p<0.001$). Serious adverse events were reported in 18% of patients given tocilizumab *versus* 13% of those given DMARDs; they consisted chiefly of infections [34].

Tocilizumab combined with an anti-inflammatory or analgesic agent

Population pharmacokinetics studies found no evidence that methotrexate, NSAIDs, or glucocorticoids affected the clearance of tocilizumab [4].

There are no published data indicating increased intolerance to tocilizumab in patients receiving concomitant treatment with a glucocorticoid, an NSAID, or an analgesic.

Tocilizumab combined with other treatments

In vitro vitro studies of cultured human hepatocytes have shown that IL-6 downregulates the expression of the isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Tocilizumab therapy normalizes the expression of these enzymes. Given the fairly long elimination half-life of tocilizumab (t1/2=8 to 14 days), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after tocilizumab discontinuation.

When initiating or discontinuing tocilizumab therapy in patients who are also taking medications that are metabolized by the CYP3A4, 1A2, 2C9, or 2C19 isoenzymes (e.g., atorvastatin, calcium channel inhibitors, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) (Table 1) and that require individual dosage adjustment, monitoring is in order, as the dosages may need to be adjusted to maintain the treatment effect :

- at tocilizumab initiation -> increase in the dosage of the concomitant drug
- 1 to 2 weeks after tocilizumab discontinuation -> decrease in the dosage of the concomitant drug.