Management of Patients with Past or Present

Hepatic Abnormalities

Evidence Based Medicine | Official recommendations | Expert opinion

Course of action before tocilizumab therapy in patients with a history of liver disease

Tocilizumab therapy, particularly when combined with methotrexate, may be associated with hepatic transaminase elevation. No studies specifically designed to assess the effects of liver failure on tocilizumab pharmacokinetics are available [4]. Consequently, the Summary of Product Characteristics [4] indicates that caution should be exercised when considering tocilizumab therapy in patients with active liver disease or liver function impairment, as the safety of tocilizumab in these patients has not been evaluated.

In practice:

- In patients who have liver disease with alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) levels >1.5 x upper limit of normal (ULN) but <5 x ULN, tocilizumab therapy initiation can be considered [4] but requires special caution. Before starting tocilizumab, the advice of a hepatologist should be sought to determine the cause and severity of the underlying liver disease. To facilitate the conduct of tocilizumab therapy, treatment directed at the cause of the pre-existing liver disease (metabolic, alcohol-related, viral, haemochromatosis...) should be given if possible. Depending on the severity of the liver disease evaluated using non-invasive tests for fibrosis (biochemical tests and elastometry), the tocilizumab dosage may need to be adjusted. If tocilizumab therapy is initiated in a patient with pre-existing liver disease, the transaminase levels should be monitored routinely, at intervals no longer than 15 days for the first 3 months and no longer than 3 months subsequently.
- Tocilizumab therapy is not recommended in patients with ALAT or ASAT levels >5 x ULN (SPC).
- In patients with chronic viral hepatitis B or C with or without transaminase elevation, tocilizumab therapy initiation can be considered, although special caution is in order. The advice of a hepatologist should be obtained before considering the initiation of tocilizumab therapy, in particular to determine whether pre-emptive treatment with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) [39] is in order to prevent viral reactivation (see also the Additional Information section).

What are the warning signs of liver disease?

The development of clinical manifestations of hepatitis or hepatocellular insufficiency has not been reported in patients receiving tocilizumab therapy. In most cases, the hepatic abnormalities were discovered fortuitously by routine laboratory tests [4, 40].

When and how should the transaminase levels be monitored and what should be done in the event of transaminase elevation?

In clinical trials, transient or intermittent mild-to-moderate elevations of the transaminase levels were common in patients receiving tocilizumab, in the absence of clinical liver injury [4]. The use of concomitant medications with potential hepatotoxic effects (e.g., methotrexate) was associated with an increased rate of transaminase elevation [4, 29, 30, 32, 35-37, 39-42].

Monitoring transaminase levels

The Summary of Product Characteristics (4) recommends that ALAT and ASAT levels be monitored every 4 to 8 weeks for the first 6 months of treatment and every 12 weeks thereafter [4].

The recommendations issued in Japan [43], where tocilizumab is usually given as monotherapy, do not mention a need for monitoring the transaminase levels.

In practice, the transaminases (ALAT and ASAT) should be assayed before each infusion during the first 3 treatment months (four infusions) and the result checked before starting the infusion. Thereafter, the interval between the transaminase assays can be extended to 3 months.

In patients with underlying viral hepatitis, if tocilizumab therapy is started, the transaminase levels must be monitored routinely, at an interval no longer than 15 days for the first 3 months and no longer than 3 months thereafter.

Course of action in patients with transaminase elevation

In practice, the first step consists in adjusting the methotrexate dosage if needed. The CRI experts developed two algorithms for managing patients with persistent transaminase elevation (Figures 1 and 2).

Other liver test abnormalities

Total bilirubin elevation to less than 3 times the ULN was noted in 0.1% to 11% of patients given tocilizumab alone or with a disease-modifying antirheumatic drug [4, 33, 35, 37]. In the clinical studies, transaminase elevation was not associated with clinically significant elevations in the conjugated bilirubin levels, the classic marker for severe hepatotoxicity [4]. An increase in the total bilirubin level (with a parallel increase in unconjugated bilirubin) does not require special monitoring tests or specific treatment.

The recommendations on tocilizumab therapy do not indicate a need for monitoring the serum levels of bilirubin, γGT, or alkaline phosphatase [4]. In the LITHE study [38], however, tocilizumab therapy was discontinued in patients with indirect bilirubin elevation to more than twice the ULN (evidence-based medicine).

Additional information on the risk of hepatic abnormalities during tocilizumab therapy

Hepatotoxicity of medications in general

All medications have the potential to induce hepatotoxicity. Nevertheless, hepatotoxicity is uncommon, with a rate of 1% to 1/100,000 depending on the drug and mechanism involved (direct toxicity or immunoallergic response). Prior liver disease, which must be detected before starting tocilizumab therapy, may increase the risk of hepatotoxicity with synergistic or additive effects. Therefore, closer monitoring is needed in these patients. With the exception of severe liver cirrhosis, liver disease is not considered a definite contraindication to the use of hepatotoxic drugs, provided the patient is appropriately monitored.

Viral hepatitis and pre-emptive treatment

For the hepatitis C virus, apart from pre-existing fibrosis of the liver associated with chronic infection, there is no definite contraindication a priori to the use of tocilizumab.

For the hepatitis B virus, a positive test for HBs does not contraindicate tocilizumab therapy, particularly when the liver tests fail to suggest significant fibrosis; however, HBs-positive patients should receive pre-emptive antiviral therapy with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) [39] to prevent viral reactivation, which can have severe consequences [41]. This strategy applies to all immunosuppressive drugs, including tocilizumab. The pre-emptive treatment should be continued as long as the immunosuppressive medication is used, if warranted by the hepatic status, in compliance with standard recommendations [42], and for 6 to 12 months after the immunosuppressive medication is stopped. Finally, in patients with underlying viral hepatitis who are started on tocilizumab therapy, the transaminase levels should be monitored routinely, at intervals no longer than 15 days for the first 3 months and no longer than 3 months thereafter.

Transaminase elevation in therapeutic trials

According to the Summary of Product Characteristics [4], 3778 patients in all received at least one dose of tocilizumab 4 mg/kg or 8 mg/kg. The long-term open-label extension studies included 2562 patients who received tocilizumab 8 mg/kg with or without DMARDs. Exposure duration was usually less than 6 months. Total exposure in the long-term safety analysis was 3685 patient-years [4].

In the clinical trials, ALAT elevation was noted in 1% to 16% of patients given tocilizumab alone or with DMARDs [4, 38].

Transient ALAT and ASAT elevation >3 x ULN was noted in 2.1% of patients given tocilizumab 8 mg/kg compared to 4.9% of patients on methotrexate, 6.5% of patients on tocilizumab 8 mg/kg plus DMARD, and 1.5% of patients on placebo plus DMARD.

The concomitant use of potentially hepatotoxic medications (e.g., methotrexate) was associated with an increased rate of transaminase elevation compared to patients on tocilizumab monotherapy. ALAT and ASAT elevation >5 x ULN was

noted in 0.7% of patients on tocilizumab monotherapy and 1.4% of those on tocilizumab plus DMARD [4]. Most of these patients were taken off tocilizumab permanently.

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE [32, 35-37] in RA patients, including 2562 patients exposed to tocilizumab for a mean of 1.5 years showed that transaminase elevation was common but usually resolved in the absence of any changes in the treatment regimen [44]. In the pooled analysis, the rate of transaminase elevation to 1-3 x ULN on two consecutive assays was 54.5% on tocilizumab 8 mg/kg + DMARD *versus* 39.5% on methotrexate alone [44]. In the same analysis, the rate of transaminase elevation to >3 x ULN was 2% (ALAT) to 6.5% (ASAT) on tocilizumab 8 mg/kg + DMARD *versus* 2.1-4.9% on methotrexate alone [45].

In the OPTION and TOWARD studies [32, 35], transaminase elevation required temporary tocilizumab discontinuation (values >3 x ULN) in 1.9% to 3.4% of patients and permanent tocilizumab discontinuation (for values >5 x ULN or >3 x ULN persistently) in 0.8% to 3.4% of patients [35]. Transaminase levels >3 x ULN returned to normal despite tocilizumab continuation in over one-third of cases in these trials [35]. A few patients who had prolonged liver test abnormalities underwent liver biopsy, which showed no evidence of aggressive hepatitis [46].

Bilirubin elevation in therapeutic trials

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE (32, 35-37) in RA patients, including 2,562 patients exposed to tocilizumab for a mean of 1.5 years showed a rate of bilirubin elevation of 9.1% with tocilizumab 8 mg/kg + DMARD *versus* 8.7% with tocilizumab 8 mg/kg alone and 1.8% with methotrexate alone [45]. Bilirubin elevation above 3x ULN was extremely rare [45]. An increase in the unconjugated bilirubin level does not require tocilizumab discontinuation.

Liver data during long-term tocilizumab therapy

In the STREAM 12-week randomized controlled trial followed by a 12-week open-label extension phase [30], patients given tocilizumab 8 mg/kg as monotherapy were monitored for up to 5 years [30]. ASAT and ALAT elevations of grade 2 or higher occurred during the study in 6.3% (n=9/143) and 9.8% (n=14/143) of patients. Transaminase elevation was usually transient; of the 143 initial patients, 2 had transaminase elevations categorized as serious adverse events. No cases of clinical hepatitis were observed [30].

The Food and Drug Administration [47] determined that the risk was not higher in patients who received long-term tocilizumab therapy. The risk of liver test abnormalities was about 1% in patients monitored after participating in controlled trials, and 8% of patients experienced at least one episode of transaminase elevation >2 x ULN. Bilirubin elevation to >2 x ULN occurred in 1% of patients.

Hepatic abnormalities recorded in registries

To date, no cases of hepatic abnormalities have been reported in the registries.

Conclusion

In sum, tocilizumab is not associated with severe hepatotoxicity. Hepatic disease is not a definite contraindication to tocilizumab therapy, except for severe hepatocellular failure, which limits the use of all drugs and requires pharmacokinetic and pharmacodynamic evaluations to define the modalities of use, if any.

However, as with all recently introduced medications, the use of tocilizumab requires regular monitoring by laboratory tests followed by dosage adjustments as indicated by the results. Patients with pre-existing hepatic risk factors require non-invasive tests for fibrosis and, in some cases, a pre-treatment liver biopsy to enable appropriate dosage adjustment and intensification of the monitoring program. Finally, as with all immunosuppressive drugs, patients considered for tocilizumab therapy should be screened for hepatitis B and C virus infections.