Management of Patients with Past or Present

Bacterial and/or Viral Infections

Evidence Based Medicine | Official recommendations | Expert opinion

Steps to be taken before tocilizumab initiation to prevent infections

Bacterial infections

- Evaluate the overall risk by looking for predisposing factors: co-morbidities (diabetes, diverticulitis, respiratory disease, and chronic wounds), foreign material in the body (prosthesis, indwelling catheter), a past or present history of treatment with immunosuppressive agents or glucocorticoids, and evidence by patient interview and/or physical examination of an overt or latent focus of infection.
- Check the immunisation record: always check that all vaccines are up to date. Consider administering the pneumococcal vaccine if possible at least 2 weeks before tocilizumab initiation, as with all biotherapies used in rheumatoid arthritis.
- Rule out contraindications to tocilizumab therapy: tocilizumab is contraindicated in patients with severe uncontrolled infections (septicaemia, opportunistic infections) or a high risk of bacterial infection (recent infection of a prosthesis, indwelling catheter) [4].
- In patients with diverticulitis: see, in particular, the sheet entitled "Management of patients with a past or present history of ileocolonic disease".
- Obtain screening tests for latent tuberculosis if not done in the past 2 years. As with other biotherapies, patients should be screened for latent tuberculosis before starting tocilizumab therapy [4], in keeping with AFSSAPS recommendations [48]: 5 U Tubertest® or *in vitro* QuantiFERON Gold® test or T-Spot-TB® test (which are being evaluated in France) and chest radiograph. Patients with latent tuberculosis should receive prophylactic anti-tuberculous therapy (isoniazid for 9 months or isoniazid plus rifampin for 3 months) and tocilizumab should be postponed for at least 3 weeks after initiation of the anti-tuberculous regimen.

Viral infections

The results of serological tests for the hepatitis B and C viruses and the HIV should be available before starting tocilizumab therapy.

A positive serological test for the hepatitis C virus in the absence of pre-existing fibrosis related to chronic HCV infection does not *a priori* constitute a definite contraindication to tocilizumab therapy.

Positive serological test for the hepatitis B virus: a positive test for HBs, particularly when the liver tests show no evidence of significant fibrosis, does not contraindicate tocilizumab therapy; however, as with other immunosuppressive drugs, patients with a positive HBs test should receive

pre-emptive treatment with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) (see the sheet entitled “Management of patients with a past or present history of hepatic abnormalities”).

Positive test for the HIV: tocilizumab therapy can be considered in the event of highly refractory and incapacitating rheumatoid arthritis, provided the plasma viral load is monitored closely throughout the treatment period.

The advice of specialists (hepatologist, infectiologist) should be obtained before choosing the treatment strategy.

What are the warning signs of infection in patients on tocilizumab?

In patients on tocilizumab, many warning signs may develop:

- a fever
- chills
- asthenia
- abdominal pain
- a cough
- dyspnea
- a skin rash
- a burning sensation during urination
- sudden recurrence of joint pain, highly inflammatory monoarthritis or oligoarthritis
- depending on the site of infection: low back pain in pyelonephritis or discitis, abdominal pain in diverticulitis
- re-ascent of the laboratory markers for inflammation
- leukocytosis.

Special vigilance for the detection of infections is in order in patients receiving tocilizumab therapy, as IL-6 inhibition, similar to TNF inhibition, may blunt the signs and symptoms of acute inflammation associated with infection: thus, IL-6 inhibition may result in the absence of fever, leukocytosis, and CRP elevation (and of elevations in other acute-phase reactants).

Course of action in the event of infection during tocilizumab therapy

As with all biotherapies, the development of an infection requires the discontinuation of tocilizumab therapy, an evaluation of the severity of the infection, the collection of microbiological specimens whenever possible and, without waiting for the results, the prompt initiation of anti-infectious therapy, whose effectiveness should be evaluated and monitored.

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elevation (and of elevations in other acute-phase reactants). In this situation, other biological markers may be useful, such as CD64 [49].

At the slightest suspicion of infection, tocilizumab therapy should be discontinued until the infection is either ruled out or, if not severe, controlled and resolved. Severe infection contraindicates tocilizumab therapy (see above) [4].

Serious infections (defined as infections requiring hospital admission or intravenous antimicrobial therapy) should be reported to the pharmacovigilance centre.

When can tocilizumab therapy be re-started?

Once the patient is fully recovered from the infection, the appropriateness of re-starting tocilizumab therapy should be evaluated based on the risk/benefit ratio. The tocilizumab re-start date depends on the severity and site of the infection but should always occur at a distance from discontinuation of the antibiotics.

Close monitoring is in order when re-starting tocilizumab therapy. Prompt recurrence of the manifestations of infection should prompt an assessment of the appropriateness of permanent tocilizumab discontinuation.

Additional information on current knowledge

Role for IL-6 in defence mechanims againts infection

IL-6 activates the macrophages and neutrophils and upregulates the expression of adhesion molecules, the chemokine profile, and antibody production. Therefore, IL-6 plays a role in defence mechanisms against infection. IL-6 decreases HBV replication [48] and IL-6-deficient mice are at increased risk for a number of infections (listeriosis, toxoplasmosis, candidiasis) [50]. IL-6 inhibition by tocilizumab may interfere with these antibacterial defence mechanisms, thereby promoting the development or reactivation of infections. The role for IL-6 in defence mechanisms against mycobacterial infections is probably ancillary, but IL-6 contributes to macrophage activation.

The precautions aimed at minimising the risk of infection are those recommended for all biotherapies.

Risk of bacterial and viral infections during tocilizumab therapy

In controlled studies, the infection rate in patients receiving tocilizumab (8 mg/kg) + DMARD was 127/100 patient-years compared to 112/100 patient-years in the placebo + DMARD groups. In the long-term open-label extension studies, the infection rate in patients receiving tocilizumab + DMARD was 116/100 patient-years [4].

Serious infections

In controlled studies (LITHE, OPTION, TOWARD, and RADIATE), the rate of serious infections in patients receiving tocilizumab 8 mg/kg + DMARD (n=1,582) was 5.2/100 patient-years (95% CI, 3.7-7.1) compared to 3.8/100 patient-years (95% CI, 2.3-5.9) in the placebo + DMARD group (n=1170) [51]. With tocilizumab monotherapy (AMBITION), the rate of serious infections was 2.9/100 patient-years in the tocilizumab group (95% CI, 0.8-7.3), compared to 1.5/100 patient-years (95% CI, 0.2-5.4) in the methotrexate group [37].

The following serious infections were reported: pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, septicaemia, and bacterial arthritis.

Van Vollenhoven et al. [40] reported that the serious infection rate in long-term studies (n=4009; mean follow-up, 2.4 years) was 4.7/100 patient-years and showed no increase with increasing exposure time.

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE [30, 45, 52, 53] in RA patients, including 2,562 patients exposed to tocilizumab for a mean of 1.5 years showed that the serious infection rate was 3.9/100 patient-years (95% CI, 3.3-4.6). Statistically significant associations were found between the risk of serious infection and diabetes, age older than 65 years, a past history of infection, and systemic glucocorticoid therapy; whereas no association was found with neutropenia [45].

In Japan, the 5-year open-label extension phase of a phase II trial (STREAM) included 143 patients, of whom 66% took tocilizumab for 5 years. The rate of serious infections during the resulting 612 patient-years of tocilizumab monotherapy was 5.7/100 patient-years [30].

Tuberculosis seems uncommon [52], with 6 cases during 10,552 patient-years of tocilizumab therapy, including 2 cases in patients who did not undergo tuberculosis screening before treatment initiation.

It is worth noting that active chronic EBV infection may be exacerbated by treatment with anti-IL-6 antibodies [53] and that no exacerbation of hepatitis occurred in a patient with chronic hepatitis B who took tocilizumab for 5 years in combination with an antiviral agent [54].

A very small number of cases of acute infection related to reactivation of herpes viruses (EBV, CMV) and complicated by macrophage activation syndrome have been reported [29, 55].