Management of patients with past or present bacterial or viral infections

Evidence-based Medicine | Official Recommendations | Expert opinion

What should be done before initiation of abatacept to prevent the risk of bacterial and viral infections?

Overall evaluation of the risk of infection in RA

Infections contribute to the excess mortality seen in patients with RA. The increased incidence and severity of infections in patients with RA is multifactorial. Multiple Factors can increase the risk of infection such as the immune system dysfunction related to RA, the disease activity and severity, its functional impact, any co-morbidities (e.g., diabetes mellitus, respiratory diseases, skin ulcers, and foreign material such as prosthetic joints, prosthetic valves, and catheters), and any concomitant immunosuppressive medications (most notably glucocorticoids and TNF antagonists) (17-19).

All these risk factors should be considered when evaluating the overall risk of infection in patients with RA, particularly before starting an immunosuppressive medication such as abatacept.

Minimizing the risk of bacterial infections

- Abatacept is contraindicated in patients who have severe uncontrolled infections such as septicemiai and opportunistic infections. Physicians should exercise caution when considering batacept therapy in patients with a history of recurrent infection (e.g., herpes virus infection) or underlying conditions which may predispose them to infections (e.g., diabetes or COPD) (20).

- Situations associated with a high risk of bacterial infection (recent prosthesis infection, skin ulcers, indwelling catheter) also contraindicate the initiation of immunosuppressive treatments such as abatacept.

- Therefore, before starting abatacept therapy, a medical history and physical examination should be performed to look for a clinical or latent source of infection (refer to the “Pre-treatment assessment ” fact sheet).

Minimizing the risk of tuberculosis

- All patients evaluated for eligibility in the abatacept clinical trials in RA first underwent an assessment of the risk of latent tuberculosis. Patients with a history of active tuberculosis within the 3 years preceding the selection visit, and those who had positive screening tests and did not receive tuberculosis chemoprophylaxis, were not included in these studies (21). Despite these precautions, 8 cases of tuberculosis were recorded (0.07/100 patient-years [0.03-0.17]) (4).

- Therefore, patient should be screened for latent or active tuberculosis before being started on abatacept according to the national recommendations on TB (20). Since 2006, specific blood tests (*in vitro* interferon gamma release assays, IGRAs) can be used instead of the tuberculin intradermal skin test.

- In patients taking prophylactic antituberculosis therapy, abatacept can be started after 3 weeks.

- If the 5 IU intradermal tuberculin test done before starting abatacept was positive and the patient received prophylactic antituberculosis therapy in compliance with local recommendations, there is no need to repeat the test.

- In contrast, if the 5 IU intradermal tuberculin test done before starting abatacept was negative and was performed more than 1 year earlier, another test should be performed. If this second 5 IU intradermal tuberculin test is positive, prophylactic antituberculosis therapy should be given according to the french national recommendations (22).

Minimizing the risk of viral infection

- There was an increased proportion of *Herpes simplex* virus infections in the five main controlled studies of the abatacept RA clinical development program (2% in the abatacept groups vs. 1% in the placebo groups).

  In contrast, there were no cases of hepatitis B or C, HIV infection, or JC virus infection during these studies (21). There is a report of 2 patients with RA and hepatitis C who were treated with abatacept and experienced no complications (23).

- However, as the safety of abatacept has not been established in patients with viral infections (24), serological tests for the hepatitis B and C viruses should be performed routinely before treatment initiation. If serological tests done within the last 5 years are available, re-testing is not necessary, except in patients with risk factors or previous high-risk medical procedure. HIV Serology can be performed (following patient consent)

- Patients with active HBV or HCV infection, should be referred to a hepatologistbefore making treatment decisions.

- Patients with HIV infection should be referred to an infectiologist before making treatment decisions.

- In patients with recurrent oral or genital *Herpes simplex* virus infection should be referred to an infectiologist before making treatment decisions to evaluate whether prophylactic valaciclovir therapy is in recommended.

Vaccinations

Check that boosters of mandatory vaccines have been administered according to standard practice.

Live vaccines are contraindicated, as with all biological agents. If the patient may travel to countries where yellow fever immunization is mandatory, administer the yellow fever vaccine before starting abatacept treatment, in the absence of methotrexate treatment and of glucocorticoid treatment in a dosage higher than 10 mg/day.
The pneumococcus vaccine (which is effective for 5 years) is recommended before abatacept initiation, as well as the annual influenza vaccine and, if appropriate, the hepatitis B vaccine.

What are the alarm symptoms of infection during abatacept treatment?

- Fever
- Chills
- Asthenia
- Weight loss
- Sudation
- Cough
- Dyspnea
- Skin rash
- Urinary burn
- Development of acute monoarthritis or sudden recurrence of inflammatory joint pain
- Flu-like syndrome with arthralgia and myalgia
- Hepatic cytolysis
- Changes in blood cell counts (leukocytosis, leukopenia, mononucleosis-like syndrome)

Course of action when clinical evidence of infection develops during abatacept therapy

- Patients with evidence of severe infection requiring emergent probabilistic antimicrobial therapy should be admitted to a specialized unit and should stop abatacept.

- In all patients with infections, bacteriological tests must be obtained before starting probabilistic antimicrobial therapy. Other tests (mycobacteriological, virological, mycological, or parasitic studies; and imaging studies) should be performed according to clinical evidence.

- The probabilistic antibiotics should be selected based on the signs of infection (site, organism, and history of infections), personal history, and co-morbidities (25).

  - In patients with community-acquired respiratory tract infections, the first-line antimicrobial treatment consists of amoxicillin-clavulanic acid or a third-generation cephalosporin. Depending on the risk factor profile, hospital admission should be considered based on the last consensus conference on lower respiratory tract infections held in 2010 (25) and national guidelines (127, 128).
    If no improvement occurs within the first 48 hours, a macrolide should be substituted for, or added to, the first antimicrobial. Depending on the context, a quinolone active against pneumococci (levofloxacin) may be preferred.

  - Evidence of interstitial pneumonia should routinely suggest the possibility of atypical pneumonia (*Chlamydia pneumoniae, Mycoplasma pneumoniae*) or of an opportunistic infection *(Legionella,*

Pneumocystis jirovecii). Serology tests should be obtained for *Chlamydia pneumoniae, C. psittaci,* and *Mycoplasma pneumoniae*, as well as a *Legionella pneumophila* antigenuria assay, and bronchoalveolar lavage should be discussed.
Chlamydiae, mycoplasms and *Legionella* are susceptible to macrolides.
Identification of *Legionella* requires hospital admission. When *P. jirovecii* pneumonia is suspected, the patient should be admitted to hospital with an initiation of cotrimoxazole therapy.

- The type and duration of the antimicrobials should be adjusted based on the results of the microbiological tests, effects on signs of infection, and its tolerance.
- All serious infections should be reported to the pharmacovigilance center.

When can abatacept therapy be resumed?

Abatacept treatment should not be resumed until full resolution of the infectious episode and monitoring to check the absence of recurrent infection. Close monitoring is required when resuming abatacept treatment. After a severe infection or an opportunistic infection, the decision to re-start a biological agent should be taken, following an evaluation of the risk/benefit ratio by a multidisciplinary team.

Current knowledge on the risk of bacterial and viral infection during abatacept therapy

- Safety data are available for 4632 patients exposed to abatacept (representing 12 375 patient-years) exposed in the five main controlled trials, three long-term studies, and a safety study of the abatacept RA clinical development program. These safety data were analyzed in an EMA report published in 2010. Although infections remain the main identified safety risk during abatacept therapy, even in the long-term, the incidence of infections did not increase over time and severe and opportunistic infections were rare (5). An analysis of safety databases suggests that the risk of infection may be lower with abatacept than with TNF-alpha antagonists or rituximab (5).

- A review article analyzed data from seven placebo-controlled trials, an open-label trial, and the extension periods of five of these studies. Treatment discontinuation related to adverse events occurred in 1.9% to 8.7% of patients with abatacept + methotrexate vs. 0.9% to 4.3% of patients with placebo + methotrexate (26). Serious infections were reported in 3% of patients with abatacept and 1.9% with the placebo and malignancies in 3.7% of patients with abatacept and 2.9% with the placebo (26).

- Another review article (27) analyzed safety data of the abatacept clinical trial experience representing 10 366 patient-years. Overall the incidence of serious infections was low although higher with abatacept than with the placebo (3.47 vs. 2.41 events/100 patient-years).

Furthermore, the rates of serious infections and of infections requiring hospital admission were similar during the four double-blind periods and the open-label extension periods (3.47 vs. 2.98

per 100 patient-years for serious infections and 3.05 vs. 2.73 per 100 patient-years for infections requiring hospital admission) (27).

The 5-year open label extension period of a Phase IIB study comparing abatacept + methotrexate to placebo + methotrexate in RA patients with an inadequate response to methotrexate (28) evaluated 130 of the 235 initially randomized patients. The incidence rates of infections and serious infections were 94.2 and 2.1/100 patient-years during the double-blind period and 77.3 and 3.0/100 patient-years during the entire study period. The most common infections were lung infections and diverticulitis. No cases of opportunistic infection or tuberculosis were observed during the study period.

The incidence rates of hospitalized infections have been evaluated in the abatacept clinical development program (29). The analysis included 1955 patients in controlled studies and 4134 patients in open-label extension studies. The incidence ratios of hospitalized infections were compared between abatacept-treated patients and patients in RA icohorts treated with synthetic DMARDs.

Overall, the risk of serious infections was lower with abatacept than with other biological agents (30).. Thus, in the ATTEST study comparing abatacept + methotrexate (n=156) to infliximab + methotrexate (n=165) for 1 year (31), the rate of severe infections was 2% in the abatacept group and 9% in the infliximab group; all 5 cases of severe opportunistic infection occurred with infliximab.

However, the risk of infection increases when abatacept is combined with another biological agent. This combination of two biological agents is contraindicated. Thus, in a study by Weinblatt et al. (32), 167 patients with RA and an inadequate response to a biological agent (TNF antagonist, 87%; and anakinra, 13%) were randomized to abatacept or placebo therapy then monitored for 1 year. Severe infections were more common with abatacept (5.8%) than with the placebo (1.6%). In a double-blind 1-year study (33), severe infections were more common with abatacept + etanercept (3.5%) than with abatacept alone (0%). Singh et al. (34) drew similar conclusions from their metaanalysis: the risk of serious adverse events was significantly lower with abatacept and anakinra than with other biological agents. Another metaanalysis included the five main controlled studies evaluating the efficacy and safety of abatacept in RA and found no statistically significant increase in the risk of serious infections with abatacept compared to a placebo (OR=1.35 [95%CI: 0.78-2.32; P=0.3]). However, the statistical power of this metaanalysis is not sufficient to conclude that abatacept is not associated with an increased risk of infection (35).

Role for the B7–CD28 co-stimulation pathway in immunity against infectious agents

- The origin of an anti-infectious T-cell response is a complex process during which cytokines and co-stimulation molecules generate signals that regulate adaptive immunity. By preventing T-cell activation via the B7/CD28 co-stimulation pathway, abatacept may inhibit the specific anti-infectious T-cell response (36).

- The crucial role for the B7/CD28 co-stimulation pathway in immunity against viruses has been demonstrated in several models of infection due to *Herpes simplex* virus and *Influenza* virus (37). The B7/CD28 pathway also makes an important contribution to immunity against parasites, most notably *Toxoplasma gondii* and *Leishmania major* (38); fungi, such as *Pneumocystis jirovecii* (39); and bacteria, particularly some of the intracellular organisms including *Listeria monocytogenes, Salmonella enterica*, and *Chlamydia trachomatis* (40).

- In mouse models, treatment with abatacept or CTLA4-murine Ig did not affect the ability of the animals to survive chronic infection with *Mycobacterium tuberculosis*, latent infection with *M. tuberculosis*, or acute infection with cytomegalovirus or *P. jirovecii* (41). However, the treatment was associated with decreased survival of mice that had acute *H. simplex* virus infection (42).