



## Management of... Specific clinical situations (dialysis, hemoglobinopathy, splenectomy)

Evidence-based Medicine

Official Recommendations

Expert opinion

### Dialysis

#### **Steps to be taken before initiation of abatacept therapy in patients on dialysis**

Although dialysis does not contraindicate abatacept therapy, the following specific steps should be taken:

- Before starting abatacept therapy, check that the dialysis port is healthy and will not require an intervention in the short term, given the risk of delayed healing and the excess risk of infection.
- The risk of fluid overload with cardiac decompensation after intravenous abatacept administration is low in hemodialysis patients, as the amount of saline given with an abatacept dose is only 100 mL and the sodium content of the infusion is only 0.375 mmol (8.625 mg) per bottle, i.e., 1.5 mmol (34.5 mg) for the four bottles needed for one infusion. However, this sodium intake should be taken into account in patients on low-sodium diet.
- Given the absence of data on the dialysability of abatacept, the drug is best administered just after each dialysis session (48). The risk of removing part of the dose is almost nul with hemodialysis but must be considered with plasmapheresis. In dialysis patients, whether abatacept therapy should be combined with a synthetic DMARD (e.g., methotrexate or leflunomide) should be discussed on a case-by-case basis, given the increased risk of adverse events associated with chronic dialysis. Accumulation of an immunosuppressant or its metabolites requires appropriate dosage adjustment in dialysis patients (48).

#### **Course of action when dialysis is required in a patient on abatacept therapy**

Patients on abatacept therapy should be considered as immunocompromised patients. Therefore, according to French High Health Authority (HAS) recommendations, abatacept-treated patients can receive hemodialysis (the reference extrarenal replacement therapy) or peritoneal dialysis. Careful attention should be given to the increased risk of infection, which may be more severe with peritoneal dialysis. The nephrologist and rheumatologist should work together in close coordination.

#### **When can abatacept therapy be resumed in dialysis patients?**

In patients who have required dialysis, the resumption of abatacept therapy depends on disease activity which may require the use of abatacept.

#### **Current knowledge**

T-cell co-stimulation blockade has been used in nephrology for several years to prevent kidney transplant rejection. The drug used is belatacept, in which differences in two amino acids compared to abatacept lead to an increased potency (49) and was shown to present a good safety profile over 5-year (50).

At present, no data are available on the use of abatacept in RA patients with chronic dialysis. Therefore, regarding this uncommon situation physicians need to be cautious given the risk of infection.

Finally, abatacept has not been studied in patients with renal failure. Consequently no recommendations can be made regarding the optimal dosage in this situation (20).

### Hemoglobinopathy

No specific recommendations or expert opinions have been published to date.

#### **Steps to be taken before abatacept therapy in patients with hemoglobinopathies (e.g., sickle cell anemia or thalassemia)**

There is no data available suggesting that abatacept initiated for inflammatory joint disease may worsen or improve the acute or chronic manifestations of concomitant hemoglobinopathy.

Optimal control of the anemia and of any exacerbating factors (e.g., dehydration) should be achieved prior to starting abatacept therapy in patients with hemoglobinopathy.

In patients with severe sickle cell anemia, the use of abatacept may increase the risk of infection, as functional asplenia is common in this situation. Long-term prophylactic penicillin V therapy (2 000 000 IU/d) is recommended in these patients, as well as the administration of conjugate vaccines against pneumococci (Pevnar®), *Haemophilus influenzae* type b (Act HIB®), and meningococci (Meningitec®, Menjugatekit®, or Neisvac®). Annual flu vaccination against is recommended.

Folic acid is consumed in large amounts during hemolytic crises and any deficiency in folic acid should be corrected, particularly in patients receiving concomitant methotrexate therapy.

#### **Course of action when hemoglobinopathy is diagnosed during abatacept therapy**

If a hemoglobinopathy is diagnosed fortuitously, regular monitoring of blood cell counts is recommended during abatacept therapy.

The risk of infection should be re-evaluated given the high prevalence of functional asplenia in patients with sickle cell anemia.

#### **Current knowledge**

Sickle cell anemia and thalassemia are autosomal recessive hemoglobinopathies. These hemoglobinopathies are due to mutations in the gene encoding one of the globin chains ( $\beta$  in sickle cell anemia and  $\alpha$  or  $\beta$  in thalassemia). Hemoglobin electrophoresis provides the diagnosis.

In sickle cell anemia, the erythrocytes are prone to sickling, particularly when hypoxia occurs. Functional asplenia may develop as a result of recurrent splenic microinfarction. Cases of RA, juvenile idiopathic arthritis, and systemic lupus erythematosus have been reported in patients with sickle cell anemia, with exacerbation of the hemolytic episodes just after the development of the rheumatic disease (51, 52). Glucocorticoid-sparing strategies are recommended in these patients

who are at high risk for infection and mortality when treated with glucocorticoids and/or methotrexate.

No cases of RA treated with abatacept in patients with sickle cell anemia have been reported to date. Studies of the pathophysiology of vaso-occlusive crisis (VOC) in patients with sickle cell anemia (53) showed differences in concentration across anti-inflammatory cytokines (with high IL-4 concentrations but low IL-10 concentrations) during VOC, as well as a significant decrease in CD4+ T cells and a low CD4+/CD8+ ratio (0.7 vs. 1.1, not significant for patients with VOC compared to other sickle cell anemia patients and 0.7 vs. 1.4 [ $p < 0.05$ ] for patients with VOC compared to healthy controls). Compared to healthy controls, sickle cell anemia patients with or without VOC had significantly higher IL-2 levels.

In addition, studies of murine models of sickle cell anemia showed a major role of natural killer cells (NK) in the development and perpetuation of the ischemia/reperfusion vascular lesions, mainly mediated by IFN- $\gamma$  and the production of CXCR3 (54). Patients with sickle cell anemia have increased counts of circulating NK cells expressing CXCR3.

However, the available data are too scarce to allow a reasonable evaluation of the risk of inducing VOC, or the possibility of preventing VOC, in patients with sickle cell anemia treated with abatacept. Close monitoring involving routine physical examinations and laboratory tests (blood cell counts) are therefore required as a precaution in this situation.

The most common form of thalassemia is  $\beta$  thalassemia, in which production of the beta chain is either decreased (beta + thalassemia) or absent (beta 0 thalassemia). Thalassemia manifests as chronic hemolytic anemia, which can be severe in homozygous patients (thalassemia major). The treatment relies on blood transfusions, iron chelation and, if needed, splenectomy. RA patient with thalassemia is rare (55, 56).

In murine models of sickle cell anemia, abatacept was used successfully for nonmyeloablative conditioning before allogeneic bone marrow transplantation (57, 58). Donor/host chimerism of circulating blood cells was noted after transplantation, as well as a significant improvement in disease activity. The advantage of T-cell co-stimulation modulation for transplantation conditioning in these murine models relied on the clinical efficacy and in its lower toxicity compared to myeloablation via irradiation.

There have been no reports of RA treated with abatacept in patient with major or minor thalassemia. Close monitoring involving routine physical examinations and laboratory tests (blood cell counts) is required as a precaution.

## Splenectomy

### **Steps to be taken before initiation of abatacept therapy in patients with splenectomy**

Abatacept is not contraindicated in patients with a history of splenectomy.

However, splenectomy is associated with an increased risk of infection, and caution must therefore be taken on two main issues.

- long-term prophylactic antibiotic therapy. The goal is to minimize the risk of infection in patients with both splenectomy and abatacept therapy. Penicillin V (2 000 000 IU/d) is the most often used antibiotic, at least during the first 2 years after splenectomy. In the absence of penicillin allergy, prophylactic antibiotic therapy should be continued or resumed in case of concomitant abatacept therapy. Importantly, cotrimoxazole is contraindicated in patients who are taking methotrexate (potentiation of the effects and hematological toxicity of methotrexate).

- Administration of conjugate vaccines. **The response to vaccines based on bacterial capsule polysaccharides (polysaccharide vaccines such as Pneumo23) is altered in splenectomized patients, who fail to develop an antibody response (59).** In this specific situation, the use of conjugate vaccines is highly recommended:

- Pneumococcal saccharide conjugated vaccine for pneumococcal infections,
- *Haemophilus influenzae* type b conjugate vaccine for *Haemophilus influenzae* type b infections, and
- Meningococcal serogroup C conjugate oligosidique vaccines for meningococcal (*Neisseria meningitidis*) infections.

**Administration of the annual influenza vaccine is also recommended (60).**

#### **Course of action in case of of splenectomy during abatacept therapy**

Abatacept-treated patients who require splenectomy are theoretically at high risk for infection after the procedure.

Splenectomy may be needed in two main settings.

- **Emergency splenectomy (e.g., after an injury):** discontinue the abatacept as soon as the need for splenectomy is confirmed. Patients who are still treated with abatacept at the time of surgery should be considered at high risk for infection.

- **Scheduled splenectomy:** the time to abatacept discontinuation should be determined based on the half-life of the drug.

Potential infections are caused by bacteria targeted by the prophylactic antibiotic treatment recommended for this type of surgery by the national guidelines.

**Special attention should be paid immediately after the surgical procedure, given the increased risk of infection and the possibility of delayed healing. Thus, prophylactic cefazolin (2 g IV before surgery then an additional 1-g dose if the operating time exceeds 4 h) is recommended to prevent immediate infectious complications (61).** In patients who are allergic to cefazolin, the recommended prophylactic regimen is a single dose of gentamicin (5 mg/kg) and clindamycin (600 mg), to be repeated if the operating time exceeds 4 h.

#### **When can abatacept therapy be resumed?**

Abatacept therapy can be resumed once healing is complete.

Long-term prophylactic penicillin V (2 000 000 IU/d) together with the administration of conjugate vaccines is recommended.

**Current knowledge**

In France, 9000 new patients undergo splenectomy each year and the overall estimate of patients with splenectomy is 250 000. The incidence rate is about 10-15/100 000 inhabitants (62).

Pneumococci (*Streptococcus pneumoniae*) are responsible for more than 50% of overwhelming postsplenectomy infections (OPSIs), which often have their lead point in the respiratory tract and progress rapidly to multiorgan failure with disseminated intravascular coagulation and a high early mortality rate (63).

In a murine model of invasive pneumococcal infection, mice lacking CD4+ T cells had higher survival rates than normal mice, as a result of a blunted inflammatory response to infection (64). In these experimental models, T-cell inhibition by cyclosporine or T-cell co-stimulation modulation by abatacept was associated with improved survival after experimental infection. These results need to be confirmed and documented in greater detail. They may then suggest a strategy involving T-cell co-stimulation modulation during the early phase of massive pneumococcal invasion in patients with splenectomy.

However, no data on the use of abatacept in RA patients with splenectomy have been published to date. Therefore, caution should be taken in this uncommon situation, given the risk of infection associated with splenectomy.