



Management of patients with past or current history of lymphoma or other hematological diseases

Evidence-based Medicine

Official Recommendations

Expert opinion

Steps to be taken before initiation of abatacept therapy in patients with a history of hematological disease

No contraindications or precautions for use of abatacept related to a history of hematological disease are given in the abatacept Summary of Product Characteristics, 2008 ACR recommendations, or 2010 EULAR recommendations (5, 8, 9).

Co-stimulation pathways play a major role in regulating T-cell responses against tumors. This fact explains that immunomodulation strategies involving the use of monoclonal anti-CTLA4 antibodies (ipilimumab and tremelimumab) to block the CTLA-4/B7 inhibitory pathway have been evaluated in patients with solid cancers (most notably malignant melanoma) or hematological malignancies (non-Hodgkin lymphoma) (10-12). To date, ipilimumab is indicated for the treatment of advanced melanoma (unresectable or metastatic) in adults who have received prior therapy. Abatacept-induced blockade of the CD28/B7 activating pathway might raise concern in patients with RA, whose lymphoma risk may be increased 2- to 3-fold compared to the general population. Consequently, we evaluated the impact of a history of hematological disease on the decision to initiate abatacept therapy.

1. History of acute leukemia

Patients with a history of acute leukemia were not included in the clinical trials evaluating the efficacy and safety of abatacept in RA.

Acute leukemia is not on the list of the more frequently adverse events reported (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in clinical trial program (5).

As of March 31, 2011, no cases of acute leukemia in abatacept-treated patients had been reported to the Pub.Med.gov database.

In practice, in the current state of our knowledge, in patients having a history of acute leukemia within the last 5 years, abatacept treatment initiation can't be recommended. Decisions to start abatacept therapy in a patient having a history of acute leukemia should be taken in conjunction with a hematologist

2. History of lymphoma

Patients with a history of lymphoma were not included in the clinical trials of the efficacy and safety of abatacept in RA.

During double-blind and open-label studies in 4149 abatacept-treated patients, with 11 658 patient-years (including 1000 patients exposed to abatacept for longer than 5 years), the incidence rate of hematological malignancies was 0.13/100 patient years. The most common hematological malignancies were lymphomas, with an incidence rate of 0.06/100 patient-years. The incidence rates of lymphomas and other hematological malignancies remained stable during the double-blind period and open-label extension periods. These incidence rates are considered consistent with those expected in a RA population adjusted for age and sex (4, 5, 13-15). Recent data show that the

annual incidence of lymphoma and other hematological malignancies is stable (with up to 7 years of treatment) and that the incidence rate of these malignancies in the long-term period or cumulative period is not increased compared to the short-term periods (4).

In practice, in the current state of our knowledge, in patients with a history of lymphoma within the last 5 years, abatacept treatment initiation can't be recommended. Decisions to start abatacept therapy in a patient with a history of lymphoma should be taken in conjunction with a hematologist.

3. History of another lymphoproliferative syndrome

Patients with a history of other lymphoproliferative syndromes (multiple myeloma, Waldenström macroglobulinemia, and chronic lymphocytic leukemia) were not included in the clinical trial program evaluating the efficacy and safety of abatacept in RA.

These lymphoproliferative syndromes are not on the list of adverse events more frequently reported (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in these clinical trials (5).

As of March 31, 2011, no cases of lymphoproliferative syndrome in abatacept-treated patients had been reported to the Pub.Med.gov database.

In practice, in the current state of our knowledge, in patients having a history of chronic lymphoproliferative disease within the past 5 years, abatacept treatment initiation can't be recommended. Decisions to start abatacept therapy in a patient with a history of chronic lymphoproliferative disease should be taken in conjunction with a hematologist.

4. History of monoclonal gammopathy of undetermined significance (MGUS) or solitary plasmacytoma

Neither MGUS nor solitary plasmacytoma are on the list of more frequently adverse events reported (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in clinical trial program evaluating the efficacy and safety of abatacept in RA (5).

As of March 31, 2011, no cases of MGUS or solitary plasmacytoma had been reported to the Pub.Med.gov database.

In the absence of adequate clinical data, it is recommended to use abatacept with caution in patients with MGUS, and the following two situations should be differentiated.

- Monoclonal gammopathy detectable only by serum protein immunofixation (monoclonal component usually <1 g/L) with no evidence of lymphoproliferative syndrome: the abnormality can be considered of marginal relevance and abatacept treatment can be started if needed, and monitored by a serum protein electrophoresis at regular intervals (every 3-6 months).
- Monoclonal gammopathy detectable by serum protein electrophoresis (monoclonal component usually >1 g/L): there are two main situations.
 - A past and stable monoclonal gammopathy, supporting a diagnosis of true MGUS. Abatacept treatment can be considered, with monitoring by a serum protein electrophoresis at regular intervals (every 3-6 months). Worsening of the monoclonal gammopathy and/or the development of another abnormality (e.g., decrease of the other immunoglobulins, cytopenia, or proteinuria) requires abatacept discontinuation and investigations for a lymphoproliferative syndrome:

- The monoclonal gammopathy was diagnosed during a pre-treatment screening with no data regarding its duration or evolution. An evaluation for lymphoproliferative syndrome is mandatory. If the results are negative, abatacept treatment can be started, with serum protein electrophoresis monitored every 3 months initially then every 6 months. Should the monoclonal component concentration increase or another abnormality develop, abatacept treatment should be discontinued.

5. History of myelodysplastic syndrome

Patients with a history of myelodysplastic syndrome (MDS: refractory anemia, idiopathic refractory sideroblastic anemia, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) were not included in the clinical trial program evaluating the efficacy and safety of abatacept in RA.

MDSs are not on the list of the more frequently reported adverse events (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in clinical trials evaluating the efficacy and safety of abatacept in RA (5).

As of March 31, 2011, no cases of MDS in abatacept-treated patients had been reported to the Pub.Med.gov database.

In practice, in the current state of our knowledge, in patients with a history of MDS in the past 5 years, abatacept treatment initiation can't be recommended. Decisions to start abatacept therapy in a patient with history of MDS should be taken in conjunction with a hematologist.

6. History of chronic myeloproliferative syndrome

Patients with a history of chronic myeloproliferative syndrome (CMS: chronic myelogenous leukemia with (9;22) translocation, chronic neutrophilic leukemia, chronic eosinophilic leukemia, polycythemia vera, chronic idiopathic myelofibrosis, and essential thrombocythemia) were not included in the clinical trials evaluating the efficacy and safety of abatacept in RA.

CMSs are not on the list of the more frequently reported adverse events (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in clinical trials evaluating the efficacy and safety of abatacept in RA (5).

As of March 31, 2011, no cases of CMS in abatacept-treated patients had been reported to the Pub.Med.gov database.

In practice, in the current state of our knowledge, in patients having a history of CMS in the past 5 years, abatacept treatment initiation can't be recommended. Decisions about whether to start abatacept therapy in a patient having a history of MDS should be taken in conjunction with a hematologist.

7. History of blood cell count abnormalities

Leukopenia and thrombocytopenia are on the list of more often reported adverse events (difference >0.2%) in abatacept-treated patients than in placebo-treated patients in clinical trials evaluating the efficacy and safety of abatacept in RA. These cytopenias were described as uncommon (rate between 0.1% and 1%) (1). Abatacept treatment was not associated with increases in autoantibody titers (antinuclear antibodies and anti-dsDNA antibodies) compared with placebo (5).

As of March 31, 2011, no cases of leukopenia or thrombocytopenia in abatacept-treated patients had been reported to the Pub.Med.gov database. A pilot study showed favorable *in vitro* effects of abatacept on the autoimmune response mechanisms underlying chronic idiopathic thrombocytopenic purpura (16).

In practice, in the current state of our knowledge, a history of cytopenia requires precautions when using abatacept. Investigations to identify the cause of cytopenia should be performed. Based on the results, several situations can be considered:

- Cytopenia revealing a hematological disease occurring concomitantly with RA: follow the specific recommendations for this hematological disease.
- Cytopenia revealing an autoimmune disease occurring concomitantly with RA: prefer rituximab, which may have favorable effects on some forms of autoimmune cytopenia.
- Cytopenia revealing an infection (due to a bacterium, mycobacterium, virus, or parasite) occurring as a complication of RA: administer specific treatment against the infectious agent before considering the initiation of abatacept treatment.

The decision to initiate abatacept treatment will take into account the results of the etiological evaluation and will be taken in conjunction with the hematologist.

8. Regarding hematological diseases, a screening before initiation of abatacept treatment should include the following:

- A physical examination to search signs suggesting an acute or chronic hematological disorder;
- Blood cell counts to look for cytopenia involving one or more blood cell lines or for an excess of normal or abnormal blood cells;
- Serum protein electrophoresis to search monoclonal gammopathy or hypogammaglobulinemia (whose presence requires assays of serum immunoglobulins and light chains by weight and immunofixation of serum and urinary proteins).

What are the alarm symptoms of hematological diseases?

1. Clinical symptoms and laboratory abnormalities depend on the disease.

● **The most common symptoms are as follows:**

- decline in general health (asthenia, weight loss, persistent fever)
- pallor, dyspnea
- recurrent infections
- petechiae, bruising, bleeding from the mucous membranes (nose and gums)
- lymphadenopathy, hepatomegaly, splenomegaly
- bone pain, pathological fractures
- night sudation

● **The following laboratory abnormalities suggest an acute leukemia:** cytopenia, circulating blasts.

● **The following laboratory abnormalities suggest a lymphoproliferative syndrome:** increase in circulating T-cells or B-cells, monoclonal gammopathy, or abnormality suggesting myeloma (cytopenia, hypercalcemia, renal failure, Bence-Jones proteinuria).

● **The following laboratory abnormalities suggest a myelodysplastic syndrome:** normocytic or macrocytic aregenerative anemia, isolated macrocytosis, neutropenia, thrombocytopenia; more rarely, leukocytosis with monocytosis (chronic myelomonocytic leukemia) or thrombocytosis.

● **The following laboratory abnormalities suggest a myeloproliferative syndrome:** polycythemia, leukocytosis with myeloma, thrombocytosis, or pancytopenia (in patients with myelofibrosis).

2. Evaluations to monitor abatacept treatment must include the following, at regular intervals:

- A physical examination to search signs suggesting an acute or chronic hematological disease;
- Blood cell counts to look for cytopenia involving one or more blood cell lines or for an excess of normal or abnormal blood cells;
- Serum protein electrophoresis every 3-6 months in patients with monoclonal gammopathy.

Course of action in patients with severe hematological disorders diagnosed during abatacept treatment

- Stop abatacept.
- Stop methotrexate and other immunosuppressants.
- Perform investigations to confirm the diagnosis, identify the cause (e.g., of cytopenia), evaluate severity, and stage the hematological disease.

When can abatacept therapy be resumed?

In the absence of recommendations, the decision to re-start abatacept treatment in a patient with a history of hematological disease should be taken in conjunction with a hematologist. The following guidance is suggested:

- 1) Development of a lymphoid or myeloid hematological malignancy (acute leukemia, myeloma, Waldenström macroglobulinemia, T-cell or B-cell chronic lymphocytic leukemia, chronic myelogenous leukemia): abatacept treatment should not be re-started, except in highly selected patients for whom no alternative treatments are available.
- 2) Detection of apparently benign monoclonal gammopathy (confirmed by serum protein electrophoresis on several occasions) by investigations performed in addition to the usual laboratory monitoring tests for abatacept-treated patients: the appropriateness of continuing abatacept treatment should be considered carefully, given the risk of transformation to myeloma. This risk is about 1% per year. Given the high frequency of detection of benign monoclonal gammopathy in patients older than 50 years (2% to 3% of the general population), this diagnosis does not preclude continued abatacept treatment with a monitoring with serum protein electrophoresis every 3 months then every 6 months. Hematological disorder must have been ruled out and the monoclonal component concentration has remained stable over time. If the monoclonal component concentration increases, abatacept treatment should be discontinued.
- 3) Myeloproliferative syndrome developing during abatacept treatment: abatacept should be discontinued, despite the absence of data suggesting a causal link between abatacept and the development of myeloproliferative syndromes.
- 4) Myelodysplastic syndrome developing during abatacept treatment: abatacept is best discontinued, despite the absence of data suggesting a causal link between abatacept and the development of myelodysplastic syndromes.
- 5) Cytopenia: the decision to re-start abatacept therapy depends on the cause, severity and reversibility of the cytopenia.

Additional information on the risk of hematological disease during abatacept treatment

In the preclinical studies of abatacept development program, no evidence of mutagenicity or clastogenicity was found by a battery of *in vitro* studies of abatacept (5).

In a mouse study of carcinogenicity, increased incidence of lymphomas and (in females) of mammary tumors were observed. These increases in the incidence of lymphomas and mammary tumors in abatacept-treated animals may be associated with a decreased control of the murine leukemia virus and of the mouse mammary tumor virus, respectively, due to prolonged immunomodulation (5).

In a 1-year toxicity study in *Cynomolgus* monkeys, abatacept was not associated with significant toxicity. Reversible pharmacological effects ranged from small and short-lived decreases in serum IgG levels to severe lymphoid depletion of the germinal centers in the spleen and/or lymph nodes. No evidence of lymphoma or pre-malignant morphological changes was seen in this study, despite the presence of the lymphocryptovirus, a virus known to cause such abnormalities in immunocompromised monkeys. Extrapolation of these data to the use of abatacept in clinical practice has not been evaluated (5).

Finally, the ISS data reported at the 2010 ACR meeting suggest that the annual incidence of lymphoma and other hematological malignancies remained stable with treatment durations of up to 7 years (4). The incidence of these malignancies in the long-term or cumulative periods has not increased compared to the short-term period (4).

In conclusion

Recommendations regarding the use of abatacept in patients with benign or malignant hematological disorders can be summarized in four points:

- One needs to be cautious in patients with a history of hematological disease, as there are no available data to consider that abatacept treatment is warranted in this situation, except in highly selected patients and in conjunction with a hematologist
- One needs to be cautious in patients with a history of myelodysplastic syndrome or chronic myeloproliferative syndrome, as the available data are not sufficient to consider that abatacept treatment is warranted in this situation, except in highly selected patients and in conjunction with a hematologist
- Patients with apparently benign monoclonal gammopathy can receive abatacept, with a tight monitoring. A diagnosis of monoclonal gammopathy during abatacept treatment does not necessarily preclude continued treatment, provided a hematological disorder is ruled out and the monoclonal component concentration remains stable
- In patients with cytopenia, abatacept treatment can be considered depending on the cause, severity, and reversibility of the cytopenia