



Use of abatacept in juvenile idiopathic arthritis

Evidence-based Medicine

Official Recommendations

Expert opinion

The pathophysiology of juvenile idiopathic arthritis (JIA) remains unelucidated. However, many lines of evidence indicate that activated T cells play a central role in the immunopathology of JIA. T-cell activation involves two events:

- 1- specific recognition of the antigen-HLA molecule pair at the surface of antigen-presenting cells (APCs) by T-cell receptor (TCR)
- 2- the second signal, or co-stimulation signal, which plays a key role via signal amplification and involves one or more ligand-receptor pairs at the surface of T cells and APCs

Full T-cell activation results in cytokine production, clonal T-cell proliferation, and T-cell differentiation to effector T cells then to memory T cells.

Under normal stimulating conditions, absence of the second signal induces a state of tolerance known as anergy, in which the T cell is no longer able to differentiate to an effector cell.

Second-signal blockade has been achieved in many animal models of autoimmunity and either prevents or decreases autoimmunity events. It relies on a blockade of the CD28-CD80/CD86 co-stimulator by a fusion molecule called CTLA4-Ig. CTLA4-Ig binds to CD80/CD86 on APCs and prevents CD28 from interacting with its CD80/CD86 ligands on APCs. Abatacept is a fully humanized recombinant version of CTLA4-Ig composed of the extracellular portion of human CTLA4 and of part of the FC domain of human IgG1 (93, 94).

Abatacept has been evaluated in the polyarticular course of JIA in an international study, and the pivotal trial described below was published in *The Lancet* in 2008 (95). Based on this trial, abatacept was licensed for use in polyarticular JIA in the US in 2008 and in Europe in 2010. However, the recognized indications differ between the US and Europe.

When is abatacept indicated?

- Abatacept is approved for use in Europe in children over 6 years who present with JIA with a polyarticular course, following one of the following initial subtype: polyarticular disease, extended oligoarticular disease, or systemic-onset disease. Abatacept can be used in polyarticular JIA in combination with methotrexate after an inadequate response to other disease-modifying drugs (DMARDs) including at least one TNF antagonist.

In the US, the FDA has approved the use of abatacept in children at least 6 years of age with moderate-to-severe polyarticular-course JIA, either as single-drug therapy or in combination with other DMARDs.

- A few case-reports and an open-label study describe the use of abatacept in chronic uveitis associated with JIA (refer to the relevant paragraph). To date, abatacept is not approved for use in this indication in children.

- No published data are available on the use of abatacept in systemic JIA with evidence of systemic disease activity, in psoriatic JIA, or in juvenile spondylarthropathy. Neither have any studies directly comparing abatacept to TNF antagonists or abatacept alone to abatacept plus methotrexate been performed. Finally, the optimal time for using abatacept has not been determined (early use of abatacept before TNF antagonists or later use after failure of a TNF antagonist).

Proof of efficacy

1- In polyarticular-course JIA

- The pivotal trial of abatacept in polyarticular-course JIA (including extended oligoarticular JIA, RF+ and RF- polyarticular JIA, and systemic-onset JIA without evidence of systemic disease activity) was conducted in 45 centers in Europe and the US between 2004 and 2006 (95). This Phase III randomized double-blind placebo-controlled trial evaluated the efficacy of abatacept in patients aged 6 to 17 years who had active JIA and an inadequate response or intolerance to at least one DMARD or TNF antagonist failure. Among DMARDs used in JIA, only methotrexate was allowed during the trial. Patients with active uveitis were excluded.

During the open-label lead-in phase, 190 patients received abatacept once a month for 4 months. The most common subtype was RF-polyarticular JIA (44%), the mean number of joints with active arthritis at baseline was 16 per patient, and mean disease duration was 4.2 years. Over 70% of patients were taking methotrexate at baseline and 30% had failed TNF antagonist therapy.

Regardless of the JIA subtype, at completion of the lead-in phase, 65% (123/190) of patients had an ACRPedi 30 response, 50% an ACRPedi 50 response, and 28% an ACRPedi 70 response.

The ACRPedi 30 response rate was twice higher in patients with no prior history of biological therapy than in patients having failed TNF antagonist therapy.

At completion of the lead-in phase, 47 patients had no response and 20 had left the study prematurely for the following reasons: lack of efficacy, n=17; failure to attend follow-up visits, n=1; and no known reason, n=1.

The randomized phase included 122 patients, who were allocated to either a placebo (n=62) or continued abatacept therapy (n=60) for 6 months. At completion of the randomized phase, a relapse had occurred in 53% (33/62) of the placebo patients compared to only 20% (12/60) of the abatacept patients (p=0.0003). The ACRPedi 50 and 70 response rates were significantly higher in the abatacept group (77% with abatacept vs. 52% with placebo and 53% with abatacept vs. 31% with placebo, respectively). At completion of the randomized phase, the disease was inactive in 13% of the abatacept patients. No differences in the abatacept response were noted across JIA subtypes. The median time to flare occurrence was 6 months in the placebo group and could not be determined with abatacept given the very small number of flares in this group.

The unexpectedly high ACRPedi response rate in the placebo group is evidence of the carry-over effect of abatacept given during the lead-in phase and shows that a washout period of at least 6 months is needed to determine response rates to abatacept. Finally, these results suggest that early abatacept therapy in patients naive to biological agents may be more effective than the use of abatacept after failure of TNF antagonist therapy.

- The long-term effects of abatacept therapy are being evaluated in the third phase of the study conducted over 5 years using an open-label design (44). This phase has 153 patients: 36 patients with initial failure to respond during the lead-in phase, 59 patients receiving the placebo during the randomized phase, and 58 patients randomized to abatacept during the randomized phase. An interim analysis on day 589 showed continued improvements in the ACRPedi response rates after the randomized phase, with comparable rates between the group given abatacept continuously (ACRPedi 50, 88%) and those who took the placebo during the randomized phase (ACRPedi 50, 83%). In the initial nonresponders, the ACRPedi response rate was lower but remained substantial (ACRPedi 50, 64%).

In this group of nonresponders (n=36), 16 patients had to stop abatacept prematurely, mainly because of inadequate efficacy.

Thus, the effect of abatacept is sustained in the medium term and even tends to improve over time. Among patients who had no response after 4 months of abatacept, the medium-term response rate was high, indicating a delayed effect. This is the first bioterapy trial to include patients with failure of TNF antagonist therapy, an indicator of severe disease. The results in this subgroup with severe disease were less dramatic than in patients naive to prior biological therapy but nevertheless established abatacept as a major treatment alternative in patients who fail TNF antagonist therapy. To date, no therapeutic trials have directly compared TNF antagonists and abatacept.

- The structural effect of abatacept has not yet been evaluated in pediatric patients
- The effect of abatacept on quality of life, pain, sleep, and activities of daily living in patients with JIA were evaluated during the lead-in and randomized phases of the pivotal trial, comparatively to healthy children (96). Abatacept therapy was associated with improvements in all the scores at the end of each of the two periods of the study, including the randomized period.

2- In chronic refractory anterior uveitis associated with JIA

- In JIA, uveitis has a fairly high prevalence ranging from 15% to 34%. Complications of chronic anterior uveitis develop in about 30% of patients with JIA-associated uveitis and cause blindness in 10% of cases (97). The first-line treatment rests on glucocorticoid eye drops, whose prolonged use can cause cataract formation and glaucoma. High doses systemic glucocorticoids and for prolonged periods have devastating effects on growth in children and should consequently be avoided if possible. Treatment options for difficult cases include synthetic DMARDs and TNF antagonists.

- Abatacept was introduced only very recently for the treatment of refractory JIA-associated uveitis. The beneficial effect of abatacept in animal models of experimental uveitis was recognized more than 5 years ago (98). In a recent case-series of 7 patients with a mean follow-up of 9.2 months, and in two reports each describing 2 patients, abatacept was beneficial in severe glucocorticoid-dependent uveitis refractory to synthetic DMARDs and to TNF antagonists (99-102). In most cases, the effect of abatacept became apparent toward the fourth week of treatment.

Thus, available data on abatacept treatment of refractory JIA-associated uveitis come only from descriptive case studies and should therefore be interpreted with caution. Abatacept seems to hold promise for the treatment of refractory JIA-associated uveitis.

Safety profile

Data on the adverse effects of abatacept come essentially from the pivotal trial and its extension phase, with a follow-up of 21 months at the time of this writing (44, 95). The safety profile of abatacept was good overall and was similar in the three periods of the study.

Adverse events can be classified into two groups:

● Immediate adverse events

- **infusion-related reactions** are uncommon (2-4%) and consist in headaches and dizziness, with rates similar to those recorded with the placebo
- headaches (13%), transient
- gastrointestinal disturbances(14%), which tend to decline with subsequent infusions
- fever (7%)

● Delayed adverse events

- **infections: the rates were similar with abatacept and the placebo (35-45%)** (influenza, bacteriuria, nasopharyngitis, upper respiratory tract infection, gastroenteritis, sinusitis, rhinitis)
 - 1 case of erysipelas, 1 of bacterial meningitis, and 1 of pyelonephritis
 - 2 cases of varicella during abatacept therapy including 1 with reversible varicella encephalitis and 1 case of shingles, followed by a full recovery
 - 1 case of dengue fever, reversible
 - no increase in the risk of tuberculosis
 - no increase in the risk of opportunistic infection
- **malignancies**
 - 1 case of acute lymphoblastic leukemia diagnosed on day 89. The chart review showed that the manifestations of leukemia were probably mistaken for JIA, as can occur in strictly rheumatic presentations of acute leukemia
- **benign tumors**
 - 4 cases of benign tumors
- **autoimmune disease**
 - 6 flares of arthritis, all during abatacept therapy (44); 1 flare of arthritis in a JIA patient given open-label abatacept for uveitis, with a skin rash and oral fungal infection (99)
 - 1 case of uveitis
 - 1 case of multiple sclerosis
 - 21% of patients with JIA developed antibodies against abatacept. These antibodies had no impact on the efficacy or safety of abatacept therapy. Antibody formation was more common when the serum abatacept levels were lower than the therapeutic range and when patients had a period of placebo therapy before resuming abatacept therapy
- **fertility**
 - potential effect unknown
- **laboratory test abnormalities**
 - no abnormalities reported to date

Administration modalities (age, dose, schedule, route)

Age

The European marketing license granted in 2010 allows the use of abatacept in children aged 6 years or older.

Dose and schedule

The approved dose is 10 mg/kg as a 30-minute infusion at weeks 0, 2, and 4 then every 4 weeks. Abatacept has a half-life of 13.1 days.

Route of administration

Intravenous

In most cases, no premedication is needed.

Drug-drug interactions

Abatacept should not be used in combination with TNF antagonists, as this combination is associated with a substantial increase in serious adverse events with no demonstrated clinical benefits (refer to the fact sheet on drug-drug interactions).

Furthermore, abatacept should be used with caution in patients with renal or hepatic failure, whose impact on abatacept pharmacokinetics has not been studied.

Cost of abatacept therapy

A study by Ungar et al. evaluated the direct and indirect costs related to abatacept therapy compared to etanercept, adalimumab, and infliximab (103). Abatacept was the less expensive biologic, with an annual cost of 16 205 Canadian dollars to induce an ACRPedi30 response in a child with polyarticular JIA refractory to methotrexate. Costs in Canadian dollars were 26 061 for etanercept, 31 209 for infliximab, and 46 711 for adalimumab.

The lower cost of abatacept compared to other biologics is a strong argument in favor of abatacept therapy.

Pre-treatment assessment

Thorough clinical examination including the components listed below.

1. An interview geared to the detection of contraindications (latent infections [e.g., tuberculosis or contact with a varicella patient], chronic infections, recurrent infections, acute infections [ENT, lower respiratory tract, urinary tract, dental], or a history of cancer, demyelinating disease, or deleterious drug-drug interactions).
2. A review of the immunization record and boosters as appropriate; the pneumococcal vaccine should be recommended; in patients without a reported history of varicella, a VZV serological test should be performed and, if the result is negative, the VZV vaccine should be given if allowed by the patient's overall health status (abatacept can be started only after at least 4 weeks have elapsed since VZV vaccination, or 3 weeks since yellow fever vaccination). If the VZV vaccine cannot be administered, the parents should be informed of the appropriate course of action in the event of contact with a varicella patient. The parents should be told about the vaccines that are contraindicated during abatacept therapy (live attenuated vaccines).

3. A thorough physical examination to look for contraindications to abatacept therapy and to evaluate the level of **JIA disease activity**.
4. **Laboratory tests:** blood cell counts, erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, serum urea and creatinine, urinary dipstick, ASAT and ALAT, antinuclear factor, rheumatoid factor, anti-citrullinated peptide antibodies, serology for the hepatitis B and C viruses and, with parental consent, serology for the HIV.
5. **5 IU intradermal tuberculin test:** read the result 48 to 72 hours later; the test is positive if (i) the induration is >5 mm in children who have not received the BCG vaccine or who have marked immunodepression; (ii) the induration is >10 mm in children vaccinated with the BCG and having only mild immunodepression; if the result is doubtful, particularly in BCG-vaccinated children, perform a QuantiFERON® or T-Spot TB®.
6. In adolescents, birth control must be discussed, particularly as concomitant methotrexate therapy is common.
7. An **ophthalmologic evaluation must be performed before starting abatacept therapy**.
8. **Radiographs** of involved joints and an anteroposterior chest radiograph must be obtained.

Evaluating the treatment response in pediatric patients

- The effectiveness of drugs for JIA should be evaluated using the ACR Pedi30, 50, 70, 90, and 100 criteria (104).
- Monitoring of drug safety includes evaluations for adverse events during treatment, most notably infections and malignancies.
- In most cases, visits are scheduled once a month at the beginning of abatacept therapy then every 3 months and later on every 6 months depending on whether a remission is obtained.