Management of pregnant women

Evidence-based Medicine | Official Recommendations | Expert opinion

Given the absence of adequate data, abatacept (CTLA-4 Ig) is contraindicated in pregnant women, and effective contraceptive methods must be used, starting at treatment initiation. However, the product characteristics and the data from animal studies allow to develop an expert opinion.

CTLA-4 and risk of spontaneous abortion

Several publications establish a beneficial effect of CTLA-4 on tolerance during pregnancy (77-79). CTLA-4 is expressed by foetal cells, including the fibroblastic cells of the placental mesenchyme at the mother-foetus interface, and the level of expression increases from the first to the second trimester of pregnancy. In addition, monoclonal antibodies to CD80 and CD86 (specific ligands of the CD28/CTLA-4 co-stimulation pathway) can induce maternal tolerance to the foetus. CTLA-4 overexpression has been documented in an abortion-prone mouse strain (80). Finally, a CTLA-4 gene polymorphism has been suspected as a cause of recurrent abortion in a population of Chinese women (81).

These preliminary data do not allow definitive conclusions but suggest a protective role of CTLA-4 against spontaneous abortion.

Available data on abatacept

Animal studies (5, 82, 83)

Abatacept is devoid of genotoxic or mutagenic effects and does not induce chromosomal abnormalities.

In rats, abatacept had no adverse effect on fertility in males or females. Embryotoxicity studies in mice, rats, and rabbits with doses corresponding to 20 to 30 times the dose used in humans (10 mg/kg), found no evidence of foetotoxicity, teratogenicity, or negative effects on neonatal development. Mild disturbances in immune functions consisting of thyroid gland inflammation or exacerbation of the T-cell-dependent humoral response were noted in rats but only with a dose of 200 mg/kg (i.e., 11 times the dose used in humans).

It should be noted that the animal toxicology studies of abatacept were conducted without concomitant medications (i.e., without concomitant methotrexate).

Pharmacological properties (5, 82, 83)

Studies in rats indicate that abatacept can cross the placental barrier (producing dose-dependent foetal serum concentrations that are 1.7 to 2.4 times lower than maternal serum concentrations). Abatacept can be detected in breast milk, in concentrations 10 times lower than in the maternal serum concentrations. In healthy volunteers given a single dose of 10 mg/kg, mean half-life was 16.8 ±4.5 days. After repeated intravenous doses of 10 mg/kg in patients with RA, mean half-life was 13.1 days (8 to 25 days).

Exposure to abatacept during pregnancy in women

During the double-blind and open-label phases of the five pivotal studies of abatacept in RA, 8 patients became pregnant while taking abatacept. Among them, 7 were on concomitant

methotrexate and 1 was on concomitant leflunomide (5). Spontaneous abortion occurred during the first trimester of pregnancy in 3 of these patients (of whom 2 had a prior history of spontaneous abortion). Elective abortion was performed in 2 patients. The remaining 3 patients were still pregnant at the time the study report was written. The spouse of a man treated with abatacept became pregnant and delivered a healthy baby.

During a phase II trial of abatacept in multiple sclerosis, 2 abatacept-treated women became pregnant, as well as the spouse of an abatacept-treated man. Of the three women, one delivered a healthy baby, one underwent elective abortion, and one experienced a spontaneous abortion at 2 months' gestational age (5).

Two registries of abatacept-exposed pregnancies have been set up:

- In the US: Organization of Teratology Information Specialists (OTIS), http://otispregnancy.org/otis_study_ra.asp
- In Europe: European Network of Teratology Information Service (ENTIS), http://www.entis-org.com

Clinical situations

Before initiating abatacept therapy

Women of child-bearing potential who are being evaluated for abatacept therapy initiation should be asked whether they want to have children. If a pregnancy is desired within the next few months, initiation of abatacept therapy is not advisable. However, the severity of the disease should be assessed, and when abatacept therapy is crucial to preserve function, the patient may be advised to postpone the pregnancy (in order to control the disease activity to allow a conception under more favorable clinical conditions). Refer to "Available data on abatacept – Pharmacological properties".

Time from the last abatacept infusion to attempted conception

Conception should not be attempted immediately after the last abatacept infusion. Furthermore, methotrexate, if used concomitantly with abatacept, must be stopped at least 1 month and 3 months before conception in women and men, respectively.

The Summary of Product Characteristics (20) contains the following recommendation about the time from the last abatacept infusion to attempted conception (that is, the time during which effective contraceptive measures must be used): "Women of child-bearing potential should use effective contraceptive methods during treatment and for 14 weeks following the last infusion".

The following should be taken into consideration:

- The wait before attempting conception recommended in the Summary of Product Characteristics (14 weeks) may lead to challenging clinical situations (e.g., joint disease flare after the initial response to abatacept), particularly as achieving a pregnancy may take time (20).
- The outcomes of the few pregnancies characterized by maternal exposure to abatacept were similar to those of pregnancies without abatacept exposure.
- Methotrexate, which is known to induce birth defects and abortions, is usually given in combination with abatacept and must be stopped at least 1 month and 3 months before conception in women and men, respectively.

Two main clinical situations may be encountered

- *The patient fails to respond to abatacept:* failure to control the joint disease usually requires a switch to another treatment option, and in most instances attempts to initiate a pregnancy must

therefore be postponed.

- *Abatacept therapy ensures control of the disease:* Methotrexate should be stopped 1 month and 3 months before conception in women and men, respectively. The elimination half-life of abatacept suggests that a 14-week wait between the last abatacept infusion and the first attempts to conceive may be adequate (as the maximal half-life is 20 days, 14 weeks is about 5 times the half-life, which allows elimination of 97% of a compound exhibiting linear kinetics).

  All these considerations suggest that waiting at least 14 weeks between the last abatacept infusion and attempts to initiate a pregnancy is reasonable in women. No specific data are available for men. In particular, the potential effect of abatacept on sperm cell production is unknown. Therefore, recommending a 14-week wait, as with female patients, may be reasonable.

Pregnancy initiation during abatacept therapy

Currently, initiation of a pregnancy during abatacept therapy requires the following measures:

- Immediate discontinuation of abatacept (and of concomitant methotrexate, if not already done)
- Sonographic monitoring
- A report to the pharmacovigilance center

If a pregnancy is initiated in an abatacept-treated woman, the decision about whether to continue the pregnancy is taken by the woman and her partner during the period when elective termination of pregnancy is legally available.
If the obstetrical investigations are normal, continuing the pregnancy can be recommended. Detailed information given at the initiation of abatacept therapy should prevent the occurrence of pregnancies during the treatment.

Initiation of abatacept therapy during pregnancy

This situation is unlikely to occur in patients with RA, a disease that usually improves during pregnancy. In the current state of our knowledge, abatacept initiation during pregnancy is not advisable.

Breast-feeding

Abatacept is detectable in milk in lactating animals (5). No data are available on abatacept excretion in human breast milk and, therefore, breast-feeding is not advisable during abatacept therapy. In practice, breast-feeding is possible, since it is started at least 13 months after the last abatacept infusion (4-month wait before attempting conception [refer to above] plus 9 months of gestation), at which time the drug has been completely eliminated from the body.
In patients who want to breast-feed and who require abatacept re-treatment, this re-treatment must be postponed until the baby is fully weaned. If the joint disease flares after delivery (a fairly common event in RA), re-treatment with abatacept and, therefore, the need to refrain from breast-feeding should be discussed on a case-by-case basis.