Management of Patients

Who Are or Want to Become Pregnant

Evidence Based Medicine | Official recommendations | Expert opinion

Given the absence of adequate data, tocilizumab is contraindicated in pregnant women. Therefore, effective contraceptive methods must be used as soon as tocilizumab therapy is initiated.

Pharmacokinetic data [4]

The half-life of tocilizumab varies with the concentration of the drug. At the steady state, after a dose of 8 mg/kg every 4 weeks, the effective half-life decreases from 14 to 8 days as the concentrations decline over the interval between infusions.

Data from the literature [4]

None of the preclinical data suggests any effect of tocilizumab on fertility. No effect on the endocrine glands or reproductive system was identified during a toxicity study in cynomolgus monkeys, and neither was reproductive capability altered in mice lacking IL-6. Tocilizumab given to cynomolgus monkeys during early pregnancy had no direct or indirect deleterious effects on the pregnancy or the embryonic or foetal development. However, small increases in abortion, embryonic mortality, and foetal mortality rates were noted after systemic exposure to high doses (more than 100-fold the exposure in humans) in a group receiving a high dose of tocilizumab (50 mg/kg/jour) comparatively to the placebo group and to the groups receiving lower doses.

In women who want to become pregnant

- **Before tocilizumab therapy**

During the tocilizumab initiation visit, women of child-bearing potential should be asked whether they want to become pregnant.

In women who plan to initiate a pregnancy within the next few months, tocilizumab initiation is not recommended.

However, the severity of the disease should be evaluated. When tocilizumab therapy is deemed crucial to preserve function, the option of postponing plans for a pregnancy should be suggested to the patient (as a means of achieving disease control and subsequently stopping tocilizumab and initiating the pregnancy under better conditions; see “During tocilizumab therapy”).

During tocilizumab therapy

Regarding methotrexate therapy, if used in combination with tocilizumab:

Women who are already receiving tocilizumab and who plan to initiate a pregnancy should discontinue tocilizumab therapy. The first step consists in stopping methotrexate therapy. The CRAT recommends stopping methotrexate at least 15 days before attempting conception [80]. **The CRI experts recommend waiting for at least one menstrual cycle (4 weeks) after methotrexate discontinuation before attempting conception.**

In male patients, methotrexate therapy should be stopped and at least one full spermatogenesis cycle (71 days) should be allowed to elapse prior to attempted conception.

Regarding tocilizumab therapy:

The Summary of Product Characteristics (4) recommends that effective contraception be used throughout tocilizumab therapy and for 6 months after the end of the treatment.

This suggested 6-month waiting period is not based on scientific data. It reflects the precautionary principle and should be assessed in the light of the product half-life.

Assuming that the waiting period should be equal to 5 times the half-life (the estimated time needed to eliminate 97.5% of the drug from the body), and using the highest reported half-life times (i.e., 5 times 14 days, 70 days) to obtain a conservative estimate, it may be reasonable to initiate a pregnancy 3 months after the end of tocilizumab therapy.

The factors listed below should also be considered:

- The long time to attempted conception recommended in the SPC may lead to challenging clinical situations (exacerbation of the joint disease), particularly as achieving a pregnancy may take time.
- The potential effects of tocilizumab on spermatogenesis are unknown. Therefore, the precautions recommended for women apply also to men (3-month wait between the last tocilizumab infusion and attempted conception).

All these considerations suggest that waiting 3 months between the last tocilizumab infusion and attempts to initiate a pregnancy is reasonable in both women and men.

Course of action in the event of a pregnancy during tocilizumab therapy

At present, occurrence of a pregnancy during tocilizumab therapy requires the measures listed below.

- immediate discontinuation of tocilizumab therapy (and of methotrexate therapy if not yet stopped);
- sonographic foetal monitoring;
- and report to the pharmacovigilance centre.

Thus, in the event of a pregnancy in a woman who has not discontinued tocilizumab therapy, a recommendation to continue the pregnancy can be made provided the obstetrical evaluation yields normal results.

In the event the pregnancy is continued, prenatal screening tests focusing on the birth defects described to date should be performed; the healthcare professionals who manage the neonate should be informed of the treatments taken by the mother [83].

Conception by a male patient taking tocilizumab therapy

At present, conception by a male patient on tocilizumab therapy requires the measures listed below.

- sonographic foetal monitoring;
- and report to the pharmacovigilance centre.

If the obstetrical evaluation shows no abnormalities, a recommendation can be made to continue the pregnancy.

Lactation

No data on potential tocilizumab excretion in human breast milk are available, and no studies have been performed in animals.

In patients who want to breast-feed, tocilizumab therapy should not be re-started until the baby is fully weaned.

If the joint disease flares after delivery (a fairly common event in rheumatoid arthritis), the appropriateness of re-starting tocilizumab therapy and, therefore, of weaning the baby should be discussed on a case-by-case basis.