Reproductive Toxicology 60 (2016) 29–32

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center

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ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
15 December 2015
Accepted 18 January 2016
Available online 21 January 2016

Keywords:
Pregnancy outcome
Spontaneous abortion
Tocilizumab
Rheumatoid arthritis
Birth defects
Biologic disease-modifying antirheumatic drugs

ABSTRACT

Tocilizumab (TCZ) is not recommended for use during pregnancy due to limited data, but pregnancies nevertheless occur and pregnant women need to be counseled about potential fetal risks. Participants of this study were recruited from the pool of callers who spontaneously contact the pharmacovigilance center "Embryotox" Berlin for risk assessment during pregnancy. Of 22 identified cases with TCZ exposure during pregnancy, 16 prospectively enrolled cases with maternal and two cases with paternal TCZ therapy could be completed. The outcomes of the 16 maternal cases were: four spontaneous abortions (SAB), one induced abortion for personal reasons and 11 live-born infants. Congenital malformations were not recorded, but one SAB at week 15 + 3 days was complicated by hydrops fetalis of unknown origin. An incidental continuation of TCZ into early pregnancy does not justify an elective termination. However, a detailed prenatal ultrasound should be offered.

1. Introduction

Biologic disease-modifying antirheumatic drugs have become a cornerstone of treatment for patients with chronic inflammatory diseases. Tocilizumab (TCZ) is a humanized monoclonal antibody (Mab) of the IgG1 subclass directed against the interleukin-6-receptor. The anti-inflammatory effect is a direct consequence of the inhibited activity of the pro-inflammatory cytokine interleukin 6 (IL-6). TCZ, marketed in the European Union since 2009, has been approved as a second-line medication for patients suffering from rheumatoid arthritis (RA) [1].

As TCZ possibly seems similar effective with or without the teratogenic methotrexate (MTX), it may become an interesting alternative for women of reproductive age, if there were more data on its safety in pregnancy.

In humans, TCZ can be administered once weekly in a dosage of 162 mg S.C. or every four week I.V. in a dosage of 8 mg/kg. Its half-life is 8–14 days, respectively, depending on the serum concentration. Pregnant monkeys treated with high intravenous doses of TCZ (50 mg/kg/d) were reported to have an increase in embryofetal death but not in malformations (product labeling and [2]). Published data on exposed human pregnancies are limited to two abstracts. Rubbert-Roth et al. [3] reported on 31 pregnancies with known pregnancy outcome resulting in 13 elective terminations, 7 SABs and 11 live-born children—all without congenital malformations. Ishikawa [4] reported on 6 pregnancies with TCZ therapy resulting in one SAB and 5 healthy newborns. In the EMA assessment report [5] seven pregnancies were mentioned, however, pregnancy outcome was only available for four, two SABs and two elective terminations.

Due to the limited experience women and men of reproductive potential are advised to discontinue TCZ three months before conception [2,6]. This recommendation is based on the assumption that the waiting period should equal 5× the highest reported half-life [2]. However, as pregnancies under maternal and paternal TCZ therapy nevertheless occur, the question arises how to counsel pregnant women about potential fetal risks in the event of an unplanned but wanted pregnancy.

Abbreviations: TCZ, tocilizumab; Mab, monoclonal antibody; IL-6, interleukin-6-receptor; RA, rheumatoid arthritis; MTX, methotrexate; LMP, last menstrual period; SAB, spontaneous abortion; CS, cesarean section; SGA, small for gestational age.

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http://dx.doi.org/10.1016/j.reprotox.2016.01.002
0890-6238/

The purpose of this study was to evaluate the effects of TCZ treatment in the first trimester of pregnancy on the frequency of congenital malformations and SABs.

2. Methods

From 2011/2012 through 2014, the Pharmakovigilanzzentrum Embryonaltoxikologie (further referred to as Embryotox Berlin) conducted a research project on pregnancy outcome after exposure to selected antirheumatic drugs (e.g., [7–10]) among which TCZ was explicitly itemized. Participants were recruited from the annual pool of approximately 13,500 consultations at Embryotox Berlin for drug risk assessment during pregnancy.

Most consultations of Embryotox Berlin take place during (early) pregnancy when a particular drug exposure raises the question of developmental toxicity, or when there is uncertainty about the best treatment option for an individual pregnant patient with an acute or chronic disease [11]. Thus pregnancy outcome is mostly recorded prospectively, i.e., neither the outcome of the pregnancy nor the results of prenatal diagnostic tests are known at the time of subject enrolment.

With informed consent data on drug exposure and pregnancy outcome are collected through structured telephone interviews and/or mailed questionnaires via the mother and/or her physician(s). These include maternal characteristics such as maternal age, pregnancy history, pre-pregnancy body mass index, prescription and over-the-counter medication including exposure interval and dosage, smoking and alcohol consumption as well as use of illicit drugs. Details regarding the course and outcome of pregnancy are focused on pregnancy complications, and birth defects. In addition, details of delivery, pregnancy loss, and gestational age at birth, sex, birth weight, length, head circumference, Apgar scores, and umbilical pH are collected. These data are obtained 8 weeks after birth including the results of the 3rd standard pediatric examination at 4–6 weeks after delivery offered to all infants born in Germany. For further details on the methodology and adaptation of the STROBE statement to the needs of pregnancy outcome studies see Schaefer et al. [12].

Gestational age is calculated by ultrasound during the 1st trimester or, if not available, from the first day of the last menstrual period (LMP). Spontaneous abortion (SAB) is defined as spontaneous pregnancy loss of a fetus <500 g or <23 completed weeks after LMP if weight is not known. Birth defects are classified into minor or major according to the EUROCAT classification system.

3. Results

To date, the institute has had 59 requests on TCZ (until 10.07.2015), of which 22 referred to an exposure during or shortly before pregnancy. Eighteen cases could be completed, among them 16 with maternal and two with paternal therapy. Two maternal cases are still pending and two lost to follow-up.

All 22 patients with exposure related to a pregnancy (Fig. 1) were treated because of RA—with TCZ infusions every four weeks except for the two pending pregnancies where it was administered subcutaneously. In all maternal cases therapy was halted latest at recognition of pregnancy. The dosage was recorded in 12 patients, seven of them received about 8 mg/kg, three the recommended highest dosage of 800 mg due to obesity (one maternal and both paternal cases), and the two patients with subcutaneous administration got 162 mg per week. One pregnancy had required assisted reproduction (ICSI).

Maternal characteristics of the 16 TCZ exposed women are shown in Table 1.

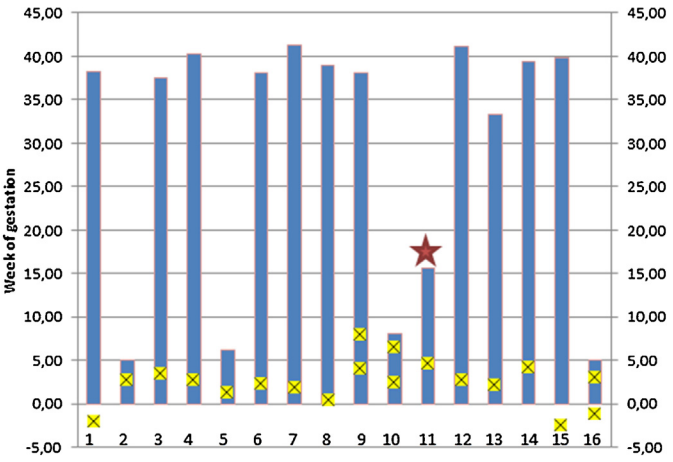

Fig. 1. Pregnancy outcome after maternal exposure and respective exposure time points.
Legend: Blue/grey bars show the duration of pregnancy; the (yellow) squares symbolize the timing of TCZ infusion during or shortly before pregnancy. The star points to the only pregnancy with pathologic fetal outcome. Four pregnancies (#2;#10;#11;#16) ended as SAB. #5 was electively terminated for personal reasons.

Table 1
Maternal characteristics of the 16 TCZ exposed women.

	TCZ ($N = 16$)
Maternal age, ($n = 16$)	
Age – years – median (min–max)	33.5 (24; 37)
Maternal BMI (pre-pregnancy), ($n = 12$)	
BMI – kg/m^2-median (min–max)	22.7 (17.7; 38.9)
Smoking, ($n = 14$)	
No – n (%)	13 (81)
Alcohol, ($n = 14$)	
No – n (%)	14 (100)
Illicit drugs, ($n = 13$)	
No – n (%)	13 (100)
Previous child, ($n = 16$)	
0 – n (%)	13 (81)
1 – n (%)	1 (6)
≥2 – n (%)	2 (13)
Previous miscarriages, ($n = 16$)	
0 – n (%)	15 (94)
1 – n (%)	1 (6)
Gestational week at first contact, ($n = 16$)	
Median gestational week	9.0
Other DMDs during pregnancy, ($n = 16$)	
No – n (%)	5 (31)
Prednisolone – n (%)	8 (50)
Other DMD – n (cases) (%)	4* (25)

BMI: body mass index, DMDs: disease-modifying drugs.
*One patient was treated with prednisolone and other DMDs; three with other DMDs than TCZ but without prednisolone. The DMDs were leflunomide ($n = 2$), low-dose MTX ($n = 1$), sulfasalazine & hydroxychloroquine ($n = 1$ pregnancy).

3.1. Pregnancy outcome after maternal TCZ therapy

Of the 16 prospectively recorded pregnancies there were 4 SABs (Fig. 1: #2; #10; #11; #16), one elective termination for personal reasons in week 6 + 1 day (#5) and 11 live-born infants. For details of drug exposure and pregnancy outcome see Fig. 1.

The high number of 7/11 cesarean sections (CS) (64%) exceeding the average CS- rate of about 30% [13] and the high rate of comorbidities are worth mentioning. Eight women (50%) had one or more of the following diseases: hypertension, fibromyalgia, depression, eating disorder, polycystic ovarian syndrome, hypothy-