

PURPOSE

The fully human, anti-tumor necrosis factor monoclonal antibody adalimumab is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), psoriasis, and juvenile idiopathic arthritis in the United States and elsewhere.

This preliminary description of outcome data from an ongoing study provides some information on the safety of adalimumab when used by patients with rheumatoid arthritis (RA) and Crohn's disease (CD) during pregnancy.

METHODS

The Organization of Teratology Information Specialists (OTIS) is a North American-wide network of telephone-based teratogen counseling services located in universities or hospitals throughout the U.S. and Canada.

- OTIS members provide information about exposures in pregnancy to approximately 80,000 health care providers and pregnant women each year.
- Since 1999, OTIS members have collaborated in conducting a pregnancy registry study focused on the safety of medications used to treat a variety of autoimmune diseases, including rheumatoid arthritis (RA).
- The OTIS Autoimmune Diseases in Pregnancy Project utilizes a single Coordinating Center to recruit and follow study subjects, drawing on OTIS member services across the network to screen and refer pregnant callers who qualify for study participation.

As part of the OTIS project, using a prospective cohort study design, women with RA and CD who have been treated with adalimumab in the first trimester of pregnancy are enrolled, interviewed on three occasions during pregnancy and once after delivery, and their infants are followed up for one year post-partum.

- Pregnancy outcome information is obtained by maternal interview and medical records review.
- All live born infants in the study are examined by one of a team of pediatric specialists who evaluate these infants for both major and minor anomalies.
- Pregnancy outcomes in the adalimumab-exposed group are compared with those in a disease-matched group of women with RA or CD who have not been treated with adalimumab in pregnancy.
- Mothers and infants in the two comparison groups are followed using the same methods and procedures as those in the adalimumab-exposed group.

In addition to conducting the cohort study, the OTIS investigators also collected information on adalimumab-exposed pregnancies that did not meet the cohort criteria, but were followed as a case series. The case-series pregnancies are presented separately as they have no comparison group. They include patients treated for diseases other than RA and CD, as well as retrospectively reported outcomes.

RESULTS

As of October 22, 2009 (5.5 years of the study), pregnancy outcomes were available for 239 women in the cohort (Table 1).

As shown in Table 2, 7 women delivered infants who had major defects (8.8%) among 94 women with first trimester adalimumab exposure and for whom pregnancy outcomes were known: 1 undescended testicle, 1 microcephaly, 1 ventricular septal defect, 1 congenital hip dysplasia with inguinal hernia, 1 congenital hypothyroidism, 1 bicuspid aortic valve and agenesis of the corpus callosum (twin pregnancy in which 2nd twin had patent ductus arteriosus), and 1 congenital hydronephrosis (twin pregnancy in which 2nd twin was spontaneously aborted).

In the case-series group (data not included in the table), of the 122 known outcomes, 5 (4.1%) resulted in major congenital defects: 2 chromosomal anomalies, 1 child with an atrial septal defect and peripheral pulmonic stenosis, 1 hip dysplasia, and 1 ventricular septal defect.

CONCLUSIONS

Based on preliminary data from this ongoing study, no concerns have been raised regarding increased risks for adverse pregnancy outcomes associated with early pregnancy exposure to adalimumab.

- The proportion of ADA-exposed pregnancies that ended in spontaneous abortion is within the expected range of 10-15% in clinically recognized pregnancies in the general population.
- The proportion of preterm deliveries in the ADA-exposed cohort group is similar to the proportion in the disease-matched comparison group.
- There is no pattern of birth defects evident in the ADA-exposed cohort group, and rates are consistent with the expected range in the general population.
- Firm conclusions await accumulation of sufficient sample size in the prospective cohort study.

TABLE 1 Pregnancy Outcomes in the Cohort Study

OUTCOME	ADALIMUMAB COHORT N=94	DISEASED COMPARISON N=58	NON-DISEASED COMPARISON N=87
Live born - n (%)	80 (85.1)	53 (91.4)	78 (89.7)
Spontaneous abortion - n (%)	13 (13.8)	3 (5.2)	1 (1.1)
Stillborn - n (%)	0	0	1 (1.1)
Elective termination - n (%)	1 (1.1)	0	0
Lost-to-follow-up - n (%)	0	2 (3.4)	7 (8.0)

TABLE 2 Known Outcomes of Prospectively Identified Pregnancies

	ADALIMUMAB COHORT N=94	DISEASED COMPARISON N=58	NON-DISEASED COMPARISON N=87
Preterm delivery <37 wks among live births - n (%)	12 (15.0)	9 (17.0)	3 (3.8)
Birth weights in full-term infants in grams - mean (SD)	3253 (480)	3340 (469)	3514 (522)
Malformations among live births - n (%)	7 (8.8)	2 (3.8)	4 (5.1)
Malformations among all pregnancies - n (%)	9 (9.6)*	3 (5.4)**	4 (5.0)***

*in addition to malformations among live births, includes one spina bifida and hydrocephalus in a pregnancy resulting in elective termination, and one ectopia cordis and caudal regression in a twin pregnancy resulting in a spontaneous abortion; **one ventricular septal defect and one bilateral metatarsus adductus among live births; one report of non-specific "chromosomal problems" in a pregnancy resulting in spontaneous abortion; one postnatal death in an infant due to an in-utero stroke (not counted as a malformation); ***one ventricular septal defect, one postaxial accessory digit, one ventricular septal defect with patent foramen ovale and patent ductus arteriosus, and one pulmonic stenosis among live births.