



Pregnancy Outcome in Women Exposed to Leflunomide: The OTIS Autoimmune Diseases in Pregnancy Project

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Purpose

Leflunomide (Arava®) is a disease-modifying antirheumatic drug approved for the treatment of rheumatoid arthritis. Based on animal studies, leflunomide has been classified as pregnancy category X. However, little information is available on the human fetal safety of this medication when women are inadvertently exposed in early pregnancy. The purpose of this report is to describe a pregnancy outcome study designed to evaluate the safety of leflunomide and to present interim results from this pregnancy registry.

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 who have been treated with leflunomide in the first trimester of pregnancy are enrolled, interviewed on three occasions during pregnancy, and their infants are followed up into the post-partum period. Pregnancy outcome information is obtained by maternal interview and medical records review. In addition, 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 leflunomide-exposed group are compared with those in a disease-matched group of women with RA who have not been treated with leflunomide in pregnancy, and a non-diseased group of women who neither have RA nor have been treated with leflunomide in pregnancy. Mothers and infants in the two comparison groups

are followed using the same methods and procedures as those in the leflunomide-exposed group.

In addition to the cohort study, OTIS registry investigators also enroll and follow leflunomide-exposed pregnancies that do not meet the criteria for inclusion in the cohort. These include women who contact the study staff after the 20th week of gestation, retrospectively reported pregnancy outcomes, pre-conception and paternal exposures.

Results

As of September 15, 2006, a total of 277 women have enrolled in the leflunomide study, of whom 229 met the cohort study criteria (63 leflunomide-exposed, 108 RA comparison women, and 58 non-diseased comparison women). An additional 48 women who did not meet the cohort study criteria have been enrolled in the leflunomide pregnancy registry, and of these 21 women were exposed to leflunomide during pregnancy. Current status of the cohort study pregnancies is shown in Table 1.

Table 1. Leflunomide (Arava®) Pregnancy Study Enrollment and Outcome Status

	Leflunomide Cohort N	Disease-Matched Comparison N	Non-Diseased Comparison N	Total N
Enrolled Pregnancies	63	108	58	229
Outcome Known	61	106	56	223
Live born	54 (87.1%)	95 (88.0%)	54 (94.7%)	203
Spontaneous Abortion	6 (9.7%)	8 (7.4%)	2 (3.5%)	16
Still born	0	1 (0.9%)	0	1
Elective Termination	1 (1.6%)	2 (1.9%)	0	3
Lost-to-follow-up	1 (1.6%)	2 (1.9%)	1 (1.8%)	4
Pending Delivery	1	0	1	2

As shown in Table 2, 2 of 54 (3.7%) live born infants in the leflunomide-exposed cohort group had major structural defects: one with occult spinal dysraphism and one with multicystic kidney disease. An additional 2 infants in this group (3.7%) had microcephaly. In the disease-matched comparison group, 4 of 95 live born infants (4.2%) had major structural defects and an additional 2 of 95 had isolated microcephaly (2.1%). The rate of major structural defects in the non-diseased comparison group was 3.7%.

Table 2. Major Structural Defects, Preterm Delivery and Birth Size in the Cohort Study Pregnancies

	Leflunomide Cohort	Disease-Matched Comparison	Non-Diseased Comparison
Major Structural Defects N (%)	2 (3.7%)	4 (4.2%)*	2 (3.7%)
Microcephaly n (%)	2 (3.7%)	2 (2.1%)	0
Functional Problems n (%)**	1 (1.9%)	1 (1.1%)	1 (1.9%)
Major Structural Defects in Terminations or Spontaneous Abortions n (%)	0	3 (2.8%)	0
Preterm Delivery n (%)	20 (37.0%)	23 (24.2%)	2 (3.7%)
Mean Birth Size (full term infants)			
Weight - g (SD)	3156 (436)	3310 (391)	3570 (441)
Length - cm (SD)	50.2 (2.3)	50.4 (2.6)	51.2 (2.2)
Head Circumference - cm (SD)	34.1 (1.6)	34.3 (1.6)	34.5 (1.4)

*one infant had a major structural defect and microcephaly

**one infant each with hydronephrosis in the leflunomide and disease-matched groups; one infant with congenital esotropia in the non-diseased comparison group

Among the 20 leflunomide-exposed pregnancies that did not meet the cohort group criteria, no major structural defects and one functional problem (hearing loss) has been reported in 14 live births.

Conclusions

Based on interim data from this ongoing study, the proportion of pregnancies with adverse outcomes is comparable between the leflunomide-exposed cohort study pregnancies and the disease-matched comparison group. Furthermore, no specific pattern of major structural defects has been noted in the leflunomide-exposed infants nor are the reported congenital anomalies consistent with those noted in animal developmental toxicity studies. These data do not suggest specific increased risks for teratogenicity with early first-trimester exposure to leflunomide (Arava®). More definitive conclusions await accumulation of sufficient sample size in the cohort study and final analyses of the data on minor structural defects.

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