

Biologics in Pregnancy Up Malformation Risk

BY AMY ROTHMAN SCHONFELD

PHILADELPHIA — Women with rheumatic disease who took etanercept during pregnancy were three times more likely to have a child with a major malformation than a disease-matched comparison group, judging from interim results from a small sample.

Most of the malformations were isolated, and no patterns of birth defect were apparent, according to Christina Chambers, Ph.D., who presented the findings from the Autoimmune Diseases in Pregnancy Project being conducted by the Organization of Teratology Information Specialists (OTIS) at the annual meeting of the American College of Rheumatology.

The OTIS study is a prospective observational cohort study with the purpose of evaluating effects of autoimmune diseases and their treatment on pregnancy outcomes and fetal development. Recruitment began in 2000, and is projected to continue through 2015. Current recruitment stands at 944, with a goal of 1,500, said Dr. Chambers, an associate professor of pediatrics and family and preventive medicine at the University of California in San Diego.

Pregnant women are typically enrolled

in the study before they reach 20 weeks of gestation. To be enrolled, the women must have current diagnoses of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis, or Crohn's disease.

Many participants are referred to the OTIS coordinating center, where they undergo multiple interviews and review of their symptom management. After birth, the infants are followed for up to a year, during which time they are assessed by their pediatricians, undergo blinded dysmorphological examination by OTIS physicians, and are photographed.

"Evaluating pregnancy outcomes following medication exposure is a not a situation that lends itself to conducting a randomized controlled trial for obvious ethical reasons," said Dr. Chambers. While the literature contains case reports, the OTIS Project is designed to give clinicians the evidence-based information they need to counsel patients who are pregnant or considering becoming pregnant.

At the time of this progress report, outcome was available for 115 women with RA who had been exposed to etanercept, compared with 55 disease-comparison controls. Outcome was available for 42 women with RA who were

exposed to adalimumab, compared with 58 disease-matched women and 84 healthy controls.

The percent of live births was higher in those treated with etanercept, compared with those with similar rheumatic diseases (92% vs. 85%) and fewer spontaneous abortions occurred in the etanercept-treated group (4% vs. 11%). One stillbirth was reported in the etanercept cohort and none in the controls. Preterm deliveries were more common in women who were taking etanercept (23% vs. 13%).

Of the major malformations among all pregnancies enrolled in OTIS, 12% (14 of 114) were reported in the etanercept group, compared with 3.8% (2 of 53) in the disease-matched controls. The defects included displaced stomach with epispadias and congenital eye defect; ventricular septal defect with peripheral pulmonary stenosis; pyloric stenosis; hypopspadias; ventricular septal defect with patent foramen ovale and patent ductus arteriosus; volvulus; patent foramen ovale; atrial septal defect with patent ductus arteriosus; microcephaly; congenital hypothyroidism; and an unspecified heart defect. Three abnormalities—Noonan syndrome, Turner syndrome, and Down syndrome—were genetic or chromoso-

mal. "Typically we would see a specific pattern of malformation with a medication that truly causes defects, but our results indicate that most of the defects were isolated with no apparent patterns," Dr. Chambers said.

For those exposed to adalimumab, the percentage of live births was lower in those receiving the drug (88%) compared with those with similar autoimmune illnesses (93%) and healthy controls (92%). The rate of spontaneous abortions also was higher in the adalimumab-treated cohort (12%) compared with the disease-matched (5%) and healthy cohorts (1%). There were no ectopic pregnancies or stillbirths in the drug-treated group.

Preterm delivery was higher in both the adalimumab-treated (14%) and disease-matched comparison (17%) groups compared with healthy controls (4%). Mean birth weight was approximately 300 grams less in full term infants whose mothers had received adalimumab compared with healthy controls but similar to full-term infants in the disease-matched comparison group.

Rates of major malformations were similar (from 4% to 5%) in all groups and within the range of expected numbers in the general population, said Dr. Chambers.

BRIEF SUMMARY

(see package insert for full prescribing information)

Atralin™ (tretinoin) gel 0.05%

For topical use only

INDICATIONS AND USAGE
Atralin Gel is a retinoid indicated for topical treatment of acne vulgaris.

Important Limitations of Use

The safety and efficacy of the use of this product in the treatment of any other disorders have not been evaluated.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using Atralin Gel. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced; if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with caution in patients with these conditions.

Topical over-the-counter acne preparations, concomitant topical medication, medicated cleansers, topical products with alcohol or astringents, when used with Atralin Gel, should be used with caution. [See Drug Interactions (7)]

Ultraviolet Light and Environmental Exposure

Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Atralin Gel. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Fish Allergies

Atralin Gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with Atralin Gel [see Clinical Studies (14)]. In these studies, 50% of the subjects who were treated with Atralin Gel reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related.

There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined, are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persist throughout the treatment period.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

Event	Atralin Gel (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	78 (12%)	7 (1%)
Skin Burning/Itching	53 (8%)	6 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

DRUG INTERACTIONS

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50-kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses.

Dose-related increases in embryo/lethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (numerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects on fetuses: Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Atralin Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with Atralin Gel were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include any subjects over age 65 to determine whether they respond differently than younger subjects.

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Answering Your Patient's Questions

There are really sparse data on the safety of biologic agents in women who are pregnant. We currently are in a situation where controlled randomized trials typically are not appropriate, yet pregnant women are using these medications. The OTIS project is a prospective, observational cohort study that should shed light on whether biologics are safe for women who are pregnant. However, it will still be several years before all results are in and the data can be statistically analyzed. In the meantime, what can you tell your patients about the use of biologics if they are pregnant or plan to become pregnant?

Q: If I take a biologic, will it be more difficult to become pregnant?

A: Information is very limited, but to date neither preclinical data nor clinical data indicate that becoming pregnant is more difficult.

Q: If I do become pregnant while on a biologic drug, do I have a chance of having a baby with a birth defect?

A: One of the principles of teratology is that known teratogens tend to cause specific patterns of malformations. To date with the limited information available, neither animal nor human data suggest that the risk for a specific pattern of defects is increased over baseline if you take a bi-

ologic agent while pregnant. While preliminary results from the OTIS project have noted that more malformations occurred in the offspring of women taking etanercept, the defects were varied and isolated.

Q: If I do become pregnant while taking this drug, will my child's immune system be compromised?

A: There are limited human data available for rituximab. To date, the results of the OTIS study do not indicate an increase in opportunistic infections, hospitalizations, or malignancies in the infants of women who have taken etanercept or adalimumab.

Q: If I do become pregnant while taking a biologic agent, do I have to discontinue the drug or can I safely continue to take the drug throughout pregnancy?

A: We really don't know the answer. In the OTIS project, approximately half of women on etanercept or adalimumab remain on the medication into the second or third trimester.

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