

No Red Flags for Early Etanercept, Adalimumab

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Preliminary data suggest no increased risk for adverse pregnancy outcomes in women exposed to either etanercept or adalimumab during the first trimester, Christina Chambers, Ph.D., reported in two posters at the annual meeting of the American Academy of Dermatology.

Although the numbers are small thus

far, no worrisome pattern has emerged. "Based on preliminary data at the present time, we don't see any big red flags," said Dr. Chambers, a perinatal epidemiologist at the University of California, San Diego, who specializes in drug safety during pregnancy.

The prospective cohort data come from the Organization of Teratology Information Specialists (OTIS), a network of telephone-based teratology counseling services based at hospitals and universities

throughout the United States and Canada. Since 1999, network members have collaborated on the OTIS Autoimmune Diseases in Pregnancy Project, a registry study focused on the safety of medications used to treat a variety of autoimmune diseases. The project is sponsored in part by research grants from several pharmaceutical companies, including Amgen Inc., the manufacturer of etanercept (Enbrel), and Abbott Laboratories, maker of adalimumab (Humira).

Both etanercept and adalimumab are self-injectable anti-tumor necrosis factor- α monoclonal antibody medications approved in the United States for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis.

Etanercept is also approved for treating psoriasis and ankylosing spondylitis. Dr. Chambers presented early data from ongoing studies of both drugs.

A total of 82 women were enrolled in the etanercept study between March 2005 and October 2006. Of those, 48 were exposed to etanercept: 28 for RA, 14 for psoriasis or psoriatic arthritis, and 6 for ankylosing spondylitis.

Another 34 women who did not take etanercept were also enrolled: 18 with RA, 14 with psoriasis or psoriatic arthritis, and 2 with ankylosing spondylitis. Mean age was about 33 years in both groups, and mean gestational age at enrollment was

11.4 weeks for the etanercept-exposed group and 12.2 weeks for the disease-matched comparison group.

As with etanercept, no increased risks for preterm delivery or malformations were seen with adalimumab exposure in the first trimester.

Outcome was known for 42 pregnancies as of October 2006. No stillbirths occurred in either group. There was one spontaneous abortion

among the 22 in the etanercept group (4.5%), far below both the 3 of 20 (15%) in the disease-matched comparison group and the 10%-15% pregnancy loss rate in the general population, Dr. Chambers noted.

Gestational age was 37.5 weeks for the etanercept group, which was not significantly different from the 37.8 weeks for the disease-matched controls.

Gestational age in both groups, however, was about a week earlier than normal, a phenomenon that has been documented previously in patients with RA. Similarly, birth weights—3,323 g for the etanercept group and 3,317 g for the nonexposed disease-matched women—were slightly lower than the 3,400-3,500 g average birth weight in the general population, but were not increased in those with etanercept exposure, she said.

Of the 21 infants born alive in the etanercept group, three had major defects: One infant, a twin, was born with malrotation of the stomach, which required surgery; a preterm infant had a unilateral inguinal hernia that required surgery; and a third, whose mother had Hashimoto's thyroiditis, was born with congenital hypothyroidism.

In the comparison group, one pregnancy was terminated following a prenatal diagnosis of Down syndrome.

The adalimumab data set comprised a total of 130 women who were enrolled in the prospective cohort study: 23 exposed to adalimumab for the treatment of RA,

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Sanctura® (trospium chloride) 20 mg Tablets

Brief Summary: please see package insert for full prescribing information.

INDICATIONS AND USAGE

Sanctura is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

CONTRAINDICATIONS

Sanctura is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Sanctura is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention: Sanctura should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility: Sanctura should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (See CONTRAINDICATIONS). Sanctura, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis.

Controlled Narrow-angle Glaucoma: In patients being treated for narrow-angle glaucoma, Sanctura should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

Patients with Renal Insufficiency: Dose modification is recommended in patients with severe renal insufficiency (CLcr < 30mL/min). In such patients, Sanctura should be administered as 20 mg once a day at bedtime (See DOSAGE AND ADMINISTRATION).

Patients with Hepatic Impairment: Caution should be used when administering Sanctura in patients with moderate or severe hepatic dysfunction (See CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations).

Information for Patients

Patients should be informed that anticholinergic agents, such as Sanctura, may produce clinically significant adverse effects related to anticholinergic pharmacological activity. For example, heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as Sanctura are used in a hot environment. Because anticholinergics such as Sanctura may also produce dizziness or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

Sanctura should be taken 1 hour prior to meals or on an empty stomach. If a dose is skipped, patients are advised to take their next dose 1 hour prior to their next meal.

Drug Interactions

The concomitant use of Sanctura with other anticholinergic agents that produce dry mouth, constipation, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

Drugs Eliminated by Active Tubular Secretion: Although demonstrated in a drug-drug interaction study not to affect the pharmacokinetics of digoxin, Sanctura has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion (e.g. procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir). Coadministration of Sanctura with these drugs may increase the serum concentration of Sanctura and/or the coadministered drug due to competition for this elimination pathway. Careful patient monitoring is recommended in patients receiving such drugs (See CLINICAL PHARMACOLOGY: Excretion, and CLINICAL PHARMACOLOGY: Drug-Drug Interactions).

Drug-Laboratory-Test Interactions

Interactions between Sanctura and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with trospium chloride were conducted in mice and rats. A 78-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats were conducted at doses of 2, 20, and 200 mg/kg/day. No evidence of a carcinogenic effect was found in either mice or rats. The 200 mg/kg/day dose in the mouse and rat represents approximately 25 and 60 times, respectively, the human dose based on body surface area. At 200 mg/kg/day in the mouse and rat after 4 weeks the AUC was 34 and 753 ng•h/mL, respectively. The exposure in the rat is 8.6-fold higher than the AUC following 40 mg daily exposure in healthy young or elderly subjects (88 ng•h/mL).

Trospium chloride was not mutagenic in tests for detection of gene mutations in bacteria (Ames test) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or in vivo in the rat micronucleus test.

No evidence of impaired fertility was observed in rats administered doses up to 200 mg/kg/day (about 10 multiples of the expected clinical exposure via AUC).

Pregnancy: Teratogenic Effects

Pregnancy Category C: Trospium chloride has been shown to cause maternal toxicity in rats and a decrease in fetal survival in rats administered approximately 10 times the expected clinical exposure (AUC). The no-effect levels for maternal and fetal toxicity were approximately equivalent to the expected clinical exposure in rats, and about 5-6 times the expected clinical exposure in rabbits. No malformations or developmental delays were observed. There are no adequate and well controlled studies in pregnant women. Sanctura should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Trospium chloride (2 mg/kg PO and 50 µg/kg IV) was excreted, to a limited extent (<1%), into the milk of lactating rats. The activity observed in the milk was primarily from the parent compound. 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 Sanctura is administered to a nursing woman. Sanctura should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

Pediatric Use

The safety and effectiveness of Sanctura in pediatric patients have not been established.

Geriatric Use

Of the 591 patients with overactive bladder who received treatment with Sanctura in the two U.S., placebo-controlled, efficacy and safety studies, 249 patients (42%) were 65 years of age and older. Eighty-eight Sanctura-treated patients (15%) were ≥75 years of age.

In these 2 studies, the incidence of commonly reported anticholinergic adverse events in patients treated with Sanctura (including dry mouth, constipation, dyspepsia, UTI, and urinary retention) was higher in patients 75 years of age and older as compared to younger patients. This effect may be related to an enhanced sensitivity to anticholinergic agents in this patient population (See CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION). Therefore, based upon tolerability, the dose frequency of Sanctura may be reduced to 20 mg once daily in patients 75 years of age and older.

ADVERSE REACTIONS

The safety of Sanctura was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients, who were treated with Sanctura (N=1673), placebo (N=1056) or active control medications (N=246). Of this total, 1181 patients participated in two, 12-week, Phase 3, U.S., efficacy and safety studies and a 9-month open-label extension. Of this total, 591 patients received Sanctura 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with Sanctura for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving Sanctura 20 mg BID and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with Sanctura or placebo, respectively, by the investigator.

Table 1 lists treatment emergent adverse events from the combined 12-week U.S. safety and efficacy trials that were judged to be at least possibly related to treatment with Sanctura by the investigator, were reported by at least 1% of patients, and were reported more frequently in the Sanctura group than in the placebo group.

The two most common adverse events reported by patients receiving Sanctura 20 mg BID were dry mouth and constipation. The single most frequently reported adverse event for Sanctura, dry mouth, occurred in 20.1% of Sanctura treated patients and 5.8% of patients receiving placebo. In the two Phase 3 U.S. studies, dry mouth led to discontinuation in 1.9% of patients treated with Sanctura 20 mg BID. For the patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

Table 1. Incidence (%) of adverse events judged at least possibly related to treatment with Sanctura, reported in ≥1% of all patients treated with Sanctura and more frequent with Sanctura (20 mg BID) than placebo in Studies 1 and 2 combined.

Adverse Event	Placebo (N=590)	Sanctura 20 mg BID (N=591)
Gastrointestinal disorders		
Dry mouth	34 (5.8)	119 (20.1)
Constipation	27 (4.6)	57 (9.6)
Abdominal pain upper	7 (1.2)	9 (1.5)
Constipation aggravated	5 (0.8)	8 (1.4)
Dyspepsia	2 (0.3)	7 (1.2)
Flatulence	5 (0.8)	7 (1.2)
Nervous system disorders		
Headache	12 (2.0)	25 (4.2)
General Disorders		
Fatigue	8 (1.4)	11 (1.9)
Renal and Urinary Disorders		
Urinary retention	2 (0.3)	7 (1.2)
Eye Disorders		
Dry eyes NOS	2 (0.3)	7 (1.2)

Abbreviations: BID=twice daily, NOS=not otherwise specified.

Other adverse events from the Phase 3, U.S., placebo-controlled trials judged possibly related to treatment with Sanctura by the investigator, occurring in ≥0.5% of Sanctura-treated patients, and more common with Sanctura than placebo are: tachycardia NOS, vision blurred, abdominal distension, vomiting NOS, dysgeusia, dry throat, and dry skin. During controlled clinical studies, one event of angioneurotic edema was reported.

Postmarketing Surveillance

Additional spontaneous adverse events, regardless of relationship to drug, reported from marketing experience with trospium chloride include: Gastrointestinal—gastritis; Cardiovascular—palpitations, supraventricular tachycardia, chest pain, syncope, "hypertensive crisis"; Immunological—Stevens-Johnson syndrome, anaphylactic reaction; Nervous System—vision abnormal, hallucinations and delirium; Musculoskeletal—rhabdomyolysis; General—rash.

OVERDOSAGE

Management of Overdosage

Overdosage with Sanctura may result in severe anticholinergic effects. Treatment should be provided according to symptoms and supportive. In the event of overdosage, ECG monitoring is recommended.

A 7-month-old baby experienced tachycardia and mydriasis after administration of a single dose of trospium 10 mg given by a sibling. The baby's weight was reported as 5 kg. Following admission into the hospital and about 1 hour after ingestion of the trospium, medicinal charcoal was administered for detoxification. While hospitalized, the baby experienced mydriasis and tachycardia up to 230 bpm. Therapeutic intervention was not deemed necessary. The baby was discharged as completely recovered the following day.

DOSAGE AND ADMINISTRATION

The recommended dose is 20 mg twice daily. Sanctura should be dosed at least one hour before meals or given on an empty stomach.

Dosage modification is recommended in the following patient populations:

- For patients with severe renal impairment (CLcr < 30 mL/min), the recommended dose is 20 mg once daily at bedtime (See PRECAUTIONS: General).
- In geriatric patients ≥75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability (See PRECAUTIONS: Geriatric Use).

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Preeclampsia, Diabetic Nephropathy Rates Linked

BY JOHN R. BELL
Associate Editor

Among women with type 1 diabetes whose pregnancies were managed at one clinic in Finland, those who had a history of preeclampsia went on to have a higher rate of diabetic nephropathy in the following years than did those with normotensive pregnancies.

In the report, researcher Daniel Gordin and colleagues at Helsinki University Cen-

tral Hospital reported findings for 203 women with type 1 diabetes who had been pregnant between 1988 and 1996 and who were followed an average of 11 years within the nationwide, multicenter Finnish Diabetic Nephropathy Study.

For purposes of the study, diabetic nephropathy was defined as microalbuminuria, macroalbuminuria, or end-stage renal disease.

Among the women with history of preeclampsia, the rate of diabetic nephro-

pathy at follow-up was 42%, versus 9% for those without such history (Diabetologia 2007 [Epub ahead of print doi 10.1007/s00125-006-0544-5]).

Women with pregnancy-induced hypertension, however, were not at significantly increased risk of microvascular disease, compared with normotensive women (10.3% vs. 8.9%).

Diabetic nephropathy at follow-up was also predicted by poor glycemic control during pregnancy. Hemoglobin A_{1c} levels

in each trimester significantly correlated with kidney disease.

These results warrant more intensive monitoring of women with type 1 diabetes and a history of preeclampsia, as well as special emphasis on early detection of microalbuminuria, the investigators concluded.

In addition, "an early start to renoprotective medication in type 1 diabetic women with prior preeclampsia could be beneficial," they suggested. ■

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48 with disease who did not take adalimumab, and 26 without disease.

Another 33 women who did not meet the study cohort criteria were also enrolled in the adalimumab pregnancy registry. These included five women treated for Crohn's disease, two treated for psoriasis or psoriatic arthritis, and two others treated for nonspecific autoimmune disorders.

Rates of spontaneous abortion among the pregnancies with known outcome were higher among all the groups with RA or other autoimmune disease: 2 (11.8%) of the 17 in the adalimumab study cohort, 5 (20.0%) of the 25 from the registry, and 3 (7.1%) of the 42 in the diseased comparison group, versus 0 of 15 pregnancies with known outcomes among healthy women who were not exposed to adalimumab. The only stillbirth occurred in the healthy nonexposed group.

As with etanercept, no increased risks for preterm delivery or malformations were seen with adalimumab exposure. There was one preterm delivery among the 15 live births in the study cohort (7%), compared with 4 of the 14 in the registry (29%), 7 of the 37 in the disease comparison group (19%), and 0 of the 14 in the nondisease comparison group.

Malformations occurred in none of the 17 total known outcomes in the study (0%), in 1 of 14 in the registry (7%), in 1 of 42 disease comparison patients (2%), and in 1 of 15 of the healthy controls (7%).

In both of these drug studies, all of the infants will be evaluated up to 1 year of age for major and minor anomalies by pediatric specialists, Dr. Chambers said.

Final results for preterm delivery, birth weight, and congenital malformations should be available in 1-2 years. In the meantime, even these small preliminary numbers are reassuring because they don't show any particular pattern.

"All the major teratogens are associated with very specific patterns of abnormal outcomes. When you don't see a pattern and you just see one of this and one of that, it makes you a little more confident that this is not an Accutane," Dr. Chambers said. ■

Physicians who prescribe etanercept and adalimumab to women of childbearing age are encouraged to enroll patients in OTIS. For more information, call 877-311-8972 or e-mail Dr. Chambers at chchambers@ucsd.edu.

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References:

1. Centers for Disease Control and Prevention (CDC). Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR*. 2006;55(RR-17):21-22. 2. CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the ACIP. *MMWR*. 2006;55(RR-3):22.

* Advisory Committee on Immunization Practices. † Tetanus, diphtheria, and acellular pertussis. ‡ 19-64 years of age. § 11-18 years of age.

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