

Herpes Reactivation Observed With TNF Inhibitors

BY NANCY WALSH
New York Bureau

BARCELONA — The risk of reactivation of herpesvirus infection is increased among patients with rheumatoid arthritis who are treated with the anti-tumor necrosis factor agents, and especially with the monoclonal antibodies infliximab and adalimumab, Dr. Anja Strangfeld said at the annual European Congress of Rheumatology.

“An increased risk of bacterial infections during treatment with the TNF-blocking drugs is well documented, but less attention has been paid to viral infection and reactivation in this regard, so we analyzed data from the German biologics register to ascertain the incidence and risk factors for reactivation of herpesvirus infection,” said Dr. Strangfeld, who is an epidemiologist with the German Rheumatism Research Center, Berlin.

Among the patients enrolled in the registry as of June 2006, 1,132 had received etanercept, 563 infliximab, and 1,155 adalimumab.

Among these patients, 160 cases of herpes in 144 patients were reported, with 84 cases being herpes zoster and 76 being herpes simplex, she said.

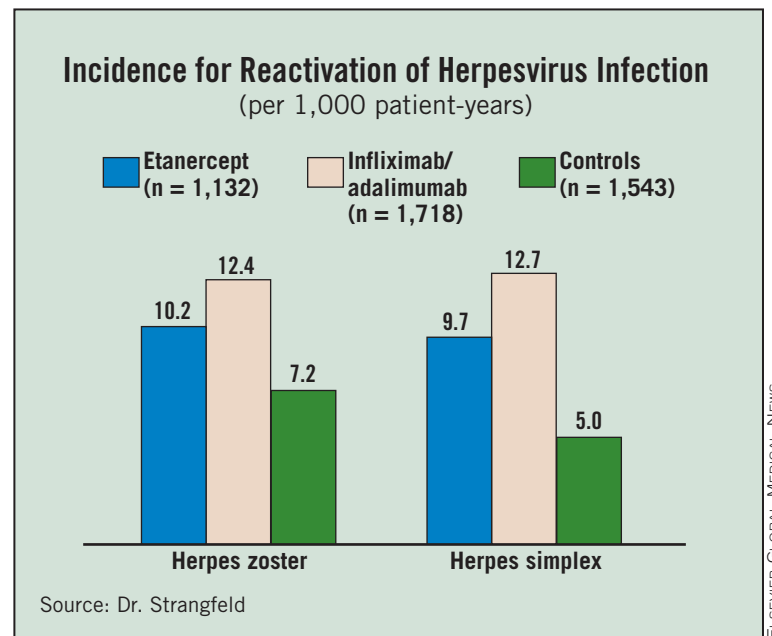
Of note, 15 of the cases of herpes zoster were serious, with 13 being the rare multidermatomal form. An additional two were serious ophthalmic herpes; this results when the virus, which remains latent and lifelong in the sensory ganglia, reactivates in the geniculate ganglion.

The incidence of zoster reactivation among patients being treated with infliximab, adalimumab, and etanercept was compared with rates among control RA patients receiving conventional disease-modifying antirheumatic drugs, and was found to be higher rates among the biologic-treated patients overall. (See box.)

“We also analyzed the rates for the TNF blockers according to their molecular type, because previous analyses of rates of tuberculosis reactivation found differences in rates among patients receiving the monoclonal antibodies infliximab and adalimumab, compared with those receiving the receptor fusion protein etanercept,” she said.

Higher rates were seen for the monoclonal antibodies than for etanercept, and particularly for the serious multidermatomal and ophthalmic infections, she noted.

Analysis of risk factors for reactivation identified higher risk for increasing age (hazard ratio 1.24) and for increased duration of disease (HR 1.10).



LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator used was for females only (N=490 Lexapro; N=404 placebo). Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Dry Mouth (3% and 5%); Sweating Increased (4% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-Like Symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%); Psychiatric Disorders: Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder^{1,2} (14% and 2%); Anorgasmia (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis, †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events:** The potential dose dependency of common adverse events (defined as an incidence rate of 8% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). †Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs:** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual performance. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes:** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes:** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro:** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3. Those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, lightheadedness, chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Frequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** increased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **H-905 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, lightheaded. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram -** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

Rev. 05/07 © 2007 Forest Laboratories, Inc.

Tetracycline Eases Cancer Therapy Rash

BY KERRI WACHTER
Senior Writer

CHICAGO — Tetracycline may reduce the severity of rashes associated with epidermal growth factor receptor inhibitors, such as gefitinib and cetuximab, but the antibiotic doesn't seem to prevent such rashes.

More than 75% of patients on epidermal growth factor receptor (EGFR) inhibitors develop an acneiform rash. The rash can be very problematic for patients, said Dr. Aminah Jatoi, a professor of on-

cology at the Mayo Clinic in Rochester, Minn.

Dr. Jatoi and her colleagues randomized 61 cancer patients to 500 mg oral tetracycline twice daily or placebo twice daily for 1 month. Patients were included if they had started an EGFR inhibitor within 7 days of enrollment and did not have a rash.

“Tetracycline did not prevent EGFR inhibitor-induced rashes. However, diminished rash severity and improved quality of life suggest this antibiotic deserves further study,” Dr. Jatoi said at the annual meeting of the American Society of Clinical Oncology.

Patients are getting a severe rash and it bothers them. Yet at the same time they're saying, 'My tumor may well be responding to this drug.'

Rashes were assessed by physicians and patients over an 8-week period. Physicians submitted monthly reports using the Common Terminology Criteria for Adverse Events v3.0. Patients submitted weekly reports, including the answers to a brief questionnaire on rash incidence (the Skindex-16), and an EGFR inhibitor compliance questionnaire.

A small portion of patients—10% in the treatment arm and 17% in the placebo arm—were being treated with gefitinib. An additional 35% and 40% were being treated with cetuximab in the treatment and placebo arms, respectively. The remaining 55% and 43% were taking other EGFR inhibitors (EGFR tyrosine kinase inhibitors) in the treatment and placebo arms, respectively.

“With regard to the primary end point [rash prevention], this was a negative study,” Dr. Jatoi said. Physician-reported rash incidence was comparable between the two arms at weeks 4 and 8. At week 4, the incidence was 70% and 76% for the treatment and placebo arms, respectively. Likewise at week 8, the incidence was 87% and 84% for the treatment and placebo arms, respectively. Patient-reported results were similar.

In terms of physician-reported rash severity, significantly fewer patients (17%) on tetracycline had rashes with grade 2 or greater at 4 weeks, compared with those on placebo (55%). However, the difference was not significant at 8 weeks—27% in the tetracycline group vs. 47% in the placebo group. Patient-reported results were similar.

Patients on tetracycline did report less itching on the Skindex-16 starting at week 2, however.

Three patients in each arm stopped taking EGFR inhibitors early because of cancer-related issues. Adverse events were comparable in both treatment arms.

“We invite caution, however, in interpreting these results for two reasons. First, this was a secondary end point not a primary end point. Secondly, the numbers are very small. Dropout rates were quite high over time,” Dr. Jatoi said.

The issue of EGFR inhibitor-induced rash is particularly troublesome for patients, because it has been suggested that the presence of skin rash may be associated with tumor response.

“Patients are sometimes finding themselves in quandary. They're getting a severe rash and it bothers them. Yet at the same time they're saying, 'My tumor may well be responding to this drug. I can't stop taking this drug and yet I want to,' ” Dr. Jatoi said.