Pregnancy Risks of Transplant Drugs Raise Alert

BY ELIZABETH MECHCATIE
Senior Writer

Rheumatologists who have been using mycophenolate mofetil off label to treat lupus and rheumatoid arthritis in women of reproductive age should be aware that the Food and Drug Administration has issued an alert about cases of birth defects and spontaneous abortions associated with its use in the first-trimester.

Mycophenolate mofetil—CellCept—is also used off label in women with erythema multiforme. The FDA's report concerns a second drug: Myfortic (mycophenolic acid). Mycophenolate mofetil (MMF) is an ester of the metabolite mycophenolic acid (MPA), which is the active drug substance in Myfortic. Both agents are approved to prevent organ rejection after transplantation.

The information about early pregnancy loss and congenital malformations was described in a letter to health care professionals and added to the black box warning in the labels of the two drugs in November 2007, when they were reclassified as pregnancy category D drugs. A classification of category D means there is positive evidence of human fetal risk, but potential benefits might warrant the use of the drug during pregnancy anyway. The drugs previously were classified as category C, meaning they were shown to be teratogenic or to have embryocidal effects in animals, but that there are no human data.

Postmarketing data on 77 women exposed to MMF during pregnancy showed 25 had a spontaneous abortion and 14 had a malformed infant.

Now, published and unpublished reports associate the drugs with an increased risk of spontaneous abortions and serious congenital malformations in humans, including bilateral microtia or anotia, sometimes with atresia of the external auditory canals; oral clefts; and other major structural malformations, according to the FDA. In most cases, the mothers were taking MMF after an organ transplant, but in some cases, the women were taking MMF for systemic lupus erythematosus, erythema multiforme, or other immune-mediated conditions.

The data include 33 pregnancies exposed to MMF in 24 transplant patients in the National Transplantation Pregnancy Registry. There were 15 spontaneous abortions (45%). Of the 18 live-born infants, four (22%) had a major structural malformation. This is compared with the 3% background rate of congenital anomalies in the United States, and a rate of 4%-5% among babies born to women in the registry who took other immunosuppressive drugs. The FDA cited postmarketing data in 77 women exposed to MMF during pregnancy between 1995 and 2007: 25 had a spontaneous abortion and 14 had a malformed infant or fetus (including ear abnormalities in six cases).

The FDA is advising health care professionals to counsel women of childbearing potential about the fetal risks associated with taking the medications, and about contraceptive options. Health care professionals should not start treatment until they confirm patients are not pregnant, using a serum or urine pregnancy test that has a sensitivity of at least 25 mIU/mL, within 1 week of starting treatment.

"If therapy is initiated in a patient who is already pregnant or the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the developing fetus," according to the FDA. "Women taking CellCept and Myfortic and who are planning to become pregnant should also talk with their doctors about the risks involved and whether alternative immunosuppressive agents can be considered," according to the release. ■

The alert, including information for patients, is on the FDA Web site at www.fda.gov/cder/drug/infopage/mycophenolate/default.htm

Type I Interferon Deemed Central to SLE Therapy

BY BRUCE JANCIN
Denver Bureau

Waikoloa, Hawaii — Recent developments underscore the critical role the type I interferon system plays in the pathogenesis of systemic lupus erythematosus, according to a dermatology and immunology researcher.

"Type I interferon may be a cornerstone of lupus therapy in the future," predicted Dr. David Fiorentino of Stanford (Calif.) University.

Type I interferon also appears to be central to the pathogenesis of numerous other autoimmune diseases, he said at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

The type I interferon system is emerging as a particularly attractive therapeutic target. There are 13 subtypes of interferon-α, all binding to the same receptor. Several companies are developing biologic agents that down-regulate the type I interferon pathway by blocking interferon-α; preliminary reports are positive, Dr. Fiorentino said.

Interferon-α appears to induce autoimmunity, and it is known that interferon-α levels are increased in the skin, blood, and kidneys of patients with SLE. Interferon levels correlate with disease activity, and interferon-α blockade results in improvement in mouse models of lupus, he said.

The most persuasive evidence that type I interferon plays a key role in lupus has come from recent genetic studies. High serum interferon-α activity has been shown to be a complex heritable trait (Genes Immun. 2007;8:492-502).

Earlier this year, two genome-wide studies resulted in identification of 10 new genetic variants conferring an increased risk of SLE (N. Engl. J. Med. 2008;358:900-9; Nat. Genet. 2008;40:204-10). Some of these genes encode components of the type I interferon pathway associated with activation of the innate immune system, while others are involved in the adaptive immune response.

Dr. Fiorentino commended an editorial by Dr. Mary K. Crow of the Hospital for Special Surgery, New York, which accompanied the gene scan studies and incorporated the findings into an updated model of SLE pathogenesis (N. Engl. J. Med. 2008;358:956-61).

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Don't Hesitate to Use Antimalarials When Treating Lupus, Expert Says

BY BRUCE JANCIN
Denver Bureau

Waikoloa, Hawaii — Every patient with lupus should be treated with an antimalarial drug, Dr. David Fiorentino said at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

"Don't be scared to use an antimalarial. I really think this is first-line therapy. You should have a really good reason not to use one," said Dr. Fiorentino, a dermatologist at Stanford (Calif.) University.

Antimalarials are effective for lupus skin disease, joint manifestations, and fatigue. They've also been shown to slow accrual of target-organ damage in systemic lupus erythematosus (SLE).

Moreover, SLE has been associated with an increased risk of malignancy, particularly non-Hodgkin's lymphoma, lung cancer, and hepatobiliary cancer. Antimalarial therapy may reduce this risk, according to Dr. Fiorentino. Antimalarials have been associated with an adjusted 85% reduction in the relative risk of cancer during a median 10-year follow-up in a series of SLE patients (Ann. Rheum. Dis. 2007;66:815-7).

Retinal toxicity is the most feared complication of antimalarials. It can be avoided by calculating the dose based on a patient's ideal rather than actual body weight. The key is to stay below 6.5 mg/kg of ideal body weight per day for hydroxychloroquine (Plaquenil) and below 4.0 mg/kg per day for chloroquine (Aralen).

"If you do that, you're very, very unlikely to run into retinal toxicity. It's a problem that's much more talked about than it is a reality," said Dr. Fiorentino.

Quinacrine (Atabrine) can safely be added to either agent for greater efficacy. Just don't combine chloroquine and hydroxychloroquine because doing so can more readily lead to retinal toxicity, he added.

Dr. Fiorentino recommended a baseline eye examination including a visual field check prior to placing a patient on antimalarial therapy.

The eye exam should be repeated annually in higher-risk patients: those who are above age 60, are obese, have renal or hepatic disease, or have been on antimalarials for more than 5 years.

Second-line systemic agents for cutaneous lupus patients who do not respond adequately to antimalarials include methotrexate and mycophenolate mofetil (CellCept). These drugs lack FDA approval for use in SLE.

"They're very effective for all types of cutaneous lupus. They're not 100% effective, but I think they are the next go-to agents if antimalarials fail," he explained.

Many lupus patients at Stanford are treated with thalidomide, according to Dr. Fiorentino. It is effective in close to 90% of patients. The clinical response is rapid: within 2 weeks at 100 mg/day, although the full response typically takes 2-3 months. Even though thalidomide is most notorious for its teratogenic effects, neurotoxicity is actually a far bigger problem.

"It's the major limiting factor. If you leave patients on thalidomide long enough, most will develop neurotoxicity," he said.

Dapsone is quite effective in lupus complicated by vasculitis or bullous lesions and in lupus panniculitis, a highly neutrophilic disorder, he continued.

Intravenous immune globulin is primarily a temporizing measure rather than a long-term strategy.

The use of biologic agents that block tumor necrosis factor–α is controversial in lupus for several reasons. There are documented cases of lupus induced by anti-TNF agents.

Plus, the drugs often cause an increase in autoantibodies (including anti–double-stranded DNA) in patients with SLE, although the clinical significance of this phenomenon is unclear because it hasn't been accompanied by disease flares.

Dr. Fiorentino said that he has employed infliximab (Remicade) off label for lupus and has found it quite effective for renal and joint disease, but less so for skin disease. He has also prescribed the B-cell–depleting biologic rituximab (Rituxan) in cutaneous lupus, but hasn't "had a lot of success."

Dr. Fiorentino disclosed that he is on the advisory boards of, and/or has been a paid investigator for, Abbott Laboratories, Amgen Inc., Centocor Inc., Genentech Inc., and MedImmune Inc.

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