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 the 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 may 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 embryopathic effects in animals, but that there are no human data.

Now published and unpublished reports associate the drugs with an increased risk of spontaneous abortions and serious congenital malformations in humans, including bilateral microtia or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 13 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 on 77 women exposed to MMF during pregnancy between 1995 and 2007: 25 had a spontaneous abortion and 14 had a malformed infant.

**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 John A. Hartford (Calif.) University.

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 the 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 commented 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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