Type I Interferon Deemed Central to SLE Therapy

BY BRUCE JANCIN
Denver Bureau

WAIKOLOA, HAWAI'I — 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 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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Postmarketing data on 77 women exposed to MMF during pregnancy showed 25 had a spontaneous abortion and 14 had a malformed infant.

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

BY BRUCE JANCIN
Denver Bureau

WAIKOLOA, HAWAI'I — Every patient with lupus who has been 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 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 83% 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.

They 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.

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 both parties agree is negative. 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 has said he hadn’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, Argenx Inc., Centocor Inc., Genentech Inc., and MedImmune Inc.

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