Novel Drug Improves Methotrexate-Resistant RA

BY MITCHEL L. ZOLER

PHILADELPHIA — Treatment with an investigational, oral, immune-modulating drug led to significant improvement in patients with active rheumatoid arthritis refractory to methotrexate in a phase II study in more than 400 patients.

"These results confirm our earlier observations of the effect of this drug on a background of methotrexate," Dr. Michael E. Weinblatt said at the annual meeting of the American College of Rheumatology.

The two tested dosages of R788 (fostamatinib disodium), 150 mg once daily and 100 mg b.i.d., each led to significantly higher rates of ACR20 responses compared with placebo, the study's primary end point, said Dr. Weinblatt, a professor of medicine at Harvard University and codirector of clinical rheumatology at Brigham and Women's Hospital in Boston.

However, the story may be different in patients with active RA who have failed a biologic. In a second phase II study with the same agent in 219 such patients, administration of R788 at 100 mg b.i.d. did not produce an ACR20 response that was significantly better than placebo, reported Dr. Mark C. Genovese, a professor of medicine/immunology and rheumatology at Stanford (Calif.) University. He noted that this negative, second study seemed potentially flawed because its placebo group had an "exceptionally high placebo response rate."

R788 is a selective inhibitor of Syk kinase, an important immunoregulating enzyme that affects mast cells, macrophages, neutrophils, and B cells. Prior studies showed that Syk kinase was present in the synovial fluid of RA patients.

The trial enrolled patients with active RA and at least 6 (out of 28) painful and swollen joints and either a C-reactive protein level above the upper limit of normal or an erythrocyte sedimentation rate greater than 28 mm/hr. Patients also had to be on a methotrexate regimen of at least 10 mg/week for at least 3 months and with a stable dosage for at least 6 weeks. Patients could also be on stable dosages of low-dose prednisone and/or NSAIDs, but other disease modifying antirheumatic drugs, including any biologic, had to be washed out. Their average age was 53 years, about 85% were women, and their mean disease duration was 9 years. Each patient had an average of 12 painful and swollen joints.

After 6 months, an ACR20 response rate occurred in 66% of 152 patients randomized to 100 mg b.i.d., in 57% of 152 patients randomized to 150 mg once daily, and in 35% of 153 placebo patients, analyzed on an intention-to-treat basis. The differences between each of the two active arms and the placebo group were statistically significant. The 100 mg b.i.d. patients also had significantly better improvements in their ACR50 and ACR70 responses compared with placebo, as well as a significantly better rate of patients with a disease activity score (DAS)-28 of less than 2.6. Patients on 150 mg once daily also fared significantly better than the placebo group for the ACR50 and DAS-28 responses, but their ACR70 response did not significant surpass the placebo group.

R788 led to significantly higher rates of ACR20 responses, compared with placebo.

DR. WEINBLATT

The incidence of serious adverse events was similar in all three groups, with 7 in the placebo arm, 5 in patients getting 150 mg daily, and 13 in those getting 100 mg b.i.d. No patient died or had an opportunistic infection. The most common adverse event on treatment was diarrhea in 3% of placebo patients, in 12% of patients on 150 mg once daily, and in 19% of patients getting 100 mg b.i.d.

Patients receiving R788 also showed small increases in the rates of neutropenia and in elevations of liver enzymes, compared with the placebo patients. The rate of patients who had a reduction in their dosage because of an adverse event was 14% in each of the R788 arms and 4% in placebo patients. Discontinuations were for blood pressure elevations, liver enzyme elevations greater than three times the upper limit of normal, neutropenia, or gastrointestinal events.

The second study included 219 patients with active RA who previously failed to respond to or tolerate a biologic treatment. Their average age was 56 years, 80% were women, and their average disease duration was 12 years. After 3 months of treatment, the 146 patients getting 100 mg R788 b.i.d. did not have a significantly better response than 73 placebo patients for any ACR response or DAS28 measure. The patients on R788 did have significantly greater reductions in their level of C reactive protein and in their erythrocyte sedimentation rate than those on placebo.

One serious adverse event, an infection, occurred in the placebo patients. Patients on R788 had 13 serious adverse events, including 3 infections, none of them opportunistic. In the placebo group, 3% of patients had to lower their dose due to adverse events as did 14% of those on the active drug. ■

Disclosures: *Rigel Pharmaceuticals, the company developing R788, sponsored both studies. Dr. Weinblatt and Dr. Genovese served as consultants to Rigel, and two of their associates on the study are full-time employees of the company.*

RA Progression Hinges on Genetics, Lifestyle, and Gender

BY SALLY KOCH KUBETIN

SANTA MONICA, CALIF. — Progression of early rheumatoid arthritis is likely in any woman who smokes, has active disease at the time of presentation, and is positive for both rheumatoid factor and anti–cyclic citrullinated peptide antibodies.

Sex and clinical disease activity are the most frequent risk factors for progression of rheumatoid arthritis (RA), and rheumatoid factor and anti–cyclic citrullinated peptide (anti-CCP) antibodies are the most frequent tests that physicians use to assess the likelihood of such progression. Other genetic tests that offer information about progression risk, such as that for HLA-DRB1, are not widely used. And yet other tests for genetic determinants of treatment response and the likelihood of developing adverse events in response to treatment are encouraging, but remain largely in the realm of research, according to Dr. Daniel E. Furst, who is the Carl M. Pearson Professor of Rheumatology at the University of California, Los Angeles.

No single marker can absolutely predict disease progression, at least in part because RA is probably more than one disease, dependent on the presence or absence of anti-CCP antibodies. Anti-CCP antibodies are the result of a genetic predisposition and a systemic stress, such as smoking. However, Dr. Furst pointed out that even among all anti-CCP antibody–positive people, the course of RA may vary because of the effects of environmental stimuli, immune events, and interventions (Annu. Rev. Immunol. 2008;26:651-75).

Citrullination is present in a wide range of inflammatory tissues, suggesting that this process is a nonspecific response to inflammation, rather than a disease-specific response, Dr. Furst noted at a meeting sponsored by RHEUMATOLOGY NEWS and Skin Disease Education Foundation. Anti-CCP antibodies are more likely to be elevated in patients who both have the susceptibility epitope and smoke.

Subset analyses of data from the PROMPT (Probable Rheumatoid Arthritis: Methotrexate vs. Placebo Treatment) study, presented by Dr. Henrike Van Dongen of Leiden (the Netherlands) University Medical Center at the 2006 congress of the European League Against Rheumatism (EULAR), demonstrated that the presence of anti-CCP determined response to methotrexate. Responses at 15 months after diagnosis in a group of 27 anti-CCP antibody–positive patients were below 10% in those on placebo, but were close to 50% in those on methotrexate. There was no treatment effect in a group of 83 anti-CCP–negative patients (Arthritis Rheum. 2007; 56:1424).

The HLA-DRB1 gene is associated with extra-articular manifestations of RA and the development of Felty's syndrome. That syndrome occurs in fewer than 1% of RA patients and is considered to be a complication of long-standing disease. It involves a triad of conditions: RA, splenomegaly, and an abnormally low white blood count. Findings from an unpublished study show that Felty's syndrome was associated with HLA-DRB1.0401.

Other extra-articular manifestations of RA (such as pericarditis, vasculitis, interstitial lung disease, and neurologic involvement) were seen not with individual alleles, but with DRB1.04SE double-dose genotypes.

Findings from numerous other studies show that multiple single nucleotide polymorphisms (SNPs) of the PTPN22 gene have a significant association with RA, as does TRAF1-C5 (on chromosome 9).

Smoking and anti-CCP antibody status seem to be associated in RA, but PTPN22 is an independent risk factor for developing RA, according to Dr. Furst. Although not yet directly applicable to clinical care, attempts are being made to predict response to RA medications using genetic signatures or gene SNPs.

For now, other factors are more practical predictors of good response.

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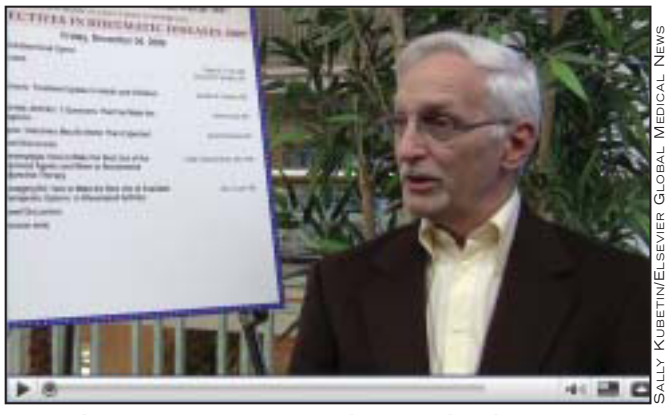

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Dr. Daniel E. Furst noted that anti-CCP antibodies are the result of a genetic predisposition and a systemic stress.

For a video interview with Dr. Furst, go to www.youtube.com/rheumatologynews.

Disclosures: *Dr. Furst reported financial relationships with numerous pharmaceutical companies and the National Institutes of Health.*