Quick ACR 20 Response Seen to Spleen Tyrosine Kinase Inhibitor

BY BETSY BATES

SAN FRANCISCO — Clinical disease activity lessened rapidly and persistently for 12 weeks in the first study of a spleen tyrosine kinase inhibitor in rheumatoid arthritis, based on findings from a phase II trial reported by Dr. Michael E. Weinblatt of the center for arthritis and joint disease at Brigham and Women's Hospital, Boston.

The double-blind, placebo-controlled study was a pivotal test of whether the novel oral molecule can inhibit inflammation by blocking activation signals in the complex kinase pathway, which serves as a facilitator of cellular activity involving neutrophils, B cells, mast cells, and microphages, he said at the annual meeting of the American College of Rheumatology.

Inhibition of the spleen tyrosine kinase (Syk) pathway is being studied in a variety of immune and inflammatory diseases, including asthma, lymphoma, and autoimmune thrombocytopenia.

In all, 189 patients who had long-standing, active RA and were on background methotrexate therapy, were randomized to receive the drug R788 at twice-daily dosages of 150 mg, 100 mg, 50 mg, or placebo at study sites in the United States and Mexico. An "adaptive" dosing regimen mandated dose reduction at any point that laboratory testing showed a decline in white blood cell count or a decline in liver function.

At 12 weeks, 84% of patients had completed the trial (122 patients who had received R788 and 36 in the placebo group). Any patient who withdrew from the study was treated as a "nonresponder" for the sake of data analysis, said Dr. Weinblatt, who is also professor of medicine at Harvard Medical School, Boston.

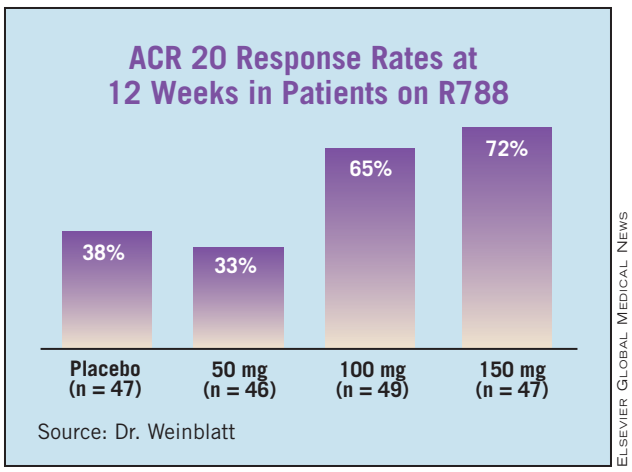
By week 1, significantly more patients on morning and evening 100-mg and 150-mg dosages showed an ACR 20 response versus those on a lower dose or placebo. A similar separation could be seen at week 1 and throughout the trial in interleukin-6 and metalloproteinase-3 levels, which were evaluated as surrogate biomarkers for inflammation and bone destruction. By week 12, the primary end point of an ACR 20 response rate was achieved by 72% of patients in the 150-mg group. (See box.) A higher bar, an ACR 70 response, was achieved in 40% of patients in the 150-mg cohort, 33% in the 100-mg group, and just 2% of the 50-mg group, versus 4% of the placebo group.

Remission, as defined by Disease Activity Score, occurred in 22 of 47 (47%) patients receiving the highest dosage, 17 of 49 (35%) patients in the 100-mg group, and 9 of 46 (20%) receiving the 50-mg, twice-daily dosage.

Diarrhea was experienced by 40% of patients receiving the highest dosage, causing one patient to withdraw from the trial. Dizziness, neutropenia, an increase in blood pressure, and a twofold increase in liver transaminases were also seen in patients receiving 150 mg twice daily, he said. Overall a "clear dose-response curve" pointed to an efficacious and safe dose of 100 mg twice daily, as opposed to relative ineffectiveness at 50 mg twice daily and unacceptable toxicity at 150 mg twice a day.

A future phase II study is planned to compare a 100-mg twice-daily dosage with a dosage of 150 mg once daily and placebo, he said.

The researchers disclosed research support from Rigel Pharmaceuticals Inc., the sponsor of the study. ■



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