Spleen Tyrosine Kinase Inhibitor Eased RA

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Adding an oral, spleen tyrosine kinase inhibitor to an existing methotrexate regimen significantly lessened rheumatoid arthritis symptoms in patients with active disease, compared with placebo.

The results, though, were not without side effects, including hypertension, neutropenia, and diarrhea.

The phase II, double-blind, placebo-controlled study was sponsored by the drug's maker, Rigel Pharmaceuticals.

Spleen tyrosine kinase (Syk) is an intracellular cytoplasmic tyrosine kinase that is present in the synovium. It is an important mediator for "immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells," the investigators noted. Syk inhibitors have previously been studied as therapeutic agents in cancers, including breast cancer and lymphoma.

The authors of the current study, led by Dr. Michael E. Weinblatt, codirector of the division of clinical rheumatology at Brigham and Women's Hospital and professor of medicine at Harvard Medical School, both in Boston, looked at 457 patients at 64 sites around the world, specifically Bulgaria, Colombia, Mexico, Poland, Romania, and the United States (N. Engl. J. Med. 2010 [doi:10.1056/NEJMoa1000500]).

All patients met the American College of Rheumatology's 1987 criteria for rheumatoid arthritis and had had active RA for at least 6 months prior to enrolling in the trial. The 1987 ACR criteria define "active" RA as involving six swollen joints, plus six tender joints, plus either an

elevated erythrocyte sedimentation rate or an elevated C-reactive protein level.

Patients also had been receiving a "stable dose" of methotrexate for at least 3 months (between 7.5 mg and 25 mg/wk), plus folic acid or folinic acid supplements.

Patients were randomized to four groups. The first group (n = 152) received the Syk inhibitor known as R788, in twice-daily doses of 100 mg. The second group (n = 152) received once-daily, 150-mg doses of the drug. The third group received placebo twice daily, and the fourth received once-daily placebo (total number of placebo patients = 153).

The majority of patients in all groups were female, and the mean age was 52 years in all groups.

Overall, 67% of patients in the R788 twice-daily, 100-mg dose group registered an ACR 20 response at 6 months; in the once-daily, 150-mg group, the response rate was 57%. Both numbers were significantly higher than among placebo patients, who had a response rate of 35% (P less than .001 for both comparisons).

The authors also found that patients taking the twice-daily Syk inhibitor responded sooner than those on the once-daily regimen or placebo. By the end of the first week, 36% of twice-daily patients had an ACR 20 response, compared with 23% in the once-daily R788 group and 14% in the placebo group (P less than .001 for the twice-daily group and P = .04 for the once-daily group, compared with placebo).

Moreover, 31% of the twice-daily R788 group achieved remission (defined by a Disease Activity Score–28 less than 2.6) by 6 months, compared with 21% in the once-daily group and 7% in the placebo group (P less than .001 for the twice-daily group and P = .003 for the once-daily group, compared with placebo).

The therapy did have adverse events. Ten patients in the once-daily group and five in the twice-daily group withdrew, mostly because of nausea and diarrhea. There were also two serious infections in the once-daily group and five in the twice-daily group, as well as neutropenia and hypertension.

Three authors, including Dr. Weinblatt, disclosed financial relationships to multiple pharmaceutical makers, including Rigel; the remaining three are employees of Rigel. ■