Preliminary Data Mixed on IL-15 as RA Target

BY NANCY WALSH
New York Bureau

SAN ANTONIO — The list of potential therapeutic targets in rheumatoid arthritis continues to expand, with preliminary evidence supporting the addition of the proinflammatory cytokine interleukin (IL)-15.

This signaling molecule, found in the synovium in those with rheumatoid arthritis (RA), appears early in the cascade of events that leads to inflammation, inducing the production of tumor necrosis factor (TNF)-α and recruiting inflammatory T cells.

A human monoclonal IgG antibody that binds to and inhibits IL-15 has been developed and is now undergoing clinical testing, Iain McInnes, M.D., said at the annual meeting of the American College of Rheumatology.

In an interim analysis of a proof-of-concept study of the antibody AMG 714, clinical effect was demonstrated at various doses in 110 patients with active RA, with the most pronounced benefit seen in the highest-dose group, he said.

Background methotrexate was permitted in stable doses of 25 mg/wk or less, but other disease-modifying drugs were not. None of the patients had previously received biologic response modifiers.

Stable limited doses of NSAIDs and corticosteroids were allowed.

Patients were randomized to receive placebo or AMG 714 in doses of 40 mg, 80 mg, 160 mg, or 280 mg, given by subcutaneous injection every 2 weeks for a 12-week period.

Among those patients in the highest dose group, 62% achieved an ACR 20 response, as did 26% in the placebo group; this between-group difference was statistically significant.

The response was maintained at week 14, though at that point, statistical significance was lost because of an increased placebo response, said Dr. McInnes, professor of experimental medicine and rheumatology at the Centre for Rheumatic Diseases, Glasgow, Scotland.

Approximately one-fourth of patients in the active treatment groups achieved an ACR 50 response, as did one patient in the placebo group. Some patients have achieved an ACR 70 response, but those data remain blinded, he said.

Statistical significance was lost after week 14 because of an increased placebo response.

DR. McINNES

A 20% reduction in CRP was seen at weeks 4 and 14 in 29% and 39% of placebo patients, respectively, and in 70% and 63% of those in the high-dose AMG 714 group.

Worsening of RA was observed in 26% of placebo patients, compared with 5% of the high-dose treatment group.

Adverse events have been closely tracked in the study. "As this is the first time IL-15 is being targeted in humans, safety is our highest priority," Dr. McInnes said.

Overall, the incidence of adverse events, such as infection, gastrointestinal complaints, and skin disorders, has been similar across the treatment and placebo groups. Approximately one-fourth of patients in the high-dose group have experienced transient injection-site reactions.

Two serious adverse events were reported. One was a case of deep venous thrombosis diagnosed 4 weeks after the last injection, and the other was sepsis following focal infection of a finger. Both resolved without sequelae, he said.

No deaths occurred during the trial.

"These are encouraging preliminary data," he said in conclusion. An additional 70 patients now have entered the ongoing study.

Dr. McInnes disclosed a commercial relationship with Genmab A/S, the Copenhagen-based manufacturer of AMG 714. ■

NEXT ISSUE

Stop the Ride!

If reading the headlines on COX-2s makes you feel like you're on an endless roller coaster, look for our story on how to manage the madness.