New B–Cell Depleting Agent Is Well Tolerated

TRU-015 resulted in ACR20 improvement in half of 36 patients studied; 25% had ACR50 responses.

ARTICLES BY NANCY WALSH
New York Bureau

PARIS — Repeated treatment with a new type of B-cell–depleting agent was well tolerated and reduced signs and symptoms of rheumatoid arthritis, according to an interim analysis of an ongoing open-label study.

Analysis of pooled clinical responses from two dosage groups found that approximately 50% of patients achieved a 20% improvement in American College of Rheumatology parameters (ACR20); 25% had ACR50 responses, and 10%-15% had ACR70 responses, Dr. Richard W. Martin said at the annual European Congress of Rheumatology.

TRU-015 is a small modular immunopharmaceutical (SMIP), a single-chain protein that is approximately one-half to one-third the size of a monoclonal antibody. It is directed against CD20 markers on the surfaces of B cells, Dr. Martin said.

TRU-015 differs from rituximab in that it is human rather than chimeric, and was designed using a custom drug assembly technology that reduces complement activation, which is thought to contribute to some rituximab-associated adverse events, such as infusion reactions, and may play a role in disease activity in RA.

In all, 36 patients have now had at least one retreatment (that is, a second infusion), and 29 have had more than one retreatment (at least three infusions).

At this point, more than 100 courses of the experimental agent have been administered, with some patients receiving up to six courses over 3 years, Dr. Martin said. Patients who had previously received an infusion of at least 5 mg/kg and who completed 24 weeks of follow-up with at least 70% of B-cell recovery were eligible for retreatment with either 5 mg/kg or 15 mg/kg of TRU-015.

The infusions have generally been well tolerated, and there have been no grade 3 or 4 adverse events. Four patients had grade 2 adverse events, including facial flushing, erythema, and pruritus, as well as worsening insomnia.

Whether these events were caused by the study agent or by pretreatment with corticosteroids is not known, said Dr. Martin, professor of medicine and rheumatology at Michigan State University, Grand Rapids.

Six patients withdrew from the study, primarily for administrative reasons. There were no withdrawals because of adverse events, and there have been no opportunistic infections or deaths.

Headache was reported by 28% of patients after their first infusion; this fell to 8% and 7% after the second and third infusions. Other adverse events, such as fatigue and edema, also decreased with repeated treatments.

Nine serious adverse events were seen in seven patients. One patient had two hospitalizations for exacerbations of chronic obstructive pulmonary disease, another patient experienced an episode of cholecystitis, and one reported shortness of breath of unknown cause.

The retreatment pharmacokinetics of TRU-015 following repeated infusions are indistinguishable from those seen with the initial treatment, suggesting that there is no significant early development of neutralizing antibodies. There also was no attenuation in B-cell depletion following retreatment.

Clinical responses have been maintained from the first treatment to the second and beyond, he added.

Dr. Martin did not say when the trial was expected to be complete.

The manufacturer of TRU-015, Trubion Pharmaceuticals Inc., is creating a pipeline of customized therapeutic products, including SMIPs, for the treatment of autoimmune and inflammatory diseases and cancer.

Additionally, Wyeth Pharmaceuticals and Trubion have a worldwide licensing and commercialization agreement for the development of TRU-015 and other CD20-targeted therapies.

Dr. Martin disclosed that he has had contracts for clinical trials with Trubion, but owns no stock in the company and is not a paid consultant. ■

Infliximab Plus Combo DMARDs Prevents Progression in Early RA

PARIS — The addition of infliximab to intensive combination disease-modifying therapy in early rheumatoid arthritis resulted in higher rates of remission and no radiographic progression at 2 years in a placebo-controlled trial of 100 patients.

Combination therapy with methotrexate, sulfasalazine, and hydroxychloroquine plus prednisone has previously been shown to be associated with a remission rate of 37% in patients with early RA, Dr. Marjatta Leirisalo-Repo said at the annual European Congress of Rheumatology.

In the current trial of 100 patients with RA of less than 1 year's duration, the patients were randomized to the regimen in the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial plus infliximab or placebo, to determine whether the addition of the tumor necrosis factor (TNF) blocking agent would increase rates of remission and influence radiographic outcome.

The intensive, remission-targeted FIN-RACo regimen includes individually tailored doses of methotrexate, up to 25 mg/wk, and sulfasalazine, at a maximum of 2 g/day, along with fixed doses of hydroxychloroquine (35 mg/kg per week) and prednisone (7.5 mg/day).

In addition to the combination disease-modifying antirheumatic drug (DMARD) regimen, patients received placebo or infliximab in doses of 3 mg/kg at weeks 4, 6, 10, 18, and 26, and were followed for 2 years.

At baseline, patients had active disease, said Dr. Leirisalo-Repo of the division of rheumatology at Helsinki University Central Hospital. The patients' mean age was 46 years, and the median duration of their symptoms was 4 months; 68% of the patients were rheumatoid factor positive, and 67% were female. The mean number of swollen joints was 15, the mean number of tender joints was 20, the mean erythrocyte sedimentation rate was 33 mm/hr, and the mean Health Assessment Questionnaire (HAQ) score was 1.

At 24 months, the remission rate was 53% among patients receiving the combination plus placebo regimen and 70% in the combination plus infliximab group. Sustained remission out to 24 months was seen in 31% and 40% of those in the placebo and infliximab groups, respectively.

"Patients in the infliximab group had an overall odds ratio of 2.24 for reaching remission," Dr. Leirisalo-Repo said.

The median total Sharp/van der Heijde score was 0 at baseline in both groups. At 2 years, the score was 1.4 in the placebo group compared with 0.2 in the infliximab group, suggesting that there had been almost no radiographic progression in the infliximab group, she said.

In conclusion, the intensive FIN-RICo combination strategy resulted in remission rates of 53% and sustained remission rates of 31%, but the addition of infliximab for 6 months further increased these rates and prevented radiographic damage, she said.

Dr. Leirisalo-Repo disclosed that she has received research grants from Schering-Plough Finland and consulting fees from Centocor Inc., and that she holds nonremunerative positions of influence with Abbott Laboratories, Bristol-Myers Squibb Co., and Roche. ■

Switch Drug Class After Anti-TNF Efficacy Failure

PARIS — Rituximab may be a better choice than another tumor necrosis factor inhibitor for patients with rheumatoid arthritis whose disease remains active despite anti-TNF therapy, according to a study of more than 300 patients.

"We and others have shown that switching to a different class of biological agents may be more effective than going to a second or third anti-TNF agent," Dr. Axel Finckh said at the annual European Congress of Rheumatology.

Patients interrupt anti-TNF therapy for various reasons, including lack of efficacy, adverse events, convenience, and preferences. To determine if the reason for discontinuation could influence the efficacy of subsequent therapy, a prospective longitudinal observational study was undertaken that included all rheumatoid arthritis (RA) patients in a Swiss national cohort who failed a course of TNF inhibitor therapy, said Dr. Finckh of Geneva University Hospital.

The primary outcome was the evolution in disease activity score 28 (DAS28) in the first year after switching, analyzed by multivariate regression models.

Among the 325 adult patients included in the study, 175 switched to another anti-TNF drug while 150 switched to the B-cell-depleting agent rituximab, according to Dr. Finckh.

Overall, the reason for discontinuation of the previous regimen was lack of efficacy in 65%. Of those, 28% were primary failures who experienced no response to therapy and 72% were secondary failures who initially responded but then lost the response.

The remaining 35% of patients switched because of adverse events, he said.

At the time of switching, there were no significant differences between the anti-TNF group and the rituximab group in terms of patient age, gender, disease duration, or concomitant steroid or conventional disease-modifying antirheumatic drug use.

Patients who switched to another anti-TNF drug had lower baseline DAS scores, however, at a mean of 4.0, compared with a mean of 4.97 in the rituximab group. After adjustment for this and other confounders, the evolution of DAS28 was overall more favorable for the rituximab group, he said.

When the motive for switching was lack of efficacy of the original TNF inhibitor, the evolution of DAS28 was significantly better for rituximab, with scores decreasing by 1.55 at 6 months, compared with a decrease of 1.03 for the anti-TNF group.

However, when the reason for switching was an adverse event, the evolution of DAS28 was similar in the two groups, with rituximab patients having a decrease in scores of 0.86 and the anti-TNF group decreasing by 0.77.

There was no effect modification by other variables, including primary versus secondary failure or concomitant DMARD use.

"This observational study suggests that patients who demonstrate therapeutic resistance to anti-TNF therapy may benefit from switching to rituximab," Dr. Finckh concluded.

The study was partially supported by Roche. ■