Rituximab combined with a TNF inhibitor and methotrexate shows no safety signal in RA treatment

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A recent trial of rituximab in combination with a tumor necrosis factor (TNF) inhibitor and methotrexate (MTX) in patients with active rheumatoid arthritis (RA) found the safety profile to be consistent with other RA trials with TNF inhibitors. While the trial reported no new safety risks, clear evidence of an efficacy advantage in RA patients receiving the combination therapy was not observed in this study sample. Results of the trial are published in the March issue of *Arthritis & Rheumatism*, a peer-reviewed journal of the *American College of Rheumatology*.

The National Arthritis Data Workgroup estimates that 1.3 million U.S. adults have RA which is characterized by systemic joint inflammation that often leads to joint damage, functional impairment and significant disability. While MTX is successfully used to treat many RA patients, the severity of the disease in some patient populations requires the use of additional disease-modifying antirheumatic drugs (DMARDs). A specific group of biologic DMARDs, called tumor necrosis factor (TNF) inhibitors and includes such therapies as etanercept and adalimumab, block the immune system response, and have been shown to be safe and effective in clinical trials.

Prior studies, however, have found that up to 40% of RA patients exhibit an inadequate response, intolerance, or inadequate slowing of the rate of joint damage with biologic therapies, and require additional treatment options. "Our objective was to assess the safety of the biologic DMARD, rituximab, in combination with a TNF inhibitor and MTX in patients with active RA," said lead study author Maria Greenwald, M.D., from Desert Medical Advances in California. This was a small exploratory study to evaluate safety with this combination due to the prolonged effect of rituximab, and the fact that RA patients may switch to an alternate biologic such as a TNF inhibitor before the effects of rituximab may have resolved.

The controlled trial enrolled 51 patients with active RA (more than 5 swollen and tender joints) who were receiving a stable dose of MTX (10-25 mg/week) and either etanercept or adalimumab for more than 12 weeks. Participants were randomized 2:1 to receive one course of rituximab or placebo (two 500-mg doses intravenously or placebo). The primary study end point was the proportion of patients developing more than one serious infection through week 24.

Researchers reported one serious infection (pneumonia) in the rituximab group compared with none in the placebo group (TNF only) at week 24. Nonserious infections were reported in 18 patients (55%) and 11 patients (61%) in the rituximab and placebo groups, respectively. Infections requiring intravenous antibiotics occurred in three patients administered rituximab and in none of the patients receiving placebo. No life-threatening, opportunistic, fungal or tuberculosis infections were observed. Dr. Greenwald noted, "The incidence of serious infections was low."

During the 24-week trial period the overall proportion of patients in the placebo and rituximab cohorts who experience an adverse event (AE) was 83% and 94%, respectively. The most common AEs reported in the rituximab group included nausea, pruritus (itching sensation), and fatigue. In the placebo group the common AEs included upper respiratory tract infections, sinusitis, headache, and exacerbation of RA. Two serious adverse effects (SAEs)-pneumonia and coronary artery occlusion-were observed in two rituximab-treated patients; no SAEs were reported in patients receiving placebo.

The research team also determined the percentage

of patients achieving an ACR201 improvement response at week 24 was 30% in the rituximab group compared with 17% in the placebo group. ACR50 responses achieved in the rituximab and placebo groups were 12% and 6%, respectively. "The safety of rituximab in combination with a TNF inhibitor and MTX was consistent with other RA trials of rituximab and MTX that did not include TNF inhibitors," concluded Dr. Greenwald. The authors noted that a larger study examining efficacy of treatment of RA using multiple biologic DMARDs is underway.

More information: "Evaluation of the Safety of Rituximab in Combination with a Tumor Necrosis Factor Inhibitor and Methotrexate in Patients With Active Rheumatoid Arthritis." Maria W. Greenwald, William J. Shergy, Jeffrey L. Kaine, Marianne T. Sweetser, Kye Gilder and Matthew D. Linnik. Arthritis & Rheumatism; Published Online: February 25, 2011 (DOI: 10.1002/art.30194); Print Issue Date: March 2011.

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