Rituximab for the Treatment of Refractory Rheumatoid Arthritis: New Information from Clinical Trials

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Introduction

In the April 2006 issue of P&T, we published an article in the Drug Forecast column entitled “Rituximab for Patients with Refractory Rheumatoid Arthritis.” In that article, we detailed numerous clinical trials involving the use of rituximab (Rituxan, Genentech) in the treatment of patients with rheumatoid arthritis (RA) who experienced an inadequate response to traditional therapies such as disease-modifying antirheumatic drugs (DMARDS) or anti–tumor necrosis factor (TNF) therapies. These trials focused primarily on determining the efficacy and safety of rituximab in this patient population.

More recently, the results of two new trials, presented at the American College of Rheumatology’s 2005 annual meeting in San Diego, were made available. These trials offer new insight into the efficacy and safety of rituximab in the management of refractory RA.

The DANCER Study

The Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) trial sought to answer questions raised in previous clinical trials as to whether glucocorticoids are necessary for the efficacy of rituximab and whether they contribute any additional toxicity or whether they enhance safety.

This 24-week trial evaluated 465 patients with active RA who were resistant to DMARDs, including biologic agents, despite ongoing treatment with methotrexate. The patients were randomly selected to receive placebo, rituximab 500 mg, or rituximab 1,000 mg as an infusion on days 1 and 15. Within each group, the patients were also assigned to receive one of three glucocorticoid treatment options, including placebo, methylprednisolone 100 mg IV prior to each infusion of either rituximab or placebo on days 1 and 15, or methylprednisolone 100 mg IV prior to each infusion of either rituximab or placebo on days 1 and 15, followed by oral prednisone 60 mg daily on days 2 through 7 and prednisone 30 mg on days 8 through 14.

Patients continued to receive methotrexate throughout the study. The primary endpoint was the proportion of rheumatoid factor–positive patients achieving a 20% improvement in the American College of Rheumatology response criteria (ACR 20) at week 24. Secondary endpoints included ACR 50, ACR 70, changes in Disease Activity Scale (DAS-28) scores, EULAR (DAS-based European League Against Rheumatism) responses, and erythrocyte sedimentation rate.

The study results showed that rituximab was superior to placebo, as measured by the ACR 20 criteria (P < .0001). Furthermore, glucocorticosteroids did not contribute additionally to the efficacy of rituximab at 24 weeks; however, the incidence and severity of first infusion reactions were reduced in patients who received intravenous (IV) methylprednisolone prior to the infusion on days 1 and 15.

No additional benefit of reduced toxicity was observed in the group receiving oral prednisone therapy on days 2 through 14.

The REFLEX Study

The Randomized Evaluation of Long-Term Efficacy of Rituximab in Rheumatoid Arthritis (REFLEX) trial evaluated 517 patients who had demonstrated an inadequate response to prior anti-TNF therapy, and the primary endpoint was an ACR 20 response at week 24. Both rheumatoid factor–positive and rheumatoid factor–negative patients were enrolled and were included in the primary efficacy analysis.

These patients received a stable dose of methotrexate (10–25 mg/week), and they were selected to receive a single course of either rituximab 1,000 mg or placebo, given by IV infusion on days 1 and 15. All patients received parenteral methylprednisolone immediately before each infusion and a tapering course of oral glucocorticoids between the two rituximab infusions.

Clinical assessments were conducted every four weeks between weeks 4 and 24. The primary endpoint was the proportion of patients in each group who achieved an ACR 20 response at week 24. Secondary endpoints included ACR 50 and ACR 70 responses, changes in DAS-28 scores, and EULAR responses.

At week 24, the responses of the rituximab group of patients (ACR 20, 51%; ACR 50, 27%; and ACR 70, 12%) were statistically superior to those of patients receiving placebo (ACR 20, 18%; ACR 50, 5%; and ACR 70, 1%). The rituximab patients also experienced statistically superior improvements in DAS scores (−1.83) compared with the placebo group (0.34). In rituximab RA placebo-controlled trials, 32% of rituximab-treated patients experienced an adverse event during or within 24 hours following their first infusion, compared with 23% of placebo-treated patients receiving their first infusion. The incidence of adverse events was significantly lower in the placebo group (0.34).

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dence of adverse events during the 24-hour period following the second infusion, rituximab or placebo, decreased to 11% and 13%, respectively.4

Acute infusion reactions were experienced by 27% of the rituximab group following their first infusion, compared with 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infection reactions following the second infusion of rituximab or placebo decreased to 9% and 11%, respectively.

In RA clinical studies, 39% of patients in the rituximab group experienced an infection of any type, compared with 34% of patients in the placebo group. The incidence of serious infections were 2% in the rituximab-treated group and 1% in the placebo group.4

In summary, rituximab was effective and well tolerated when given with methotrexate in patients with active RA who experienced an inadequate response to one or more anti-TNF-α therapies.

References