Rituximab for Rheumatoid Arthritis: A Systematic Review to Inform Knowledge Users

Lynda McGahan, MSc, Maria A. Lopez-Olivo, MD, PhD, Maksalen Amezaga Urueña, MD, Eduardo N. Pollono, MD, and Maria E. Suarez-Almazor, MD, PhD, L. McGahan Consulting, Ottawa, ON, Canada, University of Texas, Houston, TX, USA, University of Pittsburgh Medical Center, Pittsburgh, PA, USA, University of South Florida, Tampa, FL, USA.

**Background**

Rituximab (RTX) is used in combination with methotrexate (MTX) to treat refractory Rheumatoid arthritis (RA); reimbursement is criteria-based. Evidence is systematically reviewed to inform clinicians, patients and policy makers regarding the safety and efficacy of RTX.

**Objective**

To assess whether RTX alone or in combination with disease modifying anti-rheumatic drugs (DMARDS) is a safe, effective RA treatment.

**Methods**

Published literature was identified by searching electronic databases (MEDLINE, EMBASE, CINAHL, The Cochrane Library, Web of Science) and reference lists from comprehensive reviews. Two reviewers independently selected studies and assessed trial quality. Safety and efficacy data were extracted independently by two reviewers and dichotomous data were pooled as relative risk (RR). Number needed to treat (NNT) and 95% confidence intervals were calculated using the Visual Rx 3.0 NNT calculator at http://www.visualrx.net.

**Results**

Of 2,100 citations identified, five studies comparing RTX (2 x 1000mg) with MTX versus MTX, provided data for quantitative meta-analyses. Four of five studies did not report the randomization method or allocation concealment. While sample sizes ranged from 169 to 755, a total of 2,412 patients were included for this comparison.

American College of Rheumatology (ACR) clinical response rates, Disease Activity Score (DAS) and radiographic disease progression improved significantly among RTX plus MTX recipients versus MTX alone, with no differences in the rates of severe adverse events (SAEs). Acute infusion reactions were reported in 20% of RTX plus MTX patients and 16% of MTX recipients (Absolute Risk Difference (ARD) 9% (95% CI 5%, 13%).

- **Proportion of 24-week data showed 20% and 16% of RTX+MTX users achieved ACR response rates of 50 and 70, respectively versus 6% and 4% of MTX recipients.**
- **Relative risk (RR) of achieving ACR 50 or 70 response was 3.3 (95% CI 2.2, 4.6) and 3.9 (95% CI 1.8, 3.2), respectively** (Figures 1 and 2).
- **At 52 weeks, 46% of RTX+MTX users showed no radiographic disease progression compared to 16% of MTX users.** (Figure 3)
- **At 52 weeks, the RR of achieving clinical remission (DAS28<2.6) with RTX+MTX was 2.4 (95% CI 1.7, 3.5).** (Figure 4)
- **To achieve ACR response rates of 50 and 70 at 24 weeks, 6% (95% CI 4.5, 8.3) and 9% CI (5.9, 12.0) respectively** were needed to treat with RTX (2 x 1000 mg) plus MTX.
- **Out of 100 RTX+MTX recipients, 26 and 14 would achieve ACR response rates of 50 and 70, respectively.** (Figures 5 and 6).
- **To prevent radiographic disease progression or achieve clinical remission at 52 weeks, 8% (95% CI 5.1, 12) and 7% (95% CI 4.1, 12) people needed to be treated with RTX (2 x 1000 mg) plus MTX, respectively.**
- **Out of 100 RTX+MTX recipients, 62 would achieve no radiographic disease progression and 22 would achieve clinical remission (DAS28<2.6) at 52 weeks.** (Figures 7 and 8).

**Discussion**

RTX with MTX improves RA symptoms and prevents disease progression compared to MTX monotherapy. While no differences in the rates of SAEs were noted between groups, RTX recipients experienced higher rates of infusion reactions, vascular events, and cough compared to controls. Knowledge users must consider limitations in the evidence, as all trials were industry sponsored and of moderate quality. Evidence regarding radiographic disease progression is based on few studies, and small sample sizes with few events that may lead to wide confidence intervals.

**References**