

# EXPERT OPINION:

## The benefits of rituximab in rheumatoid arthritis



**Professor Paul-Peter Tak, Director, Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, answers questions about the efficacy of the novel B cell targeted therapy, rituximab**

### Q1. What is rituximab?

Rituximab is a monoclonal antibody, which selectively depletes peripheral B cells by targeting a unique cell-surface marker (CD20) found on these cells. B cells play a key role in the chain of inflammatory events in rheumatoid arthritis (RA) that lead to the damage of bone and cartilage in the joints.<sup>1</sup>

This joint damage ultimately results in the disability that may be seen in RA.

Rituximab, in combination with methotrexate (MTX), is indicated for the treatment of adult patients with severe,

active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs), including one or more tumour necrosis factor (TNF) inhibitor therapies.

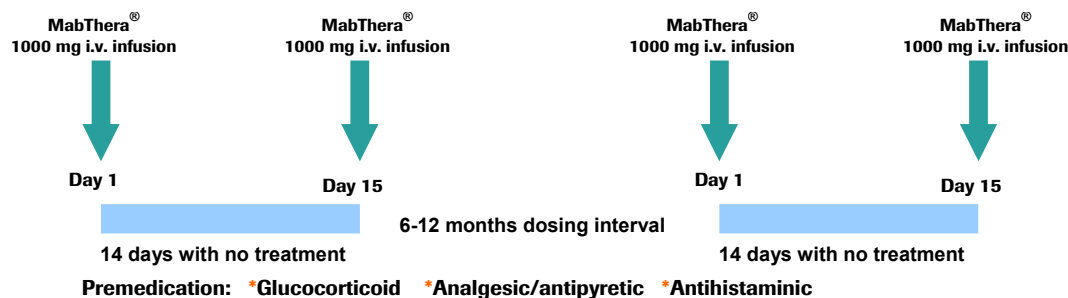
TNF inhibitor therapy is less than optimal in at least one-third of RA patients<sup>2</sup> owing to inadequate efficacy, intolerance or compliance problems. Rituximab represents a new treatment option for these patients, who until recently had limited therapeutic alternatives.

### Q2. What makes rituximab different from other RA therapies?

Rituximab is the only registered therapy for RA that targets B cells. Other RA therapies have different targets and, as a consequence, rituximab may prove effective when other therapies have not worked.

Rituximab also has a unique treatment regimen for an RA treatment: each course of treatment is administered as two 1000mg infusions, two weeks apart (Figure 1).

Positive clinical responses seen with each course of rituximab are maintained for an unprecedented duration of between 6 and 12 months. In contrast, all other biologic therapies require regular administration (at least weekly to two monthly depending on the agent) to maintain their effect



**Figure 1: Schematic of rituximab administration schedule**

### Q3. What is the evidence that supports the use of rituximab in patients with an inadequate response to one or more TNF inhibitors?

REFLEX (Randomised Evaluation of Long-term Efficacy of RituXimab in RA) was a pivotal Phase III study evaluating the effectiveness and safety of rituximab in combination with methotrexate in patients with long-standing, severe disease who had failed to respond or were intolerant to one or more TNF inhibitors. In this multi-centre, double-blind, placebo-controlled trial, 499 patients received either a single treatment course of just two infusions of rituximab two weeks apart (1000 mg IV on days 1 and 15),

or placebo infusions, in combination with continuing MTX.<sup>3</sup>

In the REFLEX study, rituximab produced impressive results leading to a significantly greater improvement in ACR and EULAR scores after 24 weeks over placebo [Figure 2].<sup>3</sup> The improvement in the DAS28 score was also statistically significant ( $p < 0.0001$ ) at every time point from week 8 to week 24, with the maximal benefit obtained by week 16 and sustained thereafter.<sup>3</sup>

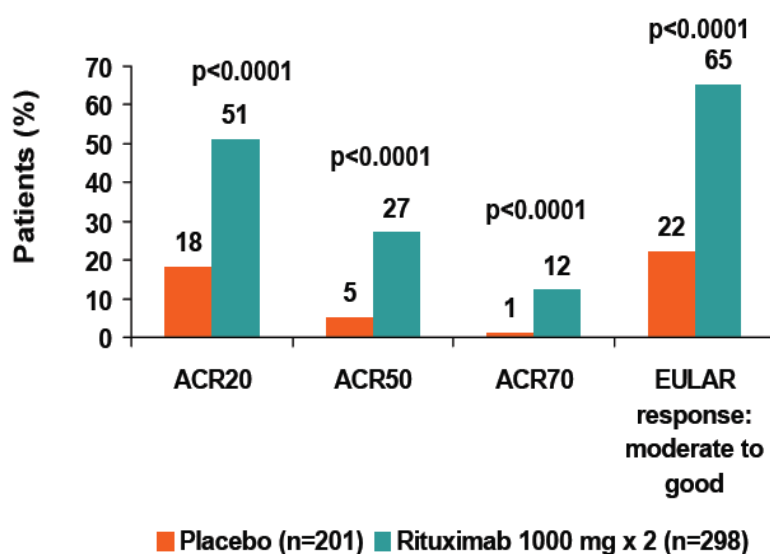


Figure 2: ACR and EULAR responses at 24 weeks in the REFLEX study<sup>3</sup>

Importantly, REFLEX also demonstrated the ability of rituximab to slow structural joint damage progression which is the predominant cause of the disability associated with RA.<sup>4</sup> Rituximab is the only RA

therapy that has demonstrated the ability to minimise the progression of joint damage in inadequate responders to TNF inhibitor therapy.

### Q4. Do improvements in disease activity translate into noticeable improvements for patients?

Major concerns for patients with RA, and their families, include pain, distress, fatigue, poor sleep quality and the inability to perform the simple tasks associated with daily living. In addition to improvements in disease activity, treatment with rituximab in the REFLEX study showed rapid, clinically and statistically significant improvements in patient-reported pain, fatigue, functional disability and, last but not least, quality of life, both in relation to physical and mental health.<sup>5</sup>

These improvements in the signs and symptoms of RA can make a dramatic difference to the lives of patients with RA. In my clinical practice, I have seen patients who have shown no response to other DMARDs including one or more TNF inhibitor therapies, whose lives have really changed after the use of rituximab. Following treatment, they have been able to go back to work and have an active social life – rituximab has made a really positive impact on their quality of life.

### Q5. Has more than one course of rituximab been investigated in clinical trials?

Yes. Patients from the Phase II and III rituximab clinical trial programme could receive repeat treatment as part of open label extension studies. To date, almost 700

patients have received two or more courses of rituximab, with some having received six or seven treatment courses.

### Q6. What is the response of patients to more than one course of rituximab?

Results from the follow-up of these patients have confirmed that rituximab produces sustained long term efficacy with repeat treatment courses. In patients with an inadequate response to one or more TNF

inhibitor, three courses of rituximab resulted in sustained or improved good EULAR response and DAS28 low disease activity and remission [Figure 3].<sup>6</sup>

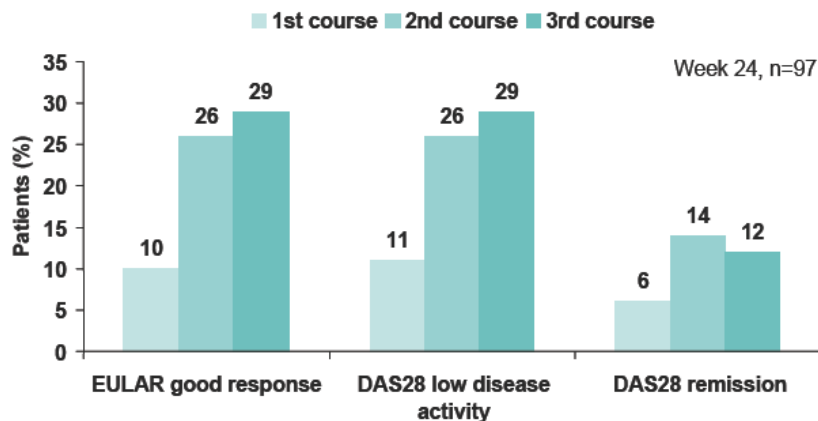


Figure 3: Achievement of EULAR good response, DAS28 low disease activity or remission at week 24 in patients who were inadequate responders to TNF inhibitors following the first and later repeat treatment courses of rituximab<sup>6</sup>

The proportion of patients achieving ACR70 responses at 24 weeks also increased from 11% with the first treatment course to 25%

following a third course.<sup>6</sup> Efficacy was sustained or improved when measured relative to the original baseline [Figure 4].<sup>6</sup>

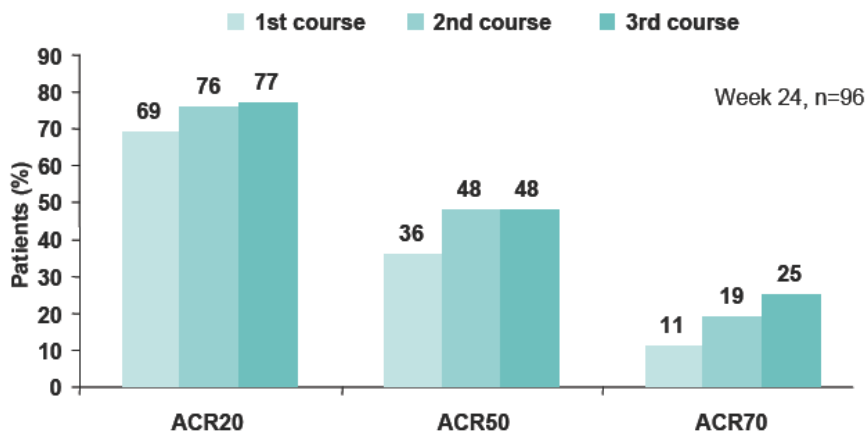


Figure 4: ACR response to rituximab at week 24 relative to the original study baseline in patients with an inadequate response to one or more TNF inhibitors<sup>6</sup>

### Q7. What is the duration of response to each course?

In my clinical experience, as well as in clinical studies, the positive responses seen with rituximab are maintained for 6 to 12 months with each course. This duration of clinical response between treatment administrations is longer than seen with other RA therapies.

Analysis of 210 patients, with a previous inadequate response to one or more TNF inhibitors and who received at least three courses of rituximab, showed that the median time between treatment courses was 37.9 weeks for courses one and two, and 42.1 weeks between courses two and three – around 9 months [Figure 5].<sup>7</sup>

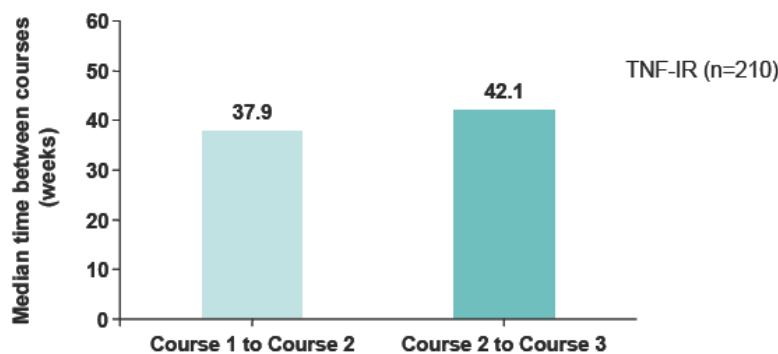


Figure 5: Median time between rituximab courses in patients with an inadequate response to one or more TNF inhibitors<sup>7</sup>

### Q8. What are the main conclusions that you take from the trials investigating the use of rituximab in RA?

There remains a real unmet need for effective treatment options for patients whose daily life continues to be affected by this serious disease after the failure of a TNF inhibitor. Rituximab is an innovative B cell targeted therapy that has proven to be an effective therapy for these patients. REFLEX showed not only that rituximab produces significant results in reducing swollen and tender joints, improving fatigue and quality of life, but that it also slows the progression of structural damage to the joints, a unique and important finding in patients who have had an inadequate response to one or more TNF inhibitors. It is also most encouraging

that repeat treatment with rituximab provides sustained or improved effectiveness for patients across all clinical measures.

The positive responses seen with each course of rituximab are also maintained for an unprecedented duration of between 6 and 12 months. This duration of response allows patients to have fewer treatments than with other RA therapies. I very much look forward to the emergence of further new data on RA patients treated with rituximab so that we can realise the full potential of this novel therapy on patients' lives.

### References:

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