



Rituximab in Rheumatoid Arthritis (RA) - Milestones

At a glance

1997 Rituximab (brand name MabThera[®] / Rituxan[®]) was the first licensed monoclonal antibody therapy, in the USA for the treatment of non-Hodgkin's lymphoma – approved a year later in Europe^{1,2}

1999 Rituximab shows benefits in RA patients

2002 First presentation of six month results for the Phase IIa randomised clinical trial of rituximab in RA at the American College of Rheumatology (ACR)

2004 Six and twelve month results of the Phase IIa study show a short course of rituximab with methotrexate (MTX) is effective for up to one year³

2004 Phase IIb DANCER study unblinded, initial results support rituximab's safety and efficacy in RA patients, and explore the role of glucocorticoids in the regimen

2005 Phase III REFLEX study unblinded (six month results) demonstrating rituximab is effective in patients who have had an inadequate response or are intolerant to anti-TNF therapies

To date More than 500,000 patients have been treated with rituximab in non-Hodgkin's lymphoma (NHL), a form of lymphatic cancer.

Rituximab for the treatment of RA

- Initial research conducted in 1999 showed that rituximab benefits RA patients, suggesting a role for B cells in the pathophysiology of RA¹
 - These results were confirmed by additional small pilot studies^{2,4,5}
 - These first studies suggested that selective B cell targeting with rituximab is a promising treatment option¹
- A randomised, controlled Phase IIa study, published in the New England Journal of Medicine in June 2004³ showed that a short course of just two infusions of rituximab administered two weeks apart, in combination with MTX, produced an

- ACR50* response in almost half of the study population (43%) at 24 weeks – the primary endpoint³
 - The same study found the control group of MTX alone produced ACR50 scores in only 13% of the study population
 - The data also showed that almost a quarter (23%) of patients receiving rituximab and MTX in combination achieved ACR70 compared to 5% in those receiving MTX alone
- The study also showed that the single, short course of treatment with rituximab - two infusions, two weeks apart - combined with MTX significantly improved symptoms in patients with severe RA for up to one year (35% of patients at 48 weeks achieved ACR50 scores at 48 weeks compared to 43% of patients at 24 weeks)³
 - In addition, the ACR70 response rate at 24 weeks was well maintained at 48 weeks 23% vs. 15% respectively.

Ongoing research into the use of rituximab in RA

The clinical trial programme exploring the use of rituximab in RA includes a number of studies to date, including a dose-defining study (DANCER), the first Phase III study (REFLEX) and an extension study looking at the benefits of further courses of treatment with rituximab. The programme will extend into broader indications in rheumatoid arthritis in the future.

- The Phase IIb study DANCER (**D**ose-ranging **A**ssessment: **i**nternational **C**linical **E**valuation of **R**ituximab in RA) was designed to explore the efficacy and safety of different doses of rituximab in RA, and the role of glucocorticoids in the regimen. DANCER is the largest study of rituximab in RA to date and included a diverse group of patients with active RA who have failed one or more disease-modifying anti-rheumatic drugs, including biologics

* The ACR response is a standard assessment used to measure patients' responses to anti-rheumatic therapies, devised by the American College of Rheumatology (ACR). It requires a patient to have a defined percentage reduction in a number of symptoms of their disease. For example, a 20 or 50 percent level of reduction (the percentage of reduction of RA symptoms) is represented as ACR20, ACR50 or ACR70. An ACR70 response is exceptional for existing treatments and represents a significant improvement in a patient's condition.

- The results from the 24-week analysis showed that both doses of rituximab were highly effective, producing significantly higher response rates than placebo
 - Patients with moderate-to-severe RA who received two infusions of rituximab over a two week period in combination with a stable dose of MTX, experienced improved symptoms compared to patients who received placebo and MTX
 - Benefits in the rituximab-treated patients were present regardless of whether additional glucocorticoids were administered
 - Analyses of safety and tolerability of rituximab found a safety profile consistent with that seen in other studies of rituximab in RA
 - The study continues for a total of two years of follow up.
- The Phase III study called REFLEX (**R**andomized **E**valuation of **F** Long-term **E**fficacy of ritu**X**imab in RA) was designed to explore the use of rituximab in RA patients who have had an inadequate response to anti-TNF therapies
 - The trial successfully met its primary endpoint in patients who had had an inadequate response or were intolerant to prior treatment with one or more anti-TNF therapies – those patients with the most difficult-to-treat RA
 - A greater proportion of rituximab-treated RA patients achieved a significant improvement of disease symptoms (ACR20 response) after 24 weeks, compared to placebo.
- An open-label extension study of patients from the Phase IIa and IIb has found that rituximab continues to be effective and safe when used as a second or third course of treatment
 - Following a second treatment course, 63% of patients maintained at least a 20% improvement in their symptoms (ACR20)* while 31% of patients maintained at least a 50% improvement (ACR50)*. After a third course of rituximab, these figures increased to 69% and 39% respectively, with 15% of patients maintaining a 70% improvement
 - In addition to the positive impact of rituximab on symptoms over the extended observation period, therapy with rituximab converted the strongly positive rheumatoid factor to negative in a proportion of patients (90% at baseline to 71% at week 120), a finding not seen with other standard RA treatment.

Heritage in oncology - safety

- Early results in RA suggest that the overall tolerability and safety profile of rituximab in RA patients is similar to that seen in non-Hodgkin's lymphoma patients.

References

1. Edwards JC, Cambridge G. Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology* 2001; 40: 205-11
2. De Vita S, Zaja F, Sacco S et al. Efficacy of selective B cell blockade in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. *Arthritis Rheum* 2002; 46:
3. Edwards J et al. Efficacy of B-cell targeted therapy with rituximab in patients with rheumatoid arthritis. *New England Journal of Medicine* 2004;350:2572-81
4. Leandro MJ, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Ann Rheum Dis* 2002;61:883-8
5. Higashida J et al. Data presented at American College of Rheumatology (ACR) Meeting 2002. LB11