



Rituximab in the treatment of rheumatoid arthritis

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Rheumatoid arthritis is a chronic, disabling condition and the most common form of inflammatory arthritis affecting approximately 1% of the population. The outlook has improved considerably over the last decade with the recognition that better outcomes accompany early and optimal suppression of synovitis. In some patients, this can be achieved with conventional, oral disease-modifying anti-rheumatic drugs. For those with more severe disease, the introduction of biologic therapies targeting the pro-inflammatory cytokine tumor necrosis factor (TNF)- α has led to further, significant improvements in outcome. However, in general, these drugs are being used for long-term maintenance therapy and are associated with a very high expense that limits their availability in most healthcare economies. Furthermore, approximately a third of patients fail to achieve clinically significant responses. There is therefore a need for new, effective approaches to therapy, in particular for those patients refractory to TNF blockade. Rituximab, a B cell-depleting antibody, is the first biologic targeting B cells to be approved in the USA and Europe for the treatment of active rheumatoid arthritis in anti-TNF non-responders. This article reviews the background to this therapeutic approach and the encouraging clinical trial data to date indicating that enduring responses can be achieved in a majority of patients after a single treatment cycle comprising two rituximab infusions given 2 weeks apart.

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Introduction to the current rheumatoid arthritis market

The outlook for rheumatoid arthritis (RA) has improved considerably in recent years. A number of factors have contributed to this. For example, as appreciation of the gravity of the social and economic burden imposed by RA has grown, so has the recognition that more favourable clinical outcomes are achieved when synovitis is optimally suppressed. In particular, there is now compelling evidence that intervention with disease-modifying combination therapy early in the course of RA results in improved remission rates, magnitude of clinical benefit, and slowing of structural damage to joints [1–8]. In addition, the armamentarium of potential therapeutics has risen. The most dramatic impact has been made over the last decade or so with the introduction and widespread use of biologic tumor necrosis factor (TNF)- α inhibitors leading to

further improvements in patient care with particularly marked benefit with respect to inhibition of structural damage to joints. However, the expense associated with biologic drugs is such that rationing of these agents is required in most healthcare economies and TNF- α inhibitors are generally not available at the earliest stages of disease where there is the highest potential to prevent joint damage, and subsequent disability despite clear evidence of such benefits in study populations [9–15] and preliminary data suggesting that early treatment with an anti-TNF agent may permit induction of biologic-free remission [16,17]. Cost-effective and optimal clinical use of expensive biologic agents is further complicated by the fact that a significant proportion of RA patients are refractory to TNF- α blockade, suggesting that other pro-inflammatory molecules or immunological pathways drive the clinical syndrome in this

population. Furthermore, serious adverse events, although relatively uncommon, can and do occur in an unpredictable manner.

In light of these considerations, it is timely that rituximab joins abatacept (Orencia[®], BristolMyersSquibb) as RA treatment approaches with mechanisms entirely different from those of the TNF inhibitors. The focus of this review is rituximab (Rituxan[®]; Genentech Inc. and Biogen Idec Inc.; and MabThera[®]; F-Hoffman LaRoche Ltd.), a B-cell depleting, therapeutic monoclonal anti-CD20 monoclonal antibody (mAb) for patients with active RA who fail to respond to, or are intolerant of, TNF α inhibitors.

B-cell depletion therapy: a new approach in the treatment of RA

B cells arise from stem cells in the bone marrow where they acquire an antibody receptor bearing a unique variable region. A number of maturation and activation steps take place as the B cells migrate from the marrow compartment through blood to perifollicular germinal centres and memory compartments in lymphoid tissue before returning to the marrow as mature plasma cells [18]. Successful maturation and survival of cells is tightly regulated and dependent on a number of trophic signals delivered via cell surface ligands, such as vascular cell adhesion molecule (VCAM)-1, and soluble factors such as B lymphocyte stimulator (B LyS) [19,20].

The role of B cells in the pathogenesis of RA is not fully understood. Nonetheless, there are a number of known B-cell functions of likely relevance, including their role in antigen presentation, secretion of pro-inflammatory cytokines, production of rheumatoid factor (RF), and thus their role in immune-complex formation and co-stimulation of T cells. Of note, immune complexes are one trigger in the production of TNF and other pro-inflammatory cytokines. B cells are also implicated in the process of ectopic lymphoid organogenesis in the rheumatoid synovium.

In the late 1990s, Edwards and colleagues suggested that the (assumed) underlying autoreactive response in RA might be driven by self-perpetuating B cells, and that initiation of inflammation results from ligation of the low-affinity IgG receptor, Fc γ IIIa, by immune complexes [21,22]. This hypothesis might account for the tissue tropisms of disease expression in the RA syndrome complex, as Fc γ IIIa is expressed in high levels in synovium and other extra-articular tissues sometimes involved in RA. RF-producing cells can capture antibodies bound to antigen prior to antigen internalization by endocytosis and subsequent presentation of peptide fragments to a T cell with provision of T-cell assistance to the B-cell. Edwards and colleagues also proposed that such RF-producing B cells might become self-perpetuating by an amplification signal arising from coligation of the B-cell receptor and small immune complexes formed by IgG RF bound to the complement component C3D, providing a survival signal [23]. In contrast, co-ligation of certain other B-cell surface receptors with the B-cell receptor may provide a negative survival signal to the parent or other B cells. The formation of such self-perpetuating, autoreactive B cells might arise as a rare event escaping normal regulatory mechanisms and this theory predicts that a B-cell depletion strategy would remove the autoreactive B-cell clones and their antibody products. Since CD20 is not internalized and is highly expressed on a range of B lineage cells, including preHB cells, immature B cells, activated cells, and memory cells but is not found on stem, dendritic, or plasma cells (FIGURE 1), it is an ideal target for B-cell depletion by mAbs. The hypothesis that B cells represent a therapeutic target in RA is also being tested in the clinic using other strategies for B-cell inhibition, as discussed below.

The CD20 antigen is located on the B cell membrane with 44 amino acids exposed to the extracellular space. Its function is unknown although it may have a role in cell signalling or in calcium mobilization [24]. Interestingly, CD20 knockout mice do not have a clear-cut phenotype or obvious B-cell defect [25]. CD20⁺ B cells represent a prominent population in the rheumatoid synovial tissue in the majority of patients.

Introduction to rituximab

Rituximab is a chimeric mouse-human mAb directed against the extracellular domain of the CD20 antigen. It initiates complement-mediated B-cell lysis and may permit antibody-dependent, cell-mediated cytotoxicity when the Fc portion of the antibody is recognized by corresponding receptors on cytotoxic cells. Rituximab may also initiate apoptosis [26] and influence the ability of B cells to respond to antigen or other stimuli [27]. Rituximab initially found a

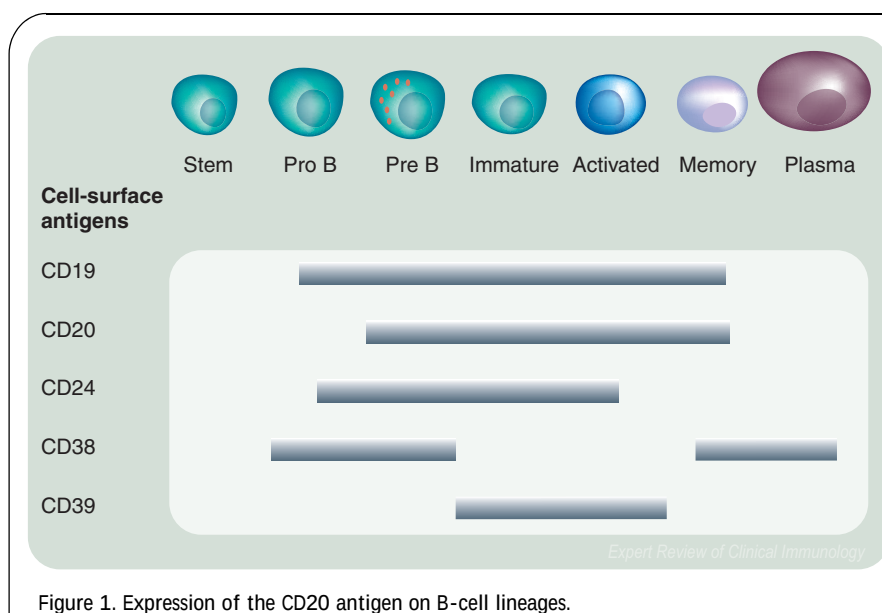


Figure 1. Expression of the CD20 antigen on B-cell lineages.

role in the clinic as a single-agent treatment for relapsed or refractory low-grade or follicular CD20⁺ B cell non-Hodgkins lymphoma, for which it was approved. There was therefore a wide experience of rituximab in hematologic oncology prior to clinical trials of this drug in RA, and its recent approval in the USA and Europe for treatment TNF inhibitor-refractory RA patients with active disease.

Clinical studies of rituximab in RA

The clinical effects of B-cell depletion therapy using rituximab in a number of different treatment regimes have been reported in patients with active RA over the last 5 years with encouraging data emerging.

In 2001, Edwards and Cambridge reported their findings in five patients with severe, long-standing refractory RA, despite treatment with at least five previous disease-modifying anti rheumatic drugs (DMARDs), following treatment with rituximab used in combination with oral prednisolone and pulsed intravenous cyclophosphamide, based on a regimen derived from the rituximab–Cytoxan, Hydroxyrubicin (Adriamycin), Oncovin (Vincristine), Prednisone (CHOP) regime used in non-Hodgkins lymphoma patients [28]. Up to four intravenous rituximab infusions were administered at 300 mg on day 2, and 600 mg on Days 8, 15, 22. Oral prednisone was given from 30–60 mg on days 1–22 and intravenous 750 mg cyclophosphamide on days 4 and 17. At 6 months, all five patients achieved ACR50 response, and of these, three patients achieved the more stringent ACR70 level responses. Of these, all maintained this response at 1 year. The two patients with ACR50 responses relapsed and both achieved ACR70 on retreatment.

In this small series there were no major adverse events and no infusion-related events. However, the use of steroids and cyclophosphamide precluded any conclusions regarding the contribution of rituximab to the observed benefit.

The findings of two further small open-label studies were published in 2002. De Vita and colleagues used rituximab (4-weekly intravenous infusions of 375 mg/m²) to treat five patients with active RA despite combination treatment with methotrexate (MTX) and cyclosporine, of whom two were non-responders to anti-TNF therapy [29]. In this study, one patient had an ACR70 response (lasting 10 months) and one had an ACR50 response (lasting 1 year). Two further patients had an ACR20 response. Leandro and colleagues reported their findings following treatment with one of five different combinations of rituximab, cyclophosphamide and oral prednisone in 22 patients with long-standing, active RA despite treatment with at least two previous DMARDs [30]. At 6 months, ACR20, 50 and 70 responses were achieved by 16, 13 and 8 patients, respectively. No major adverse events were reported but non-serious infections occurred in five patients and mild-to-moderate nausea in seven patients.

These encouraging, early efficacy findings with an acceptable safety profile pointed to a possible therapeutic potential for rituximab in RA. Confirmation of benefit required a randomized, double-blind, controlled study. In a Phase IIa study, the efficacy of rituximab in active RA was tested in 161 patients who had failed to respond adequately to treatment with MTX at a dose of at least 10 mg once weekly for a minimum of 16 weeks. Patients were assigned to one of four treatment regimens: a 1 g infusion of intravenous rituximab alone on days 1 and 15; MTX alone as a comparator arm; intravenous rituximab with cyclophosphamide infusions at a dose of 750 mg on days 3 and 17; or rituximab and MTX. All patients received 100 mg methylprednisolone just before each treatment, in addition to prednisolone 60 mg daily on day 2 and days 4–7 and 30 mg daily on days 8–14. The primary end-point was the proportion of patients achieving an ACR50 response at week 24, and exploratory analyses were undertaken at week 48 [31]. At week 24, a significantly greater proportion of patients achieved an ACR50 in the rituximab and MTX combination group (43%; *p* = 0.005), and the rituximab–cyclophosphamide combination group (41%; *p* = 0.005) than in the group receiving MTX as monotherapy (13%) (TABLE 1). Of the patients receiving rituximab alone, 33% achieved an ACR50 response, but this failed to reach statistical significance as compared with MTX alone (*p* = 0.059). In all the rituximab groups, the mean change from baseline in disease activity score was significant as compared with MTX alone.

At 48 weeks, an exploratory analysis of the ACR responses in the rituximab and MTX group demonstrated 35% of patients responding at the ACR50 level, and 15% of the ACR70 level, significantly greater than the 5% and 0% responses at ACR50 and 70% levels respectively in the MTX group. In the rituximab and cyclophosphamide treatment arm, 27% of patients achieved an ACR50 response.

Table 1. percentage of patients achieving ACR20, 50 and 70 responses at 24 weeks following treatment with either methotrexate or methotrexate plus two infusions of 1 g rituximab, 2 weeks apart in the Phase IIa, Phase IIb DANCER and Phase III REFLEX studies.

Study		ACR20	ACR50	ACR70	Ref
Phase IIa study	1 g rituximab x 2 plus MTX	65	35	15	[28]
	MTX	20	5	0	
Phase IIb study DANCER	1 g rituximab x 2 plus MTX	54	34	20	[29]
	MTX	28	13	5	
Phase III study REFLEX	1 g rituximab x 2 plus MTX	51	27	12	[30]
	MTX	18	5	1	

ACR: American College of Rheumatology; DANCER: Dose-ranging Assessment: iNternational Clinical Evaluation of Rituximab in rheumatoid arthritis; MTX: Methotrexate; REFLEX: Randomized Evaluation of Long-term Efficacy of Rituximab in rheumatoid arthritis.

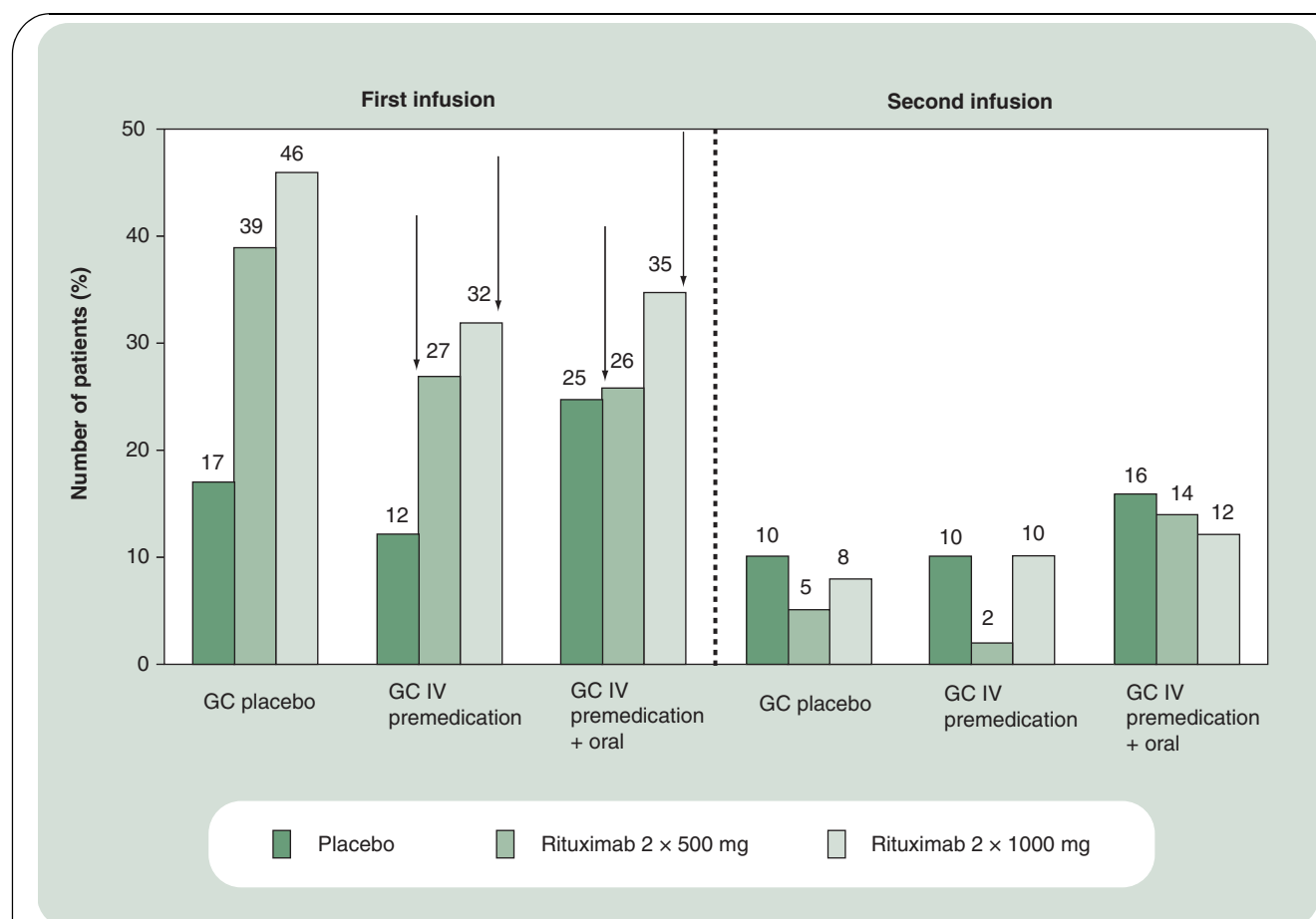


Figure 2. Chart showing occurrence of infusion reactions in the DANCER trial. The DANCER trial, a Phase IIb dose-ranging study undertaken to examine the efficacy and safety of rituximab at two doses, with or without glucocorticoids, in patients with active RA resistant to DMARDs, including biologics. Patients were randomized to receive either placebo infusions or rituximab at a dose of 500 mg or 1 g on days 1 and 15, together with one of three glucocorticoid options, comprising glucocorticoid placebo, 100 mg of intravenous methylprednisolone prior to each rituximab infusion, or 100 mg of methylprednisolone prior to each infusion in addition to oral corticosteroid. Pretreatment with methylprednisolone prior to rituximab infusions reduced the incidence and severity of reactions by approximately a third. DANCER: Dose-ranging Assessment: iNternational Clinical Evaluation of Rituximab in rheumatoid arthritis; DMARD: Disease-modifying anti-rheumatic drugs; RA: Rheumatoid arthritis. Based on data from [32].

Rituximab treatment was associated with near-complete peripheral blood B-cell depletion, persisting throughout the 24-week period of the primary analysis. Patients in the rituximab groups were noted to have a substantial and rapid reduction in the concentration of RF levels in serum, but despite peripheral B-cell depletion, Ig levels did not change substantially [31].

Surprisingly, in view of the profound peripheral B cell depletion, the overall incidence of infection reported was similar in the control and rituximab groups, at 24 and 48 weeks. By week 24, four patients in the rituximab groups had suffered a serious infection and one in the control group. Two further serious infections were reported during the extended 48-week period in the rituximab groups, one of which was fatal. Infusion reactions of any type were reported in 36% of patients receiving rituximab and 30% of patients receiving placebo, although most were characterized as mild or moderate. The reactions included hypotension, hypertension, flushing, pruritis, and rash. It has been suggested that a cytokine release

syndrome associated with marked cell lysis following rituximab might be a contributory factor, particularly in the rare cases of severe reactions.

In summary, the findings of the Phase IIa study indicated that a single course of treatment with rituximab, particularly in combination with MTX, produces an enduring response in patients with severe, seropositive, active RA. Furthermore, treatment with rituximab was well tolerated, with a favorable safety profile over 48 weeks of follow-up.

Following the success of the Phase IIa study, a Phase IIb study was undertaken to examine the efficacy and safety of rituximab at different doses, with or without glucocorticoids, in patients with active RA resistant to DMARDs, including biologics. The findings of this Phase IIb study, the Dose-ranging Assessment: iNternational Clinical Evaluation of Rituximab in RA (DANCER) trial have recently been reported [32]. A total of 465 patients with active disease were recruited. Patients were required to have failed at least one DMARD other than MTX, but no more than five, and/or biologic response modifiers, and to

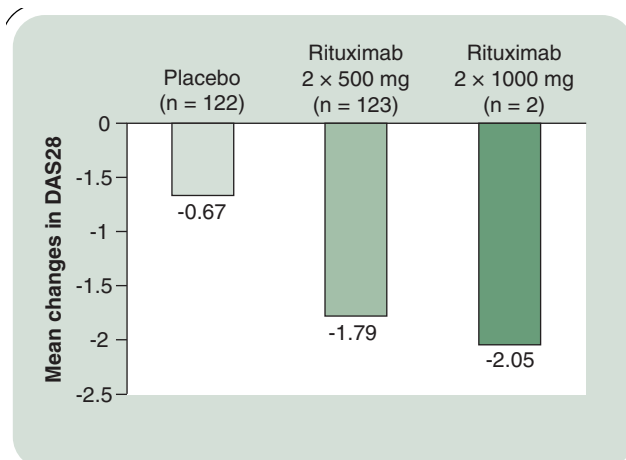


Figure 3. Mean changes in DAS28 from baseline in the DANCER study. Mean changes in DAS28 from baseline in the Phase IIb DANCER study was significantly greater in patients treated with two rituximab infusions 2 weeks apart at either 500 mg or 1 g each, as compared with placebo infusions ($p < 0.0001$). DANCER: Dose-ranging Assessment: international Clinical Evaluation of Rituximab in rheumatoid arthritis. Based on data from [32].

have been treated with MTX as a single DMARD for at least 12 weeks, with 4 weeks of stable therapy at a dose of at least 10 mg once weekly. All other DMARDs were withdrawn at least 4 weeks prior to randomization and 8 weeks for infliximab, adalimumab or leflunomide. Patients were randomized to receive either placebo infusions or rituximab at a dose of 500 mg or 1 g on days 1 and 15, together with one of three glucocorticoid options, comprising glucocorticoid placebo, 100 mg of intravenous methylprednisolone prior to each rituximab infusion, or 100 mg of methylprednisolone prior to each infusion in addition to oral corticosteroid. The results at 24 weeks confirmed the significant efficacy of a single course of rituximab in active RA when combined with continuing MTX. This benefit was independent of glucocorticoids, although methylprednisolone on day 1 reduced the incidence and severity of first rituximab infusion reactions by approximately a third (FIGURE 2). Both rituximab doses were efficacious. At the lower dose, 55% of recipients achieved ACR20 responses, as did 54% of those at the higher rituximab dose, in both cases, highly significantly greater than the 28% of those receiving placebo infusions. Similarly, there were significantly higher proportions of patients achieving ACR50, ACR70 (TABLE 1) and EULAR good responses at 24 weeks at both rituximab doses compared with patients randomized to placebo infusions (FIGURE 3). At the most stringent ACR70 response level, the difference between the percentages of responders in the placebo, lower and higher rituximab groups was most marked at the higher rituximab dose of 1 g 2 weeks apart (5, 13 and 20% respectively, $p < 0.05$). Adverse events reported up to 24 weeks were largely infusion-related, particularly at the time of the first infusion.

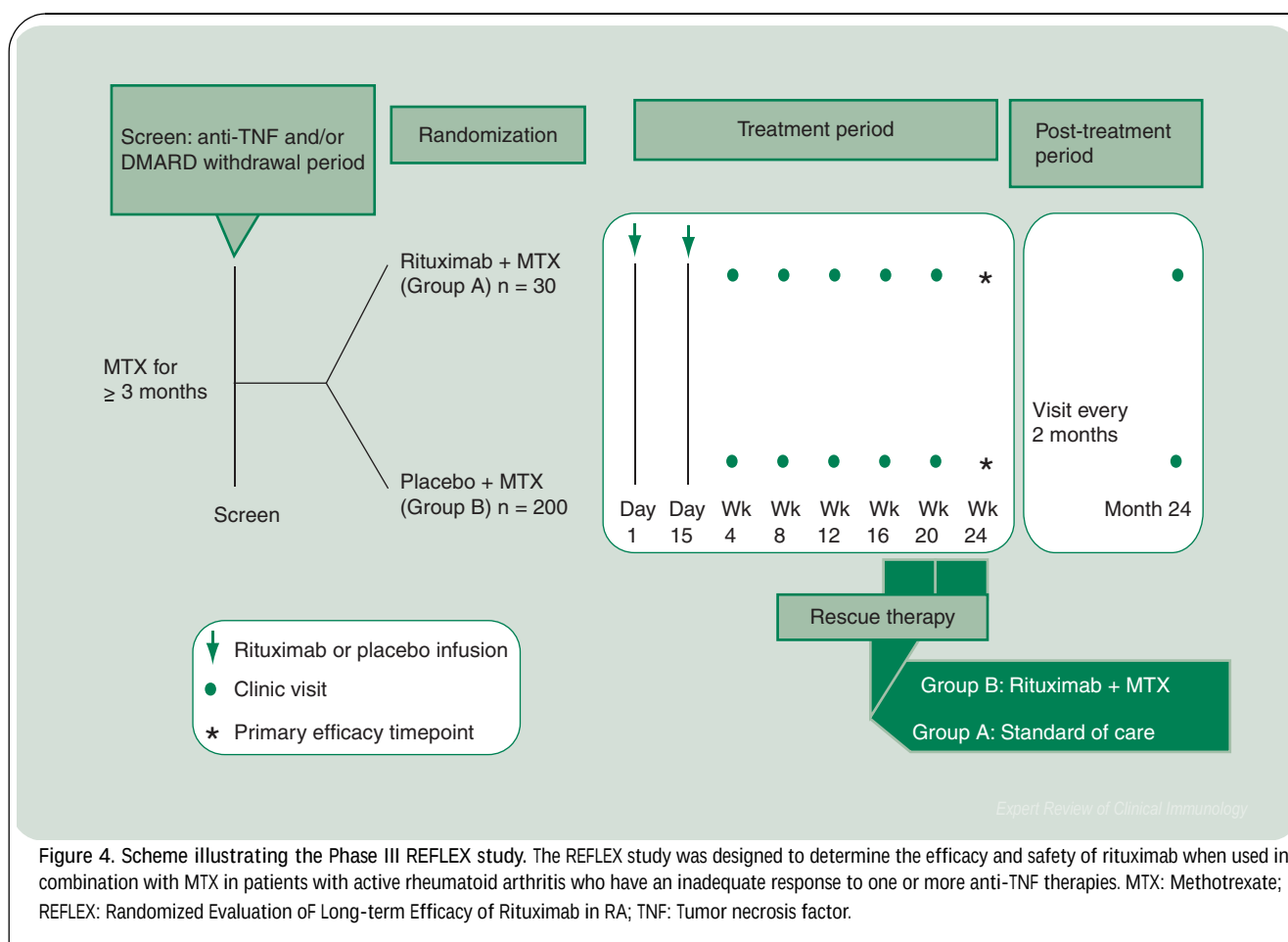
Primary efficacy and safety data at 24 weeks into a Phase III trial have recently been published [33]. Supplementary data at 12 months of follow up have been presented at international

meetings [34]. This trial, known as a Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX), was designed to determine the efficacy and safety of rituximab when used in combination with MTX in patients with active RA who have an inadequate response to one or more anti-TNF therapy (FIGURE 4), either because of lack of efficacy (90% of patients recruited) or due to toxicity (10% of patients recruited). In addition, all patients recruited had radiographic evidence of at least one joint with definite erosion attributable to RA. The recruited cohort comprised 520 patients, of mean disease duration of 12 years, on a background regime of 10–25 mg of once weekly MTX. After a washout period during which other DMARDs and anti-TNFs were withdrawn, patients were randomized to receive a single course of 1 g rituximab, or placebo, infusions on days 1 and 15. All patients were given 100 mg intravenous methylprednisolone prior to each infusion and a brief course of oral prednisolone between the two doses; 60 mg daily from days 2–7 and 30 mg daily from days 8–14 [33].

Of the patients assigned to rituximab, 82% completed 6 months compared with only 54% assigned to placebo. The major reason given for study withdrawal was lack of response reported in 40% of placebo and 12% of rituximab-treated patients. At 6 months, significantly more patients receiving rituximab achieved ACR20, 50 and 70 responses at 51, 27 and 12%, compared with 18, 5 and 1% of patients receiving placebo infusions respectively (TABLE 1). In terms of change in disease activity score (DAS28), intention-to-treat analyses showed that in patients administered placebo infusions the reduction from baseline was 0.34, less than the 0.6 point reduction from baseline considered to clinically meaningful, as contrasted with a reduction of 1.83 in the rituximab group [33].

The ACR response evaluates RA treatment based on a 20, 50 or 70% improvement in five of seven core components. However, from the patient perspective, it is not straightforward to determine where the actual benefit of an ACR20 improvement lies. In fact, in the REFLEX study there were significantly greater improvements in all components of the ACR core set measures in the rituximab group. Rituximab demonstrated a clinically meaningful benefit for RA pts in physical function evaluated by Health Assessment Questionnaire (HAQ) at all non-overlapping ACR response categories. In the active treatment arm both clinical and subjective parameters of the ACR core components contributed to the assignment of an ACR20 response whereas on placebo the subjective parameters dominated [33].

In the REFLEX study, following a single treatment course, maximal clinical responses to rituximab plus MTX were observed at 24 weeks. After this time point, patients were eligible to exit the study and receive further rituximab treatment based on clinical need. Of the patients in the rituximab plus MTX group, 37% (114/308) remained in the study over 48 weeks indicating continued clinical benefit following a single initial treatment course. The majority of patients who withdrew did so to receive further courses of rituximab



between weeks 24 and 48 of the study. In contrast, 89% of the placebo plus MTX group (185/209) withdrew prior to week 48 [34].

The extraordinary success of TNF blockade with respect to inhibition of structural damage to joints has set a height to which all new biologics must aspire in the treatment of RA. Preliminary analyses of REFLEX radiographic data set at one year have been presented recently with encouraging findings [35]. At week 56, the mean change in Genant-modified Sharp score in the placebo plus MTX arm was 2.31 compared with 1.0 in the rituximab plus MTX group ($p = 0.0043$). Significant differences were also reported for joint space narrowing and bone erosions, comprising both components of the score. The proportion of patients with no progression in erosion score was 61% in the rituximab arm, significantly higher than the 52% in the placebo arm. These represent the first data that B-cell depletion therapy can inhibit progressive destruction to joints in a population refractory to anti-TNF treatment.

Safety issues

A common concern regarding all therapies directed at B cells is the potential for toxicities related to modulation of humoral immunity. Unlike other newly introduced biologic therapies for an RA indication, rituximab has the considerable advantage of

an oncology safety database based on more than 350,000 non-Hodgkin's lymphoma patient treatments since 1997 [36]. The overall safety conclusions are that serious adverse events are infrequent and often associated with well-defined risk factors such as cardiopulmonary disease or a high numbers of circulating cancer cells. Of note, in this lymphoma population, prolonged peripheral B cell depletion has not been associated with cumulative toxicity or increased occurrence of opportunist infections [37–39]. However, it cannot be assumed that the toxicity profile will be identical in distinct disease phenotypes with differing pathogenic processes.

In RA open-label [40], Phase II [31,32] and III [33] studies, although decreases in serum total Ig levels were observed in patients receiving rituximab, concentrations remained within normal limits. Of note, existing antibody titres against tetanus toxoid appear to be unaffected by a single course of rituximab treatment [41]. However, there is some anecdotal evidence that total serum Ig concentrations fall below the normal range in those patients receiving multiple cycles of rituximab treatment over a number of years in open label studies [23]. It is unclear at this stage whether this results in increased infective risk. In the Phase II studies the majority of adverse events were mild-to-moderate and associated with infusions including headache, nausea and rigors.

In the DANCER trial, adverse events associated with rituximab were largely associated with the first infusion occurring in 39% of patients treated with 500 mg (without steroid) and 46% receiving 1 g compared with 17% administered placebo infusions. The corresponding incidence decreased with the second infusion to 5, 8 and 10 respectively (FIGURE 2). Two serious infusion reactions, hypersensitivity and generalized edema, occurred on day 1. Pretreatment with methylprednisolone prior to rituximab infusions reduced the incidence and severity of reactions by approximately a third (FIGURE 2). Infectious adverse events (largely upper respiratory tract infections) were reported in 28% of placebo and 35% of rituximab patients. There were six serious infections: two in the placebo group, four in patients receiving rituximab 1000 mg and none in patients receiving rituximab 500 mg. No opportunistic infections or tuberculosis reactivations were reported.

Immunodynamics

Among RA patients achieving clinical responses to rituximab treatment, the time to clinical relapse is heterogeneous. In some patients, relapse is closely correlated to the reappearance of peripheral blood B cells but in others, it may be delayed by years [42]. Clinical relapse is more closely associated with increases in autoantibody levels but there remains a need for better biomarkers reliably informing optimal management strategies on an individual patient basis. All B-cell populations are depleted following rituximab therapy. Of residual B lineage cells, over 80% exhibit memory or plasma cell precursor phenotype [43]. B-cell repopulation occurs at a mean of 8 months after rituximab and depends on the formation of naïve B cells of immature phenotype resembling those found in umbilical cord blood. Peripheral B cell depletion is accompanied by substantial increases in blood B lymphocyte stimulator (BLyS) concentrations that tend to fall with B cell repopulation [44]. BLyS is a naturally occurring protein required for the development of B-lymphocytes into mature plasma cells. Elevated levels of BLyS in RA are believed to contribute to the production of autoantibodies. However, in cases of prolonged clinical responses to rituximab, more gradual reductions in BLyS concentrations have been observed to extend beyond the period of B-cell depletion. Thus BLyS may contribute to survival or regeneration of pathogenic, autoreactive B cells. This hypothesis predicts a potential therapeutic role for blockade of BLyS in addition to B-cell depletion.

Expert commentary

Recent advances in the understanding of the pathogenesis of RA emphasize the critical role played by B cells in self-sustaining chronic inflammatory processes. Rituximab is a promising addition to the therapeutic armamentarium for the treatment of RA. It is not clear at this point in time whether there are differences in efficacy of rituximab in RF⁺ and RF⁻ patients although available data from the REFLEX study indicate that the effect of treatment on ACR responses was not dependent on baseline RF status [33]. The optimal and most cost-effective

dosing regime for rituximab remains a matter of some debate. However, on the basis on the DANCER study findings, it is recommended that rituximab is given in combination with one weekly MTX, usually at doses of at least 15 mg/week, to optimize efficacy. Furthermore, administration of 100 mg intravenous methylprednisolone is recommended prior to each rituximab infusion as standard of care to reduce frequency and severity of infusion reactions.

The optimal dose of each the two rituximab infusions given 2 weeks apart has been recommended as 1 g on the basis of the higher proportion ACR70 responses in DANCER, although there were a proportion of ACR20 and ACR50 responses that were essentially the same and use of the lower 500 mg dose of rituximab would have the advantages of lower cost and possibly lower serious adverse event rate. Further studies in the post-licensing phase should help clarify these issues.

It is likely that the major use for rituximab in the treatment of RA in clinical practice will be confined to the TNF inhibitor-refractory population in the short term, until there is broader experience and confidence regarding potential adverse effects. It may also have a role in those patients for whom TNF blockade is relatively contraindicated, such as those with connective tissue disease overlap syndromes. At the present time there are uncertainties regarding the implications of long-term peripheral B-cell depletion and the timing and need for redosing with rituximab in patients who respond. Current research suggests that restoration of peripheral B-cell numbers takes approximately 8 months after depletion treatment, although retreatment may need to be earlier. Preliminary results have been presented for an open-label study to evaluate response to repeated treatment courses with rituximab in patients with active RA participating in one of several Phase II/III studies and to determine the optimal frequency for repeated treatment [45]. In a series of 155 patients with prior exposure to TNF inhibitors, ACR20, 50 and 70 scores were 65, 33 and 12%, respectively, following the first course, and 72, 42 and 21%, respectively, for the second treatment course, relative to original baseline. In 82 of these patients going on to receive a third rituximab course, the median interval between first and second courses was very similar to that between second and third courses at between 30–31 weeks [45]. Further studies are needed to identify the optimum regimes that can be used for maintenance therapy that will provide efficacy and limit toxicity.

Although the available safety data for rituximab in RA is reassuring, the data need to be interpreted with caution until larger numbers have been treated and long-term safety and retreatment data become available. Furthermore, there is also a substantial body of safety data for rituximab in treatment of non-Hodgkins lymphoma where similarly low infection rates have been reported. In oncology, some of the associated adverse events are related to circulating tumour loads. Overall, this is reassuring with regard to the rheumatoid population, although close monitoring of immunocompetence and for the possibility of rare opportunistic infections is advisable.

Five-year view

Initially, rituximab, in combination with MTX, will be used as a second line biologic, after one or more anti-TNFs, in the treatment of active RA [46]. However, as physicians become more experienced with its use, assuming that no new safety signals come to light, it is likely that interest in its potential as a first-line biologic will increase over the next few years. Evidence that will support this case will include any competitive health economic data in comparison with TNF inhibitors and efficacy data in early-phase disease. A key question will be the most effective strategy in early stages of RA to induce a biologic-free remission, and whether this can be achieved safely and effectively with rituximab. In the much longer term, the continued success of rituximab will also depend on clinical trial efficacy and safety data for other antibodies targeting CD20, such as ocrelizumab, a humanized version of rituximab, and HuMax-CD 20/ofatumumab, a fully human anti-CD20, also in clinical trials but still some time away from reaching the clinic. It may conceivably be that delivery of such antibodies has a lower rate of infusion (or injection) reactions although this is unlikely to be the case if the infusion reactions observed with rituximab are the consequence of B-cell lysis. In any event, such reactions are generally mild such that any differences emerging between these agents may not be of great clinical importance.

Although many other approaches to B-cell targeted therapy are in clinical testing, it is unlikely that any of these will significantly impact on the rituximab niche over the next 5-year time span. Alternative strategies to target the B-cell compartment

include the use of antibodies to CD22 and BlyS. Belimumab, or LymphoStat-B™, is a human anti-BLyS mAb currently in clinical development for the treatment of RA and other rheumatic indications. An alternative approach to BLyS inhibition in early stages of clinical development is to block signaling through BLyS receptors using a soluble receptor, such as transmembrane activator and calcium modulator and cyclophilin ligand interactor Ig (TACI-Ig). Preliminary results of a Phase II, double-blind, placebo-controlled study of belimumab in 283 active RA patients has been presented [47]. Patients were randomized to receive intravenous belimumab at a dose of 1, 4 or 10 mg/kg or placebo infusions on days 0, 14, and 28, then every 28 days through 24 weeks. The ACR20 response at week 24 in the combined belimumab groups was 29% compared with 16% in the placebo group, with no dose response observed. The antibody was well tolerated [47]. These preliminary findings with a functional inhibitor of B cells are surprising, given the effectiveness of rituximab although it may simply represent a pharmacokinetic problem and that too low a dose of belimumab was used.

In conclusion, the rituximab clinical trial data validates CD20 as a therapeutic target in RA and endorses B-cell depletion as a successful approach to treatment that has an acceptable safety profile without unacceptable reduction in humoral immunity after a single treatment cycle. The mechanism of action is yet to be fully understood but a growing share in the RA biologic market is anticipated over the next 5-year time frame, with a potential for positioning as a first-line biologic option.

Key issues

- Rituximab is a chimeric monoclonal antibody that depletes B cells expressing CD20.
- Clinical trials in active, established rheumatoid arthritis (RA) confirm that a single cycle of rituximab administered as two infusions, together with once-weekly oral methotrexate, produces enduring clinical responses comparable to that observed with tumor necrosis factor (TNF) blockade.
- Preliminary data suggest that rituximab retards the rate of structural damage to joints.
- Rituximab has recently been approved for use in active RA refractory to TNF inhibitors.
- Current data suggest that the most appropriate interval between rituximab treatment courses is between 6 and 12 months. Repeat treatment produces American College of Rheumatology (ACR) responses that are comparable or improved relative to the first course of treatment with a comparable duration of effect.
- There is an acceptable safety record in RA trials but infusion reactions of variable severity occur, the majority being mild to moderate. The frequency and severity is reduced by administration of intravenous methyl prednisolone prior to rituximab infusions.
- There is the benefit of a reassuring long term safety experience for use of rituximab in treatment of non-Hodgkin's lymphoma.
- Current uncertainties include: how to treat rituximab failures and the lack of reliable biomarkers to inform rational choice of biologic agent.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

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