Rituximab: B-cell depletion therapy for the treatment of rheumatoid arthritis

Shouvik Dass, Edward M Vital & Paul Emery†

†Author for correspondence
Academic Unit of Musculoskeletal Disease, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, UK
Tel.: +44 113 392 4884;
Fax: +44 113 392 4991;
Email: p.emery@leeds.ac.uk

New and effective therapies are still required in rheumatoid arthritis as some patients have disease that is refractory to both conventional therapy and biological agents, such as tumor necrosis factor-α inhibitors. Such patients may respond insufficiently, lose their response or develop toxicity to these newer agents. Rituximab, a chimeric monoclonal antibody against CD20 that effectively depleted B cells in peripheral blood, has been licensed for the treatment of certain hematological malignancies for nearly 10 years. Data are now available that indicate its efficacy and safety in the treatment of rheumatoid arthritis in a variety of patient groups. The clinical outcomes from these studies, together with its safety profile, have led to the recent licensing of rituximab by the US FDA as therapy for rheumatoid arthritis for those patients who have failed to obtain benefit from antitumor necrosis factor-α agents.

Unmet needs in rheumatoid arthritis

Rheumatoid arthritis (RA) affects almost 1% of the population worldwide [1]. Patients with RA show increased morbidity and mortality, with significant detriment to quality of life. The economic burden of RA is considerable, with the direct costs of medical care, surgery and hospitalization, as well as indirect costs of disability and productivity losses [2]. A Spanish study found that cost was related to disease severity, with an increase of US$11,184/year per unit increase in the health assessment questionnaire (HAQ) [3].

Important advances have been made in recent years in the treatment of RA. Earlier and more intensive use of disease-modifying antirheumatic drugs (DMARDs), especially methotrexate, both as monotherapy and in combination with other DMARDs, has been shown to be of benefit [4]. Further understanding of the roles of key cytokines in RA, in particular tumor necrosis factor (TNF)-α [5], has led to the development of biological response modifiers. Biological therapies have been shown to have significant effects on disease outcomes, both in clinical and radiological terms. Three anti-TNF-α agents are licensed in RA – infliximab [6], etanercept [7] and adalimumab [8] – as well as anakinra [9], an interleukin-1 antagonist.

However, it is clear that not all patients derive optimum benefit from these agents [10]. Some patients appear to have disease that is unresponsive to currently available biologicals; others may have an initial response that is then lost; while still others either develop toxicity or are unsuitable for such therapy due to comorbidity. These issues have spurred the development of newer biological agents.

Both the innate and adaptive immune systems are of importance in the pathogenesis of RA [11]. The effector cells of the latter – B cells, T cells and antigen-presenting cells (APCs; such as dendritic cells, macrophages and B cells) – play a major role. Initial T-cell-directed therapy was not entirely successful, with concerns regarding the safety of anti-CD4 therapy [12]. However, recently, a new class of drugs known as co-stimulation blockers has attracted more attention. The first of these to be licensed, abatacept (CTLA4-Ig), is a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (Ig)G_1 fusion protein. Abatacept selectively modulates the co-stimulatory signal required for full T-cell activation. By binding to CD80 and CD86 on APCs, it blocks the engagement of CD28 on T cells and thus prevents T-cell activation. Clinical trials have shown evidence of benefit [13,14].

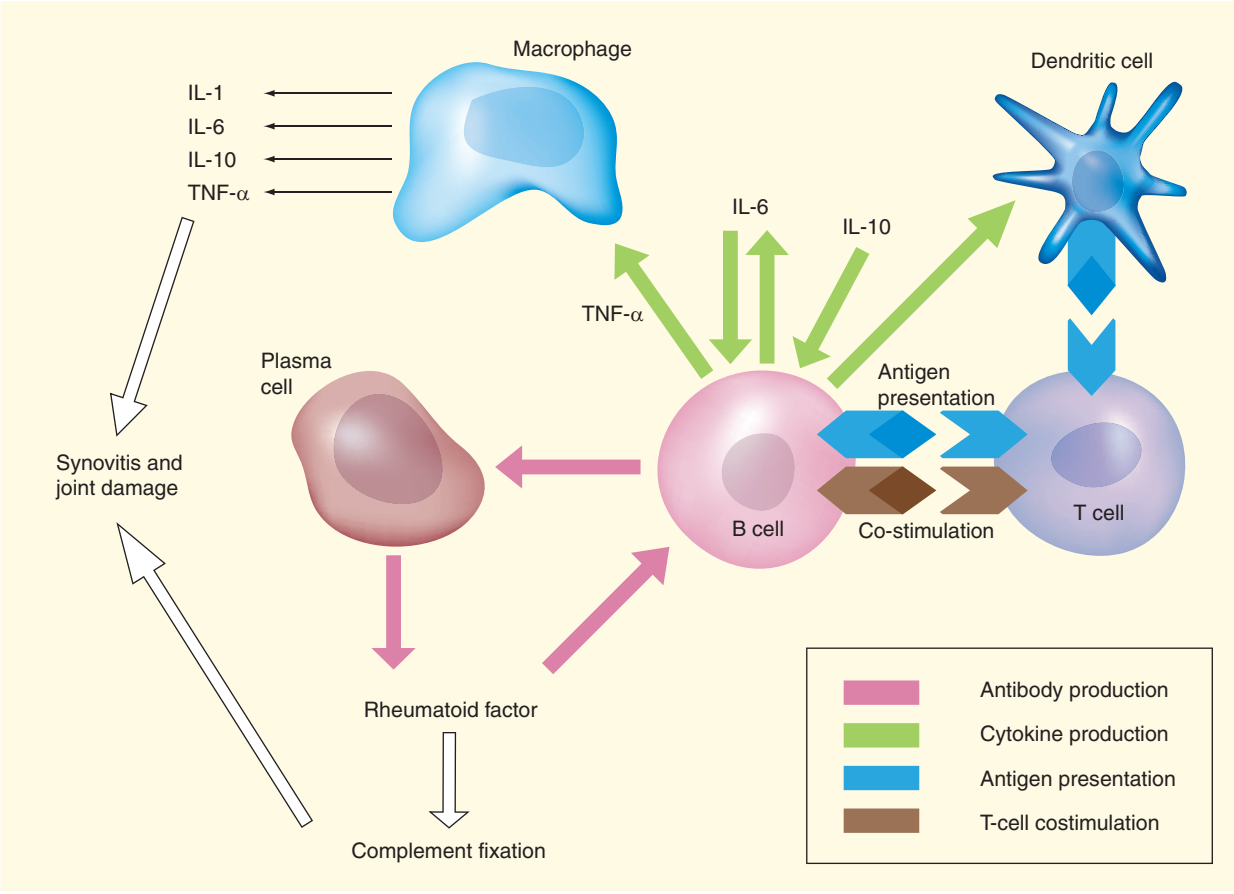
B-cell directed therapy: a novel approach in RA

Although the role of T cells in RA has been studied extensively, the role of B cells is not yet completely elucidated. However, it is apparent that they have the ability to play a number of potentially pathologically significant roles (**Figure 1**) [15]. B-cell development initiates in the bone marrow, with the progressive differentiation of stem cells into immature B cells. These cells express IgM in the bone marrow, before they migrate as mature B cells to peripheral lymphoid tissue. Within lymphoid follicles, mature B cells can be induced by antigens to proliferate and express IgA, IgG and IgM. Follicular B cells can differentiate into plasmablasts that become short-lived plasma

Keywords: B-cell depletion, rheumatoid arthritis, rituximab, targeted therapy, TNF failure

future medicine

Figure 1. Pathogenic roles of B cells in rheumatoid arthritis.



IL: Interleukin; TNF: Tumor necrosis factor.

cells. These cells produce much more Ig than plasmablasts. Short-lived plasma cells last for 2–3 days and provide an immediate response to a pathogen. Within the follicle, activated B cells can congregate tightly to form a germinal center. These cells can differentiate into either plasma cells or memory B cells. Once plasma cells derived in this way lodge in the bone marrow, they are typically long lived, with lifespans estimated at 6–12 months. The presence of structures with features of germinal centers has been found in a proportion of synovial biopsies from RA patients. In RA, large numbers of B cells have been found in the synovial membranes of some affected joints [16].

B cells are thought to have a number of pathogenic roles. They can act as highly effective APCs by processing and presenting antigenic peptides to T cells [17]. In fact, T-cell activation may be dependent on B cells [18]. B cells can also produce cytokines and chemokines indirectly, which can induce leukocyte infiltration [19]. The secretion of autoantibodies by B cells is also important in RA. In particular, rheumatoid factor (RF), an antibody reactive against antigenic determinants on the Fc fragment of IgG, correlates with RA disease severity. It has been suggested that there is a 'vicious cycle' of antibody production in RA, which leads to the development of self-perpetuating B-cell clones [20]. IgG RF has the capacity for self-association in immune complexes that directly activate macrophages by interacting with FcγRIIIa receptors on the macrophage surface, in the process producing TNF-α and enhancing chronic autoinflammatory pathways in synovitis. The variety of putative roles played by B cells may explain why B-cell depletion therapy could be of benefit to patients, regardless of autoantibody status.

Targeting CD20

A broader understanding of the pathological roles of B cells in RA has led to an interest in applying methods of B-cell depletion and,

specifically, the use of monoclonal antibody technology. CD20 (a 33–37-kDa membrane-associated phosphoprotein) is a surface antigen that is expressed solely on pre- and mature B cells [21,22]. It is not expressed on stem cells or pro-B cells, nor is it found on plasma cells [23]. Thus, it is highly specific and, as such, is a suitable therapeutic target for B-cell depletion. Upon antibody binding, CD20 does not modulate its expression, is not shed from the cell surface and is not internalized. There are no known membrane or secreted molecules that interfere with the function of CD20 and it is not found as a free antigen in the circulation [24].

Monoclonal antibodies against CD20 are effective at depleting B cells [24,25]. Rituximab is a chimeric (part human, part mouse) monoclonal antibody specific to CD20. It is genetically engineered by the fusion of the variable regions of a murine antihuman CD20 B-cell hybridoma to a human IgG_1K constant region. Following binding to CD20, B-cell lysis occurs [26]. The mechanism of this is not wholly understood, but is believed to be mediated by complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity or apoptosis [27]. The mechanism responsible for B-cell depletion may differ based on the underlying disease and/or the immune set point of the individual being treated.

Rituximab is approved for the treatment of refractory $CD20^+$ B-cell non-Hodgkin lymphoma (NHL) and has been used in the treatment of more than 500,000 patients, since 1997 in the USA and 1998 in the EU [28]. The treatment regimen in NHL consists of an intravenous infusion of 375 mg/m^2 of rituximab once weekly for 4–8 weeks. More recently, it has been approved by the US FDA for use in certain patients with RA (see Regulatory affairs).

Pharmacodynamics

Data are available from the initial Phase IIa study of rituximab in RA [29]. Depletion of peripheral blood B cells was measured by levels of CD19, a B-cell-specific marker not targeted by rituximab. This indicated that treatment with rituximab (2 × 1 g on days 1 and 15) depleted B cells to levels below 16 cells/µl (regarded as < 20% of the lower limit of normal). Depletion appeared to be achieved in most patients after the first infusion. Median peripheral B-cell counts began to recover from 24 weeks after therapy onwards, but had not reached pretreatment levels in most patients by 48 weeks after therapy. Treatment with rituximab was associated with a rapid and significant fall in RF; levels of Igs remained within normal limits, although mean IgM levels declined.

Pharmacokinetics

Data from the above study show that the mean terminal half-life of rituximab following the second infusion was approximately 20 days, with low systemic serum clearance; rituximab concentrations were still detectable in many patients 24 weeks after rituximab treatment. Data from NHL patients suggests that there is an initial rapid distribution phase followed by a slower elimination phase.

Clinical efficacy

Initial clinical experience

A small, open-label study provided the first indication of the potential efficacy of rituximab in RA [30]. Five patients with poorly controlled RA despite prior sequential treatment with at least five DMARDs were treated with a combination of rituximab (300 mg on day 2 and 600 mg on days 8, 15 and 22), cyclophosphamide (750 mg on days 4 and 17) and oral prednisolone (30–60 mg/day for 22 days). This regimen was based on the rituximab–cyclophosphamide, hydroxydoxorubicin, vincristine and prednisolone (CHOP) that has been successful in the treatment of NHL. However, the use of hydroxydoxorubicin and vincristine was considered inappropriate for RA patients.

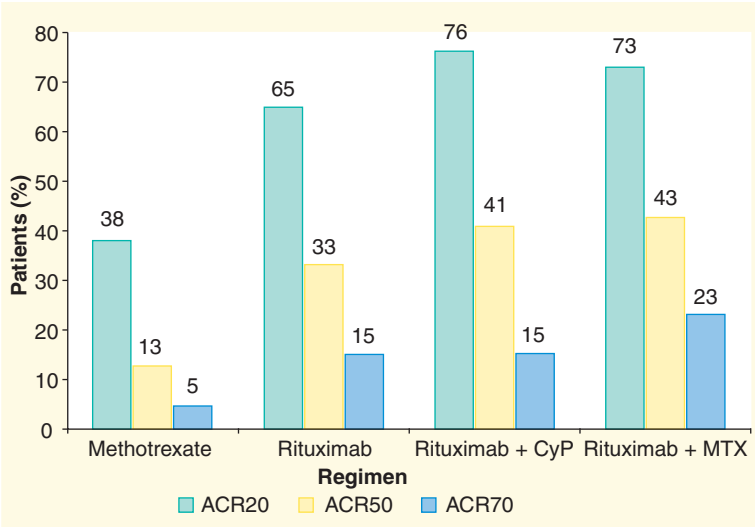
All five patients had improvements of at least 50% in the American College of Rheumatology (ACR) disease response criteria (known as ACR50 response) [31]. Three patients achieved an ACR70 response. These improvements were maintained beyond 6 months after therapy and no major treatment-related adverse effects occurred. B cells were depleted to almost undetectable levels but Ig levels remained stable.

This open-label study provided clinical evidence of the potential role of B cells in RA and of the therapeutic potential of B-cell depletion therapy.

Phase IIa study: the first randomized, controlled trial

Following publication of the open-label study described previously and the follow-up results [32], a multicenter, 24-week, randomized, controlled, double-blind study was carried out to explore the safety and efficacy of treatment with rituximab in RA [29]. The 48-week follow-up data are now available. A total of 161 patients were

Figure 2. ACR clinical responses at week 24 in the first Phase IIa randomized trial.



Data taken from [29].
ACR: American College of Rheumatology; CyP: Cyclophosphamide; MTX: Methotrexate.

enrolled; all had active disease despite treatment with methotrexate and, furthermore, had failed between one and five DMARDs other than methotrexate. All were seropositive for RF. The primary end point was the proportion of patients with an ACR50 response at 6 months.

Patients were randomly assigned to one of four arms; oral methotrexate monotherapy (10–25 mg/week, the control arm); rituximab monotherapy (1 g on days 1 and 15); rituximab with cyclophosphamide (750 mg on days 3 and 17) and rituximab with methotrexate. All groups, including the control group, received a 17-day course of concomitant corticosteroids. This consisted of infusions of 100 mg methylprednisolone before infusions of rituixmab or cyclophosphamide (or placebos for those agents) and oral prednisolone, 60 mg/day on day 2 and days 4–7, and 30 mg daily on days 8–14.

The proportion of patients achieving the primary end point was significantly higher for the rituximab–methotrexate (43%; $p = 0.005$) and rituximab–cyclophosphamide combinations (41%; $p = 0.005$) than for methotrexate alone (13%). In terms of ACR20 response, all groups treated with rituximab had a significantly higher proportion of responders (65–76 vs 38%, $p \geq 0.025$) (**Figure 2**). Some responses were maintained at week 48 (**Figure 3**). With regard to response criteria established by the European League against Rheumatism (EULAR) [33], patients receiving rituximab had a significantly higher proportion of responders (moderate and/or good) compared with those receiving methotrexate alone (83–85 vs 50%; $p \leq 0.004$).

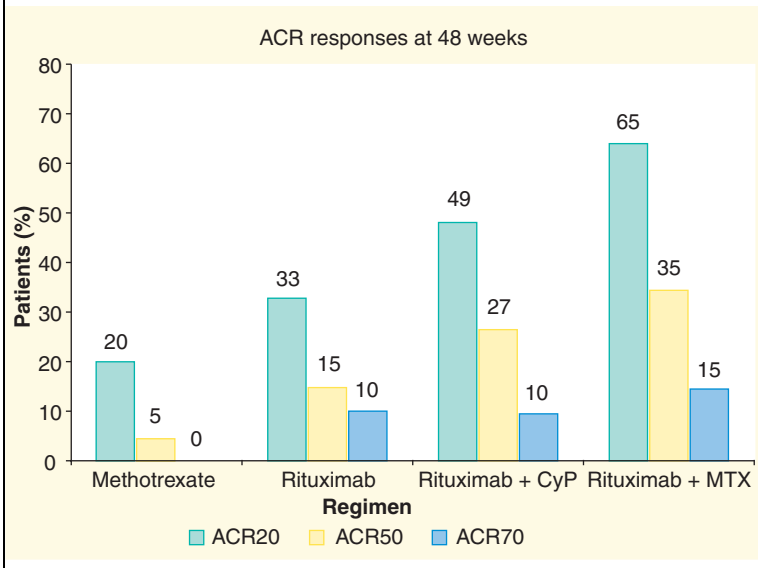
Rituximab treatment appeared to be associated with almost complete depletion of peripheral blood B cells, which lasted throughout the 24-week study period. Mean values for IgG, IgM and IgA remained within normal levels, although those of IgM did decline. There was no effect on antitetanus antibody titers.

Phase IIb study: efficacy & safety

The Dose-ranging Assessment: iNternational Clinical Evaluation of Rituximab in RA (DANCER) study was a multicenter, randomized, controlled, double-blind study of a similar patient group to that in the Phase IIa study discussed previously [34]. A total of 465 patients were treated, of whom 380 were RF positive and 85 were RF negative. All patients received background methotrexate (all had active disease despite methotrexate therapy). They were randomized to receive either placebo therapy or rituximab (0.5 or 1 g on days 1 and 15) with or without intravenous and/or oral corticosteroids. Intravenous steroids were administered as 100 mg methylprednisolone before rituximab/placebo infusions on days 1 and 15; the oral steroid regimen was 60 mg on days 2–7 and 30 mg on days 8–14. The primary efficacy end point was the proportion of RF-positive patients with an ACR20 response 24 weeks after treatment (**Figure 4**).

The proportion of patients achieving the primary end point was significantly higher in patients receiving rituximab than placebo (55.3% with lower dose rituximab and 54.1% with higher dose rituximab vs 27.9%; $p < 0.001$). The corticosteroid regimen had no significant impact on ACR response at the primary end point. ACR50 and ACR70 responses were consistent with those observed for ACR20. ACR50 responses were similar for both rituximab doses (33% with the lower dose and 34% with the higher dose), but ACR70 responses were slightly higher in the higher dose group (20 vs 13%, which was not significant). With regard to EULAR responses, rituximab treatment significantly improved responses when compared with placebo ($p < 0.001$). There was no statistically significant difference between different doses of rituximab with respect to EULAR response, although a higher proportion of patients

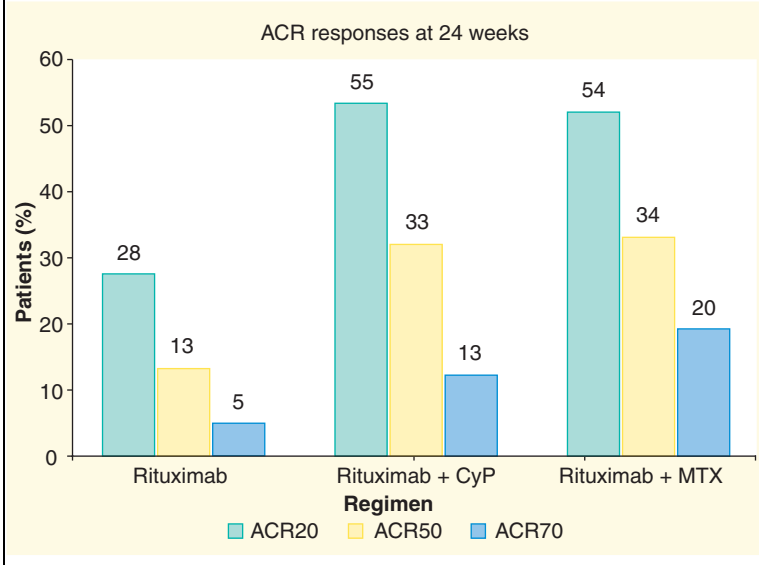
Figure 3. ACR clinical responses at week 48 in the first Phase IIa randomized study.



Data taken from [29].
ACR: American College of Rheumatology; CyP: Cyclophosphamide; MTX: Methotrexate.

treated with the higher dose of rituximab achieved a 'good' response by EULAR criteria (27.9, 13.8 and 4.1% for higher dose, lower dose and placebo, respectively).

Figure 4. ACR clinical responses at week 24 in DANCER.



Data taken from [34].
ACR: American College of Rheumatology; CyP: Cyclophosphamide; DANCER: Dose-ranging Assessment: International Clinical Evaluation of Riuximab in rheumatoid arthritis; MTX: Methotrexate.

The DANCER study confirmed the efficacy of rituximab in RA. There was no significant difference between both doses of rituximab (0.5 and 1 g on days 1 and 15) in terms of efficacy, although there were trends in favor of the higher dose for some efficacy outcome measures. The use of oral corticosteroids appeared unnecessary in terms of improving outcomes, but intravenous corticosteroids did reduce the incidence of infusion reactions.

Phase III study: efficacy & safety of rituximab in patients with an inadequate response or lack of tolerance to prior anti-TNF therapy

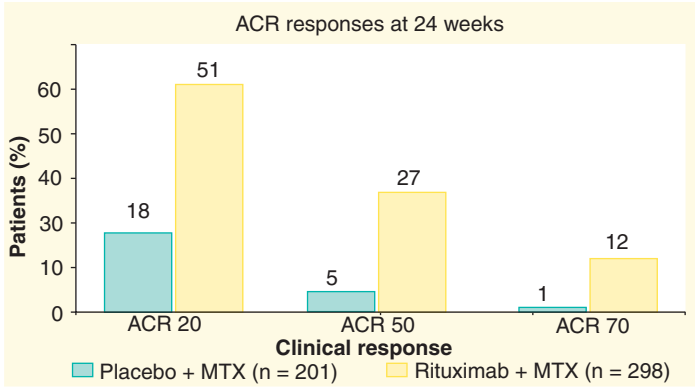
The Randomized Evaluation oF Long-term Efficacy of rituXimab in RA (REFLEX) multicenter, randomized, double-blind, placebo-controlled study was designed to evaluate the efficacy and safety of rituximab when used in conjunction with methotrexate in RA patients who had experienced an inadequate response to one or more anti-TNF-α agents (due to either inefficacy or toxicity) and had active disease, despite treatment with methotrexate and a TNF-α inhibitor [35]. Patients were randomized to either two doses of rituximab 1 g (on days 1 and 15) or placebo. All patients received 100 mg methylprednisolone prior to each infusion and oral prednisolone between each infusion (60 mg/day on days 2–7 and 30 mg/day on days 8–14). The primary end point was the proportion of patients with ACR20 response at week 24 (**Figure 5**).

A total of 499 patients comprised the primary intent-to-treat efficacy population. This included both RF-positive (81%) and -negative patients. The mean baseline data indicated that patients had severe, active disease – mean disease duration was 12 years; swollen joint count was 23; disease activity score by 28 joint count (DAS28) [33] was 6.9 (a value of 5.1 is regarded as the minimum to warrant biological therapy in some practices, 2.6 is regarded as indicating disease remission).

Efficacy of rituximab on clinical outcomes

At 24 weeks, there was a significant difference between the two arms in the proportion of patients reaching the primary end point of ACR20 response: 51 versus 18% for the rituximab and placebo arms, respectively ($p < 0.0001$). With regards to ACR50 and 70 responses, these were also significantly increased in rituximab-treated patients (27 vs 5% and 12 vs 1% for ACR50 and 70, respectively;

Figure 5. ACR clinical response at week 24 in REFLEX.



ACR: American College of Rheumatology; MTX: Methotrexate; n: Number of patients; REFLEX: Randomized Evaluation oF Long-term Efficacy of rituXimab in rheumatoid arthritis.

$p < 0.0001$ compared with placebo). Similarly, the proportion of patients with either moderate or good EULAR response was significantly higher in those who had received rituximab (65 vs 22%; $p < 0.0001$). At week 24, 12% of patients receiving rituximab had withdrawn due to lack of efficacy in comparison with 40% of those receiving placebo.

Efficacy of rituximab on patient-reported outcomes

Patient-reported outcomes included: physical function, measured by HAQ; fatigue, measured by functional assessment of chronic illness therapy – fatigue; and mental and physical health, measured using short form (SF)36. A fall in HAQ score of 0.25 or greater was defined as a clinically relevant improvement. A total of 50.7% of rituximab-treated patients achieved this compared with 19.9% of those receiving placebo. Results in the physical health domains of SF36 and fatigue were also significantly better for rituximab when compared with placebo ($p < 0.0001$).

Efficacy of rituximab on radiographic outcomes

At 24 weeks the following exploratory radiographic outcomes were studied: mean changes in Sharp–Genant total score, erosion score and joint space narrowing score. There was a significant improvement in joint space narrowing in the rituximab arm compared with placebo ($p = 0.0156$). Other scores showed a trend to improvement in the rituximab-treated group over placebo. However, it should be noted that most of the patients in both groups had no change in their erosion score. This is perhaps expected over a 6-month period in a group of patients with long-standing disease. It is also likely that the study was underpowered to show an outcome over this short period.

The results of the pivotal, Phase III, REFLEX study demonstrated the efficacy of rituximab therapy in patients with severe disease who had failed to respond to, or were unsuitable for, anti-TNF therapy.

Safety & tolerability

The overall adverse event profile in the three studies described above was consistent with that seen in the NHL population treated with rituximab [36]. No new or unexpected findings were seen in the RA population when compared with the NHL population.

In the Phase III study, the proportion of patients reporting an adverse event was similar for rituximab- and placebo-treated groups. Most of these events were mild or moderate in severity. The most common disorders in both groups were nonserious infections (i.e., not warranting hospital admission or intravenous antibiotics), which were more frequent in rituximab-treated patients (40 vs 34%).

Most of the adverse reactions occurred during or immediately after the first infusion of rituximab (15% of patients in REFLEX). Infusion-related events included pruritus, urticaria, pyrexia, throat irritation and hypertension. However, in rituximab-treated patients, it has been suggested that these reactions might be due to cytokine release following B-cell lysis. The incidence of adverse events following the second infusion is much lower than after the first. This may be because B-cell numbers are already significantly reduced after the first infusion. The lower rate of infusion reactions in RA patients compared with NHL patients is also related to this, as the latter group often have a heavier B-cell load before therapy. A small number of patients (<1%) experienced a serious infusion reaction (e.g., anaphylaxis, bronchospasm). Patients were less likely to experience an infusion reaction if they received premedication with intravenous corticosteroids and if they received the lower dose of rituximab (0.5 g). Patients who suffered an infusion reaction were treated by slowing or stopping the infusion and, if needed, antipyretics, antihistamines and corticosteroids were administered.

With regard to infections, most of those reported were minor and were largely upper respiratory or urinary tract infections. The only

infections to show an absolute increase over placebo of at least 1% were upper respiratory tract infections (7 vs 6%) and rhinitis (3 vs 2%). The incidence of serious infections compared with placebo was 2 versus 1%. Hepatitis virus reactivation has not been reported, unlike in other rituximab-treated patient groups, although screening for, and treatment of, hepatitis B and C prior to therapy is recommended. A small number of patients with either a history of tuberculosis or who had a positive purified protein derivative test have been treated with rituximab and there was no evidence of reactivation of tuberculosis.

The Phase IIa data indicate that approximately 5% of patients developed human anti-chimeric antibodies (HACA) at various time points after therapy. The presence of HACA did not appear to have significant clinical consequences, either in terms of response to or development of infusion reactions following further treatment with rituximab.

B-cell depletion, reconstitution & retreatment

Initial conventional flow cytometry analysis suggests that there is near complete depletion of B cells from the peripheral blood following rituximab therapy in almost all patients. This being so, there appears to be no correlation between B-cell depletion and clinical response. In terms of B-cell reconstitution, data from the initial Phase IIa study are most extensive, with patients now being followed for up to 2 years. The data suggest that B cells begin to rise 6–12 months after treatment in most patients. Across the enitre patient population, there appears to be no clear correlation between the return of B cells and the reactivation of disease (defined by factors such as worsening swollen and tender joint counts) at specific time points. However, in individual patients, the phenomenon of B-cell counts rising with concurrent disease relapse is well observed. Patients who experienced such relapses following the initial response were identified on clinical grounds and entered into retreatment protocols. Most patients who received retreatment did so when their B-cell levels were lower than before their first exposure to rituximab. Retreatment has generally been well tolerated and effective [37]. A significant number of patients from the initial study (45% of those receiving one cycle of rituximab with continuing methotrexate) did not appear to have reactivation of disease, as judged by a lack of requirement for additional therapy and improvements in physical function at 2 years after therapy [38,39]. However, it should also be noted that the median time to retreatment in the Phase IIa study was 12 months and this may have been biased by a slower tendency to retreat early in the study. In the small number of patients who had prolonged B-cell depletion for up to 2 years after therapy, there was no increase in the rates of infection. The median duration of B-cell depletion in patients who experienced infections was similar to that in patients who did not have infections. It is not yet known for certain how and if B-cell depletion should affect future treatment decisions in patients who have not responded to rituximab.

Regulatory affairs

Rituximab was licensed in the USA in March 2006 for use in patients with active RA refractory to treatment with anti-TNF-α agents. Licence applications under similar terms are currently being considered by the appropriate regulatory authorities in the EU.

Conclusions

Data from the the pivotal Phase III study, supported by results from the Phase II studies, indicate that B-cell depletion with rituximab may be safe and effective for the treatment of RA in a variety of patient groups. Most strikingly, rituximab appears to be of clinical benefit in patients who have disease refractory to the most effective, currently licensed therapies, including TNF inhibitors. Two infusions of either 500 mg or 1 g rituximab, with prior methylprednisolone, appear to deplete B cells successfully. Clinical responses, both objective and patient reported, can be prolonged. Retreatment with rituximab also appears to be safe and well tolerated.

The duration of response to rituximab, and factors affecting this, are not yet fully elucidated. Initial data regarding retreatment of patients who fulfilled certain clinical criteria that indicated an initial response with subsequent decline, suggest a median time to retreatment of 12 months. The effect of rituximab on the radiographic progression of the disease is not yet clear and the longer term effects of either prolonged or repeated B-cell depletion are not yet fully elucidated. No direct comparison of rituximab with anti-TNF-α agents has been undertaken. However, the efficacy of rituximab, particularly in patients with few therapeutic options, combined with its safety profile, suggest that this agent is likely to provide significant benefit for RA patients.

Future perspective

The development of anti-TNF-α therapy for RA transformed the treatment of this severe, chronic disease. At the same time, it became clear that early diagnosis and treatment was of much greater importance than previously thought. The development of rituximab as a therapy for RA has led to a shift in understanding, with increased knowledge of the potential roles of B cells in RA. Current data provide some support for the use of rituximab in severe, refractory disease, where new therapeutic options could provide for as yet unmet needs. The data set from this patient group is likely to expand in the near future. However, the novel focus on B cells in the pathogenesis of RA has wider implications, in that B-cell depletion or modulation may be most effective earlier in the disease process.

Much has yet to be understood regarding rituximab itself and its best use in RA. Data regarding use of monoclonal antibodies in hematological malignancies suggest that conventional assessment of B-cell depletion may not reveal the whole picture following treatment [40]. More sensitive methods could allow the identification of correlates of response and predictors of relapse. Furthermore, the optimal dosing regimen has yet to be confirmed, either in terms of dose or duration of therapy, as well as what factors should guide retreatment. The mechanism of action of rituximab is not completely understood and further study in peripheral blood and other tissues may shed important light on both the agent itself and pathogenic processes in RA.

When the data presented previously are considered, it seems clear that rituximab is an agent that may significantly affect the treatment of patients with RA. The first such patients for whom the agent is now licensed are those with RA who have had an inadequate response following anti-TNF therapy.

Executive summary

Mechanisms of action

- Rituximab is the first B-cell depleting agent to be used in rheumatoid arthritis (RA).
- B cells may play a variety of roles in the pathogenesis of RA: autoantibody production, antigen presentation, cytokine release and T-cell activation.

Dosage & administration

- Two intravenous infusions of rituximab are given on days 1 and 15 of treatment. Both 500 mg and 1 g rituximab at each infusion have been used in studies. Treatment with 100 mg methylprednisolone by intravenous infusion is recommended immediately prior to the infusion of rituximab.
- Rituximab is given as a slow infusion over 4–6 h.

Clinical efficacy

- The clinical efficacy of rituximab in RA has been demonstrated in randomized, placebo-controlled trials in patients who have active disease despite receiving conventional therapy and/or antitumor necrosis factor agents
- Rituximab appears to be most effective when combined with methotrexate.
- Rituximab has beneficial effects on objective and patient-reported clinical outcomes.
- Benefits can last for 12 months or longer.

Safety

- An increase in the incidence of infections of 1% above placebo is observed in B-cell depleted patients.
- Most of the adverse reactions are infusion reactions and of mild-to-moderate severity. Their incidence is reduced by the use of corticosteroids. Such reactions are much less common with the second infusion and repeated cycles.
- Retreatment with rituximab in patients who have responded to an initial course appears safe and effective, on the basis of data available so far.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. American College of Rheumatology Subcommittee on Rheumatology Guidelines: Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum.* 46, 328–346 (2002).
2. Scott DL, Symmons DP, Coulton BL, Popert AJ: Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1, 1108–1111 (1987).
3. St Clair EW, van der Heijde DMFM, Smolen JS *et al.*: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomised, controlled trial. *Arthritis Rheum.* 50, 3432–3443 (2004).
4. Suarez-Almazor ME, Osiri M, Emery P: Rheumatoid arthritis. Evidence-based rheumatology. *Br. Med. J.* 243–282 (2004).

• **Reviews the objective evidence for efficacy of conventional disease-modifying antirheumatic drugs.**

5. Chu CQ, Field M, Feldmann M, Maini RN: Localization of tumor necrosis factor α in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. *Arthritis Rheum.* 34(9), 1125–1132 (1991).
6. Maini R, St Clair EW, Breedveld F *et al.*: Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised Phase III trial. ATTRACT Study Group. *Lancet* 354(9194), 1932–1939 (1999).
7. van der Heide D, Klareskog L, Rodriguez-Valverde V *et al.*: Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* 54(4), 1063–1074 (2006).
8. Breedveld F, Weisman MH, Kavanaugh AF *et al.*: The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 54(1), 26–37 (2006).
9. Bresnihan B, Alvaro-Gracia JM, Cobby M *et al.*: Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum.* 41(12), 2196–2204 (1998).
10. Moreland L: Unmet needs in rheumatoid arthritis. *Arthritis Res. Ther.* 7(Suppl. 3), S2–S8 (2005).
11. Malmstrom V, Trollmo C, Klareskog L: The additive role of innate and adaptive immunity in the development of arthritis. *Am. J. Med. Sci.* 327, 196–201 (2004).
12. van der Lubbe PA, Dijkmans BA, Markusse HM, Nassander U, Breedveld FC: A randomised double-blind, placebo-controlled study of CD4 monoclonal antibody therapy in early rheumatoid arthritis. *Arthritis Rheum.* 38(8), 1097–1106 (1995).
13. Kremer JM, Westhovens R, Leon M *et al.*: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N. Engl. J. Med.* 349, 1907–1915 (2003).
14. Genovese MC, Becker JC, Schiff M *et al.*: Abatacept for rheumatoid arthritis refractory to tumour necrosis factor α inhibition. *N. Engl. J. Med.* 353, 1114–1123 (2005).
15. Silverman GJ, Carson DA: Roles of B cells in rheumatoid arthritis. *Arthritis Res. Ther.* 5(Suppl. 4), S1–S7 (2003).
16. Zhang Z, Bridges SL Jr: Pathogenesis of rheumatoid arthritis: role of B lymphocytes. *Rheum. Dis. Clin. North Am.* 27, 335–353 (2001).
17. Choy EH, Panayi GS: Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med.* 344, 907–916 (2001).
18. Takemura S, Klimiuk PA, Braun A *et al.*: T cell activation in rheumatoid synovium is B cell dependent. *J. Immunol.* 167, 4710–4718 (2001).
19. Edwards JC, Cambridge G, Abrahams VM: Do self-perpetuating B lymphocytes drive human autoimmune disease? *Immunology* 97(2), 188–196 (1999).
20. Edwards JC, Cambridge G: Prospects for B-cell-targeted therapy in autoimmune disease. *Rheumatology* 44(2), 151–156 (2005).

• **Review of current and novel theories regarding the role of B cells and methods of modulation.**

21. Einfeld DA, Brown JP, Valentine MA *et al.*: Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. *EMBO J.* 7, 711–717 (1988).
22. Valentine MA, Meier KE, Rossie S *et al.*: Phosphorylation of the CD20 phosphoprotein in resting B lymphocytes. Regulation by protein kinase C. *J. Biol. Chem.* 264, 11282–11287 (1989).
23. Stashenko P, Nadler LM, Hardy R *et al.*: Characterisation of a human B lymphocyte specific antigen. *J. Immunol.* 125, 1678–1685 (1980).
24. Press OW, Appelbaum F, Ledbetter JA *et al.*: Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. *Blood* 69, 584–591 (1987).
25. Reff ME, Carner K, Chambers KS *et al.*: Depletion of B cells *in vivo* by a chimeric mouse human monoclonal antibody to CD20. *Blood* 83, 435–445 (1994).
26. Demidem A, Lam T, Alas S *et al.*: Chimeric anti-CD20 monoclonal antibody sensitises a B cell lymphoma cell line to cell killing by cytotoxic drugs. *Cancer Biother. Radiopharm.* 12, 177–186 (1997).
27. Cartron G, Watier H, Golay J, Solal-Celigny P: From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 104, 2635–2642 (2004).
28. Czuczman MS: Combination chemotherapy and rituximab. *Anticancer Drugs* 12(Suppl. 2), S15–S19 (2001).
29. Edwards JC, Szczepanski L, Szechinski J *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N. Engl. J. Med.* 350, 2572–2581 (2004).

•• **First randomized, controlled trial of rituximab in rheumatoid arthritis (RA).**

30. Edwards JC, Cambridge G: Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology* 40, 205–211 (2001).
31. Felson DT, Anderson JJ, Boers M *et al.*: American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis *Arthritis Rheum.* 38(6), 727–735 (1995).
32. Leandro MJ, Edwards JC, Cambridge G: Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Ann. Rheum. Dis.* 61, 883–888 (2002).
33. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/ International League Against Rheumatism Criteria. *Arthritis Rheum.* 39(1), 34–40 (1996).

34. Emery P, Fleischmann RM, Filipowicz-Sosnowska A *et al.*: The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment:results of a Phase IIb double-blind, placebo-controlled, dose-ranging trial (DANCER) *Arthritis Rheum.* 54(5), 1390–1400 (2006).

•• **First Phase IIb study of rituximab in RA.**

35. Cohen SB, Emery P, Greenwald M *et al.*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum.* (2006) (In press).

•• **Pivotal Phase III study of rituximab in RA.**

36. Hainsworth JD: Safety of rituximab in the treatment of B cell malignancies: implications for rheumatoid arthritis. *Arthritis Res. Ther.* 5(Suppl. 4), S12–S17 (2003).

37. Fleischmann RM, Pavelka K, Baldassare AR *et al.*: Preliminary efficacy results of rituximab retreatment in patients with active rheumatoid arthritis. *Arthritis Rheum.* 51(Suppl. 9), S264 (2005).

38. Emery P, Sheeran T, Lehane PB, Saiedabadi N, Shaw TM: Efficacy and safety of rituximab at 2 years following a single treatment in patients with active rheumatoid arthritis. *Arthritis Rheum.* 50(Suppl. 9), S659 (2004).

39. Strand V, Balbir-Gurman A, Pavelka K *et al.*: Two year improvements in physical function reflect sustained benefit in rheumatoid arthritis patients receiving a single course of rituximab with methotrexate. *Ann. Rheum. Dis.* 64(Suppl. 3), 208 (2005).

40. Moreton P, Kennedy B, Lucas G *et al.*: Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *J. Clin. Oncol.* 23(13), 2971–2979 (2005).

Affiliations

- *Shouvik Dass, MA, MRCP*
  Academic Unit of Musculoskeletal Disease, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, UK
  Tel.: +44 113 392 4884;
  Fax: +44 113 392 4991;
  shouvikdass@yahoo.co.uk
- *Edward M Vital, MRCP*
  Academic Unit of Musculoskeletal Disease, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, UK
  Tel.: +44 113 392 4884;
  Fax: +44 113 392 4991;
- *Paul Emery, MA, MD, FRCP,*
  Arthritis Research Campaign Professor of Rheumatology, Academic Unit of Musculoskeletal Disease, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA,UK
  Tel.: +44 113 392 4884;
  Fax: +44 113 392 4991;
  p.emery@leeds.ac.uk