B-cell-targeted therapy in rheumatic diseases

Anna P Risselada & Cees GM Kallenberg†
†Author for correspondence
Department of Rheumatology & Clinical Immunology, University Medical Center, Groningen, and, University of Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands Tel.: +31 503 612 945; Fax: +31 503 619 308; c.g.m.kallenberg@int.umcg.nl

During the last decade, the role of B cells in the pathogenesis of autoimmune diseases has been highlighted. Treatment selectively targeting B cells has been made available through the development of (humanized) monoclonal antibodies. Rituximab (anti-CD20) depletes mature B cells and has been successfully used in several systemic autoimmune diseases. At present, only one randomized controlled trial has been performed, and more trials are planned. Additionally, other B-cell targeting monoclonals, such as epratuzumab (anti-CD22) and belimumab (anti-BLyS/BAFF) are being tested. In this article, the presently published (open) studies using these monoclonal therapies are reviewed and future perspectives in this area are discussed.

Autoantibodies are present in many autoimmune diseases, and some are thought to play an important role in their pathogenesis, as suggested by the correlation between autoantibody titers and disease activity [1]. B cells, being the progenitors of antibody-producing plasma cells, are, therefore, naturally implicated in the pathogenesis of diseases as systemic lupus erythematosus (SLE) and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. In other diseases, such as rheumatoid arthritis and Sjögren’s syndrome, emphasis has been on T cells. However, research from the last decade has demonstrated that the role of B cells in the pathogenesis of autoimmune diseases may reach beyond autoantibody production alone [2].

B cells may contribute to autoimmunity by presenting self-antigens to autoreactive T cells involved in the disease process, thereby promoting T-cell proliferation. Additionally, B cells can produce reactive oxygen intermediates and inflammatory cytokines, such as interleukin (IL)-10, and upregulate costimulatory molecules and Toll-like receptors on the cell membrane of T cells. Through these mechanisms, B cells provide support to T cells and other immune cells, and, in turn, stimulate their production of cytokines and chemokines. All these processes can enhance pathological immune responses to self-antigens, and promote germinal center formation and the production of high-affinity autoantibodies [3].

Although mortality and morbidity from autoimmune diseases have decreased over the years, the treatment of autoimmune diseases is still not satisfying. Many patients require continuous or temporary immunosuppressive therapy. The available treatment regimens suppress the whole immune system, with increased risk of serious and opportunistic infections. Therefore, therapies targeting the specific pathogenic pathways are needed. With regard to pathogenesis, it appears to be logical to try to selectively target B cells. Fortunately, developments in the research of cancer therapy have provided us with monoclonal antibodies that selectively deplete mature B cells [4].

In the past 5 years, rituximab (RTX; anti-CD 20 antibody) has been successfully applied in a number of autoimmune diseases, as will be discussed later. Although most studies were open-label studies dealing with small numbers of patients, the positive results have given way for the conduction of larger controlled trials. Successful repeated treatments with RTX in patients with relapsed SLE have also been described. Following the successful treatment of rheumatoid arthritis (RA) and SLE with RTX, other B-cell targeted therapies have been developed and are being tested; for example, epratuzumab (anti-CD 22) and belimumab (Anti B-lymphocyte stimulator [BLyS]; also termed BAFF antibodies). In this review, we discuss presently available studies of rituximab in rheumatic autoimmune diseases, and also the preliminary results of trials with epratuzumab and belimumab.

Rituximab

RTX is a chimeric anti-CD 20 monoclonal antibody, initially registered in 1997 for the treatment of B-cell non-Hodgkin’s lymphoma. CD 20 is a surface antigen that is thought to function in B-cell cycle initiation and differentiation, although its precise function is not yet completely understood. CD 20 is present only on pre-B and mature B cells. Stem cells and plasma cells do not
express CD20 and are therefore not depleted. B-cell lysis probably results from complement activation, antibody-dependent cellular cytotoxicity, induction of apoptosis and Fcγ-receptor pathways [4,5]. RTX depletes B cells from the peripheral blood for a mean duration of 6 months, although some patients remain depleted for more than 2 years (ranging from 1 month to 4 years). The safety profile of RTX appears to be favorable, with only mild infusion reactions and no clear increased risk of major infections [4]. This has made RTX an interesting option in the treatment of autoimmune diseases with a pathogenic role for B cells.

**RTX in rheumatoid arthritis**

Treatment with RTX has been successful in a few uncontrolled studies, on small numbers of RA patients resistant to other treatment [6–10]. High total dosage of RTX and concomitant treatment with cyclophosphamide appeared more successful than low dosage of RTX or RTX monotherapy [8]. In 2004, the first randomized, double-blind, controlled study has been published, which confirmed the positive results of open studies (Table 1) [11].

In a multicenter trial, a total of 161 patients were randomly assigned to treatment with methotrexate alone (control group), RTX

### Table 1. Summary of study protocols and results of relevant studies treating rheumatoid arthritis patients with rituximab.

<table>
<thead>
<tr>
<th>Study</th>
<th>n tested</th>
<th>Study design</th>
<th>Follow-up time (weeks)</th>
<th>Intervention</th>
<th>Outcome (effect n/ total n or percentage of effectiveness)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 40) RTX (2 x 1000 mg) + pr</td>
<td>ACR 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 40) RTX (2 x 1000 mg) + MTX + pr</td>
<td>ACR 20, 50, 70 (at 48 weeks: 20, 50, 70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 41) RTX (2 x 1000 mg) + CX + pr</td>
<td>ACR 20, 50 (at 48 weeks: 20,50)</td>
<td></td>
</tr>
<tr>
<td>Leandro MJ (2002)</td>
<td>22</td>
<td>Open</td>
<td>24 (including retreatment)</td>
<td>RTX (4 x 350 mg/m²) + CX + pr</td>
<td>ACR 70 (three of five), 50 (two of five)</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RTX (1 or 2 x 300 mg/m²) + pr</td>
<td>ACR 20 (one of four)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RTX (2 x 350 mg/m²) + CX + pr</td>
<td>ACR 70 (six of ten), 50 (two of ten)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RTX (4 x 350 mg/m²) + CX + pr</td>
<td>ACR 70 (two of six), 50 (two of six)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RTX (1 x 500 mg/m²) + CX + pr</td>
<td>ACR 0 (four of four)</td>
<td></td>
</tr>
<tr>
<td>Kneitz C (2004)</td>
<td>5</td>
<td>Open</td>
<td>22 + (44)</td>
<td>RTX (4 x 375 mg/m²) (MTX)</td>
<td>Five of five DAS28 ≥ 1.2 point improved (at 44 weeks: one of five DAS28 ≥ 1.2)</td>
<td>[6]</td>
</tr>
<tr>
<td>Higashida J (2005)</td>
<td>13</td>
<td>Open</td>
<td>16 + (28)</td>
<td>RTX (4 weeks, 1 x 100 mg, 1 x 375 mg/m² and 2 x 500 mg/m²) + pr (+ DMARD)</td>
<td>ACR 20: 50% (at 28 weeks: 67%); ACR 50: 42% (at 28 weeks: 33%); ACR 70: 25% (at 28 weeks: 17%)</td>
<td>[7]</td>
</tr>
<tr>
<td>de Vita S (2002)</td>
<td>5</td>
<td>Open</td>
<td>52</td>
<td>RTX (4 x 375 mg/m²) + low pr</td>
<td>ACR 70 (one of five), 50 (one of five), 20 (two of five)</td>
<td>[9]</td>
</tr>
<tr>
<td>Gottenberg J-E (2005)</td>
<td>14</td>
<td>Open</td>
<td>&gt;8</td>
<td>(n = 8) RTX (4 x 375 mg/m²) or (n = 6) RTX (2 x 1000 mg) + pr (+ DMARD)</td>
<td>ACR 50 (11 of 14)</td>
<td>[10]</td>
</tr>
</tbody>
</table>

ACR 0: No effect; ACR 20, 50, 70: American Committee of Rheumatism criteria of efficacy, percentage of disease improvement compared with baseline; CX: Cyclophosphamide; DAS 28: Disease activity score counting 28 joints; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; pr: Prednisone; RCT: Randomized controlled trial; RTX: Rituximab.
monotherapy (two infusions of 1000 mg, 2 apart), RTX plus methotrexate or RTX plus cyclophosphamide. At 24 weeks, patients treated with RTX in combination with methotrexate or cyclophosphamide achieved American Committee of Rheumatism (ACR)50 responses (50% improvement from baseline) more often than patients treated with methotrexate monotherapy (43 and 41% vs 13%, respectively). The frequency of ACR20 responses (20% improvement from baseline) was significantly higher in all RTX regimens. In the RTX–methotrexate group, significantly more patients achieved ACR70 responses (23 vs 5%). Additionally, all the RTX groups demonstrated significantly larger improvements in Disease Activity Scores (DAS) and EUropean League Against Rheumatism (EULAR) responses, measuring disease activity by counting involved joints. At 48 weeks, RTX–methotrexate still demonstrated significantly higher ACR20, 50 and 70 responses than methotrexate monotherapy, and RTX–cyclophosphamide resulted in significantly higher ACR20 and 50 responses than methotrexate monotherapy [10]. This study demonstrated that RTX, especially in combination with MTX, is more effective than MTX monotherapy in treating RA patients.

RTX in systemic lupus erythematosus

At present, only open, uncontrolled studies treating small numbers of therapy-resistant SLE patients are available [10,12–14]. The inherent heterogeneity of a group of SLE patients renders it difficult to provide general statements about effectiveness in SLE, especially since inclusion criteria regarding disease severity and specific organ involvement differed between studies. Additionally, different treatment protocols and disease activity scores were used. However, the results appear to be promising (Table 2).

In the largest study, 24 SLE patients were treated with two 500 mg RTX infusions (six patients) or 1000 mg 2 weeks apart (18 patients) in combination with pulse intravenous cyclophosphamide and corticosteroids. Of these patients, 23 reached B-cell depletion and significant clinical improvement, as measured by the British Isles Lupus Assessment Group (BILAG) score at 6 months [12].

In a dose-escalation trial, 17 SLE patients were treated with different regimens of RTX monotherapy and pretreatment with prednisone to minimize infusion reactions. Only four patients received a dosage of four weekly infusions of 375 mg/m² RTX, the remaining patients receiving less medication. B cells were successfully depleted in 11 of 17 patients, and only these patients had significant clinical improvement up to 12 months after treatment as measured by systemic lupus activity measure (SLAM) scores [13]. Several small, open studies demonstrated effectiveness in SLE patients with CNS disorders, nephritis, skin disease and other SLE manifestations [14–16]. Randomized, controlled trials are underway.

RTX in vasculitis

RTX proved to be effective in several types of autoimmune vasculitis, including Wegener’s granulomatosis (WG), giant cell arteritis and Type II mixed cryoglobulinemia. In an open study, 11 patients with therapy-resistant ANCA-associated vasculitis (Wegener’s granulomatosis and microscopic polyangiitis) were treated with four weekly infusions of 375 mg/m² RTX and prednisone. Following treatment, disease remission was achieved in all patients, as measured by Birmingham Vasculitis Activity Score (BVAS)/WG scores, and prednisone could be tapered down. During B-cell depletion remission persisted. Additionally, cANCA (PR3) antibody levels decreased in all patients, with eight out of 11 patients becoming cANCA negative. Following the return of B cells, some patients remained in remission and cANCA negative, while others experienced a relapse with increasing levels of cANCA [17].

In another open study, 15 patients with therapy-resistant Type II mixed cryoglobulinemia were treated with four weekly infusions of 375 mg/m² RTX and low- to medium-dose prednisone. Of these 15 patients, 12 had associated chronic hepatitis C virus infection. Following treatment, a rapid response in cutaneous vasculitis was observed in all patients with disappearance of purpura and urticaria, and healing of ulcers. Additionally, arthralgias and neuropathic pain improved. Levels of rheumatoid factor and cryoglobulins had decreased significantly, while levels of complement C4 had increased. In most patients, improvement lasted for more than 6 months [18].

RTX in other rheumatic diseases

Besides RA and SLE, RTX has been successfully applied in a number of other autoimmune diseases (Box 1).

In Sjögren’s syndrome (SS), successful treatment with RTX has been described. In an open-label Phase II study, eight patients with early primary SS and seven with primary SS associated with
mucosa-associated lymphoid tissue (MALT)-type lymphoma were treated with four weekly infusions of 375 mg/m² RTX. B-cell depletion led to improvement of subjective and objective parameters of disease activity, including salivary and lacrimal gland function. This was observed in patients with early primary SS as well as patients with MALT/primary SS with residual gland function [19].

In another open study, six SS patients were treated with a course of four weekly infusions of 375 mg/m² RTX and low-dose prednisone. RTX proved to be effective with partial remissions in five of six patients, who demonstrated regression of parotid swelling and articular involvement, and improvement in subjective dryness and cryoglobulinemia-related vasculitis when present before treatment [10].

In an open study, six patients with therapy-resistant dermatomyositis were treated with four weekly infusions of 375 mg/m² RTX, and continued concomitant medication (mostly corticosteroids). Following treatment, all patients demonstrated decreased creatine phosphokinase (CPK) levels and experienced a more than 12% increase in muscle strength (criterion of effectiveness), as measured by quantitative dynamometry in 18 different muscle groups. Additionally, rashes and alopecia improved. Following B-cell return, muscle strength decreased in four patients, while the other two remained in remission [20].

Mechanisms

Full B-cell depletion following RTX appears to be a requirement to achieve improvement in clinical disease. Additionally, higher dosage of RTX and combination therapy with methotrexate or cyclophosphamide are more likely to induce both full B-cell depletion and significant clinical improvement. Interestingly, the present studies indicate that RTX improves disease activity in a number of patients with rheumatic diseases (RA, SLE and WG) for a period extending the duration of B-cell depletion. Relapses were often preceded or accompanied by rises in B-cell counts and antibody titers [6–12,15–19]. The observed temporary remissions may be a result of alterations in the immune system induced by B-cell depletion.

Immunoglobulin (Ig) levels of IgG, IgA and IgM remained within the normal range in most patients, with only some minor decreases. However, levels of pathogenic antibodies as anti-double-stranded (ds)DNA antibodies, cANCA (PR3), rheumatoid factor and cryoglobulins decreased significantly [6–12,15–19]. In concordance, levels of complement factors C3 and C4 rose in SLE patients. Notably, levels of specific antiviral or antibacterial antibodies did not decrease significantly (e.g., antibodies to measles, mumps, rubella, diphtheria, pneumococcus or tetanus toxoid) [6,11,13]. These data indicate that B cells producing pathogenic antibodies are rather selectively depleted.
B-cell-targeted therapy in rheumatic diseases – REVIEW

During B-cell depletion in RA and SLE patients, a very small number of residual CD19+ B cells was detected, being mostly memory B cells and plasma cell precursors. Repopulation in RA patients occurred mainly with naive B cells, with increased expression of CD38 and CD5. Patients with high numbers of residual memory B cells experienced a clinical relapse at B-cell recovery [21]. In SLE patients, B-cell depletion normalized the disturbances in peripheral B-cell homeostasis characteristic of active disease, including naive lymphopenia, expansion of a population of IgD/CD27 double-negative cells, the presence of plasma cell precursors and expansion of autoreactive memory B-cell populations [22]. Following B-cell recovery in SLE patients treated with RTX, a downregulation of CD40 and CD80 on B cells has been demonstrated [14]. This indicates that mutual T-cell activation through these costimulatory molecules may be decreased. In another study on SLE patients, decreased expression of CD40L and activation markers CD69 and human leukocyte antigen (HLA)-DR on T cells has been observed following B-cell recovery [15]. These data indicate that RTX affects the immune system beyond B cells.

Safety

Safety profiles in patients treated for autoimmune diseases were comparable to those in patients treated for lymphoma. The risks of infusion reactions and infections were low (occurring in approximately 5–10% of patients) [6–11,13,17,18]. However, a number of infections did occur, some of which were hazardous, including septic arthritis, cystitis, maxillary sinusitis, bronchitis and pneumonia (one fatal) [7–9,11,17]. Infections occurred mostly in patients treated with combinational therapy, including cyclophosphamide or methotrexate [11]. Although these infections were mostly ascribed to the concomitant use of immunosuppressives, it raises some concerns regarding the treatment of immunosuppressed patients.

Another risk associated with RTX is the induction of human antichimeric antibodies (HACA). In patients with autoimmune diseases, the risk of developing HACA following RTX infusion appears to be greater than in patients treated for B-cell lymphoma [7,19]. Presence of HACA carries the risk of inducing serum sickness when RTX treatment is continued. In one study, HACA occurred more often in patients receiving lower RTX dosage and monotherapy, and who have less effective B-cell depletion, a high disease activity and an African-American background [13]. Recently, completely humanized anti-CD20 antibodies have become available.

Other B-cell targeted therapies

Inhibition of BLY5 is another way of targeting B cells. Belimumab is a human monoclonal antibody that inhibits soluble BLY5, a cytokine that promotes B-cell function and survival. In a randomized, double-blind Phase I study, the safety of four different doses (single and double) of belimumab (LymphoStat-B) were tested. Treated SLE patients had stable disease with mild-to-moderate disease activity as measured by SLEDAI. During the follow-up of 84–105 days, all patients in the belimumab group had significant reductions of CD20+ cells (12–47%), and some had reductions in anti-dsDNA or immunoglobulin levels. No changes in SLE disease activity (as measured by SLEDAI)
were observed [23]. Presently, Phase II clinical trials in SLE and RA have been performed, but the results have not been published to date [24]. A Phase III trial in SLE is scheduled.

Besides CD 20, other surface antigens are specific for B cells and can be targeted by antibodies. CD 22 is an inhibitory membrane molecule that causes down-modulation of B-cell receptor signaling. Anti-CD 22 has been used in the treatment of B-cell malignancies. In an open-label pilot study, humanized anti-CD 22 antibodies (epratuzumab) were tested for safety and efficacy in the treatment of SLE. A total of 14 patients with active disease were treated with four doses of 360 mg/m² of epratuzumab, administered every 2 weeks. At the time of publication, the results of 11 patients who had completed the treatment were available. B-cell levels decreased immediately upon treatment, with approximately 60% B-cell depletion at 4 and 12 weeks. Infusions were well tolerated, and three patients had related minor adverse events. There was no evidence of human antiepratuzumab antibodies. SLE disease activity, as measured by BILAG, improved in all patients, with eight of 11 patients achieving over 50% improvement in BILAG score. Levels of immunoglobulins and autoantibodies showed no consistent changes [25].

Conclusion

The importance of B cells in the pathogenesis of autoimmune diseases has gained interest over the last decade, and is underscored by the success of B-cell depleting therapies, regardless of changes in autoantibody levels. RTX (anti-CD 20) has been successfully used in several rheumatic diseases, including RA, SLE and vasculitis. However, at the moment, only one randomized controlled trial is available that demonstrates the efficacy of RTX in RA. More randomized controlled trials are underway.

Disease improvement is dependent on the success of B-cell depletion. This, in turn, appears to be more likely with RTX in combination with methotrexate or cyclophosphamide. Remission can persist while B cells have returned, with findings indicating that RTX can temporarily restore B-cell abnormalities. Relapses often occur, but successful repeated treatment with RTX has also been described.

At present, risks of infections appear to be small. However, no long-term effects are known. An additional risk lies in the formation of antibodies to RTX, which appears to be higher in autoimmune patients than in lymphoma patients. This risk may be smaller with the use of humanized monoclonal antibodies, but remains present. It carries the further risk of developing serum sickness and neutralizing the monoclonal antibodies, rendering treatment less effective.

Additionally, other B-cell-targeting therapies, such as epratuzumab (anti-CD 20) and belimumab (anti-BLyS/BAFF), are being tested. Data remain too limited to draw any conclusions regarding their effectiveness; however, treatment with anti-CD 22 appears to be promising.

Future perspective

The past 5–10 years have demonstrated rapid development of monoclonal antibodies targeting specific parts of the immune system. Initially used in the treatment of lymphoma, the antibodies form promising therapeutic options in the treatment of autoimmune diseases. RTX (anti-CD 20) has been used successfully in several autoimmune diseases. Although its effectiveness has only been established in one randomized, double-blind, controlled trial in RA, the next couple of years will provide us with information from randomized controlled trials in other diseases. Additionally, other B-cell-targeting therapies are being tested, including anti-BLyS and anti-CD 22. The selective interference with the immune system makes it possible to further investigate the precise roles of specific parts of the immune system, and helps elucidate their contributions to the pathogenesis of autoimmune diseases. This may lead to further developments in the treatment of autoimmune diseases.

Nevertheless, some questions remain to be answered. The one randomized controlled trial treating RA patients indicated that RTX monotherapy appears to be less effective than combination therapy with methotrexate or cyclophosphamide. However, treatment protocol consensus remains to be established. Furthermore, most patients demonstrate only temporary disease remissions, which require retreatment at a certain point. Although several courses of RTX have proved to be effective in some cases, the frequency and timing of retreatment remain debatable.

Should treatment be restored at a fixed interval, at the return of B cells or at clinical relapse? Since RTX was registered in 1997, no information has become available regarding the long-term consequences of (repeated) courses. Although the risk of infectious complications appears small, repeated courses or prolonged B-cell depletion may still cause immunosuppression and risk serious and/or opportunistic infections. Future investigations will hopefully answer these questions.
Executive summary

Role of B cells in autoimmune diseases
- The many roles of B cells in autoimmune diseases include the production of autoantibodies, autoantigen presentation, production of cytokines, expression of costimulatory molecules and Toll-like receptors, and supporting and stimulating T cells.

B-cell-targeted therapy
- Anti-CD20 (rituximab) depletes pre-B cells and mature B cells.
- Anti-CD22 (epratuzumab) decreases and interferes with the function of mature B cells.
- Anti-BlyS/BAFF (belimumab) decreases B cells.

Rituximab in rheumatoid arthritis
- Rituximab (RTX) appears to be successful in several small, open-label studies.
- One double-blind, placebo-controlled, randomized trial (161 patients) tested the efficacy of RTX in rheumatoid arthritis (RA).
- The American Committee of Rheumatism (ACR)50 response in RTX–methotrexate-treated patients at 24 weeks was 43%.
- The ACR50 response in RTX–cyclophosphamide-treated patients at 24 weeks was 41%.
- RTX in combination with methotrexate or cyclophosphamide, but not RTX monotherapy, was significantly more successful than methotrexate alone.
- All ACR responses were maintained at week 48 in the RTX–methotrexate group.

Rituximab in systemic lupus erythematosus
- Only a few small, open-label studies are available; RTX appears to be successful in all of these.
- A total of 23 of 24 patients demonstrated British Isles Lupus Assessment Group (BILAG) improvement at 6 months.
- All B-cell-depleted patients (11 of 17) demonstrated systemic lupus activity measure (SLAM) improvement up to 12 months.

Rituximab in vasculitis & other rheumatic diseases
- RTX provided successful treatment in Wegener’s granulomatosis (11 of 11 patients).
- RTX led to improvement in Type II mixed cryoglobulinemia (15 of 15 patients)
- RTX led to symptomatic improvement in Sjögren’s syndrome (15 of 15 and five of six patients).
- RTX led to a temporary improvement in dermatomyositis patients (six of six patients).

Mechanisms
- Disease improvement appears to be dependent upon successful B-cell depletion.
- Remissions can endure while B-cells have returned. This may reflect changes in the immune system beyond B cells.
- Levels of pathogenic autoantibodies decrease, while levels of immunoglobulins and antibacterial and antiviral antibodies remain within normal range in most patients.
- B-cell abnormalities can normalize following B-cell depletion.

Safety
- The risk of infection appears to be small.
- Formation of human antichimeric antibodies occurs more frequently in autoimmune patients than lymphoma patients, and can induce serum sickness and decrease of efficacy.

Other B-cell-targeted therapies
- Only pilot studies are available, other studies are being conducted.
- Belimumab (anti-BlyS/BAFF) proved safe in stable systemic lupus erythematosus patients.
- B cells decreased significantly following belimumab, some patients had decreases in anti-double stranded DNA.
- Epratuzumab (anti-CD22) was effective in all 11 patients, with eight of 11 patients having a more than 50% BILAG score improvement.
- B cells were depleted in 60% following epratuzumab, immunoglobulins and autoantibodies demonstrated no consistent changes.

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

Demonstrates effectiveness of RTX in a

One of the first studies testing the
efficacy of rituximab in patients with
rheumatoid arthritis refractory to disease
modifying antirheumatic drugs and
anti-tumor necrosis factor-α treatment.
J. Rheumatol. 32(11), 2067-2069
(2005).

Leandro JM, Edwards JCW, Cambridge G:
Clinical outcome in 22 patients with
rheumatoid arthritis treated with

One of the first studies testing the
effectiveness of RTX (Rituximab) in
rheumatoid arthritis (RA) in a larger
number of patients.

de Vita S, Zaja F, Sacco S, de Candia A,
Fanin R, Ferraccioli G: Efficacy of selective
B-cell blockade in the treatment of
rheumatoid arthritis - evidence for a
pathogenetic role of B cells.
Arthritis Rheum. 46(8), 2029-2033
(2002).

Gottenberg JÈ, Guillemin L, Lambotte O
et al.: Tolerance and short term efficacy of
rituximab in 43 patients with systemic
64, 913-920 (2005).

Edwards JCW, Szczepanski L, Szczekini J
et al.: Efficacy of B-cell-targeted therapy
with rituximab in patients with rheumatoid
2572-2581 (2004).

Presently the only randomized controlled
trial of RTX treatment in a rheumatic
disease, proving its effectiveness.

Leandro M J, Cambridge G, Edwards JC,
Ehrenstein MR, Isenberg DA: B-cell
depletion in the treatment of patients with
systemic lupus erythematosus: a
longitudinal analysis of 24 patients.

Demonstrates effectiveness of RTX in a
larger number of systemic lupus
erythematosus (SLE) patients, although in
an open uncontrolled series.

Looney RJ, Anolik JH, Campbell D et al.: B
cell depletion as a novel treatment for
systemic lupus erythematosus: a Phase I/II
dose-escalation trial of rituximab.

O ne of the first trials demonstrating
effectiveness of RTX in an open,
uncontrolled study, dose-escalation trial.

Tokunaga M, Fuji K, Saito K et al.: Down-regulation of CD40 and CD 80 on
B cells in patients with life-threatening
systemic lupus erythematosus after successful
treatment with rituximab. Rheumatology 44,
176-182 (2005).

Sfkakis PP, Bolotsi JN, Lionaki S et al.: Remission of proliferative lupus nephritis
following B-cell depletion therapy is preceded
by down-regulation of the T cell costimulatory
molecule CD40 ligand – an open-label trial.

Risselada AP, Kallenberg CGM:
Therapy-resistant lupus skin disease
successfully treated with rituximab.

Keogh KA, Wylam ME, Stone JH, Specks U:
Induction of remission by B lymphocyte
depletion in eleven patients with refractory
antineutrophil cytoplasmic antibody -

Demonstrates effectiveness of RTX in
rheumatoid arthritis in an open series.

Zaja F, de Vita S, Mazzaro C et al.: Efficacy and safety of rituximab in Type II
mixed cryoglobulinemia. Blood 101(10),

Pijpe J, van Hooft GW, Spijkervet FKL et al.: Rituximab treatment in patients with primary
Sjogren's syndrome: an open-label Phase II
study. Arthritis Rheum. 52(9), 2740-2750
(2005).

Demonstrates effectiveness of RTX in
Sjogren's syndrome in an open series.

Levine TD: Rituximab in the treatment of
dermatomyositis - an open-label pilot study.

Leandro M, Cambridge G, Ehrenstein MR,
Edwards JCW: Reconstitution of peripheral
blood B cells after depletion with rituximab
in patients with rheumatoid arthritis.

Affiliations

Anna P Risselada, Resident in Internal Medicine,
University of Groningen, Department of
Rheumatology & Clinical Immunology,
PO Box 30.001, 9700 RB, Groningen,
The Netherlands
Tel.: +31 503 612 945;
Fax: +31 503 619 308;
c.g.m.kallenberg@int.umcg.nl