Rituximab: Use in rheumatoid arthritis

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Abstract
RA has an intricate pathogenesis and several inflammatory mediators can be targeted with treatment. One such a mediator is the B lymphocyte.

B cells act as antigen-presenting cells, secrete proinflammatory cytokines, produce rheumatoid factor autoantibodies and activate T cells. RF autoantibodies play an important role in the pathogenesis of this disease, because they contribute to further release of inflammatory cytokines such as TNF-α. B cell treatment would therefore eliminate the cells responsible for the production of pathogenic autoantibodies and cytokines.

Rituximab is a chimeric monoclonal antibody against the CD20 surface marker on B cells and treatment with it leads to prolonged depletion of normal B cells from peripheral blood. The drug was first registered for non-Hodgkin’s lymphoma, but has been found to be helpful in a number of autoimmune conditions, including rheumatoid arthritis.

Adverse events of rituximab in rheumatoid arthritis are similar to those experienced in patients with non-Hodgkin’s lymphoma, and consist mainly of infusion reactions. Opportunistic infections like TB have not been reported in patients receiving treatment for RA, but testing for hepatitis B and C before starting with rituximab treatment should be considered.

A number of clinical studies have provided evidence of the efficacy and safety of a single course of rituximab in RA, notably the DANCER and REFLEX studies.

Many patients require subsequent treatment courses. Preliminary long-term data for patients who had received ≥ 3 courses show sustained clinical response without substantially more adverse effects, but more investigation on this is required. The average time interval for patients to receive subsequent courses of treatment varies between 6 and 12 months.

Results in terms of improved radiological outcomes after treatment with rituximab seem promising, although there is no direct comparative data with anti-TNFs. In patients who have failed treatment with one anti-TNF agent, there is currently debate as to the choice of a second or even 3rd anti-TNF agent as opposed to rituximab. An observational study seems to suggest a better outcome using rituximab, but randomised controlled trials are required before definite conclusions can be made.

At first glance, cost appears to be a problem with rituximab, but this is also the case with the anti-TNFs, which are currently widely used. It must also be noted that total treatment costs of either drug class are strongly influenced by administration costs and frequency of treatment.

Despite many questions still remaining, rituximab represents a valuable addition to current therapeutic strategies in managing RA.

Introduction
Rheumatoid arthritis (RA) is a chronic, inflammatory disease that can lead to functional disability and diminished quality of life.1,2 Worldwide, an estimated 1% of the population is affected and the condition is associated with a reduced life expectancy.3,4,5 Rheumatoid arthritis is characterised by painful inflammation and swelling of joints, fatigue, morning stiffness and by the irreversible destruction of cartilage, tendons and joints.2,6,7

RA has a complicated pathogenesis and several inflammatory mediators can theoretically be targeted with treatment.5,7,8,9,10,11 In the 1990s, the focus of research has largely been on the T cell mediated immune response and the development of tumour necrosis factor alpha inhibitors (anti-TNFs).5,8,10,11

Anti-TNFs have dramatically improved the outcomes in patients who have failed treatment with traditional disease-modifying antirheumatic drugs (DMARD)s. Yet 20–40% of patients treated with anti-TNFs do not respond adequately, become intolerant or have secondary loss of response.1,3,13 Many patients fail to achieve the goals of preserving joint structure and function and improved overall quality of life.2,3,14

During the last few years the role of B cells in RA has been explored.5,8,12,14 Results from rituximab, an agent used to treat B cell malignancies such as non-Hodgkin’s lymphoma, have been promising. Rituximab is a monoclonal antibody against...
the CD20 surface marker on B cells.\textsuperscript{12,14} It has been approved in the UK, Europe and the USA for use in RA\textsuperscript{1,6,7,15,16} and has also been approved for this indication in the RSA since January 2008.\textsuperscript{17}

Pathogenesis of RA and the role of B cells
The pathogenesis of RA is mediated by an interlinking system of cytokines, prostanoids and proteolytic enzymes. Cytokines regulate the immune response, possessing both proinflammatory and immunosuppressive antiinflammatory properties.\textsuperscript{4,5,18} An imbalance between the proinflammatory and antiinflammatory effects is thought to result in RA.\textsuperscript{2,4,9,18}

B cells act as antigen-presenting cells, secrete proinflammatory cytokines, produce rheumatoid factor (RF) autoantibodies and activate T cells.\textsuperscript{6,7,8,9,14} RF autoantibodies, produced by B cells under influence of activated T cells, play an important role in the pathogenesis of this disease.\textsuperscript{4,5,9,14,18} These autoantibodies are present in 80\% of patients with RA\textsuperscript{8} and activate macrophages, which then release inflammatory cytokines such as TNF-$\alpha$.\textsuperscript{4,5,11} They also promote survival of B cells via complement fixing, or immune complexes.\textsuperscript{11,16} The RF antibody thus appears to be the antigen fuelling T cell responses and further B cell activation. This leads to a vicious circle.\textsuperscript{5,10,11,16,19} Please refer to Diagram 1 for a representation of B cell pathways.

B lymphocytes are produced in the bone marrow.\textsuperscript{12} Phases of development are divided into pre-B, immature B cells, virgin B cells, mature B cells, memory B cells and plasma cells.\textsuperscript{12} CD20 is a cell surface glycoprotein that emerges at pre-B stage and wanes during differentiation to plasma cells.\textsuperscript{5,10,12} CD20 is therefore found on pre-B and mature B lymphocytes, but not on normal plasma cells or stem cells.\textsuperscript{5,7,10,12,14,17} The exact function of CD20 is unknown, but it is believed to be involved in signal transduction and activation of B lymphocytes.\textsuperscript{12}

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**Diagram 1: Role of B cells in pathogenesis of RA**

- **Role of B cells**
  - Antigen presentation
  - Autoantibody production
  - Cytokine production

- **B cell**
  - Cytokines (TNF-$\alpha$, IFN-$\gamma$, IL-$6$)
  - Amplification of inflammation and damage
  - Synovitis, pain and joint destruction

- **CD4 T Cell**
  - Activation of macrophage
  - Release of cytokines and inflammatory mediators

- **Macrophage**
  - Antigen presentation

- **RF**
  - +

- **IL-1, TNF-$\alpha$**
  - +

**Legend**
- IL-1 = Interleukin 1, IL-6 = Interleuken 6, TNF-$\alpha$ = Tumour necrosis factor $\alpha$, RF = Rheumatoid factor, IFN-$\gamma$ = Interferon $\gamma$
Mechanism of action of rituximab
Rituximab is a chimeric (mouse/human) monoclonal antibody that specifically binds to the antigen CD20. After binding to CD20, an immunologic reaction that results in B cell lysis is initiated. Proposed mechanisms of cell destruction are:
- Complement-dependent cytotoxicity
- Antibody-dependent cellular cytotoxicity
- Growth arrest and induction of apoptosis (programmed cell death)

The rationale for using B cell treatment is to eliminate cells responsible for the production of pathogenic autoantibodies. Furthermore, eliminating B cells decreases production of TNF-α by macrophages, decreases T cell activation and decreases T cell dependent synovial inflammation.

Treatment with rituximab leads to prolonged depletion of normal B cells from peripheral blood, but IgG serum levels are generally not altered due to the lack of CD20 on plasma cells. Similarly, IgM and IgA levels also usually remain within normal levels.

History/Indications
Rituximab was first registered for non-Hodgkin’s lymphoma. However, studies have shown benefits of rituximab in a number of refractory autoimmune disorders including rheumatoid arthritis, chronic cold agglutinin disease, systemic lupus erythematosus, haemolytic anaemia, dermatomyositis, antineutrophil cytoplasmic antibody-associated vasculitis, immune thrombocytopenic purpura and mixed cryoglobulinemia.

Dose in RA
A course of rituximab consists of two 1000 mg IV infusions in combination with methotrexate: an initial dose of 1000 mg is administered, followed 2 weeks later by a second 1000 mg dose. Pre-medication with glucocorticoids, and/or antihistamines and antipyretics should be given to lessen infusion reactions.

Further doses are given based on signs and symptoms. In clinical studies, the earliest a patient received a repeat course was 16 weeks after the first infusion. On average most patients receive a second course 6–12 months after the initial course, many even less frequently. Both the South African Rheumatism and Arthritis Association (SARAA) and the UK’s National Institute for Health and Clinical Excellence (NICE) recommend that rituximab should not be given more frequently than every 6 months and NICE states that patients requiring subsequent dosing within 6 months of initial/previous treatment are regarded as inadequate responders.

Safety profile
Contraindications to rituximab include allergy to rituximab or murine proteins, active infections, severe heart failure (NYHA class IV) and pregnancy. Rituximab has established a large safety database, with over 370 000 courses given to patients with lymphoma. It has also been used off-label for many other malignancies and is generally well-tolerated.

Adverse events in rheumatoid arthritis are similar to those experienced in patients with non-Hodgkin’s lymphoma. Labelling warnings include:
- Fatal infusion reactions
- Tumour lysis syndrome
- Acute respiratory failure
- Cardiac events
- Severe mucocutaneous reactions

The majority of infusion reactions experienced occur during the first infusion and include flu-like illness, fever, chills, nausea, urticaria, bronchospasm, hypotension, angio-oedema, headache and hypoxia. Infusion reactions are most severe with the 1st infusion and lessen with repeated infusions.

Decreasing a patient’s immune response obviously raises the question of opportunistic infections. Incidence of infections is however low and opportunistic infections like TB have not been reported in patients receiving treatment for RA. Conversely, serious and occasional fatal reactivations of viral infections have been linked to the use of rituximab in non-RA conditions.

Testing for hepatitis B and C prior to starting with rituximab treatment is recommended, as there has been an association between patients with latent hepatitis B and developing fulminant hepatitis when treated with rituximab. Vaccination against hepatitis B, pneumococcus and influenza should be considered as a precaution before rituximab treatment is initiated.

Common indices used to measure RA activity and clinical response
Several indexes are available to measure rheumatoid arthritis activity and damage. Some examples are:
- The Disease Activity Score (DAS) is calculated by using counts for tender and swollen joints (53 and 44 respectively), evaluation of general health by the patient (0–100) and circulating inflammatory markers. DAS28 uses 28 joints for measurement and eliminates the grading of joints. Interpretation of DAS28 is as follows:
  - Remission: < 2.6
  - Low activity: ≥ 2.6 ≤ 3.2
  - Moderate activity: > 3.2 ≤ 5.1
  - High activity: > 5.1

- Similarly, the Simplified Disease Activity Index (SDAI) is calculated using tender joint count and swollen joint count based on a 28 joint assessment, patient global assessment (PGA on a visual analogue scale (VAS) of 0–10cm), physician global assessment (MDGA on VAS) and C-reactive protein. Interpretation of SDAI is as follows:
  - Remission: ≤ 3.3
  - Low activity: > 3.3 ≤ 11
  - Moderate activity: between > 11 ≤ 26
  - High activity: > 26

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• The Genant-modified Sharp score is a method to assess joint damage. X-rays of joints are taken and analysed using 14 specific sites for evidence of bone erosion and 13 sites for narrowing of joint spaces. Each erosion site is scored from 0-3.5, with 0 being ‘no erosion’ and 3.5 being ‘total loss of joint space’. Similarly, the severity of joint space narrowing is assigned a score from 0–4. The two subscores are then added together to get the total score.25

Response to treatment is expressed in terms of changes in these attributes and scores:
• Using DAS2823
  - Moderate response: Either
    a) a decrease by at least 1.2, or
    b) decrease of > 0.6 points and a change in disease activity from high to moderate, or
    c) a decrease of > 0.6 points and a change in disease activity from moderate to low.
  - Good response: decrease of at least 1.2 points and resulting in DAS28 < 3.2

• Using SDAI21,23
  - Minor/ moderate improvement: SDAI decreased by ≥ 7 points
  - Major improvement: SDAI decreased by ≥ 17 points

• The American College of Rheumatology (ACR) response criteria consist of tender joint count, swollen joint count, patient and doctor assessments, pain, functional disability and circulating inflammatory markers (ESR or C-reactive protein). ACR20, ACR50 and ACR70 imply a 20, 50, or 70% improvement respectively in joint counts and 20, 50 or 70% improvement respectively in 3 of the remaining 5 domains.6,9,15,23,24

Discussion

Is rituximab effective for treatment of RA?
A number of double-blind, placebo–controlled clinical trials have provided evidence of the efficacy and safety of a single course of rituximab in RA.26

One of these trials is the DANCER study: Patients were RF positive, had moderate to severe RA and had failed methotrexate (MTX), and in some cases also ≥ 1 other DMARD, which could include an anti-TNF (27–32% of patients). All patients continued with methotrexate, but received either rituximab (a 2 x 500 mg dose was compared to a 2 x 1000 mg dose) or placebo. Refer to Table 1 for results. There was no significant difference between the two doses of rituximab, even at ACR70 response rates, but benefits of both doses were significant over placebo.27,28

The REFLEX study was conducted in patients with active RA who had an inadequate response to one or more TNF inhibitors. The objective was to further investigate the safety and efficacy of rituximab plus methotrexate (MTX). Table 2 lists the main results. Interestingly, RF seronegative patients demonstrated similar treatment effect to seropositive patients, showing that rituximab acts on several mechanisms of pathogenesis, including production of RF and autoantibodies, T cell activation and cytokine production by macrophages or B cells.3

Is the effect going to lessen after each treatment? Is it safe to use long-term?
A total of 1039 patients were enrolled in an observational trial to study the effects of repeat courses. Of these, 570 received 2 courses, 191 received 3 courses, 40 received 4 courses and 3 patients received 5 courses.26 Please refer to Table 3 for DAS28 results.

Data for patients who had received ≥ 3 courses show sustained clinical response without substantially more adverse effects, although the number of patients was too small to draw meaningful conclusions.6 Table 4 summarises the adverse events per 100 patient years.

| Table 1: DANCER study: Percentage of patients achieving ACR response at 6 months27 |
|-----------------------------------------------|----------------|----------------|
| Response                                      | Placebo plus MTX (n = 122) | Rituximab 2x500 mg plus MTX (n = 123) | Rituximab 2x1000 mg plus MTX (n = 122) |
| ACR20                                         | 28              | 55*            | 54*             |
| ACR50                                         | 13              | 33*            | 34*             |
| ACR70                                         | 5               | 13***          | 20**            |

*p<0.001 vs placebo  
**p<0.029 vs placebo  
if numerical difference, but not statistically significant

| Table 2: REFLEX study: Percentage of patients achieving ACR response at week 24* |
|-----------------------------------------------|----------------|----------------|
| Response                                      | Placebo plus MTX (n = 201) | Rituximab 2 x 1000 mg plus MTX (n = 298) |
| ACR20                                         | 18              | 51*            |
| ACR50                                         | 5               | 27*            |
| ACR70                                         | 1               | 12*            |

*p<0.0001 vs placebo

| Table 3: Mean DAS28 at various time points of therapy in patients previously treated with TNF inhibitors and receiving 3 courses of rituximab26 |
|-----------------------------------------------|----------------|----------------|
| Course 1                                      | Course 2       | Course 3       |
| Baseline (n = 81)                             | 7.07           | 6.17           | 6.01             |
| Week 8 (n = 61)                               | 5.37           | 4.66           | 4.65             |
| Week 12 (n = 53)                              | 5.07           | 4.46           | 4.57             |
| Week 16 (n = 49)                              | 4.88           | 4.58           | 4.50             |
| Week 20 (n = 25)                              | 4.48           | 4.69           | 4.23             |
| Week 24 (n = 12)                              | 5.30           | 4.66           | 4.26             |

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No correlation between B cell depletion and clinical response could be demonstrated; therefore the decision to repeat treatment should not be based solely on return of B cell levels, but rather on disease activity.26

The time interval for patients to receive subsequent courses of treatment was on average 6–9 months, compared to the REFLEX trial, where the average time interval between treatments was 307 days.3,28

**Is there any evidence of radiological outcomes?**
A recent study showed early evidence of improved radiological outcomes after treatment with rituximab plus methotrexate. Patients with inadequate response to anti-TNF therapy were randomised to either rituximab or placebo. A total of 517 patients were enrolled in the study and all received methotrexate. Radiographic evaluation was done at baseline, week 24 and week 56. The result was an overall significant reduction in joint damage progression when compared to placebo. (Mean Genant-modified Sharp score at week 56: 1 vs 2.31, p = 0.005) Trends towards retardation of structural damage with rituximab use were also seen in patients who were RF negative, as well as in patients with high C-reactive protein (CRP) levels and high DAS28 at baseline.1

**How do rituximab and a second TNF inhibitor compare?**
A study that was done to compare the use of rituximab and a 2nd anti-TNF drug showed that patients responded better to a different class of biologic therapy, e.g. rituximab, than to a second or third TNF blocker.29 Patients (n = 116) who had previously failed at least 1 anti-TNF were treated with either rituximab or another TNF inhibitor.16,25 At 6 months the average decrease in DAS28 was 1.61 for rituximab patients and 0.98 for anti-TNF patients. Significant reductions in ESR and number of tender joints were also seen in the rituximab group, as compared to the anti-TNF group. However, this was an observational study and there was no control over treatment allocated, i.e. patients receiving rituximab had used and failed treatment with significantly more anti-TNF agents than the group of patients receiving an alternative anti-TNF.29 Thus, further randomised, controlled trials are required before definite conclusions can be made.16,29

**Place in Therapy**
- Rituximab has been approved by the FDA in combination with methotrexate for use in patients with moderate to severe active RA who have had a failed response to, or are intolerant to anti-TNFs.1,16
- SARAA recommends the use of anti-TNFs after failure of at least 3 standard DMARDs, for at least 6 months at their therapeutic dosages, one of which must be methotrexate. Furthermore, SARAA recommends the use of rituximab only after failure of at least one anti-TNF. Failed response would be SDAI > 11, or less than 10–20 point SDAI improvement after 6 months of anti-TNF therapy.21
- NICE recommends rituximab under similar provisions, although the DAS28 system is used to measure disease activity and response to TNF blockers.15
- In patients who have failed treatment with one anti-TNF agent, the options would be to try a second or even 3rd anti-TNF agent or to try a different drug class such as rituximab.13,22,29 Early evidence seems to suggest a better outcome using rituximab. Whether better long-term outcomes, such as prevention of radiographic damage or deterioration of functional disability, are achieved by switching to rituximab rather than to a second anti-TNF, is not clear yet.29
- Anti-TNFs have been associated with lymphoma, although clinical data regarding these agents and an increased risk of lymphomas is mixed.9,20 Nevertheless, since rituximab is also indicated for treatment of non-Hodgkin’s lymphoma, it may be a better agent to use in RA patients at risk of lymphomas.22
- Fewer opportunistic infections are likely to occur with rituximab, due to the sparing of immunoglobulin deficiency,8 but preliminary data on infection rates are similar to those observed with other biologics.26
- Rituximab treatment requires a shorter dosage schedule, therefore less hospitalisation than treatment with infliximab.9

**Cost**
One of the major drawbacks of rituximab is the high cost.9 The cost of 1 course of treatment for rheumatoid arthritis is R59 133.48 (SEP for 4x500 mg vials, February 2009). Provided that treatment is given at an average interval of 9 months,15 it will however compare favourably with anti-TNFs administered at their registered doses. Please refer to Table 5.

Clearly, cost is a huge problem with of all the biologics, not only rituximab.9,33 However, cost cannot be compared on drug SEP alone and various factors such as administration costs and frequency of treatment need to be considered.15 Costs associated with administration of an infusion (requiring hospitalisation for half a day) are much higher than for drugs

<table>
<thead>
<tr>
<th>Adverse event (AE) per 100 patient-years</th>
<th>Course 1 (n = 1039) total pt yrs = 1152.8</th>
<th>Course 2 (n = 570) total pt yrs = 416.6</th>
<th>Course 3 (n = 191) total pt yrs = 88.5</th>
<th>Course 4 (n = 40) total pt yrs = 12.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AE</td>
<td>396.4</td>
<td>326.0</td>
<td>383.0</td>
<td>384.2</td>
</tr>
<tr>
<td>Serious AE</td>
<td>19.3</td>
<td>17.5</td>
<td>20.3</td>
<td>24.0</td>
</tr>
<tr>
<td>Infections</td>
<td>82.8</td>
<td>83.3</td>
<td>80.2</td>
<td>88.0</td>
</tr>
<tr>
<td>Serious infections</td>
<td>5.1</td>
<td>4.8</td>
<td>5.6</td>
<td>8.0</td>
</tr>
</tbody>
</table>

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formulated as a subcutaneous injection, which can be given at the doctors rooms or even self-administered. Treatment with rituximab should only be repeated if an adequate response was achieved following initiation and was sustained until at least 6 months, but this treatment interval will result in increased longterm costs.\textsuperscript{15,21,22}

**Conclusion**

The success of therapies targeting B cells has demonstrated the importance of the role of B cells in the pathogenesis of RA.\textsuperscript{5,8,10,14} Rituximab has been shown to be effective for the treatment of RA and gives new hope to patients who have failed treatment with anti-TNFs.\textsuperscript{1,2,3}

While rituximab has been on the market for a long time and has a good safety record in patients with lymphoma, long-term safety of repeated treatments in patients with RA is not clear yet.\textsuperscript{5,9,22,26,27} The optimum dose and frequency of treatment, as well as the advantages of rituximab over a second anti-TNF, still need further investigation.\textsuperscript{22,27,29}

Similar to anti-TNF agents, rituximab is not a cure for RA and relapses occur after varying periods of time.\textsuperscript{16,22,26,33} Nevertheless, rituximab constitutes an important addition to current therapeutic strategies in treating RA.\textsuperscript{22,29}

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**Table 5: Cost comparison of biologicals in first year of treatment\textsuperscript{31,32}**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose per treatment</th>
<th>Cost (SEP price) per course/infusion/injection</th>
<th>Average number of treatments per year</th>
<th>Drug cost per year (SEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>1000 mg Week 0 and 2</td>
<td>R59 133.48</td>
<td>1.35</td>
<td>R79 830</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg 2 x per week</td>
<td>R1 209.87</td>
<td>104</td>
<td>R125 826.48</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 mg/kg (week 0, 2, 6, then every 8 weeks)</td>
<td>R11 071.04*</td>
<td>8.75</td>
<td>R 96 872**</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg (every alternate week)</td>
<td>R4 255.84</td>
<td>26</td>
<td>R110 651</td>
</tr>
</tbody>
</table>

\textsuperscript{*}for 75kg patient using 2.25 vials; cost will vary with weight and will be significantly more if vials are not shared by patients not needing a full number of vials

\textsuperscript{**}cost in 2nd year will be less as no induction treatment is needed, but also highly dependent on weight and vial sharing

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