Treatment of rheumatoid arthritis with rituximab: An update and possible indications

Salvatore De Vita *, Luca Quartuccio

Rheumatology Clinic – DPMSC – University of Udine, 33100 Udine, Italy

Received 15 January 2006; accepted 10 February 2006
Available online 15 March 2006

Abstract

Based on new biologic and clinical insights, the number of drugs blocking different biologic targets in rheumatoid arthritis (RA) [e.g., tumor necrosis factor alpha (TNFα), CTLA4, interleukin (IL)-1, IL-6, IL-15, IL-18, B lymphocyte stimulator (BLyS), CD20] has increased considerably over the last decade. Rituximab, a chimeric monoclonal antibody that was developed for the treatment of B-cell lymphomas, has been used in different autoimmune diseases where B-cells are thought to play a pivotal role. However, blinded randomised controlled trials have been completed only for RA so far, indicating the clear efficacy of B-cell blockade in RA and highlighting the pathogenetic B-cell in rheumatoid synovitis. The use of rituximab in RA is herein updated, from early preliminary studies to more recent presentations in International Conferences. Key clinical and biologic issues are discussed, i.e., efficacy and safety of rituximab, role of concomitant therapies, use in the long term and retreatment strategies, differences with anti-TNFα therapy. The possible indications in RA are finally discussed, also on the ground of personal experience with rituximab in RA and other rheumatic diseases associated with B-cell lymphoproliferation. Further clinical research should go hand in hand with laboratory research, and tissue studies are now needed.

Keywords: Rheumatoid arthritis; Rituximab; TNF; Lymphoproliferation; Lymphoma

Contents

1. Preliminary studies indicating the clinical efficacy of rituximab combination therapy or monotherapy ................. 444
2. Randomized controlled studies on the efficacy and safety of rituximab in RA, and the role of steroids ......................... 444
3. Long-term management of RA with rituximab ........................................................................................................ 444
4. Differences between rituximab and anti-TNFα therapies ...................................................................................... 445
5. Possible indications for the use of rituximab in RA today ................................................................................. 446
6. Conclusions ......................................................................................................................................................... 447
Take-home messages ................................................................................................................................................... 447
References .............................................................................................................................................................. 447

* Corresponding author. Tel.: +39 0432 559800; fax: +39 0432 559472.
E-mail address: salvatore.devita@med.uniud.it (S. De Vita).

In the last 5 years, the relevant pathogenetic role of B-cells in rheumatoid arthritis (RA) has become a widely accepted notion [1]. Despite many laboratory
studies in the previous decades, in 2001, it was still believed that treatments directed at B-cells alone, if they exist, are unlikely to be effective as monotherapy in RA [2]. In the same year, the elegant paper by Takemura and co-workers clarified that T cell activation is B-cell-dependent in human RA synovium [3]. Without proof of the clinical efficacy of anti-B-cell treatments, however, many clinicians were still reluctant to believe that the anti-B-cell approach would lead to meaningful clinical results.

1. Preliminary studies indicating the clinical efficacy of rituximab combination therapy or monotherapy

Four preliminary studies demonstrating the efficacy of rituximab therapy in RA were of major value to highlight the potential of such treatment approach (then leading to larger controlled studies), and to better clarify the pathogenetic role of B-cells in this disease. These studies were produced by two groups from England and Italy [4–8]. In the earliest study in 1999 by Protheroe et al. [4], the efficacy of rituximab was shown in one patient with erosive arthritis following chemotherapy for a B-cell lymphoma. Arthritis was rheumatoid factor (RF)-negative, following lymphoma, and could not however be surely defined as RA. In any case, subsequent studies from the same group clarified the efficacy of B-cell-depleting therapy with rituximab plus cyclophosphamide plus high-dose but short-term steroid induction in RA [5,8]. Between 2001 and 2002 our group also reported the efficacy of rituximab in 4/5 cases with RA [6,7]. The latter study differs since rituximab monotherapy was employed, i.e., a selective therapy blocking only the B-cell compartment. Rather than the clinical efficacy observed in a small series, the key message was the demonstration that B-cells played a key pathogenetic role in RA responders, since other pathogenetic mechanisms did not bypass the B-cell blockade and did not maintain the level of synovitis as before treatment [7]. This study was also the first to point out the efficacy of rituximab in the absence of steroids [7], as recently confirmed by a large controlled, randomized study called DANCER [9–12].

2. Randomized controlled studies on the efficacy and safety of rituximab in RA, and the role of steroids

The first controlled, randomized study on rituximab in RA was published in 2004 by Edwards and co-workers, and demonstrated that the combination of rituximab (1 g × 2, with 1-g infusion every 2 weeks) plus methotrexate (MTX) is the most effective and convenient treatment option in RA, when compared to that of MTX alone, rituximab alone, or rituximab plus cyclophosphamide [13]. Corticosteroid induction therapy was concomitantly used. With this combination, the rates of ACR 20, 50 and 70 responses at week 24 proved to be 73%, 43% and 23%, respectively, and a significant response was still detected at week 48 [13].

The most frequently reported adverse events were infusion-related, in particular at the first infusion, but not severe [13]. Notably, these infusion reactions are mediated by complement activation and cytokine release [14], and they are significantly less frequent in RA than in lymphoma patients [13], likely due to the smaller burden of target B-cells. Rituximab proved safe, and an increase in serious adverse events was noticed only with the concomitant use of cyclophosphamide [13], an approach now abandoned in RA.

In a subsequent study vs. placebo, named DANCER [9–12], it was shown that lower doses of rituximab (0.5 g × 2) and the standard full dose (1 g × 2) are both effective in RA when combined with MTX (10–25 mg/week), but ACR70 and EULAR good responses proved to be better with the full dose of rituximab (20% and 28%, respectively, with the full dose, vs. 13% and 14% with the reduced rituximab dose). By contrast, ACR20 and ACR50 responses were similar with the two regimens (54–55% and 33–34%, respectively). A second conclusion of this study was that efficacy of rituximab treatment was not affected by steroids [11]: in fact, the RA patients had been randomized in 9 groups, by considering not only the rituximab regimen or placebo, but also the lack of concomitant steroids, steroids only as pre-medication before rituximab (100 mg of methylprednisolone i.v.) or steroids as a standard 14-day induction plus premedication). The intravenous infusion of steroids appeared, however, to be convenient before the first rituximab infusion, to reduce the risk of infusion-related side effects [11]. The safety of rituximab therapy was finally confirmed in the DANCER study. Notably, no opportunistic infections or tuberculosis reactivations were noticed [12].

3. Long-term management of RA with rituximab

The long-term management of RA with rituximab remains an open issue. Data from an open-label extension phase of the DANCER study [15,16] indicate that retreatment with a full cycle of rituximab (1 g × 2) is again effective in previous responders to rituximab, who
had relapsed in the follow-up. In addition, there was no evidence of cumulative toxicity despite ongoing B-cell depletion. Interestingly, the peripheral B-cell count at the time of retreatment did not predict response to retreatment. Overall, timing of retreatment should be based on clinical manifestations rather than on peripheral B-cell recovery.

Whether and when it may be advisable to retreat a patient with rituximab, or to start a maintenance treatment, remain open issues in all the autoimmune diseases where rituximab therapy may prove effective.

Our experience with rituximab in glomerulonephritis in the course of mixed cryoglobulinemia syndrome suggests that different options should be considered and may be of value in the single patient [17,18]. After response to rituximab, maintenance therapy with rituximab can be avoided in the responder case, but could also be used if renal flare might be hazardous. Secondly, if renal flare occurs, the patient should be retreated with a full course of rituximab, and then maintenance therapy could be avoided (since after retreatment a second relapse does not necessarily occur after the same interval) or could be used instead (to avoid a second flare) [18]. As in the case of mixed cryoglobulinemia syndrome, additional studies are needed to optimize the long-term management of RA with rituximab, also considering a flexible treatment schedule tailored to the single case.

4. Differences between rituximab and anti-TNFα therapies

The widely used biologic therapy for RA refractory to standard MTX or combination therapy with DMARDs is the one employing anti-TNFα agents.

Insufficient response of anti-TNFα agents is not rare, however [19], and rituximab has proved effective in RA non-responders. This is not unexpected considering the different biologic targets of the two approaches. Furthermore, treatment strategies combining rituximab and anti-TNFα therapy are under investigation.

The REFLEX study [20,21] compared rituximab (1 g × 2) vs. placebo (in both arms in conjunction with MTX 10–25 mg/week and with the standard 14-day steroid induction used in previous studies) in RA patients with inadequate response to etanercept (≥3 months at 25 mg biweekly), infliximab (4 infusions ≥3 mg/kg) or adalimumab (≥3 months at 40 mg every other week). The primary end point was the ACR20 response at week 24. This was reached in 51% of the 298 cases randomized in the rituximab arm, and in 18% of the 201 cases in the placebo arm, while a EULAR moderate or good response was obtained in 65% vs. 22% (p<0.0001). The ACR50 and ACR70 responses were also significantly more frequent in rituximab-treated patients (27% and 12%, respectively) [20,21]. The experience of our group is consistent with these results, since 7/8 RA patients unresponsive to anti-TNFα agents could be rescued with rituximab in our Clinic (De Vita, personal communication).

A second difference between rituximab and anti-TNFα therapy is represented by the possible long-term efficacy of the former, even after B-cell reconstitution. By contrast, suspension of TNFα blockade is generally followed by RA relapse.

A possible disease “reset”, or profound modifications on disease pathobiology leading to a long-term disease response, was also noticed in mixed cryoglobulinemia syndrome and in systemic lupus erythematosus (SLE) [18,22]. Response up to 2 years after rituximab treatment has been reported by Emery in patients treated with rituximab + MTX, i.e., in the same patients where MTX alone was previously ineffective [23]. Edwards reported his experience with RA patients treated with rituximab, and then stable (after rituximab suspension) with DMARDs previously ineffective (MTX, sulphasalazine or leflunomide) [24]. A long term response to rituximab, defined by us as >12 months of duration, is currently noticed in 6/23 (26.1%) RA patients treated with rituximab in our Clinic (range: from 13 to 25 months, persisting in all at the last follow-up; De Vita, personal communication).

Such clinical data in RA may be consistent with previous observations in SLE [25], where recovery from disease-related B-cell abnormalities was detected after rituximab treatment, thus supporting the clinical efficacy observed.

Very recently, two distinct groups have reported that B-cell repopulation after rituximab therapy in RA is characterized by an increase in naïve B-cells [26,27], while an enhanced frequency of peripheral blood memory cells is usually detected in RA [28]. In addition, memory B-cells increased in RA patients who relapsed with B-cell repopulation after response to rituximab [27]. Finally, a different use of immunoglobulin heavy chain genes and a polyclonal pattern of B-cell regeneration have been reported in the RA peripheral blood compartment after rituximab therapy [29]. These data are consistent not only with a quantitative effect, but also with a qualitative, more important biologic and therapeutic effect of rituximab on distinct B-cell clones or subpopulations. With regard to this issue, it should be stressed that RF-positive clones are sensitive to rituximab [30], since a decrease in serum RF levels.
has been reported both in RA and in mixed cryoglobulinemia syndrome after rituximab therapy [13,17]. However, rituximab efficacy has been noticed not only in RF-positive RA but also (though less frequently) in RF-negative RA by recent larger studies [20,21], while initial reports had pointed out a lack of efficacy of rituximab in such RF-negative cases [7,24].

5. Possible indications for the use of rituximab in RA today

The first, obvious indication for rituximab in RA is represented by disease unresponsive to anti-TNF\(\alpha\) therapy. Whether a switch to a different anti-TNF\(\alpha\) agent or the direct switch to rituximab therapy may be more convenient remains an open question. The rationale for the second option is stronger when a totally different biologic target becomes the first point to consider for decision. In addition, rituximab availability could be of value in the subset of RA patients with latent tuberculosis where antitubercular therapy results toxic or not tolerated [19] (Table 1).

Secondly, given that in RA patients there is an increased risk of lymphomas [31], rituximab might be safer than anti-TNF\(\alpha\) therapy in RA patients where a lymphoproliferative disorder is present or suspected (B-cell lymphoma, or non-malignant atypical lymphoproliferative disorder) (Table 1). In this regard, we recently

---

**Table 1**

Rituximab versus anti-TNF\(\alpha\) therapy in active rheumatoid arthritis unresponsive to DMARDs: what is to be gained?

<table>
<thead>
<tr>
<th>Possible indications for rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anti-TNF(\alpha) therapy inefficacy, intolerance or side effects.</td>
</tr>
<tr>
<td>2. Overlap with either systemic lupus erythematosus or undifferentiated connective tissue disease or Sjögren’s syndrome.</td>
</tr>
<tr>
<td>3. Association with clearly diagnosed or highly suspected lymphoproliferative disorders, i.e. non-malignant atypical lymphoproliferative disorder or B-cell lymphoma.</td>
</tr>
<tr>
<td>4. Association with latent tuberculosis, where anti-tubercular therapy is not tolerated or contra-indicated.</td>
</tr>
</tbody>
</table>

---

F, 76 years with longstanding rheumatoid arthritis (ref. 32)

*LPD, oligoclonal*

MTX→1993

MTX + CyA

MTX monotherapy

CyA monotherapy

Stop all immunosuppressors→1999

Rituximab→2001

No LPD, Inactive RA

Regression of LPD

Active RA

Synovitis relapsed→2002

Anti-TNFalpha→2003

Aggressive NHL after 7 months

LPD-99 (I biopsy)

LPD-01 persisted (II biopsy)

Fig. 1. Summary of RA patient history, developing an atypical lymphoproliferative disorder (LPD) after methotrexate (MTX) and cyclosporin-A (CyA) combination therapy, which regressed only after suspension of both drugs. The patient was then treated with rituximab with LPD still undetectable. At, RA relapse anti-TNF\(\alpha\) therapy was introduced, but an aggressive B-cell non-Hodgkin’s lymphoma (NHL) developed after 7 months. The histologic pictures on the left show the oligoclonal B-cell expansion at the LPD step (LPD-1999) which progressed into a monoclonal NHL (NHL-2004) [32].
reported a RA patient developing an atypical lymphoproliferative disorder after MTX and cyclosporin-A therapy, which regressed after suspension of both drugs. The patient was then treated with rituximab achieving RA amelioration [7,32] with LPD still undetectable. At RA relapse anti-TNFα therapy was used, but an aggressive B-cell non-Hodgkin’s lymphoma developed shortly after. Molecular analyses showed an oligoclonal B-cell expansion at the atypical lymphoproliferative disorder step. Notably, a minor clone present in the B-cell expansion at the atypical lymphoproliferative lesion originated the disorder step. Notably, a minor clone present in the B-cell expansion at the atypical lymphoproliferative lesion originated the monoclonal lymphoma [32] (Fig. 1).

A third subset where rituximab might be a good choice is represented by RA in overlap with SLE, Sjögren’s syndrome or with undifferentiated connective tissue diseases, where anti-TNF blockade may be hazardous [33] (Table 1).

Finally, accumulating data are consistent with the safety of rituximab in patients infected by the hepatitis C virus (HCV), although additional investigation is needed. Results available at present in larger series of patients with mixed cryoglobulinemia syndrome HCV-related are consistent with the safety initially reported ([17], and S. De Vita, personal communication).

6. Conclusions

Rituximab represents a novel, relevant biologic agent for the treatment of RA. The efficacy of rituximab therapy better pointed out the key pathogenic role of B-cells in RA, or at least in RA subsets, thus providing new clues for research and for the development of other anti-B-cell blocking strategies (e.g., anti-CD22, anti-BLyS therapies).

The use of rituximab in RA should now be optimized, and its efficacy and safety carefully evaluated in the long term, as in the case of the anti-TNFα agents currently in use.

Additional clinical issues to be addressed are the efficacy of rituximab in preventing RA erosive damage (with encouraging preliminary data coming from the REFLEX study), the reduction of patient disability in the long term, and the identification of predictors of response and of relapse, if any.

Clinical research should go hand in hand with laboratory research. Notably, tissue studies on RA synovium are presently lacking in rituximab-treated patients, and may be crucial to better predict response to treatment and to explain in detail the mechanism of action and of resistance to rituximab in disease subsets. The risk is of going on too fast with clinical trials without some crucial data on disease biology, which may greatly improve the treatment strategy. Conversely, clinical studies with rituximab in larger series of RA patients will offer again the opportunity to shed more light on key pathogenetic issues.

Take-home messages

- Rituximab appears effective and safe in RA based on recent controlled studies.
- B-cells play a crucial role in rheumatoid synovitis.
- Combination with methotrexate is more effective, combination with steroids seems irrelevant, and rescue of anti-TNFα non-responders is possible with rituximab.
- Rituximab may reset some of the immune abnormalities in RA, leading to long term response in a fraction of cases.
- Rituximab may be the drug of choice when a lymphoproliferative disorder is present or is suspected in RA.

References


TLR9/MyD88 signaling is required for class switching to pathogenic IgG2a and 2b autoantibodies in SLE

Loss of tolerance in systemic lupus erythematosus (SLE) leads the generation of autoantibodies, which accumulate in end-organs where they induce disease. Here, Ehlers M, et al. (J Exp Med 2006; 203: 553–61) show that immunoglobulin (Ig)G2a and 2b autoantibodies are the pathogenic isotypes by recruiting FcgammaRIV expressing macrophages. Class switching, but not development, of IgM anti-self B cells to these pathogenic subclasses requires the innate immune receptor Toll-like receptor (TLR) 9 and MyD88 signaling. In their absence, switching of autoreactive B cells to the IgG2a and 2b subclasses is blocked, resulting in reduced pathology and mortality. In contrast, switching of anti-self B cells to IgG1 is not perturbed and generation of nonautoreactive IgG2a and 2b antibodies is not impaired in TLR9-deficient mice. Thus, the TLR pathway is a potential target for therapeutic intervention in SLE. TLR9/MyD88 signaling is required for class switching to pathogenic IgG2a and 2b autoantibodies in SLE.