Abstract

Objectives. Rituximab (RTX) is a therapeutic option for patients with SLE or RA. We conducted a prospective, longitudinal, observational study to compare rates of RTX-related adverse events (AEs) in these two patient groups.

Methods. RTX was used in 23 patients with SLE that was refractory to conventional therapy and in 31 patients with RA that had been unsuccessfully treated with TNF-α inhibitors. Infusion-related and infectious AE rates were calculated for each group.

Results. Seven (22.5%) RA patients experienced an infusion-related reaction. These AEs involved 7/91 (7.7%) infusions administered in the RA group. None of the 102 infusions administered to SLE patients was associated with infusion-related AEs (P=0.038 vs RA group). The mean daily glucocorticoid dose administered during the week preceding RTX treatment in the SLE group was higher than that for the RA group [0.25 (0.2) vs 0.18 (0.14) mg/kg, P= not significant] and significantly higher than that received by the subgroup of the seven RA patients who experienced infusion-related AEs [0.10 (0.02) mg/kg; P=0.0017]. Infectious AE rates were also lower (but not significantly so) in the SLE group (8.7 vs 12.9% in RA).

Conclusions. Repeated cycles of RTX in combination with different immunosuppressants is a safe therapeutic option for SLE and RA patients. The lower incidence of infusion-related AEs in the SLE patients might reflect the higher dosage glucocorticoid therapy they received during the week before RTX infusion.

Key words: Rituximab, Safety, Systemic lupus erythematosus, Rheumatoid arthritis, Glucocorticoids.

Introduction

Rituximab (RTX) is a chimeric mouse/human mAb directed against the CD20 antigen, which is expressed exclusively on the surfaces of B lymphocytes [1]. B-cell hyperactivity seems to play a central role in the pathogenesis of SLE [2], and B-cell-targeted immunotherapies are providing new options for patients whose SLE is refractory to conventional immunosuppressive treatment. The efficacy and safety of RTX therapy for RA have been widely investigated in clinical trials and large patient cohorts [1], but much less is known about its use in SLE. Available data are currently based on the results of a single randomized, double-blind, Phase II/III trial and analyses of several case series, most of which have been retrospective [3–16]. In this report, we present the results of a longitudinal, observational study specifically designed to compare the safety profiles of RTX in patients with SLE and in those with RA.

Methods

In this study, we prospectively evaluated the safety of RTX treatment in 23 patients with SLE refractory to...
conventional immunosuppressant therapy. All have been followed in the Rheumatology of Policlinico Umberto I, Sapienza University of Rome, since January 2004. SLE was diagnosed in accordance with the 1982 revised ACR criteria [17]. RTX was administered i.v. according to two different protocols: 1000 mg i.v on Days 1 and 14 (Protocol A) and 375 mg/m² on Days 1, 8, 15 and 22 (Protocol B). Each protocol provided for additional cycles of treatment after an interval of at least 6 months. Thirty-one patients with RA, in whom treatment with at least one anti-TNF-α agent had been discontinued due to lack of response or intolerance, were also enrolled. These patients, diagnosed according to the revised ACR criteria [18], were followed in the same Rheumatology Unit and all treated with RTX according to Protocol A.

All patients in both groups received oral acetaminophen (1000 mg), methylprednisolone (125 mg i.v) and chlorphenamine (10 mg i.v) 30 min before each infusion to prevent infusion-related adverse events (AEs). Written informed consent was obtained according to the Declaration of Helsinki from all patients. The work has been approved by the ethical committee of Policlinico Umberto I.

All patients were evaluated by the same rheumatologist before the first cycle of RTX and every 3 months thereafter. Daily glucocorticoid doses (expressed in mg/kg of prednisone or equivalents) were recorded as the mean dose received during the week before each infusion. Glucocorticoid dosage was maintained stable from the week preceding the first infusion to the week after the last infusion. Serum gamma globulin (Ig) levels were quantified by protein electrophoresis. Clinical efficacy was evaluated 6 months after the first RTX cycle using the SLEDAI-2000 [19] and the ECLAM [20] in patients with SLE and the 28-joint DAS (DAS-28) [21] in the RA groups.

Safety evaluation

All early and late AEs were recorded in both groups of patients. An AE was defined as the appearance of any unfavourable or unintended sign, symptom or disease that could be associated with the use of RTX. Serious AEs were those resulting in death, persistent or significant disability or disease that was life-threatening and/or that could be associated with the use of RTX. Serious and non-serious AE rates and those for infusion-related AEs (those occurring during or ≤24 h after completion of the RTX infusion) and infectious AEs were calculated separately.

Statistical analysis

Calculations were made with the Statistical Package for Social Sciences 13.0 (SPSS, Chicago, IL, USA). Mean (s.d.) were calculated for all normally distributed variables. The Wilcoxon-matched pair test and the Mann and Whitney test were used to compare quantitative variables. Two-tailed $P \leq 0.05$ were considered to be statistically significant.

Results

In the 23 patients with SLE that was resistant to conventional therapies, a total of 47 RTX treatment cycles were completed. Over half (13/23, 56.5%) of the patients received two or more cycles. A total of 55 cycles of RTX therapy were administered in the RA group. Fifteen (48.4%) of these 31 patients received more than one cycle of treatment. Table 1 shows the clinical and demographic characteristics of both patient groups.

Safety evaluation

Seven (22.6%) RA patients experienced RTX infusion-related AEs (one per patient), but there were no reactions of this type in the SLE group ($P=0.038$). The RA group’s infusion-related AE rate was also higher when expressed as AEs per infusion (7/91 RTX infusions, 7.7%; $P=0.006$ vs SLE group) (Table 1). None of the seven infusion-related AEs observed in the RA group was serious. Three patients developed rash and itching during the very first RTX infusion, two others experienced mild laryngospasm with the second infusion and the remaining two reactions (chest heaviness with non-specific ECG changes in one patient, bronchospasm in the other) occurred during the first infusion of the second cycle.

Patients with SLE were significantly younger than the RA patients ($P=0.0003$). Within the RA group, there was no significant difference between the mean age of the 7 patients who had infusion-related AEs and the 24 who did not. The SLE patients received higher mean daily doses of glucocorticoids the week before RTX infusions [0.25 (0.20) vs 0.18 (0.14) mg/kg in the RA group, $P=$ not significant (NS)] (Table 1). Interestingly, the mean daily glucocorticoid dose received by the seven RA patients who suffered infusion-related AEs [0.10 (0.02) mg/kg] was significantly lower than that of the SLE group ($P=0.0017$) and appreciably lower than that of the other 24 RA patients [0.21 (0.16) mg/kg, $P=$ NS]. These two RA subgroups were not significantly different in any other respect, with the exception of the mean number of DMARDs that had been used unsuccessfully by the patients before RTX therapy, that was higher in the RA subgroup that experienced AEs ($P=0.019$ vs the other RA patients). Serum Ig levels were similar in all groups (Table 1).

Infectious AEs developed in 2 (8.7%) of the 23 SLE patients [urinary tract infection (UTI) in one, Legionella pneumophila pneumonia in the other] and 4 (12.9%) of the 31 RA patients (upper-airway infections in two, gastroenteritis and UTI in the others). No significant differences were observed between the two groups in terms of infection incidence.

RTX was effective in both the SLE and RA groups. Six months after the first RTX cycle, mean disease activity indices were significantly improved in patients with SLE [SLEDAI-2000, 5.1 (3.3) vs 4 (5) before treatment,
During the week before each RTX infusion. All the other comparisons were not significant.

The results of this study indicate that repeated cycles of RTX, in combination with different immunosuppressants, is a safe approach to the treatment of SLE. Infusion-related AEs occurred in roughly one out of four RA patients, but none of our SLE patients experienced reactions in RTX-treated patients. The incidence of infusion-related reactions drops when patients are premedicated with acetaminophen, i.v. glucocorticoids and anti-histamines [22]. However, this factor did not contribute to the differential rate of infusion-related AEs observed in our study since both groups received the same premedication.

As for the mean daily glucocorticoid dose, very few studies have considered the effect of this factor on infusion-related reactions to chimeric drugs. In our study, the mean daily oral glucocorticoid dose received the week before RTX infusion by the seven RA patients with infusion reactions (IRs) was lower than that of the other 24 RA patients and significantly lower than that of the SLE patients. This finding suggests that higher dose glucocorticoid therapy before the RTX infusion might reduce the frequency of infusion-related AEs. In a study on infliximab in patients with RA, the risk of treatment-limiting IRs was also strongly reduced by low-dose glucocorticoid therapy [23]. Several explanations can be advanced for this effect. First of all, the anti-inflammatory potential of glucocorticoids might reduce the inflammatory burden, thereby conferring protection against IRs to various drugs. Secondly, steroid-induced improvement of a chronically altered immunological state might also reduce the likelihood of immune-based AEs [23].

Infusion-related AEs might also be promoted by the for- 

Discussion

The results of this study indicate that repeated cycles of RTX, in combination with different immunosuppressants, is a safe approach to the treatment of SLE. Infusion-related AEs occurred in roughly one out of four RA patients, but none of our SLE patients experienced reactions of this type. The infusion-related AEs in the RA group were all mild, and they appeared to be unrelated to the type of immunosuppressant therapy being used, the RTX infusion rate or the amount of drug administered per infusion. Indeed, 28 of the infusions administered in the SLE group contained an RTX dose of 375 mg/m², whereas all those given to RA patients contained a dose of 1000 mg, but the incidence of infusion-related AEs in this group was still significantly lower than that of the RA group when the lower dose infusions were excluded from the analysis ($P = 0.02$).

Little is known about the factors that may favour RTX infusion-related AEs. They could be linked to staff and working conditions, and, for this reason, both of our patient groups underwent the same procedures performed assiduously by the same physicians. Short-course i.v. prophyaxis is important to prevent hypersensitivity reactions in RTX-treated patients. The incidence of infusion-related reactions drops when patients are premedicated with acetaminophen, i.v. glucocorticoids and anti-histamines [22]. However, this factor did not contribute to the differential rate of infusion-related AEs observed in our study since both groups received the same premedication.

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Infusion-related AEs might also be promoted by the formation of anti-chimeric antibodies, and, interestingly enough, it seems that this antibody response can be prevented with higher mean glucocorticoid doses [24].

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<th>Patients’ features</th>
<th>SLE ($n = 23$)</th>
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$^*$ P = 0.019 vs RA patients with infusion reactions. **P = 0.017 vs SLE patients. aIn the RA group previously failed TNF antagonists were included. bDuring the week before each RTX infusion. All the other comparisons were not significant.
The therapeutically relevant effects of glucocorticoids can be classified as genomic, specific non-genomic and unspecific non-genomic actions [25]. Very low doses produce genomic effects, which become more evident as the dosage is increased and more receptors are occupied. It has been calculated that 7.5 mg of prednisone results in receptor occupancy of ~42%, and this figure rises to 63% with a dose of 15 mg [25]. It is, therefore, conceivable that, in our patients, higher dose glucocorticoid doses may have affected glucocorticoid receptor off-loading, re-occupancy and synthesis, thereby inhibiting the transcription of key pro-inflammatory genes and reducing the incidence of IRs.

Treatment failure with a high number of DMARDs may be another predictor of RTX infusion-related reactions [23]. On average, the seven RA patients who experienced IRs in our study had been unsuccessfully treated with a higher number of DMARDs [5.3 (1.4)] compared with an average of only 4.0 (0.9) for the remaining RA population. These seven RA patients may have been more prone to IRs to various drugs, not just RTX. The RA patients were also significantly older than the SLE patients, although there was no difference between the mean ages of the RA patient subgroups who did and did not experience infusion-related AEs.

Hypergammaglobulinaemia has also been linked to a higher incidence of RTX-related IRs [26], and, for this reason, we measured serum Ig levels in all of our patients. However, no differences were observed between the SLE and RA groups or between the RA subgroups who did and did not experience IRs.

RTX therapy for patients with SLE is a recent development [27]. For this reason, most of what we know about this approach comes from retrospective analysis of relatively small case series [3–14]. Only one randomized, double-blind study, The Efficacy and Safety of Rituximab in Patients with Severe SLE (EXPLORER) trial, has been published thus far [16], and data are now available from the large study based on the French Autoimmunity and Rituximab (AIR) registry [15]. In observational studies, infusion-related AE rates range from 0 to 18.2%, and this variability may be related to any or all of the factors mentioned above. It is important to note that our patients were similar to those of the larger French AIR registry cohort [15] in terms of mean age, disease duration, rates of infections (9%) and the rate of infusion-related reactions was slightly higher (9%). Our RA population was also similar to previously published series, in which IRs occurred in 15–40% of the RTX-treated patients and the annual infection rates ranged from 4.26 to 5.2 per 100 patients [28–32].

In conclusion, our experience demonstrates that RTX can be used safely to treat both SLE and RA and that increasing glucocorticoid doses during the week before treatment may help to prevent IRs. The populations we examined in this study are relatively small, but this potential limitation is offset to some extent by the long period of follow-up and number of RTX cycles administered. Nonetheless, our findings need to be verified in larger double-blind, placebo-controlled trials.

**Rheumatology key messages**

- Repeated cycles of RTX are a safe therapeutic option for SLE and RA patients.
- SLE patients showed a lower incidence of infusion-related AEs.
- The incidence of infusion AEs may be related to the glucocorticoid dose administered during the week before RTX infusion.

**Acknowledgements**

We thank Marian Everett Kent for her assistance in editing the article.

**Disclosure statement**: The authors have declared no conflicts of interest.

**References**


