Running head: Rituximab in systemic lupus erythematosus

Title: Use of rituximab in systemic lupus erythematosus: a single center experience over 14 years

Authors:
Aguiar R¹ MD, Araújo C² MD, MSc, Martins-Coelho G³,⁴,⁵ MD, Isenberg D⁶ MD FRCP FAMS

¹Rheumatology Department - Centro Hospitalar do Baixo Vouga E.P.E.; ²Internal Medicine Department 2 - Hospital de Curry Cabral, Centro Hospitalar de Lisboa Central, E.P.E. ³Public Health Unit, Baixo Vouga Group of Primary Care Centers; ⁴Institute of Public Health, University of Porto; ⁵Clinical Epidemiology, Predictive Medicine and Public Health Department, University of Porto Medical School; ⁶Centre for Rheumatology Research, University College London Hospital

Correspondence to:
Professor David Isenberg
Room 424 The Rayne Building
5 University Street
London
WC1E 6AG

Tel: + 00 44 (0)20 3108 2148
Fax: + 00 44 (0)20 3108 2152
Email: d.isenberg@ucl.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an ‘Accepted Article’, doi: 10.1002/acr.22921
© 2016 American College of Rheumatology
Received: Jan 05, 2016; Revised: Mar 16, 2016; Accepted: Apr 19, 2016

This article is protected by copyright. All rights reserved.
Financial interests of the authors:

This study had no external commercial financial support. Professor Isenberg and the project were supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The authors gratefully acknowledge the statistical support from Dr AL Papoila and Dr M Alves from the Epidemiology and Statistics Unit, Research Centre of Centro Hospitalar de Lisboa Central.
Abstract

Objectives: To describe the clinical outcome and safety of rituximab (RTX) treatment in systemic lupus erythematosus (SLE) patients with severe manifestations or refractory to standard immunosuppressive therapy, treated at a single center.

Methods: This was a retrospective analysis of all patients with SLE treated with RTX at one center between June 2000 and December 2013. The clinical outcome was assessed by determining BILAG scores, anti dsDNA and C3 levels before and six months after RTX treatment. For safety analysis, adverse events and deaths were recorded.

Results: Of a total of 115 patients, 93.9% were female; mean age at diagnosis was 26.39±11.90 years: mean disease duration at first RTX treatment was 91.96±84.80 months. A BILAG score variation of -11.26±11.38 (p<0.001) was recorded six months after first RTX treatment; 40% of patients had a complete response and 27% had a partial response; in 36.5% of patients, C3 levels increased over 25%, and in 33.5% dsDNA levels decreased over 50%. Depletion of CD19+ cells was achieved in 94.0% of patients. Hypogammaglobulinemia was detected in 14.9% of patients, with significant reduction for IgM (p<0.001) and IgG (p=0.001) levels. Severe infections, infusion-related and hypersensitivity reactions occurred in 7%, 3.5% and 2.6% of patients. Of the 115 patients, 62 patients had repeated RTX treatments, with an average number of 1.95±1.17 cycles per patient and a mean interval between
infusions of 21.44±20.11 months. At the end of follow-up, 11 patients were deceased; 6 had cardiovascular events.

**Conclusion:** RTX treatment was effective in decreasing disease activity, with low incidence of adverse effects.
Significance and Innovations

- There is a notable absence of long-term follow-up studies about lupus patients treated with B-cell depletion [BCD] using Rituximab.
- We address this gap providing up to 14 years of follow-up data on >100 SLE patients that we have treated with BCD. To our knowledge, this is the largest single center experience ever reported.
- Rituximab was an effective and safe alternative in the treatment of patients with severe or refractory SLE, demonstrating that, although not formally approved, it should remain an option in the treatment of such patients.
Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder, which may potentially affect any organ, by inducing the production of pathogenic autoantibodies directed against cell components and the deposition of immune complexes. The therapeutic approach relies on the use of corticosteroids and other immunosuppressive agents, depending on the disease features. However, the rationale for the use of those agents comes mainly from uncontrolled studies, and only in 2008 a EULAR task force gathered some evidence-based core recommendations on the management of SLE\(^1\). More recently, the first treat-to-target recommendations were published\(^2\); however, the role of the available therapies was not discussed. Rituximab (RTX) is a chimeric monoclonal antibody that targets CD20
positive B cells, directly inducing apoptosis or promoting antibody or complement dependent cell toxicity\textsuperscript{3}.

Two double-blind controlled trials have assessed the efficacy of RTX in the treatment of SLE.

The EXPLORER trial\textsuperscript{4} was a phase II/III randomized, double-blind, placebo-controlled trial, which evaluated the efficacy and safety of RTX against placebo in the treatment of 257 patients with moderate to severe SLE, excluding lupus nephritis patients. Although a significant improvement was noted in immunologic parameters such as CD19\textsuperscript{+} B lymphocyte count, anti dsDNA antibody levels and complement level in RTX-treated patients, the study failed to meet the primary endpoint of superiority of RTX.

The LUNAR trial\textsuperscript{5}, a phase III randomized controlled trial, evaluated the efficacy of RTX in the treatment of 144 patients with class III/IV lupus nephritis, concomitantly with mycophenolate mofetil (MMF) and corticosteroids or versus MMF, corticosteroids and placebo. As in the EXPLORER trial\textsuperscript{4}, RTX achieved B cell depletion and improvement in anti dsDNA antibody and complement levels, but showed no superiority of RTX.

However, a review\textsuperscript{6} and many further retrospective and open label studies\textsuperscript{7-11} suggested that RTX is effective and safe in the treatment of moderate to severe SLE when standard treatments have failed. Some recent studies showed RTX might be a useful steroid-sparing agent in patients with lupus nephritis\textsuperscript{12-13} and in newly diagnosed patients\textsuperscript{14}.

RTX was first used as an alternative in the treatment of refractory SLE at University College London Hospital in 2000; the clinical outcome of the first fifty patients was
published in 2009\textsuperscript{7}, as well as a later assessment looking at the outcome in relation to duration of B-cell depletion\textsuperscript{15}.

The objective of this retrospective study was to examine data on the efficacy and long-term safety of RTX in patients with lupus at this center over a 14-year period of time.

**Patients and methods**

**Study Design**

This is a single center in-depth retrospective analysis of all patients diagnosed with SLE treated with RTX at the University College of London Hospital (UCLH), between June 2000 and December 2013 and followed for up to 14 years.

**Participants**

We enrolled the patients through the UCLH Rheumatology Unit database of all the SLE patients treated with RTX.

The treatment protocol consisted on two infusions of 1 g of RTX, two weeks apart, with a combination of methylprednisolone (100–250 mg), anti-histamines and, up to 2007, 500–750 mg of cyclophosphamide. After 2007 we reduced the cyclophosphamide to a single infusion (following the first dose of RTX). Following B-cell depletion [BCD] the patients continued on hydroxychloroquine and, wherever possible, a reducing dose of corticosteroids. Invariably any immunosuppressive drugs being prescribed at the time of BCD were stopped until the B-cells had returned and the patients started to flare. CD19 counts and total immunoglobulin levels were monitored approximately every 2 months post-BCD until the CD19\textsuperscript{+} B-cell
count was back to normal. As this study is an audit, it did not require hospital ethics committee approval.

**Data collection**

The clinical records of all patients enrolled were reviewed for gender, ethnicity, age at presentation, disease duration at first RTX treatment, previous immunosuppressant treatments, indication for RTX treatment, response to RTX treatment after 6, 12, 18 and 24 months, follow-up time after RTX treatment.

Other data collected included anti dsDNA antibody and C3 levels before and 6 months after RTX infusions. Both parameters were measured at the UCLH laboratory. Anti-dsDNA titers were evaluated by ELISA [n <50 u/ml] and C3 levels [n = 0.9 → 1.8mg/l] by laser nephelometry.

Data on BCD was also recorded: acknowledgement of BCD in the first 6 months after RTX treatment was reviewed.

Adverse events, including allergic/anaphylactic reactions, hypogammaglobulinemia, infections, cardiovascular and cerebrovascular events and death were reviewed.

**Measurements and calculations**

The indication for RTX treatment was dependent upon the severity of the organ/system involved (which was captured by BILAG assessments).

For the purpose of clinical outcome assessment, response to RTX treatment was classified according to the ‘classic’ BILAG score: full disease response being determined when BILAG A or B scores changed to C or D in every organ system; partial response if BILAG scores changed from A or B to C or D score in at least one
organ system but with a persistent A or B score in another organ system; no improvement when a BILAG A or B score remained unchanged after treatment.

For anti-dsDNA antibody levels, the benefit of RTX treatment was recorded when a 50% reduction of the initial titer was achieved. For the C3 levels, benefit was recorded if a 25% increase occurred.

Regarding safety analysis, the proportion of patients with adverse reactions was recorded. Adverse events were divided into the following categories: severe infections (defined as requiring hospitalization or intravenous antibiotics), hypersensitivity reactions, infusion-related reactions and others. Hypersensitivity reactions occur when the drug is recognized as an antigen by the patient immune system; these are IgE-mediated reactions and, as such, only become evident with subsequent exposures to the culprit drug. Clinically, hypersensitivity reactions lead to urticarial, rash, angioedema, bronchospasm, hypotension, and eventually anaphylaxis. Infusion reactions usually develop during the infusion or several hours afterwards, have a mild to moderate intensity and are characterized by a complex of chills, fever, nausea, asthenia, headache, hypotension; these reactions are thought to be cytokine-dependent. Hyponatremia-induced seizures due to cyclophosphamide, reactivation of hepatitis B, jugular thrombosis due to catheterization, abnormal liver function tests or cyclophosphamide-induced cytopenias were classified as other adverse reactions.

**Statistical Analysis**

Descriptive statistics was performed in terms of mean and standard deviation in continuous variables, and in percentage with 95% confidence interval in case of discrete variables.
Statistical analysis was performed using IBM SPSS® version 22.0 software. We applied paired samples Student’s t-test to compare the values of the continue variables before and after RTX treatment; ordered and multinomial logistic regression analysis were performed to compare the number of infusions according to BILAG system involved and BILAG responses after RTX treatment in the different organ involvement. Both models included all the BILAG systems.

We considered statistical significance at p < 0.05.

Results:

Baseline characteristics

Out of a total of 650 patients with an SLE diagnosis, 115 patients treated with RTX were identified after reviewing the available charts.

The baseline demographic and clinical characteristics of the patients are described in table 1.

Female gender and Caucasian ethnicity were predominant. Prednisolone and hydroxychloroquine were the most frequent previous treatments (94.8% and 70.3%, respectively), followed by azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate; other less frequent previous therapies included cyclosporine A, intravenous immunoglobulin, dapsone, sulphasalazine, and plasma exchange.

The main disease features that motivated RTX treatment were musculoskeletal, mucocutaneous and renal involvement. Although there were 54 patients that scored A or B for hematological manifestations of the disease, most of them had mild to moderate anemia or slightly low leukocyte count, not demanding aggressive intervention.
Mean follow up time after the last RTX cycle was 46.03±41.10 months; four patients were lost to follow-up.

**Rituximab infusions**

In the considered interval, among the 115 patients who had RTX treatment, 53 had only one cycle of RTX; 35 had two cycles; 14 had three cycles; and 9, 1 and 3 patients had, respectively, 4, 5 and 6 cycles. The mean number of RTX cycles was 1.95±1.18.

Mean interval between the 1\textsuperscript{st} and the 2\textsuperscript{nd} cycles of RTX was 23.81±22.65 months. Overall mean interval between two consecutive cycles was 21.75±20.23 months.

None of the indications for the first rituximab treatment was associated with a higher number of RTX cycles (p=0.691).

The reason that led to the second RTX treatment was the same as had led to the first in 85.2\% (CI\textsubscript{95\%}: 76.3-94.1\%) of patients. Overall, the principal involvement that motivated re-treatment with RTX (N=109) was the same that had led to previous treatment in 79.8\% (CI\textsubscript{95\%}: 72.3-87.4\%) of cases; in 17.4\% of cases, the new flare was distinct from the ones that were previously responsible for RTX treatment and a new RTX cycle was administered to prevent new flares in 2.8\% of the cases.

**Efficacy**

There was a significant decrease in BILAG score after treatment with RTX, both at first and subsequent cycles. The addressed serological markers of disease also demonstrated a significant improvement, as revealed on tables 2 and 3.

Reviewing the RTX treatment, of the six patients who were not successfully CD19+ lymphocyte depleted, only one had no response; partial and complete responses were observed in three and two patients, respectively. Overall, absence of depletion
and absence of response were coincident in 7 of the 15 patients who were not successfully depleted.

For RTX re-treatments (N=100), in 48% (CI$_{95\%}$: 38.2-57.8%) of cases, patients were still partially depleted of CD19+ lymphocytes at the time of the new cycle.

The response to therapy according to the different organs affected is shown on table 4. Musculoskeletal and renal manifestations were associated with higher response rate in our model (p=0.026 and p=0.001, respectively).

Rituximab effects on immunoglobulins (Ig A, M, G)

With respect to the first RTX treatment, a statistically significant decrease 6 months post-treatment was found both in IgM (1.26±1.05 g/L [0 months], 0.94±0.97 g/dL [6 months], p<0.001) and IgG levels (15.15±6.92 g/L [0 months], 13.52±6.84 [6 months], p<0.001). No such difference was found for IgA (p=0.112). At six months after first RTX cycle, low levels of IgA, IgG and IgM were detected, respectively, in 2.1% (CI$_{95\%}$: 0.0-5.0%), 14.9% (CI$_{95\%}$: 7.7-22.1%) and 23.4% (CI$_{95\%}$: 14.8-32.0%) of patients (N=94).

Considering all RTX cycles, only IgM levels decreased significantly after 6 months (1.22±1.02 g/L to 0.92±0.92 g/L, p <0.001); and low IgA, IgG and IgM levels were identified, respectively, in 3.3% (CI$_{95\%}$: 0.7-5.9%), 12.2% (CI$_{95\%}$: 7.7-17.0%) and 27.2% (CI$_{95\%}$: 20.7-33.7%) of patients (N=180).

Adverse events

Adverse events are presented on table 5.

Four severe infections occurred in patients with low IgM levels: three infections occurred within six months after first RTX cycle (one had a soft tissue infection, one
gastroenteritis and one septic shock of unknown origin) and one was registered after the second RTX cycle (cystitis). Human anti-chimeric antibodies were identified in two patients — although they were not routinely investigated.

Overall, among the 224 RTX infusions, in 80.4% (CI95%: 75.2-85.6%) no adverse events were recorded.

From 2000 to 2013, six patients had at least one cardiovascular event: one patient presented with stroke; four patients had a myocardial infarction.

During the same period, eleven patients deceased: three patients died due to disease activity; two patients committed suicide; one patient had a fatal acute respiratory distress syndrome attributed to cyclophosphamide infusion; one patient had a fatal cerebrovascular accident; one patient had a fatal myocardial infarction; and the cause of death was unknown in three patients.

**Discussion**

Although the use of B-cell depletion in lupus is not novel, there is a marked paucity of long-term follow-up data on patients treated in this way. This study attempts to fill the gap by providing ‘real world’ experience on >100 lupus patients followed for periods of up to 14 years.

To our knowledge, this report analyses the largest single-center experience of the use of rituximab in SLE.

Edwards and Cambridge, were the first to suggest that since corticosteroids, cyclophosphamide and RTX were able to reduce peripheral B-cell numbers, BCD might best be achieved by combining these drugs [16]. Their studies in patients with rheumatoid arthritis fully validated this approach [17] and we extended its use to patients with lupus. [8, 14]
In this cohort, the efficacy analysis was largely favorable. Most of the patients treated with RTX at UCLH presented with clinical features refractory to more than one immunosuppressive agent; however, a small minority, in recent years, was treated with RTX at the time of diagnosis, in patients with florid presentation of the disease or severe renal involvement. In any case, RTX was able to reduce disease activity, with a response rate (partial or complete response) of about 70%. The response to RTX was better in those patients with musculoskeletal and renal involvement. These data are in line with recent evidence suggesting that RTX is useful, not only in cases of lupus nephritis refractory to standard immunosuppressive agents, but also as a steroid sparing agent in the induction of remission\textsuperscript{12-13,19-23}.

Notably, many of the patients who flared and needed to be re-treated with RTX were still partially depleted of CD19+ lymphocytes by the time of flare. The safety profile was also favorable, with a low incidence of serious adverse events; in particular no patient developed multifocal leukoencephalopathy but there were serious infections, one case of reactivation of hepatitis B and one death due to an acute respiratory distress syndrome secondary to cyclophosphamide infusion. The infusion related and hypersensitivity reactions were mostly mild to moderate.

The limitations of this study have to be carefully taken into account. The cohort was highly heterogeneous in terms of affected systems, and interobserver variability has to be considered when judging BILAG scores. However, all the clinicians making the BILAG assessments were trained by one of us (DAI) and the single centre approach allows for uniformity of serological assessment. Disease duration also showed wide variability, as well as the number of previous immunosuppressive agents used.

There were some missing data, for several reasons. Firstly, four patients were lost to follow up. Some patients were not seen in the outpatient clinic at six months,
therefore, clinical and laboratory data could not be easily obtained for that period. In some cases, laboratory tests were not available. Another limitation was that some patients (n=4) had the last RTX cycle less than six months before data collection. The absence of a control group also limits the measure of efficacy and safety of RTX in SLE patients.

Even though a new anti-BlyS monoclonal antibody, belimumab, has been approved for the treatment of SLE, its role in the treatment of lupus nephritis and neuropsychiatric features has not yet been established. Long term data on efficacy and safety are still lacking for this drug.

Rituximab is the biologic agent with the most extensive off-label use in the treatment of refractory SLE and observational studies. Much published data seem to contradict the results from the two available randomized controlled trials\textsuperscript{4,5}, suggesting a possible role for this drug in the treatment of SLE patients. It is notable that both the American College of Rheumatology and the European League Against Rheumatism guidelines on the treatment of lupus nephritis consider rituximab a viable therapeutic option\textsuperscript{24,25}.

References:


Table 1. Baseline demographic and clinical characteristics of the SLE patients treated with RTX.

**Epidemiological features**

<table>
<thead>
<tr>
<th>Gender (Female:Male)</th>
<th>108:7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (n)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>50</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>37</td>
</tr>
<tr>
<td>South Asian</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td>Mean age at diagnosis (mean ± SD, years)</td>
<td>26.39±11.90</td>
</tr>
<tr>
<td>Mean disease duration at first RTX treatment (mean ± SD, months)</td>
<td>92.00±84.80</td>
</tr>
</tbody>
</table>

**Previous treatments (n,[%])**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count ( [%] )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>109 (94.8%)</td>
</tr>
<tr>
<td>Hydroxichloroquine</td>
<td>90 (70.3%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>74 (64.3%)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>40 (34.8%)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>39 (33.9%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>35 (30.4%)</td>
</tr>
</tbody>
</table>
Serological characterization (n, [%])

Positive antinuclear antibodies 111 (96.5%)
Positive anti-Ro antibodies 62 (53.9%)
Positive anti-La antibodies 23 (20%)
Positive anti-RNP antibodies 53 (46.1%)
Positive anti-Sm antibodies 32 (27.8%)
Positive anti-cardiolipin antibodies 21 (18.3%)
Anti dsDNA antibodies 81 (70.4%)
Lupus anticoagulant 12 (10.4%)

Clinical features: all BILAG score A and B (n)

<table>
<thead>
<tr>
<th>Category</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Neurological</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Cardiovascular and respiratory</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td>15</td>
<td>23</td>
</tr>
</tbody>
</table>
Haematological  

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

**Disease activity**

- Mean BILAG score (mean±SD) 18.29±10.62
- Mean anti dsDNA (mean±SD, unit) (n < 50 U/ml) 712.60±1410.80
- Mean C3 (mean±SD, unit) (n = 0.9 -1.8mg/L) 0.79±0.34

**Table 2.** Mean BILAG score, C3 level and dsDNA titer at baseline and 6 months after RTX therapy.

<table>
<thead>
<tr>
<th></th>
<th>1(^{st}) RTX cycle</th>
<th></th>
<th>Any RTX cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (N=109)</td>
<td>After 6 months (N=103)</td>
<td>Baseline (N=206)</td>
</tr>
<tr>
<td>BILAG score</td>
<td>18.29±10.62</td>
<td>6.79±5.55</td>
<td>16.18±8.91</td>
</tr>
<tr>
<td>C3 (N=103)</td>
<td>0.79±0.03</td>
<td>0.95±0.03</td>
<td>0.89±0.36</td>
</tr>
<tr>
<td>Anti dsDNA (N=105)</td>
<td>712.60±1410.80</td>
<td>478.06±1572.33</td>
<td>619.73±1197.61</td>
</tr>
</tbody>
</table>

Δp: p<0.001
Table 3. Response rate to therapy in terms of BILAG score, C3 level, anti dsDNA titer and depletion of CD19+ lymphocytes.

<table>
<thead>
<tr>
<th></th>
<th>1st RTX cycle (at 6 months), % (95% CI)</th>
<th>All RTX cycles (at 6 months), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with a decrease in anti dsDNA level ≥50% or normalization</td>
<td>38.2% (28.9-47.5)</td>
<td>37.7% (30.8-44.6)</td>
</tr>
<tr>
<td>% of patients with an increase in C3 level ≥25% or normalization</td>
<td>36.5% (27.2-45.8)</td>
<td>31.8% (25.5-38.1)</td>
</tr>
<tr>
<td>% of patients with complete response</td>
<td>43.0% (33.7-52.3)</td>
<td>42.4% (35.7-49.1)</td>
</tr>
<tr>
<td>% of patients with partial response</td>
<td>29.0% (20.5-37.5)</td>
<td>27.3% (21.2-33.4)</td>
</tr>
<tr>
<td>% of patients with no response</td>
<td>28.0% (19.6-36.4)</td>
<td>30.2% (23.9-36.5)</td>
</tr>
<tr>
<td>% of patients successfully CD19+ lymphocytes depleted (N=100)</td>
<td>94.0% (89.3-98.7)</td>
<td>92.0% (88.2-95.8)</td>
</tr>
</tbody>
</table>
Table 4. Changes in BILAG scores in responders to RTX treatment.

<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>Mucocutaneous</th>
<th>Neurologic</th>
<th>Musculoskeletal</th>
<th>Cardiorrespiratory</th>
<th>Vascular</th>
<th>Renal</th>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total A/B</td>
<td>33</td>
<td>41</td>
<td>12</td>
<td>55</td>
<td>15</td>
<td>8</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>A → B</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>A → C</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>A → D</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>B → C</td>
<td>9</td>
<td>11</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>B → D</td>
<td>13</td>
<td>13</td>
<td>4</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 5. Adverse events occurring 6 months within RTX therapy.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>1st RTX (n=115)</th>
<th>2nd RTX (n=62)</th>
<th>3rd RTX (n=27)</th>
<th>4th RTX (n=13)</th>
<th>5th RTX (n=4)</th>
<th>6th RTX (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe infections</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>91</td>
<td>51</td>
<td>23</td>
<td>10</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>