

# Off-label use of rituximab in systemic rheumatic diseases: case series

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## ABSTRACT

B-cells play an important role not only in cellular but also in humoral immunity through differentiation into plasma cells and antibody production. B-cell depletion may, theoretically, change the course of systemic rheumatic diseases (SRD) in which self-reactive antibodies are part of the pathogenic pathway. In Rheumatology, anti-B-cell antibody Rituximab is currently licensed for the treatment of rheumatoid arthritis, however there is growing evidence of its potential use in other SRD. The authors present a case series of eight patients in which Rituximab was used off-label including overlap syndrome Rhupus, systemic lupus erythematosus and Wegener's granulomatosis. In the end, a brief literature review about this subject is performed.

**Keywords:** Rhupus; Systemic Lupus Erythematosus; Wegener's granulomatosis; Rituximab; Off-label.

## INTRODUCTION

In the past decades, advances in immunology and molecular science have not only enriched the understanding of disease pathophysiology but also brought new light on cutting edge therapies. The role of B-cells in both innate and adaptive immunity as antigen-presenting cells, producers of chemokines and cytokines and as plasma cell precursors<sup>1</sup> has made them capital targets when abnormal immune system functioning oc-

curs, such as in lymphatic malignancies or autoimmune disorders. Therefore, B-cell depleting therapy with Rituximab, an anti-CD20 chimeric monoclonal antibody, was first approved for non-Hodgkin lymphoma in 1997<sup>2</sup> and was later licensed for treatment of rheumatoid arthritis (RA) in patients with inadequate response or intolerance to tumour necrosis factor (TNF) inhibitors<sup>3</sup>. There is also growing evidence that Rituximab may be effective and relatively safe in several other systemic rheumatic diseases (SRD), especially in patients refractory to first-line therapies.

We present a case series of eight patients with SRD other than RA who were treated with Rituximab.

## CLINICAL CASES

Rituximab was introduced in our hospital for the treatment of RA in 2007. Since then, there were eight patients with SRD treated off-label with this monoclonal antibody in our rheumatology department, seven of which were female patients. The mean age was 48,25 years (33 – 80) and they were all caucasian. Five of those patients had an overlap syndrome consisting of RA and Systemic Lupus Erythematosus (also known as Rhupus), two had systemic lupus erythematosus (SLE) and one had Wegener's Granulomatosis (WG).

The five patients with Rhupus were all female and had an mean age of 54,2 years (37 – 80). They had a mean duration of disease of 14 years (9 – 30) and they were treated with Rituximab after 11,6 years of disease onset (5 – 28). One patient had a previous diagnosis of SLE and presented with erosive polyarthritis; two patients had a previous diagnosis of RA and presented with clinical features of SLE; the other two patients presented simultaneously with clinical features of SLE and RA. By the time the diagnosis of Rhupus was made, two patients had both positive rheumatoid factor (RF) and

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anti-citrullinated protein antibodies (ACPA); one patient had only positive RF; and the other had only positive ACPA (RF and ACPA were not available in one patient). All had an elevated titer of antinuclear antibody (ANA) and positive anti-double stranded DNA antibody (anti-dsDNA). All patients had also been previously treated with methotrexate (mean dosage of 21 mg/week), hydroxychloroquine (400 mg/day) and prednisone (mean dosage of 8,5 mg/day). Four patients were treated with azathioprine (mean dosage of 125 mg/day). Only one patient received biologic therapy previous to Rituximab (Adalimumab, 40 mg every other week for 3 years, suspended for secondary failure). The reason that led to treatment with Rituximab was moderate (2 patients) and severe (3 patients) joint disease activity as indicated by the Disease Activity Score (DAS) 28, hence, the regimen used was two 1000 mg infusions two weeks apart in all 5 patients. At week 24 after infusion there was a significant decline in the mean 3-variable DAS 28 from 4,89 to 3,31 and in the mean 4-variable DAS 28 from 5,23 to 3,48. At week 24 after infusion there was also a significant reduction in mean standard treatment dosage, namely in methotrexate (from 21 mg/week to 15 mg/week), azathioprine (from 125 mg/day to 87,5 mg/day) and prednisone (from 8,5 mg/day to 5 mg/day). Three of the five Rheumatoid Arthritis patients are currently in remission, only one of them needing retreatment. The fourth patient, despite three retreatment courses, maintains severe articular disease activity). The fifth patient didn't complete her first treatment because she had a severe infusion-related reaction near the end of the treatment, which led to drug discontinuation. There were no reported infections in the follow-up period.

We also had two SLE patients who were treated with off-label Rituximab: a 33-year old female patient and a 41-year old male patient with 5 and 12 years of disease duration, respectively. The female patient was treated with Rituximab for a severe and refractory thrombocytopenia which was the presenting feature of her disease along with malar rash, photosensitivity and elevated ANA titer. Before the infusion, oral prednisone 1 mg/kg/day, intravenous methylprednisolone 1000 mg/day for three consecutive days and human immunoglobulin were used to try to reverse the severe platelet depletion, with no success. She was treated with weekly Rituximab 375 mg/m<sup>2</sup> for four consecutive weeks and a slight increase in platelet count was observed, from 10,8x10<sup>9</sup>/L to 36x10<sup>9</sup>/L. Therefore, posterior treatment with intravenous cyclophos-

phamide and mycophenolate mofetil was ensued and the patient was discharged 3 months after admittance with a platelet count of 158x10<sup>9</sup>/L<sup>21</sup>. The male patient was also treated with weekly Rituximab 375 mg/m<sup>2</sup> for four consecutive weeks for World Health Organization (WHO) class IV + V lupus nephritis (LN) resistant to intravenous cyclophosphamide, oral azathioprine and oral mycophenolate mofetil. Previous to the infusion, creatinine level was 1,02 mg/dL, 24 hour proteinuria was 1,6 g, complement levels were low and dsDNA antibody titer was high. At week 24 after treatment creatinine was 0,99 mg/dL, 24 hour proteinuria was 370 mg and both complement and anti-dsDNA levels were normal. Both female and male patient are currently in remission.

Our last case of off-label use of Rituximab refers to a 41-year old female patient with glottic stenosis as a complication of ANCA-negative WG. She had been previously submitted to several bronchofibrosopies as well as treatment with intravenous methylprednisolone, oral cyclophosphamide, azathioprine and methotrexate. At week 24 after infusion of Rituximab 375 mg/m<sup>2</sup> for four consecutive weeks there was still need for bronchofibrosopic airway dilation procedures, although an improvement in physical components like asthenia and anorexia was referred. Table I summarizes RTX off-label treatments.

## DISCUSSION

Self-reactive antibodies seem to play an important role in several SRD, although their precise mechanism of action is still subject of debate. For instance, in RA and in SLE, RF and ANA, respectively, are thought to activate complement and trigger joint and systemic inflammation leading to tissue damage<sup>4,5</sup>. Consequently, drugs that are used to deplete these antibodies may have the potential to change SRD's natural history. Based in these premises, Rituximab has been used in different clinical settings aside from those for which it has been previously approved. The results have been inconsistent.

In SLE, the two major randomized controlled trials (RCT) of Rituximab in patients without renal involvement (EXPLORER trial) and with renal involvement (LUNAR trial) failed to meet their endpoints and thus showed no benefit over standard of care therapy. Some methodological issues such as concomitant therapies, disease heterogeneity and limited follow-up might ex-

TABLE I. PATIENTS WITH SRD OTHER THAN RA, TREATED WITH OFF-LABEL RITUXIMAB

Patient	Gender	Age	Disease	Reason for RTX treatment	RTX dosage	Before RTX treatment	Week 24 after RTX treatment	24 week variation	Drug dosage variation	Current status
1	F	51	Rhupus	Severe articular disease activity	1000 mgx2	DAS 28 3v/4v: 5,46/5,47, HAQ 1,5	DAS 28 3v/4v: 2,42/2,52, HAQ ?	Δ DAS 28 3v/4v: ↓3,04/ /↓ 2,95, Δ HAQ ?	MTX: ↓5mg/w; PDN: ↓5 mg/d	Remission (after retreatment)
2	F	37	Rhupus	Moderate articular disease activity	1000 mgx2	DAS 28 3v/4v: 4,04/4,88	DAS 28 3v/4v: 0,99/0,77	Δ DAS 28 3v/4v: ↓ 3,05/ /↓ 4,11	AZT: ↓50 mg/d; HCC: ↓200 mg/d; PDN: ↓5 mg/d	Remission
3	F	58	Rhupus	Moderate articular disease activity	1000 mgx2	DAS 28 3v/4v: 3,94/4,06	DAS 28 3v/4v: 4,13/4,24	Δ DAS 28 3v/4v: ↑ 0,19/ /↑ 0,18	AZT: ↓25 mg/d; PDN: ↓5 mg/d	Remission
4	F	80	Rhupus	Severe articular disease activity	1000 mgx2	DAS 28 3v/4v: 4,84/5,17, HAQ 1,875	DAS 28 3v/4v: 4,87/5,34, HAQ 2	Δ DAS 28 3v/4v: ↑ 0,03/ /↑0,17, Δ HAQ ↑ 0,125	PDN: ↓5 mg/d	Severe articular disease activity
5	F	45	Rhupus	Severe articular disease activity	1000 mg (interrupted because of infusion-reaction)	DAS 28 3v/4v: 6,19/6,58	DAS 28 3v/4v: 4,13/4,15	Δ DAS 28 3v/4v: ↓ 2,06/ /↓ 2,43	PDN: ↓2,5 mg/d	Severe articular disease activity
6	F	33	SLE	Severe and refractory thrombocytopenia	375 mg/m2 weekly (4 weeks)	10,8x10 <sup>9</sup> platelets/L; ANA 1/640; normal C3, C4 and dsDNA antibody	158x10 <sup>9</sup> platelets/L; ANA 1/160; normal C3, C4 and dsDNA antibody	↑147x10 <sup>9</sup> platelets/L	-	Remission
7	M	41	SLE	Lupus nephritis class IV+V	75 mg/m2 3weekly (4 weeks)	Creat. 1,02 mg/dL; 24h-proteinuria 1,6 g; C3 54 and C4 6,8 mg/dL; dsDNA antibody 167 U/L	Creat. 0,99 mg/dL; 24h-proteinuria 0,37 g; C3 85 and C4 13 mg/dL; dsDNA antibody 66 U/L	↓ 1,23g 24h-proteinuria; C3 ↑ 31 mg/dL and C4 ↑ 6,2 mg/dL; dsDNA antibody ↓ 101 U/L	MMF: ↓1g/d; PDN: ↓10 mg/d	Remission

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**TABLE 1. CONTINUATION**

Patient	Gender	Age	Disease	Reason for RTX treatment	RTX dosage	Before RTX treatment	Week 24 after RTX treatment	24 week variation	Drug dosage variation	Current status
8	F	41	WG	Glottic stenosis	375 mg/m <sup>2</sup> weekly (4 weeks)	ANCA negative	ANCA negative	-	-	No change in Glottic stenosis; considerable improvement in general in status

SRD: systemic rheumatic diseases; RTX: rituximab, SLE: systemic lupus erythematosus; WG: Wegener's granulomatosis; DAS: disease activity score; HAQ: health assessment questionnaire; ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibody; MTX: methotrexate; PDN: prednisolone; AZT: azathioprine; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil.

plain this. Many open-label and retrospective studies, as well as case series and case reports, have demonstrated the clinical efficacy and safety of Rituximab in SLE<sup>6</sup>. LN is a serious complication of SLE and influences morbidity and mortality. Ramos-Casals et al<sup>7</sup> analyzed seven observational studies regarding the use of Rituximab in LN, in a total of 106 patients. There was a favorable response in 69% of them (half had a complete response, the other half had a partial response) with higher rates of response among patients with type III LN and lower among patients with type V LN. There is also no consensus on the regimen that should be used in SLE and LN. The majority of patients was treated with two infusions of 1000 mg two weeks apart, but 375 mg/m<sup>2</sup> weekly for four consecutive weeks was also used. Aside from renal involvement, Rituximab may have potential benefits in articular, cutaneous and hematologic disease<sup>6,7</sup>. So far, the adverse events profile has been acceptable (10% of serious infections)<sup>2,6,8</sup>.

The overlap syndrome Rhupus was first described by Schur in 1971<sup>9</sup> and it refers to a rare form of erosive and deforming polyarthritis in patients with SLE, resembling RA<sup>10</sup>. It affects only a minority of patients (0,01-2%)<sup>11</sup> and therefore there is scarce evidence on the efficacy and safety of treatment using conventional and biologic drugs. Reports of small series of patients show variable response to standard DMARD therapy<sup>12</sup> including methotrexate, hydroxychloroquine and low-dose corticosteroids. Prabhakaran et al<sup>13</sup> reported 3 cases of overlap syndrome Sjrupus (SLE, RA and Sjögren's syndrome) with significant clinical and laboratorial response to Rituximab, although no dosing regimen is referred.

There is also growing evidence on the role of Rituximab in ANCA associated vasculitis, namely WG. The RAVE trial (Rituximab versus cyclophosphamide for ANCA-associated vasculitis)<sup>14</sup> and the RITUXVAS trial (Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis)<sup>15</sup> are two recent prospective RCT that have shown that Rituximab is capable of inducing remission with a favorable safety profile, presenting as an alternative to cyclophosphamide and corticosteroid regimens. The RAVE trial even showed superiority of Rituximab in relapsing disease when compared to cyclophosphamide. Both trials used 375 mg/m<sup>2</sup> per week for four consecutive weeks. Several other retrospective studies confirm these auspicious data. The Spanish BIOGEAS Study Group demonstrated higher response rates for renal (100%), neurological (80%) and pulmonary (78%) involvement and lower response rates

for ear, nose and throat (67%) and cutaneous (33%) involvement<sup>16</sup>.

Promising results are also arriving from new trials and also from case series and case reports on the use of Rituximab in other refractory SRD such as inflammatory myopathies<sup>17,18</sup> and Sjögren's syndrome<sup>19</sup>. In systemic sclerosis it may have a beneficial effect in lung disease<sup>20</sup>.

The authors decided to report these 8 clinical cases to support bibliographic evidence that Rituximab may be effective and safe in SRD other than RA. However, this evidence comes mainly from uncontrolled trials since SRD are rare and heterogeneous, which makes trial design, outcome measurement and endpoint definition a difficult task. There is also no definition on which dosing regimens should be used in the different SRD settings. In most published studies, the most frequent adverse events were infections. In our small series, no infection was reported in the follow-up period although one serious infusion-related reaction occurred. One of the main limitations of studies concerning off-label use of Rituximab is the short follow-up period, which may underestimate the number of adverse events as well as the frequency of relapses and need for retreatment.

In conclusion, for the time being, off-label use of Rituximab should be restricted to severe patients with SRD that do not respond or are intolerant to first-line therapies.

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