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# Rituximab for the treatment of Churg–Strauss syndrome with renal involvement

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**Abstract**

**Introduction.** Churg–Strauss syndrome (CSS) is a small vessel systemic vasculitis associated with asthma and eosinophilia that causes glomerulonephritis (GN) in ~25% of patients. Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody that depletes B cells and is effective in

numerous autoimmune diseases including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. We aim to evaluate the safety and efficacy of RTX in inducing remission of renal disease activity in patients with CSS.

**Methods.** We conducted a single-center, open-label pilot study using RTX (375 mg/m$^2$/week × 4) for induction of remission in CSS patients with renal involvement [defined as having >25% dysmorphic red cells, red blood cell casts or pauci-immune GN on biopsy]. Written informed consent was obtained from all individuals. Patients were eligible if they were untreated, had failed glucocorticoid therapy or had failed glucocorticoid dose reductions because of disease relapses. The primary outcome was remission of renal disease activity defined as stability or improvement of creatinine clearance, absence of active urinary sediment and reduction of the glucocorticoid dose to <50% of the average dose received over 3 months before enrollment or <10 mg/day (whichever is smaller) at 6 months. Patients were followed up for 1 year.

**Results.** Only three patients (two females; ages 54, 55 and 65) were enrolled. All patients had positive myeloperoxidase-ANCA and renal involvement. Two patients had biopsy-proven pauci-immune crescentic GN. All achieved the primary end point of renal remission within the first 3 months and remained in renal remission during the year following RTX treatment. One patient experienced a non-renal relapse (eye and joint involvement) at 6 months coinciding with the reconstitution of CD19+ cells and eosinophilia. He was retreated with RTX and achieved remission within 6 weeks. No major adverse effects were recorded.

**Conclusions.** In this pilot study, RTX was safe and successful in controlling renal disease activity in three patients with CSS. This agent deserves further study in CSS.

**Keywords:** ANCA vasculitis; Churg–Strauss syndrome; glomerulonephritis; rituximab

## Introduction

Churg–Strauss syndrome (CSS) is a form of vasculitis characterized by asthma, prominent eosinophilia and angiitis [1]. The three main histologic features are the presence of extravascular granulomas, tissue eosinophilia and necrotizing vasculitis involving a number of organ systems including the lungs, heart, nervous system and kidneys [2–6]. Kidney involvement has been reported to be present in 25% of cases [7] and the typical histopathological lesion is that of a pauci-immune focal segmental necrotizing glomerulonephritis (GN) with crescent formation [8, 9].

Current recommendations for the therapy of CSS with renal involvement include the use of glucocorticoids in combination with cyclophosphamide [10, 11]. Given the high rate of side effects associated with corticosteroids and cyclophosphamide, a potentially safer treatment regimen would be desirable. Rituximab (RTX) is a genetically engineered, chimeric monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. It was approved by the Food and Drug Administration for the treatment of relapsed or refractory low-grade or follicular, CD20+ B-cell non-Hodgkin's lymphoma and rheumatoid arthritis and has an excellent safety profile in these diseases. In two recent randomized controlled trials comparing RTX to cyclophosphamide for remission induction in severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the adverse events (AE) profiles of the RTX and control treatment arms were indistinguishable [12, 13]. In some series, up to 70% of CSS patients are ANCA positive suggesting that ANCA may have a pathogenic role in this disease [7]. RTX has been effective in the treatment of a number of autoimmune diseases including ANCA-associated vasculitis [12–15]. More recently, several case reports have reported on the successful therapy of RTX in CSS patients that are refractory to standard therapy with steroids and cyclophosphamide [16–20].

No prospective study has evaluated the use of RTX in patients with CSS with renal involvement; therefore, in this single-center open-label study, we aim to evaluate the safety and efficacy of RTX in CSS patients with renal involvement.

## Materials and methods

This investigator-initiated trial was approved by the Institutional Review Board of the Mayo Clinic in Rochester, MN, and was registered on www.clinicaltrials.gov (identifier NCT00424749). All patients included in the study signed a written informed consent before entering the study. The study was a single-center, pilot open-label study using 4 weekly doses of RTX in the treatment of CSS with renal involvement. The study was planned to enroll five subjects during the study period. Complete inclusion and exclusion criteria are listed in detail in the online supplement. Briefly, patients were eligible to participate if they had CSS defined by meeting one of three sets of criteria for CSS (Lanham's criteria [21], American College of Rheumatology [22] or Chapel Hill Consensus Conference [23]) and were newly diagnosed and previously untreated or had failed steroid therapy (partial or non-responders) or could not be tapered off oral prednisone because of documented relapsing disease. In addition, evidence of active renal involvement had to be present (>25% dysmorphic red cell, red blood cell casts or pauci-immune GN on biopsy).

### *Definitions and disease assessments*

Pretreatment evaluations included complete history and physical including measures of performance status, complete blood count (CBC) with differential erythrocyte sedimentation rate, C-reactive protein, electrolytes, creatinine and blood urea nitrogen (BUN), ANCA titers, immunoglobulin levels, urinalysis and proteinuria. Physical examinations and laboratory testing were conducted following RTX infusion on Days 1, 8, 15 and 22 and subsequently, clinical follow-up at Months 2, 3, 6, 9 and 12. Evaluations posttreatment included CBC with differential glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, total protein, albumin, serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT). CD 19/20+ B-cell counts were performed at baseline, 6 weeks and Months 3, 6 9 and 12. Disease activity was assessed using the Birmingham Vasculitis Activity Score/Wegener's granulomatosis (BVAS/WG) instrument [24, 25]. Major and minor relapse definitions are described in the online supplement. Renal relapse was defined as a rise in serum creatinine of >30% from the baseline at remission that is attributable to vasculitis and/or active urinary sediment (presence of >25% dysmorphic red cells and/or red cell casts) or documented by renal biopsy. If life-threatening disease progression occurred or no improvement from the initial BVAS/WG was achieved after 2 months, patients were considered treatment failure and were removed from the study and treated according to the best medical practice. Disease relapses that occurred before 16 weeks were considered treatment failures. B-cell return was defined as CD19+ B-cell count >15/μL or >5% of baseline count.

### *Treatment protocol*

The remission induction regimen included oral prednisone and RTX. Prednisone was started at 1 mg/kg/day (not to exceed 80 mg/day) for 4 weeks followed by a taper to 0 mg by 6 months. RTX 375 mg/m$^2$ intravenously, once a week for 4 weeks, was given within 2 weeks of starting steroid

therapy. Prior to the first RTX infusion, patients were premedicated with methylprednisone 100 mg intravenously. The four doses RTX regime has been chosen because it is the only one with evidence of efficacy in other ANCA-associated vasculitides. In patients with asthma, inhaled high-dose steroids and long-acting bronchodilators were started at the latest once the prednisone dose is reduced <30 mg/day. Patients were followed up for 1 year after beginning of the remission induction regimen. RTX labeled for investigational use was provided by Genentech Inc., South San Francisco, CA.

*Outcomes*

The main outcome include safety and remission of renal disease activity as indicated by stable or falling creatinine, absence of active urinary sediment and reduction of oral prednisone dose to <50% of average dose of preceding 3 months or <10 mg/day (whichever is smaller) at 6 months. The presence of remission is supported by normalization of C-reactive protein, a negative ANCA testing and a BVAS score of 0. Safety was assessed by monitoring and recording of AE that are defined as any untoward medical occurrence in a patient participating in the investigational trial or protocol regardless of causality assessment. Secondary outcomes included normalization of eosinophil count at 6 months, defined as total eosinophil counts $<1.5 \times 10^9$/L.

## Results

The study was done between June 2007 and July 2009. Four patients signed consent and were enrolled during the study period, one patient withdrew consent after the first infusion of RTX and only three individuals completed the study and were included in the analyses. All patients were Caucasians and had positive myeloperoxidase (MPO)-ANCA. Table 1 summarizes the clinical characteristics of these three patients. Renal disease at enrollment in all patients was confirmed by active urine sediment in all three patients and two patients underwent renal biopsy that showed pauci-immune crescentic GN. The disease was newly diagnosed in two individuals, and one patient had been previously diagnosed 4 years prior to enrollment in the trial and had failed therapy with cyclophosphamide 3 years prior and more recently therapy with methotrexate and prednisone. Active peripheral neuropathy was present in all three patients: one patient also presented myopathy and one patient presented active biopsy-proven eosinophilic pneumonia. None of the patients presented with active cardiac, central nervous system or skin activity of the disease.

**Table 1.** Baseline clinical characteristics of patients included in the trial

| | Patient # 1 | Patient # 2 | Patient # 3 |
|---|---|---|---|
| Sex | Male | Female | Female |
| Age (years) | 54 | 54 | 64 |
| Duration of vasculitis (months) | 48 | New diagnosis | New diagnosis |
| ANCA type | MPO | MPO | MPO |
| Previous immunosuppressants | Cyclophosphamide Methotrexate Prednisone | None | None |
| Active organ involvement | Kidney Neuropathy | Kidney Neuropathy Lung | Kidney Neuropathy Myopathy |
| BVAS/WG score at first therapy | 6 | 6 | 8 |
| Creatinine (mg/dL) | 0.9 | 1.1 | 1.9 |
| Proteinuria (mg/24 h) | 2734 | 455 | 1301 |
| Eosinophils ($\times 10^6$/L) | 740 | 3830 | 910 |

All patients achieved the primary end point of renal remission within the first 3 months and remained in renal remission during the year following RTX treatment. In Patient # 1, proteinuria improved from 2734 to 671 mg/24 h at the end of the study. The other two patients normalized the 24-h proteinuria and all patients showed no evidence of active urinary sediment at the end of the study. The only patient with elevated serum creatinine at enrollment of 1.9 mg/dL (Patient # 3) experienced significant recovery of renal function to a new baseline serum creatinine of 1.3 mg/dL at the end of the study. Peripheral neuropathy improved in all patients.

Figure 1 summarizes the disease activity and response in all three patients during the year that the patients were followed in the trial. Patient # 1 experienced a non-renal relapse (eye and joint involvement) at 6 months coinciding with the reconstitution of CD19+ cells; the time of relapse is marked with a solid black arrow in all panels of Figure 1. This patient was retreated with 4 weekly doses of RTX and achieved remission within 6 weeks. Concomitantly with inflammatory markers, eosinophilia and lower doses of prednisone, the disease activity as measured by the BVAS/WG mirrored the results as described in Figure 1.

RTX was effective in depleting CD19+ cells at 6 weeks in all individuals; the response was sustained for all patients except for Patient # 1, whose response was previously described. There were no differences during the trial in the levels of hemoglobin, platelets, total white blood cells, electrolytes or liver function tests in all three participants. The levels of immunoglobulins A, M, G and E were measured at baseline, at 12, 24 and 48 weeks after RTX therapy. No significant changes in the levels of any of these were detected throughout the study, and their levels remained within normal ranges.

*Adverse events*

All patients completed the RTX infusion series without any AE. During the study, no major AE were recorded among the participants. One patient developed an upper respiratory tract infection that was treated with oral antibiotic therapy. None of the patients required hospitalization for any reason and all patients were alive at the end of the study.

## Discussion

In this single-center, pilot open-label study using 4 weekly doses of RTX in the treatment of CSS with renal involvement, all three subjects included in the study achieved the primary end point of renal remission within the first 3 months and remained in renal remission during the year following RTX treatment. This is among the first studies documenting efficacy of RTX in patients with CSS and renal involvement and, to the best of our knowledge, the first study utilizing RTX as first-line therapy for CSS with renal involvement. RTX was well tolerated and no major AE were documented. All patients included in the study also achieved remission of the non-renal manifestations of their disease for as long as peripheral CD19+ lymphocytes were undetectable, with the exception of Patient # 1 who required retreatment with 4 weekly doses of RTX at 24 weeks due to a

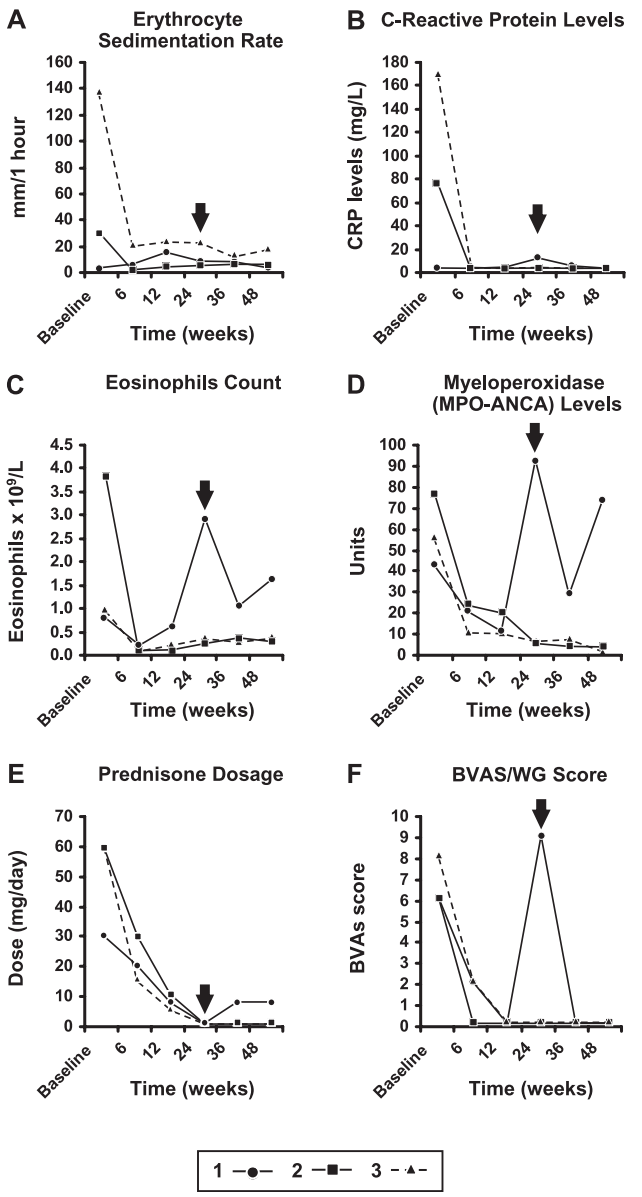


**Fig. 1.** Panels A and B describe the inflammatory markers response (sedimentation rate and C-reactive protein) with marked improvement after initiation of RTX in all the subjects. Panels C and D describe the eosinophilia response and the levels of MPO, respectively, note that with the exemption of Patient # 1, the response was sustained over the 48 weeks of the study. Prednisone therapy and BVAS scores are described in Panels E and F, respectively; prednisone was successfully discontinued in two individuals and Patient # 1 was able to lower the dosage to $<10$ mg a day.

non-renal relapse that coincided with the reconstitution of CD19+ cells and increase in MPO levels; however, this individual achieved remission again within 6 weeks. Taken together, these observations suggest that RTX is effective for remission induction of CSS with renal and non-renal involvement.

The most widely accepted standard treatment for remission induction of patients with CSS and renal involvement is corticosteroids and cyclophosphamide. The evidence of this practice is mainly based from several uncontrolled trials. The French Vasculitis Study Group recently reported on the long-term follow-up of CSS patients treated with glucocorticoid plus cyclophosphamide [10]; these patients presented significantly prolonged survival in the group with more severe disease, only patients treated with glucocorticoid alone had uncontrolled disease, and cyclophosphamide was associated with a greater frequency of side effects. However, many patients do not respond satisfactorily to glucocorticoid monotherapy. In addition, resistance to glucocorticoid therapy occurs and some patients cannot be tapered off glucocorticoids $\pm$ cyclophosphamide without prompt relapse. The overall rate of infection with the combined use of steroids and cyclophosphamide may result in the development of life-threatening complications (mainly infections) in $>20\%$ of the patients treated. In addition, there are long-term side effects as illustrated by the increased risk of urological malignancy in patients with CSS, which is $>15$–45 times in the population at large [10]. In contrast, RTX has been effective in the treatment of a number of autoimmune diseases including rheumatoid arthritis [26], ANCA-associated vasculitis [12–15, 27, 28] and systemic lupus erythematosus [29]. In ANCA-associated vasculitis, induction of remission was obtained in 11 patients with refractory ANCA-associated vasculitis that were treated with RTX [15], and in a prospective open-label trial of 10 patients treated with RTX for refractory Wegener's granulomatosis, RTX was found to be well tolerated and effective in achieving remission [14]. Furthermore, RTX was found to be not inferior to cyclophosphamide for the induction of remission in severe ANCA-associated vasculitis patients in a recent randomized controlled study [12].

Several case reports have reported on the successful therapy of RTX in CSS patients that are refractory to standard therapy, including corticosteroids, cyclophosphamide and other immunosuppressants such as methotrexate or mycophenolate [16–20, 30]. A summary of CSS cases treated with RTX is presented in Table 2; note that only one patient presented kidney involvement and all cases were treated due to relapse despite aggressive immunosuppressive therapy. Moreover, with the exemption of two cases where RTX was discontinued due to severe bronchospasm and the remainder eight cases achieved remission.

The fact that all patients remained in remission during the period of B-lymphocyte depletion supports the central pathogenic role for B lymphocytes in ANCA-associated vasculitis that has been previously reported [15, 31]. Furthermore, the patient who clinically relapsed at 24 weeks showed B lymphocyte reconstitution preceding the relapse, which provides more evidence regarding the importance of B lymphocytes in the pathogenesis of ANCA-associated vasculitis [15, 32, 33].

ANCA levels dropped in all our patients, which is consistent with reports of a variety of autoimmune diseases where autoantibodies levels are suppressed, such as rheumatoid factor in rheumatoid arthritis [34, 35] and ANCA-PR3 levels in Wegener's granulomatosis [14, 15]. In the only patient that presented a flare of the disease, there was a rise of MPO-ANCA levels which was preceded by CD19+ cell reconstitution, a finding which suggests that autoantibody production in CSS is also B lymphocyte dependent such as seen in rheumatoid arthritis [34] and Wegener's granulomatosis [15].

**Table 2.** Summary of case reports of use of RTX in CSS

| | Number of patients/age | Reason for RTX therapy | Main active organs | RTX dosing | Outcome | AE |
|---|---|---|---|---|---|---|
| Donvik and Omdal [16] | 2 cases, 50 and 35 years | 1-Refractory disease to corticosteroids, azathioprine, methotrexate, cyclosporine, infliximab and anakinra | 1-Lung, hearing loss and sinusitis | 1000 mg 2 weeks apart in both cases | Remission of active disease in both cases | None reported |
| | | 2-Refractory disease to corticosteroids and azathioprine | 2-Uncontrolled asthma and sinusitis | | | |
| Bouldouyre *et al.* [30] | 2 cases, 44 and 33 years | 1-Refractory disease to corticosteroids, methotrexate, azathioprine and cyclophosphamide | 1-Peripheral neuropathy and lung infiltrates | 375 mg/m$^2$ | Not reported due to side effects during first infusion | Severe bronchospasm during infusion despite premedication in both cases, medication was withdrawn |
| | | 2-Refractory disease to corticosteroids, mycophenolate mofetil, azathioprine and cyclophosphamide | 2-Joints and lung | | | |
| Saech *et al.* [20] | 1 case, 46 years | Refractory central nervous system involvement despite corticosteroids and cyclophosphamide | Central nervous system vasculitis | 1000 mg 2 weeks apart | Resolution of central nervous system vasculitis | None reported |
| Pepper *et al.* [19] | 2 cases, 40 and 66 years | 1-Refractory disease to corticosteroids and cyclophosphamide | 1-Skin, kidney and eyes | 1000 mg 2 weeks apart in both cases | Remission of active disease in both cases | None reported |
| | | 2-Refractory disease to corticosteroids and cyclophosphamide | 2-Skin and peripheral neuropathy | | | |
| Kaushik *et al.* [17] | 1 case, 49 years | Relapse despite azathioprine, corticosteroids and cyclophosphamide | Skin and lung | 375 mg/m$^2$ weekly $\times$ 3 weeks | Remission of skin and lung involvement | Pneumonia herpes zoster |
| Koukoulaki *et al.* [18] | 2 cases, 37 and 35 years | 1-Refractory disease to corticosteroids, cyclophosphamide, mycophenolate mofetil and alemtuzumab | 1-Peripheral neuropathy and sinusitis | 1—375 mg/m$^2$ weekly $\times$ 4 weeks | Remission in both cases, first case required repeated infusions at 7 and 16 months | Respiratory tract infection in the second case |
| | | 2-Refractory disease to corticosteroids, cyclophosphamide, mycophenolate mofetil, interpheron alfa and alemtuzumab | 2-Skin, peripheral neuropathy and arthritis | 2—1000 mg 2 weeks apart | | |

RTX was well tolerated with no major AE reported during the 48 weeks of the trial. It is possible that the concomitant high dose of corticosteroids mitigates potential mild infusion reactions. No significant changes in immunoglobulins were observed. The effect of RTX therapy on immunoglobulin levels reported in observational studies has not been consistent, and information regarding IgE and IgA levels is lacking. More is known about IgG and IgM levels. Most studies report declines of IgM and preserved levels of IgG after RTX therapy. This is consistent with short-lived plasma cells, which are dependent on B-cell precursors, being a significant source of serum IgM [36]. In contrast, most of the serum IgG is produced by long-lived bone marrow plasma cells that are not affected by RTX [37]. Our observation of preserved IgE levels suggests that short-lived plasma cells are not a significant source of IgE.

Despite these encouraging results, we acknowledge that the limited number of individuals enrolled into the study makes it difficult to draw firm conclusions that are more than hypothesis generating. Even though the open-label design can bias the assessment of subjective components of the BVAS/WG score, the main outcomes evaluated were objective demonstrations of the resolution of urinary

sediment activity, prednisone dose reduction and laboratory markers that are not subject to biased subjective interpretation. One patient had received immunosuppressants other than corticosteroids prior to enrollment. We cannot exclude that its lingering effects could have contributed to the perceived beneficial effects of RTX; however, this patient had been treated with cyclophosphamide 3 years prior to the trial and presented with a relapse while on therapy with methotrexate and prednisone. Moreover, the other two patients were treated with RTX as the first induction agent and had an excellent response. It is also important to acknowledge that all patients were MPO-ANCA positive, and it remains unknown whether a similar RTX response can be expected in ANCA-negative patients with CSS.

In conclusion, the results of this small pilot study have shown that RTX was safe and successful in controlling renal and non-renal disease activity in patients with CSS and therefore deserves further study in CSS.

## Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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*Conflict of interest statement.* None declared.

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