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# Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: a study on 8 patients

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## ABSTRACT

**Objective.** Rituximab, an anti-CD20 biotherapy, has been effective against refractory and/or relapsing Wegener's granulomatosis (WG). But the frequency of and time to responses to rituximab, and its effects on various clinical WG manifestations remain to be thoroughly evaluated.

**Methods.** Retrospective study of 8 patients with refractory/relapsing WG. In addition to their ongoing therapy, 7 patients received rituximab (375 mg/m<sup>2</sup> weekly for 4 weeks) and another received 2 rituximab infusions (1 g on days 1 and 15). Disease activity was assessed using BVAS 2003 before and 6 months after the first rituximab infusion.

**Results.** The median BVAS before rituximab was 14.3 (range 4–30). At 6 months, 5/8 patients had BVAS=0; 3/8 were in complete remission; 3/8 in partial remission (lung nodules persisted in 2 patients, scored 0 in BVAS); 2/8 did not respond. One patient relapsed 1 year after stopping rituximab and responded successfully to a second cycle. Dissociated responses of constitutional and 'vasculitis' symptoms, as opposed to granulomatous manifestations, were observed: the former regressed within days or weeks, while the latter regressed more slowly, over several months. Tolerance was good for 7 patients but 1 developed an urticarial rash during the last 3 infusions. Corticosteroids could be tapered in all patients.

**Conclusion.** Rituximab, when prescribed in conjunction with corticosteroids and immunosuppressants to treat refractory/relapsing WG, was able to improve clinical outcome. But the dissociation of response times in patients with predominantly granulomatous manifestations, as opposed to vasculitis symptoms, merits further study before

an optimal rituximab regimen can be defined.

## Introduction

Wegener's granulomatosis (WG) is characterized by around 50% relapses despite prolonged immunosuppressant therapies (1). Cyclophosphamide combined with corticosteroids (CS) remains the most effective induction regimen and should be followed by a prolonged less toxic treatment to maintain remission (2). In the case of relapses occurring under or immediately after withdrawing therapy, or when patients do not respond to several lines of immunosuppressants (IS), alternative therapies are needed. They include other combinations of IS or intensification of the previously prescribed drugs. Biotherapies, like intravenous immunoglobulins (3), anti-tumor necrosis factor- $\alpha$  (4, 5) and, more recently, anti-CD20 (6) antibodies, can also be prescribed instead of or in addition to conventional treatments. Herein, we report our experience with 8 patients who received rituximab for WG relapses occurring despite optimal conventional treatment and/or other biotherapies.

## Patients and methods

Patients' characteristics, affected organs, indication of rituximab and anti-neutrophil cytoplasm antibody (ANCA) status are reported in Table I.

## Patients

We retrospectively reviewed the medical files of the 8 patients followed in our department who received rituximab between May 2002 and December 2005. All of them fulfilled the ACR 1990 classification (7) and the Chapel Hill Nomenclature (8) criteria. WG was biopsy-proven for all patients. At diag-

nosis, all patients were c-ANCA-positive with anti-proteinase 3 specificity by enzyme-linked immunosorbent assay (ELISA). Their WG were resistant to cyclophosphamide combined with CS, had relapsed after stopping cyclophosphamide or had contraindications to cyclophosphamide. The first patient was treated in May 2002; data were censored on 30 June 2006.

#### Treatment

Six patients received rituximab intravenously once a week for 4 weeks at the dose of 375 mg/m<sup>2</sup>, based on treatment recommendations adopted from lymphoma regimens. Systematic maintenance therapy consisted of 375 mg/m<sup>2</sup> of rituximab every 4–6 months. Patient 1 received 16 rituximab infusions (375 mg/m<sup>2</sup>) within 26 months: a weekly infusion for 4 weeks, then at progressively prolonged intervals until 1 infusion every 4 months as maintenance therapy. Patient 5 received 2 infusions of rituximab, 1 g at a 2-week interval, based on the therapeutic schedule proposed for rheumatoid arthritis (9).

Concomitant treatments comprised CS, which could be transiently increased according to symptom severity, then progressively tapered until reaching 5 mg/day. IS use was adapted to each patient, i.e., maintained or modified according to disease severity with the objective to reduce and withdraw them as soon as possible. Patients 2 and 4 received plasma exchanges prior to rituximab for glomerulonephritis and mononeuritis multiplex, respectively.

All patients took trimethoprim-sulfamethoxazole (80 mg/400 mg daily) or monthly pentamidine aerosol to prevent *Pneumocystis jiroveci* infection.

#### Assessment

Retrospectively collected information included: clinical manifestations, routine biological parameters, ANCA results (Indirect immunofluorescence and ELISA); computed tomography (CT) scans of the chest, sinuses and orbits, if appropriate, were performed 4 months after the first rituximab infusion, then every 3–6 months, according to the clinical symptoms. Circulating B-lymphocyte counts, assessed by flow

cytometry, were not systematically determined and were not retained as a parameter for drug reinfusion.

All patients were evaluated at 6 months and then in a non-uniform fashion. WG activity was assessed with the 2003 version of the Birmingham vasculitis activity score (BVAS) (10). According to BVAS, complete remission was defined as 0 points, indicating the absence of new symptoms or worsening of those already present. Partial remission was defined as persistent disease activity for no more than 1 item. We considered patients with persistent lung nodules, even if they had decreased in size, to be in partial remission, even though this situation is scored BVAS = 0. The day of the first rituximab infusion was considered day 1.

#### Results

The main findings are summarized in Table I.

#### Overall response to treatment

At 6 months, 5 of our 8 patients (no. 1, 2, 4, 5 and 6) had BVAS = 0 but only patients 2, 5 and 6 were considered to be in complete remission, because patients 1, 3 and 4 had persistent lung nodules, which we defined as partial remission. Patients 7 and 8 did not respond to therapy. By the censoring date, patient 3, who had been in partial remission at 6 months, had entered complete remission.

Patient 1 entered complete remission 1 month after the first rituximab infusion. He relapsed 12 months after the 16<sup>th</sup> infusion and his pyoderma gangrenosum worsened, lung nodules appeared, and a high-degree atrioventricular block developed. Partial remission was obtained 2 months after starting a new course of a weekly rituximab infusion for 4 weeks.

#### ANCA status and biologic inflammatory parameters

Six patients were ANCA-positive at the onset of rituximab therapy and 3 became ANCA-negative at some time after starting rituximab. Rituximab contributed to complete remission for patients 3 and 6, and to partial remission for patient 1; all 3 were ANCA-nega-

tive when rituximab was administered. In contrast, patient 7's orbital pseudotumor was not affected but he became ANCA-negative.

Considering inflammatory parameters, only patients 1, 2 and 6 exhibited constitutional symptoms: respective elevated C-reactive protein values of 110, 25 and 15 mg/L (normal <5 mg/L) returned to normal within 3, 3 and 5 weeks, respectively, after starting rituximab.

#### Response of granulomatous manifestations

Patients 1, 3 and 4 had lung nodules on chest CT scans before starting rituximab. On rituximab, all their symptoms regressed dramatically except for their lung nodules, which increased in size in 1 and remained unchanged or diminished only slightly over the 6 months following rituximab administration. Leflunomide (10 mg/day) was added to patient 3's regimen. At 9 months, lung nodules remained unchanged but they had disappeared by 15 months. Because patient 4's lung nodules were unchanged at 6 months, methotrexate was added then stopped 6 months later, despite the persistence of lung nodules, because the patient had become asymptomatic since starting rituximab. At 24 months, only 1 lung nodule was still present but its size had decreased.

For patients 7 and 8, who had orbital pseudotumors, rituximab failed to achieve remission. The sizes of the orbital masses decreased only slightly in these patients, but pain relief was obtained.

#### Adverse reaction

Rituximab was well tolerated in all but patient 5, who developed an urticarial rash during the 3 last infusions.

#### Discussion

Herein, we described our experience with 8 patients with refractory/relapsing WG emphasizing the effect of rituximab on the various components of the disease. The overall response was good and complete or partial remissions were obtained in 6/8 patients. Pertinently, general symptoms tended to regress quickly, sometimes in only a few days after the first infusion. In contrast, WG

**Table 1.** Detailed individual demographic, clinical, biological and outcome characteristics of the 8 patients with refractory/relapsing WG given rituximab.

Patient	Age at RTX start/sex	Months since diagnosis	Previously prescribed IS	Ineffective regimens at RTX onset	Active organ involvement at RTX start	Total no. of RTX pulses	ANCA status		BVAS baseline/6 mo	Concomitant drugs	Status at censoring date
							Before RTX	After RTX			
1	44/M	184	oral CYC, IVIg, AZA, MMF, MTX, infliximab	MTX: 12.5 mg/wk; MMF: 3 g/d; CS: 5 mg/d	PG, ENT	16	yes	no (17 mo)	13/0 CR	MTX: 10 mg/wk; MMF: 3 g/d	CR at 2 mo; relapse 12 mo after stopping RTX
Relapse					heart, L, PG	4	no	no	15/0 PR	MTX: 10 mg/wk; MMF: 3 g/d	PR at 6 mo (persistent lung nodules)
2	42/M	30	IV then oral CYC	oral CYC: 200	E, ENT, K, CS: 90 mg/d perforation	5 rectal	yes	no (12 mo)	30/0 CR	CS 5 mg/d; MMF 2 g/d; IVIg	CR at 24 mo
3	55/M	88	IV CYC, MMF, oral CYC, MTX, IVIg, infliximab	infliximab; MTX 25 mg/wk; CS: 25 mg/d	ENT, L, PNS	5	no	no	19/3 PR	CS: 5 mg/d; MTX: 20 mg/wk; leflunomide: 10 mg/d	CR at 18 mo
4	56/M	109	IV then oral CYC, AZA, IVIg, MMF	MMF: 2 g/d; CS: 5 mg/d	L, K	8	yes	yes	13/0 PR	CS: 5 mg/d	PR at 26 mo, (persistent lung nodules)
5	44/F	160	Oral CYC, AZA, MTX, IVIg, IV CYC	IV CYC: 0.6 g/m <sup>2</sup> /15 d	ENT, 'strawberry' gingival hyperplasia	4	yes	no (3 mo)	8/0 CR		CR at 7 mo
6	71/F	52	MTX, IV then oral CYC, IVIg	oral CYC: 125 mg/d; CS: 20 mg/d	ENT, L, PNS	4	no	no	22/0 CR	CS: 10 mg/d	CR at 7 mo
7	47/M	206	IV then oral CYC, MTX, AZA, etanercept	oral CYC: 100 mg/d etanercept, IV CS	E (orbital pseudotumor), ENT, CNS	4	yes	yes	4/4 failure	CS: 20 mg/d; AZA: 150 mg/d; MTX: 15 mg/wk; IVIg	unchanged orbital pseudotumor at 13 mo
8	38/F	108	oral the IV CYC, MTX, etanercept, infliximab, IVIg, AZA	AZA: 150 mg/d	orbital pseudotumor relapse after enucleation	2	yes	no (3 mo)	4/4 failure		unchanged orbital pseudotumor at 6 mo

RTX: rituximab; ANCA: antineutrophil cytoplasm antibodies; BVAS: Birmingham vasculitis activity score; AZA: azathioprine; (IV) CYC: (intravenous) cyclophosphamide; IVIg: intravenous immunoglobulins; MMF: mycophenolate mofetil; MTX: methotrexate; PG: pyoderma gangrenosum; E: eye; ENT: ear, nose, throat; K: kidney; L: lung; CNS: central nervous system; PNS: peripheral nervous system; CR: complete remission; PR: partial remission.

granulomatous manifestations did not respond in the same way. They responded to rituximab much later. Although rituximab failed to achieve remission in patients with orbital pseudotumors, the latter continued to diminish in size and orbital pain disappeared. Concerning lung nodules, no clinically marked size changes were observed during the first months after rituximab. But the patients became completely asymptomatic and granulomas progressively disappeared. The transient adjunction of methotrexate to the treatment regimen of 1 patient and leflunomide for another did seem not to have an effect on the long-term regression of lung nodules. Notably, the rapid attenuation of constitutional and vasculitis-related symptoms was not the consequence of CS, because the prednisone dose was increased for only 2 patients at the time rituximab was administered, and 3 patients were not even taking CS.

Almost all of the patients described by Keogh *et al.* (6, 11), Eriksson (12) and Stasi *et al.* (13) had achieved complete remission by 6 months. At the time of rituximab initiation, their patients were characterized by active organ involvement, mainly due to severe vasculitis (e.g., alveolar hemorrhage) or glomerulonephritis. In contrast, Aries *et al.* (14) reported the lack of rituximab efficacy in WG patients with refractory granulomatous manifestations. However, in the latter, the therapeutic response had been evaluated 4 weeks after the completion of the 4<sup>th</sup> rituximab pulse, which might have been too early to assess the efficacy of this biologic. In light of the slow regression of granulomatous disease under rituximab that we observed in our patients, rituximab efficacy on granulomatous manifestations should not be evaluated before 3 months or even before 6 months. If this approach is correct, it would mean that rituximab might not be appropriate, at least as the sole agent, when a granulomatous mass is organ-threatening (e.g., orbital pseudotumor and retrobulbar optic neuritis). Should ongoing prospective clinical trials confirm the efficacy of rituximab, a further step would be to determine whether its combination with other treatment(s) could reduce the time to

response for threatening granulomatous manifestations and/or enhance the expected effect of the anti-CD20 therapy. BVAS is usually used to assess the activity of ANCA-associated vasculitis. The absence of new/worsening manifestations generates a score of 0, which can be considered a complete remission. However, partial and complete remissions have been defined differently, depending on investigators' choices. Based on our clinical experience, persistence of unchanged or only slightly diminished pulmonary nodules after 3 months of immunosuppressive therapy was associated with a high relapse rate. Therefore, we considered these patients to be in only partial remission. Among our 8 patients, 5 had BVAS = 0 but, in our opinion, 2 of them should be and were considered as being only in partial remission. Difficulties establishing a reliable scoring system for vasculitis activity were clearly emphasized by the Vasculitis Clinical Research Consortium (10).

We also observed that the response to treatment was sustained. One patient relapsed 1 year after stopping rituximab, despite maintenance IS therapy. But the patient responded well to a 2<sup>nd</sup> rituximab cycle. That case report might encourage clinicians to taper and/or stop IS and/or CS when patients have received/responded to rituximab because the IS maintenance therapy was ineffective and may subsequently appear unnecessary.

We observed that the response to rituximab in WG could be independent of ANCA status. Three of our patients were ANCA-negative when rituximab was administered and they responded to treatment. To the best of our knowledge, only 1 ANCA-negative patient with a sustained 3-year remission after rituximab has been reported (15). In contrast, our patient 8, who had an orbital pseudotumor, became ANCA-negative but was considered a clinical failure. These data challenge theories in which ANCA are key effectors in ANCA-associated vasculitis pathophysiology (16). In addition, our patients 2 and 5 remained ANCA-positive after rituximab treatment and throughout prolonged follow-up. Aries and colleagues (14) also found

that ANCA titers were unchanged for 6 out of 8 patients after rituximab therapy. Pertinently, Browning postulated that rituximab acts directly on B lymphocytes and short-lived plasma cells that also express CD20, resulting in the rapid blockade or decrease of ANCA production, whereas long-lived plasma cells that have lost CD20 are not affected and can continue to produce ANCA (17). The results obtained by Keogh *et al.* (11), Eriksson (12) and Smith *et al.* (18) highlighted that clinical responses to rituximab were associated with effective B-lymphocyte depletion. All reported clinical relapses had been preceded by reconstitution of the B-lymphocyte counts, 6 to 12 months after starting the rituximab cycle.

Rituximab maintenance therapy might be a new alternative but, at present, no such recommendation can be made. For example, 1 rituximab infusion of 375mg/m<sup>2</sup> could be systematically given at fixed intervals, 4-6 months, or new infusions could be prescribed only when circulating CD19-positive B cells reappeared in blood and/or when ANCA are again detected or their titer increases. Such an approach seems reasonable but relapses still occur in ANCA-negative patients. At present, we favor systematic readministration (every 4-6 months), until further experience with this agent justifies modifying this strategy.

In conclusion, rituximab, when prescribed in combination with CS and immunosuppressants for patients with refractory/relapsing WG despite optimal treatment, is able to improve dramatically the clinical outcome, especially for constitutional and vasculitis-related symptoms independently of ANCA status. In contrast, orbital pseudotumors responded late and very poorly, with responses remaining incomplete, but continued attenuation of the other granulomatous manifestations was observed.

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