Treatment of orbital inflammation with rituximab in Wegener's granulomatosis

B. Baslund[1], A.K. Wiencke[2], N. Rasmussen[3], M. Faurschou[1], P.B. Toft[4]

[1]Department of Rheumatology and Institute for Inflammatory Research, Institute for Inflammatory Research, Rigshospitalet, Copenhagen, Denmark; [2]Department of Ophthalmology, University of Copenhagen, Glostrup Hospital, Glostrup, Denmark; [3]Department of Otorhinolaryngology, Head and Neck Surgery, and [4]Department of Ophthalmology Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark.

Bo Baslund, MD, PhD
Anne Katrine Wiencke, MD, PhD
Niels Rasmussen, MD
Mikkel Faurschou, MD, PhD
Peter Bjerre Toft, MD, DMSc

Please address correspondence to:
Dr Bo Baslund,
Department of Rheumatology 4242,
Rigshospitalet,
9 Blegdamsvej,
DK-2100 Copenhagen, Denmark.
E-mail: bbaslund@gmail.com

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ABSTRACT

Objectives. *To study the efficacy of rituximab therapy for the treatment of orbital inflammation in patients with Wegener's granulomatosis (WG).*

Methods. *Ten WG patients with orbital inflammation were included in this case-series. None had symptoms suggestive of extra-orbital disease activity. Immunosuppressive medication (mycophenolate and prednisolone) was administered to 3 patients at the time of rituximab therapy. Three patients had previously been treated with anti-tumour-necrosis-factor-alpha antibodies, and one of these patients had also received cyclophosphamide as treatment for orbital inflammation. All patients were treated with 1000 mg of rituximab administered twice with an interval of 14 days between the infusions. Six months after therapy, a physical examination and a control computerised tomography (CT) scan was performed.*

Results. *All patients had orbital inflammation demonstrated by CT-scan before treatment (3 had bilateral and 7 unilateral orbital involvement). Orbital symptoms at study baseline included pain, pressure sensation behind the eyes, epiphora, diplopia, and affection of the visual acuity. Nine out of ten patients experienced subjective improvement. Four patients (seven eyes) with visual impairment responded to therapy, and the improvement in visual acuity was sustained throughout follow-up (median duration of follow-up: 17 months; range: 6–18 months). At the time of the control CT-scan, size-reduction of the orbital mass was observed in two patients, while the size of the orbital mass was unchanged in eight patients.*

Conclusion. *Rituximab therapy has positive effects on symptoms, visual acuity and/or granuloma size in some WG patients with orbital inflammation. Treatment with rituximab should be considered in WG patients with this serious manifestation of the disease.*

Introduction

Wegener's granulomatosis (WG) is an inflammatory condition characterised by granulomatous inflammation in the respiratory tract, necrotising vasculitis affecting small to medium-sized vessels, necrotising glomerulonephritis, and the presence of anti-neutrophil cytoplasmic auto-antibodies (ANCA) (1). Any organ system may be affected by the disease (2). Ophthalmic involvement is estimated to affect approximately 50% of WG patients, with clinical manifestations ranging from conjunctivitis and episcleritis to more severe inflammation with scleritis and retinal vasculitis (3). Orbital inflammation presenting as an orbital mass (orbital or retro-orbital pseudotumour/granuloma) can be detected in as many as 13% of patients with WG and is frequently associated with visual impairment (2). Orbital inflammation can occur without other organ manifestations during the course of WG, and may even be the presenting feature of the disease (4, 5). While depletion of CD20+ B cells is an effective treatment for WG patients with active vasculitis (6, 7) controversy exist as to the efficacy of anti-CD20-antibody therapy in patients with orbital disease (8-10). In this study, we used rituximab, a chimeric anti-CD20-antibody, for the treatment of ten WG patients with orbital inflammation and observed a high clinical response rate. Thus, our findings substantiate that anti-CD20 antibody therapy can be of benefit in WG patients with orbital disease involvement.

Patients and methods

From December 1, 2008, until November 31, 2009, all WG patients seen at our departments with orbital inflammation were included in the study. For patients to be considered eligible, a computerised tomography (CT)-scan should confirm the presence of an orbital mass. In total, 10 WG patients met this inclusion

Table I. Clinical characteristics of 10 patients with Wegener's granulomatosis and orbital disease involvement at the time of rituximab therapy.

Patient no./age/sex	Systemic organ involvement	Time from diagnosis to orbital inflammation (years)	Anti-TNF	AZA	MTX	CYC	MMF	Treatment at the time of RTX therapy
1/61/M	ENT	2		x	x	x		-
2/66/F	ENT, kidney	23			x	x		-
3/22/F	ENT	3		x				-
4/70/M	ENT, kidney, skin	10			x	x		-
5/68/F	ENT	5	x	x		x	x	MMF and prednisolone
6/41/F	ENT, pulmonary	9			x	x	x	-
7/29/F	ENT	8			x		x	-
8/58/M	ENT, skin, kidney, PNS	17	x	x	x	x	x	MMF and prednisolone
9/42/F	ENT, pulmonary	14	x	x	x	x		prednisolone
10736/F	ENT, pulmonary	17		x		x		-

AZA: azathioprine; CYC: cyclophosphamide; ENT: Ear, nose and throat; MMF: mycophenolate mofetil; RTX: rituximab; PNS: peripheral nerve system; F: female; M: male.

Table II. Presenting symptoms, visual acuity, computerised tomography before and after treatment, and subjective improvement.

Pt. No	Presenting ophthalmological symptoms	Visual acuity right eye Before-after treatment	Visual acuity left eye Before-after treatment	CT findings right orbit	CT findings left orbit	Orbital mass size on CT after treatment right/left orbit	Subjective improvement reported by patient
1	Right eye: pressure feeling over the eye	6/18–6/6	6/12–6/12	medial granuloma	normal	UC/UC	yes
2	Left eye: palpable tumour in the medial canthus, swollen and red eye lid	6/9–6/9	6/6–6/6	normal	medial granuloma	UC/regression	yes
3	Right eye: change in the perception of colour, two errors on Ishihara colour plates	6/6–6/6	6/6–6/6	apical granuloma	normal	Regression/UC	yes
4	Left eye: impaired motility, double vision	6/9–6/6	6/12–6/9	intra+extra conal granuloma	intra+extra conal granuloma	UC/UC	yes
5	Right eye: pressure feeling behind the eye	6/6–6/6	CF-CF	intra+extra conal granuloma	normal	UC/UC	yes
6	Right eye: pain in the medial canthus, change in the perception of colour	6/9–6/6	6/9–6/6	medial granuloma	medial granuloma	UC/UC	yes
7	Pain behind the eyes	6/9–6/6	6/36–6/18	intra+extra conal granuloma	intra+extra conal granuloma	UC/UC	yes
8	Left eye: oedema in the medial canthus	exenterated orbit	6/6–6/6	exenterated orbit before rituximab	intra+extra conal granuloma	-/UC	yes
9	Right eye: pain in the orbit	6/6–6/4.5	6/6–6/6	apical granuloma	normal	UC/UC	yes
10	Epiphora, palpable tumour	6/6–6/6	6/6–6/6	normal	medial granuloma	UC/UC	no

UC: unchanged; CF: counting fingers.

criterion. All patients were proteinase-3 ANCA positive at the time of diagnosis. Previous organ manifestations of WG experienced by the patients are summarised in Table I. The median time from diagnosis of WG to the demonstration of orbital inflammation was 9.5 years (range: 2–23 years). Three patients had been treated for orbital inflammation prior to the study. All of these patients had received anti-tumour-necrosis factor-alpha antibody therapy, and one patient had also received cyclophosphamide on this indication. These patients were regarded as refractory with respect to the orbital inflammatory disease. Patient no. 7 had received rituximab due to active pulmonary and cutaneous vasculitis one year before the current study. None of the patients presented with clinical, radiological, or laboratory findings indicating active WG outside the orbits at study baseline.

Rituximab (Mabthera, Roche, Basel, Switzerland) was given as 2 intravenous doses of 1000 mg, administered at days 1 and 14 of the study. Adjuvant medication given immediately before the infusions included anti-histamines and 100 mg of prednisolone. A second CT-scan of the orbits was performed 6 months after therapy.

Results

Symptoms at study baseline included pain and pressure sensation in the or-

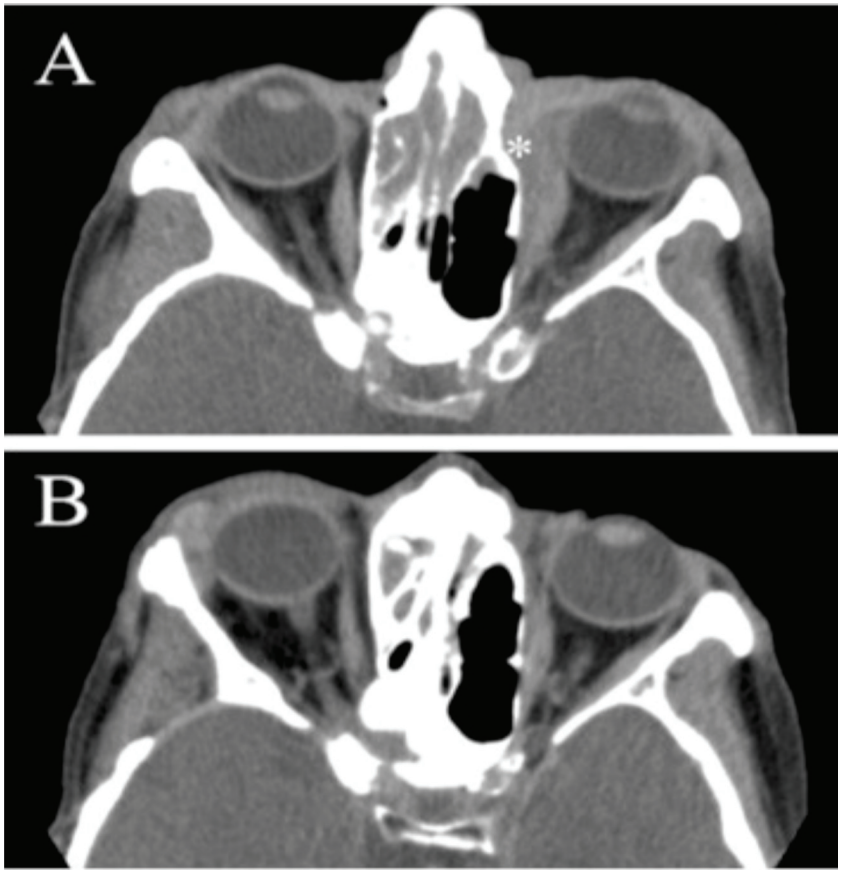

Fig. 1. Computerised tomography (CT) findings in patient no. 2 before (**A**) and six months after (**B**) treatment with Rituximab. Note that the size of the tumour (*) in the left medial orbit decreased after treatment. The CT image at 6 months after the treatment (**B**) is slightly oblique, causing the levels of images A and B to be directly comparable only at the left side.

bit, change in the perception of colour, double vision and epiphora. Objective findings included palpable tumour in the orbit (through the lids), oedema of the eye lids, mild protrusion of the eye globe, decreased visual acuity, errors on Ishiharas colour plates, impaired eye mobility, papil oedema, chronic nasal crusting and chronic nasal *Staphylococcus aureus* infection.

All patients tolerated rituximab treatment well, and serious side-effects, including macular oedema (11), were not observed. The peripheral CD20+ B cells were depleted in all cases for at least 6 months. The observed subjective and objective effects of rituximab therapy are listed in Table II. Nine out of ten patients reported subjective improvement that was sustained throughout the follow-up period (median duration of follow-up: 17 months [range: 6–18 months]). Four patients had impaired visual acuity at study baseline. Rituximab-treatment improved the visual acuity in all of these patients. (Table II). Patient no. 9 developed right-sided cataract and the visual acuity decreased to 6/12. However, it returned to 6/4.5 after cataract surgery.

At the time of the control CT-scan, progression of the orbital mass was halted in all cases, and size reduction was observed in two patients (Fig. 1).

In one of the patients who did not obtain size-reduction of the orbital mass, a biopsy of the mass was performed 11 months after treatment at a time when no CD20+ B cells could be seen in the peripheral blood. This biopsy showed the presence of both B- and T-cells in the lesion.

Eight patients had chronic nasal infection with *Staphylococcus aureus* and nasal crusts. There was no association between the location of orbital inflammation and the location of nasal crusting.

Discussion

In this case-series study, we found that depletion of CD20+ B cells is frequently beneficial in WG patients with orbital inflammation. However, a radiological size-reduction of the orbital mass was seen in only 20% of cases. Of note, we did not observe size progression of the orbital mass in any of our patients. These results are in contrast with the observations by Aries *et al*. (9), who observed a further enlargement of the orbital mass in 3 out of 5 rituximab-treated WG patients with orbital inflammation. Although Aries and co-workers used a different scheme for rituximab treatment (4 infusions of 375 mg/m^2 in 4 weekly intervals), this unlikely explains the differences in outcome, since both regimes resulted in depletion of peripheral CD20+ B cells. In a recent study, Taylor and co-workers used rituximab for the treatment of 10 patients with refractory ophthalmic manifestations of WG (8). The results of that study are comparable to our findings with regard to clinical efficacy of rituximab therapy.

The pathogenesis of orbital inflammation is unknown. The proximity of the nose and the orbit could suggest a "rhinogenic" element in the pathogenetic events leading to orbital granuloma formation in WG. However, our observations do not support this hypothesis. The granulomatous lesions in WG consist of monocytes, macrophages, giant cells and neutrophils together with T-cells and B-cells (12). The inflammatory process induces orbital contracture in some patients, probably due to inflammation-provoked fibrosis. This condition is characterised by enopthalmos, restrictive opthalmopathy, chronic orbital pain, and optic nerve disease and is not responsive to immunosuppressive treatment (13). Talar-Williams *et al*. reported orbital contracture in 6 out of 18 patients with orbital manifestations of WG. We did not observe this phenomenon in any of our patients, and to some extent this may account for the relatively high response rate to rituximab therapy in the cohort.

In conclusion, although available results are conflicting, our data suggest that rituximab treatment constitutes a therapeutic option for patients with WG and orbital inflammation.

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