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CLINICAL STUDY

Rituximab for the treatment of IgG4-related orbital disease: experience from five cases

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Abstract

Purpose **To review the clinical efficacy and safety of rituximab for treatment of IgG4-related orbital disease (IgG4-ROD).**

Design **Retrospective multicentre interventional case series.**

Methods **Chart review for five cases of biopsy-confirmed IgG4-ROD (IgG4+ >10/HPF, ratio of IgG4+/IgG+ >40%) treated with rituximab. Information retrieved included the dosing schedule, adverse events and the magnitude, temporality, and duration of the clinical response.**

Results **All cases of IgG4-ROD were either steroid dependent or steroid resistant. Rituximab doses for induction therapy included two doses of 1000 mg at 2-weekly intervals, and four doses at 375 mg/m² at weekly intervals. Two months after starting rituximab, three cases achieved complete clinical resolution and two cases achieved partial clinical resolution. Complete radiological resolution occurred in one case, and partial radiological resolution in three cases. Three cases received rituximab maintenance therapy and one case was commenced on mycophenolate. No relapse occurred during a mean follow-up of 33 months (range: 7–65 months). One disease relapse occurred when the dosing interval of rituximab maintenance therapy was extended to 6–monthly intervals; remission was swiftly achieved with rituximab reinduction therapy. The only adverse effects reported were one episode of fatigue lasting 1 week and two episodes of orbital discomfort.**

Conclusion **Rituximab may be an effective treatment option for IgG4-ROD that is steroid dependent or steroid intolerant. Rituximab therapy resulted in swift clinical and radiological improvement, many months free of relapse, and few side effects.**

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Introduction

IgG4-related disease (IgG4-RD) is a systemic disorder characterised by soft tissue mass lesions infiltrated with IgG4-bearing plasma cells.[1] The orbit is the sixth most commonly involved site, affected in approximately 3.6–12.5% of cases.[1–4] Retrospective IgG4 staining of orbital biopsies has revealed that IgG4-RD may account for 36% of cases originally diagnosed as idiopathic orbital inflammation,[5] and an even higher proportion of orbital lymphoid hyperplasia.[6,7]

Corticosteroids are considered first-line treatment for IgG4-ROD and the response is typically excellent but unsustained. A meta-analysis of published cases of IgG4-related orbital disease (IgG4-ROD) revealed that 50% of all cases treated with corticosteroids experienced disease relapse during dose taper or shortly after corticosteroid cessation.[1] A further study found that two of nine patients relapsed following tapering of corticosteroid.[8] The relapse rate following corticosteroids is similar for extra-orbital IgG4-RD. Approximately 36–59% of patients with IgG4-related pancreatitis relapse following corticosteroids,[9–12] and approximately 48% of IgG4-RD patients require additional pharmacotherapy because of steroid dependence, steroid adverse effects, or steroid-resistant disease.[4] Non-corticosteroid pharmacotherapies have included immunosuppressants (azathioprine, methotrexate, mycophenolate, 6-mercaptopurine, cyclophosphamide, cyclosporine), biological agents (rituximab, tocilizumab, infliximab, adalimumab), and anti-neoplastic agents (imatinib, bortezomib).[4,13–16]

Rituximab is a monoclonal antibody against CD20 and has been reported to be effective in controlling IgG4-RD.[4,17–26] Typically reserved as a second-line agent because of cost and potential toxicity, studies indicate that it is a useful treatment option for IgG4-RD patients who are intolerant to corticosteroids or have steroid-refractory disease.[12,17] However, the literature regarding rituximab treatment for biopsy-proven IgG4-ROD is limited to a few case reports.[18–21,27] The follow-up in these reports was generally short, often less than 10 months, and therefore the long-term efficacy of rituximab in IgG4-ROD is not known.

The aim of this study was to retrospectively review cases of biopsy-confirmed IgG4-ROD treated with rituximab, paying particular attention to the dosing regimen used, the magnitude, temporality, and duration of the clinical effect, and the occurrence of adverse reactions. Our purpose was to share our experience with this treatment modality by presenting cases that may serve as a reference for ophthalmologists who are considering initiating rituximab therapy for IgG4-ROD.

Materials and methods

This study was a retrospective multicentre non-comparative clinical case series. In May 2013, orbital surgeons in Australia were invited to contribute cases of biopsy-confirmed IgG4-ROD treated with rituximab. Cases were classified as IgG4-ROD if they presented with an orbital inflammatory syndrome, and orbital biopsy demonstrated >10 IgG4+ plasma cells per high-power field (HPF) and a ratio of IgG4+/IgG+ cells $>40\%$ in the setting of morphology consistent with the diagnosis of IgG4-RD. These inclusion criteria are based on previously suggested diagnostic criteria.[28] An elevated serum IgG4 (≥ 135 mg/dl) was considered supportive of the diagnosis but was not required for inclusion. There were no exclusion criteria.

A chart review was undertaken for all cases. The following information was retrieved: demographic information (age, gender); medical history (atopic or autoimmune disease); clinical features of IgG4-ROD (presenting features, symptom duration, laterality); radiological data (orbital and extra-orbital structures involved by IgG4-ROD radiologically); laboratory data (serum IgG4 concentration, blood eosinophilia); non-rituximab treatment data (treatment(s), response); and rituximab treatment data (dose, response, adverse reactions). Institutional Human Research Ethics Committee approval was obtained.

Results

Five cases fulfilled the inclusion criteria. All patients were Caucasian, and four of the five patients were living in rural areas at the time of their orbital biopsy. Only one case (Case 2) had a history of allergic or autoimmune disease (asthma). A synopsis of the clinical and radiological data at presentation is presented in Table 1. Table 2 provides a summary of treatment details.

Case 1

A 46-year-old woman presented with a 3-month history of painless left upper lid swelling and proptosis. Orbital biopsy showed 266 IgG4+ cells/HPF, a ratio of IgG4+/IgG+ cells of 94%, and lymphoid hyperplasia.

Two doses of triamcinolone (40 mg) were injected into the left orbit 6 weeks apart, associated with complete clinical resolution. Six weeks after the second dose, bilateral, multifocal orbital disease developed, which was confirmed to be IgG4-ROD on repeat biopsy. Bone marrow biopsy demonstrated no evidence of monoclonality and whole-body 18-Deoxyglucose Positron Emission Tomography revealed no extra-orbital

Table 1 Clinical and radiological data at presentation

Case/Age/Gender	*Clinical findings*	*Orbital structures involved on imaging*	*Extra-orbital swellings on imaging*
1/46/F	L proptosis and L upper lid swelling	L side: MR, SR, fat Subsequent bilateral multifocal orbital disease	None
2/49/M	Bilateral (L>R) proptosis and upper lid swelling	Bilateral: LG, LR, preseptal tissues	Bilateral SMGs, cervical LNs
3/64/M	Bilateral upper lid swelling and proptosis	Bilateral: LG, fat, SR, LR L side: frontal nerve	L parotid gland, cervical and mediastinal LNs
4/83/M	L upper lid swelling and L proptosis	L side: LG Bilateral: LR	Bilateral parotid glands
5/48/F	L upper lid swelling and L ptosis	L side: LG, preseptal tissues	None

Abbreviations: LG, lacrimal gland; LNs, lymph nodes; LR, lateral rectus; MR, medial rectus; SMGs, submandibular glands; SR, superior rectus.

Table 2 Rituximab treatment details

Case	*Induction rituximab*	*Maintenance therapy*	*Outcome*	*Time to clinical response*	*Duration of follow-up since first dose of rituximab (months)*
1	375 mg/m^2 (600 mg) IV, 4 doses at weekly intervals	Rituximab (same dose as induction) at 3, 4, and then 6-monthly intervals	Success, no relapse	Complete response at 4 weeks	65
2	375 mg/m^2 (800 mg) IV, 4 doses at weekly intervals	Rituximab (same dose) at 3 and then 6-monthly intervals	Success, 1 relapse successfully treated with rituximab reinduction and maintenance therapy	Complete response at 4 weeks	57
3	375 mg/m^2 (700 mg) IV, 4 doses at weekly intervals	4 doses of rituximab (same dose) at 2-monthly intervals	Success, no relapse	Complete response at 3 weeks	38
4	500 mg IV, 1 dose	None	Success, no relapse	Partial response at 2 months, minor symptoms at 4 months	7
5	100 mg IV, 2 doses at 2 weeks apart	Mycophenolate BD (ongoing, gradually reduced) and prednisolone OD (20 months)	Success, no relapse	Partial response at 2 months, minor symptoms at 6 months	30

FDG-avid lesions. Oral prednisolone was started at 1 mg/kg/day and slowly tapered. The initial clinical response was good, but dose tapering resulted in recrudescence of symptoms. Corticosteroid side effects included hypertension, glucose intolerance, and insomnia.

Four doses of 375 mg/m^2 rituximab (600 mg) IV were given at weekly intervals by an oncologist. Pre-medications with each dose included IV hydrocortisone (100 mg), oral loratadine (10 mg) and oral paracetamol (1 g). Complete clinical resolution was achieved by 4 weeks and partial radiological resolution was achieved at 2 months. Rituximab maintenance therapy (600 mg IV) with the same doses of pre-medications was given in the following regimen: 3-monthly dosing intervals for 30 months, 4-monthly dosing intervals for 16 months, followed by 6-monthly dosing intervals (ongoing). The only side effect was one episode of fatigue lasting 1 week. No relapses have occurred during 65 months of follow-up since starting rituximab. Improvement in disease was shown on orbital computed tomography scans prior to treatment at 2 months follow-up and at 2 years follow-up (Figure 1).

Case 2

A 49-year-old man presented with a 5-month history of bilateral upper lid swelling and proptosis. Orbital biopsy demonstrated 280 IgG4+ cells/HPF, a ratio of IgG4+/IgG+ cells of 93%, and lymphoid hyperplasia. The patient had a past history of asthma and a blood eosinophilia at presentation of 0.65×10^9/l (normal: $< 0.5 \times 10^9$/l).

Oral prednisolone was started at 1 mg/kg/day and tapered by 10 mg/day each week. The clinical response was initially excellent, but dose tapering resulted in recrudescence of inflammation. The patient suffered eight disease flares during 5 years of treatment and could not be weaned from corticosteroids. A single intraorbital injection of triamcinolone (40 mg) resulted in a moderate but unsustained improvement. Corticosteroid side effects included weight gain.

Four doses of 375 mg/m^2 rituximab (800 mg) IV were given at weekly intervals by an oncologist. Pre-medications with each dose included IV hydrocortisone (100 mg), oral loratadine (10 mg), and oral paracetamol (1 g). Complete clinical resolution was achieved by 4 weeks. Repeat computed tomography scan of the orbits at 2 months demonstrated partial radiological resolution with persistent soft tissue thickening in the left superolateral orbit. Maintenance rituximab therapy (800 mg IV) with the same doses of pre-medications was given at 3 monthly intervals. At 24 months, the patient remained in clinical remission and the decision was made to extend maintenance therapy to 6 monthly dosing intervals. Just prior to his first-scheduled 6-monthly dose, the patient suffered a disease relapse. Symptoms included left eyelid swelling, erythema, and pain. Repeat computed tomography scan demonstrated diffuse enlargement of the left lacrimal gland.

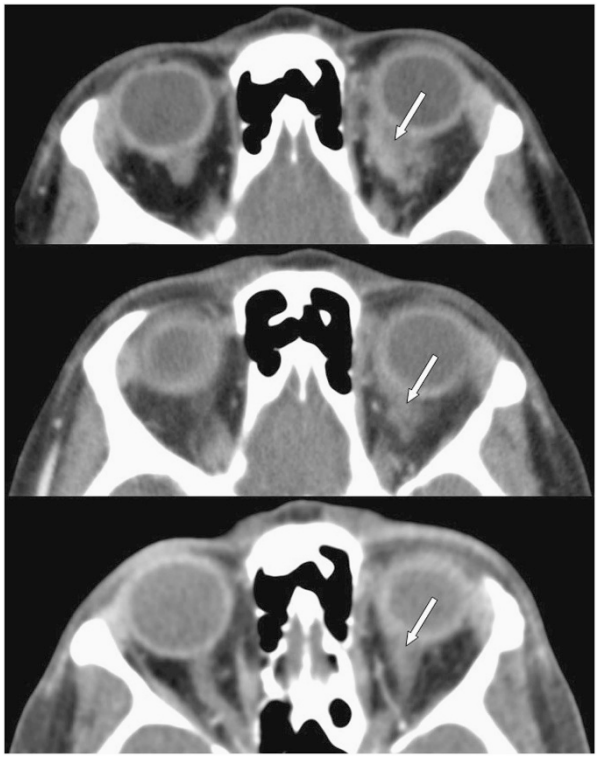

Figure 1 Left superior orbital mass (white arrow) in Case 1 significantly reduced in size following rituximab treatment. No abnormality detected at 2-year follow-up. Axial computed tomography pre-treatment (top); computed tomography at 2-month follow-up (middle); and computed tomography at 2-year follow-up (bottom).

The patient was commenced on a tapering dose of oral prednisolone (1 mg/kg/day) followed 1 week later by rituximab reinduction therapy (four doses of 800 mg IV at weekly intervals). A partial clinical resolution was achieved just 1 week after the first rituximab dose. Rituximab maintenance therapy was continued at 3-monthly dosing intervals and complete clinical remission has been sustained for another 27 months. The patient has reported no adverse effects to rituximab during a total follow up of 57 months.

Case 3

A 64-year-old man presented with painless swelling of the left upper lid and proptosis. Orbital biopsy demonstrated 266 IgG4+ cells/HPF, a ratio of IgG4+/IgG+ cells of 94%, and sclerosis. The patient had blood eosinophilia at presentation of 0.8×10^9/l (normal: $<0.5 \times 10^9$/l).

Orbital symptoms were controlled with a tapering dose of oral prednisolone (1 mg/kg/day), but the patient relapsed soon after prednisolone cessation. The disease was relentlessly recurrent to both orbits with seven disease flares occurring in 12 years, each treated with oral prednisolone. The patient also developed cervical and mediastinal lymphadenopathy, and biopsy-confirmed IgG4-RD of the left parotid gland. Bone marrow biopsy demonstrated no evidence of monoclonality.

Four doses of 375 mg/m^2 rituximab (700 mg) IV were given at weekly intervals by an oncologist. With each dose, the patient was given one oral dose of chlorambucil (20 mg) and prednisolone (100 mg) OD for 4 days. The patient was admitted to hospital overnight for observation for his first dose. Complete clinical resolution was achieved by the third week of treatment. Repeat head computed tomography scan at 6 weeks demonstrated complete radiological resolution of all orbital, parotid, and cervical lymph node swellings. A residual 1 cm mass on the left cheek was treated with radiotherapy 30 G given in 15 fractions during 3 weeks. The maintenance therapy given was four doses of rituximab only (700 mg) at 2-monthly intervals. The patient has maintained complete clinical remission for 38 months since starting rituximab. No adverse effects of rituximab have been reported.

Case 4

An 83-year-old man presented with a 2-month history of painful left upper eyelid swelling. Orbital biopsy showed >100 IgG4+ cells/HPF, a ratio of IgG4+/IgG+ cells of 100%, and sclerosis. Serum IgG4 was elevated at 271 mg/dl (normal: <135 mg/dl).

Three courses of prednisolone were given (tapering dose starting at 1 mg/kg/day); however, the patient suffered disease relapse each time the prednisolone was stopped. Corticosteroid side effects included epistaxis.

One dose of rituximab (500 mg) IV was administered by a haematologist. At 2 months, partial clinical response and partial radiological response were achieved. By 4 months, there was minimal lacrimal gland swelling, mild ptosis, and full extraocular movements. No maintenance therapy was given and no relapse occurred during 7 months of follow-up. No adverse effects of rituximab were reported.

Case 5

A 48-year-old woman presented with left upper eyelid swelling and left medial canthus irritation. Orbital biopsy showed 73 IgG4+ cells/HPF, a ratio of IgG4+/IgG+ cells of 48%, and sclerosis. Serum IgG4 was elevated at 152 mg/dl (measured after systemic and intraorbital corticosteroid treatment, normal: <135 mg/dl).

Prior to orbital biopsy, the patient was treated with chloramphenicol 0.5% eye drops QID, oral amoxicillin/clavulonate (500/125 mg BD) and loratadine (10 mg daily)

without response. One month after presentation, the eyelid swelling had progressed to a complete mechanical ptosis. The patient was commenced on oral cephalexin (500 mg QID) and prednisolone (50 mg/day), and experienced a partial clinical response but relapsed upon prednisolone cessation. Three intraorbital injections of triamcinolone acetonide (20, 40, 40 mg) were given during the subsequent 2 months. The clinical response was good but unsustained. A slowly tapering dose of prednisolone (25 mg/day) was started. Oral azathioprine (100 mg/day) was given for 2 weeks and then stopped because of side effects of nausea and vomiting.

Two doses of rituximab (1000 mg) IV were given 2 weeks apart by an immunologist. The patient experienced orbital discomfort for 48 h after each infusion. Two months after starting rituximab, partial clinical resolution was achieved. The patient reported symptom resolution at 3 months. On examination at 6 months, proptosis had resolved and extraocular movements were full. Orbital imaging was not repeated. Mycophenolate maintenance therapy was given in the following regimen: 1.5 g BD for 6 months, 1 g BD for 12 months, 750 mg BD for 5 months, followed by 500 mg BD. Prednisolone was ceased 20 months after starting rituximab. Two months after starting rituximab, the B-cell count was low at $<12\times10^6$/l (normal: $>100\times10^6$/l). At 23 months, B-cell count had recovered to 112×10^6/l. During follow-up, serum IgG4 levels remained within normal limits. Clinical remission has been maintained for 30 months since starting rituximab.

Discussion

This case series is the largest review of rituximab therapy amongst patients with biopsy-confirmed IgG4-ROD. Our results suggest that rituximab may be an effective treatment for cases of IgG4-ROD that are steroid resistant or steroid intolerant. Rituximab treatment resulted in swift clinical and radiological improvement, many months free of relapse, and few side effects.

Corticosteroids were used as first-line anti-inflammatory treatment in all cases, producing a clinical response that was excellent but unsustained. Disease flares during corticosteroid dose tapering were common, resulting in corticosteroid dependence in all cases. Three cases also experienced significant corticosteroid side effects. After starting rituximab, clinical and radiological response was dramatic and swift. Within 2 months, partial clinical response had occurred in all cases. Complete radiological response occurred in one case and partial but significant radiological response occurred in the other three cases for which post-treatment imaging was performed. Rituximab maintenance therapy was given in three cases, with a dose frequency ranging from 2 months (given four times) to 6 months (ongoing). All cases have been free of relapse during a mean follow-up of 33 months (range: 7–65 months). Rituximab adverse effects included one episode of fatigue (Case 1) and two episodes of orbital discomfort (Case 5). Induction dose regimens used for Cases 1, 2, 3, and 5 were consistent with regimens used in the past for IgG4-RD and other conditions.[18,19,21,23,26,29] However, as Case 4 required a lower dose of rituximab, further study may help to determine the optimal regimen for treatment of IgG4-ROD.

Our results corroborate the results of large case series ($n=24$ in total) reporting the efficacious and safe treatment of IgG4-RD with rituximab.[12,17,18] To the best of the authors' knowledge, only 13 cases of biopsy-confirmed IgG4-ROD treated with rituximab have been reported in the literature.[18–21,27] Over half of these cases did not specify the dosing regimen. In three of these cases, the treatment regimen was two doses of rituximab (1000 mg) 15 days apart, and with each dose, methylprednisolone (100 mg), diphenhydramine (25 mg), and acetaminophen (650 mg) were also given. In eight cases, complete clinical response was achieved and no relapses occurred. Unfortunately, the duration of follow-up for these cases was short, often less than 10 months. As such, limited conclusions could be drawn about the long-term efficacy of rituximab in treating IgG4-ROD.

Although few side effects were reported in our series, rituximab has been associated with a range of adverse drug reactions.[29,30] Anaphylactoid and anaphylactic infusion reactions are the most common side effects[31] and typically occur within 2 h of starting the infusion. Symptoms may include chills, nausea, urticaria, angioedema, bronchospasm, and hypotension. The risk of an infusion reaction occurring can be reduced by premedicating with antihistamines, paracetamol, and glucocorticoids.[32] Owing to the risk of serious drug effects and the need for close monitoring during infusions, rituximab is usually administered by oncologists, haematologists, and rheumatologists experienced with its use, side effects, and toxicities. However, studies involving rheumatoid arthritis patients have found that rituximab therapy is generally safe and well tolerated during 9.5 years of observation.[33,34]

Rituximab is a monoclonal antibody against the CD20 antigen, which is located on normal pre-B and mature B lymphocytes. It is used to treat conditions including non-Hodgkin lymphomas, chronic lymphocytic leukaemia, and rheumatoid arthritis. The mean terminal half-life is approximately 20 days.[29] Rituximab acts by inducing apoptosis of CD20-bearing cells by triggering a cytotoxic immune response.[35] The resultant B-cell depletion is rapid and persists for approximately 6 months. B-cell levels usually return to normal within 12 months.[30]

The mechanism by which rituximab controls inflammation in IgG4-RD is unclear. Anecdotal reports indicate that clinical response is paralleled by a decline in serum IgG4 concentration.[36] It has been suggested that this decline results from depletion of the CD20-positive B cells destined to differentiate into IgG4-producing plasma cells.[18] Additionally, although CD20 is normally lost following maturation of B cells into plasma cells,[36] a study found that IgG4-producing plasma cells in IgG4-RD may still express CD20 and therefore be targeted by rituximab.[37] However, because IgG4 antibodies are generally regarded as non-inflammatory, plasma cell depletion cannot solely account for the anti-inflammatory effects of rituximab in IgG4-RD. B cells maintain T cells by presenting antigen to them and it has been suggested that rituximab's anti-inflammatory action in IgG4-RD is primarily through the inhibition of T cells that can result from B-cell depletion. This may lead to a decrease in activated T cells, the profibrotic cytokines secreted by T cells, and inflammatory cellular infiltrate.[38] This hypothesis is supported by the finding that T-cell suppression may have a role in the treatment of IgG4-RD.[19]

It may be helpful to have a reliable indicator of relapse that informs the decision to use maintenance therapy. It has been suggested that an increase in serum IgG4 concentration after B-cell reconstitution is a biomarker predictive of impending disease flare.[18] Measurement of serum IgG4 was not routinely performed in our cases; the decision of whether to give maintenance rituximab therapy was made by the treating oncologist and ophthalmologist, and was empiric. Maintenance rituximab therapy was given to three patients, and the frequency of administration was gradually decreased if remission was maintained.

In this case series, we present our shared experiences of treating IgG4-ROD with rituximab. In our experience, rituximab treatment resulted in swift clinical and radiological improvement, many months free of relapse, and few adverse effects.

Summary

What was known before

- Rituximab is a monoclonal antibody against CD20 and has been reported to be effective in controlling IgG4-related disease.

What this study adds

- Rituximab may be an effective treatment option for orbital manifestation of IgG4-related disease that is steroid dependent or steroid intolerant.

Conflict of interest

The authors declare no conflict of interest.

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Authors Contributions

Design and conduct of the study (NA, AT, PT, AG, DS); collection, management, analysis, and interpretation of the data (AW, NA, AT, PT, AG, DS); preparation, review, or approval of the manuscript (AW, NA, AT, PT, AG, DS).

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