Can Rituximab Induce Long-Term Disease Remission in Patients with Intra-Ocular Non-Infectious Inflammation?

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Key Words

Rituximab · Uveitis · Intra-ocular inflammation · CD20 · Birdshot chorioretinopathy · Remission

Abstract

Treatment of non-infectious uveitis is based primarily on the use of systemic corticosteroids and second-line immunosuppressive drugs. However, their extensive side effect profile, particularly for steroids, has led to the increased use of other immunosuppressive drugs, as sparing capacity agents. Rituximab is an anti-CD20 chimeric antibody, often given as a single course of 2 infusions, resulting in complete depletion of peripheral mature B cells. While it is licensed to treat refractory systemic lymphoma patients, it has also shown promising results in systemic auto-immune diseases, where a single course of treatment is able to achieve long-term clinical remission. Treatment with rituximab has been reported for various ocular conditions, suggesting it may be effective in inducing long-term disease control and other systemic immunosuppressive agents can be reduced or discontinued. When disease relapse occurs, a further course or courses can be given with good results. This review summarizes the current evidence regarding the role of rituximab in treating non-infectious uveitis.

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Introduction

Non-infectious uveitis accounts for up to 10% of pathologies leading to blindness [1]. Treatment is primarily centred on controlling the inflammation and preventing any lasting damage that may result in reduced vision. Corticosteroids remain the mainstay treatment of non-infectious uveitis achieving rapid control of ocular inflammation [2]. However, their attendant side effects have led to the continued search for 2nd-line immunosuppressive drugs that can act as steroid-sparing agents. Many different drugs originally used for systemic autoimmune and neoplastic diseases are available to help control ocular inflammation and lower steroid levels. Most of these systemic immunomodulatory drugs used in ophthalmology have been adopted from other specialties, such as rheumatology, and while their safety profiles make them valid alternatives to long-term high-dose corticosteroids, systemic side effects still prove problematic for a significant proportion of patients [3]. Biological agents target specific molecules, making them effective immunomodulating agents with a relatively high safety profile. Of these, rituximab, a chimeric monoclonal antibody directed against CD20 achieves disease control after a single course, with patients symptom free under either no or significantly reduced treatment. Here we present a short case report demonstrating our use of rituximab for

non-infectious uveitis and review the current literature. The aim of this review is to examine the recent evidence regarding treatment with rituximab in ocular non-infectious inflammation, describe treatment regimes and consider the role of this drug in controlling non-infectious uveitis.

Case Report

A 62-year-old man diagnosed with birdshot chorioretinopathy presented to the clinic in 2008. His main complaints were recurrent episodes of anterior and intermediate uveitis together with cystoid macular oedema. Best-corrected visual acuity (BCVA) at presentation was 6/6 and 6/7.6 for the right and left eyes, respectively. Over the entire follow-up period, he suffered from recurrent bilateral asynchronous flares presenting with increased vitritis and cystoid macular oedema (up to 498 and 396 μm , right and left eyes, respectively) and resulting in decreased BCVA, down to 6/12 and 6/15, right and left eyes, respectively. While both eyes were involved, his left eye was more severely affected, requiring intensive treatment in the form of systemic prednisolone starting at a dose of 60 mg o.d. to which were later added 2nd-line agents, first methotrexate 25 mg $\times$ 1/week and then mycophenolate mofetil (MMF) up to a dose of 1.5 g b.i.d. This was augmented by repeated orbital floor injections of depomedrone 40 mg (3 injections in the left eye), intravitreal injections of triamcinolone acetate 4 mg (1 in the left eye) and an ozurdex implant (1 in the left eye). The combined treatment resulted in temporary improvement in inflammation and BCVA lasting several weeks to months, with relapses occurring as the effect of the local therapy subsided. The use of long-term high-dose systemic steroids resulted in decreased bone density, requiring the initiation of alendronate therapy.

In an attempt to achieve inflammatory control and reduce the requirement for systemic steroids and MMF, a course of rituximab was begun. Two infusions of 1,000 mg were given 2 weeks apart, with subsequent blood analysis demonstrating a complete eradication of peripheral B cells. Three months after treatment his ocular inflammation subsided, his inflammation remained controlled with no vitritis, the cystoid macular oedema reduced, his prednisolone was reduced to 5 mg and MMF to 500 mg b.i.d. At his final follow-up, 9 months after rituximab had been started, the inflammation was controlled and his BCVA was maintained at 6/6 in both eyes. His immunosuppressive treatment remained at prednisolone 5 mg o.d. and MMF 500 mg b.i.d.

Rituximab and CD20

CD20 antigen is a tetraspan membrane protein that acts as a calcium channel and is expressed on the surface of only mature B lymphocytes. While its naive ligand remains unknown, its activation is connected to B cell activation and proliferation [4]. In vitro studies using anti-CD20 antibodies have suggested that CD20 may activate intracellular signalling pathways, leading to cell cycle ar-

rest, apoptosis or lysosome-mediated cell death [5, 6]. It has a variable expression, appearing first in the late stages of B cell maturation; it later disappears when B cells differentiate into plasma cells. By targeting CD20, only mature B cells are affected and precursor stem cells remain unaffected. Furthermore, long-living plasma cells found in the bone marrow are also left unharmed, that way antibody production remains intact and immune memory against previously fought infectious agents is preserved.

Rituximab is a chimeric (murine and human) monoclonal antibody directed against the CD20 antigen [7, 8]. Antibody connection to the receptor initiates a signal cascade that results in B cell death. The exact mechanism of cell death remains unclear; however, it is thought to be caused by a combination of pathways including antibody-dependent cell-mediated cytotoxicity, complement-mediated lysis, growth inhibition and apoptosis [4, 9]. Animal models suggest that antibody-dependent cell-mediated cytotoxicity is the most important pathway [10]. By inducing peripheral B cell depletion, it has been found to be effective in inducing remission of B cell monoclonal proliferation as well as systemic autoimmune diseases. It is usually given in the form of a single course of intravenous infusions that results in rapid, long-lasting depletion of peripheral B cells. Furthermore, as B cells act as antigen-presenting cells, their removal has an impact on T cell activation, extending rituximab's potential use also to T-cell-mediated conditions such as Behçet's disease (BD) [11, 12].

Rituximab in Systemic Disease

While rituximab was approved by the Food and Drug Administration in 1997 for treatment in relapsed or refractory non-Hodgkin lymphoma [13], it is now also used for various systemic inflammatory diseases, including rheumatoid arthritis, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), antineutrophil cytoplasmic antibody-associated vasculitis, systemic lupus erythematosus and microscopic polyangiitis [14–20]. Its widest use in autoimmune disease is for the treatment of refractory rheumatoid arthritis patients who have not responded to other immunosuppressive agents [21–23]. Treatment protocols differ among the various conditions with weekly treatments for 2–4 weeks at doses ranging from 500 to 2,000 mg. These achieve peripheral CD20 B cell depletion and clinical remission, which may last from 6 to 12 months. In cases of relapse, retreatment is able to induce further disease remission.

Table 1. Rituximab in intra-ocular inflammation clinical studies

Paper	Year	Disease	Cases n	Rituximab treatment regime	Outcome	Mean follow- up time months
Iaccheri et al. [51]	2010	Anterior nodular scleritis	1	2 × 1,000 mg, 2-week interval	Remission	9
Ahmadi-Simab et al. [42]	2005	Anterior scleritis	1	4 × 375 mg/m ² , 4-week interval	Quiescence under immunosuppressive therapy	6
Taylor et al. [29]	2009	Ophthalmic GPA	10	2 × 1,000 mg, 2-week interval	Quiescence under immunosuppressive therapy	12
Joshi et al. [43]	2011	Ophthalmic GPA	20	2 × 1,000 mg, 2-week interval	Quiescence under immunosuppressive therapy	18
Cheung et al. [31]	2005	Scleritis associated with GPA	1	2 × 1,000 mg, 2-week interval	Quiescence under immunosuppressive therapy	7
Onal et al. [30]	2008	Scleritis associated with GPA	1	2 × 1,000 mg, 2-week interval	Remission	12
Chauhan et al. [52]	2009	Scleritis associated with rheumatoid arthritis	3	2 × 1,000 mg, 2-week interval	Remission	6–24
Baslund et al. [37]	2012	Idiopathic orbital inflammation associated with GPA	10	2 × 1,000 mg, 2-week interval	4 of 10 clinical improvement	17
Foster et al. [38]	2010	Ocular cicatricial pemphigoid	12 in 2 treatment arms	2 × 1,000 mg, 2-week interval + intravenous immunoglobulin; systemic immunosuppression	Stabilization of BCVA and disease progression	57.5
Heiligenhaus et al. [34]	2011	Uveitis associated with juvenile idiopathic arthritis	10	2 × 1,000 mg, 2-week interval	70% remission	11
Miserocchi et al. [35]	2011	Uveitis associated with juvenile idiopathic arthritis	8	2 × 1,000 mg, 2-week interval + 3rd at 12 months as needed + 4th at 21 months as needed	2 patients in remission 5 patients quiescence under immunosuppressive therapy	11.75
Miserocchi et al. [36]	2011	Uveitis associated with juvenile idiopathic arthritis	8	2 × 1,000 mg, 2-week interval + 3rd at 12 months as needed + 4th at 21 months as needed	1 patient in remission 6 patients quiescence under immunosuppressive therapy	14.87
Sadreddini et al. [11]	2008	Uveitis associated with BD	1	2 × 1,000 mg, 2-week interval	Quiescence under immunosuppressive therapy	24
Davatchi et al. [41]	2010	Uveitis associated with BD	20 in 2 treatment arms	2 × 1,000 mg, 2-week interval; systemic immunosuppression	Improvement in clinical indices	6

Treatment with Rituximab for Ocular Disease

Rituximab has been successfully used to treat ocular disease relating to systemic inflammatory conditions as well as others affecting the eyes alone (table 1). There is some evidence that it may be used as an intravitreal agent in cases of relapsing primary vitreoretinal lymphoma [24, 25], and it has been further reported for use in cases of peripheral ulcerative keratitis [26–28], scleritis related to rheumatoid arthritis and GPA [29–31], juvenile idiopathic arthritis (JIA) [32–36], orbital inflammation [37], ocular cicatricial pemphigoid [38] and BD [11, 39–41]. Most reports suggest their patients achieved clinical remission, in some reflecting quiescent disease with treat-

ment [11, 29, 31, 35, 36, 42, 43]. According to the Standardization of Uveitis Nomenclature, the definition of remission is reserved for inactive disease for at least 3 months after discontinuing all treatments for eye disease [44]. Therefore we have divided the outcome of all the reports into drug-free remission or quiescence under immunosuppressive therapy.

Intra-Ocular Lymphoma

Primary vitreoretinal lymphoma may involve the vitreous, retina, optic nerve and subretinal structures [45]. It mainly develops in elderly people and is regarded as a part of central nervous system lymphomas that are a subset of non-Hodgkin lymphoma. Over 15% of primary

central nervous system lymphoma patients develop intra-ocular lymphoma, with 65–90% of primary vitreoretinal lymphoma patients later diagnosed with central nervous system involvement [24]. Primary vitreoretinal lymphomas are typically classified as a diffuse large B cell lymphoma, and therefore use of rituximab has been explored. Animal models and preliminary clinical studies have suggested that an intravitreal injection of 1 mg rituximab has no untoward ocular effects [46, 47]. It penetrates the entire retina [48], and has a half-life of approximately 5 days, meaning it is effective for up to 3–4 weeks [24]. Clinical trials have indicated it is effective in inducing disease remission alone or in combination with other chemotherapeutic agents [24], and may be used for re-inducing remission in patients with disease relapse that were formerly treated with radiotherapy and systemic chemotherapy [25, 49].

Scleritis and Orbital Inflammation

Inflammation of the sclera may present as an isolated pathology or as part of systemic diseases such as GPA or rheumatoid arthritis. It involves the anterior or posterior sclera and in some cases can result in sclera necrosis. Treatment aims at controlling the inflammation and preventing sclera thinning. Use of rituximab in these systemic conditions has prompted further investigation into its use among patients with refractory scleritis. In patients suffering from GPA involving the sclera, optic nerve or orbital inflammation, who were refractory to combinations of systemic steroids and immunosuppressive agents, the addition of 2 intravenous infusions of rituximab resulted in lasting disease control in all patients [29–31, 37, 42]. These patients had depletion of peripheral B cells, reduction in titers of cytoplasmic-pattern antineutrophil cytoplasmic antibodies and improvement in clinical signs. Other immunosuppressive agents were then lowered or discontinued [29–31]. In a recent case series, Joshi et al. [43] demonstrated efficacy of rituximab treatment among 20 patients with ophthalmic GPA refractory to immunosuppressive therapy. Two doses of 1,000 mg rituximab, given 2 weeks apart, resulted in complete disease control in all patients within 6 months. Disease relapse occurred in a third of patients within 18 months, and retreatment resulted in re-establishing disease control. While these studies demonstrated rituximab is effective for treating scleritis, a recent study has suggested rituximab has limited response in patients with refractory scleritis and orbital inflammation, possibly due to fibrotic changes in the orbit [50]. Results among patients with scleritis associated with

rheumatoid arthritis have been reported where use of rituximab resulted in disease remission and systemic steroids and immunosuppressive agents were discontinued [51, 52].

Juvenile Idiopathic Arthritis

JIA is a systemic condition that involves inflammation of joints as well as ocular involvement. It is the most common systemic disorder associated with uveitis in childhood and up to a third of children suffer from poor long-term visual outcome [53]. While most children have no ocular symptoms during acute bouts of anterior uveitis, repeat flares can lead to progressive ocular complications including cataract, posterior synechiae, glaucoma and maculopathy leading to visual impairment [54]. Oligo-articular JIA and uveitis are associated with up-regulation of immature B cells, generation, activation, and differentiation of clonal B cells and the release of pathogenic auto-antibodies [55]. This is suggested by elevated levels of antinuclear antibodies found in this condition [56]. Use of rituximab has been demonstrated in cases with joint involvement that were refractory to systemic steroids and immunosuppression, including methotrexate, cyclosporin and tumour necrosis factor α inhibitors. Following a single treatment course of 2 infusions, most patients responded by lasting disease remission, with resolution of symptoms and reduction or discontinuation of other immunosuppressive agents [32, 33]. Treatment of ocular involvement was also explored in several small case series demonstrating a positive effect [34–36]. In a case series of 10 JIA patients with ocular involvement, a single treatment course of 2 rituximab 1,000-mg infusions, 2 weeks apart, resulted in uveitis remission in 7 of these patients [34]. Systemic and local immunosuppressive treatments were then tapered with complete withdrawal of all other drugs in some cases. In another case series, a single treatment course resulted in a decrease in inflammatory activity that was noted to begin up until the 4th–5th month after treatment [35, 36]. Disease control lasted 6–25 months with patients who relapsed responding to additional repeat infusions of rituximab [25].

Behçet's Disease

BD is a T-cell-driven systemic auto-immune disorder affecting multiple organs, and is related to severe intra-ocular inflammation [40]. Ocular involvement is paramount to the clinical diagnosis of the condition and is related to a high incidence of visual loss. While historically BD has been treated with high-dose systemic ste-

roids and immunosuppressive agents, recently rituximab has emerged as a possible treatment option. This has forced clinicians to reconsider the role of B cells in classically T-cell-related conditions. It is thought that mature B cells, in their role as antigen-presenting cells, play an important part in T cell activation and disease activity. By depleting mature B cells, lasting disease control was achieved in BD patients who were not responsive to other forms of immunosuppression [11, 39, 40]. In a group of 20 BD patients with retinal vasculitis and oedema, treatment with rituximab resulted in improved disease control at 6 months compared to patients who received a combined cytotoxic treatment including cyclophosphamide, azathioprine and prednisolone [41]. A single course of 2 rituximab 1,000-mg infusions (2 weeks apart) reduced retinal oedema and disease activity scores. Although patients responded to treatment with B cell depletion and inactive disease, they continued to require low-dose systemic steroids and other immunosuppressive drugs [41]. This was both to maintain remission, as well as to prevent rituximab-related side effects, primarily an infusion reaction.

Dosage and Side Effects

While rituximab is widely accepted for treatment of lymphoma and systemic auto-immune conditions, evidence from ocular conditions is less available (table 1). In adults with ocular inflammation most treatment protocols include a single course of two 1,000-mg infusions, 2 weeks apart. This generally results in completed peripheral B cell depletion and disease control with time. In cases when complete response is not achieved or if patients relapse, an additional infusion is given after several months, resulting in renewed disease quiescence [36, 43, 57]. Information regarding paediatric dosage mainly comes from JIA patients. The reported regime in these children is a course of 2 infusions, 2 weeks apart, at a dose of approximately 375 mg/m² body surface [32, 34].

While rituximab has a favourable adverse reaction profile, it is a chimeric antibody that may stimulate the production of human antichimeric antibodies, which can induce hyperreactivity responses [58]. Patients generally tolerate rituximab well with infusion reaction the most frequent adverse event, occurring in most patients during the first infusion, but rarely following subsequent treatments [59]. Most of these patients experience immediate mild reactions (fever, rigor and chills) that can be treated symptomatically. Severe reactions including se-

rum sickness can be avoided using concomitant intravenous corticosteroids [60]. Other serious side effects, reported in patients treated for systemic disease included an increased risk of systemic infections [59], progressive multifocal leucoencephalopathy [61] and hepatitis B reactivation [62]. Of these, the risk of systemic infection, occurring in patients receiving additional immunosuppressive drugs, is of some concern and has even been reported to result in fatal septicaemia [59]. Therefore patients require a continued close follow-up with repeated blood tests.

Conclusions

Rituximab has been shown to be effective in controlling orbital conditions and external ocular inflammation (scleritis). It has also shown efficacy in controlling intra-ocular inflammation in JIA-associated uveitis. In most patients a single course results in inactive disease and other immunosuppressive treatment can be reduced or discontinued. While information regarding the effectiveness of this treatment in intra-ocular inflammation remains limited, results from our own patients, as demonstrated in the case report, indicate that rituximab treatment can result in disease quiescence allowing discontinuation of other immunosuppressive treatment, similar to that achieved in external ocular disease [23, 29].

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