

## Concise report

## Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab)

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## Abstract

**Objective.** Rituximab (RTX), a chimeric mAb directed against the B-cell marker CD20, was investigated for its anti-inflammatory effect in treating refractory uveitis associated with JIA.

**Methods.** Case series, retrospective multicentre. JIA patients with severe uveitis with vision-threatening complications ( $n = 10$ ) and with insidious onset. All patients were treated with RTX for active uveitis refractory to topical and systemic CSs, immunosuppressives and at least one of the TNF- $\alpha$  inhibitors. All had active arthritis. Uveitis and arthritis course were assessed before and after RTX treatment.

**Results.** After one RTX cycle (mean follow-up 11 months, range 7–18 months), uveitis inactivity was achieved in seven oligoarthritis patients (ANA<sup>+</sup>, HLA-B27<sup>-</sup>) for a prolonged period of time (mean 7.5 months, range 6–9 months). Therefore, CSs and immunosuppression could be spared. In three of four patients responding to RTX, uveitis recurred thereafter, and RTX re-treatment led to inactivity again. In another three patients (ANA<sup>+</sup> polyarthritis,  $n = 1$ ; ANA<sup>+</sup> HLA-B27<sup>+</sup> oligo- or polyarthritis,  $n = 2$ ) uveitis activity persisted after RTX therapy. In seven patients, arthritis improved or was inactive after RTX treatment (PedACR30/50/70).

**Conclusion.** RTX may represent a rescue therapy option for severe JIA-associated uveitis refractory to CSs, immunosuppression and TNF- $\alpha$  inhibitors.

**Key words:** Uveitis, Juvenile idiopathic arthritis, Rituximab, B cells, Biologicals.

## Introduction

JIA is observed in patients with onset of disease before the age of 16 years, and in ~10% of individuals, chronic anterior uveitis develops [1, 2]. JIA-associated uveitis is a major cause of visual loss [3, 4]. About 25% of the uveitis patients who experience a severe chronic course require immunosuppressive agents. In addition to the first-choice agent, MTX, CSA, AZA and MMF are commonly used [5–8].

With the development of therapies targeting TNF- $\alpha$ , inactivity of uveitis was achieved in patients who were refractory to these classic immunosuppressive agents [9, 10]. However, a subgroup of patients still does not respond to treatment.

The aetiology of JIA-associated uveitis remains elusive. The pathogenesis is most probably multifactorial. Histopathologically, non-granulomatous inflammatory cell infiltration in the iris and ciliary body has been reported [11]. Some T lymphocytes and monocytes have also been found, but the cell infiltrate was dominated by B cells and plasma cells, with a heavy infiltration of CD20<sup>+</sup> cells [12].

Rituximab (RTX) is a genetically engineered, chimeric murine/human mAb directed against the CD20 antigen [13]. CD20 is found on the surface of normal and malignant B lymphocytes, but not on plasma cells. Rituximab can deplete CD20<sup>+</sup> B cells for a period of 6–9 months [14].

Owing to the notion that B cells might be critical to the development of autoimmune disease, B-cell depletion was extended to a variety of diseases, including RA [15] and

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lupus [16]. We have now evaluated the use of RTX for the treatment of JIA-associated uveitis refractory to conventional immunosuppressants and to one or more TNF- $\alpha$  inhibitors.

## Methods

We treated 10 patients with JIA-associated chronic uveitis and with insidious onset of flares that were refractory to conventional immunosuppression and at least one TNF- $\alpha$  inhibitor. These 10 patients were treated with RTX and followed up at one of the three tertiary uveitis centres between 2007 and 2009, and data was reviewed retrospectively to ascertain effectiveness of this therapy. Written consent was obtained from all patients/parents according to the Declaration of Helsinki. The design of the work conforms to standards currently applied in our countries.

JIA was classified according to the ILAR criteria [17]. All patients had developed uveitis before the age of 16 years. All patients were clinically monitored by the same paediatric rheumatologist in each referral centre with complete physical examination assessing the number of involved joints and routine laboratory test that included ANA, RF and major histocompatibility antigen B27 (HLA-B27). Infections or malignancies were excluded. The uveitis classification applied in the present study is in accordance with previously published criteria [18].

Treatment was initiated with a trial of topical prednisolone-acetate 1%. If active uveitis persisted despite low-dose topical steroids ( $\leq 3$  drops daily), oral steroids were given and MTX was added. If uveitis activity continued or in the presence of significant agent-related side effects, one of the other immunosuppressives or biologicals was applied.

If active uveitis persisted under these treatment regimens, RTX was instituted. Two RTX infusions were given at 2-week intervals. Patients received  $\sim 375$  mg/m<sup>2</sup> body surface. Methylprednisolone i.v. was given to all patients 30 min before each infusion at dosages of 100–250 mg as adapted to body weight. B-cell depletion was confirmed by flow cytometry (less than one CD19<sup>+</sup> cell per microlitre).

The epidemiological data, course of visual acuity and presence of uveitis complications were recorded before and after institution of RTX. Concomitant use of topical CSs and systemic immunosuppressive agents was documented. Sparing of systemic CSs and immunosuppressive agents with RTX was assessed [9]. Additionally, sparing of topical steroids was assessed. Arthritis activity was determined by means of PedACR30/50/70 criteria before and after RTX treatment [19].

Patients were followed up at least at 3-month intervals by ophthalmologists and paediatric rheumatologists. Ophthalmological tests included determination of best-corrected visual acuity, slit-lamp examination, applanation tonometry and ophthalmoscopy. Visual acuity and change of more than two lines (improvement or worsening) and occurrence of uveitis complications during and at the end of the follow-up were documented. Glaucoma was

diagnosed when glaucomatous disc change or visual field defect was present.

Activity of anterior uveitis was graded by means of chamber (AC) cells [18]. Having a grade of  $< 0.5+$  AC cells was considered as inactive disease [18].

## Results

Ten female JIA patients with a mean age of 20 years (range 14–32 years) were treated with RTX for active uveitis between 2007 and 2009. Eight suffered from oligoarthritis and another two had polyarthritis (Table 1). All patients were ANA<sup>+</sup> and RF<sup>-</sup>. HLA-B27 was negative in eight and positive in the other two patients. All patients had a long-term and chronic course of disease with early onset of arthritis (mean 4.8 years, range 2–13 years) and uveitis (mean 4.0 years, range 2–14 years). Nine patients had anterior uveitis and one had anterior and intermediate uveitis. All but one of the patients had a bilateral uveitis. All patients had chronic severe uveitis with insidious onset, with the presence of at least one vision-threatening complication (Table 1). All of the patients had active uveitis before receiving RTX. The patients had also received topical and oral prednisone, various immunosuppressives and at least one of the TNF- $\alpha$  inhibitors (Table 2).

After the RTX treatment, uveitis improved in seven patients. All of them had oligoarthritis and were ANA<sup>+</sup>, but HLA-B27<sup>-</sup>. Uveitis inactivity defined as a grade  $< 0.5+$  AC cells was noted after a mean of 3.1 months (range 2–6 months) following the RTX treatment cycle. CSs and other immunosuppressives could be spared and steroid eye drops could be tapered down. Mean (s.d.) best-corrected visual acuity did not differ before [0.5 (0.49)] or after [0.5 (0.52)] RTX therapy. During the follow-up period (mean 11 months, range 7–18 months) after RTX therapy, none of the patients developed additional vision-threatening complications.

Uveitis recurred in four of the seven treatment responders between 6 and 9 months (mean 7.5 months) after the RTX treatment. Three of the four patients received RTX re-treatment, leading again to inactivity of uveitis. The other patient responded to an increased adalimumab dosage. However, uveitis activity persisted after RTX treatment in three patients. Among these individuals, one had ANA<sup>+</sup> polyarthritis and the other two had ANA<sup>-</sup> and HLA-B27<sup>+</sup> oligo- or polyarthritis.

In all of the patients in this series, arthritis was active before RTX treatment. After RTX, arthritis improved in two patients or became inactive in another five, but was persistently active in another two. Arthritis activity after RTX therapy was not documented in one patient. While arthritis activity persisted after RTX treatment in two of the three uveitis patients who did not respond to RTX treatment, arthritis became inactive after this therapy in one. No serious adverse events were encountered during the follow-up period in our patients treated with RTX.

**TABLE 1** Rituximab therapy in 10 patients with JIA-associated uveitis: patient characteristics

Patient	Age, years/ gender	ILAR classification	HLA-B27/ ANA/RF	JIA diagnosis age, years	Uveitis diagnosis, years	Uveitis type <sup>a</sup>	Eyes involved	Complications
1	20/f	Oligoarthritis, ext.	Neg./pos./neg.	2	2	Anterior	Both	Syn, gl, cat, ME
2	15/f	Oligoarthritis, ext.	Neg./pos./neg.	4	3	Anterior	Both	Syn, cat, gl
3	21/f	Oligoarthritis, ext.	Neg./pos./neg.	11	2	Anterior + interm.	Both	Syn, cat, gl, band, ME
4	16/f	Oligoarthritis, ext.	Neg./pos./neg.	2	2	Anterior	Both	Syn, band
5	32/f	Polyarthritis	Neg./pos./neg.	4	4	Anterior	Both	Syn, band
6	14/f	Oligoarthritis, ext.	Neg./pos./neg.	2	3	Anterior	Both	Syn, cat, gl, band
7	22/f	Oligoarthritis, persist.	Neg./pos./neg.	2	2	Anterior	Left	Syn, cat, gl
8	18/f	Oligoarthritis, ext.	Neg./pos./neg.	4	4	Anterior	Both	Cat, gl
9	24/f	Oligoarthritis, ext.	Pos./pos./neg.	13	14	Anterior	Both	Cat
10	15/f	Polyarthritis	Pos./pos./neg.	4	4	Anterior	Both	Cat, ME

Age at the time of therapy. <sup>a</sup>SUN classification [18]. f: female; cat: cataract; syn: synechiae; gl: glaucoma; ME: macular oedema; band: band keratopathy; interm.: intermediate uveitis; ext.: extended; persist.: persistent; neg.: negative; pos.: positive.

## Discussion

Only a few publications have reported the effect of RTX on the course of severe immune-mediated inflammatory eye disease. RTX has been successfully used to treat refractory Sjögren's disease [20], ulcerative keratitis [21] and scleritis associated with WG [22]. Only one previously published study has reported that RTX may be helpful in selected patients with chronic uveitis refractory to CS and immunosuppression [23]. Herein, the B-cell depletion in the peripheral blood and the positive effect on the uveitis was transient so that inflammation and macular oedema recurred after 9 months. RTX re-treatment led to improvement.

We observed that RTX was capable of inducing inactivity in 7 of 10 patients with JIA-associated uveitis who were refractory to other second-line immunosuppressives. Importantly, sparing of topical and systemic CSs and immunosuppression was achieved after RTX infusions. The good response to RTX treatment is in agreement with previous immunohistochemical observations in JIA-associated uveitis. The focal aggregates mainly consisted of CD20<sup>+</sup> B cells [12]. However, as the infiltrate at enucleation may not reflect those conditions during early active disease, the therapeutic implications of end-stage histology are limited. Although the patients in this series had ongoing disease at an earlier stage, the good response after RTX suggests an important role of B cells in the pathogenesis of JIA uveitis.

After one RTX cycle, sustained B-cell depletion of naïve and autoimmune cells was achieved: peripheral blood CD20 cells were low or could not be detected for up to 6 months, returning to pre-treatment levels within 12 months [24]. In accordance with these observations, the effect of RTX on JIA-associated uveitis in four patients in our case series was also transient, with uveitis relapses being observed after 6–9 months. It is our impression that these relapses occurred in conjunction with B-cell

restoration, as CD19 cells were below detection level initially after RTX infusions and subsequently increased (data not shown).

Only in two patients with a favourable response to RTX therapy were the laser flare photometry (LFM) values in the AC analysed before and after RTX treatment. LFM is a reproducible, non-invasive tool for measuring a break in the blood–aqueous barrier and the AC protein content [25]. Interestingly, the LFM values fall after the treatment, corresponding with the disappearance of AC cells. Previously, a high content of immunoglobulins was detected in an eye with JIA uveitis [26]. We can only speculate that the decrease in LFM values during uveitis improvement may be due to reduced immunoglobulin production in the AC. However, this issue must be studied in a larger number of patients.

Relapses have been seen previously after RTX in patients with other autoimmune diseases; however, a good response to RTX re-treatment was described. This finding was also noted in the RTX-re-treated patients with JIA-associated uveitis in this case series. The lack of RTX efficacy in previous clinical trials on autoimmune disease has been attributed to the survival of long-lived autoreactive plasma cells, which do not harbour CD20 antigen [27]. A previous histological study found significant numbers of plasma cells in an eye from a patient with JIA-associated uveitis. The poor response to RTX in some of our uveitis patients may be related to the important role of plasma cells as the predominant producers of the antibodies.

Our observations suggest that different manifestations of disease show differing responses to treatment. A good response of uveitis to RTX treatment was observed in a subgroup of patients with oligoarthritis, who are ANA<sup>+</sup> and HLA-B27<sup>-</sup>. In contrast, RTX therapy did not induce an adequate response of uveitis in one patient with ANA<sup>+</sup> polyarthritis and in another two with ANA<sup>+</sup> oligo- or polyarthritis, who were HLA-B27<sup>+</sup>. It is of note, however, that all patients included in this series had insidious onset of

**TABLE 2** Rituximab therapy in 10 patients with active JIA-associated uveitis: response to treatment

Patient	Treatment prior to RTX <sup>a</sup>	Uveitis activity after RTX	Months until inactive	Sparing of other immunosuppressives after RTX	Steroid eye drops baseline/after RTX (n = times daily)	Uveitis recurrence after RTX, months	RTX re-treatment at months: uveitis response	Arthritis activity prior to RTX	Arthritis activity after RTX
1	Pred <sup>a</sup> , MTX <sup>a</sup> , CSA, Eta, Ada <sup>a</sup>	Inactive	2	Yes	7/2	9	9 months: inactive	Yes	Inactive
2	Pred <sup>a</sup> , MTX <sup>a</sup> , CSA, Infi, Ada <sup>a</sup>	Inactive	2	Yes	h/1	No	No re-RTX	Yes	Improved
3	Pred <sup>a</sup> , MTX <sup>a</sup> , CSA, Eta, Infi <sup>a</sup> , Ada	Inactive	3	Yes	4/0	7	12 months: inactive	Yes	Inactive
4	Pred <sup>a</sup> , MTX, CSA, Eta, Infi, LEF <sup>a</sup> , Ana <sup>a</sup>	Inactive	3	No <sup>b</sup>	4/2	8	8 months: inactive	Yes	Inactive
5	Pred <sup>a</sup> , MTX, CSA <sup>a</sup> , Eta, Infi, Ada <sup>a</sup>	Active	6	No	2/2	Ongoing	No re-RTX	Yes	Active
6	Pred <sup>a</sup> , MTX, CSA <sup>a</sup> , AZA, Infi, Ada <sup>a</sup>	Inactive	2	Yes	6/1	No	No re-RTX	Yes	Inactive
7	Pred <sup>a</sup> , CSA <sup>a</sup> , AZA, Infi <sup>a</sup>	Inactive	2	Yes	3/3	No	No re-RTX	Yes	ND
8	Pred <sup>a</sup> , MTX <sup>a</sup> , CSA, Infi, Ada <sup>a</sup>	Inactive	4	Yes	2/1	6	No re-RTX	Yes	Improved
9	Pred <sup>a</sup> , MTX, CSA <sup>a</sup> , Aza, Ada <sup>a</sup>	Active		No	h/h	Ongoing	No re-RTX	Yes	Inactive
10	Pred <sup>a</sup> , MTX, CSA <sup>a</sup> , MMF, Eta, Infi, Ada <sup>a</sup>	Active		No	6/6	Ongoing	No re-RTX	Yes	Active

The dosages applied were within the generally used ranges, e.g. for MTX 15 mg/m<sup>2</sup> body surface, CSA 3 mg/kg body weight, AZA 2 mg/kg body weight, adalimumab 24 mg/m<sup>2</sup> body surface, infliximab 6 mg/kg body weight. <sup>a</sup>Baseline treatment. <sup>b</sup>No other immunosuppression directly before and after RTX due to intolerance. Pred: prednisolone; Ana: anakinra; Eta: etanercept; Infi: infliximab; Ada: adalimumab; ND: not determined.

flares, which is typical for the anterior uveitis type in the oligoarthritis subgroup of JIA. It is speculative that the differing responses may reflect differing pathogenesis of uveitis in these subgroups of JIA patients.

For this first trial, JIA patients with long-standing disease and uveitis persisting into adulthood were chosen. Indeed, 5 of the 10 patients were already older than 18 years of age at the first RTX cycle. However, the response to RTX treatment was not related to patient age. No significant side effects from RTX were noted during the observation period in this small case series. However, the follow-up was relatively short. Therefore, we refer to other publications on this important issue. The safety profile appears to be well defined, including, for example, infusion reactions, haematological events, interstitial lung fibrosis, infectious complications and risk of malignancy [28–30].

In summary, we show for the first time that RTX is capable of inducing improvement and inactivity of uveitis and arthritis in JIA patients refractory to topical and systemic CSs, immunosuppressives and TNF- $\alpha$  inhibitors. RTX may represent a rescue therapy option in a severe course of JIA-associated uveitis with complications. Indications and treatment protocols for initial and maintenance therapy must be studied in future trials.

#### Rheumatology key message

- RTX may represent a rescue therapy option for severe JIA-associated uveitis refractory to CSs, immunosuppression and TNF- $\alpha$  inhibitors.

*Disclosure statement:* The authors have declared no conflicts of interest.

#### References

- 1 Carvounis PE, Herman DC, Cha S *et al*. Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Arch Clin Exp Ophthalmol* 2006;244:281–90.
- 2 Heiligenhaus A, Niewerth M, Ganser G *et al*. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology* 2007;46:1015–9.
- 3 Edelsten C, Reddy A, Stanford MR *et al*. Visual loss associated with paediatric uveitis in English primary and referral centers. *Am J Ophthalmol* 2003;135:676–80.
- 4 Thorne JE, Woreta F, Kedhar SR *et al*. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. *Am J Ophthalmol* 2007;143:840–6.
- 5 Heiligenhaus A, Mingels A, Heinz C *et al*. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. *Eur J Ophthalmol* 2007;17:743–8.
- 6 Doycheva D, Deuter C, Stuebiger N *et al*. Mycophenolate mofetil in the treatment of uveitis in children. *Br J Ophthalmol* 2007;91:180–4.

- 7 Tappeiner C, Roesel M, Heinz C *et al.* Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. *Eye* 2009;23:1192–8.
- 8 Goebel JC, Roesel M, Heinz C *et al.* Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. *Br J Ophthalmol* 2011;95:209–13.
- 9 Saurenmann RK, Levin AV, Rose JB *et al.* Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology* 2006;45:982–9.
- 10 Tynjälä P, Kotaniemi K, Lindahl P *et al.* Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology* 2008;47:339–44.
- 11 Merriam JC, Chylack LT Jr, Albert DM. Early onset pauciarticular juvenile rheumatoid arthritis: a histopathologic study. *Arch Ophthalmol* 1983;101:1085–92.
- 12 Parikh JG, Tawansy KA, Rao NA. Immunohistochemical study of chronic nongranulomatous anterior uveitis in juvenile idiopathic arthritis. *Ophthalmology* 2008;115:1933–6.
- 13 Press OW, Appelbaum F, Ledbetter JA *et al.* Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. *Blood* 1987;69:584–91.
- 14 McLaughlin P, Grillo-Lopez AJ, Link BK *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsing indolent lymphoma: half of the patients respond to a four-dose treatment program. *J Clin Oncol* 1998;16:2825–33.
- 15 Edwards JCW, Szczepanski L, Szechinski J *et al.* Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572–81.
- 16 Sfikakis PP, Boletis JN, Tsokos GC. Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005;17:550–7.
- 17 Petty RE, Southwood TR, Manners P *et al.* International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
- 18 Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol* 2005;140:509–16.
- 19 Ruperto N, Ravelli A, Falcini F *et al.* Performance of the preliminary definition of improvement in juvenile chronic arthritis patients treated with methotrexate. Italian Pediatric Rheumatology Study Group. *Ann Rheum Dis* 1998;57:38–41.
- 20 Dass S, Bowman SJ, Vital EM *et al.* Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomized, double-blind, placebo-controlled pilot study. *Ann Rheum Dis* 2008;67:1541–4.
- 21 Ahmadi-Simab K, Lamprecht P, Nolle B *et al.* Successful treatment of refractory anterior scleritis in primary Sjögren's syndrome with rituximab. *Ann Rheum Dis* 2005;64:1087–8.
- 22 Taylor SRJ, Salama AD, Joshi L *et al.* Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum* 2009;60:1540–7.
- 23 Tappeiner C, Heinz C, Specker C *et al.* Rituximab as a treatment option for refractory endogenous anterior uveitis. *Ophthalmic Res* 2007;39:184–6.
- 24 Stasi R, Stipa E, Del Poeta G *et al.* Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology* 2006;45:1432–6.
- 25 Ladas JG, Wheeler NC, Morhun PJ *et al.* Laser flare-cell photometry: methodology and clinical applications. *Surv Ophthalmol* 2005;50:27–47.
- 26 Nguyen QD, Humphrey RL, Dunn JP *et al.* Elevated vitreous concentration of monoclonal immunoglobulin manifesting as schlieren in juvenile rheumatoid arthritis-associated uveitis. *Arch Ophthalmol* 2001;119:293–6.
- 27 Lamprecht P, Till A, Steinmann J *et al.* Current state of biologicals in the management of systemic vasculitis. *Ann NY Acad Sci* 2007;1110:261–70.
- 28 Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005;7(Suppl. 3):19–25.
- 29 Stoll ML, Gotte AC. Biological therapies for the treatment of juvenile idiopathic arthritis: lessons from the adult and pediatric experiences. *Biologics* 2008;2:229–52.
- 30 Khraishi M. Comparative overview of safety of the biologics in rheumatoid arthritis. *J Rheumatol Suppl* 2009;82:25–32.