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ORIGINAL ARTICLE

Long-Term Follow-Up of Patients with Scleritis After Rituximab Treatment Including B Cell Monitoring

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ABSTRACT

Purpose: We report the long-term effect of rituximab (RTX) in scleritis and determine the value of B-cell monitoring for the prediction of relapses.

Methods: We retrospectively studied 10 patients with scleritis, who were treated with RTX. Clinical characteristics were collected, and blood B-cell counts were measured before the start of RTX, and at various time points after treatment.

Results: Clinical activity of scleritis decreased after RTX treatment in all patients within a median time of 8 weeks (range 3–13), and all reached remission. The median follow-up was 101 months (range 9–138). Relapses occurred in 6 out of 10 patients. All relapses, where B-cell counts were measured (11 out of 19), were heralded by returning B cells. However, B cells also returned in patients with long-term remissions.

Conclusions: RTX is a promising therapeutic option for scleritis. Recurrence of B cells after initial depletion does not always predict relapse of scleritis.

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B cells; B-cell depletion; refractory scleritis; rituximab; systemic immunosuppressive treatment

Scleritis is a rare and potentially sight-threatening inflammation of the sclera, characterized by redness, severe pain, scleral edema, and cellular infiltration.[1–3] It can present at any age, with a peak onset between the third and fifth decades of life. Scleritis may manifest as an isolated organ-specific disease, or occur concomitantly with a systemic immune-mediated inflammatory disease.[4] The most common systemic diseases include rheumatoid arthritis (RA) and granulomatosis with polyangiitis (GPA). Sporadically, infectious disorders, trauma, medication, or malignancies may cause scleritis.[2,3] Untreated scleritis can lead to blindness and may occasionally result in perforation of the globe when left untreated. Adequate and timely treatment is therefore paramount.[2,3]

Treatment of scleritis is challenging because topical corticosteroids or non-steroidal anti-inflammatory drugs often have limited effects.[5] Systemic immunosuppressive and/or chemotherapeutic treatments are often required but associated with systemic side effects, such as systemic infections.[5,6] Despite these aggressive regimens, a long-standing remission of scleritis is difficult to achieve.

Rituximab (RTX) is a chimeric (human/murine) monoclonal anti-CD20 antibody that targets the transmembrane protein CD20 that is specifically expressed on B cells.[7] Binding of RTX to CD20 induces a significant depletion of (peripheral) B cells for a duration of three up to 44 months.[8,9] Over the past decade, RTX showed promising results in the treatment of scleritis associated with several autoimmune diseases, as well as in idiopathic cases.[10–13] Repopulation of B cells after initial depletion following RTX administration might represent a possible relapse predictor in systemic diseases.[14–16] However, data on the B cell dynamics and its correlation with clinical activity in patients with scleritis are lacking.

In this case series, we describe the long-term disease course and B-cell monitoring in 10 patients with severe scleritis, who were eventually treated with RTX.

Materials and methods

Patients and data collection

We performed a retrospective cohort study of all consecutive patients with severe scleritis who started RTX treatment between December 2006 and March 2013 at the department of Internal Medicine at the Erasmus MC (Rotterdam, the Netherlands). Clinical follow-up continued up to

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September 2021, or discontinued in patients, who required the switch to immunosuppressive medications for non-ocular causes (after the initial cycle of RTX). One additional patient was treated with RTX in the given time period, but the indication for RTX therapy encompassed a combination of various systemic and ocular disorders, and was therefore not included in the present study. The study was performed in accordance with the Declaration of Helsinki and with the approval of the local review board of our institution.

All included patients underwent a work-up for scleritis according to national guidelines, including full ophthalmic evaluation and systemic evaluation by experienced uveitis and internal medicine specialists.[17] Baseline characteristics and relevant clinical data, including comorbidities and medication use, were extracted from medical files. Thereby, all relevant data regarding RTX treatment was gathered, including drug administration, interval between onset scleritis and RTX treatment, remissions, reactivations, and need for re-infusions of RTX. Remission was defined as the absence of active ocular inflammation and subjective symptoms including pain with (despite scleromalacia) or without treatment. Relapse was defined as activity of scleritis after a period of remission. Durable remission was defined as remission lasting more than 2 years.

Medication and laboratory examinations

RTX was administered as 1000 mg intravenously at day 1 and 14 and repeated on demand if a relapse occurred, but not earlier than 6 months after the first cycle. Before the administration of RTX, 100 mg prednisolone and 2 mg clemastine were administered intravenously to prevent infusion-related reactions. Peripheral blood B-cell counts were monitored before and after RTX treatment, at various time points. A diagnostic lyse-no-wash protocol was used to count the absolute numbers of CD19+ B cells,[18] and 8-color flow cytometry was performed for B-cell subset analysis in naive and memory populations.[19] The repopulation of B cells was considered in patients when these reached a level of at least 0.01×10^9/L.

Statistical analysis

Categorical data is presented as numbers and percentages, while continuous data is presented as median ± range.

Results

Ten patients started rituximab between December 2006 and March 2013. The baseline characteristics of the included patients are illustrated in Table 1. The median age at scleritis onset was 44 years (range 36–62). Four out of 10 patients (40%) had an associated autoimmune disease. The median time interval from the onset of scleritis to the first cycle of RTX treatment was 27 months (range 1–111 months). The median duration of follow-up after the first cycle of RTX was 101 months (range 9–138 months). Follow-up was discontinued in four patients, after a median follow-up of 67 months, because of the switch to immunosuppressive medication for non-ocular causes.

Responses

All patients showed a beneficial response after the first cycle of RTX, within a median time of 7 weeks (range 2–14 weeks), and subsequently all patients reached remission (Table 2). Three patients (30%) reached durable remission lasting for the entire follow-up duration after one cycle of RTX, in one patient follow-up was discontinued 9 months after the last RTX. Relapses occurred in six patients (60%), within a median interval of 15 months (range 7–20). Patients 4, 5, 9, and 10 reached remissions after two or three cycles of RTX (Table 2). Seven patients with remissions were able to cease other immunosuppressive medications for scleritis before the end of follow-up, while one required a low dose of methotrexate (MTX) for cutaneous psoriasis. Infrequently, patients needed bridging therapy between the initial infusion of RTX and clinical response (solumedrol, dexamethasone, mycophenolic acid (MPA), or intravenous immunoglobulin (IVIG)) before other immunosuppressant agents could be tapered or stopped. Two patients (patients 6 and 7) required RTX reinfusions every 6 months, because of relapses of scleritis. This maintenance treatment with RTX showed good effect with no further relapses of scleritis in the last 18 and 19 months of follow-up, respectively (Table 2).

B cell levels

Prior to treatment, the average B cell count was 0.21 ± 0.09 (SD) x10^9/L (Table 2). In all but one patient, B cells decreased to $<0.01 \times 10^9$/L within 5 or 6 weeks after the first infusion of RTX. One patient still had 0.01×10^9/L peripheral B cells 7 weeks after RTX administration.

The repopulation of B cells $\geq 0.01 \times 10^9$/L occurred after a median interval of 6 months. After RTX reinfusions, the B cells decreased again to $\leq 0.01 \times 10^9$/L. Relapse of scleritis occurred 18 times in six patients, and in 14 cases the relapse was directly followed by a repeated RTX infusion. All relapses of scleritis, in which the levels of B cells were measured (n = 11), were heralded by returning B cells. In patient 4, the relapse emerged in the presence of returning antigen-experienced B cells (natural effector and IgD-memory, Figure 1). Figure 2 shows the timeline of the B-cell levels and relapses of scleritis. No relapses were seen when B cells were depleted. A correlation between the duration of returning B cells to relapse of scleritis was not determined. Finally, whenever measured, B cells returned to pre-treatment levels in all patients.

Side-effects of RTX treatment were not encountered in our cohort.

Discussion

We demonstrate beneficial and long-lasting outcomes of RTX treatment in 10 patients with severe scleritis, who all had extensive follow-up period after RTX administration. Remission of scleritis after initial RTX cycle occurred in all patients (100%). However, six patients (60%) developed relapse of scleritis that necessitated retreatment with RTX, which had a good effect in all. Relapses of scleritis were in all

Table 1. Characteristics and treatment schedules of patients with severe therapy refractive scleritis treated with rituximab (RTX).

Patient No	Age at scleritis onset years	Interval onset scleritis and RTX (months)	Gender	Laterality	Subtype	Systemic disease	Prior immunosuppressive treatment	Immuno-suppressive therapy at start RTX[a]	Systemic immunosuppressive therapy after first RTX cycle[a]		Follow-up duration months
									At 1 year	At last follow up	
1	60	51	F	1	Anterior	No	CYC, AZA, MTX, MPA, IVIG	Pred 12, MPA 1440	Pred 5	None	111
2	40	111	M	1	Anterior + posterior	No[b]	CYC, Anti-TNF, AZA, MTX, SCIG	Pred 10, CYC 1000	Pred 2.5, Dapsone 100, SCIG 9.6 g	None	94[d]
3	36	4	F	2	Anterior	SLE	CYC, AZA, MTX, IVIG	Pred 30	Hydrochloroquine 200	None	122
4	36	22	F	1	Anterior + posterior	RPC	CYC, Anti-TNF, AZA, MTX, MPA, IVIG	IVIG 25 g, MPA 1440	RTX, MPA 1440	MPA 1440	39
5	39	10	M	1	Anterior + posterior	No	Anti-TNF, AZA	Pred 5	Pred 5	None	107
6	57	33	M	2	Anterior	No[c]	Anti-TNF, AZA, MTX, MPA	Pred 20, MPA 1440	RTX, MPA 1440	Pred 6.25, RTX 1000/6 months	107[d]
7	58	101	F	2	Anterior _ posterior - necrotizing	RPC	CYC, MTX, MPA, IVIG	Pred 30, CYC 600	Pred 5, IVIG 50 g	Pred 7.5 RTX 1000/6 months	138
8	36	22	F	1	Anterior sclero-uveitis	No	MTX, MPA	Pred 20, MPA 1440	Pred 5	MTX 15[e]	9[d]
9	48	32	M	1	Anterior + posterior	No	CYC, MTX, MPA	Solu 500, CYC 1000	None	MPA 2000	83
10	62	1	M	2	Anterior	GPA	CYC, MTX, AZA	Pred 30, AZA 100	Pred 5, Aza 150	None	40[d]

[a]Doses of immunosuppressive therapies are given in total daily doses in milligrams unless specified otherwise. All patients had been pretreated with steroids locally and orally.
[b]Patient developed neuromyelitis optica, where-after follow up was discontinued.
[c]Patient developed polymyalgia rheumatic, where-after follow up was discontinued.
[d]Follow up was discontinued for this study as patient switched to immunosuppressive medication for primarily non-ocular causes.
[e]This patient was initially treated for psoriasis with MTX after which she developed scleritis. Scleritis was treated with rituximab and MTX was ceased. After 9 months MTX was restarted because of recurrence of psoriatic articular involvement. A mild recurrence of scleritis occurred after 35 months which was treated locally, and she remained scleritis free for 10 years after the last Rituximab dose.
SLE= Systemic lupus erythematosus; RPC= Relapsing polychondritis; GPA= Granulomatosis with poly-angiitis; CYC= cyclophosphamide iv generally following the vasculitis protocol[30]; anti-TNF= anti-tumor necrosis factor α; SCIG= Subcutaneous Immunoglobulin, weekly, IVIG= intravenous immunoglobulin, monthly; AZA = azathioprine; MTX= methotrexate, weekly; MPA= mycophenolate acid or mycophenolate mofetil; RTX= rituximab; Pred= prednisolone; Solu: monthly intravenous high dose solumedrol; Dexa = dexamethasone.

Table 2. Clinical and biochemical courses after rituximab in patients with severe therapy refractory scleritis.

Patient No	Time to clinical response (weeks)	Recurrence of scleritis after first RTX (months)	Recurrences requiring repeat of RTX (number)	Rituximab cycles[a]	B-cells before 1st cycle of RTX (10^9/L)	First re-occurrence of B cells after first cycle of RTX and level (months/10^9/L)		Minimal duration complete remission after last RTX until last follow up (months)
1	3	No	0	1	0.22	10 (fully depleted at 8 m)	0.01	111
2	11	No	0	1	0.14	6 (first time measured)	0.01	94
3	11	No	0	1	Nm	11 (first time measured)	0.15	122
4	14	7	1	2	0.38	5 (fully depleted at 4 m)	0.02	32
5	4	18	2	3	0.26	18 (fully depleted at 14 m)	0.01	56
6	8	13	7	7 + 2×1000	0.16	9 (fully depleted at 5 m)	0.01	NA[c]
7	13	17	5	5 + 3×1000	Nm	6 (fully depleted at 3 m)	0.01	NA[d]
8	4	No	0	1	Nm	2 (first time measured)	0.01	9
9	5[b]	20	1	2	0.13	Nm	Nm	5
10	2	13	1	2	0.17	Nm	Nm	25

[a]Dosing of RXT was 500 or 1000 mg per infusion. Scheduling was 2000 mg per cycle and 1000 mg bi-annually (+n x1000) when maintained for 2 years.
[b]Subconjunctival steroids were given in addition to RTX in the first year after RTX infusion.
[c]Patient 6 experienced a last recurrence of scleritis 18 months before the end of follow up. However, he developed a polymyalgia rheumatic in this period of time which required oral corticosteroids.
[d]Patient 7 experienced five recurrences of scleritis, the last 19 months before the end of follow up, eventually indicating a prolonged response.
RTX= Rituximab; Nm= Not measured; NA= Not applicable.

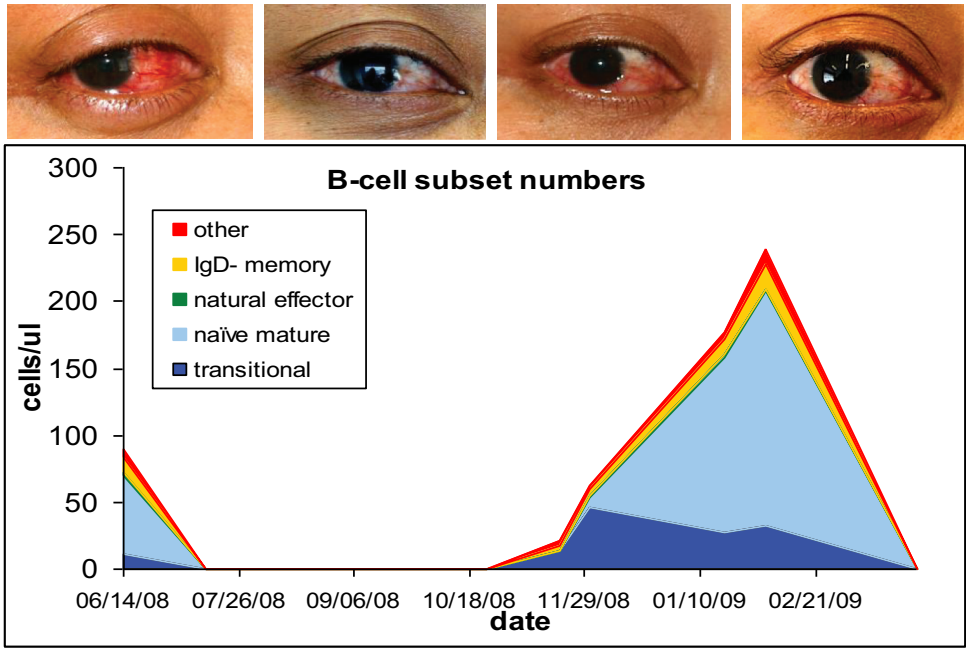

Figure 1. B-cell subset counts before and after two cycles of RTX for anterior scleritis in patient 4. The presence of B-cell subsets including transitional B cells, naive mature B cells, natural effector memory B cells, and IgD^+ memory B cells during the course of scleritis. Transitional and naive mature B cells are highly represented during a recurrence of scleritis.

cases heralded by returning B cells, however patients with durable remissions also exhibited a repopulation of B cells.

The beneficial effect of RTX treatment in scleritis was already noted in several case series.[11–13,20–28] These studies showed predominantly good RTX effect on activity of scleritis in standard treatment-refractory cases, however, relapses occurred frequently. Therefore, it is not yet clear how to manage patients with refractory scleritis after the initial cycle of RTX. It is especially unknown whether treatment with RTX has to be maintained or repeated to induce durable remissions and prevent relapses.[11,12,16] To the best of our knowledge, the longest average follow-up period in previous studies was 59 months.[10,27] Our case-series has a more extended follow-up period (median 101 months), and we observed that the initial RTX infusion induced durable remission in 4 out of 10 patients and additional retreatment with two or three cycles of RTX could induce durable remission in four out of six cases with disease relapses. Long-term 6-monthly administration of RTX was only needed in two patients.

Beneficial results of RTX given in fixed intervals were reported for patients with ANCA associated vasculitis compared to "on demand" treatment.[29] The results of our study suggest that not all patients with scleritis require continued RTX therapy and that the treatment "on demand" probably represents an appropriate initial approach.

RTX induced B-cell depletion after the initial treatment occurred in all, which is consistent with previous observations.[12,13,16,20] Only two studies monitored the

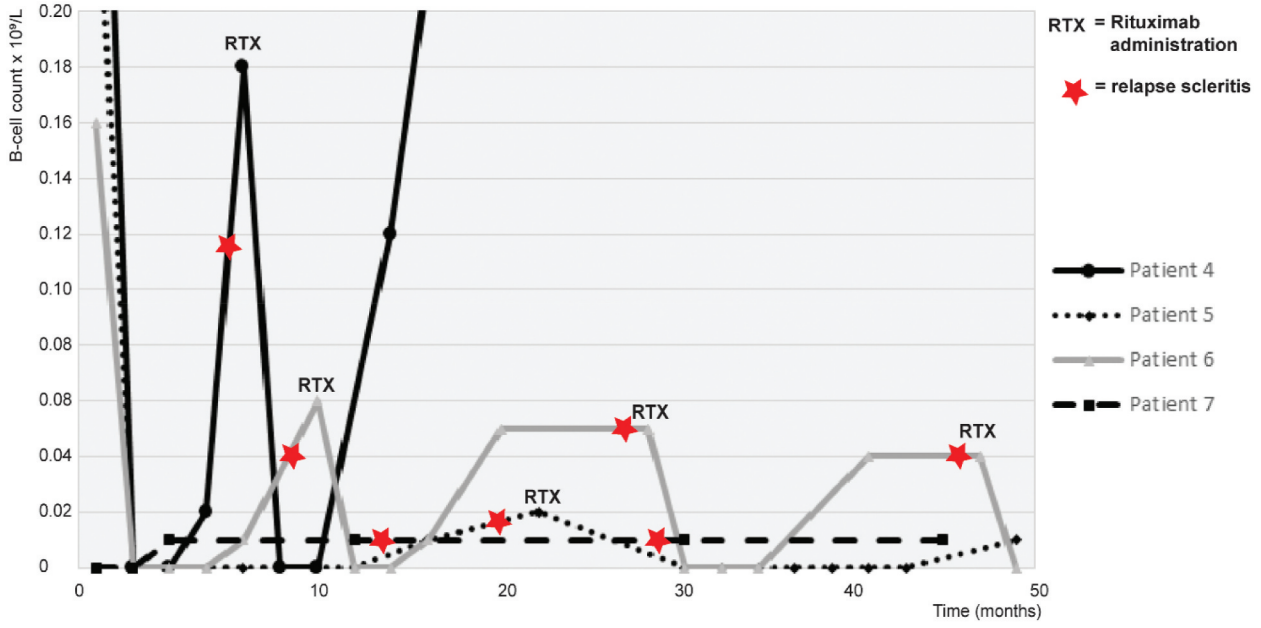

Figure 2. B-cell dynamics and recurrences of patients with treatment-refractory scleritis ($N = 4$). B-cell counts during the course of scleritis visualized in a selection of four patients out of our cohort with 10 patients. In all recurrences of all patients wherein B-cell count was measured, B cells were higher than zero or rising.

effect of B cells on relapses of scleritis after initial depletion of B cells, without an association between relapses, and B-cell repopulation.[12,16] In contrast, we observed that returning B cells heralded all relapses, and no relapses were seen with absent B cells in our limited series. Reoccurring B cells did not differentiate between relapse and remission, since B cells also returned in patients who remained in remission. This phenomenon was also noted in a study of patients with granulomatosis with polyangiitis.[15] In another study, 2 out of 66 patients with GPA suffered a relapse despite B cells remaining absent.[14] There might be a role for B cells in protective niches and localized lymph nodes that are not completely depleted, in contrast to the peripheral B cells.[16,29] Furthermore, we may hypothesize that clinical relapse might be associated with expansion of specific memory B cells, whereas B-cell repopulation in patients in remission is the result from neogenesis of transitional and naïve B cells. To clarify the role of B cells in scleritis, a more extensive study would be necessary, which is not easy to achieve in this uncommon disorder and would require (inter)national collaborations. Our study is limited by the small number of patients and their retrospective character. B cells were measured regularly, however, not at predefined time points.

Our case series illustrates that RTX can induce prolonged remissions even in patients with longstanding scleritis, resistant to conventional immunosuppressive drugs. As some of the remissions obtained were longstanding even after a single cycle of RTX, and relapses responded promptly when re-treated with RTX, we conclude that continued treatment with RTX is not necessary in all patients. Our data indicate that RTX treatment "on demand" might represent an appropriate initial approach in patients with scleritis. Repeated B-cell monitoring might be of value to exclude a relapse, but recurrence of B cells does not predict relapse of disease.

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Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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