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ORIGINAL ARTICLE

Anti-CD20 therapy for multiple sclerosis-associated uveitis: A case series

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Abstract

Background and purpose: Approximately 1% of patients with multiple sclerosis (MS) have uveitis, but data on the effects of immunotherapies for MS on MS-associated uveitis are scarce. The aim of this study was to investigate the ophthalmological outcomes in patients with MS-associated uveitis treated with anti-CD20 therapy.

Methods: A retrospective study of 12 eyes of six patients with MS-associated uveitis, refractory to previous immunotherapies, was conducted. Uveitis activity was assessed before initiation of anti-CD20 therapy and at regular follow-up visits. Primary outcome measures were: vitreous haze score; retinal vasculitis score, determined on fluorescein angiography images; macular edema, as quantified by central retinal thickness (CRT) on optical coherence tomography; and visual acuity (VA). Secondary outcomes included number of annualized uveitis or MS relapses, disease activity on cerebral magnetic resonance imaging (cMRI) and Expanded Disability Status Scale (EDSS) score.

Results: After a median (interquartile range [IQR]) treatment time of 28.5 (8–43) months, anti-CD20 therapy was associated with an improvement of vitreous haze score ($p = 0.002$), retinal vasculitis score ($p = 0.001$), CRT ($p = 0.002$), and VA ($p = 0.007$). The median (IQR) annualized uveitis relapse rate declined from 0.59 (0.56–0.94) before to 0 (0–0.49) after the start of anti-CD20 therapy. The median (IQR) annualized MS relapse rate declined from 0.62 (0.26–2.84) before to 0 (0–0) after the start of anti-CD20 therapy. After initiation of anti-CD20 therapy, there was no disease activity on cMRI, and EDSS score improved ($n = 2$) or remained stable ($n = 4$). No severe adverse events were observed.

Conclusion: These findings suggest that anti-CD20 therapy may be a valuable treatment option for MS-associated uveitis.

KEYWORDS
anti-CD20 therapy, multiple sclerosis, ocrelizumab, retinal fluorescein angiography, rituximab, uveitis

Frauke Stascheit, Anne Rübsam, Klemens Ruprecht and Uwe Pleyer contributed equally to this study.

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INTRODUCTION

Although visual impairment in patients with multiple sclerosis (MS) typically results from inflammatory demyelinating lesions of the optic nerve, approximately 1% of patients with MS have uveitis, an intraocular inflammation of the uveal tract [1]. Intraocular inflammation can be subclassified according to the Standardization of Uveitis Nomenclature (SUN) criteria with respect to the predominantly affected anatomical structures into anterior (iris and ciliary body), intermediate (vitreous), posterior uveitis (retina, choroid), and panuveitis (all of the aforementioned structures) [2]. MS-associated uveitis most often presents as bilateral intermediate uveitis and frequently follows a relapsing course [3]. Characteristic ophthalmological findings in intermediate uveitis comprise inflammation within the vitreous cavity without lesions of the retina or choroid. Inflammatory cells in the vitreous may become so dense as to obscure the retina, referred to as vitreous haze, and may present as mobile, yellow white "snowballs". Another characteristic finding in MS-associated intraocular inflammation is peripheral retinal vasculitis [4]. This primarily involves retinal venules, may present as sheathing or irregularity in vessel caliber, and can best be detected by retinal fluorescein angiography (FA) [5]. Of note, intermediate uveitis bears a high risk of sight-threatening macular edema (ME) [6].

Similarly to acute MS relapses, acute recurrences of MS-associated uveitis are usually treated with systemic corticosteroids [3]. However, data on the effects of the currently available disease-modifying therapies for MS on MS-associated uveitis are scarce. Former retrospective studies have reported improvement of MS-associated uveitis following treatment with interferon-beta or glatiramer acetate [7] as well as mycophenolate mofetil [8]. Furthermore, case reports suggested improvement of refractory MS-associated uveitis following treatment with natalizumab [9], alemtuzumab [10], and the interleukin-1-receptor antagonist anakinra [11].

B-cell depleting anti-CD20 therapies, such as rituximab, ocrelizumab and ofatumumab, have proven highly effective in the treatment of MS [12–14]. However, to the best of our knowledge, treatment of MS-associated uveitis with anti-CD20 therapy has so far only been described in one recent case report of a 40-year-old woman with panuveitis and primary progressive MS, who responded favorably to anti-CD20 therapy, but has otherwise not been analyzed systematically so far [15]. Here, we report on a series of 12 eyes of six patients treated with anti-CD20 therapy for previously treatment-refractory MS-associated uveitis.

PATIENTS AND METHODS

According to the ethics committee of Charité – Universitätsmedizin Berlin, no formal ethical approval for reporting of case series is required. All patients provided written informed consent for publication of this report in accordance with the Declaration of Helsinki in its currently applicable form.

Patients

This retrospective observational study was conducted at the Department of Ophthalmology, Charité Campus Virchow Klinikum, and the MS outpatient clinic, Department of Neurology, Charité Campus Mitte, Charité – Universitätsmedizin Berlin, which jointly manage patients with MS-associated uveitis. Patients with MS-associated uveitis were treated with anti-CD20 therapies at the Department of Neurology and were followed longitudinally and evaluated during routine visits at the Departments of Ophthalmology and Neurology between September 2017 and October 2020. Inclusion criteria comprised age 18 years, a diagnosis of MS according to the McDonald 2017 criteria [16], a diagnosis of uveitis of any type according to the SUN criteria [2] and treatment with at least three infusions of anti-CD20 therapy (rituximab or ocrelizumab) over a period of at least 6 months.

Ophthalmological assessments

Ophthalmological assessments were performed before the start of anti-CD20 therapy and at follow-up visits every 2–3 months and included visual acuity (VA) testing using a decimal chart, anterior and posterior segment examination, spectral-domain optical coherence tomography (OCT; Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) and retinal FA (Heidelberg Spectralis). Evaluation of vitreal inflammatory activity (vitreous haze) was graded by indirect ophthalmoscopy utilizing a slit lamp and comparing the current view onto the fundus with a series of photographs representing various degrees of vitreous haze, according to the Nussenblatt standardized score, which ranges from Grade 0 (no haze) to Grade 4 (optic nerve being obscured) [17]. ME, a fluid accumulation within the macula, was assessed on OCT. Central retinal thickness (CRT) in µm was automatically calculated by the device software (software version 5.1.2.0) as distance from the retinal pigment epithelium to the inner limiting membrane at the highest point with a circle of 1-mm radius, centered on the fovea. Changes in CRT therefore directly reflect the amount of ME. We considered a reduction of CRT >20% as clinically meaningful [18]. Retinal vasculitis was scored on FA images as previously described by a standardized scoring form, which scores: (i) the extent of vitreous opacities obscuring the view on the fundus; (ii) the extent of extravasation of fluorescein dye from the optic disc; (iii) the macular region; (iv) the peripheral vasculature outside their borders; (v) the extent of diffuse leakage; and (vi) the integrity of the choroidal blood circulation in late images on FA. Each of these six variables is assessed by a score from 0 (no abnormalities) to 3 (severely affected), resulting in a maximum score of 18 [19].

For Kaplan–Meier analysis, remission of uveitis activity was defined according to the SUN working group as an improvement of the vitreous haze and vasculitis scores of at least two steps [2] and any reduction of CRT.

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Neurological assessments

Neurological assessments were performed before the start of anti-CD20 therapy and at follow-up visits every 6 months and comprised a detailed history including potential adverse effects of the medication and neurological examination with determination of the Expanded Disability Status Scale (EDSS) score [20]. Cerebral magnetic resonance imaging (cMRI) was performed as part of routine care prior to initiation of anti-CD20 therapy as well as during the course of anti-CD20 therapy. Presence of disease activity on cMRI was defined as new or enlarging T2-weighted hyperintense lesions on cMRI obtained after start of anti-CD20 therapy as compared to a cMRI obtained before initiation of anti-CD20 therapy.

Statistical analysis

The primary outcome measures of this study were changes in uveitis activity variables (vitreous haze score, retinal vasculitis score on FA images, extent of ME as measured by CRT on OCT, and VA) before initiation of anti-CD20 therapy and at last follow-up. The main secondary outcome measure was annualized uveitis relapse rate, calculated as the number of uveitis relapses per patient during the observation time divided by the observation time in years, before and after start of anti-CD20 therapy. Observation times were from diagnosis of uveitis to start of anti-CD20 therapy and start of anti-CD20 therapy to last follow-up. Further secondary outcome measures were annualized MS relapse rate, calculated by analogy to the uveitis relapse rate, MS activity on cMRI and EDSS score before initiation of anti-CD20 therapy and at last follow-up.

Results of VA testing were converted to the logarithm of the minimum angle of resolution (LogMAR) scale. Note that lower LogMAR values indicate better VA.

Continuous data are presented as median and interquartile range (IQR) or absolute range and categorical variables as absolute frequencies and percentages. The Wilcoxon signed ranked test was used to assess the statistical significance of differences before and after start of anti-CD20 therapy. Mann–Whitney *U*-tests were used to assess the statistical significance of differences between eyes treated with anti-CD20 therapy alone and eyes treated with anti-CD20 and additional corticosteroid therapies. The Kaplan–Meier method was used to calculate the probability of remission of ophthalmological signs of MS-associated uveitis over time. All statistical analyses were performed using PRISM (version 9.0.1, GraphPad Software). p values <0.05 were taken to indicate statistical significance. Due to the exploratory nature of this study no correction for multiple testing was performed.

RESULTS

Patients

A total of 12 eyes of six patients, who were treated with anti-CD20 therapy for previously treatment-refractory MS-associated uveitis, were included in this study. Demographic and treatment characteristics as well as neurological findings of these six patients (five women, one man; median [range] age at start of anti-CD20 therapy 51.5 [36–62] years) are summarized in Table 1. Disease duration of MS until start of anti-CD20 therapy ranged between 0.3 and 23 (median 8.7) years.

The patients' ophthalmological findings are summarized in Table 2. The time point of diagnosis of uveitis relative to diagnosis of MS varied from 63 months before to 156 months after the diagnosis of MS (Table 2). Diagnosis of uveitis preceded diagnosis of MS in three of six patients (50%). Intermediate uveitis was the most common anatomical localization (10/12 eyes; 83%), followed by panuveitis (2/12 eyes; 17%). Except for one patient with chronic uveitis, uveitis followed a relapsing course in all other patients. While all patients had bilateral uveitis, severity of uveitis frequently differed between both eyes (Table 2).

The median (range) observation time from diagnosis of uveitis to start of anti-CD20 therapy was 70.2 (39.6–123.6) months. Before initiation of anti-CD20 therapy, all patients had been treated for uveitis and/or MS with at least two different immunotherapies, including ciclosporine A, oral or pulsed intravenous corticosteroids, glatiramer acetate, daclizumab, interferon-beta, and mycophenolate mofetil (Table 1, Figure 3). In addition, due to uveitic ME, six eyes of three patients (Patients #4–6) had received intravitreal injections of a dexamethasone insert (Ozurdex or Iluvien) prior to anti-CD20 therapy. Furthermore, cataract surgery had been performed prior to anti-CD20 therapy in both eyes of Patients #4–6 (Table 2). Cataract formation was considered to be most likely related to intravitreal and/or systemic steroid therapy. Reasons for switching prior immunotherapies for uveitis to anti-CD20 therapy were uncontrolled active uveitis (all patients) and MS activity on MRI (one patient). Additionally, three patients had side effects under previous therapies, including allergies ($n = 1$, mycophenolate mofetil), fatigue ($n = 1$, interferon-beta) or migraine ($n = 1$, interferon-beta). After initiation of anti-CD20 therapy, anti-CD20 therapy was the only systemic immunotherapy in five patients. In one patient (Patient #1) concomitant oral prednisolone (60 mg/day) was initiated 2 months after the start of anti-CD20 therapy and was subsequently tapered to a maintenance dose of 7.5 mg/day (Table 1).

Ophthalmological outcomes

The median (range) observation time on treatment with anti-CD20 therapy was 28.5 (8–43) months, during which patients were treated with a median (range) of 6 (3–8) infusions of anti-CD20 therapy (Table 1).

At baseline, vitreous haze was detectable in 11 of 12 eyes (92%) with a median (interquartile range [IQR]) vitreous haze score (all 12 eyes) of 1 (0.5–2). On the last follow-up visit, the median vitreous haze score (all 12 eyes) had decreased to 0 (0–0.125; $p = 0.002$ [Figure 1a, Table 2]). Altogether, vitreous haze score had improved in all 11 eyes, in which vitreous haze was initially present, at last follow-up.

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TABLE 1 Demographic and treatment characteristics as well as neurological findings in patients with multiple sclerosis-associated uveitis treated with anti-CD20 therapy

Patient #	Sex	Age at start of anti-CD20 therapy, years	MS type	Duration of MS until start of anti-CD20 therapy, years	MS relapses until start of anti-CD20 therapy, number	Treatments before anti-CD20 therapy	Type of anti-CD20 therapy	Number of infusions of anti-CD20 therapy[a]	Concomitant therapy during anti-CD20 therapy	FU time, months	EDSS at baseline	EDSS at last FU	T2-weighted lesions on cMRI at baseline, number
1	F	36	RRMS	0.3	1	CSA, PRED	RTX	4	PRED	27	1.0	0	2
2	F	39	RRMS	3.4	3	GLAT, DAC, IFN	OCR	6[b]	none	30	3.5	3.5	15
3	F	53	RRMS	0.75	2	CSA, MMF, IFN, PRED	OCR	7	none	39	1.0	0	60
4	F	50	RRMS	23	6	IFN, CSA,	RTX	8	ODX (OS)	43	2.5	2.5	50
5	M	62	SPMS	17	4	Methylprednisolone[c], MMF, PRED	RTX	3	none	8	7.0	7.0	9
6	F	58	RRMS	14	5	Methylprednisolone[c], IFN	OCR	7	ODX (OD), ILU (OS)	22	2.5	2.5	9

Abbreviations: cMRI, cerebral magnetic resonance imaging; CSA, ciclosporine A; DAC, daclizumab; EDSS, Expanded Disability Status Scale; f, female; FU, follow-up; GLAT, glatiramer acetate; IFN, interferon-beta; ILU, Iluvien (intravitreal); m, male; MMF, mycophenolate mofetil; *n*, number; OCR, ocrelizumab; OD, right eye; ODX, Ozurdex (intravitreal); OS, left eye; PLK, panretinal laser photocoagulation; PRED, oral prednisolone; RRMS, relapsing remitting multiple sclerosis; RTX, rituximab; SPMS, secondary progressive multiple sclerosis; VA, visual acuity; y, yes.

aInfusion scheme for both, rituximab and ocrelizumab, consisted of infusions on Day 0 and Day 14 and every 6 months thereafter.

bAfter the first three infusions of anti-CD20 therapy, the infusion interval was shortened to every 5 months due to remaining uveitis activity (see Figure 2).

cPulsed methylprednisolone administered intravenously every 3 months.

Active retinal vasculitis was defined as presence of disc leakage or retinal vascular leakage or diffuse leakage on FA images. According to this definition, 12 eyes of six patients had active retinal vasculitis at the start of anti-CD20 therapy. The median (IQR) retinal vasculitis score (all 12 eyes) at the beginning of anti-CD20 therapy was 6 (4.75–7.25). On the last follow-up visit, the median retinal vasculitis score (all 12 eyes) had decreased to 3.5 (2–5; $p = 0.001$ [Figure 1b, Table 2]). Altogether, the retinal vasculitis score had improved in 11 of 12 eyes (92%) at last follow-up. Of note vitreous opacity ranged between 0 and 2 in all FA examinations, allowing accurate determination of fluorescein leakage, that is, the fundus view was not obscured by vitreous opacities [18]. Representative FA images of one patient (Patient #2) showing a decrease of retinal vascular leakage on retinal FA images under anti-CD20 therapy are shown in Figure 2.

Macular edema, as assessed on OCT, was present in eight eyes of four patients. The baseline median (IQR) CRT of all 12 eyes was 336 (308–377) µm. At the last follow-up visit, the median CRT (all 12 eyes) had decreased to 266 (237.8–333.5) µm ($p = 0.002$; Figure 1c, Table 2). Thus, there was a 20.8% reduction in median CRT between baseline and last follow-up. CRT had decreased in all eight eyes, in which ME was detected at baseline, at last follow-up. Nevertheless, three eyes had been treated with additional intravitreal corticosteroids because of residual ME under anti-CD20 therapy (see also below).

The median (IQR) VA at baseline (all 12 eyes) was 0.2 (0.1–0.3) LogMAR, corresponding to a VA of 0.57 decimal. Importantly, the median VA had improved to 0.1 (0.1–0.125) LogMAR, corresponding to a VA of 0.75 decimal at last follow-up ($p = 0.007$; Figure 1d, Table 2). Altogether, at last follow-up, VA had either improved (eight eyes) or stayed stable (four eyes) in all eyes investigated in this study.

Figure 3 shows the number of uveitis (and MS) relapses before and after start of anti-CD20 therapy for each individual patient. The median (IQR) annualized uveitis relapse rate decreased from 0.59 (0.56–0.94) before the start of anti-CD20 therapy to 0 (0–0.49) after the start of anti-CD20 therapy. A total of three uveitis relapses were detected in two patients after anti-CD20 therapy initiation. All of these relapses represented flares of uveitic ME. The latest uveitic ME relapse occurred 11 months after anti-CD20 treatment was initiated. Thereafter, no further uveitis relapses were observed.

To analyze the effect of the duration of anti-CD20 therapy on ophthalmological signs of MS-associated uveitis, we performed a Kaplan–Meier analysis (Figure 4). To this end, we used remission of ophthalmological signs of MS-associated uveitis, defined as improvement of vitreous haze and vasculitis scores of at least two steps, and any reduction of CRT as outcome measures. According to this definition, the probability of remission of ophthalmological signs of MS-associated uveitis after start of anti-CD20 therapy was 50% after 11.5 months and 100% after 21 months of treatment (Figure 4). Thus, ophthalmological signs of MS-associated uveitis decreased with increasing treatment duration of anti-CD20 therapy and eventually resolved in all 12 investigated eyes. The time point after which

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TABLE 2 Ophthalmological findings in patients with multiple sclerosis-associated uveitis treated with anti-CD20 therapy

Patient #	Diagnosis of uveitis relative to diagnosis of MS, months	Type of uveitis OD/OS	Ocular surgery until start of anti-CD20 therapy	Uveitis relapses until start of anti-CD20 therapy, number	Vitreous haze score OD/OS		Vasculitis score OD/OS		ME OD/OS		CRT OD/OS, µm		VA OD/OS, LogMAR	
					BL	last FU	BL	last FU	BL	last FU	BL	last FU	BL	last FU
1	−36	int./int.	None	Chronic	2+/2+	0/0	5/6	3/4	n/n	n/n	305/329	286/231	0.1/0.1	0.1/0.1
2	−26	int./int.	None	3	2+/2+	0/1+	4/5	2/2	y/y	Reduced both eyes	334/395	326/344	0.1/0.2	0.1/0.1
3	−63	int./int.	None	5	0.5+/0.5+	0/0	8/6	6/4	n/n	n/n	377/338	365/330	0.2/0.1	0.0/0.0
4	+156	int./int.	Cat. surgery, ODX (OD/OS)	6	0/0.5+	0/0	2/8	2/5	y/y	OD reduced, OS reduced ≥20%	291/308	246/238[a]	0.2/0.1	0.1/0.1
5	+108	int./int.	Cat. surgery, ODX (OD/OS), PLK	5	1+/0.5+	0.5+/0	7/7	5/5	y/y	Reduced both eyes	239/445	225/400	1.3/1.1	0.8/1.0
6	+109	pan./pan.	Cat. surgery, ODX (OD/OS)	5	1+/2+	0/1+	3/8	2/3	y/y	Reduced ≥20% both eyes	369/476	237[a]/239[b]	0.3/0.3	0.2/0.1

Abbreviations: BL, baseline; Cat., cataract; CRT, central retinal thickness; FU, follow up; int., intermediate uveitis; LogMAR, logarithm of the minimum angle of resolution; m, months; ME, macular edema; MS, multiple sclerosis; *n*, no; OD, right eye; ODX, Ozurdex (intravitreal); OS, left eye; pan., panuveitis; PLK, panretinal laser photocoagulation; VA, visual acuity; y, yes.

[a]Eye was also treated with intravitreal dexamethasone insert.

[b]Eye was also treated with intravitreal fluocinolone implant.

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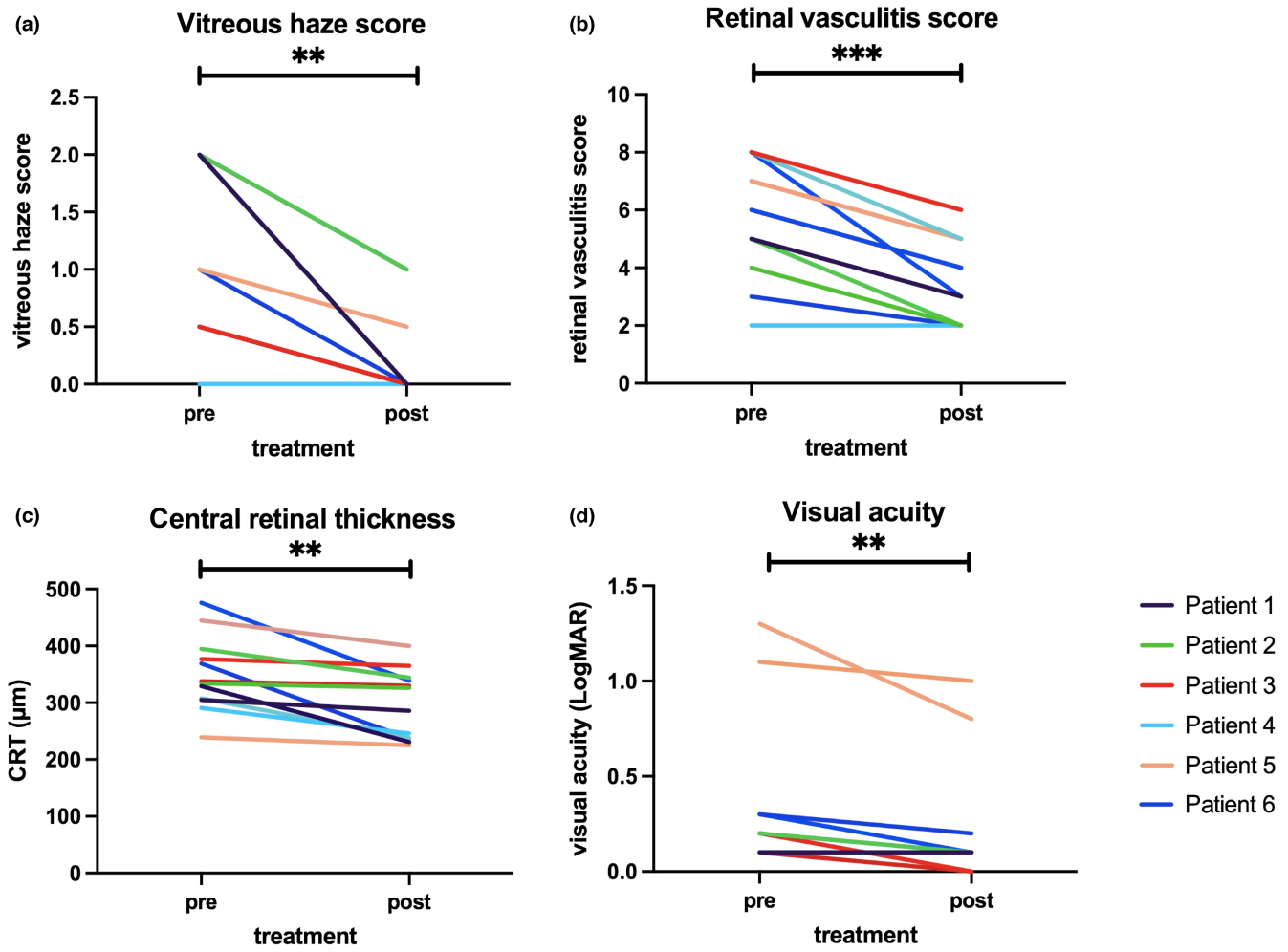

FIGURE 1 Spaghetti plots representing intraeye changes in vitreous haze score (a), retinal vasculitis score (b), central retinal thickness (c), and visual acuity (d) in 12 eyes of six patients with multiple sclerosis-associated uveitis before start of anti-CD20 therapy (= pre), and at last follow-up after initiation of anti-CD20 therapy (= post). Visual acuity is provided as LogMAR values. Note that lower LogMAR values indicate better visual acuity. Each line represents one eye. Eyes of the same patient are represented by the same colour. Note that, since the lines sometimes overlap, the total number of lines does not always add up to 12. $^{**}p < 0.01$. $^{***}p < 0.001$. CRT, central retinal thickness; LogMAR, logarithm of the minimum angle of resolution [Colour figure can be viewed at wileyonlinelibrary.com]

ophthalmological signs of MS-associated uveitis were in remission, according to the definition above, is also indicated in Figure 3 for each individual patient.

In one patient (Patient #1), oral prednisolone (60 mg/day, tapered to a maintenance dose of 7.5 mg/day) was initiated because of remaining uveitis activity in both eyes (vitreous haze and vasculitis activity) 1 month after start of anti-CD20 therapy. In addition, because of persistent ME despite anti-CD20 therapy, three eyes of two patients (Patients #4 and #6) were treated with dexamethasone (Ozurdex, two eyes) or fluocinolone acetonide (Iluvien, one eye) intravitreal implants between 3 and 12 months after start of anti-CD20 therapy. Thus, a total of five eyes of three patients were treated with systemic ($n = 2$ eyes) or local corticosteroids ($n = 3$ eyes) in addition to anti-CD20 therapy. To evaluate potential influences of concomitant corticosteroid therapies on ophthalmological outcomes, we compared ophthalmological outcome variables at the last follow-up visits in the seven eyes that were exclusively treated with anti-CD20 therapies and the five eyes that had received additional corticosteroids (Figure 5). At last follow-up, the median (IQR) vitreous haze score in eyes with anti-CD20 therapy only was 0 (0–0.25) compared to a median vitreous haze of 0 (0–0) in eyes treated with additional corticosteroids ($p > 0.999$). The median vasculitis score in eyes with anti-CD20 therapy only was 4 (2.5–4.5) compared to a median vasculitis score of 5 (4–5) in eyes with additional corticosteroids ($p = 0.420$). The median CRT in eyes with anti-CD20 therapy only was 330 (286–354.5) µm compared to a median CRT of 238 (237–239) µm in eyes with additional corticosteroids ($p = 0.07$). ME resolved in all three eyes treated with intravitreal steroids. The median VA value in eyes with anti-CD20 monotherapy was 0.1 (0.05–0.45) compared to a VA of 0.1 (0.1–0.1) in eyes with additional corticosteroids ($p = 0.902$).

We also evaluated all ophthalmological outcomes after omission of the five eyes with concomitant steroid therapies. In the remaining seven eyes, which were exclusively treated with anti-CD20 therapy,

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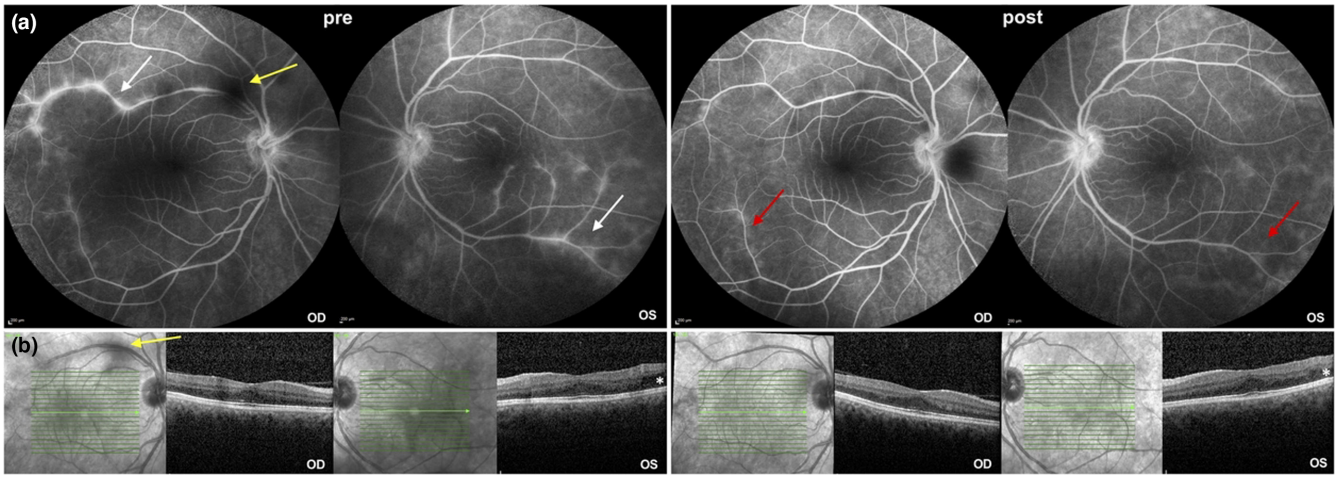

FIGURE 2 Fluorescein angiography (FA) images (a) and optical coherence tomography (OCT) images (b) at baseline (= pre) and after four infusions of anti-CD20 therapy (= post) in a 39-year-old female patient with multiple sclerosis (MS)-associated uveitis (Patient #2) showing a decrease in the extent of retinal vascular leakage (white arrows) on FA. En-face OCT images of the macula with 19 horizontal scans of the macular region (green lines, left panel) and the representative OCT scan of the foveal region (right panel), depicting a decrease in intraretinal fluid (marked with an asterisk) pre- as compared to post-therapy on the left eye. Furthermore, a decrease in vitreous haze, as seen as black shadows (yellow arrows) and a blurred image quality of the foveal OCT scans on the "pre" images, is visible. Due to remaining vasculitic activity (red arrows), infusion intervals were shortened to 5 months. OD, right eye; OS, left eye [Colour figure can be viewed at wileyonlinelibrary.com]

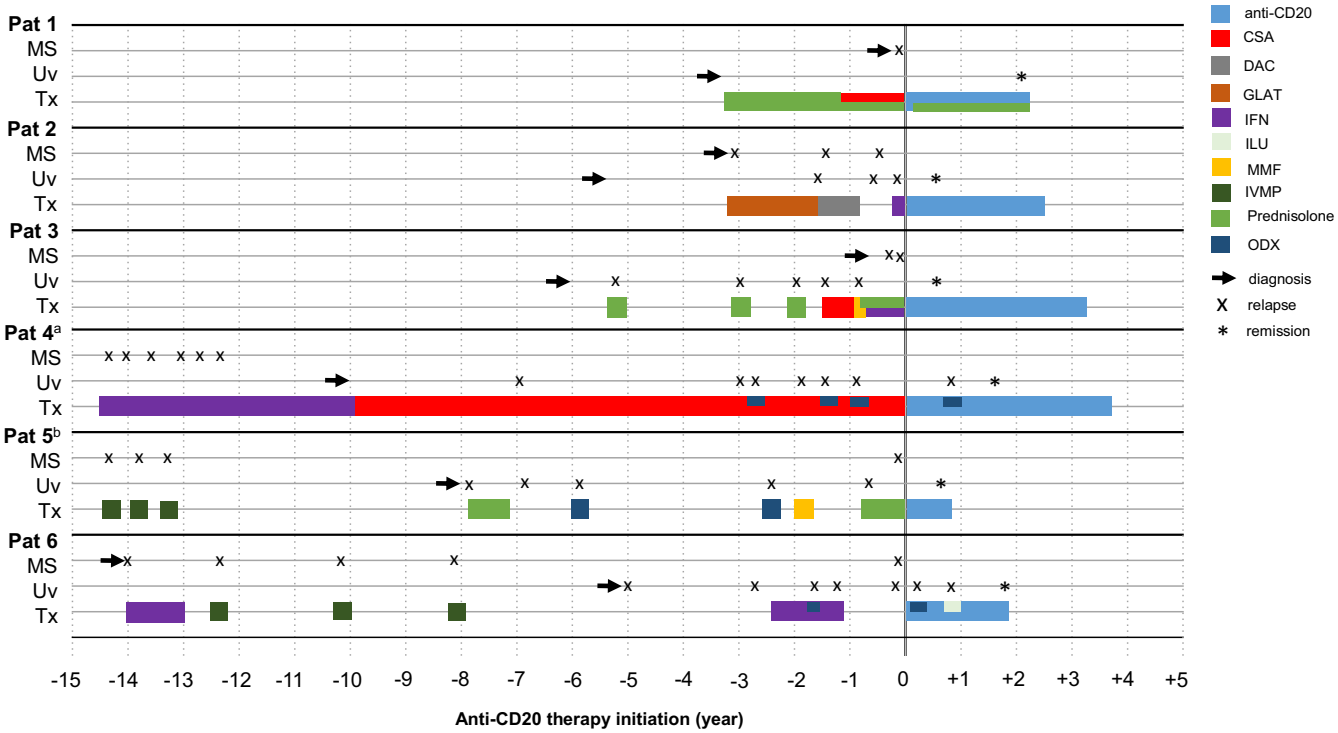

FIGURE 3 Frequency of uveitis and multiple sclerosis (MS) relapses before and after start of anti-CD20 therapy (timepoint 0) in six patients with MS-associated uveitis. The timepoints of diagnosis of uveitis or MS relative to the start of anti-CD20 therapy are indicated by arrows. Relapses are indicated by X. Asterisks indicate the timepoint after start of anti-CD20 therapy when ophthalmological signs of MS-associated uveitis were in remission, as defined by an improvement of vitreous haze and vasculitis scores of at least two steps and any reduction of CRT. Treatments before and after initiation of anti-CD20 therapy are shown. Note that all uveitis relapses under anti-CD20 therapy represented uveitic macular edema. CSA, ciclosporin A; DAC, daclizumab; GLAT, glatiramer acetate; IFN, interferon-beta; ILU, Iluvien (intravitreal); IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; ODX, Ozurdex (intravitreal); Pat, Patient; Pred, prednisolone; Tx, therapy; Uv, uveitis. [a]Diagnosis of MS was made 23 years before start of anti-CD20 therapy. [b]Diagnosis of MS was made 17 years before start of anti-CD20 therapy [Colour figure can be viewed at wileyonlinelibrary.com]

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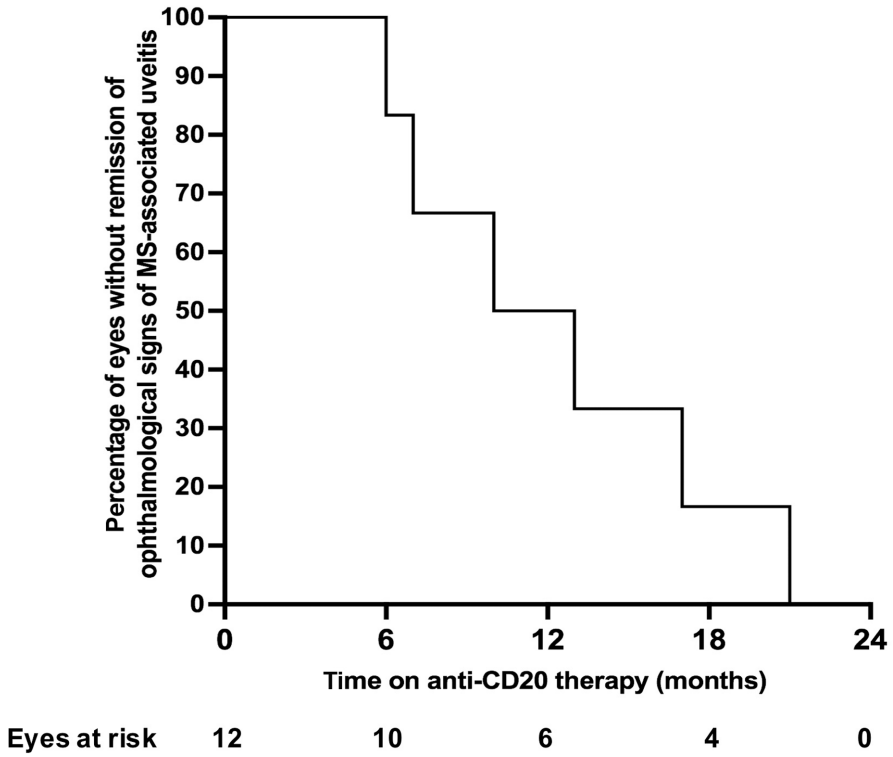

FIGURE 4 Kaplan–Meier analysis depicting the percentage of eyes without remission of ophthalmological signs of multiple sclerosis (MS)-associated uveitis, as defined by an improvement of the vitreous haze and vasculitis scores of at least two steps and any reduction of central retinal thickness after initiation of anti-CD20 therapy. The number of eyes at risk is indicated below the plot

vitreous haze (baseline vs. last follow-up) decreased from a median (IQR) of 0.5 (0.5–1.5) to 0 (0–0.25; $p = 0.03$). The median vasculitis score decreased from 6 (4.5–7) to 4 (2.5–4.5; $p = 0.05$). The median CRT decreased from 338 (312.5–386) μm to 330 (286–354.5) μm ($p = 0.01$) and the median VA improved from 0.2 (0.15–0.65) to 0.1 (0.05–0.45) LogMAR ($p = 0.03$).

Taken together, these analyses indicate that, except for a potential influence of concomitant corticosteroid therapy on CRT, the improvement in ophthalmological outcome variables under anti-CD20 therapy was not significantly distorted by concomitant systemic or local corticosteroid therapy.

Neurological outcomes

The median (IQR) annualized MS relapse rate decreased from 0.62 (0.26–2.84) before the start of anti-CD20 therapy to 0 (0–0) after the start of anti-CD20 therapy (Figure 3). The EDSS score at baseline and at the last follow-up visit remained stable in four out of six patients (67%), while in two patients (33%) the EDSS score improved from 1.0 to 0 (Table 1). The median (range) time between baseline cMRI before initiation of anti-CD20 therapy and last follow-up cMRI was 10 (9–13) months. A comparison of last follow-up and baseline MRI revealed no radiological disease activity in any of the investigated patients.

Side effects of anti-CD20 therapy, as reported by the patients, were recorded during each patient visit. Except for one patient who reported hair loss, no side effects were noted. In particular, no severe adverse events were observed during the follow-up period.

DISCUSSION

The key finding of this study was a significant decrease of intraocular inflammatory activity and a gain in VA following initiation of anti-CD20 therapy in patients with previously treatment-refractory MS-associated uveitis.

While previous retrospective case series suggested favorable responses to anti-CD20 therapy in Behçet's disease [21] and in some types of non-infectious uveitis [22–24], to the best of our knowledge, the present study represents the first case series analyzing the effects of anti-CD20 therapy in patients with MS-associated uveitis.

We used three different well-established morphological criteria, namely, vitreous haze (assessed by indirect ophthalmoscopy), retinal vasculitis (assessed on FA images), and CRT (assessed by OCT) to monitor intraocular inflammatory activity. Improvement of intraocular inflammatory activity after initiation of anti-CD20 therapy was largely consistent across these three different morphological outcome variables and, most importantly, was accompanied by functional improvement, as measured by VA. Furthermore, similarly to the marked reduction of MS relapses under anti-CD20 therapy observed in controlled clinical trials [12–14], we observed a clear decrease in the frequency of uveitis (and MS) relapses following initiation of anti-CD20 therapy.

Whereas this retrospective uncontrolled study cannot formally prove that improvement of MS-associated uveitis was directly related to anti-CD20 therapy, the consistent improvement in the various ophthalmological outcome variables evaluated in our study, as well as the decrease in the uveitis relapse rate, appear compatible with a beneficial effect of anti-CD20 therapy

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in MS-associated uveitis. Furthermore, the fact that all patients had active uveitis which previously did not respond to different immunotherapies suggests that spontaneous remission of MS-associated uveitis following start of anti-CD20 therapy is an unlikely alternative explanation.

A comparison of eyes treated with anti-CD20 therapy alone ($n = 7$) and eyes treated with additional local or systemic corticosteroids ($n = 5$) found no significant differences in opthalmological outcome variables, however, there was a trend ($p = 0.07$) towards lower CRT values in the five eyes treated with concomitant steroids as compared to the seven eyes treated exclusively with anti-CD20 therapy. Nevertheless, a subgroup analysis of the seven eyes treated exclusively with anti-CD20 therapy clearly demonstrated improvements in ophthalmological outcome variables, including CRT. Altogether, acknowledging that the number of eyes treated with anti-CD20 therapy alone ($n = 7$) was limited, these findings indicate that, except for a potential influence of concomitant corticosteroid therapy on CRT, the results of our study were not significantly distorted by concomitant systemic or local corticosteroid therapy applied in five of 12 eyes.

Although the proven efficacy of anti-CD20 therapies in MS indicates a key role of B-cells in the pathogenesis of MS, the precise mechanisms underlying the effect of anti-CD20 therapies in MS are currently not completely understood [25]. Likewise, the potential mechanisms underlying the reduction of intraocular inflammatory activity by anti-CD20 therapy in patients with MS-associated uveitis presently remain elusive. Nevertheless, whereas we are not aware of histopathological studies demonstrating B cells in MS-associated uveitis [26], a role of B cells in MS-associated intraocular inflammation is strongly suggested by the frequent detection of an intravitreal immunoglobulin synthesis in patients with MS-associated intraocular inflammation [27, 28]. Assuming that, as in MS, B cells play a pathogenic role in MS-associated uveitis, anti-CD20 therapies could thus exert their effect in MS-associated uveitis either by directly targeting intraocular B cells or by reducing the likelihood that B cells from the systemic circulation migrate into the eye.

It has long been debated whether MS-associated uveitis is a manifestation of the disease process of MS in the uveal tract or whether it could represent a co-occurrence of two different immune-mediated diseases in one individual [3]. Arguments

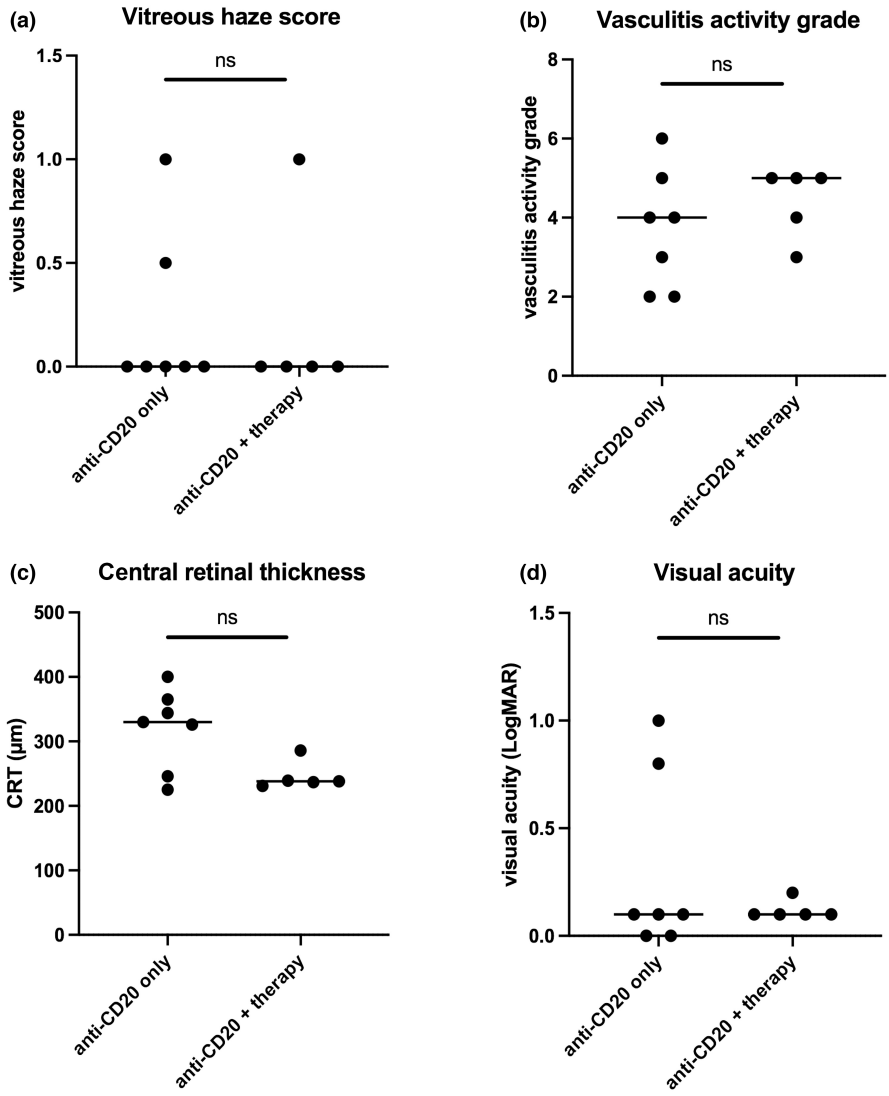

FIGURE 5 Dot plots representing vitreous haze score (a), retinal vasculitis score (b), central retinal thickness (c), and visual acuity (d) in seven eyes treated exclusively with anti-CD20 therapy (= anti-CD20 only), and five eyes treated with anti-CD20 therapy and additional intravitreal or systemic corticosteroids (= anti-CD20+ therapy). Visual acuity is provided as LogMAR values. Horizontal bars indicate the median. CRT, central retinal thickness; LogMAR, logarithm of the minimum angle of resolution

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suggesting that MS-associated uveitis may represent a manifestation of MS comprise similarities in the course of both diseases and, in particular, the detection of an intravitreal immunoglobulin synthesis in patients with MS-associated uveitis, which is reminiscent of the intrathecal immunoglobulin synthesis in MS [27, 28]. As the improvement of MS-associated uveitis under anti-CD20 therapy observed in the present study is suggestive of similar pathophysiological mechanisms operating in MS and MS-associated uveitis, our findings support the concept that MS-associated uveitis is simply a manifestation of MS in the uveal tract.

With regard to clinical practice, the results of this study suggest that, in patients with established MS and MS-associated uveitis, anti-CD20 therapies may be considered as a potentially beneficial treatment option. However, in three patients included in our work, uveitis presented before the clinical onset of MS. This is a more challenging scenario, since at this point it may not be clear whether uveitis occurs in the setting of MS. Future studies will be needed to clarify whether, in this situation, the detection of typical features of MS-associated uveitis, such as bilateral intermediate uveitis and retinal periphlebitis, may justify taking treatment with anti-CD20 therapy into consideration.

Among the strengths of this single-center study are the frequent and thorough ophthalmological assessments, including FA and OCT, as well as the median follow-up period of 28.5 months. However, this work is limited by its retrospective approach, lack of a control group and the overall low number of included patients. To increase patient numbers, future studies on the role of anti-CD20 treatment in MS-associated uveitis should thus ideally be performed in a multicenter setting. Furthermore, as only side effects spontaneously reported by the patients were recorded, but not all potential side effects of anti-CD20 therapy were systematically enquired about, it cannot be excluded that minor adverse events could have been missed. Nevertheless, it appears unlikely that any major side effects could have gone unnoticed.

In conclusion, the findings of this study suggest a beneficial effect of anti-CD20 therapy on MS-associated uveitis. Anti-CD20 therapies may thus be considered as a treatment option in patients with MS-associated uveitis. Furthermore, the results of this work are consistent with the concept that uveitis in patients with MS represents a manifestation of MS rather than the co-occurrence of a separate disease. Future studies investigating the effects of anti-CD20 therapies in independent and larger cohorts of patients with MS-associated uveitis appear warranted.

AUTHOR CONTRIBUTIONS

Frauke Stascheit: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Anne Rübsam:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Carolin Otto:** Data curation (equal); writing – review and editing (equal). **Klemens Ruprecht:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal). **Andreas Meisel:** Funding acquisition (equal); writing – review and editing (equal). **Uwe Pleyer:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal).

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CONFLICT OF INTEREST

Frauke Stascheit received speaking honoria from Biogen and Alexion. Anne Rübsam receives research support from the Deutsche Forschungsgemeinschaft (DFG; RU 2020/3–1) and has received speaking honoraria from Bayer Healthcare and Novartis. Carolin Otto reports no conflicting interests. Andreas Meisel has received speaker honoraria from Alexion, GRIFOLS and Hormosan, honoraria from Alexion, MorphoSys and Vitaccess for consulting services, and financial research support from Octapharma and Alexion. He is chairman of the medical advisory board of the German Myasthenia Gravis Society. Klemens Ruprecht has received research support from Novartis Pharma, Merck Serono, the German Ministry of Education and Research, the European Union (821283–2), Stiftung Charité (BIH Clinical Fellow Program) and the Arthur Arnstein Foundation, speaker honoraria from Bayer, and travel grants from Guthy Jackson Charitable Foundation. Uwe Pleyer has served as principal investigator or consultant for: Abbvie, Alcon, Alimera, Allergan, Bayer, Dompé, Heidelberg-E., Janssen, Novartis, Pfizer, Santen, Shire, Thea, Winzer, Abbvie, Allergan, Lilly, Novartis, Santen, and Thea and has received research support from BMBF, DOG, the DFG, and the European Union. He holds patents (PCT/EP2019/066419, C75928WOUS) and shares in Bayer, Novartis, BioNtec and Zeiss.

DATA AVAILABILITY STATEMENT

All analyzed data are presented in the manuscript and available on reasonable request from qualified investigators.

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