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Rituximab therapy for primary central nervous system vasculitis: A 6 patient experience and review of the literature

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ABSTRACT

Objectives: To assess the efficacy and safety of Rituximab (RTX) in adult primary central nervous system vasculitis (PCNSV).

Methods: We retrospectively assessed the effect of RTX in 6 patients with PCNSV. Five of the 6 were refractory to high dose glucocorticoids (GCs) and/or conventional immunosuppressants (IS). The sixth was newly diagnosed and received RTX in combination with GCs. Clinical evaluation, laboratory tests, and imaging modalities were performed at initial RTX administration and during the follow-up. Treatment response was assessed using the treating physician's global opinion regarding response and the degree of disability using the modified Rankin scale (mRS). We also performed a literature review for previous use of RTX in PCNSV using PubMed, Ovid Medline, and the Cochrane library.

Results: The six patients (3 females) had a median age at diagnosis of 50.5 years (range 17–68 years). All had active disease when RTX was started. In 4 patients, RTX administration was associated with a marked reduction in the number of flares (from 18 before starting RTX to 3 after). One patient, after an initial improvement, had 2 flares when B cells were depleted and he was not able to reduce prednisone below 20 mg/day. A 6th patient had a flare when B cells recovered and retreatment with RTX re-induced and maintained remission. The median mRS score at last visit (median: 2; range 0–4) was lower than that prior to treatment (median 3; range 1–5). The median prednisone daily dose before RTX administration was significantly higher than that at last follow-up ($p = .006$). In the literature review, we identified 5 papers describing 7 patients treated with RTX. Six patients responded to RTX with clinical and MRI improvement with no reported flares after RTX treatment.

Conclusions: Our data support a potential role for RTX treatment in selected patients with PCNSV.

1. Introduction

Primary central nervous system vasculitis (PCNSV) is an uncommon form of vasculitis that is restricted to the brain and spinal cord [1–4]. Glucocorticoids (GCs) alone or combined with traditional immunosuppressive agents, mainly cyclophosphamide (CYC), have been

Abbreviations: PCNSV, primary central nervous system vasculitis; GCs, glucocorticoids; CYC, cyclophosphamide; RTX, rituximab; IV, intravenous; IS, immunosuppressive; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; CSF, cerebrospinal fluid; MMF, micophenolate mofetil; AZA, azathioprine; PDN, prednisone; mRS, modified Rankin Scale

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used successfully to treat this vasculitis [5–9]. However, some patients are intolerant or refractory to this regimen and may have a progressive course with potential fatal outcome in spite of usual therapy [10,11]. Therefore, other treatment options are needed for patients with intractable disease and/or toxicity from current therapies [2].

Anti-CD20 therapy with rituximab (RTX) has been used successfully for the treatment of systemic vasculitides [12–15] and in several CNS inflammatory conditions [16–18]. We investigated the efficacy and safety of RTX treatment in a series of 6 patients with PCNSV. In addition, we reviewed the literature reporting the use of RTX in PCNSV.

2. Patients and methods

2.1. Identification of the patients and treatment protocols

We report findings in 6 patients with PCNSV who were treated with RTX. Four patients had a brain biopsy showing vasculitis and the other 2 had cerebral angiogram and clinical findings highly suggestive of vasculitis.

Four of 6 patients belonged to the cohort of 191 consecutive patients seen at Mayo Clinic (Rochester, MN) over the 35-year period from 1982 to 2017 [19], while the other two were followed at Reggio Emilia Hospital. The study was approved by the Mayo Clinic Institutional Review Board and written informed patient consent to perform the study was obtained. Diagnostic and exclusion criteria, data collection and evaluation have previously been described in detail elsewhere [6–8].

Five of the 6 patients had refractory disease and had received high-dose oral GCs, intravenous (IV) pulse methylprednisolone therapy and conventional immunosuppressive agents before RTX; in all of these 5 cases RTX was given due to the lack of efficacy of previous therapies. Only one newly diagnosed patient who was treatment-naïve received RTX in combination with GCs at diagnosis as remission-induction therapy.

RTX was administered as follows: two infusions of 1000 mg, 15 days apart, in 4 patients, and four weekly infusions of 375 mg/m2 in 2 patients. Three patients had multiple courses of RTX: the first had maintenance treatment with repeat infusions of 1000 mg, 6 months and 12 months, respectively, after the 1st course; the second had a second course (two infusions of 1000 mg, 15 days apart) 13 months after the first course for a disease flare, when CD19 + cells recovered; the third received a second course (two infusions of 1000 mg, 15 days apart) 27 months after the first course for a disease flare when B cells repopulated, and 6 months later as maintenance treatment with one infusion of 500 mg.

2.2. Review of biopsy specimens, angiograms, and magnetic resonance imaging (MRI)

Clinical evaluation, laboratory tests including erythrocyte sedimentation rate (ESR) levels and spinal fluid examination, as well as imaging modalities were performed both at first RTX administration and during the follow-up. All patients had a complete neurologic examination performed by a neurologist at the time of diagnosis, RTX administrations, and at other visits, including the last visit. Imaging studies included brain magnetic resonance imaging (MRI), conventional digital subtraction angiogram, and magnetic resonance angiography (MRA).

Cerebral biopsy specimens were reviewed by one pathologist (CG) without knowledge of clinical information. Angiograms and MRI were reviewed by a neuroradiologist. Conventional digital subtraction angiograms and brain MRI and MRA were performed and interpreted according to clinical protocols used by the Divisions of Neuroradiology at the Mayo Clinic and at the Reggio Emilia Hospital.

Relapse was defined as a recurrence of or worsening of symptoms of PCNSV, or evidence of worsening of existing lesions and/or new lesions on repeat MRI examinations, while the patient received no medication or received a stable dosage of medication. Patients with relapse required an increase in therapy. To assess the effect of treatment, we used the treating physician's global assessment of the response to therapy as based on the review of the detailed clinical, radiological, and laboratory data in the medical records. The degree of disability at presentation and at the last visit was defined by a review of the detailed clinical data in the medical record and was categorized using the modified Rankin scale (mRS) [20], a standardized and commonly used scale which measures disability or dependence in activities of daily living in stroke patients. The scale consists of grades 0–6: 0 corresponds to no signs or symptoms; 1, no significant disability (able to carry out all usual activities, despite some symptoms); 2, slight disability (able to look after own affairs without assistance, but unable to carry out all previous activities); 3, moderate disability (requires some help, but able to walk unassisted); 4, moderately severe disability (unable to attend to own bodily needs without assistance, and unable to walk unassisted); 5, severe disability (requires constant nursing care and attention, bedridden, incontinent); and 6, death.

Subjects were followed until their death or last follow-up visit (median follow-up duration: 51 months; range: 16–105 months).

2.3. Literature review

A detailed literature search was performed to evaluate the current published evidence on RTX use in PCNSV. The following databases were searched since their inception of the database until 28th October 2018: PubMed, Ovid MEDLINE and Cochrane Library. Key words included Rituximab, angiitis, vasculitis, arteritis, and central nervous system. We also reviewed the reference sections of published studies and identified papers known to the authors.

3. Results

3.1. Patients characteristics

The median age at diagnosis of the six study patients (3 females) was 50.5 years (range 17–68 years). The mean duration of the disease at the onset of RTX therapy was 15 months (range 4–90 months). The most common symptoms at presentation were headache and confusion (3 patients), followed by cognitive dysfunction (2 patients). One patient had symptoms related to spinal cord involvement, while one patient had Hodgkin's lymphoma which occurred simultaneously. Cerebrospinal fluid (CSF) examination was abnormal (protein > 45 mg/dL or white cell count > 5 cells mm^3) in all 6 patients. Morphologic evaluation and/or immunocytochemical studies and/or flow cytometric immunophenotyping were negative in all 6 patients. Serological and molecular tests and cultures excluded infection. ESR at diagnosis was normal in all 6 patients. Cerebral angiography or MRA was performed in 5 of the 6 patients, and in 2 showed changes characteristic of vasculitis. Multiple bilateral infarcts on MRI were observed in 2 patients, while 2 other patients had diffuse leptomeningeal enhancement which in one patient also involved the thoracic spine. One patient had a tumor-like mass on MRI with edema and mass effect, and another had enhancing multiple cortical hemorrhagic lesions. Cerebral stereotactic biopsy was performed in 4 patients and was positive in all cases. Lymphocytic vasculitis was found in 3 patients and granulomatous vasculitis in one. Vascular deposits of β-amyloid peptide were not observed.

3.2. Results of treatment and outcome

Table 1 summarizes the main results of our study. Prior to RTX therapy 4 of 6 patients had received one or more conventional immunosuppressants (IS): cyclophosphamide (CYC) [4], mycophenolate mofetil (MMF) [3], and azathioprine (AZA) [2]. As mentioned above,

Table 1
Parameters of disease activity before and after Rituximab treatment.

Case	Age/sex	Disease duration, before RTX	Previous therapy	Indication for RTX	Clinical findings and status at initiation of RTX	Imaging at initiation of RTX	RTX courses	Concomitant therapy	Response (clinical/MRI)	Outcome 6 months after first RTX	PDN dose before/ after RTX	Therapeutic changes after RTX	No. of flares before/ after RTX	Last follow-up visit (time after starting RTX and status)
1	48/F	90 months	PDN, oral CYC, MMF	Flare	Confused, disoriented and drowsy; mRS: 5	New acute infarcts at MRI and more marked vascular lesions at MRA	1	IV MTP (1 g/day for 5 days); PDN (60 mg/day) and MMF (2 g/day)	Alert, some memory impairment, walking with assistance -	mRS: 4	20/ 5 mg/ day	–	5/0	15 months; mRS: 3
2	17/M	33 months	IV MTP, PDN, IV CYC, MMF, AZA	Flare	Seizures, optic neuritis; mRS: 2	New multifocal linear and punctate enhancement throughout both cerebral hemispheres, new leptomeningeal enhancement in the right occipital and posterior temporal lobes, and recurrent enhancement in the intraconal right optic nerve	3	PDN (20 mg/ day)	No neurological manifestation. Notable reduction in gadolinium enhancing foci, no leptomeningeal and optic nerve enhancement	mRS: 0	20/ 19 mg/ day	–	3/1	14 months; mRS: 0
3	68/F	4 months	–	Starting therapy	Headache, gait imbalance, paresthesias of the right side of the lips and fingers, cognitive dysfunction; mRS: 2	Multiple infarcts of varying ages in all vascular distributions, leptomeningeal enhancement in both cerebral hemispheres	1	PDN (60 mg/ day)	Some gait and cognitive impairment. No evidence of additional infarcts	mRS: 1	60/ 20 mg/ day	AZA stopped for inefficacy, added MTX	−/2	12 months; mRS: 1
4	54/M	7 months	IV MTP, PDN	Flare	No new neurological manifestations; mRS: 1	New areas of infarction in the right dentate nucleus and right anterior temporal lobe	2	IV MTP (1 g/day for 3 days); PDN (80 mg/day)	Some headaches. No evidence of new infarctions	mRS: 1	70/ 0 mg/ day	Stop PDN	1/1	21 months; mRS:1
5	53/M	7 months	IV MTP, PDN, IV CYC	No response	Confusion, drowsiness, cognitive dysfunction; mRS: 5	Increased extension of the mass-like enhancing lesion in the left cerebral hemisphere and vasogenic edema	1	PDN (50 mg/ day)	Neurological manifestations improved. Improvement with decreased parenchymal enhancement and resolution of vasogenic edema	mRS: 4	50/ 5 mg/ day	Added MMF	5/0	48 months; mRS: 4
6	39/F	23 months	IV MTP, PDN, IV CYC, oral CYC, MMF, AZA	Flare	Headache, confusion, right hemiparesis; mRS: 4	Increase in size of the enhancing and hemorrhagic lesions in the left hemisphere and vasogenic edema	3	IV MTP (1 g/day for 3 days); PDN (50 mg/day); AZA(150 mg/ day)	Neurological manifestations improved. Reduction in size of some enhancing lesions, increase in size of left temporo-occipital hemorrhagic lesion and reduction of vasogenic edema	mRS: 3	50/ 25 mg/ day	–	5/2	33 months; mRS:3

RTX = rituximab; PDN = prednisone; CYC = cyclophosphamide; MMF = mycophenolate mofetil; MTP = methylprednisolone; AZA = azathioprine; MTX = methotrexate; IV = intravenous; mRS = modified Rankin score; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography.

one newly diagnosed PCNSV patient received RTX and oral prednisone (PDN) as initial remission-induction treatment.

All patients received oral prednisone therapy (median dosage at the time of RTX initiation: 55 mg/day, range: 20–80 mg/day) in addition to RTX. Three patients also received intravenous pulse methylprednisolone 1 g/day for 3 to 5 days, while in 2 patients RTX was added to the ongoing treatment with MMF and AZA. The median PDN dose before RTX treatment was 50 mg/day (range: 20–70 mg/day), while the median dosage at the last follow-up visit was 12 mg/day (range: 0–25 mg/day) ($p = .006$). One patient was able to discontinue prednisone.

At the initiation of RTX, all patients had active disease according to presence of symptoms of PCNSV and/or worsening of existing lesions and/or appearance of new lesions on MRI/MRA examination. All patients initially improved after the combined RTX and PDN treatment with a median time to obtain response of 1 month (range: 1–1.5 months). In 4 patients the RTX administration was associated with a marked reduction in the number of flares (from 18 before starting RTX to 3); one of the 3 flares occurred 27 months after the first course when CD19 + cells recovered, while the other 2 flares occurred 6 months after the first course of RTX and 3 months after the second course of RTX, respectively, when CD19 + cells were depleted. In both flares an increased in the PDN dosage resolved the neurologic findings, after which the two patients were treated with 1 course and 2 courses of RTX maintenance treatment, respectively; both were in remission at the last follow-up visit.

One patient did not respond to RTX treatment. This patient received RTX as initial remission-induction treatment, but after an initial improvement, had 2 flares of encephalopathy when B cells were depleted and she was not able to reduce PDN below 20 mg/day. The patient was subsequently treated with AZA that was suspended due to lack of efficacy, and then with MTX. At the last visit, 12 months after starting RTX, she was stable and had been able to reduce the PDN dose to 10 mg/day.

A 6th patient started on RTX due to the appearance of new areas of infarction on a follow-up brain MRI, while he was treated with oral PDN. Eleven months later, he suspended GC therapy, however B cells recovered and he had a disease flare. The patient had a second course of RTX and restarted PDN at the dosage of 30 mg/day. Eight months later he was in remission, his CD19+ count was 0, and he was able to discontinue PDN therapy. Fig. 1 shows the reduction of the enhancement of the vessel walls of the right middle cerebral artery on follow-up brain MRI after the second course of RTX which paralleled the improvement of neurological findings.

In one patient RTX was added to ongoing MMF treatment. Fifteen months after RTX therapy, at the last visit, she was on PDN 5 mg/day and MMF 1.5 g/day and she was in remission. In another patient RTX was used as adjunctive to AZA therapy which had previously been started as maintenance therapy after induction with IV CYC (6 monthly infusions). One patient started MMF (2 g/day) as remission maintenance treatment 13 months after RTX; 35 months later, at the last visit, he was in remission and he was able to reduce PDN to 5 mg/day and continued with MMF at a dosage of 1 g/day.

In these 6 patients, the median mRS score at last visit was 2 (range 0–4). This was lower than before RTX administration (median 3; range 1–5) and similar to the score observed 6 months after first RTX administration (median: 2; range 0–4).

3.3. Literature review

To our knowledge, there are only 8 earlier published cases of PCNSV patients treated with RTX, 7 of which are summarized in Table 2 [21–25]. Six patients had adult PCNSV, while one was 3-year old at vasculitis onset. The eighth case (case 3) has previously been described by our group [23] and is reported with a longer follow-up in this case series.

RTX was started in 3 patients because of a disease flare, in 2 for lack of response to the initial treatment, and in 2 as induction therapy. Five patients had one course of RTX and two 2 courses. In 5 patients the vasculitis was not controlled by the previous therapy that included IV MTP and oral PDN, oral and/or IV CYC, MMF, and AZA. Three patients had concomitant therapy with oral PDN alone and one with IV MTP and oral PDN. In one patient concomitant therapy was not defined. In one case the first course of RTX was given in combination with oral CYC and MMF apparently without increase of oral PDN, while the second course was administered 3 months later in association with low-dose oral CYC (50 mg daily) for a disease flare during MMF treatment. In another patient RTX was associated with IV MTP and IV CYC, 9 months later he was stable with no neurological symptoms on MMF maintenance therapy. In 2 other patients RTX was followed by AZA maintenance treatment without disease flares, while in a third patient a second course of RTX was administered 9 months after the first for maintaining remission.

All the patients appeared to respond well to RTX with clinical and MRI improvement, except for one, who at last follow-up, 3 months after the second course of RTX, was stable but presented with a small new area of T2 intensity at follow-up MRI. The other 6 patients reported no flares after RTX treatment with a median follow-up of 10 months (range: 6–20 months) after starting RTX. After RTX treatment, considering all 7 patients, there was a marked reduction in the number of flares (from 17 before starting RTX to 1 after).

No side effects were reported during RTX treatment in our cases and in the published 7 cases.

4. Discussion

Treatment for PCNSV has been derived from therapeutic strategies used in other vasculitides [5,26–28]. Earliest reports suggested a poor outlook with fatal outcome in most patients, and transient or doubtful effectiveness of GCs [1,26,29]. In 1983, Cupps et al. reported the effectiveness of CYC in combination with GCs [5]. Two recent retrospective cohort studies, which represent the two largest reported series of cases with adult PCNSV, have described the treatment and outcomes of patients with PCNSV [8,9]. Although the majority of the patients (> 60%) responded to therapy with GCs alone or in combination with CYC and tended to improve during the follow-up period, an overall increased mortality was observed.

Emerging evidence suggests that PCNSV is an heterogeneous condition and that not all patients with PCNSV need the same treatment [1,2]. Angiography negative, biopsy positive patients, characterized by vasculitic involvement of small vessels and leptomeningneal enhancement on MRI, respond favorably to GC therapy and have a good neurological outcome [30,31]. The most severe end of the clinical spectrum of PCNSV is represented by patients with angiographic evidence of multiple bilateral large vessel lesions and MRI evidence of multiple cerebral infarctions [7,8,10,11]. These patients had a rapidly progressive course and responded poorly even to an aggressive treatment with GCs and CYC. Furthermore, relapses/recurrences occur in more than one-quarter of PCNSV patients and effective immunosuppressive strategies remain to be defined for improving long-term neurological outcome in these patients [8,9,32]. Therefore, there is the unmet need to identify therapeutic agents that may be helpful in patients who are intolerant of, or respond poorly to traditional IS treatment, in particular to GCs and CYC. We demonstrated that MMF, an immunosuppressive agent successfully used to treat other vasculitides, and TNF-alpha blockers may also be effective and safe therapies for adult PCNSV [33,34]. MMF may represent a less toxic alternative to CYC for inducing remission in PCNSV.

Rituximab is a chimeric human/murine monoclonal antibody that acts by depleting CD-20 + B-cells. It is an emerging novel therapeutic option in several autoimmune neurological disorders [16–18]. In PCNSV, the inflammatory infiltrate is typically composed of lymphocytes, and the presence of granulomas is frequent [4,35]. In our

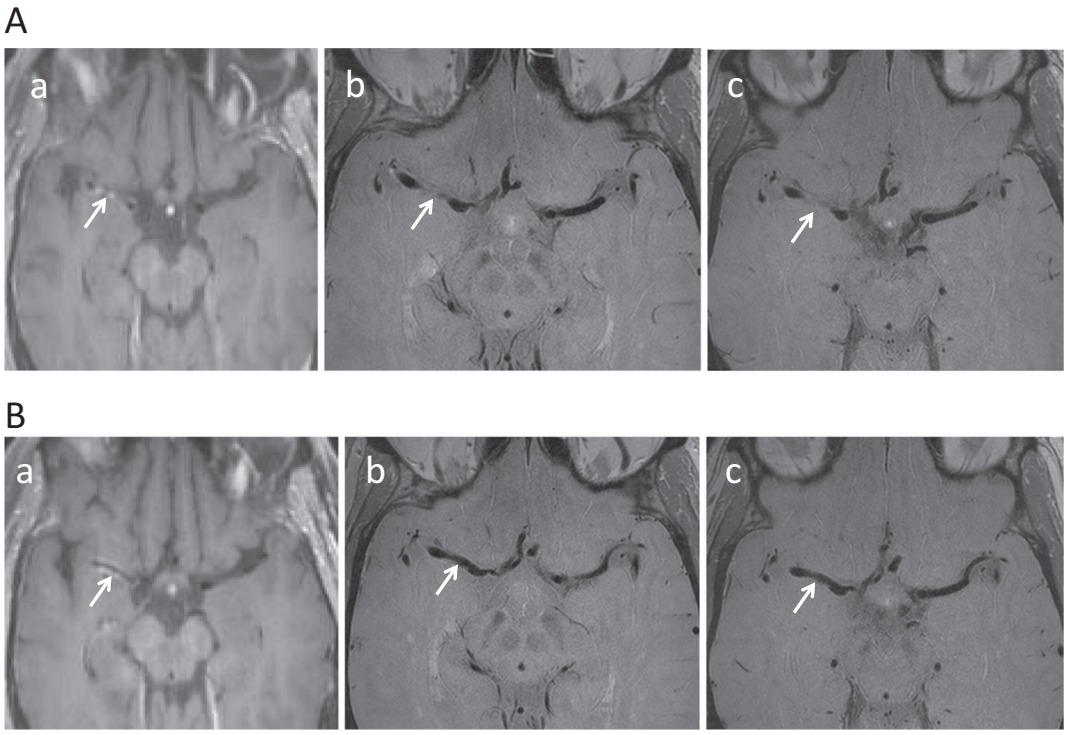

Fig. 1. A and B. Magnetic resonance imaging of patient 4. (a), at the moment of the second flare, when B cells recovered and the patient repeated rituximab (RTX) and prednisone (PDN) was restarted at 30 mg/day. Axial T1 Space Post Contrast sequence: abnormal enhancement of the vessel walls of the right middle cerebral artery (arrow) consistent with vasculitis. (b), 3 months later, the vasculitis was in remission. Gadolinium Axial Proton Density Space Black Blood imaging: decreased vessel wall enhancement (arrow) involving the right M1 segment extending to the trifurcation. (c), 7 months after RTX administration, the vasculitis was in remission, PDN was suspended and CD19+ count was 0. Gadolinium Axial Proton Density Space Black Blood image: minimal vessel wall enhancement (arrow) involving the right M1 segment extending to the trifurcation.

cerebral biopsy series, immunohistochemical stains occasionally included CD3 and CD20 as markers of T and B lymphocytes, respectively. The presence of B lymphocytes in the inflammatory infiltrate (unpublished data) supports a rationale for using RTX in PCNSV.

Four previous case reports described 5 patients with active PCNSV who despite traditional immunosuppressive agents, mainly CYC, received RTX with good reported outcomes in 4 of 5 cases [21,22,24,25]. Two additional patients were successfully treated with RTX from the beginning and RTX was able to induce the remission with improvement of neurological status and MRI findings. The only patient who did not respond had two RTX courses, at a 3-month interval, for a flaring disease. Three months after the second course at the last visit he was clinically stable, but the MRI showed a small new area of T2 hyperintensity. Except for this patient, the length of follow-up after RTX administration was adequate to evaluate the efficacy of this drug. In particular, RTX was very effective in reducing the number of flares, 6/7 patients did not have any flare after starting RTX treatment over a median follow-up of 10 months.

A reporting bias may be present in the published cases showing the efficacy of RTX in PCNSV. However, in our series, which included all patients treated with RTX in two centers, 5 of the 6 patients responded to RTX treatment with improvement of their neurological status. These 5 patients had vasculitis refractory to previous immunodepressive treatment. The patient who received RTX as initial remission-induction treatment had, after an initial improvement, 2 flares of vasculitis, when B cells were depleted, and therefore he was considered a non-responder to RTX treatment. MRI findings were improved in 3 patients and remained stable without progression in 2. In these 6 patients, RTX was started for a disease flare in 4 patients, lack of response to previous treatment in one, and as initial remission-induction therapy in one. Four of these 6 patients had previously been unsuccessfully treated with traditional IS. After RTX therapy prednisone dosage was significantly reduced and 6-month and last follow-up neurological outcome improved in most patients. As in the published cases, RTX markedly reduced the number of flares. As observed in other vasculitides [12,36], some disease flares occurred when the CD19 + count was restored, but retreatment with RTX was able to induce and maintain the remission. RTX was well tolerated by all patients. In particular, no serious adverse events such as severe infections or infusion-related reactions occurred [37].

Our study has several limitations, including the retrospective nature, the small number of patients treated, the absence of controls and the relatively short follow-up duration on RTX. Therefore, our results should be taken with caution. In addition, it is unclear how the response achieved using RTX should be best maintained over time. However, PCNSV is a rare disease and there are only sporadic case reports describing the efficacy of the biological treatment on this condition, particularly in patients refractory to traditional immunodepressants. The response to RTX of patients with refractory disease and its ability to allow tapering of GCs and to reduce the number of flares are encouraging findings, although they require confirmation in further studies. Although a randomized controlled trial would be ideal to assess the efficacy of RTX, the rarity of PCNSV makes this improbable.

5. Conclusions

Considering our results and those previously reported, we suggest that RTX may be an effective and safe therapeutic option in patients with PCNSV refractory to conventional immunodepressants. Anecdotal reports indicate a potential role for RTX as a first line therapy, but should be considered preliminary. Additional studies evaluating the use of RTX for treatment of PCNSV are needed.

Table 2
Characteristics of the published cases of Primary Central Nervous System Vasculitis treated with Rituximab.

Author	Cases	Age/sex	Disease duration before RTX	Previous therapy	Indication for RTX	Clinical/MRI findings at initiation of RTX	RTX courses	Concomitant therapy	Response (clinical/MRI)	PDN dose before/ after RTX	Therapeutic changes after RTX	No. of flares before/ after RTX	Last follow-up visit (time after starting RTX and status)
De Boysson et al. [22]	1	42/M	5 months	PDN, IV CYC	No response	Worsening of ataxia, and upper limb paresthesia; MRI: increased number of enhancing cerebral and cervical spine lesions	1	ND	Reduced paresthesias and ataxia and fewer lesions at MRI	ND/ND	AZA	1/0	12 months/no relapse
	2	57/F	2 weeks	–	Starting therapy	Balance disorder, dysarthria, focal motor deficit of the right arm, and cognitive decline; MRI: multiple infarctions;	1	PDN (70 mg/ day)	Improvement of neurologic status and decreased size and nuber of lesions at MRI	–	–	−/0	20 months/no relapse
Anis et al. [24]	1	64/M	6 months	IV MTP, PDN, IV CYC	No response	Resolution of papilledema; MRI: 2 new enhancing left frontal lobe lesions and a new right periventricular lesion;	2	PDN (ND)	Symptomatic improvement, the patient returned to his activities of daily life including his profession of teaching music; MRI: reduced periventricular and frontal lobe lesions	ND/ND	–	1/0	8 months/no relapse
El M'Kadden et al. [21]	1	3/F	9 years	IV MTP, PDN, AZA, IV CYC	Flare	ND/ND	1	PDN	Improvement, mild incoordination in all limbs and mild cognitive impairment	ND/ND	–	8/0	11 months/no relapse
Patel et al. [25]	1	41/M	ND	IV MTP, PDN, IV CYC, oral CYC	Flare	Recurrence of headache and elevated CSF protein; MRI: no further infarcts	2	PDN (15 mg/ day), oral CYC, MMF	Improvement of headache, no new neurological symptoms; MRI: new foci of acute ischemia in the left internal capsule and right occipital lobe	15/ 10 mg/ daily	MMF (stopped for new lesions at MRI); low-dose oral CYC started after MMF suspension	3/1	6 months/clinically stable but a small new area of T2 hyperintensity at MRI
	2	47/M	ND	PDN, AZA, IV MTP, oral CYC, MMF	Flare	Right-sided facial droop and elevated CSF protein; MRI: areas of cerebral white matter signal abnormality	1	IV MTP, IV CYC, PDN	Clinically stable, no new neurological symptoms; MRI: not performed	ND/ND	MMF	4/0	9 months/no relapse
	3	68/F	2 weeks	–	Starting therapy	Global aphasia, lethargy, labile mood; MRI: solitary enhancing mass with vasogenic edema	1	IV MTP, PDN	Clinically improved with normal speech and mood; MRI: no recurrence of vasculitis	ND/ND	AZA	−/0	6 months/no relapse

RTX = rituximab; PDN = prednisone; CYC = cyclophosphamide; MMF = mycophenolate mofetil; MTP = methylprednisolone; AZA = azathioprine; MRI = magnetic resonance imaging; ND = not defined.

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Conflicts of interest

None.

Author contributions

All authors were involved in drafting and in critical revisions of the article. Carlo Salvarani had full access to all of the data in the study and takes responsibility for the integrity and the accuracy of the data.

Ethics and consent

The study was approved by the Mayo Clinic Institutional Review Board and written informed patient consent to perform the study was obtained. Formal approval from Reggio Emilia Hospital Ethic Committee was not required for this type of observational study. The ethic committee confirmed the observational non-interventional retrospective nature of our cohort.

References

[1] Salvarani C, Brown Jr. RD, Hunder GG. Adult primary central nervous system vasculitis. Lancet 2012;380:767–77.
[2] Salvarani C, Brown Jr. RD, Hunder GG. Adult primary central nervous system vasculitis: an update. Curr Opin Rheumatol 2012;24:46–52.
[3] Salvarani C, Brown Jr. RD, Calamia KT, Christianson TJH, Huston 3rd J, Meschia JF, et al. Primary CNS vasculitis with spinal cord involvement. Neurology 2008;70:2394–400.
[4] Giannini C, Salvarani C, Hunder G, Brown RD. Primary central nervous system vasculitis: pathology and mechanisms. Acta Neuropathol 2012;123:759–72.
[5] Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. prospective diagnostic and therapeutic experience. Am J Med 1983;74:97–105.
[6] Salvarani C, Brown Jr. RD, Calamia KT, Christianson TJH, Weigand SD, Miller DV, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 2007;62:442–51.
[7] Salvarani C, Brown Jr. RD, Christianson TJH, Miller DV, Giannini C, Huston 3rd J, et al. An update of the mayo clinic cohort of patients with adult primary central nervous system vasculitis:description of 163 patients. Med (Baltimore) 2015;94:e738https://doi.org/10.1097/MD.0000000000000738.
[8] Salvarani C, Brown Jr. RD, Christianson TJH, Huston 3rd J, Giannini C, Miller DV, et al. Adult primary central nervous system vasculitis treatment and course: analysis of one hundred sixty-three patients. Arthritis Rheumatol 2015;67:1637–45.
[9] De Boysson H, Zuber M, Naggara O, Neau J-P, Gray F, Bousser M-G, et al. French vasculitis study group and the french neurovascular society. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the french cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol 2014;66:1315–26.
[10] Salvarani C, Brown Jr. RD, Calamia KT, Christianson TJH, Huston 3rd J, Meschia JF, et al. Rapidly progressive primary central nervous system vasculitis. Rheumatology (Oxford) 2011;50:349–58.
[11] Salvarani C, Brown Jr. RD, Morris JM, Huston 3rd J, Hunder GG. Catastrophic primary central nervous system vasculitis. Clin Exp Rheumatol 2014;32(Suppl. 82):S3–4.
[12] Guillevin L. Rituximab for ANCA-associated vasculitides. Clin Exp Rheumatol 2014;32:S118–21.
[13] Roccatello D. "How I treat" autoimmune diseases: State of the art on the management of rare rheumatic diseases and ANCA-associated systemic idiopathic vasculitis. Autoimmun Rev 2017;16:995–8.
[14] Danlos FX, Rossi GM, Blockmans D, Emmi G, Kronbichler A, Durupt S, et al. French vasculitis study group. Antineutrophil cytoplasmic antibody-associated vasculitides and IgG4-related disease: a new overlap syndrome. Autoimmun Rev 2017;16:1036–43.
[15] Kronbichler A, Windpessl M, Pieringer H, Jayne DRW. Rituximab for immunologic renal disease: what the nephrologist needs to know. Autoimmun Rev 2017;16:633–43.
[16] Dalakas MC. B cells as therapeutic targets in autoimmune neurological disorders. Nat Clin Pract Neurol 2008;4:557–67.
[17] Alexopoulos H, Biba A, Dalakas MC. B-cell therapies in autoimmune neurological diseases: rationale and efficacy trials. Neurotherapeutics 2016;13:20–33.
[18] Thiebaut M, Launay D, Rivière S, Mahévas T, Bellakhal S, Hachulla E, et al. Efficacy and safety of rituximab in systemic sclerosis: french retrospective study and literature review. Autoimmun Rev 2018;17:582–7.
[19] Salvarani C, Brown RD, Christianson TJH, Huston J 3rd, Morris JM, Giannini C, Hunder GG. Primary central nervous system vasculitis mimicking brain tumor: comprehensive analysis of 13 cases from a single institutional cohort of 191 cases. J Autoimmun, [in press].
[20] Sulter G, Steen C, DeKeyser J. Use of the barthel index and modified rankin scal in acute stroke trials. Stroke 1999;30:1538–41.
[21] El M'Kaddem B, Clapuyt P, de Bruycker JJ, Lauwerys B, Raftopoulos C, Godfraind C, et al. Primary cerebral arteritis in a young girl: an unusual cause of acute recurrent neurological deterioration. Eur J Paediatr Neurol 2012;16:196–9.
[22] De Boysson H, Arquizan C, Guillevin L, Pagnoux C. Rituximab for primary angiitis of the central nervous system: report of 2 patients from the French COVAC cohort and review of the literature. J Rheumatol 2013;40:2102–3.
[23] Salvarani C, Brown Jr. RD, Huston 3rd J, Morris JM, Hunder GG. Treatment of primary CNS vasculitis with rituximab: case report. Neurology 2014;82:1287–8.
[24] Anis S, Sharabi A, Mina Y, Klein A, Cagnano E, Elkayman O, et al. Rituximab as a second-line treatment for lymphocytic vasculitis of the central nervous system. Isr Med Assoc J 2016;18:630–2.
[25] Patel S, Ross L, Oon S, Nikpour M. Rituximab treatment in primary angiitis of the central nervous system. Intern Med J 2018;48:724–7.
[26] Moore PM. Diagnosis and management of isolated angiitis of the central nervous system. Neurology 1989;39:167–73.
[27] Salvarani C, Pipitone N, Hunder GG. Management of primary and secondary central nervous system vasculitis. Curr Opin Rheumatol 2016;28:21–8.
[28] Muratore F, Pazzola G, Soriano A, Pipitone N, Croci S, Bonacini M, et al. Unmet needs in the pathogenesis and treatment of vasculitides. Clin Rev Allergy Immunol 2018;54:244–60.
[29] Harrison Jr. PE. Granulomatous angiitis of the central nervous system. Case Rep Review J Neurol Sci 1976;29:335–41.
[30] Salvarani C, Brown Jr. RD, Calamia KT, Christianson TJ, Huston 3rd J, Meschia JF, et al. Angiography-negative primary central nervous system vasculitis: a syndrome involving small cerebral vessels. Med (Baltimore) 2008;87:264–71.
[31] Salvarani C, Brown Jr. RD, Calamia KT, Christianson TJ, Huston 3rd J, Meschia JF, et al. Primary central nervous system vasculitis with prominent leptomeningeal enhancement: a subset with a benign outcome. Arthritis Rheum 2008;58:595–603.
[32] De Boysson H, Arquizan C, Touzé E, Zuber M, Boulouis G, Naggara O, et al. Treatment and long-term outcomes of primary central nervous system vasculitis. Updated results from the French registry. Stroke 2018;49:1946–52.
[33] Salvarani C, Brown Jr. RD, Christianson TJ, Huston 3rd J, Giannini C, Miller DV, et al. Mycophenolate mofetil in primary central nervous system vasculitis. Semin Arthritis Rheum 2015;45:55–9.
[34] Salvarani C, Brown Jr. RD, Calamia KT, Huston 3rd J, Meschia JF, Giannini C, et al. Efficacy of tumor necrosis factor alpha blockade in primary central nervous system vasculitis resistant to immunosuppressive treatment. Arthritis Rheum 2008;59:291–6.
[35] Miller DV, Salvarani C, Hunder GG, Brown Jr. RD, Parisi JE, Christianson TJ, et al. Biopsy findings in primary angiitis of the central nervous system. Am J Surg Pathol 2009;33:35–43.
[36] Day J, Limaye V, Proudman S, Hayball JD, Hissaria P. The utility of monitoring peripheral blood lymphocyte subsets by flow cytometric analysis in patients with rheumatological diseases treated with rituximab. Autoimmun Rev 2017;16:542–7 [available].
[37] Tudesq JJ, Cartron G, Rivière S, Morquin D, Iordache L, Mahr A, et al. Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders. Autoimmun Rev 2018;17:115–24.