Original Contribution

Treatment and Long-Term Outcomes of Primary Central Nervous System Vasculitis

Updated Results From the French Registry

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Background and Purpose—We aimed to analyze the long-term outcomes of patients with primary central nervous system vasculitis according to the different therapeutic strategies used to induce remission.

Methods—We assessed the rate of prolonged remission (defined by the absence of relapse at ≥12 months after diagnosis) and the functional status at last follow-up in patients with primary central nervous system vasculitis included in the French cohort, who achieved a first remission according to the 3 main groups of treatments administered: glucocorticoids only (group 1); induction treatment with glucocorticoids and an immunosuppressant, but no maintenance (group 2); and combined treatment with glucocorticoids and an immunosuppressant for induction followed by maintenance therapy (group 3). Good functional status was defined as a modified Rankin Scale score ≤2 at the last follow-up.

Results—Remission was achieved with the initial induction treatment in 106 (95%) of the 112. Prolonged remission without relapse was observed in 70 (66%) patients after 57 (12–198) months of follow-up. A good functional status at last follow-up (ie, modified Rankin Scale score ≤2) was observed in 63 (56%) patients. Overall mortality was 8%. The initial severity and the radiological presentations were comparable in the 3 treatment groups. More prolonged remissions (P=0.003) and a better functional status at the last follow-up (P=0.0004) were observed in group 3. In multivariate analysis, the use of maintenance therapy was associated with prolonged remission (odds ratio, 4.32 [1.67–12.19]; P=0.002) and better functional status (odds ratio, 8.09 [3.24–22.38]; P<0.0001).

Conclusions—This study suggests that maintenance therapy with an immunosuppressant combined with glucocorticoids lead to the best long-term clinical and functional outcomes in patients with primary central nervous system vasculitis after having achieved remission with either glucocorticoids alone or in combination with another immunosuppressant. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021878.)**

Key Words: glucocorticoids ■ maintenance ■ multivariate analysis ■ odds ratio ■ prognosis

Primary central nervous system vasculitis (PCNSV) is a heterogeneous and polymorphic inflammatory disease affecting CNS vessels. In the absence of treatment, the disease course can result in morbidity and mortality. A small number of adult cohorts exist with different therapeutic management. The use of glucocorticoids has become standard in different cohorts, but tapering schedules or treatment durations are not similar. In the US cohort from Salvarani et al,[1,2] glucocorticoids are maintained <1 year and are not associated with any immunosuppressant in 46% of patients. In opposition to this, other cohorts report a longer glucocorticoids duration of almost 2 years and an associated prescription of an immunosuppressant in 80% of patients. Consequently, the need and indication for additional immunosuppressant(s) to induce and maintain remission are not well defined, resulting in a wide heterogeneity in physicians' practices.[1–8]

In this study, we aimed to update the characterization and in-depth analysis of the long-term outcomes of the patients included in the French register of PCNSV based on their treatments. We also aimed at determining the main parameters predictive of prolonged remission and good functional outcomes.

Methods

Data that support the findings of this study are available from the corresponding author on reasonable request.

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Patients From the Register

In 2010, we initiated a French register (cohort of primary cerebral vasculitis) of PCNSV patients. Physicians belonging to 3 main networks (French Vasculitis Study Group, French Neurovascular Society, and French Internal Medicine Society) proposed for the inclusion patients with a diagnosis of PCNSV. However, definite inclusion in the register was retained if patients satisfied the 3 following criteria: (1) involvement of CNS vessels was evidenced on a biopsy or based on imaging (on digital subtraction angiography or magnetic resonance [MR] angiography), showing intracranial arterial stenoses, occlusions, or fusiform dilations); (2) a complete workup was performed in all patients, including infectious and immunologic serologies (HIV, hepatitis B virus, hepatitis C virus, syphilis, tuberculosis, antinuclear and antineutrophil cytoplasmic antibodies), echocardiography and whole body imaging, to exclude other alternative conditions affecting CNS vessels; (3) a >6 months follow-up was required (unless the patient died before 6 months of a biopsy-proven PCNSV) to prevent the inclusion of other vasculopathies, such as reversible cerebral vasoconstriction syndrome where vascular lesions reverse within the first months.[9,10] Atherosclerotic lesions were excluded on a combination of criteria (location of the intracranial stenoses, the absence or the small number of associated vascular risk factors, the absence of other typical atherosclerotic lesions on other vascular territories, such as cervical carotid, the improvement of repeated imaging under treatment).

All our patients underwent clinical visits and repeated imaging (MR imaging and MR angiography) during follow-up at a rhythm based on the treating physician's preference.

Data from patients enrolled before 2010 were collected retrospectively. Data from patients enrolled after 2010 were collected prospectively. Patients were informed of their inclusion in the register and their right to request the exclusion and deletion of their data. The Paris-Cochin institutional review board approved this study (No. 12541).

Studied Parameters and Definition

A computerized database was used to record the data. Until 2014, all data were collected in each center from medical records by the same investigator (Dr de Boysson). After 2014, a standardized electronic form was completed by each physician including a patient in the register and then sent to the investigator (Dr de Boysson) for incorporation into the database. For all patients, we collected the following information: demographics; past medical history (including previous treatments or drug exposure); clinical manifestations at onset; delay between first symptoms and diagnosis; results of laboratory tests; cerebrospinal fluid analysis if available; CNS imaging, including MR imaging and neurovascular imaging; and biopsy results if available.

We retrieved information about the treatments administered (including glucocorticoids and immunosuppressant), their doses, and durations.

Neurological status was assessed after diagnosis at hospital discharge using the modified Rankin Scale (mRS; calculated on the basis of medical charts for patients enrolled retrospectively). The mRS score ranges from 0 (no symptom at all) to 6 (death). Favorable functional outcome was defined by mRS score ≤2, which corresponds to no or slight disability (but not requiring help for own affairs).[11,12] Neurological status was assessed at months 6 and 12 and every year thereafter until the last follow-up.

We differentiated large/medium-sized vessel PCNSV and small-vessel PCNSV.[13] Intracranial internal carotid and proximal and second divisions of cerebral arteries were considered large/medium-sized vessels and were observed on neurovascular imaging, whereas subsequent branches were considered small sized and assessable only on biopsy. Patients with isolated small-vessel PCNSV thus had negative neurovascular imaging studies and positive biopsies.

For the purpose of this study, we assessed the rate of prolonged remission, defined by the absence of relapse at ≥12 months after diagnosis, and the functional status at last follow-up. Relapses and death occurring from the diagnosis until last follow-up were also considered.

We defined the remission, assessed, and determined by the patients' treating physicians, as the absence of disease activity attributable to PCNSV (ie, no worsening or new clinical symptoms) after at least 3 consecutive months of induction therapy. In patients who achieved remission, we analyzed and distinguished outcomes according to the different therapeutic sequences. In group 1, we included patients who only received a treatment with glucocorticoids without any other immunosuppressant for induction or maintenance. In group 2, we included patients who received glucocorticoids combined with an immunosuppressant for induction but no maintenance. In group 3, we included patients who received an induction treatment with glucocorticoids and an immunosuppressant followed by maintenance therapy. All patients included in the 3 groups had achieved remission after induction. Few patients received other therapeutic schedules and were not included in a predefined group given their small number (eg, patients who received glucocorticoids alone for induction followed by maintenance therapy with an immunosuppressant or patients who only received an immunosuppressant without glucocorticoids). In this study, maintenance therapy referred to the use of an immunosuppressant for maintenance. A single use of glucocorticoids during follow-up was not included in the definition of maintenance therapy.

Relapse was defined as a new neurological event (ie, stroke) associated with new significant radiological abnormalities (new cerebral infarct, extension of white matter lesion, appearance of gadolinium enhancements, and worsening of arterial stenosis), leading to an intensification of treatment by the treating physician.

Our primary end point was the analysis of factors associated with prolonged remission without relapse until the last follow-up. Our secondary end point was an analysis of factors associated with good functional status at the last follow-up. Primary and secondary end points were analyzed in view of the treatments the patients received.

Statistical Analyses

Categorical variables are expressed as numbers (%), and quantitative variables are expressed as medians (range). Categorical variables were analyzed with the χ^2 or Fisher exact tests as appropriate, and quantitative variables were analyzed with Wilcoxon rank-sum test. Repetitive mRS overtime among the same subjects was compared using the Wilcoxon matched-pairs signed rank test for quantitative variables.

Multivariate logistic regression analysis was performed to determine factors independently associated with prolonged remission and those associated with good functional status using variables that reached $P<0.2$ in univariate analysis.

Statistical analyses were computed with JMP 9.0.1. (SAS Institute Inc, Cary, NC). A P value ≤0.05 defined statistical significance.

Results

At the time of this study, 5 of 117 patients in this register were excluded because, even whether they achieved remission (without occurrence of relapse or death) with induction treatment, they did not reach the 12 months of follow-up to be considered in prolonged remission. We thus analyzed clinical outcomes of 112 patients, who were followed-up >12 months or who relapsed or died before 12 months. The diagnosis was retained in these 112 patients via biopsy in 33 (29%), digital subtraction angiography in 68 (61%), and MR angiography in 11 (10%). Patients were obtained from the departments of neurology (n=69) and internal medicine (n=43). One hundred and nine patients from the cohorts have already been reported.[8,14,15] The main characteristics of these 112 patients at diagnosis are indicated in Table 1. Therapeutic management and outcomes are presented in Table 2 and the Figure.

Table 1. Characteristics at Diagnosis of 112 Patients With PCNSV in the French Registry

Demographics	
Female	52 (46)
Age	47 (18–81)
Clinical manifestations	
Headaches	60 (54)
Motor deficit	83 (74)
Sensory deficit	39 (35)
Dysphasia/aphasia	57 (51)
Seizures	36 (32)
Cognitive disorders	52 (46)
Vigilance impairment	30 (27)
Neuroimaging	
White matter changes	108 (96%)
Acute ischemia	84 (75)
Parenchymal hemorrhage	24 (21)
Meningeal hemorrhage	18 (16)
Parenchymal gadolinium enhancements	42/92 (46)
Meningeal gadolinium enhancements	25/92 (27)
Vascular stenosis on MRA	68/103 (66)
Vascular stenosis on DSA	74/95 (78)
Large and medium vessel involvement	85 (76)
Isolated small-vessel involvement	27 (24)
Positive biopsy	33/53 (62)
Abnormal CSF analysis	73/104 (70)
White blood cell count, per mm^3	9 (0–425)
Protein level, g/L	0.7 (0.1–4.1)

Values are the number (%) or median (range). CSF indicates cerebrospinal fluid; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; and PCNSV, primary central nervous system vasculitis.

Induction of Remission

All but 2 patients received glucocorticoids, including 68 (61%) who received previous intravenous pulses of methylprednisolone. The median initial oral dose of prednisone was 0.95 (0.42–1.7) mg/kg per day. Ninety-two patients (82%) received an immunosuppressant, including 2 patients who did not receive glucocorticoids. Cyclophosphamide was administered in 89 patients (intravenous pulses in 86, median dose: 0.7 [0.45–0.75] g/m^2 per pulse, median number of pulses: 6 [2–12] pulses, median duration: 6 [2–10] months; and 3 patients received oral cyclophosphamide), and the 3 remaining patients received weekly rituximab for 4 weeks (375 mg/m^2). Twenty patients initially received glucocorticoids without another immunosuppressant for induction (and 5 of them further received maintenance therapy).

Remission was achieved in 106 (95%) patients. Among the 6 patients who did not achieve remission, 1 had received glucocorticoids alone and the other 5 patients had received glucocorticoids and an immunosuppressant for induction only. Four of them died (neurological deterioration in 3, septic shock in 1) within the first few weeks during the induction period (while under glucocorticoids and cyclophosphamide in 3 and glucocorticoids alone in 1); the remaining 2 experienced a relapse at 2 and 4 months, while under glucocorticoids and cyclophosphamide.

The 106 patients who achieved remission were distributed as follows: group 1 included 14 patients, who received only glucocorticoids without immunosuppressant for induction or maintenance; group 2 included 40 patients, who received glucocorticoids and an immunosuppressant for induction only; group 3 included 45 patients, who received glucocorticoids and an immunosuppressant for induction followed by maintenance therapy with another immunosuppressant; the 7 other patients were not classified into these groups (5 patients received glucocorticoids alone for induction then maintenance with an immunosuppressant, and the remaining 2 patients did not receive glucocorticoids but received an immunosuppressant for induction then maintenance with another immunosuppressant).

In the 3 groups, the choice of the therapeutic sequence was not associated with the clinical or radiological presentation at onset (data not shown). The initial severity was comparable in the 3 groups with a median mRS score of 4 (P=0.79).

Prednisone Use

Table 3 presents glucocorticoids therapy according to the 3 predefined treatment groups. More patients from group 3 received intravenous methylprednisolone pulses at the time of diagnosis (P=0.005). However, there was no difference about the subsequent glucocorticoids dosages after diagnosis and at month 6 in the 3 groups. The discontinuation rates and glucocorticoids duration did not differ in the 3 groups. However, at month 12, patients from group 3 were on a significantly reduced daily dose of glucocorticoids (P=0.04).

Maintenance Treatment With an Immunosuppressant

Among the 106 patients who achieved remission, 52 (46%) subsequently received maintenance therapy with an immunosuppressant. Among them, 45 were still receiving glucocorticoids. Moreover, 43 and 2 patients previously received cyclophosphamide and rituximab, respectively. Five patients were still receiving glucocorticoids and had not received cyclophosphamide or rituximab previously. Two patients did not received glucocorticoids but were prescribed azathioprine after achieving remission with cyclophosphamide alone.

Maintenance therapy was started after a median of 4 (3–18) months from glucocorticoids initiation (4 and 6 weeks after the last pulses of cyclophosphamide in the 2 patients, respectively, who did not receive glucocorticoids). Azathioprine was prescribed in 41 patients (2 mg/kg per day), methotrexate in 7 (0.3–0.5 mg/kg per week), and mycophenolate mofetil in 4 (2 g/d). The median duration of maintenance therapy with these immunosuppressants was 24 (6–72) months.

No association between the initiation of maintenance therapy and the initial disease severity was noted (no difference regarding the clinical symptoms or the mRS at discharge; data

Table 2. Treatment and Outcomes of Patients With PCNSV

GC	110 (98)
Intravenous methylprednisolone pulses	68 (61)
Initial oral dosage, mg/kg prednisone-equivalent	0.95 (0.42–1.7)
Discontinuation of GC at last follow-up	85 (76)
GC duration, mo	24 (3–198)
Use of an immunosuppressant to induce remission	92 (82)
Cyclophosphamide	89 (79)
Rituximab	3 (3)
Maintenance therapy after first flare	52 (46)
Azathioprine	41/52 (79)
Methotrexate	7/52 (14)
Mycophenolate mofetil	4/51 (8)
Rituximab	0
Outcomes	
Remission	106 (95)
Patients who relapsed (after a first remission)	36/106 (34)
Delay to first relapse, mo	16 (3–132)
Patients in prolonged remission without relapse	70 (63)
Follow-up, mo	53 (0–198)
Death	9 (8)
mRS	
At discharge (first flare)	4 (1–5)
At month 6	2 (0–5)
At month 12	2 (0–5)
At month 24	2 (0–5)
At last follow-up	2 (0–5)
Improvement of mRS score >2	52 (46)
mRS score <2 at last follow-up	63 (56)

Values are the number (%) or median (range). GC indicates glucocorticoids; mRS, modified Rankin Scale; and PCNSV, primary central nervous system vasculitis.

not shown[15]). No difference about prescription of maintenance was also observed among patients included retrospectively or prospectively.

Prolonged Remission Without Relapse

Among the 106 patients who achieved remission with their first induction treatment and with a median follow-up of 57 (12–198) months, 36 (34%) relapsed (4 [29%] in group 1, 20 [50%] in group 2, 9 [20%] in group 3, 2 out the 5 patients who received glucocorticoids then maintenance and 1 of 2 patients who did not receive glucocorticoids). Five patients died at the time of relapse consecutively to a neurological deterioration.

Overall, 70 (66%) surviving patients were in prolonged remission at last follow-up, including 10 (71%) patients in group 1, 19 (48%) in group 2, and 37 (82%) in group 3 (P=0.003). The 4 other patients in prolonged remission who were not included in the 3 groups corresponded to 3 patients who received glucocorticoids and maintenance and 1 patient who received cyclophosphamide then azathioprine without glucocorticoids.

Glucocorticoids treatment and long-term outcomes of patients did not differ between groups 1 and 2 (Table I in the online-only Data Supplement).

Factors associated with prolonged remission in univariate and multivariate analysis are presented in Table 4. Maintenance therapy was associated with prolonged remission (odds ratio [OR], 4.32 [1.67–12.19]; P=0.002). Conversely, gadolinium-enhanced lesions on MR imaging represent a significant disadvantage for prolonged remission (OR, 0.20 [0.07–0.51]; P=0.0007).

In patients from groups 1 and 2 (ie, who did not receive maintenance therapy), we did not identify any factors associated with prolonged remission without relapse (Table II in the online-only Data Supplement).

On management of relapses, all relapsing patients resumed or increased glucocorticoids. Seventeen patients (2 from the group 1, 11 from the group 2, and 4 from the group 3) received a new induction treatment with cyclophosphamide in 9 and rituximab in 8. Fourteen patients, who did not initially receive maintenance, received azathioprine or rituximab as maintenance in 8 and 6 patients, respectively. Among the 9 relapsing patients from group 3, 2 continued azathioprine, 2 received rituximab as maintenance, 3 and 2 were switched to methotrexate or mycophenolate mofetil, respectively.

Functional Status

A good functional status at last follow-up (ie, mRS score ≤2) was achieved in 63 (56%) patients. As shown in Table 3, more patients from group 3 had a mRS score ≤2 at last follow-up (80% versus 43% and 40% in the group 1 and 2, respectively; P=0.0004); however, the initial severity was similar in the 3 groups.

Factors associated with a good functional status at last follow-up in univariate and multivariate analysis are presented in Table 5. Maintenance therapy and headaches at onset were significantly associated with a better functional status at last follow-up (OR, 8.09 [3.24–22.38]; P<0.0001 and OR, 3.46 [1.41–9.12]; P=0.006, respectively). Conversely, patients with initial vigilance impairment exhibited poorer functional status at last follow-up (OR, 0.32 [0.12–0.85]; P=0.02).

When analyzing only patients from groups 1 and 2, that is, who did not receive maintenance therapy, we also observed that headaches at initial presentation were associated with a better functional status (OR, 6 [1.76–24.42]; P=0.004). Conversely, patients with initial vigilance impairment also exhibited poorer functional status at last follow-up (OR, 0.23 [0.05–0.89]; P=0.03; Table III in the online-only Data Supplement).

In Table IV in the online-only Data Supplement, we analyzed glucocorticoids management or clinical outcomes in patients with biopsy-proven diagnosis or those with abnormal cerebrospinal fluid analysis, who achieved remission and who were classified within the 3 groups. Similarly, more prolonged remission and better functional status were observed in patients from group 3, that is, those receiving

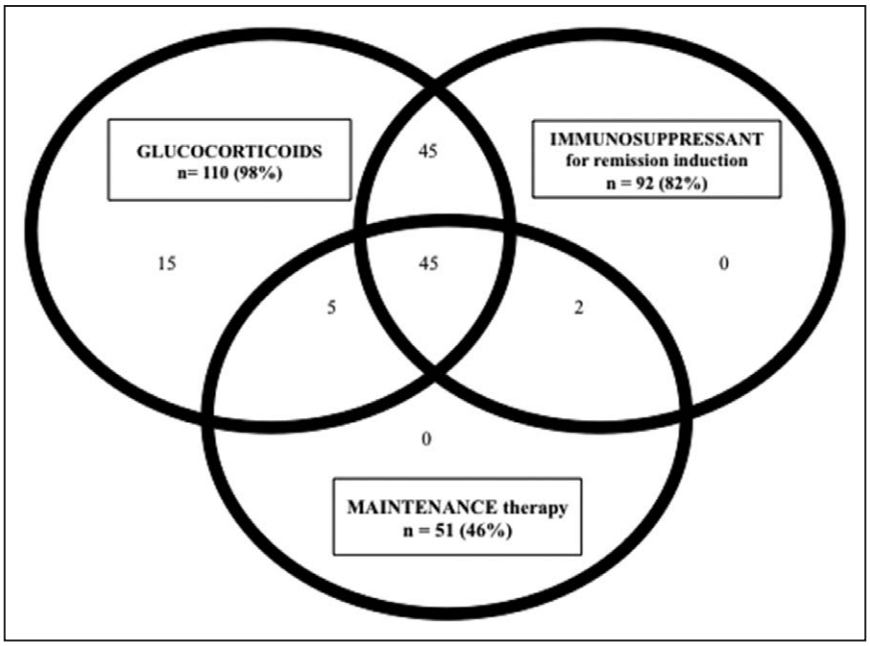

Figure. Treatments administered in 112 patients with primary angiitis of the central nervous system.

glucocorticoids+an immunosuppressant for induction followed by maintenance therapy.

Discussion

PCNSV is an inflammatory life-threatening disease, which can lead to morbidity. In addition, relapses may affect 30% to 50% of patients, thereby increasing the risk of progressive neurological deterioration with severe disability.[2,15–17] Treatments aim at suspending the initial inflammatory process and avoiding subsequent disease flares. Our study confirms that an induction strategy using high glucocorticoids doses alone or with an immunosuppressant, mainly cyclophosphamide, allowed remission to be achieved in 95% of our patients. The combination of a long-lasting glucocorticoids use and the administration of maintenance therapy with an immunosuppressant (mainly azathioprine in our study) achieved long-term remission without significant disability in three-fourths of patients who received such treatments.

Glucocorticoids remain the mainstay of treatment and act as an induction treatment, especially when combined with another immunosuppressant. Although, we observed a good remission rate in the few patients who only received glucocorticoids for induction (group 1), which is concordant with the results observed by Salvarani et al,[2] the small sample size of this group precludes any conclusion on the single use of glucocorticoids for induction. The usefulness of methylprednisolone pulses is unknown. However, our study suggests a possible beneficial effect in terms of functional outcomes. Cyclophosphamide remains the most prescribed drug for induction in France, mainly via the intravenous route. Minimal information on the other agents exists. Rituximab is likely a good alternative for patients with progressive disease who previously received cyclophosphamide or with a contraindication for cyclophosphamide.[18,19] In the French registry, no other agent was used as first-line induction treatment. However, various observations report good outcomes with mycophenolate mofetil[20] or infliximab,[21,22] which are not commonly used at first.

Our study further suggests that maintenance therapy with an immunosuppressant is probably required. Although long-term low-dose glucocorticoids use may act as a maintenance agent, we observed better outcomes, especially about disability, in patients who received an additional immunosuppressant for maintenance, mainly azathioprine. In addition, the duration of glucocorticoids therapy did not differ between our studied groups. Although ≈40% of patients from groups 1 and 2 had a mRS score ≤2 at last follow-up, 2-fold more patients were observed in group 3, where patients received a maintenance therapy with an immunosuppressant. Multivariate analyses, confirmed the protective effect of maintenance therapy about prolonged remission and good functional status at last follow-up. Although azathioprine was the most commonly used agent in our register, methotrexate or mycophenolate mofetil (especially in children) might represent other alternatives.[23] Treatment should probably be maintained for a long time. Most of our patients received glucocorticoids for 2 years, which is twice as long compared with patients from the American cohort.[2] Although direct comparison between both cohorts is difficult, the reduced death rate observed in our cohort might be attributed to more prolonged treatment and more frequent use of an immunosuppressant for induction and maintenance.

Once remission is achieved, relapses are the most feared outcomes, and new neurological flares can worsen neurological disability. Early identification of patients at risk of relapse may be useful to strengthen treatments and disease monitoring. We previously identified some subgroups of patients at increased risk of relapse, especially those with isolated involvement of small vessels.[14,15] In the univariate model, isolated small vessel involvement was associated with reduced prolonged remission. However, in the multivariate model, the best predictive factor against prolonged remission was gadolinium enhancements, which were more frequently associated with small-vessel involvement. However, in other studies, gadolinium-enhanced lesions were associated with less

Table 3. Glucocorticoid Treatment Characteristics and Long-Term Outcomes of PCNSV Patients Who Achieved Remission Based on Induction Treatment

	Group 1 (n=14)	Group 2 (n=40)	Group 3 (n=45)	*P* Value
GC				
Intravenous methylprednisolone pulses	5 (36)	23 (58)	36 (80)	0.005
Initial oral dosage, mg/kg prednisone-equivalent	0.97 (0.53–1.5)	0.95 (0.70–1.5)	0.94 (0.42–1.7)	0.85
Dosage at month 6, mg/kg	0.30 (0–0.45)	0.43 (0–0.75)	0.22 (0–0.77)	0.17
Dosage at month 12, mg/kg	0.22 (0–0.38)	0.19 (0–0.33)	0.1 (0–0.6)	0.04
Discontinuation of GC at last follow-up	12 (86)	27 (68)	35 (78)	0.33
GC duration, mo	21 (5–175)	23 (0–198)	25 (2–103)	0.21
Outcomes				
Follow-up, mo	87 (12–175)	49 (6–198)*	55 (9–143)*	0.23
Relapse	4 (29)	20 (50)	9 (20)	0.01
mRS after relapse	4 (2–5)	4 (2–5)	3 (2–5)	0.02
Death	…	4 (10)	1 (2)	0.17
Prolonged remission	10 (71)	19 (48)	37 (82)	0.003
mRS score				
At discharge	4 (2–5)	4 (1–5)	4 (2–5)	0.85
At month 6	3 (0–5)	3 (0–5)	2 (0–5)	0.01
At month 12	3 (0–5)	3 (0–6)	2 (0–5)	0.01
At month 24	3 (0–5)	3 (0–6)	1 (0–5)	0.005
At last follow-up	3 (0–5)	3 (0–6)	1 (0–6)	0.0004
Improvement of mRS score >2	5 (36)	12 (30)	32 (71)	0.0004
mRS score ≤2 at last follow-up	6 (43)	16 (40)	36 (80)	0.0004

Values are the number (%) or median (range). Group 1, GC alone; Group 2, GC+immunosuppressant for induction without maintenance therapy; Group 3, GC+immunosuppressant for induction followed by maintenance therapy. GC indicates glucocorticoids; mRS, modified Rankin Scale; and PCNSV, primary central nervous system vasculitis.

*Some patients died before 12 months of follow-up.

Table 4. Factors Associated With Prolonged Remission in Patients With PCNSV (Who Achieved Remission With the Induction Treatment) in Univariate and Multivariate Analyses

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Abnormal angiogram	2.85 (1.12–7.25)	0.02		
Isolated small-vessel PCNSV	0.35 (0.14–0.89)	0.02		
Dysphasia	2.06 (0.93–4.58)	0.07		
Seizures	0.41 (0.18–0.96)	0.04		
Acute infarctions on MRI	2.07 (0.85–5.03)	0.10		
Gadolinium enhancements	0.24 (0.10–0.58)	0.001	0.20 (0.07–0.51)	0.0007
Maintenance therapy	3 (1.33–6.90)	0.007	4.32 (1.67–12.19)	0.002

MRI indicates magnetic resonance imaging; OR, odd ratio; and PCNSV, primary central nervous system vasculitis.

relapses,[1] or with more continued treatment at the last follow-up encounter.[2] The prognostic value of gadolinium-enhanced lesions has thus to be reassessed in other studies.

This study is the first to specifically focus on the treatments of PCNSV and their impact on long-term outcomes. Our patients undergo long-term follow-up, and greater than three-fourths of these patients discontinued any PCNSV-related treatment at last follow-up. However, some limitations must be acknowledged. The retrospective design of the study is associated with possible selection biases and imbalance in unknown confounding factors that influenced therapeutic choices. One intrinsic limitation of our study is the absence of uniform criteria for the PCNSV diagnosis as some patients were diagnosed based on histological evidence of vasculitis and others on neurovascular changes on imaging that can be less specific. However, all patients had complete work-up performed at onset and a long follow-up (median of nearly 5 years) limiting the risk to have included cases of noninflammatory vasculopathy, for which immunosuppressants are not expected to improve clinical and radiological findings.

Another limitation is the relative heterogeneity of therapeutic practices among the different participating centers, as consensual guidelines or validated institutional protocols are lacking for the management of PCNSV (eg, glucocorticoids starting

Table 5. Factors Associated With Good Functional Status at the Last Follow-Up in Patients With PCNSV (Who Had Achieved Remission With the Induction Treatment) in Univariate and Multivariate Analyses

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Headaches	2.47 (1.14–5.31)	0.02	3.46 (1.41–9.12)	0.006
Vigilance impairment	0.48 (0.20–1.14)	0.09	0.32 (0.12–0.85)	0.02
Meningeal hemorrhage	3.67 (1.21–11.12)	0.02		
Methylprednisolone pulses	3.20 (1.43–7.18)	0.004		
Aspirin use	0.51 (0.24–11.08)	0.08		
Maintenance therapy	5.6 (2.51–12.80)	<0.0001	8.09 (3.24–22.38)	<0.0001
Relapses	0.35 (0.15–0.81)	0.01		

OR indicates odd ratio; and PCNSV, primary central nervous system vasculitis.

doses, tapering schedule and duration). However, we did not observe significant differences regarding doses at initiation and during the first 6 months. The combination of glucocorticoids and an immunosuppressant for induction was relatively consensual in the French register. Although our study suggests a beneficial effect of maintenance, no further conclusion can be made as to which specific immunosuppressive drug is best, as most of our patients received azathioprine. Other prospective studies are needed to answer this point. The potential effect of methylprednisolone pulses on relapses has to be determined in other studies, especially in patients who receive glucocorticoids alone. The small sample size of group 1 did not allow such analysis.

In conclusion, according to our results, PCNSV prognosis may be improved in patients receiving glucocorticoids combined with an immunosuppressant for induction and maintenance therapy. Cyclophosphamide in combination with glucocorticoids for induction and azathioprine for maintenance were the 2 main immunosuppressants used in our registry. Whether other combinations or sequences can achieve better results must be determined.

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Disclosures

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Treatment and Long-Term Outcomes of Primary Central Nervous System Vasculitis: Updated Results From the French Registry

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Comparison of treatment and outcomes in PCNSV patients from groups 1 and 2.

	Group 1 (n=14)	Group 2 (n=40)	P
GC			
Intravenous methylprednisolone pulses	5 (36)	23 (58)	0.16
Initial oral dosage, mg/kg prednisone-equivalent	0.97 [0.53—1.5]	0.95 [0.70—1.5]	0.92
Dosage at month 6, mg/kg	0.30 [0—0.45]	0.43 [0—0.75]	0.64
Dosage at month 12, mg/kg	0.22 [0—0.38]	0.19 [0—0.33]	0.07
Discontinuation of GC at last follow-up	12 (86)	27 (68)	0.19
GC duration, months	21 [5—175]	23 [0—198]	0.34
Outcomes			
Follow-up, months	87 [12—175]	49 [6—198] †	0.11
Relapse	4 (29)	20 (50)	0.16
Prolonged remission	10 (71)	17 (43)	0.06
mRS			
At discharge	4 [2—5]	4 [1—5]	0.66
At month 6	3 [0—5]	3 [0—5]	0.28
At month 12	3 [0—5]	3 [0—6]	0.39
At month 24	3 [0—5]	3 [0—6]	0.38
At last follow-up	3 [0—5]	3 [0—6]	0.72
Improvement of mRS >2	5 (36)	12 (30)	0.69
mRS≤2 at last follow-up	6 (43)	16 (40)	0.85

Values are the number (%) or median [range]. PCNSV: primary central nervous system vasculitis; GC: glucocorticoids; mRS: modified Rankin scale. †Some patients died before 12 months of follow-up.

Group 1: GC alone; Group 2: GC + immunosuppressant for induction without maintenance therapy.

Supplemental Table II. Factors associated with prolonged remission in patients with PCNSV from group 1 and 2 (who achieved remission with the induction treatment) in univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	P	OR [95% CI]	P
Dysphasia	2.25 [0.76—6.61]	0.14		
Isolated small-vessel PCNSV	0.43 [0.11—1.66]	0.19		
Positive biopsy	6 [0.60—60.4]	0.10		
Gadolinium enhancements	0.42 [0.13—1.44]	0.17		
Induction treatment	0.28 [0.08—1.06]	0.05		

OR: odd ratio; CI: confidence interval; PCNSV: primary central nervous system vasculitis.

Group 1 included 14 patients out of 15 who received only GC without immunosuppressant for induction or maintenance, and who achieved remission after induction; Group 2 included 40 out of 45 who received GC and an immunosuppressant for induction without maintenance therapy and who achieved remission

Supplemental Table III. Factors associated with good functional status in patients with PCNSV from group 1 and 2 (who achieved remission with the induction treatment) in univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	P	OR [95% CI]	P
Female sex	2.22 [0.74—6.68]	0.15		
Headaches	4.61 [1.37—15.52]	0.01	6 [1.76—24.42]	0.004
Vigilance impairment	0.34 [0.09—1.24]	0.10	0.23 [0.05—0.89]	0.03
Acute infarctions on MRI	3.17 [0.77—13.06]	0.10		
Methylprednisolone pulses	2.1 [0.69—6.35]	0.19		

OR: odd ratio; CI: confidence interval; PCNSV: primary central nervous system vasculitis.

Group 1 included 14 patients out of 15 who received only GC without immunosuppressant for induction or maintenance, and who achieved remission after induction; Group 2 included 40 out of 45 who received GC and an immunosuppressant for induction without maintenance therapy and who achieved remission

Supplemental Table IV. Glucocorticoid treatment characteristics and long-term outcomes of PCNSV patients with positive biopsy and/or abnormal CSF analysis who achieved remission based on induction treatment

	Group 1 (n=10)	Group 2 (n=30)	Group 3 (n=34)	P
GC				
Intravenous methylprednisolone pulses	4 (40)	18 (60)	27 (79)	0.04
Initial oral dosage, mg/kg prednisone-equivalent	0.92 [0.53—1.2]	0.95 [0.70—1.5]	0.96 [0.42—1.7]	0.70
Dosage at month 6, mg/kg	0.45 [0—0.45]	0.43 [0—0.75]	0.22 [0.05—0.55]	0.22
Dosage at month 12, mg/kg	0.32 [0—0.41]	0.21 [0—0.33]	0.07 [0—0.6]	0.17
Discontinuation of GC at last follow-up	9 (90)	21 (70)	27 (79)	0.39
GC duration, months	20 [5—175]	24 [2—198]	26 [2—103]	0.36
Outcomes				
Follow-up, months	88 [12—175]	51 [6—192] †	61 [9—143] †	0.25
Relapse	3 (30)	15 (50)	7 (21)	0.04
mRS after relapse	4 [2—5]	4 [2—5]	3 [2—5]	0.03
Death	-	1 (3)	1 (3)	0.86
Prolonged remission	7 (70)	13 (43)	26 (76)	0.02
mRS				
At discharge	4 [2—5]	4 [1—5]	4 [2—5]	0.63
At month 6	3 [0—5]	3 [0—5]	2 [0—5]	0.08
At month 12	3 [0—5]	3 [0—6]	2 [0—5]	0.02
At month 24	3 [0—5]	3 [0—6]	1 [0—5]	0.01
At last follow-up	3 [0—5]	3 [0—6]	1 [0—6]	0.001
Improvement of mRS >2	3 (30)	10 (33)	23 (68)	0.01
mRS≤2 at last follow-up	3 (30)	12 (40)	26 (76)	0.003

Values are the number (%) or median [range]. PCNSV: primary central nervous system vasculitis; GC: glucocorticoids; mRS: modified Rankin scale. †Some patients died before 12 months of follow-up.

Group 1: GC alone; Group 2: GC + immunosuppressant for induction without maintenance therapy; Group 3: GC+ immunosuppressant for induction followed by maintenance therapy.

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