L38. How to treat primary vasculitis of the central nervous system

We lack clear-cut and consensual recommendations for managing primary CNS vasculitis (PCNSV) because no prospective therapeutic trial has determined the most effective therapeutic strategy. Available information on outcomes and treatments are from only expert opinion, literature reviews and a few retrospective studies, although their number and sample size have been increasing. Thus, therapeutic decision-making remains a challenge, perhaps even more so for patients with a diagnosis of PCNSV based on clinical and imaging findings but with no definite histological confirmation.

From earlier reports, the prognosis of PCNSV was poor, with death occurring in almost every case within a maximum of a few years after the diagnosis, as for the first eight patients described by Cravioto and Feigin [1,2]. Most of the reported patients who did not receive treatment but had better outcomes, initially defined as having a benign form of PCNSV, were indeed more likely to have reversible cerebral vasospasm rather than PCNSV. Corticosteroids, alone or with cyclophosphamide since the late 1980s, were found to greatly improve the overall and neurological outcomes of PCNSV [3–8]. However, in practice, questions that are relatively simple, in theory – whether to add an immunosuppressant and/or for which specific patient subset(s) – remain unanswered as is which parameters the treatment response should be based on [6,8].

In the 2007 study by Salvarani et al. [9], involving 101 North American patients with PCNSV diagnosed between 1983 and 2001, mortality and relapse rates after a mean follow-up of 13 months were 17% and 26%, respectively, and only three patients had a Rankin score greater or equal to 4 (moderately severe or severe disability) at the last follow-up. In that study, 43 patients received corticosteroids alone and 81% of these had good outcomes; 54 received corticosteroids and cyclophosphamide, with a similar 81% showing good outcome. In the Oon et al. study [7], four of five Australian patients who received corticosteroids alone as induction treatment showed improvement by the Rankin score at the last assessment as compared with five of seven who received corticosteroids with cyclophosphamide (mean follow-up for the 12 patients was 30 months). In the French COVAC cohort, 29 (56%) of our first 52 patients enrolled and diagnosed between 1992 and 2012 achieved sustained therapeutic response, with no relapses during the 3 years of follow-up; the overall mortality and relapse rates were just 6% and 27%, respectively [10]. Of note, more than 80% of these patients received corticosteroids and cyclophosphamide as first-line therapy.

As for severe systemic vasculitides, with PCNSV, corticosteroids should be started in adults at a high dose (i.e., 1 mg/kg/d prednisone-equivalent), possibly preceded by 1 to 3 methylprednisolone pulses (7.5–15 mg/kg/d) [11–13]. The corticosteroid dose should then be tapered, by approximately 10%, every 2 to 4 weeks. If combined administration of cyclophosphamide is decided, as first-line therapy or in patients without response to corticosteroids alone, it can be given orally (2 mg/kg/d) or with serial infusions (15 mg/kg per infusion, every 2 weeks for the first 3, then every 3 to 4 weeks), for a minimum of 3 to 6 months and at least until sustained improvement or stabilization of the disease manifestations (the definition of remission for PCNSV lacks consensus). To limit the toxic effects of these treatments, adjunctive and prophylactic measures must be prescribed (e.g., cotrimoxazole to prevent pneumocystosis, calcium and vitamin D supplementation, prescription of mesna combined with cyclophosphamide infusions to prevent hemorrhagic cystitis). Azathioprine, methotrexate or mycophenolate mofetil, all less toxic than cyclophosphamide, have been given as first-line therapy, combined with corticosteroids, to a few patients with newly diagnosed or refractory or relapsing PCNSV, with good outcome [9,14]. However, to date, we lack definite data on their efficacy as compared with cyclophosphamide. Their prescription should be restricted to patients with minor and not rapidly progressing disease, in whom the balance between cyclophosphamide-associated toxicity and benefit would contraindicate its use.

The concomitant prescription of antithrombotic drugs has yet to be considered, as well as anticoagulants for patients with ischemic stroke, unless if contraindicated (e.g., recent cerebral hemorrhage or massive and large infarction [9,15,16]). However, the usefulness of such agents for PCNSV with no ischemic manifestations has not been demonstrated.

One of the remaining issues is that more than one-quarter of surviving patients who achieve what is considered good therapeutic response will experience relapse [9,17]. The optimal duration of induction therapy for adult PACNS is unknown, and whether maintenance therapy following induction treatment is needed and beneficial remains to be determined. Most groups and experts recommend maintenance therapy with azathioprine (2 mg/kg/d), methotrexate (15–25 mg/week) or mycophenolate mofetil (2–3 g/d) for at least 1 or 2 years, as for systemic vasculitides [5,6,8]. Most of the COVAC cohort patients received azathioprine, but some did not receive maintenance therapy, without overt differences in outcome [10]. Differences between PCNSV in children and adults remains to be further studied. None of the 62 children reported by Benseler et al. [18] died within a mean follow-up of 20 months, but only 34% recovered without any neurological damage. All received antithrombotic therapy (aspirin, heparin, or warfarin), combined with immunosuppressive treatment for 21 (34%) (13 [65%] of 20 with progressive PCNSV and 9 [21%] of 42 with...
nonprogressive PCNSV). Neurocognitive dysfunction, multifocal parenchymal lesions on MRI, and evidence of distal stenoses on angiography predicted poor functional outcome, which suggests two subgroups: medium-to-large-vessel PCNSV (abnormal angiography) and small-vessel PCNSV (normal angiography, abnormal biopsy). In a subsequent study from the same group, Hutchinson et al. [19] reported that 14 of 19 children with small-vessel PCNSV completed induction therapy with corticosteroids (intravenous pulses, then 2 mg/kg prednisone daily, to a maximum of 60 mg/d, weaned gradually on a monthly basis for 12–18 months) and pulses of intravenous cyclophosphamide (500–750 mg/m² every month for a total of 7 pulses), followed by maintenance therapy with mycophenolate mofetil (n = 5; 800–2000 mg/d) or azathioprine (n = 9; 2–3 mg/kg/d, to a maximum of 150 mg/d). Eight of 19 patients experienced disease flares, including two with poor control of disease during induction and five who switched from azathioprine to mycophenolate mofetil during maintenance therapy because of PCNSV flare, whereas no patients showed flare with mycophenolate mofetil. Among the 13 patients who completed 24 months of follow-up, nine had good neurological outcome. A total of five patients achieved remission (defined as the complete absence of disease activity in clinical symptoms, examination findings, laboratory markers, and imaging for at least 3 months) and discontinued medication. One showed disease flare after 14 months of treatment. In a different series from Malik et al. [16], all 68 children with medium-to-large-vessel PCNSV received corticosteroids (and/or intravenous immunoglobulin, 400 mg/kg/d, for 5 days for some) combined with oral azathioprine (1 mg/kg/d, started on day 5–30, for a total of 2 years) for patients with obliterate angiopathic stroke, and heparin followed by oral anticoagulants for those with recent and non-large infarction stroke for 30 days. Aspirin (3 mg/kg/d) was also prescribed for children with ischemic stroke and no contraindication (n = 56). Mortality rate was 18.6% (5 of 10 patients with hemorrhagic stroke died as compared with 5 of 8 with ischemic-haemorrhagic lesions and just 2 of the 50 with ischemic stroke and progressive arteriopathy). In all, 56 children completed the induction protocol and continued maintenance therapy based on aspirin and azathioprine for 2 years.

The identification of patient subgroups and predictors of mortality or neurological damage might also help determine the best treatment and its intensity for individual adult PCNSV patients [6,20]. Salvarani et al. identified several disease subgroups with some outcome differences [6,9,21–23], finding that patients with focal neurological deficits, multiple bilateral cerebral infarction and/or large-vessel involvement had increased risk of death. We await similar studies from other groups.

Finally, alternative treatments are needed for the few patients who are refractory to conventional treatments, as mentioned above. Use of intravenous immunoglobulin has been reported sporadically, mainly in children and combined with another immunosuppressant [15,24]. Tumor necrosis factor α blockers were effective in two adults [25] and two children, all unresponsive to cyclophosphamide [24]. Rituximab was recently successful in a 3-year-old girl with remitting–relapsing biopsy-proven PCNSV after failure of corticosteroids, azathioprine and cyclophosphamide [26]. In the ongoing COVAC’ cohort, three patients have received rituximab.

In current practice, we recommend treating PCNSV patients, at least those with biopsy-proven and severe disease, similar to those with severe forms of systemic vasculitides, that is, with corticosteroids combined with conventional cyclophosphamide for induction. The decision to add cyclophosphamide might be more difficult for patients without histological confirmation of disease. Maintenance therapy should probably be prescribed for at least 1 or 2 years thereafter. Future findings from ongoing international and/or multicentric registries may support the existence of patient subsets with different outcomes and treatment responses. Better understanding of the pathogenesis of PCNSV may help identify other therapies.

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**References**


L39. Fulminant anca vasculitis

Introduction

ANCA-associated vasculitis (AAV) is a systemic disease that may affect many different organs and present with various symptoms. According to the recently published Chapel Hill Consensus Conference Nomenclature of vasculitides [1], AAV includes three different types of small-vessels vasculitis: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA or former Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA or former Churg-Strauss vasculitis). Besides slowly progressive and chronic presentations, some patients develop rapidly progressive and sometimes fulminant symptoms with severe pulmonary, renal, intestinal, cardiac or central nervous system (CNS) involvement. These life-threatening complications often require admission in the Intensive Care Unit. Early diagnosis of AAV is necessary in order to initiate as soon as possible the specific immunosuppressive treatment, which includes short-term life-saving procedure and control of the disease in order to limit the organ lesions and long-term consequences. Even though the extent of these fulminant forms is not fully defined, it is possible to describe renal, pulmonary, gastro-intestinal, cardiac and neurological clinical presentations.

Renal presentation: acute renal failure

Rapidly progressive glomerulonephritis (RPGN) is the most typical renal presentation of AAV. It combines rapid deterioration of renal function – which may lead to dialysis within a few days –, micro- or macro-hematuria and usually non-nephrotic glomerular proteinuria. Renal failure is not always easy to detect, especially when extra-renal symptoms are mild or absent. Specific clinical symptoms, such as oliguria, uremia or fluid overload appear only at the very last stages of the renal disease and this point explains why diagnosis of the kidney involvement in AAV is sometimes too late. Although ANCA positivity during an episode of acute renal failure with RPGN features is sufficient to start urgent immunosuppressive treatment, the renal biopsy is recommended in order to confirm the renal vasculitis, exclude differential diagnosis and give the prognosis of renal failure. The classical glomerular lesion is crescentic necrotizing glomerulonephritis with extracapillary proliferation of epithelial cells. The lesions are frequently focal and segmental with a mixture of normal glomeruli, glomeruli with active necrosis and cellular crescents, and glomeruli which are already partially or globally sclerosed, with presence of fibrotic crescents. Immunofluorescence microscopy study of the renal biopsy demonstrates little or no staining for complement or immunoglobulins, defining the so-called pauci-immune pattern. Numerous clinicopathologic studies have shown that kidney pathology can predict renal

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