Treatment of Vasculitis of the Nervous System

David S. Younger, MD, MPH, MS[a,b,*]

KEYWORDS

• Immune suppression • Vasculitis • Nervous system • Clinical trials

KEY POINTS

- There is general agreement on 5 principles in the diagnosis and treatment of nervous system vasculitides.
- Vasculitides of the nervous system is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction.
- Undiagnosed and therefore untreated, there is a likelihood of excess morbidity and mortality.
- A favorable response to an empiric course of immunosuppressive and immunomodulating therapy should never be considered a substitute for the absolute proof of the laboratory diagnosis of vasculitis.
- Histopathologic confirmation of vasculitis is essential for accurate diagnosis.
- Treatments are initially guided toward stabilization of the blood-brain or blood-nerve barriers, followed by maintenance immunosuppressive therapy directed at the humoral and cell-mediated autoimmune inflammatory mechanisms.

INTRODUCTION

The Revised International Chapel Hill Consensus Conference (CHCC) nomenclature[1] provides a useful framework for the distinction of specific vasculitides based on the caliber of the vessels involved, both arteries and veins. So defined, small vessel vasculitis (SVV) includes granulomatosis with polyangiitis (GPA) (Wegener type), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome [CSS]), known collectively as antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV). Vasculitic disorders associated with immune complexes (ICs) include immunoglobulin (Ig) A vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies. Vasculitis without a

Disclosure: The author has nothing to disclose.

[a] Department of Neurology, Division of Neuro-Epidemiology, New York University School of Medicine, New York, NY, USA; [b] School of Public Health, City University of New York, New York, NY, USA

* 333 East 34th Street, Suite 1J, New York, NY 10016.

E-mail address: youngd01@nyu.edu

Website: http://www.davidsyounger.com

Neurol Clin 37 (2019) 399–423

https://doi.org/10.1016/j.ncl.2019.01.014

neurologic.theclinics.com

predominant vessel size and caliber, respectively from small to large, involving arteries, veins, and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome. Medium vessel vasculitides (MVV) includes polyarteritis nodosa (PAN) and Kawasaki disease (KD). Large vessel vasculitides (LVV) are represented by giant cell arteritis (GCA) and Takayasu arteritis (TAK). Vascular inflammation confirmed to a single organ system, such as vasculitis restricted to the central nervous system (CNS) and peripheral nervous system (PNS), and IgG4-related aortitis (IgG4-related disease [RD]), are collectively referred to as single organ vasculitides (SOV).

At the turn of the twentieth century, granulomatous angiitis of the nervous system[2] was the prototypical form of a vasculitis restricted to the CNS, recognized not only for its clinical heterogeneity in association with a variety of comorbid illnesses such as cancer, sarcoidosis, amyloid, human immunodeficiency virus, and zoster varicella virus infection, but also for the predilection for cerebral vessels of varying caliber from small meningeal to named cerebral vessels. Decades later,[3] recognition of the caliber of cerebral vessels involved by cerebral angiography and histopathologic examination of brain and meningeal tissue provided valuable clues to effective treatment and prognosis of primary CNS vasculitides (PCNSV). Adult[4] and childhood isolated CNS angiitis,[5] primary angiitis of the CNS (PACNS),[6] granulomatous angiitis of the brain (GAB),[7] and granulomatous angitis of the nervous system (GANS)[2]; and adult[8] and childhood PACNS (cPACNS)[9] are equivalent terms for a prototypical primary vasculitic disorders restricted to the CNS.

Similarly, identification of necrotizing arteritis in arteriae nervorum was synonymous with peripheral nerve vasculitis (PNV), whereas inflammatory involvement in or around smaller epineurial blood vessels defined microvasculitis (MV) and perivasculitis (PV).[10] Although diabetes was not been considered a predisposing factor in PNV, MV became a defining feature in lumbosacral radiculoplexus neuropathy (LSRPN)[11,12] with or without diabetes, and the classification and treatment of patients with systemic and nonsystemic PNV (NPNV) expanded in parallel with systemic vasculitides, incorporating the electrodiagnostic and clinicopathologic features in well-defined observational cohorts and subsets of patients determined in large part by the caliber of vessels involved.[13]

The Pediatric Rheumatology European Society (PRES), the European League against Rheumatism (EULAR), and the Pediatric Rheumatology International Trials Organization (PRINTO) reported methodology and overall clinical, laboratory, and radiographic characteristics for several childhood systemic vasculitides[14] followed by a final validated classification[15] also based on vessel size, similar to the CHCC nomenclature.[1]

Insight into effective therapies of systemic vasculitides have been guided by collaborative evidence-based randomized controlled trials (RCTs) or observational cohorts by the French Vasculitis Study Group (FVSG) database, United States–Canadian Vasculitis Clinical Research Consortium, European Vasculitis Study Society (EUVAS), EULAR, The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System (COVAC), Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), the Pediatric Vasculitis Initiative (PedVas), DCVAS, and the Web-based network BrainWorks.

Physicians treating patients with clinically definite CNS vasculitides, whether primary or secondary, must now choose the sequence and combination of induction and maintenance immunosuppression available from available corticosteroid (CS) preparations, cyclophosphamide (CYC), azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), the pyrimidine synthesis inhibitor leflunomide (LEF),

plasma exchange (PE), high-dose intravenous immunoglobulin (IVIg), and diverse biologic therapies using humanized monoclonal antibodies (mAbs), including the anti-CD20 mAb rituximab (RTX); anti–tumor necrosis factor (TNF) alpha agents infliximab, etanercept, and adalimumab; and anti–interleukin (IL)-6 receptor agents such as tocilizumab (TCZ). Other drugs contemplated for use, but not rigorously used, such as antithymocyte globulin, fusion protein of cytotoxic T-lymphocyte antigen-4 (CTLA4)–Ig, the B-cell-activating factor of the TNF family (BAFF) belimumab, the anti-CD52 mAb alemtuzumab, and the anti–interleukin 5 mAb mepolizumab are not reviewed.

Since the first RCT in tuberculosis,[16] the design and complexity have evolved to include various study designs, often large numbers of study subjects, and an emphasis on multicenter studies. The past 2 decades have witnessed extraordinary progress in the conduct of RCTs in vasculitides. This progress has occurred because of several factors. First, the widespread adoption of standardized nosology, classification criteria, and improved standardization leading to eligibility criteria for participating in RCTs. Second, the use of validated outcome measures for vasculitis.[17,18] However, many forms of vasculitis still lack well-validated measures of disease activity or state for use in clinical trials. Advances in standardized approaches to conducting clinical trials are advocated by EULAR.[19]

The Vasculitis Working Group of the Outcome Measures in Rheumatology (OMERACT) initiative actively pursues a variety of projects to advance development of valid measures in the vasculitides.[20] Disease-specific self-reported patient-related outcomes applicable to AAV can distinguish treatments of varying efficacy, including health-related quality-of-life (HRQoL) measures, further separable by the caliber of vessels involved.[21,22] Children's self-reported HRQoL measured by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL) generic scores scales repeatedly measured over time in pediatric inflammatory brain diseases (IBrainDs)[23] including cPACNS that reflected poor HRQoL in more than half of patients at diagnosis seemed to correlate with cognitive dysfunction as the most presenting symptom and small vessel cPACNS (SV-cPACNS) as the most common diagnosis.[24] The inclusion of online resources such as the UK Biobank that foster research in the genetic predisposition and environmental exposures relevant to development of disease has widened the prospects for public health awareness and applicable research in the prevention and predisposition to vasculitic illnesses.

One other important advance in vasculitis has been the recognition of predictive clinical factors that are associated with disease course. For example, the clinical pattern, disease phenotype, and history of relapse in patients with GPA and MPA are each predictive of prognosis with treatment. Patients seropositive for anti–proteinase 3 (PR3) or c-ANCA are at substantially higher risk of relapse than patients with antimyeloperoxidase (MPO) or p-ANCA,[25] although patients with GPA are more likely to relapse than patients with MPA, a finding that is not surprising given the much higher prevalence of anti-PR3 c-ANCA among patients with GPA. A history of relapse in AAV is highly predictive of future relapse. Thus, these prognostic factors are taken into consideration when developing a treatment regimen for patients with AAV, including duration of therapy.

The Five-Factor Score (FFS), a prognostic tool created by the FVSG,[26] exemplifies how severity and specific organ involvement serves not only as a prognostic tool but also helps direct the therapeutic choice in systemic necrotizing vasculitis. The revised FFS comprises age greater than or equal to 65 years, cardiac involvement, gastrointestinal involvement, renal insufficiency (stabilized peak creatinine level $\geq$150 μmol/L), and absence of ear-nose-throat involvement.[26]

This article examines the treatment of systemic, CNS, and PNS vasculitides, and the specific agents used. Whenever possible, it informs the reader of the underlying concepts guiding treatment of vasculitides, clinical trial standards and individualization of therapy, and the results of clinical studies where applicable with detailed references to the literature. **Box 1** summarizes the recommended approach to the treatment of vasculitides.

Systemic Vasculitides

Corticosteroids

CSs are used alone or in combination and are the single most commonly used therapeutic agent for the treatment of systemic vasculitides. The clinical benefit of CSs

Box 1
Recommendations for the treatment of vasculitides

Large vessel vasculitis
GCA, TAK: CS, AZA, RTX, infliximab, anti-TNF-α, anti-IL-6R, tocilizumab, and MMF
Adjunctive therapy: ASA and AC

Medium vessel vasculitis
PAN, KD: CS and CYC; MMF.

SVV, AAV type
GPA, EGPA, MPA: induction with CS + CYC, CS + RTX or CS + MMF and maintenance RTX, AZA, or MMF

SVV, IC type
CV: MMF; INF-alfa, and PegINF-alfa plus ribavirin or RTX in HCV-associated MC
IgAV: CS and/or MMF, and supportive care

Hypocomplementic-C1q: antihistamines, IVIg, PE

Variable vessel vasculitis
Cogan syndrome: CS
BD: CS, MMF; colchicine or anti-TNF-α

Single organ vasculitis-isolated aortitis, PACNS
Isolated aortitis: CS, AZA, MMF, MTX
PCNSV: induction with CS, CS + CYC, followed by maintenance with AZA, MTX, or MMF
cPACNS: induction with CS, CS + CYC, followed by maintenance with AZA, MTX, or MMF

Vasculitis associated with systemic collagen vascular disease: SLE, RAV
SLE: CS, MMF; and AC
RAV: CS, RTX, infliximab, and AZA or MTX

Vasculitis associated with illicit substance abuse
Avoid illicit substance

Vasculitis associated with infection
Antimicrobial agents chosen specifically to treat a given causal organism

Abbreviations: AC, anticoagulation; ASA, aspirin; AZA, azathioprine; BD, Behçet disease; cPACNS, childhood primary angiitis of the central nervous system CS, corticosteroids, CV, cryoglobulinemic vasculitis; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HCV, hepatitis C virus; IC, Immune complex; IgAV, IgA vasculitis; INF, interferon; IL, interleukin; IVIg, intravenous immune globulin; KD, Kawasaki disease; MC, mixed cryoglobulinemia; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis nodosa; PCNSV, primary central nervous system vasculitis; PE, plasma exchange; RAV, rheumatoid arthritis vasculitis; RTX, rituximab; SLE, systemic lupus erythematosus; TAK, Takayasu arteritis; TNF, tumor necrosis factor.

stems from their inhibitory properties on inflammatory and immune responses. Their broad antiinflammatory properties include the ability to decrease vascular permeability, inhibit the migration of inflammatory cells to sites of injury or untoward inflammation, inhibition of polymorphonuclear and mononuclear cell function, and a variety of mediators important in the inflammatory response, such as kinins, histamine, and prostaglandins. They are potent inhibitors of the immune response with broad effects on antigen processing and immune activation, including lymphocyte proliferation mediator release, as well as lymphocyte trafficking.

There is general agreement on the beneficial and deleterious effects of differing CS dosing schedules. First, therapeutic efficacy and toxicity are related to the administered dose, duration of therapy, and frequency of administration, with more serious side effects during sustained daily long-term therapy without tapering. Second, divided doses of daily prednisone are probably more potent than a single high morning dose of greater than 80 mg of prednisone. Third, daily low doses of 15 mg or less of prednisone incur many of the same problems as high-dose therapy, in particular hypothalamic pituitary adrenal (HPA) axis suppression with incipient adrenal failure. Fourth, pulse therapy of 1000 mg of methylprednisolone daily for several days is generally well tolerated and is associated with fewer effects than long-term therapy with an equivalent degree of immunosuppression and short-term antiinflammatory benefit. Fifth, alternate day therapy, typically reserved for patients whose disease activity is under good control, reduces long-term toxicity, in particular HPA suppression, CS myopathy, and osteoporosis. Sixth, although the different therapeutic options for CS administration generally relate to the best ratio of benefits to risk, when the disease is life threatening or fulminant, as in systemic vasculitides, it would be most reasonable to institute pulse therapy followed by daily high doses if monotherapy is used, whereas the inverse may be more applicable if CSs are combined with an alkylating cytotoxic agent such as CYC.

Early intensive therapy has been suggested in patients with LVV, including TAK and GCA (also known as large vessel GCA [LV-GCA]), to induce remission. CSs are the mainstay of therapy in GCA; however, their use is associated with predictable and occasionally serious side effects even with an initial dose of 0.5 to 0.7 mg/kg/d of prednisone in the absence of eye involvement, or 1 mg/kg/d in the presence thereof, both of which are continued for 1 month before gradual tapering.[27,28]

There are no clinical trials of the efficacy of CSs in patients with MVV and SVV.[29] CSs used in almost all clinical trial and cohort studies to obtain remission or induce cure alone or in association with other agents for AAV are given at the dose of 1 mg/kg/d of prednisone for 3 to 4 weeks according to the EUVAS study group.[30] The FSVG[31] recommends pulse methylprednisolone for life-threatening organ involvement because of its rapid onset of action and favorable safety index.

The use of CS in the treatment of many types of vasculitides other than LVV and systemic necrotizing vasculitides is controversial. Pulse methylprednisolone was alternative therapy given over 1 to 3 days in children with KD compared with 1 or more IVIg infusions to alleviate fever and acute inflammation.[32] A prospective randomized open-label Japanese study of KD[33] that used IVIg therapy plus CSs showed significantly less coronary artery abnormality than those treated with IVIg and aspirin. Side effects of CSs in PAN and associated chronic hepatitis B virus (HBV) infection included enhancement of viral replication and progressive cirrhosis. Such patients treated with PE and antiviral therapy in addition to CSs to avert severe life-threatening manifestations allows discontinuation of CSs. They are safely administered with IFN-α to treat hepatitis C virus (HCV)–related cryoglobulinemia.[34]

Cyclophosphamide

CYC is a member of the alkylating class of cytotoxic drugs that covalently binds cross-linked DNA strands and interferes with mitosis and cell replication. The immunosuppressive effects of CYC include absolute suppression of B- and T-cells as well as suppression of both cell-mediated and humoral immunity. Interest in the use of CYC emerged in early studies by Fauci and Wolff[35] of GPA so treated with combination prednisone and oral CYC at doses of 2 mg/kg/d, showing improved long-term benefit despite severe kidney disease and treatment-related morbidity. The latter included increased propensity for infection, hemorrhagic cystitis, bladder fibrosis, bone-marrow suppression, ovarian failure, bladder cancer, and hematologic malignancies.[36] A prospective, multicenter, randomized trial comparing steroids and pulse CYC versus steroids and oral CYC in GPA[37] showed equal efficacy of pulse CYC in achieving initial remission of GPA, with fewer side effects and lower mortality. However, treatment with pulse CYC did not maintain remission or prevent relapses as well as oral CYC.

A meta-analysis by EULAR[29] concluded that pulsed CYC was more likely to result in remission status than continuous oral therapy, with a lower risk of side effects. A meta-analysis of 3 studies of intravenously pulsed CYC[38] showed that pulsed regimens reduced cumulative CYC exposure by 50%, and were at least as effective at inducing remission, with fewer infective and myelosuppressive side effects; however, there was possible increased risk of relapse.

The recommended initial dose of CYC varies from 0.5 to 0.7 g/m^2 at 2-week intervals given initially on days 1, 15, and 30, and continued every 3 weeks until remission is obtained, followed later by maintenance therapy. CYCLOPS, a randomized trial of daily oral versus pulse cyclophosphamide as therapy for ANCA-associated systemic vasculitis, enrolled 149 patients with generalized AAV to receive either pulse CYC 15 mg/kg at 2-week intervals for the first 3 doses and every 3 weeks thereafter, or daily oral CYC 2 mg/kg/d,[39] noting that pulse therapy was equally effective as daily oral CYC with a lower cumulative dose and fewer instances of leukopenia. Patients age 65 years and older with newly diagnosed PAN, GPA, MPA, and EGPA who receive low-dose intravenous pulse CYC with faster CS dose tapering have reduced rates of severe adverse events and similar remission and relapse rates.

Apart from AAV, CYC has been used in other systemic vasculitides, including severe IgAV and CV, although these indications are controversial. A multicenter, prospective, randomized, open-label trial[40] found that the addition of CYC to CS provided no further benefit compared with steroids alone in treating adult patients with severe IgAV. In patients with HBV-related PAN and HCV-related CV, treatment with PEG-IFN-α plus ribavirin was associated with a good prognosis, whereas immunosuppressive agents, including CS, were associated with a poor outcome and increased mortality.[41]

Azathioprine

Azathioprine is an antimetabolite and purine analogue that interferes with DNA synthesis. Long-term AZA immunosuppression leads to decreased numbers of B- and T-cells, as well as decreased B-cell proliferative responses and antibody synthesis. It also inhibits natural killer cell activity.[42] The Cyclophosphamide versus Azathioprine for Early Remission Phase of Vasculitis (CYCAZAREM) trial[30] studied patients with a new diagnosis of GPA and MPA and a serum creatinine concentration of 5.7 mg/dL (500 μmol/L) or less. All patients received at least 3 months of therapy with oral CYC and prednisolone. After remission, patients were randomly assigned to

continued CYC therapy of 1.5 mg/kg of body weight per day or a substitute regimen of AZA of 2 mg/kg/d. Both groups continued to receive prednisolone and were followed for 18 months from study entry. Relapse was the primary end point. It concluded that patients with at least 3 months of oral CYC and prednisolone for AAV, and randomly assigned to continued CYC therapy at the dose of 1.5 mg/kg of body weight per day or a substitute regimen of AZA of 2 mg/kg/d, in addition to prednisolone, and followed 18 months from study entry, with an end point of relapse, showed no increase in the rate of relapse. The relapse rate was lower among the patients with MPA than among those with GPA ($P = .03$) and the withdrawal of CYC and the substitution of AZA after remission did not increase the rate of relapse. Thus, the duration of exposure to CYC may be safely reduced with the addition of AZA after initial remission in AAV.

Methotrexate

MTX is an antimetabolite that inhibits folic acid and has been used in LVV and AAV. A meta-analysis by Mahr and colleagues[43] assessed 3 randomized placebo-controlled trials in patients with newly diagnosed GCA[44–46] in whom treatment consisted of initial high-dose CS and randomly assigned oral MTX therapy of 7.5 to 15 mg/wk versus placebo, and a comparison of time to event, and continuous outcomes. Adjunctive treatment of GCA with MTX lowered the risk of relapse and reduced exposure to CS, thus MTX could be considered as a therapeutic option in addition to standard-of-care treatment with CS.[43]

A randomized, multicenter trial that enrolled 98 patients from 16 with newly diagnosed GCA to determine whether MTX reduced relapses and cumulative CS requirements and diminished disease-related and treatment-related morbidity did not support the adjunctive use of MTX to control disease activity or to decrease the cumulative dose and toxicity of CS in patients with GCA.[44]

Findings from the Wegener's granulomatosis-Entretien Trial (WEGENT) in 2008[47] suggested that AZA or MTX could effectively maintain remission of GPA or MPA. A subsequent long-term study with 10 years of follow-up for 112 of the 126 original trial participants found no between-treatment differences with regard to rates of relapse, adverse events, damage, survival without severe side effects, and survival without relapse and severe side effects. Thus, AZA and MTX are comparable treatment options for maintaining remission of GPA or MPA.

Mycophenolate mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase (required for the synthesis of DNA), thereby affecting proliferating T- and B-cells.[48] The open-label RCT, International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial[49] randomly assigned 156 patients to AZA starting at 2 mg/kg/d or MMF starting at 2000 mg/d after induction of remission with CYC and CS. The patients were followed for a median of 39 months. Relapses were more common in the MMF group compared with the AZA group; however, severe adverse events did not differ significantly between groups. Thus, among patients with AAV, MMF was less effective than azathioprine for maintaining disease remission, but both had similar adverse event rates.

Between 2007 and 2013, the Clinical Trial of Mycophenolate versus Cyclophosphamide in ANCA Vasculitis (MYCYC) evaluated MMF compared with intravenous CYC in the induction of remission in new cases of AAV, noting that MMF was not inferior to CYC. However, the inferiority of MMF to AZA in maintenance therapy will probably reduce the use of MMF only in patients with AAV refractory to intravenous and oral CYC, and RTX. A recent comparison of guidelines and recommendations on

managing AAV[50] found that patients with nonsevere and non–organ-threatening disease should be recommended a milder regimen than CYC or RTX, with the British Society for Rheumatology (BSR), British Health Professionals for Rheumatology (BHPR),[51] and EULAR[52] including CS with either MTX or MMF (grade B recommendation for MTX and grade C recommendation for MMF, where grade A is highest and D is lowest).[53]

Leflunomide

The pyrimidine synthesis inhibitor LEF was evaluated in an open-label study to show improvement in disease activity and acute phase reactants with 20 mg/d of leflunomide in patients with TAK who were refractory or intolerant to conventional therapy with CSs and immunosuppressive agents,[54] noting that LEF was safe with a steroid-sparing effect. A multicenter, prospective, randomized controlled clinical trial[55] treated patients with GPA either with oral LEF 30 mg/d or oral MTX (starting with 7.5 mg/wk reaching 20 mg/wk after 8 weeks) for 2 years following induction of remission with CYC. The primary end point was the incidence of relapses. The investigators concluded that LEF was effective in the prevention of major relapses in GPA; however, this was associated with an increased frequency of rapidly progressive glomerulonephritis, pulmonary hemorrhage, and cerebral granuloma adverse events.

Plasma exchange

PE was initially used in systemic vasculitides considering the contributory pathogenic role of ANCA and anti–glomerular basement membrane (GBM) antibodies, cryoglobulins, cytokines, and ICs. It is presently used as a second-line agent in the treatment of PAN refractory to conventional regimens. PE improves renal survival in patients with severe renal disease as defined by a serum creatinine level greater than 500 μmol/L when used as an adjunct to daily oral CYC and CS in the prospective randomized Plasma Exchange for Renal Vasculities (MEPEX) trial.[56] A total of 137 patients with a new diagnosis of AAV confirmed by renal biopsy and serum creatinine level greater than 500 μmol/L (5.8 mg/dL) were randomly assigned to receive 7 PEs or 3000 mg of intravenous methylprednisolone; both groups received oral CYC and oral prednisolone. The primary end point was dialysis independence at 3 months. PE was associated with a reduction in risk for progression to end-stage renal disease (ESRD) of 24% at 12 months compared with methylprednisolone (95% confidence interval [CI], 6.1%–41%). Patient survival and severe adverse event rates at 1 year were 76% and 48% in the intravenous methylprednisolone group compared with 73% and 50% in the PE group. The risk reduction of 24% for ESRD with PE was clinically important in view of the cost, morbidity, and mortality of end-stage renal failure, such that the additional costs of PE were outweighed by these savings. The improvement in renal recovery rates with PE was consistent with the hypothesis that PE was most likely to be of benefit in those with the most severe disease. This study excluded patients who had been dialysis dependent for more than 2 weeks because they were considered to have little chance of renal recovery.

The protocol of the Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis (PEXIVAS) Trial[57] is a 2-by-2 factorial randomized trial begun in 2013 that has been evaluating adjunctive PE and 2 oral CS regimens in severe AAV. Patients receive PE or not and a standard or reduced oral CS dosing regimen. All patients receive immunosuppression with either CYC or RTX. The primary outcome is the time to the composite of all-cause mortality and ESRD. The PEXIVAS study was due to report its findings in 2018. The primary

composite outcome, death from any cause or ESRD, occurred in 28% of patients receiving PE compared with 31% in the no-PE group (hazard ratio, 0.86; 95% CI, 0.65–1.13; $P = .27$). The primary outcome occurred in 28% of patients in the reduced CS group and 26% in the standard CS group (absolute risk difference, 2.3%; 90% CI, –3.4% to 8.0%), meeting the noninferiority hypothesis. Serious infections in the first year occurred less often in the reduced CS group compared with the standard group (incidence rate ratio, 0.70; 95% CI, 0.52–0.94; $P = .02$). The investigators concluded that, in the largest ever trial in AAV, a reduced dose of CS was noninferior to a standard dose and resulted in fewer serious infections.

Levy and colleagues[58] examined the long-term outcome of severe anti-GBM antibody disease in patients who received PE, prednisolone, and CYC. Those with a serum creatinine level less than 5.7 mg/dL had patient and renal survival respectively of 100% and 95%, and patient and renal survival of 84% and 74% at last follow-up. Those with a creatinine level greater than or equal to 5.7 mg/dL but did not require immediate dialysis, and were treated with PE, prednisolone, and CYC, had comparative patient and renal survival of 83% and 82% at 1 year, and 62% and 69% at last follow-up. Patients with the anti-GBM disease and severe renal failure should be considered for urgent immunosuppression therapy, including PE, to maximize the chance of renal recovery.

Intravenous immunoglobulin

High-dose IVIg is a safe and well-tolerated therapy compared with standard CS and immunosuppressive therapy. Its use in systemic vasculitides was first established in the prevention of coronary artery aneurysms and in the reduction of systemic inflammation in children with KD.[59,60] A later study[61] showed the superiority of a single infusion of IVIg compared with 4 infusions in the treatment of acute KD. Improvement of patients with AAV was associated with a mean reduction in pretreatment ANCA levels by 51% in patients so treated.[62] It was alternative treatment in patients with GPA and MPA without threatened systemic organ involvement,[63] leading to full clinical remission lasting 1 year before commencing conventional immunosuppressive therapy. A placebo-controlled trial of a single course of 2 g/kg per kg of IVIg in AAV with persistent disease activity[64] noted reduced disease activity as judged by a reduction in the Birmingham Vasculitis Activity Score (BVAS), along with C-reactive protein and ANCA levels in subjects randomized to IVIg compared with placebo. However, the effect of a single course of IVIg was not maintained beyond 3 months, and mild reversible side effects following therapy were frequent. A multicenter, prospective, open-label study[65] for relapses of GPA and MPA during treatment or in the year following discontinuation of CS or immunosuppressive therapy led to complete remissions, some lasting up to 2 years after treatment with high-dose IVIg for up to 6 months.

Rituximab

Rituximab is a genetically engineered chimeric murine-human monoclonal IgG1k that is directed against the CD20 antigen expressed on the surface of B-cells. In 2010, 2 randomized clinical trials, RTX in ANCA-associated Vasculitides (RAVE)[66] and RTX versus CYC for ANCA-associated Vasculitides (RITUXVAS),[67] provided initial RCT evidence that, at 6 to 12 months of follow-up respectively, RTX was as safe and effective as conventional immunosuppressive therapy to control active MPA and GPA. A subgroup of 63 of 197 enrolled patients in RAVE with either GPA or MPA[66] treated with 375 mg/m^2 of body surface area per week for 4 weeks, compared with 2 mg/kg/d of CYC in those who reached the primary end point of remission of disease

without use of prednisone at 6 months, showed that RTX was not inferior to daily CYC for induction of remission in severe AAV, and might even be superior to CYC in relapsing disease. A single course of RTX was as effective as continuous conventional immunosuppressive therapy with CYC followed by AZA for the induction and maintenance of remission of patients with severe organ-threatening AAV over the course of 18 months in the Rituximab in ANCA-Assocated Vasculitis (RAVE) Trial.[25] The primary outcome was complete remission of disease by 6 months, with remission maintained through 18 months. Guillevin and colleagues[68] studied 115 patients with newly diagnosed or relapsing GPA, MPA, and renal-limited AAV in complete remission after a CYC-CS regimen who were randomly assigned to receive either 500 mg of RTX on days 0 and 14 and at months 6, 12, and 18 after study entry or daily AZA until month 22. The primary end point at month 28 was the rate of major relapse (the reappearance of disease activity or worsening, with a BVAS >0, and involvement of 1 or more major organs, disease-related life-threatening events, or both). More patients with AAV had sustained remission at month 28 with RTX than with AZA. At month 28, major relapses had occurred in 29% of the AZA group compared with 5% in the RTX group, with similar frequencies of severe adverse events.

In a 24-month phase III RCT of 115 patients over time who received RTX or AZA for AAV maintenance therapy and completed a Health Assessment Questionnaire (HAQ),[69] there were mean improvements of HAQ scores, from baseline to month 24, that were significantly better for the RTX than the azathioprine group.

Zaja and colleagues[70] found that RTX was a safe and effective alternative to standard immunosuppressive therapy for type II mixed cryoglobulinemia (MC). Sansonno and colleagues[71] studied patients with MC and HCV-positive chronic active liver disease resistant to interferon alfa (INFα) therapy, noting that 80% of patients treated with an intravenous infusion of 375 mg/m^2 of RTX once a week for 4 consecutive weeks showed a complete response characterized by rapid improvement of clinical signs and decline of the cryocrit and anti-HCV antibody titers. Roccatello and colleagues[72] found that RTX was a safe and effective option in symptomatic patients with HCV-associated MC and glomerulonephritis and signs of systemic vasculitis. Saadoun and colleagues[73] found that 94% of patients with severe refractory HCV-related MC vasculitis showed clinical improvement, 63% of whom were complete responders with undetectable HCV RNA and serum cryoglobulins. Terrier and colleagues[74] found that RTX combined with PEG-INFα-2b plus ribavirin induced a complete and partial clinical response respectively in 80% and 15%; a complete and partial immunologic response was respectively noted in 67% and 33% of patients, and a sustained virologic response in 55% of patients so treated, making RTX combined with PEG-INFα-2b plus ribavirin safe and effective treatment in severe refractory HCV-associated mixed CV.

Ignatova and colleagues[75] studied the efficiency of traditional CS and CYC and selective RTX therapy for HCV-associated CV over an average follow-up period of 2.8 years, noting that combined therapy for RTX and antiviral therapy was most effective in patients with severe forms of vasculitis.

Anti–tumor necrosis factor alpha

The anti-TNF-α monoclonal antibody infliximab or the analogue of its receptor, etanercept, has been proposed to treat primary systemic vasculitides. Infliximab, a chimeric anti–TNF-α monoclonal antibody in combination with conventional therapy led to clinical remission in 88% of the patients with acute or persistently active AAV enrolled in an open, prospective trial.[76] In 2002, Bartolucci and colleagues[77] reported their findings of infliximab treatment in 7 patients with severe refractory GPA, all of whom

obtained complete or partial remissions, with cutaneous eruption being the only adverse effect.

Etanercept, another TNF-α blocker, composed of a soluble protein derived from the p75 TNF receptor fused to the Fc portion of IgG, has been tested in AAV and in conjunction with conventional therapy to reduce relapse rate. The Wegener's Granulomatosis Etanercept (WGET) trial[78] compared etanercept with placebo in addition to receiving standard therapy of CS plus CYC or MTX. After sustained remission, the primary outcome was defined as a BVAS of 0 for at least 6 months and tapering of standard medications according to an established protocol. Of 174 patients, 72% had a sustained remission; however, there were no significant differences between the etanercept and control groups in the rates of sustained remission (69% vs 75%; $P = .39$) or in the relative risk of disease flares per 100 person-years of follow-up. The Infliximab versus Ritaximab in Systemic Necrotizing Vasculitides with Positive ANCA after Relapse or Resistant Immunosuppressant Therapies (RATTRAP) trial,[79] which compared efficacy and tolerance of infliximab versus RTX to treat refractory GPA, showed the usefulness of infliximab to obtain remission of refractory GPA, with a trend at 12 months favoring RTX. During long-term follow-up, RTX was better able to obtain and maintain remission.

Seror and colleagues[80] studied the effect of adding a 10-week course of 40 mg on alternate weeks of subcutaneous adalimumab for 10 weeks to a standard treatment of 0.7 mg/kg/d of prednisone, with a primary end point of the percentage of patients in remission on less than 0.1 mg/kg of prednisone at week 26. Among near-equal numbers of study and control subjects, there was no difference between adalimumab and prednisone in increasing the number of patients in remission on less than 0.1 mg/kg of CS at 6 months. Mekinian and colleagues,[81] who reported the findings of a multicenter retrospective tolerance study of infliximab in refractory TAK, noted a significant decrease in clinical biological activities within 3 months, with a decrease in the median CS dose at 12 months.

Tocilizumab

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was evaluated in retrospective series in patients with refractory LVV showing evidence of clinical and serologic improvement in patients with refractory and relapsing disease. The multicenter, randomized, double-blind, placebo-controlled study, Giant-Cell Arteritis Actemra (GiACTA) trail, began recruiting patients with GCA for evaluation of the safety and efficacy of 162 mg of subcutaneous TCZ administered weekly or every 2 weeks versus placebo for 52 weeks, with tapering of the oral daily dose of prednisone over 26 weeks compared with placebo with 52 weeks of prednisone (NCT01791153). The primary outcome measure is the proportion of patients in sustained remission at week 52, comparing TCZ plus 26 weeks of prednisone taper with placebo plus 26 weeks of prednisone taper.

Insights into treatment of antineutrophil cytoplasmic antibody–associated vasculitis

Fifty years ago, AAV had a mortality of 93% within 2 years, primarily caused by renal and respiratory failure.[82] The introduction of CSs in 1948 and CYC in the 1960s, together with adjunctive therapies such as antihypertensive and renal replacement therapies, transformed the outcome of AAV, with 5-year rates approaching 80%.[83] This therapeutic revolution transformed AAV into a chronic relapsing disorder with progressive organ damage and disability. The cumulative exposure to CS and immunosuppressive drugs, which contributes to organ damage, has raised concerns of CYC-related toxicity involving chronic myelosuppression, infection, urothelial

malignancy, and infertility.[36,84] The equivalence of RTX to CYC in the induction of remission of AAV,[66,67] and the licensing of RTX for treatment of AAV, have been significant achievements. The optimal treatment strategy following RTX induction still needs to be addressed. Rates of cardiovascular disease and malignancy in AAV were increased as well as underlying patterns of disease such as accelerated atherosclerosis,[85] raising concerns that there may be nontraditional risk factors such as endothelial activation and excessive vascular remodeling to take into account as predominant causes of death, rather than uncontrolled vasculitis.[86] It is uncertain whether increasing use of RTX can remedy these unforeseen problems.

Insights into disease pathogenesis have influenced the approach to treatment. Genetic susceptibility and environmental exposures are now known to contribute to the autoimmune etiopathogenesis of AAV. Animal models of AAV show that the transfer of murine MPO-ANCA IgG without functioning B or T-cells results in a pauci-immune, necrotizing crescentic glomerulonephritis similar to that seen in AAV in humans.[87] There are also several lines of investigation linking infections to ANCA formation through molecular mimicry.[88] Fimbriated bacteria induce novel ANCA antibodies to human lysosome membrane protein-2 (LAMP-2), which in turn leads to crescentic glomerulonephritis in animals,[89] and infection with *Staphylococcus aureus* is associated with relapse of GPA.[90] Proteinase 3 ANCA binding levels are predictive of outcome with an increase in antibody titers before clinical relapse. However, patients who are consistently ANCA seronegative fit the clinical phenotype of AAV, and the efficacy of B-cell depletion with rituximab is not associated with ANCA status. Despite the pauci-immune nature of the histology in ANCA vasculitis, there is increasing evidence for the role of both cell and humoral immunity, with immune complex deposition and complement activation in renal involvement. Components of the alternative pathway are detected in glomeruli and small blood vessels in kidney biopsy tissue specimens from patients with AAV, which colocalize with C3d and the membrane attack complex.[91] The contribution of cell-mediated immunity is exemplified by activation of circulating T- and B-cells, with infiltration of plasmoblasts into affected tissues.[92] Autoreactive B-cells, necessary for the development of autoantibody producing cells, seem to play the important role of supporting autoreactive T-cell activity through antigen presentation, costimulation, and direct production of proinflammatory cytokines, including IL-6 and TNF-α. In view of their role as precursors of ANCA-secreting plasma cells, B-cells are a therapeutic target in AAV and T-cells play an important role in the eventual pathogenesis of AAV.[93] Class-switched IgG autoreactive antibodies receive cognate T-cell help, and T-cells cause damage via direct cytotoxicity and recruitment and activation of macrophages.[94]

Current and future treatment strategies in AAV are addressing optimization of existing therapies and the introduction of novel agents. With a greater understanding of the disease pathogenesis, and the advent of highly specific biological molecules, a targeted approach is now possible, with the ultimate goal of controlling the underlying disease process while eliminating or minimizing disease side effects associated with broad-spectrum immunosuppression. The desire to minimize CYC exposure has dominated clinical studies for the last 20 years.[36] Nonetheless, CYC remains a relatively safe and effective induction agent in AAV and is a component of the standard of care in consensus guidelines for the treatment of generalized disease.[29] Between 2003 and 2009, 3 adjustments in the administration of CYC in clinical trials showed that it could be given even more safely. First, the sequential replacement of CYC by AZA once remission was achieved, as in the CYCAZAREM study.[30] Second, the replacement of CYC by MTX for early systemic disease without critical organ manifestations in the Nonrenal Wegener's Alternatively Treated with Methotrexate (NORAM)

study.[95] Third, the use of pulsed intravenous CYC with dose reductions for patients aged more than 60 years and renal impairment rather than daily oral CYC in the CYCLOPS study,[39] enabling a cumulative dose reduction of approximately one-half.). In long-term follow-up of patients in the CYCLOPS study,[96] reduced CYC was associated with a higher risk of relapse, whereas MTX was associated with less effective disease control than CYC induction therapy in the NORAM study.[97] However, in neither were long-term morbidity and mortality increased.

However, early outcome results for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues[98] on behalf of A Registry for Childhood Vasculitis (ARCHiVe) Investigators Network and the Pediatric Vasculitis (PedVas) Initiative were less encouraging. Among 105 children with AAV, mainly GPA, who received CS, CYC, MTX, or RTX for remission induction, and PE in conjunction with CYC and/or RTX, 42% achieved remission at 12 months (Pediatric Vasculitis Activity Score of 0, CS dose <0.2 mg/kg/d), 21 (48%) of whom discontinued CS by 12 months; all but 3 remained on maintenance treatment at 12 months receiving AZA, MTX, RTX, MMF, and CYC. However, up to 63% had a Pediatric Vasculitis Damage Index score of 1 or more by 12 months, with the presence of renal; ear, nose and throat; or pulmonary damage. Moreover, 41% of children reported hospitalizations. Thus, a significant proportion of patients were not in remission at 12 months, and more than one-half of the patient cohort experienced damage early in the disease course. The 12-month remission rate of 42% in the cohort was significantly lower than that found by Sacri and colleagues,[99] who reported 73% remission at postinduction and 90% overall remission rate (including secondary remissions after a median time of 6.7 months). Disappointing early outcomes in the PedVas treatment study for GPA[98] may pose some difficulty in applying the same immunosuppressant treatment strategy to cPACNS, pediatric IBrainDs, pediatric autoinflammatory diseases,[100] neuroimmune disorders,[101] and childhood autoimmune encephalitides.[102]

Primary central nervous system vasculitides

Adult As originally defined, PACNS,[6] like IACNS,[4] relied on either classic angiographic or histopathologic features of angiitis within the CNS in the absence of systemic vasculitis or another cause for the observed findings. Younger and colleagues[2,7] emphasized the etiologically diverse associations with comorbid disorders and the prototypical histopathology of granulomatous giant cell and epithelioid cell infiltration involving the walls of arteries of various caliber, from named cerebral vessels to small arteries and veins, which, when present in combined meningeal and brain biopsy, predicted similar widespread features at postmortem examination.

Patients with PCNSV typically present with headache of gradual onset, often accompanied by the signs and symptoms of dementia, and only later develop focal neurologic symptoms and signs. The clinical course may be rapidly progressive over days to weeks, or insidious over many months with prolonged periods of stabilization. By comparison with PCNSV, patients with granulomatous angiitis[2,7] present with headache, mental change, and increased cerebrospinal fluid (CSF) protein content with or without pleocytosis. Hemiparesis, quadriparesis, and lethargy, associated with a poor prognosis, mandate the need for prompt diagnosis combining brain neuroimaging and cerebral angiography to choose the best site for meningeal and brain biopsy in an effort to establish the diagnosis with certainty. Nonetheless, 38% of adults with clinically definite PCNSV[3] and 8% of CNS tissue biopsies in children with SV-cPACNS[103] may show negative or nonspecific inflammation, which may be caused by prolonged time to biopsy, nonlesional biopsy, prior CS treatment, or inadequate specimen sampling. Among 79 cases of suspected PACNS at the Hospital of

the University of Pennsylvania from 2005 to 2013,[104] 9 (11%) leptomeningeal and/or cortical brain biopsies were diagnostic of PACNS, 14 (18%) showed nondiagnostic perivascular inflammation, and 24 (30%) showed alternative diagnoses (cerebral amyloid angiopathy [CAA], lymphoma, demyelination, Alzheimer disease, tauopathy, posterior reversible encephalopathy syndrome, small vessel vasculopathy, and progressive multifocal leukoencephalopathy), and the remainder were negative. Moreover, 13 patients (16%) experienced postbiopsy complications: 6 (8%) had intracerebral hemorrhage, 2 (3%) had seizures, 3 (4%) experienced transient altered mental status, and 1 each sustained cerebral infarction and CSF leak.

Physicians treating childhood and adult PCNSV should proceed with caution in choosing the sequence and mode of immunosuppressive therapies, for the present, based on a single historical survey of clinicopathologically verified adult cases, and 2 cohort observational studies in North America and France. The only historical survey of histologically confirmed granulomatous angiitis including 54 diagnosed antemortem (30 cases) or postmortem (24 cases) reported by Younger and colleagues[2] more than 2 decades ago, had a selection bias of the most severe form of PCNSV. Twenty-eight were treated with CS alone (11 patients) or with oral CYC (in 16 patients), or AZA (in 1 patient), and followed for up to 1 year, of whom 18 (64%) improved, 7 (25%) were unchanged, and 3 (11%) died with roughly equally satisfactory outcomes after treatment with CS with or without CYC. Three patients diagnosed antemortem died while taking CS and CYC, and 2 had serious sequelae of the therapy, including fatal lymphoma, immunosuppression and opportunistic infection, or pneumonia and leukopenia. Of 24 patients diagnosed postmortem, 7 (29%) received treatment with CS alone (in 6 patients) or with CYC (in 1 patient) and 17 (71%) were untreated. Thus, 17 of 18 (94%) untreated patients died, indicating that, without therapy, the disease was usually fatal. Treatment with CS, alone or in combination with CYC, was associated with a considerable reduction in mortality; 24 of 34 (70%) so treated that survived either improved (50%) or were clinically unchanged. In this historical survey, there was no appreciable benefit in the addition of CYC; however, the numbers were small; unmatched for age, disease activity, or other factors; and follow-up was not uniform. Based on this historical survey, the investigators suggested that CYC be reserved for histologically confirmed cases of PCNSV, especially those patients who continue to progress or fail to improve on CS alone, and who can be monitored closely for serious medication side effects.

Two cohorts, one retrospective[3] and the other prospective,[105] have stratified cases based on clinical, neuroradiographic, and histopathologic laboratory features, offering additional insights into the management of CNS vasculitis. Over nearly 3 decades from 1983 to 2011, 163 patients at the Mayo Clinic with PCNSV were retrospectively analyzed by Salvarani and colleagues,[3] enrolling 105 patients (64%) who met inclusion criteria similar to those used by Calabreses and Mallek[6] and the proposed changes thereof by Birnbaum and Hellmann[106] for the diagnosis of probable CNS vasculitis based on cerebral angiography manifesting areas of smooth-wall segmental narrowing or dilatation, and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis (or other causes); 58 patients (36%) met the definite diagnosis based on a CNS tissue biopsy showing transmural vascular inflammation involving leptomeningeal or parenchymal vessels. This histopathology was granulomatous in 35 patients (60.3%), lymphocytic in 13 (22.4%), and necrotizing alone in 10 (17.2%). These histologic patterns seemed to identify subsets of disease rather than different stages of the same process because no individual patient had histologic evidence of more than 1 pattern. A favorable response to therapy including CS (prednisone) alone or in association with CYC was observed in 85% of patients. Three

patients treated with biologic agents, including RTX (1 patient) and TNF-α inhibitor (2 patients) for treatment refractory disease, were also improved. Relapses were observed in 27% of patients, and 25% of patients had discontinued therapy by the time of the last follow-up visit. Although response to treatment was not associated with any histologic pattern of the biopsy specimen, treatment with CS alone was associated with more frequent relapses (odds ratio [OR], 2.90), whereas large named vessel involvement (OR, 6.14) and cerebral infarcts at the time of diagnosis (OR, 3.32) were associated with a poor response to treatment. Among the patients diagnosed exclusively by angiography alone, relapses were more frequent when there was large vessel involvement (30%) than only small vessel changes (9%), with an increased mortality because of fatal neurovascular problems caused by PCNSV. Subsets of patients with PCNSV showed equally interesting insights. Salvarani and colleagues[107] noted granulomatous vasculitis in all 8 (100%) cerebral biopsies of patients with lymphoma and PCNSV, 2 of whom had concomitant CAA. Among 131 consecutive patients with PCNSV, 11 (8.4%) had a rapidly progressive course that was resistant to immunosuppressive therapy resulting in severe disability or death. Such patients had bilateral cortical and subcortical infarction on initial brain MRI and LVV on cerebral angiography with granulomatous and necrotizing vasculitis in brain tissue biopsies. All 11 patients failed to respond to aggressive immunosuppressive therapy, only 1 of whom survived, with major fixed neurologic deficits.

In 2018, De Boysson and colleagues[105] described the treatment and long-term outcomes of an observational cohort of 112 patients with PCNSV derived from 3 main networks: the FVSG, French Neurovascular Society, and the French Internal Medicine Society. The 3 main inclusion criteria were (1) involvement of CNS vessels as shown by biopsy or based on imaging (digital subtraction angiography or magnetic resonance [MR] angiography), of intracranial arterial stenoses, occlusions, or fusiform dilations; (2) a complete work-up, including infectious and immunologic serologies (human immunodeficiency virus, HBV, HCV, syphilis, tuberculosis, antinuclear and ANCA, echocardiography, and whole-body imaging, to exclude other alternative conditions affecting CNS vessels; and (3) a follow-up at more than 6 months (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 in which vascular lesions reverse within the first months.[108,109] The rate of prolonged remission was defined by the absence of relapse at 12 months or longer after diagnosis, as was the functional status at last follow-up in accordance with 3 main groups of treatments administered: CS (group 1); induction treatment with CS and an immunosuppressant, but no maintenance (group 2); and combined treatment with CS and an immunosuppressant for induction followed by maintenance therapy (group 3). Good functional status was defined as a modified Rankin Scale score less than or equal to 2 at the last follow-up. Among the 112 patients reported by De Boysson and colleagues,[105] 33 (29%) patients were included with a diagnostic CNS tissue biopsy, and 68 (61%) and 11 (10%) respectively had digital subtraction angiography or MR angiography consistent with PCNSV. Remission was achieved with the initial induction treatment in 106 (95%) of the 112 patients. Prolonged remission without relapse was observed in 70 (66%) patients after a mean of 57 months (range, 12–198 months) of follow-up. A good functional status at last follow-up (ie, modified Rankin Scale score $\leq$2) was observed in 63 (56%) patients. The overall mortality was 8%. More prolonged remissions (P = .003) and a better functional status at the last follow-up (P = .0004) were observed in group 3. In multivariate analysis, the use of maintenance therapy was associated with prolonged remission (OR, 4.32 [1.67–12.19]; P = .002) and better functional status (OR, 8.09 [3.24–22.38]; P<.0001). These findings suggest

that maintenance therapy with an immunosuppressant combined with CS leads to the best long-term clinical and functional outcomes in patients with PCNSV after having achieved remission with either CS alone or in combination with another immunosuppressant. In that regard, CYC in combination with CS for induction and azathioprine for maintenance, were the 2 main immunosuppressants used in this registry. Whether other combinations or sequences can achieve better results remains to be ascertained.

Childhood With a minority of positive leptomeningeal and cortical brain biopsies in established series of adult cases of PCNSV, and an estimated annual incidence rate of 2.4 cases per 1 million person-years,[8] there are no satisfactory prevalence or incidence data or evidence-based guidelines to treat cPCNSV,[110] so the results of The PedVas Initiative, a Canadian and United Kingdom collaborative study (ARChiVe Investigators Network within The PedVas Initiative [ARChiVe registry], BrainWorks, and DCVAS) of pediatric and adult cases of AAV (GPA) and PACNS (National Institutes of Health identifier, NCT02006134), are awaited. The PedVas Initiative has been prospectively collecting clinical and biobank data since January 2013 of registered cases, within 12 months of study entry, and expected completion is in December 2019. The approach to cPACNS is incorporated into the larger area of IBrainD (IBD),[23] thereby excluding angiography-positive mimics of cPACANS; and angiography-negative, brain biopsy–positive mimics of SV-cPACNS. It is difficult to reconcile the applicability of the results from The PedVas Initiative for childhood to cPACNS[98] using CS, CYC, MTX, or RTX for remission induction, and PE in conjunction with CYC and/or RTX; and AZA, MTX, RTX, MMF, and CYC for up to 12 months for remission maintenance, with the disappointing rate of remission status of 42%, and a rate of visceral organ damage of 63%.[98]

The aim of treatment in IBD has nonetheless been to rapidly control the underlying inflammatory response and stabilize the blood-brain barrier while protecting the brain from further insults. Methylprednisolone has been the first-line agent administered intravenously at a dose of 30 mg/kg/d to a maximum of 1 g/d for 3 to 5 days[111] followed by 1 to 2 mg/kg/d of oral CS to a maximum of 60 mg/d of prednisone.[101,112] After stabilization the choice of immunosuppressive treatment is directed at the inflammatory pathways involved by the primary inflammatory or vasculitic process. Induction therapy with CS and pulse CYC followed by maintenance therapy with AZA or MMF has been recommended in cPACNS.[113] Children with SV-cPACNS were treated in an open-label study[113] with CYC in doses of 500 to 750 mg/m^2 as monthly infusions for 6 months, and followed with maintenance therapy with AZA of 1 mg/kg/d and a target dose of 2 to 3 mg/kg/d, and MMF at titrated doses of 800 to 1200 mg/m^2/d followed for up to 24 months using pediatric stroke outcome measures (PSOM). Among 19 such patients, 13 completed 24 months of follow-up, of whom 9 had a good neurologic outcome by PSOM scoring, 8 experienced disease flares, and 4 achieved remission of disease. MMF was more effective than AZA. Rituximab may be appropriate therapy at doses of 375 mg/m^2 for 4 consecutive weeks or 500 mg/m^2 weekly for 2 weeks in cPACNS, as was recently reported in SV-cPACNS.[114]

Nonsystemic Vasculitic Neuropathy

The vasculitic neuropathies are heterogeneous disorders that present in the setting of systemic vasculitis or in the absence thereof, where necrotizing arteritis may remain clinically and pathologically restricted to the peripheral nerves as SOV. The Peripheral Nerve Society[115,116] established respective guidelines for the classification, diagnosis, investigation, and treatment of nonsystemic vasculitic neuropathy (NSVN) and

vasculitic peripheral neuropathy. Pathologically definite vasculitic neuropathy is defined by active or chronic peripheral nerve and muscle tissue lesions that show cellular invasion of the walls of blood vessels with accompanying acute vascular damage (fibrinoid necrosis, endothelial loss/disruption, internal lamina loss/fragmentation, smooth muscle media loss/fragmentation/separation, acute thrombosis, vascular/perivascular hemorrhage, or leukocytoclasia) or chronic vascular damage (intimal hyperplasia, fibrosis of media, adventitial/periadventitial fibrosis, or chronic thrombosis chronic thrombosis with recanalization), without evidence of another primary disease process that could mimic vasculitis pathologically, such as lymphoma, lymphomatoid granulomatosis, or amyloidosis. Patients with NSVN lack symptoms, signs, or laboratory evidence of involvement of other organs (demonstrable by laboratory evidence of PR3-ANA, MPO-ANA, mixed cryoglobulins, anti-Sjögren's antibodies syndrome-related antigen A and B (SSA, SSB), Smith (Sm), ribonuclear protein (RNP), SCL-70, centromere, double-stranded DNA, or citrullinated protein (CCP) serology; erythrocyte sedimentation rate >100 mm/h, or tissue biopsy evidence of vasculitis in another organ other than muscle; serologic, polymerase chain reaction, or culture evidence of a specific infection associated with vasculitis), and no predisposing factors (other than diabetes) of a connective tissue disease, sarcoidosis, inflammatory bowel disease, active malignancy, HUV, cutaneous PAN, or exposure to drugs likely to cause vasculitis. Inflammation of microvessels less than 40 to 70 μm in diameter without vascular damage is broadly referred to as MV.

The management of NPNV has remained uncertain because the concept presumes that the vasculitic disease process is widespread within the nerves and not elsewhere in the body. This assumption has been called into question by six lines of evidence. First, the reports of equally silent lesions in medium-sized muscular arteries in patients with clinically isolated vasculitic neuropathy.[117] Patient 1 in the series of pathologically confirmed cases of PAN by Kernohan and Woltman[118] was a 54-year-old man with 5 years of progressive generalized painful peripheral neuropathy that was so severe before death that he was partially paralyzed and unable to speak or swallow. Postmortem examination showed PAN limited to the nerve trunks of the arms and legs. The brain, cranial nerves, and spinal cord were normal except for early acute changes without evidence of vasculitis. Examination of all other organs failed to reveal a single vascular lesion, except 1 small artery in the capsule of the prostate gland. Torvik and Berntzen[119] described a 76-year-old woman with diffuse fever, pain, and central scotoma of the eye that improved with CSs. A biopsy of the temporal artery and pectoralis muscle disclosed necrotizing small arteries and arterioles in small adventitial vessels of the temporal artery without frank temporal arteritis. However, postmortem examination showed evidence of healed vasculitis in numerous small arteries and arterioles of muscle and nerve tissue measuring 50 to 200 μm in diameter without vasculitis in visceral organ or the CNS.

Second, the lack of long-term follow-up in most case series ranging from 6 months to 22 years.[120]

Third, the report of only 2 proposed cases, both with foci of vasculitis outside the PNS in a visceral organ[118] or the temporal artery.[119]

Fourth, vasculitis in muscle tissue is included in the definition of NPNV,[115] making the disorder perhaps more appropriately termed PNS vasculitis or PNSV.

Fifth, finding of vasculitis in a cutaneous nerve or muscle tissue specimen aids in the diagnosis of systemic vasculitides, particularly when no other site of vasculitis can be found. An example is the FVSG database, which used nerve and muscle tissue biopsy to establish systemic vasculitis in a retrospective study cohort of PAN in the absence or presence of symptomatic peripheral neuropathy.[121] Of 129 patients who underwent

nerve biopsy, including 108 with peripheral neuropathy and 21 without peripheral neuropathy, vasculitic lesions were noted respectively in 83% and 81% of patients compared with muscle biopsy, which showed vasculitis respectively in 68% and 60%.

Sixth, the exclusion of patients with diabetes according to the 2010 guidelines[115] may allow another selection bias of ascertainment. Over the years, there has been increasing support for the contribution of an autoimmune mechanism in the pathogenesis of diabetic neuropathy. Diabetes seems to be caused by autoimmune mechanisms directed at insulin-producing pancreatic beta cells, and a variety of autoantibodies have been detected in patients with type 1 diabetes or insulin-dependent diabetes mellitus, including anti–islet cell cytoplasmic antibodies, present in up to 80% of newly diagnosed patients[122]; and glutamic acid decarboxylase antibodies, also present in patients with autoimmune stiff person syndrome.[123] Younger and colleagues[10] reported the clinicopathologic and immunohistochemical findings of sural nerve biopsy tissues in a cohort of 20 patients with heterogeneous forms of diabetic neuropathy. That series was continued to a total of 107 patients,[124] 3 of whom (3%) showed MV and 3 (3%) showed necrotizing arteritis. Although diabetes has not been considered a predisposing factor in PNV, the presence or absence of diabetes became a defining feature of patients with LSRPN.[11,125] In the only postmortem case of LSRPN described by Younger,[12] sural nerve biopsy showed mononuclear inflammatory cells surrounding a small epineurial artery with extension into the vascular wall, with reactive luminal connective tissue suggesting recanalization of a thrombus. An adjacent nerve fascicle showed marked loss of myelinated nerve fibers. The patient was treated for painful diabetic lumbosacral plexopathy and PNV according to prevailing standards with 2 g/kg intravenous immunoglobulin for 5 days, followed by 750 mg of intravenous CYC and 1000 mg of methylprednisolone intravenously for 3 additional days. Acute tubular necrosis, increasing lethargy, unresponsiveness, and aspiration pneumonia supervened and the patient expired 4 weeks after admission. General autopsy showed no evidence of systemic or PNV. The brain showed diffuse loss of neurons in all sampled cortical areas, including the cerebellum, consistent with anoxia secondary to cardiac arrest. Sections of extradural lumbar plexus, sciatic, and femoral nerve tissue showed perivascular epineurial inflammation with infiltration of adjacent endoneurium. This case suggests that the restricted LSRPN may be considered a good example of true NSVN.

There are no RCTs or ongoing observational cohort studies to guide the treatment of NPNV. However, published recommendations for the treatment of NSVN[115] suggest the use of oral CS therapy at the dose of 1 mg/kg/d, with tapering over 1 year to a low dose, unless there is rapidly progressive neuropathy that warrants combination therapy with CYC, MTX, and AZA. Other agents, such as IVIg and PE, are probably effective as both initial and adjunctive therapy. Careful monitoring should be performed to observe desired therapeutic responses and to avoid potentially serious drug side effects.

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65:1–11.
2. Younger DS, Calabrese LH, Hays AP. Granulomatous angiitis of the nervous system. Neurol Clin 1997;15:821–34.
3. Salvarani C, Brown RD Jr, Christianson TJH, et al. Adult primary central nervous system vasculitis treatment and course. Analysis of one hundred and sixty-three patients. Arthritis Rheum 2015;67(6):1637–45.

4. 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.
5. Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. Neurology 2001;56:837–42.
6. Calabrese HL, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988;67:20–39.
7. Younger DS, Hays AP, Brust JCM, et al. Granulomatous angiitis of the brain: an inflammatory reaction of nonspecific etiology. Arch Neurol 1988;45:514–8.
8. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 2007;62:442–51.
9. Benseler SM, Silverman E, Aviv RI, et al. Primary central nervous system vasculitis in children. Arthritis Rheum 2006;54:1291–7.
10. Younger DS, Rosoklija G, Hays AP, et al. Diabetic peripheral neuropathy: a clinicopathologic and immunohistochemical analysis of sural nerve biopsies. Muscle Nerve 1996;19:722–7.
11. Dyck PJB, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve 2002;25:477–91.
12. Younger DS. Diabetic lumbosacral radiculoplexus neuropathy: a postmortem studied patient and review of the literature. J Neurol 2011;258:1364–7.
13. Gwathmey KG, Burns TM, Collins MP, et al. Vasculitic neuropathies. Lancet Neurol 2014;13:67–82.
14. Rupert N, Ozen S, Pistorio A, et al. EULAR/PINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: overall methodology and clinical characterization. Ann Rheum Dis 2010;69:790–7.
15. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PReS criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis. Ankara 2008. Part II: final classification. Ann Rheum Dis 2010;69:798–806.
16. British Medical Research Council. Streptomycin treatment of pulmonary tuberculosis: a medical research council investigation. BMJ 1948;2:769–83.
17. Direskeneli H, Aydin SZ, Kermani TA, et al. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. J Rheumatol 2011;38:1471–9.
18. Stone J, Hoffman G, Merkel P, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham vasculitis activity score. Arthritis Rheum 2001;44:912–20.
19. Hellmich B, Flossmann O, Gross W, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605–17.
20. Merkel P, Aydin S, Boers M, et al. Current status of outcome measure development in vasculitis. J Rheumatol 2014;41:593–8.
21. Robson JC, Dawson J, Doll H, et al. Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. Ann Rheum Dis 2018;77:1157–64.
22. Robson JC, Dawson J, Cronholm PF, et al. Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure. Patient Relat Outcome Meas 2018;9:17–34.

23. Twilt M, Benseler SM. Childhood inflammatory brain disease: pathogenesis, diagnosis and therapy. Rheumatology (Oxford) 2014;53:1359–68.
24. Liu E, Twilt M, Tyrrell PN, et al. Health-related quality of life in children with inflammatory brain disease. Pediatr Rheumatol Online J 2018;16:73.
25. Specks U, Merkel PA, Seo P, et al, for RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.
26. Guillevin L, Pagnoux C, Seror R, et al. The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011;90:19–27.
27. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68:318–23.
28. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234–45.
29. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–7.
30. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.
31. Guillevin L, Rosser J, Cacoub P, et al. Methylprednisolone in the treatment of Wegener's granulomatosis, polyarteritis nodosa and Churg-Strauss angiitis. APMIS Suppl 1990;19:52–3.
32. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747–71.
33. Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379:1613–20.
34. Dammacco F, Sansonno D, Han JH, et al. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study. Blood 1994;84:3336–43.
35. Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine 1973;52:535–61.
36. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.
37. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187–98.
38. De Groot K, Adu D, Savage CO. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. Nephrol Dial Transplant 2001;16:2018–27.
39. de Groot K, Harper L, Jayne DR, et al, EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.

40. Pillebout E, Alberti C, Guillevin L, et al. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein purpura. Kidney Int 2010;78:495–502.
41. Terrier B, Semoun O, Saadoun D, et al. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis Rheum 2011;63:1748–57.
42. Maltzman JS, Koretzky GA. Azathioprine: old drug, new actions. J Clin Invest 2003;111:1122–4.
43. Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007; 56:2789–97.
44. Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309–18.
45. Spiera RF, Mitnick HJ, Kupersmith M, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol 2001;19:495–501.
46. Jover JA, Hernandez-Garcia C, Morado IC, et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. Ann Intern Med 2001;134: 106–14.
47. Pagnoux C, Mahr A, Hamidou MA, et al, for the French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790–803.
48. Fulton B, Markham A. Mycophenolate mofetil. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in renal transplantation. Drugs 1996;51:278–98.
49. Hiemstra TF, Walsh M, Mahr A, et al, European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381–8.
50. Geetha D, Jin Q, Scott J, et al. Comparisons of guidelines and recommendations on managing antineutrophil cytoplasmic antibody-associated vasculitis. Kidney Int Rep 2018;3(5):1039–49.
51. Ntatsaki E, Carruthers D, Chakravarty K. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306–9.
52. Yates M, Watts RA, Bajema IM. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.
53. Dougados M, Betteridge N, Burmester GR. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172–6.
54. De Souza AW, da Silva MD, Machado LS, et al. Short-term effect of leflunomide in patients with Takayasu arteritis: an observational study. Scand J Rheumatol 2012;41:227–30.
55. Metzler C, Miehle N, Manger K, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. Rheumatology 2007;46:1087–91.
56. Jayne DR, Gaskin G, Rasmussen N, et al, on behalf of the European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180–8.

57. Walsh M, Merkel PA, Peh CA, et al, PEXIVAS Investigators. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials 2013;14:73.
58. Levy JB, Turner AN, Rees AJ, et al. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med 2001;134:1033–42.
59. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;2:1055–8.
60. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315:341–7.
61. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633–9.
62. Jayne DR, Davies MJ, Fox CJ, et al. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet 1991;337:1137–9.
63. Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. Br J Rheumatol 1996;35:1150–3.
64. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 2000;93:433–9.
65. Martinez V, Cohen P, Pagnoux C, et al, French Vasculitis Study Group. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum 2008;58:308–17.
66. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
67. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.
68. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
69. Pugnet G, Pagnoux C, Terrier B, et al. Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. Clin Exp Rheumatol 2016;34(3 Suppl 97):S54–9.
70. Zaja F, De Vita S, Mazzaro C, et al. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood 2003;101:3827–34.
71. Sansonno D, De Re V, Lauletta G, et al. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood 2003;101:3818–26.
72. Roccatello D, Baldovino S, Rossi D, et al. Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis. Nephrol Dial Transplant 2004;19:3054–61.
73. Saadoun D, Resche-Rigon M, Sene D, et al. Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis. Ann Rheum Dis 2008;67:1431–6.
74. Terrier B, Saadoun D, Sene D, et al. Efficacy and tolerability of rituximab with or without PEGylated interferon alfa-2b plus ribavirin in severe hepatitis C virus-related vasculitis: a long-term followup study of thirty-two patients. Arthritis Rheum 2009;60:2531–40.

75. Ignatova TM, Kozlovskaya LV, Gordovskaya NB, et al. Hepatitis C virus-associated cryoglobulinemic vasculitis: a 20-year experience with treatment. Ter Arkh 2017;89:46–52 [in Russian].
76. Booth A, Harper L, Hammad T, et al. Prospective study of TNFα blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004;15:717–21.
77. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology 2002;41:1126–32.
78. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351–61.
79. De Menthon M, Cohen P, Pagnoux C, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. Clin Exp Rheumatol 2011;29:S63–71.
80. Seror R, Baron G, Hachulla E, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis 2014;73(12):2074–81.
81. Mekinian A, Neel A, Sibilia J, et al. Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. Rheumatology 2012;51:882–6.
82. Frohnert PP, Sheps SG. Long-term follow-up study of periarteritis nodosa. Am J Med 1967;43:8–14.
83. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism Systemic Vasculitis Task Force. Ann Rheum Dis 2008;67:1004–10.
84. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84.
85. de Leeuw K, Kallenberg C, Bijl M. Accelerated atherosclerosis in patients with systemic autoimmune diseases. Ann N Y Acad Sci 2005;1051:362–71.
86. Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 2010;69:1036–43.
87. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest 2002;110:955–63.
88. Little MA, Al-Ani B, Ren S, et al. Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. PLoS One 2012;7:e28626.
89. Kain R, Exner M, Brandes R, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med 2008;14:1088–96.
90. Popa ER, Stegeman CA, Kallenberg CG, et al. *Staphylococcus aureus* and Wegener's granulomatosis. Arthritis Res 2002;4:77–9.
91. Xing GQ, Chen M, Liu G, et al. Complement activation is involved in renal damage in human antineutrophil cytoplasmic autoantibody associated pauci-immune vasculitis. J Clin Immunol 2009;29:282–91.
92. Popa ER, Franssen CF, Limburg PC, et al. In vitro cytokine production and proliferation of T cells from patients with anti-proteinase 3- and antimyeloperoxidase-associated vasculitis, in response to proteinase 3 and myeloperoxidase. Arthritis Rheum 2002;46:1894–904.

93. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003;349:160–9.
94. Lamprecht P. Off balance: T-cells in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. Clin Exp Immunol 2005;141:201–10.
95. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9.
96. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis 2012;71:955–60.
97. Faurschou M, Westman K, Rasmussen N, et al. Brief report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3472–7.
98. Morishita KA, Moorthy LN, Lubieniecka JM, et al. Early outcomes in children with antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2017;69:1470–9.
99. Sacri AS, Chambaraud T, Ranchin B, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. Nephrol Dial Transplant 2015;30 Suppl 1:i104–12.
100. Ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis 2015;74:1636–44.
101. Golumbek P. Pharmacologic agents for pediatric neuroimmune disorders. Semin Pediatr Neurol 2010;17:245–53.
102. Graus F, Titulaer MJ, Balu R, et al. A clinical approach of autoimmune encephalitis. Lancet Neurol 2016;15:391–404.
103. Elbers J, Halliday W, Hawkins C, et al. Brain biopsy in children with primary small-vessel central nervous system vasculitis. Ann Neurol 2010;68:602–10.
104. Torres J, Loomis C, Cucchiara B, et al. Diagnostic yield and safety of brain biopsy for suspected primary central nervous system angiitis. Stroke 2016;47:2127–9.
105. De Boysson H, Arquizan C, Touze E, et al. Treatment and long-term outcomes of primary central nervous system vasculitis. Stroke 2018;49:1946–52.
106. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol 2009;66:704–9.
107. Salvarani C, Brown RD Jr, Christianson TJH, et al. Primary central nervous system vasculitis associated with lymphoma. Neurology 2018;90:e847–55.
108. Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 2007;130:3091–101.
109. Singhal AB, Topcuoglu MA, Fok JW, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. Ann Neurol 2016;79:882–94.
110. Twilt M, Benseler SM. Central nervous system vasculitis in adults and children. Handb Clin Neurol 2016;133:283–300.
111. Cellucci T, Benseler SM. Central nervous system vasculitis in children. Curr Opin Rheumatol 2010;22:590–7.
112. Twilt M, Benseler SM. The spectrum of CNS vasculitis in children and adults. Nat Rev Rheumatol 2012;8:97–107.

113. Hutchinson C, Elbers J, Halliday W, et al. Treatment of small vessel primary CNS vasculitis in children: an open-label cohort study. Lancet Neurol 2010;9: 1078–84.
114. Deng J, Fang G, Wang XH, et al. Small vessel-childhood primary angiitis of the central nervous system: a case report and literature review. Zhonghua Er Ke Za Zhi 2018;56:142–7.
115. Collins MP, Dyck PJ, Gronseth GS, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J Peripher Nerv Syst 2010;15:176–84.
116. Hadden RDM, Collins MP, Zivkovic SA, et al, the Brighton Collaboration Vasculitic Peripheral Neuropathy Working Group. Vasculitic peripheral neuropathy: case definition for collection analysis, and presentation of immunization safety data. Vaccine 2017;35:1567–78.
117. Said G, Lacroix C, Fujimura H, et al. The peripheral neuropathy of necrotizing arteritis: a clinicopathologic study. Ann Neurol 1988;23:461–5.
118. Kernohan JW, Woltman HW. A clinicopathologic study with special reference to the nervous system. Arch Neurol Psychiatry 1938;39:655–86.
119. Torvik A, Berntzen AE. Necrotizing vasculitis without visceral involvement. Postmortem examination of three cases with affection of skeletal muscles and peripheral nerves. Acta Med Scand 1968;184:69–77.
120. Dyck PJ, Benstead TJ, Conn DL, et al. Nonsystemic vasculitic neuropathy. Brain 1987;110:843–53.
121. Pagnoux C, Seror R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum 2010;62:616–26.
122. Atkinson MA, Caclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994;331:1428–36.
123. Grimaldi LME, Mertini G, Braghi S, et al. Heterogeneity of autoantibodies in stiffman syndrome. Ann Neurol 1993;34:57–64.
124. Younger DS. Diabetic neuropathy: a clinical and neuropathological study of 107 patients. Neurol Res Int 2010;2010:140379.
125. Dyck PJ, Norell JE, Dyck PJ. Non-diabetic lumbosacral radiculoplexus neuropathy: natural history, outcome and comparison with the diabetic variety. Brain 2001;124:1197–207.