**When Should Immunosuppressants Be Prescribed to Treat Systemic Vasculitides?**

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**Abstract**

Steroids and immunosuppressants are indicated to treat systemic vasculitides. However, the therapeutic strategy is different from one disease to the other. Treatment choice should be adapted to the predictable outcome, severity, pathogenic mechanisms and patient’s general condition. In polyarteritis nodosa, Churg Strauss syndrome, and microscopic polyangiitis we have demonstrated that immunosuppressants should not be systematically prescribed. Immunosuppressants should be only prescribed in the most severe patients, when factors of poor prognosis are present. In Wegener’s granulomatosis, immunosuppressants should be systematically prescribed together with steroids. The optimal treatment duration is of 12 months for polyarteritis nodosa and Churg-Strauss syndrome. A more prolonged treatment is mandatory in Wegener’s granulomatosis, at least 18 months. The new therapeutic strategies comprise also new immunosuppressants and new immunomodulating agents which could replace or be associated to the “older drugs”

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**Key words:** vasculitis, immunosuppressants

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**Introduction**

In 1979, Fauci et al (1) demonstrated the efficacy of adjunctive cyclophosphamide (CYC) in patients whose vasculitis was not controlled with corticosteroids (CS) alone. The combination of CS and CYC has since been widely prescribed to treat polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and Wegener’s granulomatosis (WG). Nevertheless, many points concerning the use of CYC remained to be clarified: dose, duration, route of administration, associated treatments. A new era has also been opened by new agents originally designed for the field of transplantation and anti-cytokines which appear to be promising drugs to treat several rheumatic diseases.

The decision to prescribe immunosuppressants should also be adapted to several factors and optimization achieved after careful analysis of classification, predictable outcome, etiology, pathogenesis, severity, age and organ(s) involved. The prospective studies on PAN, MPA and CSS organized by the French Vasculitis Study Group (FVSG), examined the indications of CYC and, based on the results obtained and those reported in the literature, we review herein the therapeutic strategies now being applied to treat severe systemic vasculitides.

**Classification**

Inflammation and necrosis of blood-vessel walls are characteristic of systemic vasculitides. All sizes of blood vessels from the aorta to capillaries may be affected by the vasculitic process. Since the first description by Kussmaul and Maier (2), different vasculitides have been identified and different classification systems have been proposed. The American College of Rheumatology has defined different classification criteria for vasculitides (3–5) but the classification that has been unanimously adopted by the scientific and medical community to differentiate PAN from MPA, is the Chapel Hill Nomenclature (6).

**Predictable Outcome**

The outcome of vasculitis differs from one disease to another and the relapse rate also varies, from 5% for hepatitis B virus-related PAN (HBV-PAN) (7) to 23.4% for CSS (8), 34.1% for MPA (9) and more than 50% in WG (10, 11). The duration of treatment should probably be determined, at least in part, according to the risk of relapse. Shorter-term treatments might be suitable for mild forms of PAN, which is a “one-shot-disease”, but not for the most severe forms, for
which 1 year of treatment seems to prevent relapses. For WG, the prolonged therapy presently recommended, 18 to 24 months, does not seem to be able to lower the relapse rate below 50%, although treatments lasting less than 1 year are almost always associated with a high relapse rate, ranging from 50 to 100%.

**Etiology**

The etiologies of some forms of vasculitides have been identified (12), with infections, viral or bacterial, proven or suggested. HBV is considered to be the etiologic agent for a minority of patients with systemic vasculitides (less than 1% in Europe since the dissemination of vaccination and the increased safety of blood transfusion), though it has been considered to be of major importance in PAN and held responsible for the disease in more than one-third of the patients (7): Human immunodeficiency virus (HIV), parvovirus B19 and Epstein-Barr virus (EBV) have been observed in rare cases and thus should be actively sought. Hepatitis C virus (HCV) is now considered to be the etiologic agent for more than 90% of the patients with mixed cryoglobulinemia (14, 15). Treatments recommended for virus-associated vasculitides are based on neutralizing the virus, combined with plasma exchange (PE) for HBV-PAN (7) and in some patients affected by severe manifestations of HCV-related cryoglobulinemia vasculitis (14, 15).

These patients can take steroids only for a short period, and immunosuppressants are contraindicated because both stimulate viral replication and can favor vasculitis relapses. Immunosuppressants are prescribed only to patients who do not respond to the antiviral strategy, or those with glomerulonephritis associated with cryoglobulinemia vasculitis.

**Disease Severity**

The indications of immunosuppressants are different for WG and other systemic vasculitides. In WG, CYC is indicated for all the patients with systemic manifestations. In other vasculitides, like PAN, CSS or MPA, the choice is not so clear and we now recommend adapting the treatment to disease severity.

**First-line therapy**

It now seems reasonable to adapt the initial treatment to the severity of the vasculitis and not to propose systematically a standard treatment. To help the clinician choose the most effective therapy and to avoid overtreatment, we have established a five-factor score (FFS), which has significant prognostic value (16) and whose parameters, defined as below, were responsible for higher mortality: proteinuria >1 g/day, renal insufficiency (creatininemia ≥140 μmol/l), cardiomyopathy, gastrointestinal (GI) manifestations and central nervous system (CNS) involvement. When FFS=0, mortality at 5 years was 12%; when FFS=1, mortality was 26%; when FFS≥2, mortality was 46%. In a study on 278 patients (17) presenting with PAN, MPA or CSS, we demonstrated that the combination of CYC and CS was beneficial for patients with an FFS≥2. The patients who died from severe vasculitides had more often been treated with CS than with the combined regimen. Other criteria, like the Birmingham vasculitis activity score (BVAS) (18), are also used to determine the intensity of treatment and are being tested in the prospective trials proposed by the European Vasculitis (EUVAS) group.

**Indications of CS and CYC in PAN and CSS**

The prognoses of the different vasculitides have been transformed by CS and immunosuppressive drugs, especially CYC. CS alone has increased the 5-year survival rate from 10% for untreated patients to about 55% in the mid-to-late 1970s (19).

**CS**

The initial management of PAN without HBV infection should include high doses of CS. The administration of methylprednisolone pulses (usually 15 mg/kg IV over 60 minutes repeated at 24-h intervals for 1 to 3 days) has become widely used at the initiation of therapy for severe systemic vasculitis because of its rapid action and relative safety, especially in the presence of life-threatening organ involvement or the extension phase of mononeuritis multiplex. Dosing of pulse methylprednisolone is empirical and doses below 1,000 mg may be as effective. CS are given at the dose of 1 mg/kg/day of prednisone or its equivalent of methylprednisolone. CS can be prescribed in a single morning dose or in two daily doses. After 1 month of the full dose, the prednisone dose should be progressively decreased and, in the absence of relapse, CS can be stopped after 9 to 12 months. When combined with CYC, prednisone dose tapering should be more rapid to reduce the number of infectious complications. The EUVAS group recommends the rapid tapering of the prednisone dose for all antineutrophil cytoplasm antibody (ANCA)-associated vasculitides.

Decreasing treatment intensity while maintaining the therapeutic effect is now a major concern for clinicians, since it is likely that some patients have been overtreated. It is probable that patients without factors of poor prognosis (FFS=0) at the time of diagnosis could be successfully treated with prednisone alone and CYC administered only as the second-line treatment in the case of persistent disease activity or relapse despite CS therapy. A similar therapeutic scheme was tested in one of our previous trials (20). Despite the high relapse rate observed in patients treated with prednisone alone, the 7-year survival rate was 79%, very similar to that observed for other patients also receiving immunosuppressive agents.

**CYC**

For PAN and CSS patients with factors of poor prognosis (FFS≥1) (16), CYC is indicated and IV pulses should be preferred to oral administration (21). The IV route gives a more
rapid clinical response than oral CYC which is important in patients with active disease. When compared, the two CYC regimens were equally effective at controlling disease activity. Oral CYC has been successfully introduced when IV pulses failed to control disease activity or for relapse within the first 6 months of treatment (22). Treatment duration with CS and CYC should not exceed 1 year. To reduce toxicity resulting from prolonged CYC therapy, shorter therapeutic protocols were evaluated (23) and, for severe PAN/MPA, a regimen comprising 12 pulses of CYC provided better control; and fewer relapses and deaths occurred. Pulse CYC therapy is now being used more frequently for systemic necrotizing vasculitides and should, in our opinion, be preferred over oral CYC, for first-line therapy. The CYC content of each pulse, as well as the total number and frequency of the pulses, should be adjusted to the patient’s condition, renal function, hematological data and the disease’s response to prior therapies, including previous CYC pulses. The CYC-pulse dose recommended in our protocols is 0.6 g/m² delivered monthly for 1 year. Higher IV CYC doses may be particularly dangerous in patients with renal insufficiency, suggesting that dose adjustment according to renal function would be prudent (24). Intense hydration and, for some authors, the use of sodium 2-mercapto-ethanesulfonate (mesna) are recommended during pulse therapy, despite some sometimes severe allergic reactions. Pulse CYC therapy allows a lower cumulative dose to be given and exposes the patient to less potential toxicity for shorter periods.

**Treatment of WG**

CS are common to every treatment regimen for systemic vasculitides. We will therefore concentrate on cytotoxic agents. For WG, a consensus has not yet been reached concerning CYC, even though its indication is universally accepted. The oral route is prescribed at 2 mg/kg/d (10). The dose should adapted according to the therapeutic response, the occurrence of side effects, renal function and age. The overall treatment duration for WG varies but should last at least 18 months and should reflect the therapeutic strategy applied and maintenance regimen choices. EUVAS group obtained equivalent results with 3 months of oral CYC followed by 12 months azathioprine or 12 months of oral CYC (25).

CYC pulses, have also been used every 3 to 4 weeks, 0.5 to 0.7 g/m² (11, 26). The clinical results were comparable and showed that administration gave results comparable to those observed with the oral route. However, the number of relapses was high after stopping treatment (11). In our opinion, pulse treatment is effective in obtaining remission but is not able to maintain it. Other therapeutic strategies should therefore be prescribed to maintain remission. Should pulses fail, oral CYC can be given successfully. Conversely, pulse CYC is usually less or not effective when administered after failure of oral treatment.

Although oral CYC is effective for the treatment of vasculitic disease, it has a low therapeutic/toxic index and severe side effects minimize the therapeutic benefit of using it. Major side effects associated with daily CYC administration include hemorrhagic cystitis, bladder fibrosis, bone marrow suppression, ovarian failure, neoplasm (bladder cancer and hematological malignancies). Long-term side effects, especially the risk of developing cancer, are correlated with the cumulative CYC dose. Severe infections represent a major cause of mortality of patients with systemic vasculitis, especially while they are receiving high doses of CS with adjunctive immunosuppressive agents. Since maximal immunosuppression is given at the beginning of treatment, prevention of opportunistic infections, like *Pneumocystis carinii* pneumonia, may be necessary and should be prescribed on an individual basis.

**Treatment of MPA**

We now recommend treating MPA with poor-prognosis factors like WG, based on the presence of putative common pathogenetic mechanisms and the preliminary results of ongoing trials.

Considering the high frequency of renal involvement in MPA, most of the patients should be considered as having factors of poor prognosis and treated intensively with high-dose CS and CYC. A therapeutic scheme, combining CYC for induction therapy and azathioprine for maintenance therapy once remission is achieved (usually after 4 to 6 months), can be proposed. The clinical presentation of fulminant MPA is usually that of pulmonary-renal failure. Treatment of massive alveolar hemorrhage requires immediate fluid resuscitation, with hemodynamic and respiratory support. Deterioration of renal function often necessitates hemodialysis. The prognosis of fulminating MPA, like other vasculitides, is poor. Savage et al (27) reported 34 MPA patients, whose actuarial survival and kidney survival at 5-year follow-up were, respectively, 65 and 55%. Two-thirds of the deaths had been caused by active vasculitis complicated by renal failure and lung hemorrhage or were due to treatment side effects. Age over 50 years and severe creatininemia >500 μmol/l are factors of poor prognosis. The high number of relapses that can occur in patients with MPA could justify prolonged immunosuppressive treatment.

A high percentage of MPA patients who relapse do so when treatment is discontinued, but relapses during treatment are also frequent, particularly when the dose is being tapered. Relapses are generally milder than the initial disease. However, relapses can occur with major organ involvement. In patients who are still on first-line therapy, mild relapses occurring during dose-tapering might be managed by a transient increase of the CS dose. Major relapses may require a return to initial doses and introduction of other treatments, oral CYC, new drugs (see below). PE could also be considered when treatment fails.

**Miscellaneous treatments**

**Plasma exchanges**

There is presently no argument to support the systematic...
prescription of PE at the time of diagnosis of PAN without HBV infection, even for patients with factors of poor prognosis. However, PE can be a useful tool, as second-line treatment, in PAN refractory to conventional therapy. For patients with crescentic glomerulonephritis responsible for severe renal insufficiency (creatininemia>500 µmol/l), Pusey and coworkers (28), unlike others, consider that PE can improve renal function and enable patients to stop dialysis. This hypothesis is now being tested through a prospective controlled trial comparing patients ANCA-positive vasculitides and presenting renal insufficiency (>500 µmol/l) at entry. The preliminary results of EUVAS group prospective trial showed that, at 3 months, the number of dialysis-dependent patients was significantly lower in the PE-group treated vs the group receiving methylprednisolone pulses (unpublished data). Those results need to be confirmed by the final analysis.

**Intravenous immunoglobulins**

Interest in the use of IVIg to treat systemic vasculitis was stimulated by their successful prevention of coronary artery aneurysms in Kawasaki disease (29). The obvious advantage of IVIg is that they generate few severe side effects. IVIg have essentially been used in WG and MPA. Jayne et al reported the results of an open study on vasculitis patients (30): all of them appeared to improve, with sustained benefit and reduced requirement for immunosuppression for most of them. However, IVIg cannot be used in place of immunosuppressants as a first-line therapy. IVIg could be prescribed for patients with disease resistant to CS and immunosuppressants, in place of or in combination with the previous treatments. IV Ig could also be tested as maintenance treatment instead of immunosuppressants, but no data on this point are available.

**Other immunosuppressive agents; new drugs**

Azathioprine is commonly used as maintenance therapy, and seems to be effective and well tolerated. It induces fewer long-term side effects than CYC. The initial dose ranges from 2 to 3 mg/kg/day. The dose should be adapted as described above for CYC. The EUVAS group obtained comparable results at 18 months for patients with ANCA-related vasculitides (25) given 12 months of oral CYC then azathioprine or 3 months of CYC followed by oral azathioprine.

Methotrexate has also been proposed for maintenance or relapsing patients (31). The initial dose is 0.3 mg/kg, delivered once weekly. The efficacy is inferior to that of CYC but good results have been obtained and this drug is now being evaluated through prospective trials FVSG. However, methotrexate is also responsible for side effects, usually minor: liver toxicity, hypersensitivity pneumonia, and transient bone-marrow failure. Langford et al (31) systematically treated WG patients in CS-induced remission with methotrexate maintenance. The remission was obtained after 3 months and it was possible to stop therapy after 8 months, but 16% of the patients relapsed.

Mycophenolate mofetil or deoxyspergualine has been tested in a very limited number of patients for maintenance treatment, relapse or vasculitis refractory to CS and CYC. The initial results have been promising but cannot be confirmed at present.

Despite favorable anecdotal reports, intensive chemotherapy followed by autologous bone-marrow transplantation cannot be recommended, for severe vasculitis. Anti-tumor necrosis factor (TNF) monoclonal antibodies (infliximab or etanercept) have been successfully prescribed in patients with severe relapses or multidrug refractory vasculitides (32). Although, the preliminary results have been promising, it seems probable that anti-TNF antibodies cannot replace immunosuppressants and that the two agents should be combined.

Immunosuppressants are the fundamental treatment for most systemic necrotizing vasculitides. They are able to control the most severe diseases and to prevent relapses. However, their side effects remain a major concern and limit their widespread use. Treatment optimization is the objective of most prospective trials and new strategies include the evaluation of new drugs, as well as the combination and sequential administration of drugs from different pharmacological families. Although not fully satisfactory, this approach has dramatically increased the survival rate of patients with vasculitis.

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