Immunosuppressants in Systemic Necrotizing Vasculitides

Loïc Guillevin MD

Department of Internal Medicine, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Nord, Bobigny, France

Key words: immunosuppressants, polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, cyclophosphamide

IMAJ 2001;3:749–754

Immunosuppressants have dramatically improved the prognosis of systemic vasculitides. The survival outcome of patients in the polyarteritis nodosa group 5 years before the treatment era was 13%, whereas half of the patients survived when steroids were prescribed [1]. However, the benefit provided by immunosuppressants in PAN and Churg-Strauss syndrome was not so clear: Cohen et al. [2] did not observe any benefit from cyctotoxic agents, but Leib and colleagues [3] reported an 80% survival at 5 years. In contrast, for systemic Wegener's granulomatosis the benefit of treatment with cyclophosphamide has been clearly established. In fact, while immunosuppressants may be beneficial to a large number of patients, their prescription does not respond to a common rule and standardization should take into account some principles determined from prospective trials.

In this paper, under the term "immunosuppressants" we will consider cytotoxic drugs and not steroids, which also possess the power of immunosuppression, especially when administered in high dose intravenous pulses or over several months. They decrease the total number of B and T cells and the production of antibodies. Given alone or in association with cytotoxic drugs, they facilitate the occurrence of infectious side effects, especially viruses (herpes zoster virus for instance) or *Pneumocystis carinii* infection [4].

When deciding on treatment, it is crucial that the clinician carefully evaluate the respective immunosuppressive power of steroids and cytotoxic agents. Differences in the strategies adopted by specialists in the field frequently derive from a different appreciation of the respective roles of steroids and cytotoxic drugs. In the United States, the usual practice is to treat patients with alternate-day steroids following short intensive oral treatment. In many European countries, steroids are administered daily but rapidly tapered to reduce the number and severity of side effects. In France, the clinical practice for decades was to administer steroids at an initial dose of 1 mg/kg/day for one month [5] and then to progressively and very slowly taper the treatment. These different strategies indicate that treatment with cytotoxic agents differs from one country to another: in the USA, patients received high and prolonged doses of oral cyclophosphamide [6], while in many European countries, CYC was given orally but within shorter periods and maintenance treatment consisted of fewer cytotoxic drugs [7]. In France, the intensity of CS treatment facilitated the administration of lower dose cyclophosphamide and a general recommendation to use pulses as the first cytotoxic treatment [8]. As with all things, the "truth" probably lies somewhere in the middle. In this paper, we will try to establish recommendations that could become a consensus.

CYC and CS in medium-sized artery vasculitides

Cyclophosphamide is not recommended for every medium-sized vasculitis. In Kawaski's disease, the recommended treatment comprises high dose immunoglobulins [9]. In PAN, the administration of CYC depends on the etiology of the disease. When PAN is the consequence of hepatitis B virus infection, immunosuppressants are contraindicated as the first-line treatment [10] and the reference treatment is a combination of antiviral treatment (lamivudine, interferon gamma) and plasma exchange [10].

Initial therapeutic choice

It is now considered feasible to adapt the initial treatment to the severity of the vasculitis, instead of routinely proposing a standard treatment. To help the clinician choose the most effective therapy and to avoid over-treatment, we have established [11] a five-factor score that has significant prognostic value and whose parameters were responsible for a higher mortality. These parameters include: proteinuria > 1 g/day, renal insufficiency (creatininemia > 140 μmol/L), cardiomyopathy, gastrointestinal manifestations, and central nervous system involvement. Mortality at 5 years was 12% when FFS = 0, 26% when FFS = 1, and 46% when FFS = 2 or more. In a recent study of 278 patients presenting with PAN, microscopic polyangiitis or Churg-Strauss Syndrome, we demonstrated that

PAN = polyarteritis nodosa

CYC = cyclophosphamide
CS = corticosteroids
FFS = five-factor scale

the association of cyclophosphamide and corticosteroids was beneficial for patients with a FFS of 2 or more. The patients who died from severe vasculitides had more often been treated with CS than with the association of CS and CYC. Other criteria, like the Birmingham vasculitis activity score [12], are also used to determine the intensity of treatment and are currently being tested in prospective trials conducted by the European Vasculitis (EUVAS) group.

Association of CS and CYC

The indications of prolonged treatment with CS and cytotoxic agents are limited to the vasculitides that are not due to viral infection.

- ***Steroids***

The initial management of PAN without hepatitis B infection could include high doses of CS. The use of methylprednisolone pulses (usually 15 mg/kg IV over 60 min repeated at 24 hour intervals for 1–3 days) at the initiation of therapy for severe systemic vasculitis is popular 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 empiric and doses below 1,000 mg may be as effective. CS is given at a dose of 1 mg/kg/day 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 9–12 months. When combined with CYC, prednisone dose tapering should be more rapid to reduce the number of infectious complications. The EUVAS group recommends that all vasculitides would benefit from the rapid tapering of the prednisone dose.

Decreasing treatment intensity while maintaining the therapeutic effect is now a major concern for clinicians, since some patients may have been over-treated. It is likely that patients without factors of poor prognosis (FFS = 0) at the time of diagnosis could be successfully treated with prednisone alone, with CYC administered only as 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 [13] and in one of our ongoing trials devised for good-prognosis vasculitides. Despite the high relapse rate observed in patients treated with prednisone alone, the 7 year survival rate was 79%, very similar to that observed in other patients also receiving immunosuppressive agents.

- ***Cyclophosphamide***

CYC is indicated in patients with factors of poor prognosis (FFS$\geqslant$1). An IV bolus is preferred to oral administration since the IV route enables a more rapid clinical response than oral CYC and is important in patients with active disease. When compared [14], the two CYC regimens were equally effective at controlling disease activity. Oral CYC was successfully introduced when IV pulses failed to control disease activity or in the case of relapse within the first 6 months of treatment [15]. Treatment duration with CS and CYC should not exceed 1 year. To reduce toxicity resulting from prolonged CYC therapy, further studies (not published) evaluating shorter therapeutic protocols were undertaken and, for severe PAN/MPA, a regimen comprising 12 pulses of CYC was deemed preferable. Pulse CYC therapy is now being used increasingly for systemic necrotizing vasculitis [14,16] and, in our opinion, is preferable to oral CYC. The CYC content of each pulse, as well as both the total number and frequency of the pulses, should be adjusted according to the patient's condition, renal function, hematological data, and the disease's response to previous therapies including previous CYC pulses [17]. Initial doses range from 0.5 to 2.5 g at intervals of 1 week to 1 month, and up to 3 months for maintenance therapy. In the protocols of the French Vasculitis Study Group [14], the CYC pulse dose was 0.6 g/m^2 delivered monthly for 1 year. High dose intravenous CYC may be particularly dangerous in patients with renal failure, suggesting that dose adjustment according to renal function would be prudent. Recent studies by our group also show that the pharmacokinetics of CYC and its metabolite, when compared at the first and fifth infusion, vary significantly [18]. These differences could explain a different clinical response to the treatment and the recurrence of clinical manifestations in some patients, however it is too early to use pharmacokinetic parameters for dose adjustment. Intense hydration and, for some authors [19,20], the use of sodium 2-mercapto-ethanesulfonate (mesna) is recommended during pulse therapy, despite some allergic reactions that are sometimes severe. Pulse CYC therapy allows a lower cumulative dose to be given and exposes the patient to less potential toxicity for shorter periods.

CYC and CS in small-sized artery vasculitides

This group of vasculitis, like others, is not homogeneous and different pathogenic mechanisms are involved in their occurrence. Mixed cryoglobulinemia is an immune complex disease due to hepatitis C virus infection in more than 80% of patients [21]. Like other vasculitides due to viruses, immunosuppressants are not indicated as a first-line treatment and their prescription is restricted to patients with severe, relapsing or resistant forms of the disease.

Antineutrophil cytoplasmic antibodies-related vasculitides belong to the group of small-sized vessel vasculitides. The strategy adopted by the EUVAS is to treat all these vasculitides in a common manner, independent of their severity and clinical form. While this approach may be valid for severe disease with an FFS > 1, it does not seem suitable for benign forms, except for Wegener's granulomatosis which requires a more extensive

EUVAS = European Vasculitis (group)

MPA = microscopic polyangiitis

prescription of immunosuppressants. The consensus has not yet been established for mild forms of MPA and CSS, but the preliminary results of our prospective trials (not published) show that steroids alone are able to control the course of both diseases. Physicians attending to CSS patients have observed that the response to steroids was easily and quickly obtained, sometimes within a few days, and more than 90% of our patients do not need additional immunosuppression (not published).

Treatment of Wegener's granulomatosis

A consensus has not been reached concerning CYC treatment for WG, even though its indication is universally accepted. The oral route is prescribed at 2 mg/kg/day [6], and the dose can be adapted depending on the therapeutic response, occurrence of side effects, renal function, and age. Treatment duration varies from one country to another: 18 months in France and the USA [6,22], and 3–9 months in Britain [23]. It is now clear that the duration of treatment with cyclophosphamide should be chosen as a part of the general strategy to treat the disease and that the choice of the maintenance regimen is essential to establish a complete and prolonged remission.

Pulse CYC has also been proposed [22], with CYC given every 3–4 weeks at a dose of 0.5–0.7 g/m^2. The clinical results were comparable to those observed with the oral route. Nevertheless, the number of relapses was high after treatment was discontinued. In our opinion, pulse treatment is effective in obtaining the 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 with a successful outcome [15]. Conversely, pulse CYC is usually less or not effective when administered after failure of oral treatment [24].

Although oral CYC is effective for the treatment of vasculitic disease, it has a low therapeutic/toxic index. Moreover, severe side effects minimize its therapeutic benefit. Major side effects associated with daily CYC administration include hemorrhagic cystitis, bladder fibrosis, bone marrow suppression, ovarian failure, and neoplasm (bladder cancer and hematological malignancies). Long-term side effects, especially the risk of developing cancer, are correlated with the cumulative dose of CYC. Severe infections represent a major cause of mortality among patients with systemic vasculitis, especially while they are receiving high doses of CS with adjunctive immunosuppressive drugs.

Treatment of microscopic polyangiitis

We now recommend that the treatment for WG be used for MPA patients with a FFS $\geqslant$ 1, 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 patients should be considered as having factors of poor prognosis and, accordingly, should be treated intensively with high dose CS and CYC. A therapeutic scheme could combine CYC for induction therapy and azathioprine for maintenance therapy once remission is achieved (usually after 4–6 months). The clinical presentation of fulminant MPA is usually that of pulmonary or 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. [25] reported on 34 MPA patients whose actuarial survival and kidney survival at 5 year follow-up were 65 and 55% respectively. Two-thirds of the deaths were due to active vasculitis complicated by renal failure and lung hemorrhage or to treatment side effects. Age over 50 and plasma creatinine > 500 μmol/L are also factors of poor prognosis [25]. 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 (34%) [26]. Relapses during treatment are also frequent, particularly when the dose is being tapered, but are generally milder than the initial disease. However, relapses can occur with major organ involvement. In patients who are still on initial therapy, mild relapses may be managed by a temporary increase of the CS dose. Major relapses may require a return to initial therapy and introduction of other treatments, oral CYC, and new drugs (see below). Plasma exchange could also be considered when treatment fails.

Other immunosuppressive agents: new drugs

Azathioprine

Azathioprine is commonly used as a maintenance therapy and seems to be effective and well tolerated [27]. It induces fewer long-term side effects than CYC. The initial dose ranges from 2 to 3 mg/kg/day and should be adapted as described above for CYC. In the EUVAS trial proposed for ANCA-related vasculitides [7], comparing 18 months CYC to 6 months CYC + 12 months azathioprine, the analysis at 18 months after inclusion showed a comparable response to treatment and number of relapses in both groups. A prolonged follow-up and a separate analysis in the long term of WG and MPA patients is needed to confirm the encouraging preliminary results.

Methotrexate

Methotrexate has also been proposed for maintenance [28,29] and for relapsing patients. The initial dose is 0.3 mg/kg delivered once weekly. Its efficacy is inferior to that of CYC but good results have been obtained and this drug is now being

WG = Wegener's granulomatosis

ANCA = antineutrophil cytoplasmic antibodies

evaluated through several prospective trials (National Institutes of Health and the French Vasculitis Study Group). In a recent prospective study, Langford for the NIH group [30] demonstrated the effectiveness of this drug in the maintenance treatment of WG. The side effects, although frequent, were minor and acceptable compared to other drugs. Nonetheless the treatment does have side effects: namely liver toxicity, hypersensitivity, pneumonia, and transient bone marrow failure. Langford [30] has systematically treated WG patients with methotrexate for remission maintenance. The treatment was effective but complications noted with other drugs were also observed. The EUVAS Group recently demonstrated in ANCA-related vasculitides that at 18 months the results were comparable when patients received 12 months of oral CYC then azathioprine, or 3 months of CYC followed by oral azathioprine [7].

Mycophenolate mofetil

Mycophenolate mofetil, deoxyspergualine and leflunomide have been tested in a very limited number of patients [31,32], always for maintenance treatment or in patients who relapsed or were refractory to the combination of CS and CYC The initial results are promising but cannot be extrapolated at this point. Some authors [33] propose intensive chemotherapy followed by autologous bone marrow transplantation but it is too early to comment on the long-term results of this treatment.

Anti-tumor necrosis factor antibodies

Recently, anti-TNF antibodies (infliximab) or analogues of the TNF receptors (etanercept) have been proposed for the treatment of systemic diseases and are approved for rheumatoid arthritis and Crohn's disease. Because TNF is involved in the pathogenesis of vasculitides, infliximab, anti-TNF antibodies and etanercept, an analogue of the TNF-receptor, are proposed in selected cases and are being tested in WG. It is too early to conclude what their potential role in this new therapeutic approach is, but promising short-term results have been obtained. When infliximab is prescribed an additional immunosuppressive treatment is mandatory to prevent the occurrence of antibodies directed against the drug, a humanized mouse antibody.

Intravenous immunoglobulins

Interest in the use of IVIGs to treat systemic vasculitis was prompted by their successful prevention of coronary artery aneurysms [9] in Kawasaki disease. The obvious advantage of IVIG is that it generates few severe side effects. IVIG has essentially been used in WG and MPA [34]. In their open study on 12 vasculitis patients, Jayne and Lockwood (34) reported an improvement in all the patients, with sustained benefit and reduced requirement for immunosuppression in 11 of them after a mean follow-up of 12 months. The mean ANCA level fell by 50%. Other strategies that can be applied include maintenance treatment in ANCA-related vasculitis, in place of immunosuppressants, and steroid sparing during the initial period of treatment. Further trials are needed to establish the indications of IVIG in vasculitides.

Monoclonal antibodies

Monoclonal antibodies that target T cells offer an alternative to conventional immunosuppressive drugs for the management of autoimmune diseases and have been used to treat systemic vasculitis [35], but this type of therapy needs further evaluation before it can be used more extensively in the future.

Non-pharmacologic treatments

Despite the use of immunosuppressants, a minority of patients do not respond adequately to the treatment or relapse soon or immediately after withdrawal. In such cases, other strategies are needed, such as an association of drugs, new drugs, or non-pharmacologic immunointervention.

Plasma exchange

There is presently no argument to support the routine prescription of plasma exchange at the time of diagnosis of PAN without HBV infection [13,36,37], even for patients with factors of poor prognosis [37]. However, plasma exchange can be a useful tool as a second-line treatment in PAN refractory to conventional therapy. For patients with crescentic glomerulonephritis leading to severe renal insufficiency (creatininemia > 500 μmol/L), Pusey and co-workers [38], unlike others [39,40], contend that plasma exchange can improve renal function and enable patients to stop dialysis. This hypothesis is now being tested through a prospective controlled trial.

Bone marrow transplant

The need for chemotherapy intensification associated with bone marrow infusion in systemic and autoimmune diseases is debated. A large number of patients with diseases like scleroderma, lupus, and multiple sclerosis have been thus treated and the preliminary results are encouraging in the very short term. The experience in vasculitides is very limited however. Apart from Bacon's report [33] on the successful treatment of a patient with WG, no other experiences have been published. We also successfully treated a patient affected with PAN-associated leukemia. Nevertheless, such experiences should remain limited since the majority of patients do not necessitate such treatment. In PAN, whose duration is usually brief and is associated with few relapses, bone marrow transplant should not be proposed even if intensive chemotherapy is sometimes indicated. In contrast, in chronic diseases like WG, bone marrow transplant could theoretically be indicated. Nevertheless, in addition to the indication of such treatment, other factors should be taken in account, such as the side effects of treatment as well as the ability to treat patients who

TNF = tumor necrosis factor
IVIG = intravenous immunoglobulin

underwent previous prolonged immunosuppressive treatments. We are therefore extremely cautious with regard to this therapeutic approach.

References

1. Frohnert P, Sheps S. Long term follow-up study of polyarteritis nodosa. *Am J Med* 1967;43:8–14.
2. Cohen R, Conn D, Ilstrup D. Clinical features, prognosis and response to treatment in polyarteritis. *Mayo Clin Proc* 1980;55:146–55.
3. Leib E, Restivo C, Paulus H. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med* 1979; 67:941–7.
4. Jarrousse B, Guillevin L, Bindi P, Hachulla E, Leclerc P, Nilson B, Remy P, Rossert J, Jacquot C. Increased risk of *Pneumocystis carinii* pneumonia in patients with Wegener's granulomatosis. *Clin Exp Rheumatol* 1993;11(6):615–21.
5. Guillevin L, Lhote F, Jarrousse B, Fain O. Treatment of polyarteritis nodosa and Churg-Strauss syndrome. A meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. *Ann Méd Interne (Paris)* 1992;143:405–16.
6. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Radem M, Fauci AS. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116(6):488–98.
7. Luqmani R, Jayne D, Group EVS. A multicentre randomised trial of cyclophosphamide versus azathioprine during remission in ANCA-associated systemic vasculitis (CYCAZAREM). *Arthritis Rheum* 1999;42(9,Suppl):928.
8. Guillevin L, Lhote F. Treatment of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum* 1998;41(12):2100–5.
9. Newburger J, Takahashi M, Burns J. Kawasaki syndrome with intravenous gammaglobulin. *N Engl J Med* 1986;315:341–7.
10. Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, Noel LH, Trépo C. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. *Medicine (Baltimore)* 1995;74(5):238–53.
11. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Cassassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17–28.
12. Luqmani R, Exley A, Kitas G, Bacon P. Disease assessment and management of the vasculitides. *Baillere's Clin Rheumatol* 1997;11: 423–46.
13. Guillevin L, Fain O, Lhote F, Jarrousse B, le Thi Huong Du, Bussel A, Léon A. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. *Arthritis Rheum* 1992;35:208–15.
14. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, Godeau P, Ruel M, Vidal E, Pointud M, Ducroix JP, Lasoued S, Christoforov B, Babinet P. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. *Br J Rheumatol* 1997;36:1290–7.
15. Généreau T, Lortholary O, Leclerq P, Grenet D, Tubery M, Sicard D, Caubarrere I, Guillevin L. Treatment of systemic vasculitis with cyclophosphamide and steroids: daily oral low-dose cyclophosphamide administration after failure of a pulse intravenous high-dose regimen in four patients. *Br J Rheumatol* 1994;33(10):959–62.
16. Adu D, Pall A, Luqmani RA, Richards NT, Howle AJ, Emery P, Michael J, Savage CO, Bacon PA. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *QJM* 1997;90(6):401–9.
17. De Vita S, Neri R, Bombardieri S. Cyclophosphamide pulses in the treatment of rheumatic diseases: an update. *Clin Exp Rheumatol* 1991;9:179–93.
18. Belfayol L, Guillevin L, Louchahi K, Perrin P, Cherrier P, Lortholary O, Bosio AM, Fauvelle F. Pharmacokinetics of cyclophosphamide in patients with systemic necrotizing angiitis. *Fundam Clin Pharmacol* 1994;8(5):458–62.
19. Gross WL. New developments in the treatment of systemic vasculitis. *Curr Opin Rheumatol* 1994;6(1):11–19.
20. Guillevin L, Lhote F. Classification and management of necrotising vasculitides. *Drugs* 1997;53(5):805–16.
21. Agnello V, Romain PL. Mixed cryoglobulinemia secondary to hepatitis C virus infection. *Rheum Dis Clin North Am* 1996;22(1):1–21.
22. Guillevin L, Cordier J, Lhote F, Cohen P, Jarrousse B, Royer I, Lesavre P, Jacquot C, Bindi P, Bielefeld P, Desson JF, Detree F, Dubois A, Hachulla E, Hoen B, Jacomy D, Seigneuric C, Lauque D, Stern M, Longy-Boursier M. 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.
23. Pusey CD, Gaskin G, Rees AJ. Treatment of primary systemic vasculitis. *Apmis Suppl* 1990;19(48):48–50.
24. Reinhold-Keller E, Kekow J, Schnabel A, Schwarz EM, Schmitt WH, Gross WL. Effectiveness of cyclophosphamide pulse treatment in Wegener's granulomatosis. *Adv Exp Med Biol* 1993;336(483):483–6.
25. Savage C, Winearls C, Evans D, Rees A, Lockwood C. Microscopic polyarteritis: presentation, pathology and prognosis. *QJM* 1985;56:467–83.
26. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Calard P, Amouroux J, Casassus P, Jarrousse B. Microscopic polyangiitis: clinical and laboratory findings in 85 patients. *Arthritis Rheum* 1999;42:421–30.
27. Cameron J. Renal vasculitis: microscopic polyarteritis and Wegener's granulomatosis. *Contrib Nephrol* 1991;94:38–46.
28. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. *Arthritis Rheum* 1992;35(11):1322–9.
29. de Groot K, Reinhold-Keller E, Tatsis E, Paulsen J, Heller M, Nolle B, Gross WL. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996;39: 2052–61.
30. Langford C. A staged approach in the treatment of Wegener's granulomatosis: induction with glucocorticoids and daily cyclophosphamide switching to methorexate for remission maintenance. *Arthritis Rheum* 1999;42:S284.
31. Nowack R, Birck R, van dWF. Mycophenolate mofetil for systemic vasculitis and IgA nephropathy [Letter]. *Lancet* 1997;349:9054.
32. Metzler C, Löw-Friedriech I, Reinhold-Keller E, Schmitt W, Gross W. Leflunomide, a new promising agent in maintenance of remission in Wegener's granulomatosis [Abstract]. *Clin Exp Immunol* 1998; 112:S154.
33. Bacon P, Exley A, Carruthers D. Immune ablation with peripheral stem cell rescue in Wegener's: systemic vasculitis [Abstract]. *Clin Exp Immunol* 1998;112:S156.

34. Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. *Br J Rheumatol* 1996;35(11):1150–3.
35. Mathieson P, Cobbold S, Hale G, Clark MR, Oliveira DM, Lockwood CM, Waldmann H. Monoclonal-antibody therapy in systemic vasculitis. *N Engl J Med* 1990;323:250–4.
36. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Généreau T, Léon A, Bussel A. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum* 1995;38(11):1638–45.
37. Guillevin L, Lhote F, Gherardi R. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: clinical aspects, neurologic manifestations, and treatment. *Neurol Clin* 1997;15(4):865–86.
38. Pusey C, Rees A, Evans D, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* 1991;40:757–63.
39. Guillevin L, Cevallos R, Durand Gasselin B, Lhote F, Jarrousse B, Callard P. Treatment of glomerulonephritis in microscopic polyangiitis and Churg-Strauss syndrome. Indications of plasma exchanges, meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis. *Ann Méd Interne (Paris)* 1997;148:198–204.
40. Madore F, Lazarus M, Brady H. Therapeutic plasma exchange in renal diseases. *J Am Soc Nephrol* 1996;7:367–86.

Correspondence: Dr. L. Guillevin, Département de Médecine Interne, Ancien Hôpital, Assistance Publique-Hôpitaux de Paris, Université Paris Nord, 125 rue de Stalingrad, 93000 Bobigny, France.
email: loic.guillevin@avc.ap-hop-paris.fr