Allergology International. 2007;56:105-111
DOI: 10.2332/allergolint.R-07-144

REVIEW ARTICLE

Therapeutic Strategies for Systemic Necrotizing Vasculitides

Loïc Guillevin[1] and Christian Pagnoux[1]

ABSTRACT
Treatments of vasculitides have progressed markedly over the past few decades. The first attempts to obtain better-adapted therapeutic strategies evaluated the indications of conventional drugs, and their abilities prolong survival and reduce the number of relapses, while decreasing the severity and number of side effects. Many prospective clinical trials were organized by the French Vasculitis Study Group and the European Vasculitis Study group, and have contributed to optimizing targeted treatment strategies. Recent therapeutic strategies include immunomodulating methods, like plasma exchanges, or products, like intravenous immunoglobulins, or, more recently, new agents called biotherapies. Some of them have achieved promising positive effects, for example, anti-CD20 monoclonal antibodies, and are now being evaluated in prospective trials.

KEY WORDS
ANCA, immunosuppressants, polyarteritis nodosa, vasculitis, Wegener's granulomatosis

INTRODUCTION

Over the past few decades, treatment of systemic necrotizing vasculitides (SNV) has become more effective and the outcomes of all these vasculitides improved. Several advances explain this improvement: better knowledge of the classification of these diseases, treatments adapted to their respective etiologies and pathogeneses when they could be determined, progress in the care of severe and life-threatening manifestations, treatment adapted to patient's condition and age. Herein, we review the different therapeutic strategies that are currently applied to patients and report on the new drugs that are currently being evaluated for SNV treatment.

CLASSIFICATION

Inflammation and necrosis of blood-vessel walls are characteristic of SNV. All sizes of blood vessels—from the aorta to capillaries—can be affected by the vasculitic process. Different vasculitides have been identified and several classification systems have been proposed. The American College of Rheumatology defined different classification criteria for vasculitides[1-3] but the classification that has been unanimously adopted by the scientific community to differentiate polyarteritis nodosa (PAN) from microscopic polyangiitis (MPA), is the Chapel Hill Nomenclature (Table 1).[4] This nomenclature defines, among small-sized-vessel vasculitides a group of diseases characterized by the presence of antineutrophil cytoplasm antibodies (ANCA): Wegener's granulomatosis (WG), MPA, Churg-Strauss syndrome (CSS) and renal-limited vasculitis. The frequency of ANCA positivity differs from one vasculitis to another: ANCA are present in more than 80% of WG patients,[5] around 75% of MPA[6] but only 40% of those with CSS.[7,8]

PREDICTIBLE OUTCOME

The outcomes of SNV also differ from one entity to another and their respective relapse rates also vary, from less than 10% for hepatitis B virus-related PAN (HBV-PAN)[9] to 23.4% for CSS,[10] 34.1% for MPA[6] and more than 50% for WG.[11] Treatment duration should probably be decided, at least in part, according to the risk of relapse. Shorter-term treatments might be suitable for mild forms of PAN. For WG, prolonged therapy does not seem able to lower the relapse rate below 50%,[11] although treatments given for less than 1 year are almost always associated with a high relapse rate, ranging from 50 to 100%.

[1]Department of Internal Medicine, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris-René-Descartes.
Correspondence: Loïc Guillevin, Department of Internal Medicine, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris-René-Descartes, 27 rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France.
Email: loic.guillevin@wanadoo.fr
Received 21 February 2007.
©2007 Japanese Society of Allergology

Table 1 Names and definitions adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides*.

Large-vessel vasculitides	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients over 50 years old and often is associated with polymyalgia rheumatica.*
Takayasu's arteritis	Granulomatous arteritis of the aorta and its major branches. *Usually occurs in patients younger than 50.*
Medium-sized vessel vasculitides	
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph-node syndrome. *Coronary arteries are often involved. Aorta and veins can be involved. Usually occurs in children.*
Small-vessel vasculitides	
Wegener's granulomatosis **	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles and/or arteries). *Necrotizing glomerulonephritis is common.*
Churg-Strauss syndrome **	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, associated with asthma and eosinophilia.
Microscopic polyangiitis ** (microscopic polyarteritis)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (*i.e.*, capillaries, venules and/or arterioles). *Necrotizing arteritis involving small- and medium-sized vessels can be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Henoch-Schönlein purpura	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (*i.e.*, capillaries, venules and/or arterioles). *Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.*
Cryoglobulin-associated vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (*i.e.*, capillaries, venules and/or arterioles), and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

* Adapted from[4]. Large vessels refers to the aorta and its largest branches directed toward major body regions (e.g. to the extremities and the head and neck); medium-sized vessels refers to the main visceral arteries (e.g. renal, hepatic, coronary and mesenteric arteries); small vessels refers to venules, capillaries, arterioles and the intraparenchymal distal arteries that connect with arterioles. Some small- and large-vessel vasculitides can involve medium-sized arteries, but large- and medium-sized — vessel vasculitides do not involve vessels smaller than arteries. Essential components are represented by normal type; italics represent usual, but not essential, components.

** Strongly associated with antineutrophil cytoplasm autoantibodies.

ETIOLOGIES

The etiologies of a few SNV cases have been identified, with viral or bacterial infections proven or considered likely. HBV is recognized as the etiological agent of a minority of patients with systemic vasculitides (less than 1%) but it could be of major importance in PAN for which it has been incriminated as being responsible for more than one-third of the cases.[9] Human immunodeficiency virus (HIV),[12] parvovirus B19 and Epstein-Barr virus have been observed in rare cases and thus should be actively sought. Hepatitis C virus (HCV) is now considered to be the etiological agent of mixed cryoglobulin-associated vasculitis in more than 90% of the patients.[13]

TREATMENT OF HBV- AND OTHER VIRUS-RELATED PAN

HBV-PAN

In the context of chronic hepatitis B, corticosteroids and immunosuppressive agents, despite having proven efficacy against the vasculitis symptoms, also have deleterious effects: they enhance virus replication, and, over the long term, they perpetuate chronic HBV infection and facilitate progression towards cirrhosis, which may be complicated later by hepatocel-

lular carcinomas.

Based on the efficacy of antiviral agents against chronic hepatitis and of plasma exchanges (PE) for PAN, we combined the two therapies to treat HBV-PAN. The rationale of the therapeutic sequence was as follows: initial corticosteroids to rapidly control the most severe life-threatening PAN manifestations, which are common during the first weeks of the disease, and their abrupt stoppage to enhance immunological clearance of HBV-infected hepatocytes and favor HBe antigen (Ag) to anti-HBe antibody (Ab) seroconversion; with PE to control the course of PAN.

In HBV-PAN, the combination of an antiviral agent (vidarabine, interferon-alpha 2b (IFNα2b) or, more recently, lamivudine) and PE gave excellent overall therapeutic results, and should be preferred to the more dangerous (in this setting) conventional regimens.[9] However, that strategy does not improve short-term survival compared to corticosteroids and cyclophosphamide (CYC), but increases the HBeAg-to-HBeAb seroconversion rate from 14.7% with conventional treatment to 49.4% when patients were treated with an antiviral agent and PE.[9]

HCV-RELATED CRYOGLOBULIN-ASSOCIATED VASCULITIS

This vasculitis is asymptomatic in the majority of patients but persists for decades and its duration could be a factor associated with the occurrence of clinical symptoms. No treatment is able to cure all cases of mixed cryoglobulin-associated vasculitis and an optimal therapeutic strategy has not yet been clearly defined. In asymptomatic patients, close monitoring could suffice but early treatment can also be considered. For patients with moderate symptoms (arthralgias, purpura, sensory peripheral neuropathy, for instance), a combination of IFNα and ribavirin or newer antiviral agents should be prescribed and may suffice to obtain clinical improvement and suppression of virus replication.[14] For patients with severe symptoms of mixed cryoglobulinemia, PE could be useful. Although PE are considered a symptomatic therapy, they are able to cure leg ulcers and to help reverse other manifestations. However, once started, PE cannot be discontinued for the majority of patients. Rituximab, an anti-CD20 monoclonal Ab, could be an effective treatment when combined with ribavirin and IFNα. Rituximab acts on the B-lymphocyte clone(s) producing cryoglobulin(s) and, simultaneously, the antiviral agent lowers or suppresses virus replication. This strategy is promising and can obtain vasculitis regression. At the moment, we have data on only a few small series of patients[15,16] and the results of prospective controlled trials would be a major contribution in this setting.

HIV-RELATED VASCULITIS

Although rarely observed, HIV has been identified as the cause of few rare cases of SNV, which mainly affected small-sized vessels. Most patients had skin, peripheral nerve or central nervous system involvement. Large-, medium- and small-sized arteries can be affected. The pathogenesis of virus-associated vasculitis is heterogeneous, but at least two general mechanisms have been incriminated: virus replication might induce direct injury of the vessel wall and vascular damage might be the result of an immune mechanism. These mechanisms may be cellular and/or humoral and include deposition of circulating immune complexes and/or their *in situ* formation.

Vasculitis has also been described during diffuse infiltrative CD8 lymphocytosis syndrome and angiocentric immunoproliferative lesions.

The therapeutic approach[12,17] should be adapted to the etiological factors: combining antiretroviral drugs and PE for vasculitis directly caused by HIV infection, or antiretroviral(s) in combination with another antiviral or antiparasite drug for vasculitis resulting from other opportunistic agents in HIV-positive patients. Usually, vasculitides observed during HIV infection are acute and, once remission has been obtained, do not relapse.

TREATMENT ACCORDING TO DISEASE SEVERITY

FIRST-LINE THERAPY

It is reasonable to adapt first-line therapy to SNV severity and not systematically prescribe a conventional regimen. To help the clinician choose the most effective therapy and to avoid overtreatment, we established the five-factor score (FFS),[18] which has significant prognostic value, and whose parameters, defined as follows, were responsible for higher mortality: proteinuria >1 g/day, renal insufficiency (creatininemia >140 μmol/l), cardiomyopathy, gastrointestinal manifestations and central nervous system involvement. When FFS =0, 5-year mortality was 12%; when FFS =1, 5-year mortality was 26%; when FFS ≥2, 5-year mortality was 46%. Indeed, the results of our study on 278 patients[19] with PAN, MPA or CSS demonstrated that the combination of CYC and corticosteroids was beneficial for patients with an FFS ≥2. The patients who died from severe SNV had more often been treated with corticosteroids alone than with corticosteroids and CYC. Other criteria, like the Birmingham vasculitis activity score (BVAS),[20] are also used to determine the intensity of treatment required and are being tested in the prospective trials proposed by the European Vasculitis Study (EUVAS) group.

INDICATIONS OF CORTICOSTEROIDS ALONE

Steroids are effective when prescribed alone to treat PAN and CSS without poor prognosis factors, *i.e.* FFS =0, with the results of one of our studies[19] demonstrating that the survival rate was the same as when patients received a combination of corticosteroids

and CYC. Based on two recent CHUSPAN trials, we were able to show that remission could be obtained with corticosteroids alone and that relapses or patients whose SNV failed to respond to steroids alone could benefit from the adjunction of immunosuppressant (CYC or azathioprine).[21]

INDICATIONS OF CORTICOSTEROIDS AND CYCLOPHOSPHAMIDE FOR PAN

PAN prognosis has been transformed by corticosteroids and immunosuppressants, especially CYC. Corticosteroids alone were able to increase the 5-year survival rate from 10% for untreated patients to about 55% in the mid-to-late 1960s.[22] Survival was further prolonged by adding immunosuppressants, either azathioprine or CYC to the treatment regimen.

Cyclophosphamide

When CYC is indicated for PAN and CSS patients with factor(s) of poor prognosis (FFS $\geq$1),[23] an IV pulse should be preferred to oral administration. The IV route may achieve a more rapid clinical response than oral CYC which is particularly important for patients with active disease. When combined with corticosteroids, IV CYC should not exceed 12 pulses. In a prospective study on PAN patients with poor-prognosis factors, we showed that a 6-pulse regimen not relayed by maintenance therapy was associated with more relapses than when treatment comprised 12 CYC pulses.[23] At present, we recommend pulse CYC until remission is obtained and then prescribe maintenance therapy, with azathioprine or methotrexate for 12 to 18 months, since its efficacy against ANCA-positive SNV was demonstrated.[24]

TREATMENT OF ANCA-ASSOCIATED SYSTEMIC NECROTIZING VASCULITIDES

ANCA-associated SNV require treatments that are more substantially codified. However, CSS can be treated differently from WG and MPA. The recommendations that we have established for PAN treatment can also been applied to CSS and some MPA patients, with the regimen adapted to disease severity.

TREATMENT OF WEGENER'S GRANULOMATOSIS

Corticosteroids and CYC treatments are presently mandatory for every patient with systemic WG. In this setting, even though the indication of CYC administration is universally accepted, consensus has not yet been reached concerning which route should be used. Oral CYC is prescribed at 2 to 3 mg/kg/day,[11] and the dose can be adapted according to the therapeutic response, the occurrence of side effects, renal function and/or age. Treatment should be continued for at least 18 months, but the results of more recent studies demonstrated that short-term CYC administration until remission followed by azathioprine was as effective as prolonged oral CYC. Shortening exposure to CYC has a major impact by sharply reducing side effects.

Based on the results of an as yet unpublished trial, once remission of ANCA-positive WG was obtained with pulse CYC, it was maintained with azathioprine or methotrexate, with equivalent outcomes for both treatment arms. Patients improved equally in both groups and relapse rates were comparable. The results of our study also validate methotrexate as a maintenance therapy but it should not be given as an induction treatment. However, methotrexate was evaluated for induction in non-renal WG: although it was as effective as CYC in the short term, it was less effective over the long term and relapses occurred more frequently in the methotrexate arm.[25]

Among immunosuppressants, mycophenolate mofetil (MMF) was prescribed for maintenance therapy for 14 WG patients: results were encouraging but its ability to prevent relapses remains to be proven.[26] The EUVAS group is evaluating MMF for maintenance treatment with a regimen comprising pulse or oral CYC for induction (6 months), then randomized prescription of azathioprine or MMF to maintain remission (3 years); results of the trial are expected at the end of 2008.

Pulse CYC, given every 3 to 4 weeks at a dose of 0.5 to 0.7 g/m^2, was shown to be as good as oral CYC to induce initial remission,[27] but did not maintain it or limit the high number of relapses after stopping treatment as well as oral CYC. Several other studies have confirmed our initial results[28,29] and recently the CYCLOPS (daily oral *vs* pulse CYC during induction therapy for generalized vasculitis) study, organized by the EUVAS group, confirmed that pulse and oral CYC are equally able to achieve remission and that pulses dramatically lowered the rate of side effects (unpublished data).

TREATMENT OF MICROSCOPIC POLYANGIITIS

We now recommend treating MPA like WG, based on the putative common pathogenetic mechanisms and preliminary results of ongoing trials. However, we also demonstrated that, when MPA had no poor-prognosis factors, it could be effectively treated with corticosteroids alone. Because the majority of MPA patients have glomerulonephritis, that therapeutic option can only be prescribed to the fewer than 20% with only minor symptoms.[6]

NEW TREATMENTS

In addition to the therapeutic approaches that have been refined over the past few decades, new drugs and strategies to treat SNV have been developed and will, in the near future, dramatically modify the care of these patients.

Manipulation of the immune system to obtain remission or cure SNV emerged two to three decades

ago with the use of PE and intravenous immunoglobulins (IVIg) to treat these systemic diseases. More recently, new drugs targeting cytokines or B lymphocytes have emerged and deserve evaluation in patients with disease resistant to conventional regimens or, perhaps also, those with newly diagnosed SNV.

PLASMA EXCHANGES

PE can be a useful tool, as second-line therapy, in PAN refractory to conventional regimen(s). Pusey and coworkers showed that PE can improve renal function in patients with crescentic glomerulonephritis responsible for severe renal insufficiency (creatininemia >500 μmol/l) and enable them to stop dialysis.[30] A prospective trial organized by the EUVAS group confirmed that PE were able to improve renal function significantly but had no effect on survival.[31]

INTRAVENOUS IMMUNOGLOBULINS

Because of their efficacy, safety and good tolerance, IVIg alone or as add-on therapy should be considered for patients with relapsed ANCA-associated SNV and perhaps to maintain their remissions. In small prospective studies, complete to partial responses, respectively, were observed in 45% to 75% of the patients given IVIg alone or in combination with other immunosuppressant(s) and/or corticosteroids.[32-34] However, in a study on 15 patients,[35] only 6 obtained clinically significant benefits, confined to single-organ manifestations, without complete disease remission. Furthermore, the authors showed that the inhibitory effect of IVIg on anti-proteinase 3 activity was not associated with clinical improvement. Hence, the optimal role of IVIg in the treatment of ANCA-associated vasculitis remains to be determined.

One placebo-controlled trial on relapsed ANCA-associated SNV demonstrated better vasculitis outcomes for IVIg-treated patients.[32] That study evaluated the efficacy, for at least for 2 months, of a single cycle of IVIg (0.4 g/kg/day for 5 days) for patients with persistent disease activity despite conventional therapy. Seventeen patients were randomized to each arm to receive a single IVIg cycle or a placebo. After 12 months, responses had been obtained in 14 and 6 patients in the two treatment groups, respectively.

Recently, we conducted a prospective, open, multicenter trial on French patients with relapsed ANCA-associated SNV who received a monthly infusion of IVIg for 6 months in addition to conventional treatment.[36] Complete remission was obtained in 13 (59%) of the 22 patients, without any severe adverse events. Thus, IVIg might be used in combination with corticosteroids and immunosuppressive therapy for patients experiencing a vasculitis flare under treatment or shortly after treatment termination.

IVIg are safe and well-tolerated compared with standard corticosteroids and immunosuppressive therapy. Although transmission of HCV infection has been described in the past with this therapy,[37] this possibility has been largely eliminated by the use of solvent-detergent inactivation of the virus. In addition, no HBV or HIV transmission has been reported. Adverse effects occur in 0% to 36% of IVIg recipients and are usually mild, transient and reversible, consisting most frequently of headaches, low-grade fever, chills, low-back pain, transient hypotension, nausea and/or intense perspiration; they generally regress after simply slowing the infusion speed.[38]

The ability of IVIg to achieve lasting remission of ANCA-associated SNV was associated with decreased ANCA titers.[39,40] However, that finding was not confirmed by others, who reported discrepancies between the ability of IVIg to neutralize ANCA activity *in vitro* and a therapeutic benefit.[35]

ANTI-TUMOR NECROSIS FACTOR-ALPHA

Anti-TNFα monoclonal Ab (infliximab) or analogues of its receptor (etanercept) have been proposed to treat SNV.[41] Infliximab, a chimeric anti-TNFα monoclonal Ab, in combination with conventional therapy, led to clinical remission in 88% of the patients with acute or persistently active ANCA-associated SNV enrolled in an open, prospective trial.[42] In that study, a number of infections, including mycobacteria and some life-threatening, were observed. In 2002, we reported on our experience with infliximab in 10 patients with severe refractory SNV, including 7 with WG. All 7 patients obtained complete or partial remissions, with cutaneous eruption being the only adverse effect.[41] Ongoing trials on infliximab use in refractory ANCA-associated SNV may lead to its use for specific subgroups of patients with refractory or relapsed disease.

Etanercept, another TNFα blocker, which is comprised of a soluble protein derived from the p75 TNF receptor fused to the Fc portion of IgG, has been tested in ANCA-associated SNV, also in conjunction with conventional therapy, but with a different aim—to reduce relapse rate. Indeed, compared with placebo (WGET trial) and in combination with induction therapy (CYC or methotrexate for limited disease), etanercept did not confer any advantage for relapse prevention.[43] Etanercept, and perhaps other TNFα blockers, should probably not be considered for maintenance therapy but, rather for some refractory SNV. Moreover, six cases of cancer were diagnosed during that trial, all in the etanercept arm, and three more cancers were diagnosed thereafter, two of which occurred in the placebo group.[43]

ANTI-CD20 MONOCLONAL ANTIBODIES

Rituximab is a genetically engineered chimeric murine-human monoclonal IgG1 kappa directed against the CD20 antigen expressed on the surface of B lymphocytes. Rituximab seems promising based on

the results obtained in the first open trials on patients with refractory and/or relapsed ANCA-associated WG.[44] However, some differences occur in the time to and extent of the therapeutic responses for constitutional and 'vasculitic' manifestations of the disease, as compared to granulomatous lesions, such as WG lung nodules or orbital pseudo-tumors, with the latter regressing more slowly, sometimes only 4 to 6 months after the first rituximab administration.[45] Results of a prospective ongoing North American randomized trial will determine whether rituximab may also be prescribed as an induction agent, hence replacing CYC, and whether it can avoid the need for another immunosuppressant as maintenance therapy.

At present, and other than the results of the abovementioned controlled trials, all these biotherapies should clearly be restricted to refractory and/or relapsed disease. Although the rituximab safety profile seems good, only long-term results will be able to determine the extent of its applicability. Moreover, the dose and administration schedules of this biologic, especially the real need for it, and the exact interval before reinfusion are not well established.

OTHER BIOTHERAPIES

Anti-thymocyte globulin polyclonal antibody preparations have also been prescribed and tested in a study on 15 patients with extremely refractory WG, with some good primary responses in 13 patients, that was not sustained in 7 of them.[46]

Other biological agents are under development and close to entering phase II/III trials, for example, abatacept, a fusion protein (cytotoxic T-lymphocyte antigen-4 (CTLA4)-Ig) that binds to CD80 and CD86 on antigen-presenting cells, thereby inhibiting optimal T-cell activation by blocking the costimulatory signal.[47] Anti-CD22 monoclonal Ab, another biotherapy directed against B-lymphocyte proliferation-inducing soluble factors (BAFF, B-cell-activating factor of the TNF family, also called BLyS, B-lymphocyte stimulator),[48] and/or other forthcoming agents, may also have a place in the future therapy of ANCA-associated SNV.

REFERENCES

1. Lightfoot RW Jr., Michel BA, Bloch DA *et al*. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum.* 1990;**33**: 1088-1093.
2. Masi AT, Hunder GG, Lie JT *et al*. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990;**33**:1094-1100.
3. Leavitt RY, Fauci AS, Bloch DA *et al*. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum.* 1990;**33**: 1101-1107.
4. Jennette JC, Falk RJ, Andrassy K *et al*. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994;**37**:187-192.
5. Kallenberg CG, Brouwer E, Weening JJ, Tervaert JW. Anti-neutrophil cytoplasmic antibodies: current diagnostic and pathophysiological potential. *Kidney Int.* 1994;**46**:1-15.
6. Guillevin L, Durand Gasselin B *et al*. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum.* 1999;**42**:421-430.
7. Sinico RA, Di Toma L, Maggiore U *et al*. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.* 2005;**52**: 2926-2935.
8. Sable-Fourtassou R, Cohen P, Mahr A *et al*. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann. Intern. Med.* 2005;**143**:632-638.
9. Guillevin L, Mahr A, Callard P *et al*. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine* (Baltimore) 2005;**84**:313-322.
10. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine* (Baltimore) 1999;**78**:26-37.
11. Hoffman GS, Kerr GS, Leavitt RY *et al*. Wegener granulomatosis: an analysis of 158 patients. *Ann. Intern. Med.* 1992;**116**:488-498.
12. Gisselbrecht M, Cohen P, Lortholary O *et al*. HIV-related vasculitis: clinical presentation and therapeutic approach on six patients [letter]. *Aids* 1997;**11**:121-123.
13. Ferri C, Greco F, Longombardo G *et al*. Antibodies to hepatitis C virus in patients with mixed cryoglobulinemia. *Arthritis Rheum.* 1991;**34**:1606-1610.
14. Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette J. PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum.* 2005;**52**:911-915.
15. Garini G, Allegri L, Vaglio A, Buzio C. Hepatitis C virus-related cryoglobulinemia and glomerulonephritis: pathogenesis and therapeutic strategies. *Ann. Ital. Med. Int.* 2005;**20**:71-80.
16. Zaja F, De Vita S, Mazzaro C *et al*. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. *Blood* 2003; **101**:3827-3834.
17. Gisselbrecht M, Cohen P, Lortholary O *et al*. Human immunodeficiency virus-related vasculitis. Clinical presentation of and therapeutic approach to eight cases. *Ann. Méd. Interne.* (Paris) 1998;**149**:398-405.
18. Guillevin L, Lhote F, Gayraud M *et al*. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* (Baltimore) 1996;**75**:17-28.
19. Gayraud M, Guillevin L, le Toumelin P *et al*. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. French Vasculitis Study Group. *Arthritis Rheum.* 2001;**44**:666-675.
20. Luqmani RA, Bacon PA, Moots RJ *et al*. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Qjm* 1994;**87**:671-678.
21. Ribi C, Cohen P, Pagnoux C *et al*. Treatment of Churg-Srauss syndrome without poor prognostic factors. A prospective randomized study in seventy two patients. In press 2007.
22. Frohnert P, Sheps S. Long term follow-up study of polyarteritis nodosa. *Am. J. Med.* 1967;**43**:8-14.
23. Guillevin L, Cohen P, Mahr A *et al*. Treatment of polyar-

teritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum.* 2003;**49**:93-100.

24. 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.

25. 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**:2461-2469.

26. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. *Arthritis Rheum.* 2004;**51**:278-283.

27. Guillevin L, Cordier J, 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**:2187-2198.

28. Adu D, Pall A, Luqmani RA *et al*. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *Qjm* 1997;**90**:401-409.

29. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J. Am. Soc. Nephrol.* 1996;**7**:33-39.

30. Pusey C, Rees A, Evans D *et al*. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int.* 1991;**40**:757-763.

31. Jayne D, Gaskin G, Rasmussen N *et al*. Randomised trial of plasma exchange versus methyl prednisolone for severe renal vasculitis. 2006.

32. Jayne DR, Chapel H, Adu D *et al*. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Qjm* 2000;**93**:433-439.

33. Jayne DR, Lockwood CM. Intravenous immunoglobulins as sole therapy for systemic vasculitis. *Br. J. Rheumatol.* 1996;**35**:1150-1153.

34. Levy Y, Uziel Y, Zandman GG *et al*. Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. *Ann. Rheum. Dis.* 2003;**62**:1221-1223.

35. Richter C, Schnabel A, Csernok E, De Groot K, Reinhold KE, Gross WL. Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin. *Clin. Exp. Immunol.* 1995;**101**:2-7.

36. Martinez V, Pagnoux C, Mahr A, Mouthon L, Guillevin L, et le Groupe Français d' Etudes des Vascularites. Intravenous immunoglobulins for relapses of ANCA-associated systemic vasculitides: final analysis of a prospective, open and multicenter trial. American College of Rheumatology, San Diego, poster 1752. *Arthritis Rheum.* 2006.

37. Bjoro K, Froland S, Yun Z, Samdal H, Haaland T. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N. Engl. J. Med.* 1994;**331**:1607-1611.

38. Sherer Y, Levy Y, Langevitz P, Rauova L, Fabrizzi F, Shoenfeld Y. Adverse effects of intravenous immunoglobulin therapy in 56 patients with autoimmune diseases. *Pharmacology* 2001;**62**:133-137.

39. Jayne DR, Esnault VL, Lockwood CM. ANCA anti-idiotype antibodies and the treatment of systemic vasculitis with intravenous immunoglobulin. *J. Autoimmun.* 1993;**6**:207-219.

40. Guilpain P, Chanseaud Y, Tamby MC *et al*. Pathogénie des vascularites systémiques primitives (I): Les vascularites ANCA positives. *Presse. Med.* 2005;**34**:1013-1022.

41. 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* (Oxford) 2002;**41**:1126-1132.

42. Booth A, Harper L, Hammad T *et al*. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J. Am. Soc. Nephrol.* 2004;**15**:717-721.

43. The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* 2005;**352**: 351-361.

44. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am. J. Respir. Crit. Care Med.* 2006;**173**: 180-187.

45. Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. *J. Intern. Med.* 2005;**257**:540-548.

46. Schmitt WH, Hagen EC, Neumann I, Nowack R, Flores-Suarez LF, van der Woude FJ. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int.* 2004;**65**: 1440-1448.

47. Steiner K, Moosig F, Csernok E *et al*. Increased expression of CTLA-4 (CD152) by T and B lymphocytes in Wegener's granulomatosis. *Clin. Exp. Immunol.* 2001; **126**:143-150.

48. Krumbholz M, Specks U, Wick M, Kalled SL, Jenne D, Meinl E. BAFF is elevated in serum of patients with Wegener's granulomatosis. *J. Autoimmun.* 2005;**25**:298-302.