Therapeutic Strategies for Systemic Necrotizing Vasculitides

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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 vasculitides¹³ 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 MPA⁶ but only 40% of those with CSS.⁷⁸

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 MPA⁶ 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%.

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

<table>
<thead>
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<th>Large-vessel vasculitides</th>
<th>Medium-sized vessel vasculitides</th>
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<td>Giant cell (temporal) arteritis</td>
<td>Polyarteritis nodosa (classic polyarteritis nodosa)</td>
<td>Wegener’s granulomatosis **</td>
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<td>Takayasu’s arteritis</td>
<td>Kawasaki disease</td>
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Large-vessel vasculitides
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
Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. 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
Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles and/or arteries).

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).

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 from4. 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. 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.

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. 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 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 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), 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 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), 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 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 ≥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 be 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/m², 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 results²⁸,²⁹ 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 (creatinemia >500 μmol/L) and enable them to stop dialysis. A prospective trial organized by the EUVAS group confirmed that PE were able to improve renal function significantly but had no effect on survival.

**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. However, in a study on 15 patients, 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 vasculitides remains to be determined.

One placebo-controlled trial on relapsed ANCA-associated SNV demonstrated better vasculitis outcomes for IVIg-treated patients. 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. 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. Although transmission of HCV infection has been described in the past with this therapy, 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.

The ability of IVIg to achieve lasting remission of ANCA-associated SNV was associated with decreased ANCA titers. 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.

**ANTI-TUMOR NECROSIS FACTOR-ALPHA**

Anti-TNFα monoclonal Ab (infliximab) or analogues of its receptor (etanercept) have been proposed to treat SNV. 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. 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. 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. 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.

**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. 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. 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 above-mentioned 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 BIOOTHERAPIES

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.

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. Anti-CD22 monoclonal Ab, another biotheraphy directed against B-lymphocyte proliferation-inducing soluble factors (BAFF, B-cell-activating factor of the TNF family, also called BLYS, B-lymphocyte stimulator), and/or other forthcoming agents, may also have a place in the future therapy of ANCA-associated SNV.

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