Even though systemic necrotizing vasculitides (SNV) are rare diseases, the joint endeavors of clinicians, over the past few decades, have led to the codification of treatments that have subsequently improved outcomes dramatically. Several other advances could also explain these improvements: better knowledge of disease classification, treatments adapted to their respective etiologies and pathogeneses, progress in the...

Treatments of systemic necrotizing 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 to prolong survival and prevent relapses, while decreasing the severity and number of side effects. Most of the 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 the latter have achieved promising effects, for example, anti-tumor necrosis factor-alpha and anti-CD20 monoclonal antibodies, and are now being evaluated in prospective trials.
care of severe and life-threatening manifestations, and treatment adapted to each patient's condition and age. Several groups have designed prospective therapeutic trials, mainly the French Vasculitis Study Group (FVSG), the European Vasculitis Study (EUVAS) Group and the Vasculitis Clinical Research Consortium (VCRC). Herein, we review the different therapeutic strategies that are currently applied to patients and report on the new drugs that are being evaluated as SNV therapies.

**Disease specificities and predictable outcomes**

SNV outcomes differ from one entity to another and their respective relapse rates also vary, from around 10.6% for hepatitis B virus-related polyarteritis nodosa (HBV–PAN) [1] to 23.4% for Churg–Strauss syndrome (CSS) [2], 28% for PAN without HBV infection [3], 34.1% for microscopic polyangiitis (MPA) [4], and 63.8% for Wegener’s granulomatosis (WG) [5]. Treatment duration should probably be decided, at least in part, according to the risk of relapse. Shorter-term treatments might be suitable for HBV–PAN. For the main SNV, treatments given for 1 year or less are almost always associated with a high relapse rate, ranging from 50 to 100% but more prolonged therapy does not seem able to lower the relapse rate below 50% [6–8]. An ongoing therapeutic trial (the REMAIN study, now including patients) is evaluating the indications of 2 versus 4 years of immunosuppressants.

**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 in a minority of SNV patients (less than 1%) but is a major cause of PAN, for which it has been incriminated as being responsible for more than one-third of the cases [3]. Hepatitis C virus (HCV), the main cause of mixed cryoglobulin-associated vasculitis, is found in 90% of these patients.

**Treatment of hepatitis B virus (HBV) and other virus-related polyarteritis nodosa (PAN)**

Virus-associated vasculitides require specific treatments.

**HBV–PAN**

In the context of chronic hepatitis B, corticosteroids and immunosuppressants can effectively treat vasculitis and the short-term outcome is comparable to strategies comprising plasma exchanges (PE) and antiviral agents [1]. However, immunosuppressants 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 hepatocellular carcinoma. Based on the efficacies of antiviral drugs against chronic hepatitis and 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 withdrawal to enhance immunological clearance of HBV-infected hepatocytes and favor HBs antigen to anti-HBs antibody seroconversion; with PE to control the course of PAN. A regimen combining an antiviral agent (vidarabine, interferon-α2b or, more recently, lamivudine) and PE to treat HBV–PAN obtained excellent overall therapeutic results in a few weeks [1]. The antiviral strategy increases the HBs antigen-to-HBe antibody seroconversion rate from 14.7% with conventional treatment to 49.4% for patients receiving an antiviral agent and PE [1].

**HCV-related cryoglobulin-associated vasculitis**

HCV–cryoglobulinemia is asymptomatic in the majority of patients but persists for decades and its duration could be a factor associated with the occurrence of vasculitis. The optimal therapeutic strategy has not yet been clearly defined. For patients with minor or moderate symptoms, close monitoring could suffice but antiviral treatment alone, comprising pegylated interferon and ribavirin can also be considered [9]. For patients with severe symptoms of mixed cryoglobulinemia, first-line treatment with anti-CD20 monoclonal antibodies should be considered and combined with an antiviral agent. Rituximab acts on the B-lymphocyte clone(s) producing cryoglobulin(s) and, simultaneously, the antiviral agent slows or suppresses virus replication. This strategy is promising and can facilitate vasculitis regression. At present, only results obtained with a few small series of patients have been published [10–12] and data from prospective controlled trials would be a major contribution in this setting.

**Human immunodeficiency virus (HIV)-related vasculitides**

SNV are a rare but major manifestation of HIV infection, with an incidence of less than 1%, excluding adverse drug reactions.
A broad spectrum of SNV has been observed concomitantly with HIV infection, reflecting almost every pattern and type of vasculitis of small-, medium- and large-sized vessels. Vasculitis in HIV-infected patients can arise due to infection with a known pathogen or in response to a triggering factor, but may also arise in the absence of any identifiable cause. Although the SNV seen in HIV-infected individuals are varied, one feature—namely vessel-wall inflammation—is common to all. Various pathogenic mechanisms have been implicated in the induction of vasculitis, including cell-mediated inflammation, immune complex-mediated inflammation and autoantibody-mediated inflammation. Therefore, treatment of these SNV will depend on the stage of the HIV infection: early during the course of HIV disease, HIV-specific antiviral agents can suffice, being effective against the virus and the SNV; however, during the later stages of acquired immunodeficiency syndrome, appropriate therapy will most likely need to be directed against HIV and any coexisting infectious pathogen. Due to the rarity of HIV-related SNV, only short series of patients have been described [13] and no therapeutic trial has been conducted.

**Treatment according to disease severity**

**First-line therapy**

It is reasonable to adapt first-line therapy to SNV severity and not systematically prescribe a combined corticosteroid-and-immunosuppressant regimen. To help the clinician choose the most effective therapy and avoid overtreatment, we established the five-factor score (FFS) [14], which has significant prognostic value, and whose parameters (proteinuria > 1 g/day), renal insufficiency (creatinemia > 140 μmol/L), cardiomyopathy, gastrointestinal manifestations and central nervous system involvement) were responsible for higher mortality. When FFS = 0, 1 or ≥2, respective 5-year mortality rates were 12%, 26% and 46%. Indeed, the results of our study on 278 patients [15] with PAN, MPA or CSS demonstrated that the combination of cyclophosphamide and corticosteroids was beneficial for patients with FFS ≥2. The patients who died from severe SNV had more often been treated with corticosteroids alone than with corticosteroids and cyclophosphamide. The new version of the FFS, also tailored for WG, associated that severe SNV had more often been treated with corticosteroids and cyclophosphamide. Based on the results of those two recent CHUSPAN trials [17,18], we were able to show that remission could be obtained with corticosteroids alone and that relapses or SNV unresponsive to steroids alone could benefit from the adjunction of an immunosuppressant (cyclophosphamide or azathioprine). A new prospective trial (CHUSPAN2: corticosteroids alone or combined with azathioprine) aims to determine whether an immunosuppressant is for PAN, CSS or MPA without factors of severity, useful for steroid-sparing. Recruitment is ongoing.

**Indications of corticosteroids and cyclophosphamide for polyarteritis nodosa and Churg–Strauss syndrome**

PAN prognosis has been transformed by corticosteroids and immunosuppressants, especially cyclophosphamide. 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 [19]. Survival was further prolonged by adding immunosuppressants, either azathioprine or cyclophosphamide, to the treatment regimen.

**Cyclophosphamide**

When cyclophosphamide is indicated for PAN and CSS patients, an IV pulse should be preferred to oral administration. The IV route achieves a more rapid clinical response than oral cyclophosphamide, which is particularly important for patients with active disease. When combined with corticosteroids, IV cyclophosphamide 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 cyclophosphamide pulses [6,7]. At present, we recommend pulse cyclophosphamide until remission is obtained and then prescribe 12 to 18 months of maintenance therapy, with azathioprine or methotrexate, since the former’s efficacy against antineutrophil cytoplasm antibody (ANCA)-positive SNV was demonstrated [20].

**Treatment of ANCA-associated systemic necrotizing vasculitides (SNV)**

Eforts to codify treatments have been made, especially for ANCA-associated SNV. Here, we cover WG and MPA, but not CSS, whose pathogenesis is complex and probably attributable only in part to ANCA. Prospective trials have been specifically devoted to CSS or included PAN [7,17,21].

**Treatment of Wegener’s granulomatosis**

Corticosteroids and cyclophosphamide are presently mandatory for every patient with systemic WG. In this setting, even though the indication of cyclophosphamide administration is universally accepted, consensus has only recently been reached concerning which administration route should be used. Oral cyclophosphamide is prescribed at 2 to 3 mg/kg/day [5,8], and...
the dose can be adapted to the therapeutic response, the occurrence of side effects, renal function and/or age. Treatment was continued for at least 18 months but the results of more recent studies demonstrated that short-term cyclophosphamide administration until remission, followed by azathioprine, was as effective as prolonged oral cyclophosphamide [20]. Shortening exposure to cyclophosphamide has a major impact by sharply reducing side effects, especially infections and malignancies.

Consensus has recently been reached to prescribe pulse instead oral cyclophosphamide. The first prospective trials demonstrating that cyclophosphamide pulses were able to induce remission as well as oral treatment were published in the 1990s [22–24] and were recently confirmed by a EUVAS trial [25]. A 0.5- to 0.7-g/m² pulse is administered every 3 to 4 weeks. Usually six to nine pulses are sufficient to induce remission. However, cyclophosphamide pulses, especially when their intervening intervals were lengthened after remission was obtained [22], did not maintain remission, once again emphasizing that a continuous-but-less-toxic therapy should be prescribed once remission is achieved [20].

Once remission of ANCA-positive WG is obtained with pulse cyclophosphamide, it can be maintained with azathioprine or methotrexate, with equivalent outcomes for both treatment arms. In the prospective randomized WEGENT trial [26], patients improved equally in both groups and relapse rates were comparable. The results of our study also validated methotrexate as a maintenance therapy, but it should not be given for induction to patients with renal forms of the disease. However, methotrexate was evaluated for induction in non-renal WG [27]: although it was as effective as cyclophosphamide in the short term, it was less effective over the long term and relapses occurred more frequently in the methotrexate arm.

Among immunosuppressants, mycophenolate mofetil (MMF) was prescribed as maintenance therapy for 14 WG patients: results were encouraging but its ability to prevent relapses remains to be proven [28]. The EUVAS group is evaluating MMF maintenance therapy with a regimen comprising pulse or oral cyclophosphamide for induction (6 months), then randomized prescription of azathioprine or MMF to maintain remission (3 years). The preliminary trial results did not demonstrate the MMF superiority at maintaining remission [29].

**Treatment of microscopic polyangiitis**

We recommend treating MPA like WG, based on the putative partly shared pathogenetic mechanisms and preliminary results from ongoing trials. However, we also demonstrated that, when MPA had no poor-prognosis factors, it could be effectively treated with corticosteroids alone [18]. Because the majority of MPA patients have glomerulonephritis, that therapeutic option can only be prescribed to the fewer than 20% with only minor symptoms.

**Other treatments**

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 et al. [30] 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 superior to pulse corticosteroids 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 and partial responses, respectively, were observed in 45% and 75% of the patients given IVIg alone or combined with other immunosuppressant(s) and/or corticosteroids [32–35]. However, in a study on 15 patients [36,37], only six 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 SNV 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 six patients from the respective treatment arms. 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 [38]. 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. 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 [39]. However, that finding was not confirmed by the same group, when measurement was made after a single infusion [32], who reported discrepancies between the ability of IVIg to neutralize ANCA activity in vitro and their therapeutic benefit.

**Anti-tumor necrosis factor-alpha**

Monoclonal antibodies to TNFα (infliximab) or analogues of its receptor (etanercept) have been used to treat SNV. Infliximab, a humanized anti-TNFα monoclonal antibody, in combination with conventional therapy, induced clinical remission in 88% of the patients with acute or persistently active ANCA-associated SNV enrolled in an open, prospective trial [40]. In that study, a number of infections, some life-threatening, including mycobacteria, were observed. In 2002, we reported on our experience with infliximab given to 10 patients with severe refractory SNV, including seven with WG. All seven patients obtained complete or partial remissions, with cutaneous eruption being the only adverse effect [41]. In the long term, infliximab is merely suspensive, as it does not cure vasculitis. We recommend infliximab for flares or difficult-to-treat cases of ANCA-associated vasculitis, but only for a few weeks or months, and not as maintenance therapy [42]. Ongoing trials on infliximab to treat refractory ANCA-associated SNV may lead to its use for specific subgroups of patients with refractory or relapsed disease [43].

Etanercept, another TNFα blocker, which is comprised of the soluble protein of an epitope, 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 lower the relapse rate. Indeed, compared with placebo (WGET trial) and in combination with induction therapy (cyclophosphamide or methotrexate for limited disease), etanercept did not confer any advantage for relapse prevention [44]. Etanercept, and perhaps other TNFα blockers, should probably not be considered an option for maintenance therapy but rather as an add-on treatment for some refractory SNV. Moreover, six cases of cancer were diagnosed during that trial, all in the etanercept arm, and three additional cancers were diagnosed thereafter, two of which occurred in the placebo group [44].

**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 [45,46]. However, some differences appeared 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 [47]. The preliminary results of a prospective ongoing North American randomized trial showed that rituximab is as effective as oral cyclophosphamide for remission induction [48]. For the time being, 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 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, but they were not sustained in seven of them [49]. 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 [50]. Anti-CD22 monoclonal antibody, another biotherapy directed against B-lymphocyte proliferation–inducing soluble factors (B-cell–activating factor of the TNF family [BAFF], also called B-lymphocyte stimulator [BLYS]) [51], and/or other forthcoming agents, may also have a place in the future therapy of ANCA-associated SNV.

**Conflict of interest statement:** none

**References**


