Treatment of Refractory and/or Severe ANCA-Associated Systemic Necrotizing Vasculitides

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Abstract

Treatment of vasculitides has progressed markedly over the past few decades. Recent therapeutic strategies in severe and refractory anti-neutrophil cytoplasmic antibodies-associated vasculitides include immunomodulating methods (e.g., plasma exchanges), products (such as intravenous immunoglobulins) and, more recently, new agents called biotherapies. Some of them (e.g., anti-tumor necrosis factor-alpha and anti-CD20 monoclonal antibodies) have achieved promising results and are now often used to treat severe cases.

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Over the past few decades, the treatment of systemic necrotizing vasculitides has become more effective and the outcome has improved. This can be attributed to better knowledge of the classification of these diseases, treatments adapted to their respective etiologies and pathogeneses when determinable, progress in the management of severe and life-threatening manifestations, and treatment adapted to the patient's condition and age. In this report we review the different therapeutic strategies that can be applied in patients with refractory and severe anti-neutrophil cytoplasmic antibodies-associated vasculitides.

ANCA-associated SNV require treatments that are more substantially codified. However, Churg-Strauss syndrome can be treated differently from Wegener's granulomatosis and microscopic polyangiitis. Patients are considered to be refractory to therapy when they do not respond to corticosteroids and immunosuppressants at optimal doses. Those who do not respond to conventional therapies are usually patients with WG. Corticosteroids and cyclophosphamide treatments are mandatory for every patient with systemic WG. Refractory and severe vasculitides occur mainly in patients with WG. Relapse is not rare despite the combination of corticosteroids and immunosuppressants, and it is often difficult to determine the proper treatment because all the major drugs have already been administered. In some patients, it is possible to optimize conventional therapy and to choose more powerful conventional immunosuppressants. When this option is not available, new drugs and especially biotherapies are recommended.

Manipulation of the immune system to obtain remission or cure of SNV emerged two to three decades ago with the use of plasma exchange and intravenous immunoglobulins to treat these systemic diseases. More recently, new drugs targeting cytokines or B lymphocytes have emerged and warrant evaluation in patients with disease resistant to conventional regimens and, possibly also, in those with newly diagnosed SNV.

Immunosuppressants

When the combination of corticosteroids and immunosuppressants fails to achieve remission, treatment intensification is theoretically warranted. However, the risk of infections from those treatments is a limiting factor that must be kept in mind. When patients had been treated solely with pulse cyclophosphamide, oral cyclophosphamide should be prescribed. This route of administration delivers a higher dose of the cytotoxic agent [1].

Anti-tumor necrosis factor-alpha

Anti-TNFα monoclonal antibody (infliximab) or analogue of its receptor (etanercept) has been proposed to treat SNV [2]. Infliximab, a humanized anti-TNFα monoclonal antibody, in combination with conventional therapy, led to clinical remission in 88% of patients with acute or persistently active ANCA-associated SNV enrolled in an open prospective trial [3]. In that study, a number of infections, including with *Mycobacteria* ssp., were observed, some of them life threatening. In 2002, we reported our experience with infliximab in 10 patients with severe refractory SNV, including 7 with WG. All seven patients achieved complete or partial remission, with cutaneous eruption being the only adverse effect in one patient [2]. More recently, we reported on our long-term experience in 15 patients with refractory or relapsed disease that confirmed the efficacy of infliximab in the short term but showed also that its beneficial effect was suspensive because patients relapsed after its discontinuation [Submitted for publication].

Etanercept, another TNFα blocker, which is comprised of a soluble protein of an epitope derived from the p75 TNF receptor fused to the Fc portion of immunoglobulin G, has been tested in ANCA-associated SNV, also in conjunction with conventional therapy, but with a different aim – to reduce the relapse rate. Indeed, compared to placebo (the WGET trial) and in combination with induction therapy (cyclophosphamide or methotrexate for limited disease), etanercept did not confer any advantage for

ANCA = anti-neutrophil cytoplasmic antibodies
SNV = systemic necrotizing vasculitides
WG = Wegener's granulomatosis

TNFα = tumor necrosis factor-alpha

relapse prevention [4]. Etanercept and perhaps other TNFα blockers should probably not be considered for maintenance therapy, but rather as a potential rescue therapy for some patients with refractory SNV. Moreover, six cases of cancer were diagnosed during this latter trial with etanercept, all in the experimental arm, and three more cancers were diagnosed later, two of them in the placebo group [4].

anti-CD20 monoclonal antibodies

Rituximab is a genetically engineered chimeric murine-human monoclonal IgG-1 kappa antibody 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 [5]. 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 4–6 months after the first rituximab administration [6]. Results of a prospective ongoing North American randomized trial will determine whether rituximab may also be prescribed as an induction agent, hence replacing cyclosphosphamide, and whether it can obviate the need for an immunosuppressant as maintenance therapy.

Although the safety profile of rituximab 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, and the exact interval before re-infusion are not well established.

Other biotherapies

At present, and apart from the results of the above-mentioned controlled trials, all these biotherapies should clearly be restricted to refractory and/or relapsed disease.

Anti-thymocyte globulin polyclonal antibody preparations have also been prescribed and tested. Of the 15 patients with extremely refractory WG who were studied, 13 had a good primary response but it was not sustained in 7 of them [7].

Other biological agents are under development and close to entering phase II/III trials, for example, abatacept, a fusion protein (CTLA4-Ig, cytotoxic T lymphocyte antigen-4-Ig) that binds to CD80 and CD86 on antigen-presenting cells, thereby inhibiting optimal cell activation by blocking the co-stimulatory signal [8]. Anti-CD22 monoclonal antibody, biotherapy directed against B lymphocyte proliferation-inducing soluble factors (BAFF, a B cell-activating factor of the TNF family, also called BLyS, B lymphocyte stimulator) [9], and/or other forthcoming agents may also have a place in the future therapy of ANCA-associated SNV.

Plasma exchange

The long-term outcome of glomerulonephritis occurring in WG is poor. Our study [10] confirmed the poor survival and functional outcome associated with renal involvement of WG and highlights the strong prognostic impact of renal impairment at diagnosis and of renal relapses during follow-up. Pusey and co-workers [11] showed that plasma exchange can improve renal function in patients with crescentic glomerulonephritis responsible for severe renal insufficiency (creatininemia > 500 µmol/L) and enables them to discontinue dialysis. A prospective trial organized by the EUVAS group confirmed that adjunctive plasma exchanges were able to improve renal function significantly but had no effect on survival [12].

Intravenous immunoglobulins

Because of their efficacy, safety and good tolerance, IVIg alone or as add-on therapy should be considered for patients with refractory and/or relapsed ANCA-associated SNV and perhaps to maintain remission. In small open prospective studies, complete to partial responses were observed in 45–75% respectively of the patients given IVIg alone or in combination with other immunosuppressant(s) and/or corticosteroids [13-15]. However, in a study of 15 patients [16], only 6 obtained clinically significant benefits, confined to single-organ manifestations, but not complete disease remission. Furthermore, the authors showed that the inhibitory effect of IVIg on anti-proteinase 3 ANCA activity was not associated with clinical improvement.

One placebo-controlled trial on relapsed ANCA-associated SNV demonstrated better outcomes in vasculitis patients treated with IVIg [13]. That study evaluated the efficacy of a single cycle of IVIg (0.4 g/kg/day for 5 days) in patients with persistent disease activity despite conventional therapy. After 12 months, responses had been obtained in 14/17 and 6/17 patients in the single IVIg or the placebo groups, respectively, at 2 months.

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 [17]. Complete remission was obtained in 13 (59%) of the 22 patients, without any severe adverse event.

They are safe and well-tolerated compared with standard corticosteroids and immunosuppressive therapy. Although transmission of hepatitis C virus infection has been described in the past with this therapy [18], this possibility has been largely eliminated by the use of solvent-detergent inactivation of the virus. In addition, no transmission of hepatitis B or human immunodeficiency virus has been reported. Adverse effects occur in 0–36% of IVIg recipients but they 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 speed of infusion [19].

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

Ig = immunogloublin

IVIg = intravenous immunoglobulins

[20,21]. 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 [16].

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