L44. Management of relapses in vasculitis

ANCA-associated vasculitis (AAV) represents a heterogeneous group of diseases including granulomatosis with polyangiitis (GPA) (formerly called Wegener’s granulomatosis), microscopic polyangiitis (MPA) and Churg and Strauss syndrome [1]. AAV are conventionally treated with a strategy of remission induction using glucocorticoids combined with cyclophosphamide (CYC) followed by maintenance therapy, in order to prevent relapses. The reference maintenance treatments are azathioprine and methotrexate [2]. Very recently, the results of the MAINRITSAN study were reported, providing evidence for the superiority of maintenance rituximab treatment over azathioprine, although these results are not published yet. Despite maintenance treatment, relapses may occur in patients with AAV, which have been the object of a limited number of studies [3]. We will review treatments that can be proposed in the setting of relapsing AAV, the choice of which will be influenced by the treatments received in the past and the severity of the disease flare.

Corticosteroids

Despite the introduction of glucocorticoids into treatment strategies for vasculitis more than 50 years ago, no randomised controlled trials have been conducted to support their use. High doses of intravenous methylprednisolone, up to 3 g are proposed for severe disease flares/relapses [4]. Although they improve disease control, high-dose steroids contribute to morbidity [5].

Cyclophosphamide

For sure, a combination of corticosteroids (CS) and CYC remains the standard treatment for inducing remission of GPA and MPA in patients with severe renal failure, but there is a potential risk of side effects, particularly with long-term CYC. Because intravenous CYC has been shown to be as effective as oral CYC in achieving remission of antineutrophil cytoplasm autoantibody (ANCA)-associated vasculitides and is less toxic, it is now widely considered an alternative to oral CYC for remission induction [6,7]. Although 75 to 90% of the patients achieve remission with oral or intravenous CYC, few data are available on therapeutic strategies for patients with disease refractory to this first-line treatment. Interestingly, oral CYC can be proposed as a rescue treatment for patients refractory to intravenous CYC. In patients newly diagnosed with systemic or renal WG or MPA with ≥ 1 poor prognosis factors, eligible in the Wegener’s Granulomatosis-Entretien (WEGENT) trial, most patients (n = 126, 79.2%) achieved remission and 32 were induction-refractory (24 GPA and 8 MPA) [2]. Induction was switched to oral CYC in 20 patients among which 15 (75%) achieved remission or low disease activity state. Alveolar haemorrhage and a creatinine level > 200 µmol/l were independently associated with induction-refractory disease [8]. Among patients with induction-refractory disease, massive alveolar haemorrhage was associated with higher mortality. Thus, switching to oral CYC can be an effective rescue treatment for patients with systemic forms of GPA or MPA who fail to achieve remission with first-line CS and intravenous CYC.
Intravenous immunoglobulins

The evidence for a benefit of IVIg in patients with ANCA-associated vasculitides initially came from small studies, with however discrepancies in the results obtained [9, 10]. Mechanisms of action of IVIg in patients with ANCA-associated vasculitides include among others neutralisation of ANCA through idiotypic mechanisms, modulation of Fcγ receptors expression and of neutrophil activation [11]. Thirty-four patients with persistent disease activity were randomised to receive either IVIg (a single course at 2 g/kg) or placebo in a double-blind trial. Fourteen of 17 patients in the IVIg group as compared with six patients over 17 who received placebo had a reduction in disease activity, but this effect was not sustained beyond 3 months [12]. IVIg have been proposed for the treatment of a first relapse of AAV in 22 patients who were either under treatment or less than one year following discontinuation of CS and/or immunosuppressants. All patients experiencing relapse were treated with the same drug(s) plus IVIg. All patients initially responded to IVIg therapy. IVIg induced complete remissions of relapsed ANCA-associated vasculitides in 13 of 22 patients at month 9. Because of the good safety and tolerance profiles of IVIg, these agents can be included in a therapeutic strategy with other drugs used to treat relapses of WG or MPA [13]. Interestingly, IVIg is the only treatment available that allows controlling relapse and does not increase immunosuppression. It will be the treatment of choice in patients with a history of sepsis or in pregnant women. Although the tolerance is excellent, IVIg should not be proposed to patients with glomerular filtration rate lower than 30 ml/min.

Plasma exchanges

Plasma exchanges have been demonstrated recently to improve the prognosis of patients with AAV and severe renal failure. The mechanisms of action of plasma exchange are still poorly understood. Removal of complement, coagulation factors, ANCA and other circulating factors probably contribute to its efficacy. In patients with AAV, advanced renal failure at presentation correlates with an increased risk of end-stage renal failure and death, and the aims of therapy are both to control disease and recover organ function. The MEPEX trial compared adjunctive therapy with plasma exchange or i.v. methylprednisolone in 137 patients with AAV and serum creatinine > 500 μmol/l (5.8 mg/dl) at presentation [14]. Both groups received oral CYC and steroids. Plasma exchange decreased the risk of progression to end-stage renal failure by 24% at 12 months, but had no effect on longer-term renal function or survival [15]. Thus, patients presenting with a severe renal relapse with a serum creatinine > 500 μmol/l (5.8 mg/dl), the prognosis is improved by the addition of plasma exchanges to the CYC and corticosteroid treatment. The use of plasma exchanges in AAV is not commonly accepted in patients with plasma creatinine < 500 μmol/l (5.65 mg/dl), and the ongoing pexivas study, focussing on this group of patients, will help to determine at what severity of renal failure plasma exchange is beneficial. Pulmonary renal syndrome, defined as a combination of diffuse pulmonary hemorrhage and glomerulonephritis, represents a severe syndrome for which minimal outcome data are available in the literature. In these patients, plasma exchanges might improve the prognosis when added to intravenous methylprednisolone and CYC [16]. Severe alveolar haemorrhage is the most common vasculitic cause of early death, and, in view of similarities in pathogenesis with renal vasculitis, plasma exchange has been recommended [17].

PE has been proposed in case of relapse involving other organs such as severe peripheral neuropathy, central nervous system involvement [18] or in case of recurrence of antineutrophil cytoplasmic antibody vasculitis in the kidney allograft [19].

Methotrexate

Methotrexate has been proposed in the induction of remission of patients with non-severe AAV. Thus, in the NORAM study conducted in 100 patients with a new diagnosis of early systemic AAV, without critical organ manifestations and with creatinine < 150 μmol/l [20], methotrexate was not inferior at inducing remission, but remission was slower than with CYC in those patients with more extensive disease or pulmonary involvement. In patients with GPA presenting with a limited granulomatous disease and/or in patients with AAV with a non-severe relapse, methotrexate can be proposed, particularly in patients who have a past history of high cumulative dose of CYC.

TNF blockade

Although TNF blockade has been shown to improve vasculitis in experimental models of AAV, a beneficial effect of TNF blockade in human disease has been more difficult to demonstrate. Thus, the dimeric soluble TNF receptor, etanercept failed to improve the rates of stable remission in GPA when added to glucocorticoids and CYC or methotrexate in prospective randomised study [21]. More than 50% of patients in both groups experienced serious adverse events and a possible increase in solid malignancies was recorded in the etanercept group [22], although all patients were previously treated with CYC. Both infliximab and adalimumab have been proposed as adjunctive agents in renal vasculitis and a potential for steroid sparing has been demonstrated [23–25]. Prolonged infliximab for refractory AAV has been complicated by infection and relapse. Finally, infliximab is efficacious against systemic necrotising vasculitides (SNV) re-fractory to conventional treatment [26,27].

Rituximab

Rituximab is a chimeric, monoclonal anti-CD20 antibody that selectively depletes B lymphocytes, but not plasma cells. Since 2006, rituximab is licensed in the treatment of rheumatoid arthritis. Two pivotal studies examined the efficacy of rituximab.
A number of treatments are available for patients with relapsing azathioprine, although these results are not published yet. The superiority of maintenance rituximab treatment over the MAINRITSAN study were reported, providing evidence for masses than for vasculitic manifestations. Finally, the results of is less effective for granulomatous lesions, especially orbital warranted to better define treatment options in these patients.

**Conclusion**

A number of treatments are available for patients with relapsing AAV (Box 1). Although CYC remains the standard treatment for inducing remission, rituximab may thus represent an important option, particularly in patients who received high cumulative doses of CYC. Rituximab seemed to be more effective than CYC in the relapsing subgroup of the RAVE trial [29], although a retrospective series suggests it is less effective for granulomatous lesions, especially orbital masses than for vasculitic manifestations. Finally, the results of the MAINRITSAN study were reported, providing evidence for the superiority of maintenance rituximab treatment over azathioprine, although these results are not published yet.

**Disclosures of interest:** L.M. has relationships with drug companies including CSL Behring and LFB Biotechnologies, including consultancy service, membership on scientific advisory boards, and investigator in trials.

**Box 1**

**Treatments proposed for relapses in ANCA-associated vasculitis**

- Corticosteroids
- Cyclophosphamide (intravenous, oral)
- Intravenous immunoglobulins
- Methotrexate
- Plasma exchanges
- Rituximab
- TNF blockade

**References**


IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells; a typical pattern of sclerosis that is termed “storiform fibrosis”; a tendency to form tumefactive lesions; and the capability of involving multiple organs either simultaneously or metachronously. A majority of patients with IgG4-RD have elevated serum IgG4 concentrations. However, some patients have diagnostic histopathologic and immunostaining features on organ biopsies yet normal serum IgG4 concentrations.

IgG4-RD can affect essentially any organ system [1]. The pancreas was the first organ recognized in this context, in the form of an entity once termed “lymphoplasmacytic sclerosing pancreatitis”, now called type 1 (IgG4-related) autoimmune pancreatitis. The biliary tree, salivary glands, peribronchial tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid gland, pericardium, and skin are also known to be involved [2]. Regardless of the site of disease, the histopathologic features are strikingly similar.

A high percentage of plasma cells within the lesion stain for IgG4. More specifically, ratio of IgG4-positive plasma cells to the total number of plasma cells — the IgG4-total IgG ratio — is elevated, typically on the order of more than 0.3 but often much higher. Elevations of IgG4 in both tissue and serum are helpful diagnostic markers when IgG4-RD is a consideration, but neither tissue nor serum IgG4 levels are entirely specific for this condition [3,4]. Correlation with specific histopathology findings as well as the clinical presentation is essential, regardless of the serum IgG4 concentration, the number of IgG4-positive plasma cells in tissue, or the tissue IgG4:IgG ratio.

Although IgG4-RD was identified initially in glands such as the pancreas and salivary glands [5], reports since 2008 have indicated that this disease can affect the full extent of the aorta as well as surrounding tissues; for example, the retroperitoneum [6–15]. A significant minority of thoracic and abdominal aortic aneurysms, in fact, are associated with inflammatory disease that has no association with any primary form of vasculitis (e.g., giant cell arteritis, Takayasu arteritis). The relevant entity has been termed “isolated aortitis” when found in the thoracic aorta and “inflammatory abdominal aortic aneurysm” when involving the abdominal segment.

The ability of IgG4-RD to affect blood vessels of a wide range in size, with not only large-vessel involvement but also microscopic findings of obliteratorive phlebitis and arteritis, warrants consideration of this condition as a primary form of systemic vasculitis. For most organs affected by IgG4-RD, veins tend to be involved to a greater extent than arteries (figure 1). Arterial inflammation is also well described, however, particularly in the lung [16]. Veins and arteries are classically affected by an obliteratorive process. Necrosis, especially fibrinoid necrosis, is not characteristic of IgG4-RD.

Recognition of the vascular nature of IgG4-RD has caused a re-consideration of the classification of both thoracic and abdominal aortitis and triggered a re-examination of the disorders known as inflammatory abdominal aortic aneurysm (IAAA) and retroperitoneal fibrosis (RPF). This review will focus...