Review

Maintenance treatment of ANCA-associated vasculitides

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ABSTRACT

ANCA-associated vasculitis (AAV) covers a group of systemic necrotising vasculitides characterised by inflammation of small vessels, sometimes with granuloma, and associated with autoantibodies to neutrophil cytoplasmic proteases (proteinase-3 or myeloperoxidase). Potentially lethal if not promptly diagnosed and treated, AAV in most patients can be induced into remission with the current treatment modalities. However, the risk of relapse remains high, necessitating prolonged immunosuppressive or immunomodulating maintenance therapy, whose optimal duration remains undetermined. Herein, we review only maintenance treatments for AAVs.

Introduction

ANCA-associated vasculitides (AAVs) are characterised by inflammation of small vessels and fibrinoid necrosis of the media. For most patients, they are typically associated with circulating autoantibodies to neutrophil cytoplasmic proteases, mainly proteinase-3 (PR3-ANCA), a cationic proteolytic enzyme physiologically present in neutrophil cytoplasmic granules, in granulomatosis with polyangiitis (Wegener's) (GPA) and primarily myeloperoxidase (MPO-ANCA) in microscopic polyangiitis (MPA). AAVs comprise three diseases: GPA, MPA and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA). MPO-ANCA can also be found in a minority of GPA patients.

Treatment modalities achieve remission in most patients. However, the risk of relapse is high and the efficacy of remission-maintenance therapy, whose optimal duration remains undetermined, needs to be improved.

Do patients need maintenance treatment?

It is commonly accepted that maintenance therapy is necessary for AAV patients whose induction treatment combined corticosteroids (CS) and immunosuppressants, mainly CS and azathioprine (1), or methotrexate (2) or mycophenolate mofetil (3). The real need to prescribe a maintenance regimen was never adressed when patients had received CS and immunosuppressants, because treatment termination when remission was obtained was rapidly followed by relapse. We compared 6 *versus* 12 months of cyclophosphamide in patients with different necrotising vasculitides and observed that patients given the shorter treatment had a higher relapse (4).

In the 18-month follow-up of the RAVE study (5), comparing induction rituximab without subsequent maintenance to cyclophosphamide followed by azathioprine, relapse rates were comparable for both groups, demonstrating that azathioprine was not useful when remission had been obtained with rituximab. However, the relapse rate was high with around 30% of patients who relapsed in both groups.

Our approach to keeping patients in remission for a longer time was tested in the MAINRITSAN 1 trial, which compared, once patients had achieved remission, azathioprine for 22 months to 5 rituximab infusions (500 mg each) over 18 months (6).

Therapeutic strategies

Before the advent of CS use to treat AAV, then other immunosuppressants, the prognoses were very poor. Most patients died without available treatment, especially those with systemic disease. Currently used treatments can obtain remission in more than 80% of the patients, with the 5-year overall mortality rate at 10–15% (7, 8). The main causes of deaths are infections and poor disease control during the first year post-diagnosis, and cardiovascular complications, infections or cancers thereafter (9).

The risk of relapse, sometimes multiple in a given patient, remains a main AAV

feature. Relapses are more frequent in GPA than MPA or EGPA, with 5-year relapse rates ranging from 35% (EGPA) (8) to around 50% (GPA) (7).

Treatment should be adapted to the entity, its severity and risk of relapse. Based on the prognostic Five-Factor Score (FFS) (10), treatment options have been designed to find the most effective regimen with the least toxicity. Only MPA and EGPA were initially analysed because it was already known that GPA must be treated with CS and an immunosuppressant or biotherapy. For MPA and EGPA patients with FFS=0, CS alone could suffice to obtain and maintain remission. However, our group's recent results challenged our initial results, highlighting that no relapse-rate difference was observed but that the risk of late relapses was higher for patients who had received only CS, especially those with peripheral neuropathy (11). Although FFS=0 predicted good and comparable overall survival of EGPA, polyarteritis nodosa (PAN) or MPA patients, 45% of them required adjunctive treatments for relapse, CS failure or corticodependence, with most having had more frequent initial mononeuritis multiplex and sequelae. Those findings support prospective evaluation of initial immunosuppressant use combined with CS to prevent treatment failure, relapses and sequelae in FFS=0 patients with mononeuritis multiplex at diagnosis (11).

The impact of induction therapy on relapse

The remission-induction regimen influences maintenance treatment choices. Combined CS and cyclophosphamide achieves remission in most patients by 6 months (2, 7, 12). However, long-term follow-up (median, 4.3 years) data from patients enrolled in the prospective CYCLOPS trial, comparing continuous oral *versus* IV pulse cyclophosphamide for induction, suggested that the subsequent relapse rate after infusions was lower, probably because of the higher cumulative dose exposure during the 6 months of continuous oral intake (13).

The RAVE study (5) provided important information on the indication of maintenance treatment demonstrating that, when patients initially received rituximab, the relapse risk was comparable to that when patients had been given cyclophosphamide for induction, followed by azathioprine (respectively 32% and 29%). However, patient follow-up lasted only 18 months and the high relapse rates in both groups plead for maintenance therapy with efficacy superior to that of azathioprine.

What agents to select and how to maintain remission?

For AAVs, rituximab now rivals conventional maintenance treatments and will probably replace azathioprine, methotrexate and mycophenolate mofetil. However, many aspects remain unresolved: 1) systematic maintenance treatment, 2) treatment adapted to ANCA categories, 3) rituximab dose and administration schedule, and 4) how long to treat?

First, conventional maintenance therapy after cyclophosphamide-based induction is usually based on azathioprine (2–3 mg/kg/day, orally) or methotrexate (0.3 mg/kg/week, orally or subcutaneously, up to a maximum of 25 mg/week) (1, 2). Both drugs can cause some side effects (*e.g.* opportunistic infections, liver toxicity or myelosuppression), but much less frequently than cyclophosphamide (2). In the long term follow up of the WEGENT study (14), ≥1 relapses occurred in ~60% of AZA-group and 54% of MTX-arm patients before the 10-year censoring date, with respective first relapses in 31/38 (81.6%) and 30/34 (88.2%). Leflunomide or mycophenolate mofetil, also evaluated for maintenance, were equally or less effective at preventing relapses, respectively.

The MAINRITSAN trial results demonstrated rituximab's efficacy at maintaining remission. That prospective trial compared azathioprine (2 mg/kg/day until month 22) to fixed-dose rituximab infusions (500 mg every 6 months for 18 months). At month 28, 29% of the azathioprine-treated patients had relapsed *versus* only 5% of those systematically reinfused with rituximab (p=0.02) (6). At 60 months, the relapse-free survival rate was around 57% for rituximab-treated patients and 37% in those given azathioprine (unpublished data).

Second, the ANCA specificity could be a major item guiding treatment. The results of the prospective RAVE and MAINRITSAN (5, 6) trails demonstrated that relapse rates varied according to ANCA type. In the RAVE study, the relapse rate was higher in anti-PR3 - than anti-MPO-positive patients at 18 months follow up ($p<0.001$). After 60 months, the relapse rate in the MAINRITSAN study was higher for patients anti-PR3+ at diagnosis than those anti-MPO+ or ANCA-negative at diagnosis (unpublished data). Although it has never been shown that maintenance treatment could be shorter for anti-MPO+ than anti-PR3+ patients, shortening its duration deserves prospective evaluation.

Third, the optimal rituximab maintenance dose and scheduling have been studied only in the MAINRITSAN trial, with 500 mg being infused systematically every 6 months for a total of 2.5 grams over 18 months. That dose was arbitrarily chosen, hypothesising that the maintenance dose could be lower than that for remission induction. The MAINRITSAN 2 trial compared two maintenance-therapy strategies: either a 500-mg rituximab infusion every 6 months for 18 months (5 infusions) or rituximab infusions guided by an ANCA titre rise or reappearance of CD19+ circulating cells. Its preliminary results showed that a smaller total rituximab dose (1.5 instead of 2.5 grams) effectively prevented relapses. They also demonstrated that trying to adapt the infusion schedule to ANCA titres and/or the presence of circulating CD19+ cells was not reliable for relapse prevention. Other rituximab-administration regimens are under evaluation. The RITAZAREM trial addresses patients with initially severe and relapsing AAVs, and is evaluating a total dose of 5 grams for maintenance administered over 18 months (1 gram every 4 months). We can easily foresee that, in the future, other biological or cellular parameters reflecting different genotypes could become the markers to guide our therapeutic choices.

Fourth, How long should patients be treated? Importantly, despite all these gradual refinements of maintenance-therapy strategies, its optimal duration remains elusive. Especially for patients with the greatest risk(s) of relapse, treat-

ment lasting more than 2 years could be useful. However, such a recommendation is premature even though it is obvious that patients receiving rituximab relapse less frequently than those who had received azathioprine. The French Vasculitis Study Group has organised a prospective trial comparing 2 to 4 years rituximab administration to prevent relapses. Recruitment is already closed and the results are expected in 2019.

Other therapeutic approaches have been advanced to prevent relapses. Co-trimoxazole (trimethoprim-sulfamethoxazole) cannot replace immunosuppressive maintenance therapy, but prescribed at "high doses" (320 mg/1600 mg daily of trimethoprim/sulfamethoxazole), together or after the standard immunosuppressive regimen for GPA, can lower the relapse rate (15).

Maintenance treatment for limited GPA forms

It is possible to prescribe a "lighter" regimen for patients with localised and/or limited non-life-threatening GPA, primarily when only granulomatous ear, nose & throat (ENT) manifestations are present. CS can obtain some attenuation in more than 50% of them but sustained remission is very rarely achieved. Because these forms are often recurrent, can be locally erosive and tend to evolve eventually into more generalised disease, it seems reasonable to treat them more systematically with a combined regimen of CS and immunosuppressant, *e.g.* methotrexate. When methotrexate is effective, it must be continued for several years.

Because of the high number of relapses and flares in patients with subglottic stenoses, and/or tracheal stenoses or orbital tumour, maintenance therapy, usually lasting several years, is needed. The therapeutic strategies are not codified: all immunosuppressants can be tried and biotherapies have also been proposed with different clinical responses. Prospective trials are needed to determine the best induction-remission and maintenance treatment(s).

Treating relapses occurring during or after maintenance treatment

Relapses while on maintenance therapy or when immunosuppressants are no longer being taken could be treated according to the same remission-induction strategies described above or with rituximab.

Treating subglottic stenosis is also complex, especially because this manifestation can recur or worsen in the absence of other signs of active disease. Systemic agents, including CS, cyclophosphamide or rituximab, can be effective for about a third of these GPA patients. For most of the remaining two-thirds, whose chronic lesions are composed of fibrotic scar tissue, only local treatments, based on dilations combined with local submucosal CS injections, provide some symptomatic relief.

Intravenous immunoglobulins have mostly been prescribed to treat refractory or relapsing GPA, with concurrent serious infections or contraindication(s) to receiving other immunosuppressants, or during pregnancy for patients with active AAVs. They are contraindicated when renal insufficiency is severe (creatinine clearance <30 ml/min) (16).

When severe rapidly progressive glomerulonephritis and/or alveolar haemorrhage are present, plasma exchanges are sometimes prescribed together with other remission-induction treatments. When renal impairment is severe (defined as oliguria), necessitating dialysis, and/or serum creatinine exceeds 500 µmol/l, plasma exchanges contributed to improved renal function and recovery at 12 months, but these improvements were not sustained (17).

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