Update on the treatment of ANCA associated vasculitis

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Summary

The introduction of glucocorticoids and cyclophosphamide has transformed ANCA associated vasculitis (AAV) from a fatal to a largely treatable condition. Over the past 40 years, considerable progress has been made in refining immunosuppressive regimens with a focus on minimising toxicity. As knowledge of the pathogenesis of AAV grows, it is mirrored by the availability of biological agents. Lymphocyte and cytokine targeted agents have been evaluated for the treatment of AAV and are entering the routine therapeutic arena with the potential to improve patient outcomes. Rituximab has transformed management of AAV in the past decade. However, there remains unmet need in the treatment of AAV; the majority of patients will relapse within five years of diagnosis despite maintenance immunosuppression; a small number of patients remain refractory to current therapies and treatment toxicity continues to contribute to mortality and chronic disability. As in rare diseases, treatment advances in vasculitis depend on international collaborative research networks to both establish an evidence base for newer agents and develop recommendations for optimal patient management.

ANCA associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (formerly Wegener’s Granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome). These small vessel vasculitides have diverse clinical manifestations that are characterised by leucocyte infiltration of blood vessel walls, fibrinoid necrosis and vascular damage with occlusion or aneurysm formation. Prior to effective treatment, AAV had a mortality of 93% within two years, primarily due to renal and respiratory failure [1]. The introduction of glucocorticoids in 1948 and cyclophosphamide in the 1960s, together with adjunctive therapies, such as antihypertensive drugs and renal replacement therapy, has transformed survival, with approximately 90% of patients surviving one year, and 75% ten years [2]. This therapeutic revolution has converted AAV into a chronic relapsing disorder with progressive organ damage and disability, eventually affecting the majority of patients. Thus, in recent years, attention has focused on refining existing immunosuppressive regimens with the aim of minimising toxicity, in parallel with the introduction of newer targeted biological agents. This review concentrates on data pertaining to the use of both conventional and targeted...
immunosuppressive agents in AAV, published in recent years. In particular, the literature on rituximab, the first agent ever to be licensed for treatment of AAV, is critically appraised. In view of the different clinical manifestations and response to treatment, eGPA is considered separately to GPA and MPA.

As more biological agents become available, the management of AAV is likely to become more complex for the physician. In addition to demonstrating efficacy, it is important to consider the target population for any new therapy, and we should continue to strive to discover biomarkers that could predict treatment response and subsequent disease course, including relapse risk. Then, rather than selecting treatments according to disease stage and severity as we do now, individually tailoring therapy, in terms of particular agent, dose and frequency, becomes a real possibility. Personalised medicine will maximise efficacy and minimise toxicity for the individual patient, and at a population level, make the best use of valuable resources.

Pathogenesis

Many of the developments in treatment approaches to AAV, in particular the introduction of targeted biologics, have come as a consequence of advances in our understanding of the pathogenesis of AAV. Both genetic susceptibility and environmental exposures contribute to the aetiology of AAV. ANCA have been demonstrated to be pathogenic in animal models, although their contribution to human disease remains less clear [3-5]. B cells are thought to play a key role in the pathogenesis of AAV and are present in granulomata in GPA [6,7]. Not only are B cells the precursors of ANCA secreting plasma cells, but they also act as antigen presenting cells for auto-reactive T cells, providing co-stimulatory support and initiating T cell activation. In AAV, the auto-antibodies are class switched (mainly IgG), which means the auto-reactive B cell has received cognate T cell help. Further evidence for the role of T cells in the pathogenesis of AAV comes from their presence in biopsy specimens, where T cells cause damage via direct cytotoxicity and the recruitment and activation of macrophages [8-10] and that a CD8 T cell gene expression signature has been associated with relapse frequency in AAV [11]. Despite AAV being characterised by the presence of pauci-immune vasculitic lesions on histology, it is becoming increasingly apparent that this complement plays an important part in the pathogenesis of disease [3,12-14].

Key principles

Two key principles underlie the management of patients with AAV, irrespective of the specific therapy utilised.

Sequential management approach

A two stage sequential management approach should be employed, with an initial 3 to 6 month induction phase of intensive immunosuppression followed by a longer period of remission maintenance therapy. There is ongoing debate as to the optimal duration of maintenance treatment, but current guidelines suggest at least 24 months [15]. Data from the REMAIN study, comparing relapse rates following either 24 or 48 months of conventional remission maintenance therapy, and the proposed MAINRITSAN 3 trial (comparing an 18 month extension of a fixed interval repeat dose rituximab maintenance approach to placebo) are likely to inform the duration of remission maintenance strategies over coming years.

Grading of disease severity

GPA and MPA have been subdivided into ‘limited’ or ‘non-severe’ versus ‘generalised’ or ‘severe’ disease [16] in order to define eligibility for a sequence of randomised controlled trials aimed at defining the optimal standard of care. The use of such an approach in routine clinical practice enables early identification of individuals with life- or organ-threatening disease who may benefit from early augmented immunosuppression, and those with milder disease, in whom less toxic induction agents may be considered.

Treatment

Induction of remission

Current remission induction strategies use high-dose glucocorticoids together with cyclophosphamide or rituximab, as well as plasma exchange for individuals with vital organ- or life-threatening disease. Methotrexate and possibly mycophenolate mofetil (MMF) are also options for individuals without any organ-threatening disease.

Glucocorticoids

Despite the introduction of glucocorticoids into treatment strategies for vasculitis over 50 years ago, there are no randomised controlled trials to support their use. Evidence is also lacking to guide dosage and overall duration of therapy [17]. However, glucocorticoids remain an integral part of induction regimens in AAV, although there is increasing evidence that high-dose steroids contribute to the significant morbidity that AAV patients suffer [18]. The PEXIVAS trial, currently recruiting 500 patients worldwide, aims to address the efficacy of a rapidly reducing glucocorticoid regimen, as well as the place of plasma exchange in severe AAV [19].

Cyclophosphamide

Cyclophosphamide was introduced empirically for induction treatment of AAV over 40 years ago, and remains one of the two recommended induction strategies (alongside rituximab) for patients with severe disease. The use of cyclophosphamide has been refined, employing strategies to reduce exposure and cumulative toxicity. From the sequential replacement of cyclophosphamide by azathioprine in the CYCAZAREM trial [20]; to the replacement of cyclophosphamide by methotrexate for early systemic disease without critical organ manifestations in the NORAM trial [21]; to the use of pulsed intravenous rather than daily oral cyclophosphamide in the CYCLOPS study [22], cyclophosphamide has become a much safer drug to use. However,
more recently it has become apparent that administering less cyclophosphamide has drawbacks, although their significance remains unclear. In long-term follow-up of patients in the CYCLOPS and CYCAZAREM studies, less cyclophosphamide was associated with a higher risk of relapse, and in the NORAM study, methotrexate was associated with less effective disease control, although ultimately there was no increase mortality or long-term morbidity [23-25].

**Rituximab**

Rituximab, as with many therapeutic agents, was first used in individuals with AAV who had proved refractory to existing treatment strategies. A number of uncontrolled case series showed rituximab to be highly effective, and thus two randomised controlled trials comparing rituximab to cyclophosphamide were designed, leading to the license of rituximab for remission induction in AAV in 2011 in the USA and 2013 in the EU [26]. The 'Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis' (RAVE) trial recruited 197 patients with severe AAV, although individuals with alveolar haemorrhage requiring mechanical ventilation or a serum creatinine greater than 354 μmol/L were excluded [27]. Patients were randomized to either weekly rituximab (375 mg/m² x 4) with no maintenance immunosuppression or oral cyclophosphamide followed by azathioprine. The primary endpoint, complete remission of disease at 6 months in the absence of any glucocorticoid therapy, was achieved by 64% of the patients in the rituximab group compared to 53% in the cyclophosphamide group, meeting criteria for non-inferiority. In the subgroup of 101 relapsing patients, rituximab was more efficacious than cyclophosphamide, with 67% of the patients in the rituximab group achieving the primary endpoint compared with 42% in the cyclophosphamide limb. The 'Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis' (RITUXVAS) trial studied 44 patients with newly diagnosed renal AAV [28]. Patients were randomized 3:1 to either receive a rituximab-based induction regimen (375 mg/m² x 4, as well as two intravenous cyclophosphamide pulses, with no maintenance agent) or pulsed IV cyclophosphamide followed by azathioprine. Patients requiring dialysis were eligible for enrolment and 25% of patients also underwent plasma exchange, reflecting disease severity. Sustained remission was achieved by 76% of patients in the rituximab group versus 82% in the control group, again meeting criteria for non-inferiority. Neither the RAVE nor RITUXVAS study reported a reduction in severe adverse events with the use of rituximab, suggesting that high-dose glucocorticoids and the disease itself are the main contributors to these events, and that current cyclophosphamide regimens, in expert centres, are reasonably safe. It is also notable that 18% of patients in the RITUXVAS trial died in the study period, highlighting, that although huge progress has been made in the management of AAV over recent years, it remains a potentially fatal disease, particularly in the elderly and those requiring dialysis, and thus further refinement of induction strategies are still required. On extended follow-up in the RAVE study, the rates of sustained remission were similar between the two groups at 12 and 18 months, with 48% and 39% respectively, maintaining complete remission in the rituximab treated group, and 39% and 33% respectively, in the cyclophosphamide-azathioprine group [29]. Similarly in the RITUXVAS trial, relapse rates were comparable between groups at 2 years, albeit lower (26% and 20% in the rituximab and cyclophosphamide limbs respectively) than observed in the RAVE trial, probably reflecting the rapid and complete withdrawal of glucocorticoids by 6 months in the former study [30]. Retrospective data suggests that lower dose rituximab induction therapy, namely a single 375 mg/m² dose effectively depletes CD19 B cells and induces clinical remission [31]. However, many patients also received additional maintenance immunosuppression, so whether an economically favourable low-dose rituximab alone strategy is sufficient to induce and sustain remission requires further exploration.

**Mycophenolate mofetil**

The MYCYC (MMF versus cyclophosphamide for remission induction in AAV) non-inferiority trial compared MMF to pulsed IV cyclophosphamide, followed by azathioprine maintenance in 140 patients with newly diagnosed AAV. The primary endpoint was complete remission at 6 months with adherence to the glucocorticoid tapering regimen. Preliminary data suggests that MMF is not non-inferior to cyclophosphamide, with non-adequacy to the glucocorticoid-tapering regimen being a major issue. And at 18 months of follow-up, there were more relapses in the MMF group [32], and based on this evidence, MMF should not be recommended as first-line induction immunosuppression, but may have a place in selected cases.

**Abatacept**

Abatacept, a fusion protein of CTLA-Ig which blocks co-stimulation via CD28 has been shown to be efficacious in 20 patients with limited relapsing GPA. Abatacept, in addition to glucocorticoids and an immunosuppressant (either azathioprine, methotrexate, or MMF) was well tolerated with 90% of patients experiencing disease improvement and 80% achieving remission, and it was possible the discontinue prednisolone in 11 of the 15 patients taking glucocorticoids [33]. The randomised, placebo-controlled ABROGATE trial (ClinicalTrials.gov Identifier NCT02108860) will further explore the role of abatacept in AAV.

**Maintenance of remission**

The successful introduction of glucocorticoids and cyclophosphamide into treatment regimens has transformed AAV in a chronic relapsing condition. Relapse risk is increased by upper respiratory tract involvement, nasal carriage of *Staphylococcus aureus* infection and the absence of renal disease. Persistent ANCA
positivity at the time of remission and a subsequent rise in ANCA level can be predictive of relapse [34-36]. Withdrawal of immunosuppression or glucocorticoids is associated with a higher relapse rate [17,20,21]. Consensus guidelines advocate continuation of maintenance immunosuppression for 24 months [15,37]. However, practice with glucocorticoids is highly variable, although results of the TAPIR study (Clinical Trials.gov Identifier NCT01933724) comparing the effect of 5 mg prednisolone compared to complete withdrawal on relapse rates, may inform practice.

**Azathioprine**

The CYCAZAREM trial compared continued cyclophosphamide 1.5 mg/kg/day after remission induction to a switch to azathioprine 2 mg/kg/day [20]. No difference in relapse rate was seen at 18 months although longer-term follow-up has suggested poorer outcomes for those switched to azathioprine, and the optimal timing of transition from induction to maintenance therapy has come back into question [24].

**Methotrexate**

The WEGENT study compared methotrexate to azathioprine as maintenance therapy after successful induction of remission with cyclophosphamide [38]. There were no differences between groups in terms of either relapse rates or toxicity. Use of methotrexate is usually restricted to those with creatinine < 150 μmol/L.

**Mycophenolate mofetil**

Following its success in the field of transplantation, MMF has been considered as an alternative to azathioprine for remission maintenance therapy in AAV. The IMPROVE trial which compared MMF to azathioprine after cyclophosphamide induction, however, found an increased hazard ratio of 1.7 for relapse in the MMF group, and a shorter time to relapse [39]. MMF cannot be recommended as a first-line remission maintenance agent in AAV but it may have a role for patients intolerant of azathioprine or for whom methotrexate is contraindicated by renal failure.

**Rituximab**

Neither the RAVE nor RITUXVAS trials employed a maintenance agent, and in longer-term follow-up, remissions were not sustained mirroring earlier retrospective experience showing that the majority of relapsing or refractory patients treated with rituximab eventually relapse again [40], although further treatment with rituximab is effective [40,41]. However, uncertainty remains whether repeated rituximab treatment to avoid relapse should be guided by biochemical parameters – peripheral blood B cell counts or ANCA levels or to follow a fixed interval strategy [42,43]. A two-year fixed interval repeat dose rituximab regimen has been shown to be highly effective at reducing relapse rates. Only 5/43 (12%) of patients relapsed by 24 months in the group that received repeated doses of rituximab, compared to 19/26 (73%) of patients that received just a single course. Based on this retrospective data, an international randomised controlled trial, RITAZAREM (ClinicalTrials.gov identifier: NCT01697267), has opened recruitment.

The MAINRITSAN trial, a prospective randomised controlled trial comparing lower dose repeat rituximab maintenance therapy (500 mg doses at 0 and 2 weeks and a further 500 mg at 6, 12 and 18 months) to azathioprine (2 mg/kg/day for 22 months) in 115 patients (79% newly diagnosed) following cyclophosphamide induction therapy, has shown rituximab to be superior to azathioprine, with 5% of patients in the rituximab group compared to 29% in the azathioprine group relapsing by 28 months [44]. The difference was sustained during extended follow-up, with 12.7% of patients in the rituximab limb, compared to 48.1% in the azathioprine arm suffering at least one major relapse, after 39 months follow-up [45].

**Refractory disease**

Patients with refractory disease encompass those who have disease progression or inadequate disease control despite induction therapy; those who relapse on maintenance immunosuppression, and those who are intolerant of standard therapy, most commonly cyclophosphamide. Despite rituximab now being the preferred agent for refractory disease [40], a minority of patients fail to respond, or the efficacy of rituximab wanes over time despite repeated doses, and therefore alternative agents, such as intravenous immunoglobulin [46-49], alemtuzumab [50], anti-tumour necrosis factor (anti-TNF) agents [51-54] and gusperimus [55-57] remain potential approaches in refractory AAV, but detailed discussion is beyond the scope of this review.

**Management of eGPA**

Although a form of AAV, eGPA is often considered separately as the clinical phenotype and treatment response has a number of distinct features. Glucocorticoid therapy alone may be sufficient, and patients are stratified on the basis of the Five Factor Score (FFS). Ninety-three percent of patients with a FFS of 0 achieved remission with glucocorticoids alone, although 35% relapsed on prednisolone taper, and many required long-term maintenance glucocorticoids to control asthma [58]. For those with any adverse prognostic features, cyclophosphamide remains the first-line therapy, with maintenance strategies following those for GPA and MPA [59]. More recently, rituximab has been shown to be efficacious [60-62]. In the largest case series, 83% had improved by 6 months with remission in 34% and partial response in 49%, which was sustained at 12 months. Infusion reactions were common, although the majority were mild-given prophylactic administration of intravenous glucocorticoids and antihistamines. The role of rituximab as a maintenance agent in eGPA requires further exploration and in contrast to GPA and MPA, only 6% of patients were able to completely withdraw glucocorticoids by 12 months, suggesting that in eGPA, rituximab has a limited steroid sparing effect.
With the development of mepolizumab, an IgG monoclonal antibody specific for interleukin-5 (IL-5), and the launch of a phase III trial, the first randomised controlled trial specifically for patients with eGPA, the future role of rituximab in eGPA has become less clear. IL-5 is a cytokine, which regulates the growth, activation and survival of eosinophils. IL-5 levels are increased in patients with eGPA and are associated with disease activity [63]. Two pilot studies, using monthly mepolizumab infusions but involving only 17 patients, have demonstrated the efficacy and steroid sparing potential of mepolizumab [64,65]. A randomized, double-blind placebo-controlled study investigating the efficacy and safety of 300 mg monthly subcutaneous mepolizumab over 52 weeks in 130 patients with relapsing refractory eGPA receiving standard of care therapy including background glucocorticoids is presently recruiting (ClinicalTrials.gov identifier NCT02020889).

**Emerging agents in AAV**

**Belimumab**
The B lymphocyte stimulating protein, (BlyS, also known as BAFF), a B cell survival factor is a potential target in AAV. Patients with active untreated GPA have higher serum BlyS levels than healthy controls [7]. Also, following B cell depletion with rituximab in SLE, BlyS levels significantly increase and then normalise as B cell populations recover [66]. Belimumab is a humanised monoclonal antibody that inhibits BlyS. Efficacy and tolerability when added to standard therapy, but without a steroid sparing effect, have recently been demonstrated in two-phase III clinical trials in patients with SLE, without significant renal involvement [67,68]. Recruitment to an industry sponsored, phase III, multicentre, international, randomised, double-blind, placebo-controlled trial investigating the effect of belimumab in combination with azathioprine as a remission maintenance strategy in AAV (BREVAS) (ClinicalTrials.gov identifier NCT01663623) is underway.

**CSa inhibitor (CCX168)**
Demonstration of the role of the alternative complement pathway in the pathogenesis of AAV has led to the evaluation of an oral CSa inhibitor (CCX168) as a novel induction approach. The preliminary results of a small phase II trial evaluating efficacy and safety indicate that CCX168 plus cyclophosphamide is at least as effective, if not more effective, as full dose steroids plus cyclophosphamide in patients with newly diagnosed renal AAV [69]. Since high-dose glucocorticoids are increasingly believed to be the major contributor to early toxicity and infectious adverse events, the possibility of a steroid-sparing agent, with the convenience of oral administration is an extremely exciting development. The CLEAR (ClinicalTrials.gov identifier NCT01363388) and CLASSIC (ClinicalTrials.gov identifier NCT02222155) studies will further evaluate the role of CCX168 on both the renal and non-renal manifestations of AAV.

**Other potential agents**
Since plasma cells are the source of ANCA, then specifically depleting them is a potential therapeutic approach. Using the proteasome inhibitor, bortezomib, anti-MPO titres were reduced and the development of necrotising crescentic glomerulonephritis was prevented in a mouse model of MPO AAV [70]. Clinical studies in patients failing current treatments may be a future option.

ANCA stimulation of neutrophils leads to degranulation of the lytic granule contents, including neutrophil serum proteases (NSPs). NSPs are involved in activating the pro-inflammatory cytokine, IL1β, in monocytes stimulated with ANCA IgG. Blocking IL1β by anakinra in a mouse model of MPO AAV reduced the severity of necrotising crescentic glomerulonephritis [71]. Anakinra has been trialled in a number of inflammatory human conditions, and could be a potential therapeutic agent in AAV.

IL17 has been implicated in a number of autoimmune conditions. Mice deficient in IL17 are protected from MPO AAV and Th17 cells can induce a proliferative glomerulonephritis in mice [72,73]. IL17 blockade is already being evaluated in conditions such as Crohn’s disease and psoriatic arthritis, and may have a role in the treatment of AAV in the future.

Spleen tyrosine kinase (syk) transmits activating signals within B cells, and thus inhibiting it would seem a logical approach to treating autoimmune diseases, given the central role of B cells. Syk inhibition, using fostamatinib, attenuates autoantibody production and reverses autoimmune glomerulonephritis in a rodent model [74]. Syk inhibitors are presently being evaluated in clinical trials of arthritis.

IL2 promotes regulatory T cell (Treg) survival and low-dose IL2 led to Treg recovery with concomitant clinical improvement was noted in a small study recruiting patients with hepatitis C induced vasculitis, a condition which is associated with low levels of Tregs [75]. TRANSREG (ClinicalTrials.gov Identifier NCT01988506) will assess the safety and biological efficacy of low-dose IL2 as a Treg inducer in a set of 11 autoimmune and auto-inflammatory diseases, GPA being one of them, with the aim to select diseases in which further therapeutic development will be pursued.

**Other important management aspects**

**Treatment of infection**
Infection is thought to play an important role driving AAV, particularly the association of *Staphylococcus aureus* with the initiation and relapse of GPA [76,77]. It is unclear how *Staphylococcus aureus* induces relapses, but one theory is that persistant low-grade infection releases pro-inflammatory cytokines, which prime neutrophils for activation by ANCA. Aggressive treatment of any infectious drive is key to the successful management of AAV.
Minimising accrual of damage

Now AAV is a chronic relapsing rather than fatal condition, it is important to consider the impact of damage as a result of periods of disease activity and the cumulative effects of immunosuppression on patients’ long-term health and quality of life. Clinicians must not only manage the disease, but also proactively take steps to address the increased cardiovascular and malignancy risks that these patients experience, and consider the impact of disease and therapy on quality of life measures. Since such complications often occur late in the disease course, it is important that we strive to include all patients with rare diseases in long-term registry follow-up. Such follow-up is imperative for those patients being treated with one of the many emerging biological agents, when rare and late side effects, such as the development of progressive multifocal leucoencephalopathy (PML), an opportunistic infection caused by the JC virus, with an incidence of 1 in 25,000 patients, are likely to be missed in short clinical studies.

Future directions

One disease or two separate conditions?

Historically, GPA and MPA have been considered together as both conditions share many clinical features and treatment approaches have been similar. However, recent data from epidemiological, long-term follow-up, and in particular, genetic studies have highlighted important differences. A recently completed Genome Wide Association Study has demonstrated clear genetic differences between GPA and MPA, which become even stronger when disease is categorised as either PR3 ANCA or MPO ANCA positive vasculitis [78], which may go some way to explaining the geographical variations in GPA and MPA [79]. This genetic evidence, together with data illustrating PR3 ANCA positivity is associated with a higher relapse risk [80] raises important questions when interpreting data from currently published studies, and more importantly when designing future studies. It is likely that in future classifications, AAV will be categorised by immunological phenotype (PR3 or MPO ANCA disease) rather than clinical phenotype (GPA or MPA). Ideally, studies should be powered to evaluate outcomes in PR3 ANCA vasculitis and MPO ANCA vasculitis independently. With such geographical variation in disease frequency and clinical phenotype, it is important that consideration is given to stratifying patients according to geographic location as we enter an era of collaborative networks and multi-centre international clinical trials.

Combination immunosuppression

The use of combinations of immunosuppressive drugs targeting different parts of the immune system has been highly effective in the field of renal transplantation, and combination induction therapy is the current gold standard [81]. The use of combinations of drugs in systemic vasculitis is a rarity, but as we learn more about the pathogenesis of these diseases, then combining agents may be a highly effective strategy. Patients with active, untreated GPA have significantly higher serum BlyS levels, when compared with healthy controls [7]. And following rituximab, BlyS levels significantly increase and then normalise as B cell populations recover possibly contributing to the return of auto-reactive B cells [82]. It may be that the combination of a B cell depleting agent with a BlyS inhibitor will produce a more sustained B cell depletion, with a corresponding clinical effect, although this must be balanced against the possible increased risk of adverse events with augmented immunosuppression.

Individually tailored therapy

To date, patients have generally been categorised into broad groups, such as those with ‘localised’ or ‘non-severe’ disease versus ‘generalised’ or ‘severe’ disease to facilitate treatment decisions [16]. Treatment has then been divided into a remission induction phase, followed by a longer period of remission maintenance therapy. In order to tailor immunosuppressive therapies to individual patients, thereby minimising drug toxicity, whilst enhancing efficacy and cost effectiveness, more sensitive and specific biomarkers than our current clinical and biochemical markers of disease response and remission are required.

Despite its limited sensitivity, ANCA is currently being used as a biomarker to guide treatment decisions in clinical trials (ClinicalTrials.gov identifiers: NCT00128895 and NCT01731561). A number of serum, urinary and cell surface biomarkers aimed at defining disease severity, remission and relapse risk have been proposed, including a CD8 T cell gene expression signature that has been associated with relapse frequency in AAV; urinary MCP-1 (monocyte chemoattractant protein 1) which correlates with degree of active vasculitis on renal biopsy and falling CDS expression on repopulating B lymphocytes indicating relapse risk [11,83-85]. However, no biomarker has been validated and entered routine clinical practice, and thus truly individualised therapy remains an aspiration rather than a reality at present.

Conclusion

As the number of therapeutic options grows, it is likely that the treatment of AAV will become more complex for clinicians. However, with the introduction of biomarkers to more accurately assess disease activity and relapse risk, we should aim to simplify treatment for patients by individually tailoring their immunosuppressive regimen. As disease control improves, we should focus more on longer-term causes of morbidity, such as cardiovascular disease and important patient-centred outcomes, including quality of life. International collaborations are vital when studying a rare condition such as AAV, in order to facilitate patient recruitment to studies, but also share clinical experience and build clinician expertise. Whilst evaluating new therapeutic strategies, research into diagnostic tests and disease
classifications, tools for the assessment of disease activity and damage and potential biomarkers must continue in parallel, as these are key components of the holistic management of patients.

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