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REVIEW

The management of anti-neutrophil cytoplasmic antibody-associated vasculitis: what has changed in the last 10 years?

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Abstract

The management of anti-neutrophil cytoplasmic antibody-associated vasculitis has substantially improved in the last decade. For the induction of remission, rituximab is increasingly used in place of cyclophosphamide, particularly for patients with proteinase 3 (PR3)-associated vasculitis or relapsing disease, and those wishing to preserve their fertility. A lower dose regimen of glucocorticoids, with a more rapidly tapering schedule, is preferable and is as effective and safer than the standard-dose regimen. Avacopan, the complement C5a receptor inhibitor, is effective in the treatment of associated vasculitis and may replace glucocorticoids in the future. Plasma exchange provides no additional benefit for patients with severe anti-neutrophil cytoplasmic antibody-associated vasculitis, although it is still used in selected patients on a case-by-case basis. Rituximab is preferred for the maintenance of remission, repeated at fixed time intervals. The duration for which immunosuppressive therapy should be given is uncertain, but is generally longer for patients with PR3 disease or persistent anti-neutrophil cytoplasmic antibody positivity. The anti-interleukin 5 monoclonal antibody, mepolizumab, is effective for the treatment of non-severe eosinophilic granulomatosis with polyangiitis. Several other targeted therapies are in the pipeline and further progress is expected in the coming years.

Key words: ANCA; Anti-neutrophil cytoplasmic antibody; Avacopan; Mepolizumab; Plasma exchange; Rituximab; Vasculitis

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Introduction

The anti-neutrophil cytoplasmic antibody-associated vasculitides include granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Jennette et al, 2013). These conditions are characterised by inflammation of the small and medium-sized blood vessels and the presence of anti-neutrophil cytoplasmic antibodies, which are autoantibodies that target antigens located in the cytoplasmic granules of neutrophils and monocytes. The target antigen for anti-neutrophil cytoplasmic antibodies is either proteinase 3 (PR3) or myeloperoxidase and thus, these vasculitides are classified into PR3-associated or myeloperoxidase-associated vasculitis (Lionaki et al, 2012).

Until a decade ago, the standard management of severe anti-neutrophil cytoplasmic antibody-associated vasculitides (organ- or life-threatening disease) included high-dose glucocorticoids and cyclophosphamide for the induction of remission, followed by azathioprine or methotrexate with gradually tapered glucocorticoids for the maintenance of remission. Plasma exchange was added for patients with rapidly progressive glomerulonephritis or diffuse alveolar haemorrhage (Lapraik et al, 2007). The combination of glucocorticoids and cyclophosphamide substantially improved the outcome for all three forms of anti-neutrophil cytoplasmic antibody-associated vasculitides, from a mortality rate of 80% at 12 months to cumulative survival rates of 88%, 85% and 78% at 1, 2 and 5 years respectively (Phillip and Luqmani, 2008; Flossmann et al, 2011). However, there remained several gaps in the management:

- Cyclophosphamide was the only available option for patients with severe anti-neutrophil cytoplasmic antibody-associated vasculitides

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- The risks of treatment with cyclophosphamide included infection, leucopoenia, bladder toxicity, cancer and ovarian failure, of which the latter was especially undesirable in young women
- Patients continued taking glucocorticoids for several years, which was problematic because a higher cumulative glucocorticoid dose was correlated with an increased risk of long-term damage in vasculitis (Robson et al, 2015)
- Mortality in these patients during the first year was mainly caused by treatment-related adverse events, rather than active vasculitis (Little et al, 2010; Flossmann et al, 2011)
- Anti-neutrophil cytoplasmic antibody-associated vasculitides was essentially converted from a rapidly fatal to a chronic grumbling disease, with a relapse rate as high as 42% over a median duration of 44 months (Hogan et al, 2005).

Several trials published in the last decade have tried to improve outcomes and reduce treatment-related toxicity. This article discusses some key advances in the management of anti-neutrophil cytoplasmic antibody-associated vasculitides. Although most trials only included patients with granulomatosis with polyangiitis and microscopic polyangiitis, changes to the management of eosinophilic granulomatosis with polyangiitis are also highlighted.

Rituximab for induction of remission

Cyclophosphamide was first used for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitides in the mid-1970s, and was the only agent available for the induction of remission for nearly four decades. During that time, efforts were mainly directed towards reducing its toxicity. The publication of some key trials in the 2000s led to:

- Shortening of the duration of treatment with cyclophosphamide to 3 months and switching to the less toxic azathioprine thereafter (Jayne et al, 2003)
- Reducing the cumulative dose of cyclophosphamide by using intermittent intravenous pulses instead of daily oral treatment (de Groot et al, 2009)
- Using methotrexate for early systemic anti-neutrophil cytoplasmic antibody-associated vasculitides with no organ or life-threatening disease (de Groot et al, 2005).

The next major advance came with the introduction of rituximab as an alternative agent for the induction of remission of anti-neutrophil cytoplasmic antibody-associated vasculitides. Rituximab is an anti-CD20 monoclonal antibody that depletes B-lymphocytes. B-cells and B-cell derived anti-neutrophil cytoplasmic antibodies have been implicated in the pathogenesis of anti-neutrophil cytoplasmic antibody-associated vasculitides (Falk and Jennette, 2002).

RAVE was a double-blind trial that randomised 197 patients with new or relapsing anti-neutrophil cytoplasmic antibody-associated vasculitides to receive either rituximab or oral cyclophosphamide followed by azathioprine (Stone et al, 2010). Both groups received the same regimen of glucocorticoids. Patients with serum creatinine levels of >354 µmol/litre and those with diffuse alveolar haemorrhage who required mechanical ventilation were excluded. The results showed that rituximab was not inferior to cyclophosphamide for inducing remission at 6 months (64% for rituximab vs 53% for cyclophosphamide, $P<0.001$). For those with relapsing disease, rituximab was superior to cyclophosphamide (67% vs 42%, $P=0.01$). There were no major differences between the two groups in overall adverse events during the 6 months of follow up.

In RITUXVAS, an open-label trial, 44 patients with severe anti-neutrophil cytoplasmic antibody-associated vasculitides and renal involvement were randomised to receive rituximab or cyclophosphamide followed by azathioprine, along with glucocorticoids (Jones et al, 2010). Patients in the rituximab arm also received two infusions of cyclophosphamide. The rates of sustained remission at 12 months (76% with rituximab vs 82% with cyclophosphamide, $P=0.68$) and serious events (42% with rituximab vs 36% with cyclophosphamide) were similar in both groups.

The American College of Rheumatology guidelines recommend rituximab over cyclophosphamide for the induction of remission, as it is less toxic, and for cyclophosphamide to be considered only when rituximab needs to be avoided or there is continued active disease despite the use of rituximab (Chung et al, 2021). Rituximab is particularly suitable

for younger women who wish to preserve their fertility. The availability of biosimilar versions of rituximab has considerably reduced the costs of treatment. A retrospective study that compared the rituximab biosimilar (Truxima) and bio-originator (MabThera) for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitides demonstrated equivalent efficacy and safety (Antonelou et al, 2021).

For eosinophilic granulomatosis with polyangiitis, the evidence for the use of rituximab is only based on retrospective studies. Complete or partial remission was reported in 83% of patients at 12 months in one study (Mohammad et al, 2016), and 77% of patients at 6 months in another (Teixeira et al, 2019). Anti-neutrophil cytoplasmic antibody-positive patients had a better response than those who were anti-neutrophil cytoplasmic antibody-negative. The American College of Rheumatology guidelines therefore recommend rituximab for patients with eosinophilic granulomatosis with polyangiitis who have either glomerulonephritis or positive anti-neutrophil cytoplasmic antibodies, and those who are at risk of gonadal toxicity (Chung et al, 2021).

Plasma exchange for severe associated vasculitis

Plasma exchange involves the extracorporeal separation of plasma from cells using a plasma separator. Plasma components, including autoantibodies like anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody (anti-GBM) and anti-double stranded deoxyribonuclease antibody (anti-DNA), cryoglobulins, complement proteins and cytokines, are removed by this process.

Plasma exchange was first introduced as a treatment for patients with anti-GBM disease in the 1970s (Lockwood et al, 1975). It was then extended to patients with anti-neutrophil cytoplasmic antibody-associated vasculitides, particularly those with rapidly progressive glomerulonephritis and serum creatinine levels >500 µmol/litre, or those with severe diffuse alveolar haemorrhage. International guidelines on vasculitis (Ntatsaki et al, 2014; Yates et al, 2016) recommended its use, based on the results of the MEPEX trial which demonstrated short-term benefits from plasma exchange in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides and serum creatinine levels >500 µmol/litre (Jayne et al, 2007). A higher proportion of patients who received plasma exchange-based induction therapy had achieved dialysis independence at 3 months (69% vs 49%) and reduced progression to end-stage renal disease at 12 months (19% vs 43%). However, these benefits were not sustained in the long term, with similar mortality rates between the two groups (Walsh et al, 2013).

PEXIVAS, the largest trial to be conducted in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides, sought to find out if plasma exchange would reduce progression to end-stage renal disease if used at an earlier stage in the disease (Walsh et al, 2020). In this study, 704 patients with granulomatosis with polyangiitis or microscopic polyangiitis and estimated glomerular filtration rate of less than 50 ml/min were randomised to receive plasma exchange or no plasma exchange, along with glucocorticoids and either cyclophosphamide or rituximab. The sample included 191 patients with pulmonary haemorrhage. The results suggested that plasma exchange provided no additional benefit in reducing the risk of the composite of progression to end-stage renal disease and death (28.4% vs 31.4%, hazard ratio 0.86, 95% confidence interval 0.65–1.13), after a median follow-up period of 2.9 years. There was no benefit noted in the sub-groups of patients with serum creatinine level >500 µmol/litre or those with pulmonary haemorrhage. These findings had a major impact in the field of vasculitis, and the American College of Rheumatology guidelines conditionally recommended against the routine addition of plasma exchange to remission induction therapy for patients with anti-neutrophil cytoplasmic antibody-associated vasculitides who have active glomerulonephritis or pulmonary haemorrhage (Chung et al, 2021).

The negative results of PEXIVAS led to a lot of debate (De Vriese and Fervenza, 2021; Kronbichler et al, 2021; Specks et al, 2021;). One criticism was that the proportion of patients with interstitial fibrosis and tubular atrophy was not known, as renal biopsy was not done in all the patients (these patients are unlikely to respond to plasma exchange). The opposing view was that it was unlikely that there were many patients without active

renal inflammation, as patients who were not biopsied were included only when there were active sediments in the urine, and all those with estimated glomerular filtration rate <50 ml/min for longer than 3 months were excluded. The protocol-driven use of alternate-day plasma exchange for 14 days, instead of daily, was also criticised, as it may have been insufficient to have an effect in some patients. It was also felt that no conclusions could be drawn regarding the usefulness of plasma exchange for diffuse alveolar haemorrhage, as the composite of progression to end-stage renal disease and death was not a pulmonary outcome measure. In one large cohort study, there was no difference in the duration of mechanical ventilation, length of stay in the intensive care unit or the rate of remission after 6 months, between patients who received plasma exchange and those who did not (Cartin-Ceba et al, 2016).

Despite the negative results of PEXIVAS, there are some situations where plasma exchange is recommended:

- Double-positive disease (positive for both anti-GBM and anti-neutrophil cytoplasmic antibody), as the outcome for these patients is far worse than that of those with anti-neutrophil cytoplasmic antibody alone (McAdoo et al, 2017)
- Patients at higher risk of progression to end-stage renal disease.

Based on the American College of Rheumatology guidelines (Chung et al, 2021), patients with rapidly worsening renal function, crescents on renal biopsy, poor response to induction therapy and reduced risk of serious infection could be considered for plasma exchange. For patients with severe diffuse alveolar haemorrhage, it may be difficult to justify the use of plasma exchange although physicians will probably continue to consider this on a case-by-case basis.

Minimising the exposure to glucocorticoids

As discussed earlier, early mortality in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides was linked to glucocorticoid-related adverse events and infection (Little et al, 2010). Reducing exposure to glucocorticoids was therefore desirable.

The PEXIVAS trial had a 2 x 2 factorial design, meaning patients who were randomised to receive plasma exchange or no plasma exchange were further randomised to receive either a reduced-dose or the standard-dose regimen of glucocorticoids (Walsh et al, 2020). Patients in the reduced-dose arm received 50% of the standard dose from the second week onwards, and the dose was rapidly tapered to 5 mg/day as early as the fourteenth week. There was no difference between the two groups with respect to the composite of progression to end-stage renal disease and death (27.9% in the reduced dose group vs 25.5% in the standard dose group) over up to 7 years of follow up. Importantly, serious infections at 1 year were less common in the reduced-dose group than in the standard-dose group (incidence rate ratio 0.69, 95% confidence interval 0.52–0.93).

Another prospective trial of 49 patients with anti-neutrophil cytoplasmic antibody-associated vasculitides demonstrated that an even more rapid withdrawal of glucocorticoids within 1–2 weeks was feasible, when used in conjunction with rituximab and low-dose cyclophosphamide (Pepper et al, 2019). All patients were able to achieve remission and there was a reduced risk of infection and diabetes, when compared to matched cohorts from other vasculitis trials.

The ADVOCATE trial went a step further and used a glucocorticoid-free regimen to treat anti-neutrophil cytoplasmic antibody-associated vasculitides (Jayne et al, 2021). In this double-blind trial, 331 patients with granulomatosis with polyangiitis or microscopic polyangiitis were randomised to receive avacopan, an oral small molecule inhibitor of the complement C5a receptor or oral prednisolone, along with cyclophosphamide or rituximab. About 80% of patients had renal vasculitis, but those on dialysis or with diffuse alveolar haemorrhage were excluded. The rationale for using avacopan was that activation of the alternative complement pathway, which results in the generation of C5a, plays a key role in the pathogenesis of anti-neutrophil cytoplasmic antibody-associated vasculitides by recruiting and activating neutrophils. Glucocorticoids were used by patients in the avacopan group during the screening phase, but the mean total daily dose was only one-third of that used by those in the prednisolone group. The results showed that avacopan was non-inferior

to glucocorticoids in inducing remission at 6 months (72.3% for avacopan vs 70.1% for prednisolone) and superior to glucocorticoids in inducing sustained remission at 52 weeks (65.7% for avacopan vs 54.9% for prednisolone). There were more glucocorticoid-related side effects, serious adverse events, deaths and infections in the prednisolone group than in the avacopan group.

In light of these findings, there has been a major shift towards the use of lower doses of glucocorticoids and a more rapid tapering schedule. In future, therapies that target the innate immune mechanisms may completely replace glucocorticoids, further improving the safety.

Rituximab for maintenance of remission

As mentioned earlier, maintenance of remission has been a major challenge in the management of patients with anti-neutrophil cytoplasmic antibody-associated vasculitides. The risk of relapse is particularly high for patients with granulomatosis with polyangiitis or positive anti-PR3 (Walsh et al, 2012). Azathioprine and methotrexate were not sufficient to maintain long-term remission in a majority of patients (Puechal et al, 2016), and neither was rituximab if it was only used for induction (Specks et al, 2013).

Continuing rituximab treatment beyond 6 months was therefore explored as an option for maintaining remission in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides. In the MAINRITSAN 1 trial, 115 patients with new or relapsing granulomatosis with polyangiitis or microscopic polyangiitis were randomised to receive 6-monthly rituximab for 18 months or azathioprine for 22 months, following the induction of remission with cyclophosphamide. The results at 28 months were impressive, with only 5% of patients in the rituximab arm experiencing a relapse as opposed to 29% in the azathioprine arm (Guillevin et al, 2014). In the RITAZAREM trial, which included only patients with relapsing anti-neutrophil cytoplasmic antibody-associated vasculitides, patients were randomised to receive rituximab or azathioprine, following the induction of remission with rituximab. The results were similar, with rituximab again proving to be superior to azathioprine in preventing relapses (13% for rituximab vs 38% for azathioprine, after 24 months) (Smith et al, 2019). The American College of Rheumatology guidelines (Chung et al, 2021) therefore recommend rituximab over azathioprine or methotrexate for maintenance of remission in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides, and giving rituximab at fixed time intervals (every 6 months) rather than waiting for a flare.

What has not been resolved yet is the duration of treatment for maintenance of remission. The challenge is to balance the risk of disease flare with the risk of adverse effects from continued exposure to immunosuppressive treatments. In the MAINRITSAN 3 trial, 97 patients who were in remission after completing 18 months of rituximab were randomised to receive rituximab for a further 18 months or switch to a placebo. After 28 months from randomisation, relapse-free survival was higher among patients who continued rituximab for 36 months (96% vs 74%), and there were no differences in the incidence of adverse reactions between the two groups (Charles et al, 2020). In the REMAIN trial, 117 patients with anti-neutrophil cytoplasmic antibody-associated vasculitides were randomised to continue azathioprine for 48 months or withdraw after 24 months, following the induction of remission with cyclophosphamide. The relapse rate was higher in the withdrawal arm than in the continuation arm (63% vs 22%, $P<0.0001$). Positive anti-neutrophil cytoplasmic antibody at randomisation and PR3-associated disease were risk factors for relapse. As expected, there were more adverse events in the continuation arm than in the withdrawal arm (Karras et al, 2017).

In summary, rituximab is an effective agent for maintenance of remission among patients with granulomatosis with polyangiitis or microscopic polyangiitis. There is evidence for continuing treatment at fixed time intervals for up to 36 months. Patients with PR3-associated vasculitis or those who remain anti-neutrophil cytoplasmic antibody positive should receive treatment for longer (Hogan et al, 2005). For patients with eosinophilic granulomatosis with polyangiitis, there is less experience with rituximab, hence either azathioprine, methotrexate or mycophenolate is recommended for maintenance of remission (Chung et al, 2021).

Mepolizumab for eosinophilic granulomatosis with polyangiitis

The manifestations of eosinophilic granulomatosis with polyangiitis include both 'vasculitic' (for example glomerulonephritis or mononeuritis multiplex) and 'eosinophilic' (for example sinusitis, asthma, pulmonary infiltrates or myocarditis) components. Interleukin-5 (IL-5), which helps with the production and maturation of eosinophils, plays a key role in the pathogenesis of the eosinophilic manifestations of eosinophilic granulomatosis with polyangiitis (Rothenberg, 1998). Hence, mepolizumab, the anti-IL5 monoclonal antibody, has been explored as a treatment for eosinophilic granulomatosis with polyangiitis.

In one large double-blind trial, 136 patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis, but without organ- or life-threatening manifestations, were randomised to receive subcutaneous mepolizumab every 4 weeks or placebo (Wechsler et al, 2017). All patients also received glucocorticoids with or without immunosuppressive therapy. The results showed that after 52 weeks, patients in the mepolizumab group had a significantly greater accrued remission for at least 24 weeks (28% vs 3%, odds ratio 5.91, 95% confidence interval 2.68–13.03, $P<0.001$). Overall, 53% of the patients in the mepolizumab group achieved remission as opposed to only 19% in the placebo group. Patients in the mepolizumab group had fewer relapses and a higher proportion of them were able to taper the dose of prednisolone to less than 4 mg after 48 weeks (44% vs 7%, $P<0.001$). There was no difference between the two groups in the occurrence of adverse events, which were generally mild.

On the basis of these results, the American College of Rheumatology guidelines recommend mepolizumab for patients with active and non-severe eosinophilic granulomatosis with polyangiitis, especially those with eosinophilic manifestations such as asthma, rhinitis or sinusitis (Chung et al, 2021). However, the cost of mepolizumab is prohibitive, with each injection costing about £840, and there is also no evidence yet for its use in patients with severe eosinophilic granulomatosis with polyangiitis (for example neurological, cardiac, gastrointestinal or renal involvement).

The original Five Factor Score, which was derived from patients with polyarteritis nodosa, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis included cardiac, gastrointestinal and central nervous involvement, a plasma creatinine level >141 µmol/litre and proteinuria >1 g/day (Guillevin et al, 1996). The 5-year mortality rates for a Five Factor Score of 0, 1 and ≥2 were 12%, 26% and 46% respectively. The recommendation was to treat those with a Five Factor Score of 0 with glucocorticoids alone, and those with a Five Factor Score of ≥1, alveolar haemorrhage or mononeuritis multiplex with glucocorticoids and cyclophosphamide (or rituximab). The Five Factor Score was revised in 2011 (proteinuria and CNS involvement were removed and replaced with an age over 65 years and an absence of ear, nose and throat symptoms) (Guillevin et al, 2011), but the original Five Factor Score is still used to make treatment decisions.

Case studies 1 and 2 discuss some of the main management options for two fictional patients with differing forms of vasculitis.

Case study 1. Severe associated vasculitis with pulmonary-renal syndrome

A 28-year-old woman presented with a 2-day history of cough, haemoptysis, breathlessness and oliguria. Her past medical history shows nothing of note and she is on no regular medication. Her vital parameters show normal temperature, heart rate 96/min, respiratory rate 24/min, blood pressure 154/102 mmHg and oxygen saturation of 96% on 4 litres of oxygen. There is palpable purpura in her legs.

Her chest X-ray shows diffuse alveolar shadowing. Urinalysis shows 2+ protein, 3+ blood, numerous red cells and red cell casts. Her haemoglobin level is 94 g/litre and serum creatinine level is 224 µmol/litre (no previous blood test results are available for comparison). Anti-neutrophil cytoplasmic antibody is positive for myeloperoxidase and negative for PR3. Anti-nuclear antibody and anti-GBM antibody are negative. Renal biopsy

Case study 1. (Continued)

shows pauci-immune, crescentic and necrotising glomerulonephritis*. Two days later, she is mechanically ventilated because of increasing oxygen requirements and her creatinine level rapidly rises to 546 µmol/litre. Bronchoalveolar lavage confirms the presence of alveolar haemorrhage.

Management of this patient, based on current evidence, would include:

- High dose glucocorticoids (pulse intravenous glucocorticoids, followed by gradually tapered, standard dose of oral glucocorticoids†)
- Rituximab for induction of remission, especially considering her young age
- Plasma exchange may be considered because of the higher risk of progression to end-stage renal disease (based on the presence of crescents on renal biopsy and rapidly worsening renal function)
- Pneumocystis and anti-fungal prophylaxis, screening for hepatitis B and appropriate prophylaxis to prevent reactivation, bone protection and vitamin D replacement, gastroprotection, cardiovascular risk assessment, and vaccinations against influenza and pneumococcus
- Rituximab for maintenance of remission, given at fixed time intervals, every 6 months.

Her anti-neutrophil cytoplasmic antibody level should be tested every 6 months (Ntatsaki et al, 2014). Her risk of relapse is lower than that of patients with PR3-associated vasculitis, but the duration of treatment should be prolonged if she remains persistently anti-neutrophil cytoplasmic antibody-positive. If she wishes to get pregnant in the interim, she should be advised to start trying only after at least 6 months have elapsed since the last dose of rituximab (Flint et al, 2016). If maintenance immunosuppression is indicated, azathioprine would be the drug of choice, as methotrexate and mycophenolate are both contraindicated in pregnancy.

**In severely ill patients, it may be necessary to begin treatment even before a biopsy could be performed or the biopsy results are available.*

†The sub-group analysis of PEXIVAS favoured the standard-dose regimen over the reduced-dose regimen for patients with pulmonary haemorrhage (Jayne et al, 2007).

Case study 2. Anti-neutrophil cytoplasmic antibody-positive eosinophilic granulomatosis with polyangiitis with mononeuritis multiplex

A 43-year-old man presents with inflammatory joint pains in his wrists, knees and ankles. He has necrotic skin lesions over his shins. Six months earlier, he was diagnosed with asthma. He moved to the UK from Myanmar 2 years ago. His eosinophil count is 9.36×10^9/litre (normal value $<0.35 \times 10^9$/litre) and erythrocyte sedimentation rate is 76 mm/hour. His chest X-ray, urinalysis and renal function are normal. A two-dimensional echocardiogram is normal. Anti-neutrophil cytoplasmic antibody is positive for myeloperoxidase and negative for PR3. Three days after presentation, he develops a right foot drop and, within the next few hours, a left wrist drop. Nerve conduction studies confirm mononeuritis multiplex.

Management of this patient would include:

- High dose glucocorticoids (typically administered as intravenous methylprednisolone pulses for 3–5 days, followed by high dose oral prednisolone)
- Rituximab for induction of remission, as he is anti-neutrophil cytoplasmic antibody positive
- Ivermectin for prophylaxis against disseminated Strongyloides infection, given his previous residence in Myanmar
- Pneumocystis and antifungal prophylaxis, screening for hepatitis B and appropriate prophylaxis to prevent reactivation, bone protection and vitamin D replacement, gastroprotection, cardiovascular risk assessment and vaccinations against influenza and pneumococcus
- Azathioprine, methotrexate or mycophenolate for maintenance of remission.

Future developments

Several targeted therapies, such as those that target spleen tyrosine kinase, B-cell activating factor, T-cell co-stimulation and tolerogenic peptides, are being tested (Kitching et al, 2020).

Key points

- Rituximab is increasingly being used in place of cyclophosphamide for induction of remission in anti-neutrophil cytoplasmic antibody-associated vasculitis.
- A lower-dose regimen of glucocorticoids with a more rapid tapering schedule is preferable.
- Plasma exchange provides no additional benefit for patients with severe anti-neutrophil cytoplasmic antibody-associated vasculitis.
- Avacopan, the C5a inhibitor, may replace glucocorticoids in the future.
- Mepolizumab is effective in patients with non-severe eosinophilic granulomatosis with polyangiitis.

It has been suggested that once the innate immune system has been fully activated by anti-neutrophil cytoplasmic antibody, the therapeutic removal of anti-neutrophil cytoplasmic antibody becomes inconsequential, thus explaining the lack of benefit for plasma exchange in the PEXIVAS trial (Specks et al, 2021). Hence, the development of therapies that target the innate immune system are eagerly awaited, especially as they might completely replace glucocorticoids in the future (Brilland et al, 2020).

Conclusions

The main objectives in the management of patients with anti-neutrophil cytoplasmic antibody-associated vasculitides are to make an early diagnosis, rapidly suppress the disease activity, maintain long-term remission, minimise treatment-related toxicity and reduce the overall morbidity and mortality. Although clinicians are nowhere close to meeting all these objectives, progress has been made in the last decade.

There are several unmet needs and unanswered questions. First, there are no reliable biomarkers for measuring disease activity and predicting relapse. Second, the length of time after which immunosuppressive treatments can be safely withdrawn is still not clear. Third, there is a paucity of trials in eosinophilic granulomatosis with polyangiitis because of the heterogenous nature of the disease. Lastly, biologic therapies are not widely available in all countries and even the biosimilar versions may be too expensive for many patients, especially in developing countries. Fortunately, international collaboration, which is essential because of the rarity of these conditions, has enabled research to flourish and further exciting advances are likely to be seen in the coming years.

Conflicts of interest

The author declares that there are no conflicts of interest.

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