Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Achieving and Sustaining Remission while Reducing Organ Damage

Interviews with Three Key Opinion Leaders

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Due to advances in treatment, antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is no longer a universally fatal condition; however, difficulties remain in managing its chronic relapsing-remitting course. Current standard of care[1] aims to control the multi-system damaging vasculitis but exposes patients to the risk of severe treatment toxicities in the short and long-term, particularly from high-dose or prolonged steroid use. Moreover, a lack of knowledge around disease recognition in real-world clinical practice often impedes patient access to the required specialist care. In this article, three experts in the field of AAV, Prof Annette Bruchfeld, Prof Kirsten de Groot, and Prof David Jayne, offer their views on the current status of disease assessment and management. In a series of interviews conducted by the European Medical Journal in June and July 2019, the experts identified present challenges and future goals, and discussed the impact of remission and relapse on patients with AAV. In particular, they voiced their concerns over the clinical risks of therapy versus sustained disease control and suggested how improvements in healthcare services and communication could transform patient care.

CURRENT CHALLENGES

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare inflammatory diseases including microscopic polyangiitis, granulomatosis with polyangiitis (previously known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome).[2] AAV can cause inflammation and damage to small blood vessels throughout the body, with the kidneys, ears, nose, sinuses, lungs, and skin being most commonly affected. Although treatments are available to induce remission of AAV, the current standard of care, typically involving immunosuppressants and high-dose steroids,[1] is associated with significant clinical risk.

Prof Bruchfeld commented on the ideals of providing effective treatment for AAV, while limiting the patient's exposure to severely toxic side effects. "The goal would be to deliver effective treatment early, with medications that are less toxic than those we have today. We also need to find a way to reduce the number of relapses which, in time, would serve to reduce organ damage."

"Maintenance of remission is the major challenge," agreed Prof de Groot, "Especially for patients who are at high risk of relapse – for those patients, we don't have so many options. Also, we don't currently have treatment-free long-term remission." Identifying patients at greatest risk of relapse was seen as a key area for improvement, with potential stratifying parameters including renal involvement; ANCA target proteins (e.g., myeloperoxidase versus proteinase 3); granulomatosis versus vasculitic disease; persistent microhaematuria; and ANCA conversion at remission.

In Prof Jayne's view, two further main issues at present are access to expert advice, and delays in diagnosis. "Unless they have very characteristic presentations, rare diseases usually result in diagnostic delay. This is compounded by the fact that AAV can present in many different ways, with different parts of the body involved, and it often takes 3–6 months before the diagnosis is made. Also, general practitioners (GP), to whom patients first present, don't tend to do the necessary tests, which is inevitable with a rare disease." Prof Bruchfeld and Prof de Groot concurred, emphasising the importance of physician awareness and education around AAV. Although the situation was said to have improved notably over the last 20 years, educating physicians (especially primary care doctors) to recognise the signs of the disease would further facilitate patient referral to specialist centres for diagnosis and management. "This is very important. The nephrology and rheumatology communities know the disease well now, but it needs someone to send the patient to these specialists, and that person is not so well educated in terms of AAV. We have to transfer our knowledge," said Prof de Groot.

CLINICAL ASSESSMENT

Whilst clinical trial endpoints for assessment of AAV are well described, the means of evaluating disease in the clinic are less clearly defined. The experts highlighted what they felt should be best practice in this area.

Prof Jayne outlined the two typical types of patient presentation: firstly, the patient who is admitted to hospital as an emergency, usually with either kidney or severe lung disease as a presenting feature, and who is diagnosed in hospital; secondly, there is the non-emergency patient who is referred to hospital, typically without a particular diagnosis but with a set of symptoms that are subsequently diagnosed by the hospital as AAV. "The key threshold is suspicion," commented Prof Jayne, and once the physician suspects AAV, the experts agreed that the actual assessment process is fairly standard, involving: X-rays, computed tomography (CT) scans, blood and urine tests, plus other investigations related to the main manifestations of disease, for example renal biopsies. "The ANCA blood test is of particular importance," commented Prof Jayne. "It is positive in around 95% of patients, relatively specific for AAV, and widely available. If the ANCA test is positive and the patient has symptoms suggestive of AAV that essentially confirms the diagnosis," he explained.

Prof de Groot emphasised the importance of an interdisciplinary team in achieving the full clinical assessment. In addition to the treating specialist (nephrologist/rheumatologist), there may be need for a radiologist, neurologist, and likely also an ENT doctor, pulmonologist, and

ophthalmologist. "It is quite a challenge to establish a stable team with experience of the disease," she commented. Prof Bruchfeld added that, in her view, patients should be at the heart of the assessment process. "Often the patient is forgotten. Doctors don't always understand that patients need the best information possible so that they are clear about their disease status and long-term prognosis. For example, if the patient has a lot of chronic renal damage, it is important they understand that the disease can be stabilised but, in the future, they may need to start dialysis," she clarified.

Prof Bruchfeld also pointed out that many of her patients at the University Hospital are enrolled in clinical and surveillance studies and that, in this environment, the use of rating scales is part of the standard patient assessment. She cited the Birmingham Vasculitis Activity Scale (BVAS)[3] as a helpful tool for following disease activity and detecting remission but commented that it is not often used outside clinical research, although she frequently uses BVAS as an educational tool and also advocates its use in smaller centres. While Prof Jayne doesn't believe these scales are suited to routine clinical practice, he agreed that BVAS is a useful tool for education and training, helping physicians to recognise and understand the range of disease manifestations.

Determining Remission

Current European guidelines[1] consider treatment for AAV in terms of remission induction and maintenance therapy, and subsequently, treatment of relapse. This raises the issue of how remission should be defined or recognised, in order to direct ongoing treatment.

"It is important to have a clear picture of when the patient is in remission, so to minimise exposure to the toxicities of initial treatment," said Prof Bruchfeld. Together with Prof de Groot, she advised that a BVAS score of zero is often the predefined target for remission, along with clinical observations that vessel inflammation has ceased in all organ systems. In Prof Jayne's view, assessment most often relies upon pattern recognition and experience. "Each organ system needs to be considered in turn, in order to work out whether persistent symptoms/abnormalities reflect ongoing disease in those areas of the body – and this is part of the skill of managing AAV," he explained. "Tests such as inflammatory markers (CRP [C-reactive protein], ESR [erythrocyte sedimentation rate], etc.) have a certain value, but they also have problems. Can we rely on them? What does it mean if the ANCA test is negative? Then there are patient symptoms that don't necessarily relate to AAV activity. It is a complex picture."

Prof de Groot further articulated these difficulties: "The more precisely you look, the less the patient appears in remission. For example, if you do an MRI of the sinuses every 3 months, you will see that the sinusitis never disappears, so you can never say that the patient is in remission. On the other hand, if you don't do these detailed assessments/radiology exams, then it's clinical judgement alone and the patient is more likely to appear in remission. So we really need to define whether we want to use CT and MRI as remission parameters or just keep to clinical tests and BVAS score." Prof Jayne agreed, pointing out that the division of remission induction and maintenance therapy is slightly artificial. "There's quite a lot of evidence to suggest that the disease is continuing, even though we're labelling people as being in remission. A lot of this has been driven historically by the desire to limit the use of cyclophosphamide (a standard immunosuppressant treatment for AAV) to only 3–6 months because it's a toxic drug – and so the remission induction period has been labelled accordingly. The bottom line is that relatively inexperienced centres may over-treat patients while more experienced centres may be better at determining remission and switching patients to maintenance therapy," he concluded.

Concerning the long-term impact of assessing and achieving remission, Prof de Groot stated, "If a patient is judged as not being completely in remission then they remain on induction treatment for longer. If induction of remission takes >3–6 months, we know that the outcome is worse; so achievement of full remission, rather than partial, within 3–6 months is important." It was also acknowledged that some patients recover more quickly than others, and the experts concurred that the greatest benefits of prompt symptom control are less organ damage and less exposure to the toxicities of treatment (steroids, in particular). Prof Jayne commented, "Steroid doses tend to be tapered along with improved control of the disease, so increased exposure is a

consequence of delayed disease control. Further to this, the organ we are most interested in is the kidney, and we know that we control kidney disease quite slowly, over months. If there was a treatment that could control kidney disease within days, this would have a long-term protective effect on organ function."

RELAPSE – TREATMENT AND IMPACT

Relapse is common in patients following conventional immunosuppressive therapy. After treatment has stopped, the experts estimated that by 2 years, 20–30% of patients will have relapsed, rising to 50–70% of patients within 5–10 years. "Those figures would be higher if you stopped the treatment earlier, and lower if you continued the treatment for longer," said Prof Jayne. It was explained that the rate of relapse also varies according to diagnosis, with granulomatosis with polyangiitis patients more prone to relapse than patients with microscopic polyangiitis, for example. In addition, it is important to distinguish the relapse rates achieved with conventional therapy (as above) from those observed more recently with rituximab, which postpones relapse further. Prof Bruchfeld commented that "we also have to be aware that patients can relapse beyond 10 years. This is why we continue specialist monitoring without fully discharging patients to GP care. It gives a better chance of recognising relapse, and we educate patients to contact us if they have specific symptoms that could indicate relapse." Prof Bruchfeld feels that this monitoring practice is likely to continue for the foreseeable future. "There may well be a group of patients who will have this disease once and never again, but we don't yet know who they are," she said.

The impact of relapse is significant, exposing patients to the risk of further organ damage and greater burden of medication and associated side effects. "About a third of relapses are what we would consider major relapses, which have long-term consequences in terms of mortality risk, and risk of end-stage renal disease," said Prof Jayne. "In contrast, minor relapses don't tend to result in significant organ damage, but they cause patient distress, making them feel unwell and, perhaps most critically, they commit the patient to a lot more treatment and associated toxicity. This is not only due to treating the relapse, but also because the physician is a lot more reluctant to stop the drugs in the future, and patients can remain on treatment for years." Prof Jayne outlined how these more and less severe states of relapse could present in practice: "For example, if you had a patient with known renal involvement, and they had a return of blood and protein in the urine, but with unchanged blood tests, that relapse could be regarded as relatively non-severe because you know it can be controlled and the patient hasn't suffered. In contrast, if your patient with renal disease presents with a relapse in which their renal function has seriously declined, you know that they are going to struggle to recover again, and the consequences from this relapse will be much worse."

Distinguishing between major and minor states of relapse was said to be difficult and could also be seen as an arbitrary divide in what is essentially a continuum of disease. Prof Jayne commented, "The reality is that minor relapses tend to be followed by other minor relapses or major relapses. Any relapse is a bad thing, and minor relapses are often major relapses just picked up early." Prof Bruchfeld concurred, "Deciding how to treat more minor relapses is problematic, as it is uncertain whether a minor relapse will precede a major relapse." However, she also pointed out that in clinical study centres, the major/minor divide is often defined using BVAS scoring, with major relapse being a more severe manifestation of disease that would, in turn, require more aggressive treatment. Prof de Groot added, "It is the difference between whether you reintroduce steroids at a low dose or whether you do a full re-induction treatment with more steroids and probably a more potent immunosuppressant. There is a difference, in terms of severity of disease, in terms of damage accrual, and in terms of need for a more potent immunosuppressant."

The experts confirmed that in patients without contraindicatory comorbidities (e.g., diabetes, osteoporosis) minor relapses are routinely treated by increasing steroid dose: "Even though there are strong data showing that this is not a good approach, and that almost all relapses treated in this way will be followed by further relapses," said Prof Jayne. "Rheumatologists, especially, spend their lives inventing therapies to enable us to avoid the use of steroids, but at the moment we don't have a better concept," added

Prof de Groot. Prof Bruchfeld agreed, "In general, I think most vasculitis doctors would like to find a way out of using so many steroids, because we know that the short and long-term side effects are not good for the patient." As a consequence, said Prof Jayne, there is a move towards the routine use of rituximab as an immunosuppressant treatment for all patients with relapse, whether deemed minor or major. He added, "Steroids are a major driver of long-term damage, so if you look 5–10 years on, about 50% of patients will have an aspect of steroid-induced damage, and that is directly related to relapse driving continuation of steroid dosing."

ADVERSE EVENTS OF THERAPY

Considering the clinical risks of therapy for AAV, infection was said to be the major problem in the short term (first year), strongly correlated to immunosuppression and steroid use. It is a predictor of early death, and the risk of infection is raised in patients who are older, have renal failure, and/or display comorbidities. Although other short-term issues such as steroid-dependent diabetes were noted, the experts were clear that infections dominate in the short term and remain a risk as long as steroid treatment continues. Prof de Groot clarified: "Mortality is high in the first year of treatment. Almost 11% of patients die within the first year, and half of them die from infections – very few die from active disease. This illustrates the issue of (probable) overtreatment within the first year, putting patients at risk of dying from the side effects of treatment."

In terms of more long-term adverse events, Prof Jayne believes that they should be generally viewed as being in one of two groups: either immunosuppressant-related or steroid-related. "Conventional immunosuppressive treatment (cyclophosphamide followed by oral immunosuppressants) is associated with an approximate 3-fold increase in malignancies (particularly skin malignancies) and, in younger patients, fertility problems due to cyclophosphamide," he said. Concerning steroid-related effects, Prof de Groot stated, "We know that every gram of steroids adds to the accrual of damage, and there are a lot of side effects from steroids, like diabetes, osteoporosis, weight gain, cataracts, thinning of the skin; and with every steroid course you add to these side effects."

Another long-term risk of the current standard of care is cardiovascular disease, as outlined by Prof Bruchfeld: "Many of these patients are older and may, due to vasculitis, have hypertension, reduced renal function, or residual proteinuria, all of which increase the risk of cardiovascular disease. So, long-term, we often face a cardiovascular quandary which is important, but difficult to prevent."

Among the many adverse effects, Prof Jayne thinks that the biggest concern for physicians is any event that leads to hospital readmission. This is most likely to be related to an infection, a cardiovascular or thromboembolic event, or symptoms of major relapse/inability to control the disease. Another specific concern is patients having to enter dialysis, said Prof Bruchfeld. However, she believes that this can be an abstract concept to patients, who are themselves likely to be more immediately concerned about steroid-related adverse events and fatigue: that is, aspects which affect their daily life. Prof Jayne agrees that patients simply want to feel better and to survive. "At the outset, patients aren't often made aware of the long-term complications of the disease. Usually, their concerns are functional; they want to be back at work, they want to be looking after their children, and they want relief from symptoms," he explained. In addition, they are concerned about the use of steroids: "Patients hate steroids," acknowledged Prof de Groot. "They know they work well and act very quickly but, longer term, higher dose steroids are disliked not only by doctors, but by patients in particular."

The ability to sustain remission while limiting adverse events is key to the current and future treatment of AAV. The best means of achieving this depends upon the patient profile but there was general agreement that, for a relapsing patient, an immunosuppressant regimen with rituximab dosed just once or twice a year, avoiding (or at very least tapering) steroids and other oral medications, is the best option at present. Prof de Groot added, "Very often we have a steroid-free long-term remission, but there is still continuous use of immunosuppressants. Treatment-free remission, which is what we would wish to have, is not yet available."

LOOKING AHEAD

Considering the future of treatment for AAV, the experts identified several key targets. Prof Jayne listed two main goals: to control the disease more quickly, and to reduce the risk of relapse (essentially curing the disease), giving the patient confidence that there will be no need for further treatment. Furthermore, he believes that better organisation of healthcare systems and resources is another major unmet need. "The reality is that most patients with AAV are treated by generalists, and not vasculitis specialists. So inevitably, there is going to be variability in quality of care. Countries that have made efforts to improve these healthcare services, particularly France, have demonstrated that this directly improves long-term outcomes for patients," he said.

Prof Bruchfeld believes that there should be greater investment in patient concerns; for example, related to treatment toxicities and fatigue. "Fatigue is a continual side effect of the disease and its treatment. If it's from the treatment we should change it, so that the patient can live a more normal life. Taking more interest in patient concerns will give us the incentive to develop their treatment in different ways, and not just focus on inflammation," she explained. Prof Jayne reiterated that patients also need better access to advice, both during the route to diagnosis (which is often long and delayed), and once diagnosis is confirmed. "What I hear about, on almost a daily basis, is patients struggling to access advice in which they feel confident," he noted.

Steroid-free treatment was highlighted by Prof de Groot as another critical need, in addition to immunosuppressant-free long-term remission. "Steroids are something that, in 20 years of vasculitis research, we cannot renounce," she said, "We still can't go without steroids."

CONCLUSION

Prof Bruchfeld, Prof de Groot, and Prof Jayne clearly highlighted the many existing issues in the management of AAV, largely centring on the lack of disease awareness in primary care, the maintenance of remission, and the toxicities of existing treatment (high-dose steroids in particular). Long-term use of steroids and continued immunosuppressant treatment through remission were cited as specific problems. Resulting effects such as infection and organ or tissue damage are strongly associated with a poor prognosis and a raised mortality risk in this complex condition. They represent a key focus for the development of future therapies, alongside a need for improved access to specialist interdisciplinary healthcare services. In addition, the experts felt that greater focus on patient concerns was needed. Indeed, keeping patients central to the management of disease was cited as an overall priority, in order to help manage expectations, deliver trusted advice, and improve daily life for those living with AAV.

Biographies

Prof Annette Bruchfeld

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Prof Bruchfeld received her MD at Karolinska Institutet, Stockholm, Sweden, and is currently a Senior Consultant and Associate Professor in the Renal Medicine Department at Karolinska University Hospital. Her clinical and research interests are mainly in inflammatory kidney diseases, ANCA-associated vasculitis, and hepatitis C in chronic kidney disease and transplantation. She has extensive experience in conducting academic and sponsored clinical trials in these areas. Prof Bruchfeld is a long-standing member of the European Vasculitis Society (EUVAS), and is currently a member of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) council and a board member of the Immunonephrology Working Group and the ERA-EDTA Scientific Advisory Board.

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Prof de Groot is a trained internist, rheumatologist, and nephrologist, who worked in the Universities of Lübeck and Hannover, Germany, before becoming Head of the Department of Nephrology and Rheumatology at Sana Klinikum Offenbach, the largest teaching hospital of the University of Frankfurt. She is a specialist in systemic autoimmune diseases. The majority of her scientific career has been devoted to clinical research in the field of ANCA-associated vasculitis and clinical therapeutic trials for these diseases. She is a long-standing member of EUVAS.

Prof David Jayne

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Prof Jayne is a clinical scientist with over 30 years of drug development and clinical trials experience in rare autoimmune diseases. He is a professor in clinical autoimmunity at the University of Cambridge, with extensive experience in teaching and in translational research. He has been involved in the evaluation of over 20 therapeutic agents for the care of multi-system autoimmune diseases, as well as the optimisation of standard-of-care regimens, the construction of global collaborative research networks, and the reorganisation of healthcare delivery for complex immunologic disease. Prof Jayne is President and Founder of EUVAS, and acts as an advisor to governments, regulatory and research bodies, industry, and patient-led organisations.

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