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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Treatment Strategies in ANCA-Associated Vasculitis

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Abstract

Purpose of Review The long-term survival of patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) has improved dramatically as a direct result of evolving therapy. This review summarizes evidence-based treatment strategies with currently approved immunosuppressive medications to serve as a guide for practitioners in the management of patients with AAV.

Recent Findings Targeted therapy aimed at minimizing treatment-related adverse effects while optimizing effectiveness is a propagated approach. Such tailored therapy considers disease severity and is especially warranted in those at high risk for relapsing vasculitis.

Summary As treatment options for AAV become available, the need to tailor therapy has become increasingly relevant to optimize patient outcomes.

Keywords Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis · Remission induction, remission maintenance · Cyclophosphamide · Rituximab · Mycophenolate mofetil · Plasma exchange

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are a heterogenous group of systemic diseases characterized by the presence of circulating autoantibodies directed against antigenic components of neutrophil cytoplasm and by inflammation of small to medium caliber blood vessels. These diseases include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and organ-limited AAV such as renal-limited vasculitis. Although rare, AAV are the most prevalent primary systemic vasculitis at over 200 cases per million and with an estimated annual incidence of 20 per million [1].

The antineutrophil cytoplasmic antibodies of concern are directed against proteinase 3 (PR3) or myeloperoxidase (MPO) and can be found in most patients with AAV. PR3 ANCA is most common in GPA (75% frequency) and least common in EGPA (5% frequency), whereas MPO ANCA positivity is observed more frequently in patients with renal-limited vasculitis (70% frequency) and less frequently in GPA patients (20% frequency) [2]. EGPA tends to be treated as a separate entity because it displays different pathogenetic mechanisms, genetic associations, and clinical manifestations than the other diseases in this group.

The two-stage treatment of AAV consists of remission induction followed by a longer period of maintenance of remission as soon as the treatment goal is achieved. Mortality (primarily due to renal and pulmonary involvement) in AAV approached 93% within 2 years prior to effective therapy. The introduction of glucocorticoids in 1948 and cyclophosphamide in the 1960s along with adjunctive therapies such as antihypertensive medications and renal replacement therapy has transformed survival [3•]. Rates of remission currently exceed 90% in many cases with a 5-year survival rate as high as 80% [4]. Unfortunately, treatment success is complicated by medication toxicity including infection, myelosuppression, infertility, and malignancy. Additionally, prolonged treatment is needed to control the disease and despite maintenance therapy, over 50% of patients experience relapses [3•, 5].

Variability in the quality of care patients with AAV receive is in part a result of the heterogeneity of disease manifestations. Advances have been made in the classification of the diseases based on severity, organ system involvement, and the presence of certain prognostic factors. Severity in AAV can be assessed by the Five-Factor Score with a score > 1 indicating a

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need for aggressive immunosuppressive therapy. A prediction of treatment outcome may be influenced by the status of new versus relapsed disease or ANCA specificity. Theoretically, this organization could improve standardization in care and facilitate the adoption of a tailored therapeutic approach to minimize the toxicity associated with immunosuppressive therapy in patients with AAV.

This review aims to summarize evidence-based treatment strategies with currently approved immunosuppressive medications to serve as a guide for practitioners in the management of patients with AAV. Treatment considerations for EGPA are dealt with separately.

Remission Induction

To date, the combination of high dose glucocorticoid and cyclophosphamide (CYC) therapy remains an important option for remission induction therapy in AAV. However, not all patients respond to CYC and at least 50% of those who respond experience a relapse within 5 years [6].There are no randomized controlled trials guiding dosage of glucocorticoids, but current regimens start with up to 1 g of intravenous methylprednisolone or 1 mg/kg/day of oral prednisone (or equivalent) for severe presentations. In spite of efficacy, there is evidence that high-dose glucocorticoid therapy impacts morbidity and studies have sought to address the efficacy of rapidly tapering the dose of glucocorticoids in AAV. For example, the Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis (PEXIVAS) trial revealed that the use of reduced glucocorticoid doses (< 60% of the standard regimen by 6 months) in severe AAV was non-inferior to a standard (high dose) regimen of glucocorticoids. However, participants that received reduced glucocorticoid doses had a significant reduction in serious infections in the first year [7]. In the CLEAR study, avacopan, an oral selective C5a receptor inhibitor, was used successfully as a glucocorticoid-sparing agent in a phase 2 randomized, double blind, placebo-controlled trial. A phase 3 trial is under way.

Similarly, lymphocyte depleting therapy with CYC has been tailored over time to reduce exposure and toxicity. The medication can be utilized in oral or intravenous pulse regimens, and intravenous CYC has several advantages including reduced exposure, bladder protection, and improved compliance [3•]. Both formulations have been shown to be of clinical equivalent efficacy. The CYCLOPS and CORTAGE trials assessed the reduction of cyclophosphamide-associated toxicity by employing intravenous pulse regimens rather than daily oral therapy in AAV. Where pulse CYC is associated with a lower risk of medication-related adverse effects such as leukopenia, a trend towards more frequent relapses in patients treated with pulse CYC compared with those who received the oral formulation was demonstrated in these studies. This increased risk of relapse primarily occurred in patients with anti-PR3 ANCA [8]. The CYCLOPS protocol additionally standardized dose adjustments of cyclophosphamide for patients over 60 years of age and those with renal impairment to improve safety of this treatment regimen [3•].

A recent addition to the strategy for remission induction in AAV is B cell targeted therapy. B cell activation and the level of B cell activating factor (BAFF) appear to correlate with disease activity [9]. Furthermore, ANCAs are known to be involved in the pathogenesis of AAV by stimulating neutrophils to release BAFF which subsequently increases the survival of autoreactive B cells [9]. Rituximab (RTX) is a chimeric monoclonal antibody to the CD20 receptor on the surface of B cells. It induces depletion of B cells expressing surface CD20.

In the RAVE study, patients with new or relapsing AAV were randomized to receive either CYC or RTX [10••]. RTX was administered at a dose of 375 mg/m^2 of body-surface area per week for 4 weeks while the dosing of cyclophosphamide was 2 mg/kg of body weight per day (adjusted for renal function). The primary end point was remission of disease without the use of prednisone at 6 months. Patients in the control group who had a remission between 3 and 6 months were eligible to switch from CYC to azathioprine (2 mg/kg/day). Patients in the RTX group with a remission during the same 3- to 6-month period were switched from placebo−cyclophosphamide to placebo−azathioprine.

In the RITUXVAS trial, participants with newly diagnosed AAV and renal involvement were randomized in a 3:1 ratio to receive either RTX or intravenous CYC for 3–6 months followed by azathioprine. All participants received glucocorticoids and about a quarter of participants in both groups received plasma exchange before trial enrollment [11••]. Analysis after a 6-month and a 12-month period, respectively, indicated that RTX was as effective as CYC for induction of remission in newly diagnosed cases of GPA and MPA. RTX appeared to be superior in patients with relapsing disease, and the short-term adverse event rate for both medications was not significantly different. Information garnered from the RAVE and RITUXVAS randomized controlled trials in 2010 supported the consideration of RTX as an option for induction therapy in AAV. In April 2011, RTX was licensed in the USA, and in March 2013 in Europe for the treatment of adults with GPA and MPA in combination with glucocorticoids.

As mentioned earlier, the success of CYC induction regimens comes with a risk of adverse effects such as infertility, infection, and malignancy. RTX use on the other hand has been associated with hypogammaglobulinemia and may be limited by availability and cost. Mycophenolate mofetil (MMF) is an alternative for remission induction in selected patients with AAV. In a recent trial, MMF (2 g/day with dose increase to 3 g/day for uncontrolled disease) was non-inferior to CYC for remission induction in randomized patients with

newly diagnosed AAV over a 6-month treatment period [12•]. Patients on dialysis or with life-threatening disease were excluded from this study, and it should be noted that relapses occurred earlier and more frequently in the MMF group compared to the CYC group. Selection of MMF as a therapeutic agent for use in combination with glucocorticoids for non-organ threatening AAV is supported by the European League Against Rheumatism (EULAR) recommendations [13].

With the information above, unique disease features can be identified and knowledge of these determinants of clinical outcome considered in the selection of the most appropriate therapeutic agent for remission induction. Table 1 summarizes these induction options.

ANCA Presence and Specificity

ANCA specificity may be more important than clinical features in defining homogenous groups of patients with AAV. The clinical correlation with ANCA is closest for alveolar and glomerular capillaritis, both lesions capable of being induced by ANCA in experimental models [3•]. MPO antibodies are present in more than 80% of patients with isolated pauci-immune necrotizing crescentic glomerulonephritis (PINCGN), whereas patients with PR3 antibodies have more extra-renal organ manifestations [8]. Although poorer renal outcomes have been associated with MPO, many studies have shown more frequent disease relapses in patients with PR3 positivity. While the RAVE study was designed as a non-inferiority trial, in a post hoc analysis, RTX demonstrated superiority over CYC in patients with PR3 positivity as well as in those with relapsing disease [10••]. Efficacy of B cell depletion with RTX is not associated with ANCA status [3•].

Renal Involvement

Renal involvement is estimated to occur in more than 70% of patients with GPA and MPA but in only 25% of cases of EGPA [8, 14]. It is generally characterized by a pauci-immune necrotizing and crescentic glomerulonephritis with a very rapid decline of renal function (rapidly progressive glomerulonephritis). The presence and severity of renal involvement at vasculitis diagnosis have an important impact on both renal and patient survival. Advanced renal failure at presentation correlates with an increased risk of end-stage renal failure and death [3•]. The most important predictors of renal outcome in AAV include older age, serum creatinine at diagnosis, treatment resistance, relapses, and the presence of chronic lesions on kidney biopsy [14]. CYC (combined with glucocorticoids) is generally recommended as the standard of care in those with severe renal involvement [8, 14], but there is data supporting efficacy of RTX. Approximately 50% of patients enrolled in the RAVE trial had significant renal disease defined by active biopsy-proven glomerulonephritis, a 30% or more increase in serum creatinine, a decrease in creatinine clearance of greater than 25%, or the presence of red blood cell casts on urine microscopy.

Table 1 Treatment strategies for remission induction in AAV

	Severe AAV	Non-severe AAV
PR3 ANCA	RTX or CYC	MTX† or RTX
MPO ANCA	CYC, RTX or MMF	MTX†, MMF or RTX
ANCA negative	CYC	MTX† or CYC
Severe renal disease*	CYC or RTX ± PLEX$^{\Delta}$	
Refractory disease◊	Switch from CYC to RTX	
	Switch from RTX to CYC	
	MMF if refractory to CYC and RTX	
	Consider combination CYC and RTX	
Concomitant infection	IVIG bridge	
Relapsing disease	RTX, CYC if advanced renal disease	

Immunosuppressive medication should be used in combination with glucocorticoids

AAV ANCA-associated vasculitis, *CYC* cyclophosphamide, *eGFR* estimated glomerular filtration rate, *EULAR* European League Against Rheumatism, *IVIG* intravenous immune globulin, *MMF* mycophenolate mofetil, *MPO ANCA* myeloperoxidase ANCA, *MTX* methotrexate, *PLEX* plasma exchange, *PR3 ANCA* anti proteinase 3 ANCA, *RTX* rituximab

*eGFR <20 ml/min per 1.73m^2 or Cr > 500 μmol/l

◊ Distinguish active vasculitis from chronic damage and exclude factors such as malignancy or infection

$^{\Delta}$ EULAR (2016) Grade B recommendation for the use of PLEX

† MTX use only if eGFR > 30 ml/min per 1.73m^2

Although patients with advanced renal disease (creatinine > 4 mg/dl) were excluded from the RAVE trial, the RITUXVAS study enrolled patients with severe disease including some requiring dialysis at trial entry. In both studies, RTX was as effective as cyclophosphamide for remission induction in newly diagnosed cases of GPA and MPA and superior in patients with relapsing disease [10••, 11••]. In 2016, the EULAR recommendations for the management of AAV were updated to recommend treatment with a combination of glucocorticoids and either CYC or RTX for remission induction of new onset or major relapse of organ-threatening GPA and MPA. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend the use of RTX as an alternative to CYC only in patients without severe renal disease or in whom CYC is contraindicated [8]. Other situations in which RTX could be considered first-line therapy for remission induction in AAV with severe renal disease include patients with refractory or relapsing disease, patients of child-bearing potential, and patients previously treated with CYC at risk of side effects from cumulative doses of the medication.

Treatment with plasma exchange (PLEX) in addition to glucocorticoids and CYC has been touted in patients with generalized vasculitis and renal involvement. The rationale for PLEX is that removal of ANCAs and other inflammatory components involved in the pathogenesis of AAV from plasma could reduce further tissue damage [8, 14]. In a randomized controlled trial of a subgroup of patients with a serum creatinine higher than 500 μmol/l (5.7 mg/dl), PLEX led to a higher rate of renal function recovery than methylprednisolone pulses. This methylprednisolone vs plasma exchange (MEPEX) trial treated all patients with cyclophosphamide plus glucocorticoids and subsequently randomized patients to receive either seven PLEX sessions or three 1000-mg pulses of methylprednisolone. It should however be noted that although the risk of progression to end-stage renal disease at 12 months was lower in the PLEX group, overall, the rates of survival and adverse events were similar in both groups at 1 year of follow-up [3•, 8, 15•]. This finding was substantiated in the recent Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis (PEXIVAS) trial in which PLEX did not reduce the risk of end-stage renal disease or death in patients with AAV [7]. PLEX continues to be a controversial therapeutic option, but the most recent EULAR recommendations for AAV suggest that it should be considered for patients with a serum creatinine level > 500 μmol/l (grade B recommendation). Anti-proteinuric treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers is warranted in patients with chronic renal impairment, in order to prevent or delay ESRD.

Refractory Disease

In spite of the therapeutic advances in the treatment of AAV, not all patients achieve disease remission with standard induction regimens. In broad terms, refractory disease encompasses those with disease progression despite induction therapy, those who are intolerant of standard therapy, and those with frequent relapses on maintenance therapy. For the purpose of distinction, this section refers only to those with inadequate control after optimal induction therapy. It is estimated that 10–30% of patients pursue a refractory course [3•]. The management of refractory vasculitis remains a challenge. In such patients, it is important to identify driving factors such as malignancy or infection and to distinguish active vasculitis from permanent tissue damage due to previous inflammatory injury. Subsequently, clinicians should consider if further immunosuppressive therapy is warranted. Many of these refractory cases are represented by those with atypical disease manifestations such as orbital granuloma and pachymeningitis. Granulomatous forms of AAV in open-label studies responded less well to RTX than vasculitic disease [16] although RTX is an important consideration for refractory disease. An approach suggested by experts (grade 2C recommendation) is to transition from CYC to RTX if resistant to therapy with CYC and from RTX to CYC if resistant to RTX. In patients who have been treated with both CYC and RTX but continue to have active disease, therapy with MMF or concurrent therapy with both CYC and RTX may be considered [17].

AAV with Concomitant Infection

As with other autoimmune disorders, active vasculitis with a concomitant infectious process presents a management conundrum. Treatment elevates infection risk due to relative immunosuppression. Intravenous immunoglobulins (IVIg) are primarily composed of immunoglobulin G and have several postulated mechanisms of action. IVIg therapy in AAV decreases the ANCA titer, inhibits ANCA-induced neutrophil activation, and interferes with ANCA binding to antigens. It has been shown to be clinically effective in disease treatment and can be particularly helpful as a bridge in patients with active AAV and active infections [9]. The use of IVIg is however limited by relapses when the infusion is discontinued [9] as well as cost and availability.

Non-SEVERE Manifestations

The selection of a treatment regimen should ideally match disease severity in an effort to circumvent toxicity. In non-severe forms of AAV, methotrexate (MTX) has been used with success in achieving remission. The NORAM study

randomized 100 patients with a new diagnosis of AAV without critical organ manifestations to receive either MTX 25 mg weekly or CYC. Both groups received a similar glucocorticoid regimen and at the end of 12 months, MTX was not inferior at inducing remission [3•]. However, remission was slower in the MTX group (among patients with more extensive disease) and these patients had a higher relapse rate.

Remission Maintenance

After remission induction goals are achieved (usually within 3–6 months), remission maintenance ensues to reduce the risk of disease relapse. Glucocorticoid withdrawal has been identified as a strong predictor for relapse [18]; therefore, it is common practice to keep patients on a low dose of prednisone (or equivalent) as part of the maintenance regimen. Table 2 is a summary of the options for maintenance therapy discussed in detail below. Azathioprine (AZT) and MTX are the most commonly used immunosuppressive agents for maintenance therapy because they have proven to be as effective as (and less toxic than) CYC [5]. This effectiveness was explored in the CYCAZAREM trial where 155 patients were randomized to receive either 1 year of oral CYC or 3 to 6 months of oral CYC followed by AZT. There was no difference in relapse rates between the two groups at 18 months. AZT and MTX showed comparable benefit as maintenance treatment options for AAV in the WEGENT randomized trial [5, 19•]. However, there remains no clear consensus on MTX dose adjustment in kidney disease so MTX should be avoided in patients with renal impairment due to the increased risk of myelotoxicity.

The IMPROVE trial explored the role of MMF as maintenance therapy in AAV by randomizing patients to receive either AZT (starting at a dose of 2 mg/kg/day) or MMF (starting at 2000 mg/day). Relapses were more common in the group treated with mycophenolate mofetil suggesting that it was less effective than azathioprine in the maintenance of disease remission [20•]. Still, MMF may be beneficial in certain patients—those intolerant of AZT for whom MTX is contraindicated as a result of kidney disease and those with a low predicted relapse risk, such as those who are MPO positive [12•]. RTX has recently been added to the armamentarium for maintenance therapy. In the MAINRITSAN trial, RTX demonstrated superiority over AZT for remission maintenance. In that study, RTX at a dose of 500 mg administered on day 0 and 14 and subsequently at 6-month intervals was compared to AZT in patients who had achieved remission after pulse CYC-glucocorticoid induction therapy. AZT was administered to the control group at a dosage of 2 mg/kg/day for 12 months, and then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months. At month 28, 3% of recipients of RTX had experienced a major relapse compared to 29% of those receiving AZT. Although tempting to attribute the higher relapse rate in the AZT group to the tapering of this medication, about 50% of those who relapsed did so within the first 12 months of maintenance therapy [21••].

Comparative studies have sought to determine the optimal duration of maintenance therapy, but this remains unknown. Consensus guidelines recommend maintenance immunosuppressive medication for at least 18–24 months from the initiation of immunosuppressive medication. In the REMAIN trial, prolonged maintenance therapy with low-dose glucocorticoids and AZT beyond 24 months after diagnosis reduced the frequency of relapse and improved renal survival, when compared with the withdrawal of immunosuppressive medication 24 months after diagnosis [22•]. Notably, patients in the REMAIN trial received remission induction with a cyclophosphamide regimen as the study was conducted prior to widespread use of rituximab. The availability of B cell depleting therapy for both induction and maintenance therapy could affect treatment duration, but this decision should take into account the presence or absence of risk factors for vasculitis relapse.

Relapsing Disease

Relapses are quite common in AAV with an estimate of 50% of patients who relapse within 5 years despite continued immunosuppression [3•]. Identifying determinants of AAV relapse facilitates the tailoring of immunosuppressive therapy to those at high risk for disease relapse while sparing those at low-risk unnecessary treatment. Risk factors for relapse include a diagnosis of GPA, previous relapse, PR3 positivity, upper respiratory tract involvement, and persistently positive ANCA titers [3•]. The treatment of relapsing disease can be challenging but should be guided by the severity of the relapse, organ system involvement, and whether the patient is on maintenance therapy at the time of the relapse. Mild, non-organ-threatening relapses that occur after discontinuation of maintenance therapy may be controlled by resuming the prior maintenance therapy [8]. A severe relapse should be treated

Table 2 Treatment strategies for remission maintenance in AAV

	No renal impairment	Renal impairment	Relapsing disease
PR3 ANCA	AZT, MTX, or MMF	RTX or AZT	RTX > AZT
MPO ANCA	AZT, MTX, or MMF	RTX, AZT, or MMF	RTX > AZT

AAV ANCA-associated vasculitis, *AZT* azathioprine, *MMF* mycophenolate mofetil, *MPO ANCA* myeloperoxidase ANCA, *MTX* methotrexate, *PR3 ANCA* anti proteinase 3 ANCA, *RTX* rituximab

with a regimen used for remission induction. If the relapse occurred after successful treatment with a CYC-based regimen, RTX should be considered based on the results of the RAVE trial which demonstrated superiority of RTX over CYC for relapsing disease [3•, 8]. RTX use is also associated with a reduced risk of the toxicity associated with cumulative doses of CYC. For those who relapse after previously achieving remission with RTX, RTX is the therapy of choice [8]. An exception to the above may be those whose relapse is characterized by advanced renal disease in whom CYC should be considered.

Some studies suggest that in a subset of patients with renal disease or alveolar hemorrhage, an increase in PR3 ANCA levels after remission induction conveys a risk of vasculitis flare [23]. However, a return to ANCA positivity or a rising ANCA titer after induction of remission (on conventional maintenance therapy) are not reliable markers of disease relapse. As such, routine ANCA monitoring in current practice is not recommended. Although circulating B cell detection does not reliably predict AAV relapse after induction therapy with rituximab, relapses are rare when B cells are undetectable and ANCA remains negative [24]. The MAINRITSAN2 trial was undertaken to evaluate the utility of monitoring levels of ANCA and circulating CD19+ B cells as indicators for retreatment with rituximab to maintain disease remission. After the completion of induction therapy (with methotrexate, cyclophosphamide, or rituximab) and randomization, the tailored-arm patients in this trial received 500 mg of rituximab followed by reinfusion when the ANCA reappeared, ANCA titer rose markedly, or CD19+ B cells reappeared. Those in the control group received a fixed dose of rituximab 500 mg at randomization (days 0 and 14) then at 6, 12, and 18 months. The primary endpoint was analyzed after 28 months. As expected, individually tailored-arm patients received fewer rituximab infusions than the control arm; however, AAV relapse rates did not differ significantly between both groups [25•].

Targeted Therapy for EGPA

Glucocorticoid monotherapy remains the mainstay for EGPA therapy. Cardiac, gastrointestinal, and central nervous system involvement as well as significant renal disease with proteinuria > 1 g in 24 h are poor prognostic features. In cases where stratification by the five factor score indicates a poor prognosis or in relapsing disease, CYC is indicated as first-line induction therapy. Maintenance therapy is similar to that recommended for other AAV.

Interleukin-5 (IL-5) plays a key role in the pathogenesis of EGPA by stimulating eosinophil activation, maturation, and survival. In December 2017, the Food and Drug Administration approved mepolizumab, a humanized monoclonal antibody that antagonizes IL-5, for the treatment of adults with EGPA. Maintenance therapy with mepolizumab, although of unclear benefit for the vasculitic manifestations of EGPA, is effective in decreasing the glucocorticoid requirements and in alleviating asthma and sinonasal symptoms of patients [9].

Additionally, based on treatment success in case reports, RTX is being evaluated as an induction and maintenance agent for EGPA (REOVAS trial ClinicalTrials.gov NCT02807103; MAINRITSEG trial ClinicalTrials.gov **NCT03164473)**.

Conclusion

Treatment of AAV has evolved, and with currently available immunosuppressive therapy, up to 85–90% of patients will achieve remission. Tailored therapy that circumvents most of the toxicity associated with care should be the goal. In addition to disease-specific therapy, key management concepts for all patients include prophylaxis and monitoring for conditions, including *Pneumocystis jiroveci* infection, fungal and other opportunistic infections, osteoporosis, cardiovascular disease, and malignancy. The disease characteristically follows a relapsing course, and in order to select an optimal regimen for affected patients, healthcare providers should be aware of unique features that may influence treatment efficacy. It is an exciting time in the management of ANCA-associated vasculitis as scientists investigate safer regimens for remission induction and maintenance, and we anticipate newer therapy on the horizon.

Compliance with Ethical Standards

Conflict of Interest The author declares no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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