ANCA-associated vasculitis (AAV) is a group of diseases encompassing granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg–Strauss disease (eosinophilic GPA). Patients often present with a rapidly progressive GN associated with focal necrotizing and crescentic lesions on renal biopsy and a lack of significant deposition of Igs in glomeruli (pauci-immune). Extrarenal vasculitis, especially sino-pulmonary, and peripheral nervous system involvement may be present. Although AAV can occur in young patients, it is primarily a disease of older adults, with the peak age between 65 and 74 years old (1,2). In the very elderly (age >80 years old), AAV accounts for 19% of kidney biopsies performed and is the most common cause of biopsy-proven AKI in this population (3). The reasons for this older age of presentation remain unclear. One might have considered the senescent immune system to be less likely to promulgate an autoimmune disorder in the same way that acute transplant rejection is less common in older patients.

The clinical presentation in older patients (>65 years old) is similar to that in younger patients (<65 years old) with AAV, although certain features may be more common (1,4). In older patients, studies have noted that the clinical presentation is more consistent with MPA rather than GPA and that anti-myeloperoxidase (MPO-ANCA) is more common (1,4–6). Renal disease may be more prominent, with fewer systemic features (in particular, less upper respiratory tract involvement), although lung involvement is not uncommon. Older patients often have nonspecific symptoms, and diagnosis is often delayed, by which time there may be very significant and irreversible renal injury. The presence of myalgias and headaches may be misdiagnosed as polymyalgia rheumatica (4,7). Notably, AAV in the elderly occurs on a background of more comorbidities (e.g., cardiovascular disease, diabetes, and malignancy), and there may be substantial CKD at baseline. The true frequency of CKD in the elderly is debated, partly related to difficulties with definitions, but creatinine clearance decreases by approximately 0.75 ml/min per year over the age of 40 years old in a normal population (8). Immunosuppressive therapy has been described to be both equally (1) or less (4,9) efficacious in attaining remission in older populations, and relapse rates are similar (1,4,10) or lower (5) (Table 1). Prior studies have confirmed that older age is a strong risk factor for death and ESRD (1,4,5,11); however, older patients are more prone to the adverse effects of immunosuppressive therapy (1,4). It should, of course, be recognized that the overall health status of individuals with the same chronological age can vary considerably.

Despite being predominantly a disease of the elderly, many studies of AAV have excluded patients >75 years old. Indeed, in two recent studies of rituximab therapy in AAV, the mean age was 54 ± 16.8 years old (RAVE), and the median age was 68 (range = 56–75) years old (RITUXVAS). In this issue of CJASN, Weiner et al. (6) describe a retrospective observational study of 151 consecutive patients ages 75 years old or older with AAV who presented to one of six centers in Sweden, the United Kingdom, and the Czech Republic. The median age was 79 years old (46% were older than 80 years old), and the majority had advanced renal disease (mean creatinine of 3.2 mg/dl), with 31% of subjects requiring dialysis. Compared with younger patients, comorbidities were more common, particularly diabetes (15%), malignancy (15%), hypertension (46%), heart failure (8%), and stroke (13%).

As noted in prior studies of older patients, MPO-ANCA was more common (60%) than anti-proteinase 3 (PR3)-ANCA (39%), and the majority of subjects had a clinical pattern consistent with MPA (70%) according to the European Medicines Agency algorithm (12). AAV is more commonly classified according to the revised 2012 Chapel Hill criteria (13), but it should be recognized that there is substantial overlap in the phenotypes of MPA and GPA and that it is often difficult to confidently ascribe one of these diagnoses to an individual patient (14). We should also recognize that MPO-ANCA and PR3-ANCA are biomarkers that do not stratify perfectly with MPA and GPA (for example, GPA is anti-MPO positive in approximately 10% of patients) and that the clinical features associated with the presence of each of these antibodies are quite variable (15). Genetic susceptibility to AAV has been identified in two large genome wide association studies (GWAS) performed in cohorts from the United Kingdom (16) and North America (17). The United Kingdom study identified the strongest association of PR3-ANCA disease with variants in the MHC region HLA-DP and the genes SERPINA1 (encodes α1-antitrypsin) and PRTN3 (encodes proteinase 3) loci. MPO-ANCA disease was associated...
Table 1. Outcomes for treated elderly patients with ANCA-associated vasculitis

<table>
<thead>
<tr>
<th>Country</th>
<th>No.</th>
<th>United Kingdom (1)</th>
<th>United States (9)</th>
<th>China (4)</th>
<th>United States (5)</th>
<th>Hungary (10)</th>
<th>Europe (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td>&gt;65</td>
<td>&gt;75</td>
<td>&gt;65</td>
<td>≥80</td>
<td>&gt;65</td>
<td>&gt;75</td>
</tr>
<tr>
<td>Inclusion</td>
<td></td>
<td>65–90</td>
<td>78±3</td>
<td>72±5.6</td>
<td>83±2.7</td>
<td>72±6</td>
<td>79 (77–82)</td>
</tr>
<tr>
<td>Creatinine (mean), mg/dl</td>
<td></td>
<td>7.5</td>
<td>2.4</td>
<td>4.5</td>
<td>4.5</td>
<td>6.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Proteinuria, g/24 h</td>
<td></td>
<td>—</td>
<td>—</td>
<td>1.67</td>
<td>1.5</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>GPA/MPA (%)</td>
<td></td>
<td>—</td>
<td>—</td>
<td>21±6.7</td>
<td>21±5</td>
<td>15 (12–19)</td>
<td>30/70</td>
</tr>
<tr>
<td>MPO/pANCA (%)</td>
<td></td>
<td>More common</td>
<td>—</td>
<td>94</td>
<td>68</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>PR3/cANCA (%)</td>
<td></td>
<td>Less common</td>
<td>—</td>
<td>5</td>
<td>21</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Outcomes (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (1 yr)</td>
<td></td>
<td>29</td>
<td>32</td>
<td>—</td>
<td>47</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Death (2 yr)</td>
<td></td>
<td>—</td>
<td>36</td>
<td>48</td>
<td>56</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>ESRD* (1 yr)</td>
<td></td>
<td>30</td>
<td>—</td>
<td>31</td>
<td>36</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Remission*</td>
<td></td>
<td>94</td>
<td>—</td>
<td>76</td>
<td>49</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td>26</td>
<td>—</td>
<td>15</td>
<td>4.3</td>
<td>19</td>
<td>—</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>38</td>
<td>39</td>
<td>—</td>
</tr>
</tbody>
</table>

Only data from elderly patients who were treated with immunosuppression are included. BVAS, Birmingham vasculitis score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear ANCA; PR3, proteinase-3; cANCA, cytoplasmic ANCA.

*Surviving patients.

with the HLA-DQ locus. Notably, these associations were stronger for the antigenic specificity of the ANCA (PR3 versus MPO) than with the clinical syndrome (GPA versus MPA). Given the significant overlap in clinical presentations and prognosis and the separate genetic associations, consideration is being given to reclassifying AAV according to the type of antibody specificity (MPO versus PR3) rather than the traditional clinical phenotype (MPO versus GPA). A new endeavor, the Diagnostic and Classification Criteria for Vasculitis Study (DCVAS), aims to collect and analyze >2000 patients with primary systemic vasculitis and >1500 controls with other forms of autoimmune disease to develop a new classification of vasculitis validated in different populations (18).

The study by Weiner et al. (6) addresses the safety and potential benefits of immunosuppressive therapy for AAV in older patients. The overall 1- and 2-year survival rates were 71.5% and 64.6%, respectively, showing that most deaths occur within the first 1 year. It was noted that subjects in the Swedish cohort who survived to the second year had a similar death rate as the general age-matched population. As in previous studies, age and GFR were the strongest predictors of survival; however, the cause of death was not clearly defined. Studies from the European Vasculitis Study Group showed a 1-year mortality of 11.1% (in all age groups), which was attributed to active vasculitis in only 19% of patients but caused by adverse events from therapy in 59% of patients (11).

Subjects (n=102) who were treated with standard immunosuppressive regimens (oral or intravenous cyclophosphamide or intravenous rituximab) had a significantly better survival than those (n=28) who were treated with nonstandard or no immunosuppressive regimens. There were no obvious differences between these two groups in terms of age, renal function, or comorbidities, although, as discussed by Weiner et al. (6), it is very difficult to retrospectively compare these two heterogeneous groups because of the risk of confounding by indication (i.e., sicker or more frail patients may have been selected to receive nonstandard or no immunosuppressive therapy because of concerns over the risk of adverse events from therapy).

Similar findings to this study have been noted in the work by Bomback et al. (5), which described outcomes in a very elderly population (>80 years old) (6); 78 subjects were studied, of whom 72% were anti-MPO positive, and all had severe renal impairment (mean baseline creatinine = 4.3 mg/dl). The majority (n=50) was treated with immunosuppression (mostly steroids and either oral or intravenous cyclophosphamide). In the treated group, disease remission was achieved in 49%, although mortality was high (1-year survival was 53%), 36.2% reached ESRD at 1 year, and infectious complications were common (38%). Notably, relapse rates were low (4%); this was partly explained by the higher rate of MPO-ANCA–associated disease, which may permit a lower-dose maintenance therapy. The French MAINRITSAN Study (n=115) recently compared rituximab with azathioprine in patients with AAV who received induction therapy with pulse intravenous cyclophosphamide (19). The rate of relapse at 28 months was significantly better in the rituximab group (5%) versus the azathioprine group (29%) with similar adverse events.

What clinical lessons can we glean from these studies of AAV in older patients? There is a high death rate in the first 1 year of therapy, particularly in the first 3 months, with the
majority of patients dying from complications of therapy (infection) rather than the underlying disease. Cyclophosphamide needs to be dose-adjusted in older patients for age and GFR. Rituximab may offer some advantages in this age group, but we still have limited data in this older population (20–22), and the side effect profile in recent studies was not superior compared with cyclophosphamide. In the RAVE Study, there was less leukopenia in the rituximab group (3% versus 10%); however, the rates of infection were the same (7%), similar to in the RITUXVAS Study (18%). These disappointing results may have been partly related to the accompanying high doses of steroid. Rituximab may also be a good option for maintenance therapy, although relapse rates may be lower in the very elderly (5).

High-dose steroids are often poorly tolerated in the elderly, and we need to consider how best to minimize this exposure. Infection, hyperglycemia, osteoporosis, and hypertension are all common adverse effects. Low-dose steroid protocols and steroid avoidance using inhibitors of the CsA receptor are currently being studied (23). Prophylactic medications (trimethoprim-sulfamethoxazole, vitamin D, bisphosphonates, antacid therapies, aspirin, and statins) and appropriate vaccinations should be used. In conclusion, this study by Weiner et al. (6) adds additional support to the idea that selected elderly patients can benefit from immunosuppressive therapy for AAV, despite the higher risk of adverse effects from these medicines in this population. Careful attention to monitoring, prophylaxis, and appropriate modification of the treatment regime may further reduce these risks.

Disclosures
None.

References


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