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Compassionate Use Of Avacopan In Difficult-To-Treat ANCA-Associated Vasculitis

Running head: Compassionate use of avacopan in AAV patients

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Introduction

Avacopan is a new, promising treatment for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and can potentially significantly reduce steroid use. Two phase 2 trials\(^1,2\) and one phase 3 trial\(^3\) concluded avacopan was safe with no higher incidence of adverse events in AAV patients. Compared to steroids added onto standard immunosuppression with cyclophosphamide or rituximab, avacopan has demonstrated non-inferiority for treatment response at 12 weeks\(^1\) and 26 weeks.\(^3\) Avacopan proved superior for sustaining remission at 52 weeks and reducing relapses within the first 52 weeks from 21% to 10% compared to a prednisone tapering schedule of 20 weeks.\(^3\) Patients using avacopan showed greater improvement on health-related quality of life\(^1,3\) which was likely related to avoidance of steroid-related adverse effects.\(^2,3\)

Most recently, avacopan was approved for the treatment of AAV by the U.S. Food and Drug Administration and approval is recommended by a committee of the European Medicines Agency (EMA) to the European Commission.\(^4,5\) In addition to currently available data of randomized trials, we now report the clinical experience with avacopan in difficult-to-treat AAV patients in the setting of a compassionate use program.

RESULTS

Cases

Eight adult GPA and MPA patients were treated within the avacopan compassionate use program at our institute. Patient and AAV relevant characteristics are summarized in Table 1. In four cases (1-4) the indication to apply for avacopan was refractory disease with steroid resistance, characterized by continuous or worsening disease despite recent induction therapy with high dose steroids. In two cases the indication was steroid dependence due to relapsing (case 5) or grumbling disease (case 6) when prednisone was reduced below 15mg per day. Two cases (7, 8) started avacopan because of necessity to avoid steroid-related toxicity based on the patient’s medical history with obesity and/or diabetes and previous severe steroid-related toxicity. Briefly, six patients had generalized disease and two patients had ear-nose and throat (ENT) limited disease at the start of avacopan. Typically, patients had relapsing disease (numbers of flares ranging from 0-3) and received multiple previous remission induction therapies (ranging from 1-6) as specified in Table 1. The median time between the start of latest induction therapy and start of avacopan was 7.7 [0.4-15.9] weeks coinciding with a median supply time of avacopan of 5.5 [2.9-7.9] weeks. During this time all patients received prednisone as a bridge to avacopan initiation. Concomitant to avacopan four patients (cases 3, 5, 6, 7) received maintenance treatment with rituximab and one patient received rituximab induction therapy.
Treatment responses and steroid-related toxicity

Disease courses of individual patients before and after the initiation of avacopan are depicted in figure 1a illustrating frequent severe relapses requiring remission-induction treatment before avacopan was initiated. This contrasted with the time after avacopan was started: all patients achieved clinical remission within 6 months and accordingly the Birmingham vasculitis activity score (BVAS) returned to 0 in all patients (figure 1b). Noteworthy, only one patient (case 5) experienced a major flare with pulmonary involvement 6 months after avacopan start. The event coincided with a reduction of avacopan dosing to 20mg bd which was necessary due to delayed supply of avacopan related to transport restrictions during the second wave in the COVID-19 pandemic. The patient’s flare was successfully managed with intravenous rituximab, a single intra-articular steroid injection for arthritis of the knee and re-institution of avacopan 30mg bd without the additional use of oral steroids. With respect to renal involvement in 5/8 patients, eGFR ranged from 32-90 ml/min at start of avacopan and slightly improved in 4 patients (range +5 to +9ml/min) and decreased in none. Noteworthy, long-standing hematuria in case 2 disappeared (<18 per ml) after 4 months of avacopan treatment.

As shown in figure 1c steroid tapering was successful in all patients with five patients discontinuing prednisone and three patients (case 1,2,6) using low dose prednisone (2.5-7.5mg/day). With respect to steroid-related toxicity effects, as defined by the Glucocorticoid Toxicity Index (GTI), patients had a median of 3 [1-5] affected items at avacopan start (figure 1d). After one year of avacopan use the GTI improved in four patients related to improvement of BMI, glucose tolerance, blood pressure or lipid metabolism and GTI remained stable in three patients. In one patient (case 8) GTI worsened related to weight gain despite improved glucose intolerance. Noteworthy, 2 patients (case 1 and 4) had steroid-related depressive symptoms which improved in both patients on avacopan and one patient (case 1) could stop antidepressant therapy.

Even though during compassionate use adverse events are not structurally registered, no adverse events, side effects or infections related to avacopan were reported. Six patients are currently satisfactorily continuing avacopan. Case 1 participated in the initial stages of the compassionate use program were avacopan use was allowed for 1 year only. Case 3 stopped avacopan because of a pregnancy wish.

Discussion

The present study describes real-life practice data on the compassionate use of avacopan in difficult-to-treat AAV patients. Avacopan contributed to achieving and maintaining remission in these AAV
patients while breaking through steroid dependency and allowing steroid reductions. Obviously, it is impossible to determine the clinical efficacy of avacopan due to prior and concomitant intensive remission-induction immunosuppression and concomitant Rituximab maintenance treatment in four patients. However, avacopan demonstrated beneficial and added-value in the treatment of our difficult-to-treat AAV cases with respect to improved disease control and reduced steroid-related toxicity.

During the avacopan compassionate use program at our center, we applied for avacopan in cases 1-4 because of insufficient response to prior intensive remission-induction therapy including high dose steroids. All four patients achieved clinical and persistent remission upon avacopan initiation. Also, cases 5 and 6 achieved full remission for the first time since their diagnoses during avacopan treatment, in contrast to previous continuous active disease with steroid dependence. Noteworthy, in one patient (case 5) we experienced that re-institution of avacopan successfully diverted a major disease flare. The latter is corroborated by early phase-1 study data demonstrating a dose-related, pharmacological C5a-R inhibition.7

With respect to steroid use, only 3 out of 8 patients required prednisone in a low dosage after one year of avacopan treatment. Additionally, in two cases of steroid-dependency, steroids could not be tapered below 15mg/day. With avacopan treatment, steroids were fully tapered to zero in one patient (case 5) and a clinically relevant reduction to 7.5 mg/day in the second patient (case 6). Taken together, compassionate use avacopan allowed to ameliorate disease and compassionate use avacopan allowed to significantly reduce and stop steroid use in difficult-to-treat AAV patients while observed improvement of steroid-related toxicity was observed.

Lastly, the present study on a case series of compassionate use avacopan provide guidance to future observational studies with avacopan. The challenge to identify beneficial effects of avacopan in clinical data of AAV patients is defined by the absence of disease activity, disease flares, steroids and steroid-related toxicity. It requires careful considerations to firmly determine benefit by proving the absence of clinically relevant events that physicians automatically strive for in routine clinical practice. Also, it will remain a significant challenge to prove the clinical efficacy of avacopan on the background of highly intensive immunosuppression necessary for remission-induction in AAV. Thus, to further investigate the potential benefits of avacopan in AAV patients in observational studies, we would emphasize assessing accurate medical histories with emphasis on disease courses, steroid dosing, steroid-related toxicity using validated GTI scores and disease relevant patient-reported outcomes.
In conclusion, we here provide the first real-life practice observations on the compassionate use of avacopan in difficult-to-treat AAV patients. Our study describes the clinical added value of avacopan in AAV treatment and that beneficial effects of avacopan are predominantly determined by the absence of adverse events such as persistent disease activity, steroid dependence and steroid-related toxicity.
Disclosures
The work of YKOT was supported by the Dutch Kidney Foundation (17OKG04) and by the Arthritis Research and Collaboration Hub (ARCH) foundation. ARCH is funded by Dutch Arthritis Foundation (ReumaNederland). YKOT received an unrestricted research grant and consultancy fees from Vifor Pharma.


Supplementary Material
Supplementary Methods (PDF)
STROBE checklist (PDF)

Supplementary information is available at KI Report’s website.
References

Figure legends

Figure 1: Treatment outcomes

a: Disease course per patient shown in relation to start of avacopan (black line). Columns start at moment of diagnoses and end at current date or stop of avacopan (x). Note that the x-as changes at -1yr (dotted line) from 6years to 6 months per thick. For some periods of time it couldn’t be reconstructed if or when remission was achieved (unknown disease activity). * reduction of avacopan dosing to 20mg bd.

b: Birmingham vasculitis activity score (BVAS) per patient at different time points.

c: Prednisone dosage in mg/day per patient at different time points.

d: Composite items of GTI. Per patient is shown if the item was affected at the start of avacopan and the GTI index is scored after one year of avacopan use. Scores can range from -36 to 439, with increasing scores relating to an increase in glucocorticoid toxicity burden and negative scores reflecting an improvement in toxicity. Last row shows total affected items and total GTI score.

Yr, year; mo, month; BVAS, Birmingham vasculitis activity score; mg, milligram; GTI, Glucocorticoid Toxicity Index; BMI, body mass index; N/A, not applicable; Tot, total.
### Table 1: Patient, AAV and treatment characteristics

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before start avacopan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td>54</td>
<td>67</td>
<td>27</td>
<td>37</td>
<td>38</td>
<td>54</td>
<td>23</td>
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<tr>
<td><strong>Gender</strong></td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
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<td><strong>ANCA serology</strong></td>
<td>MPO</td>
<td>MPO</td>
<td>PR3</td>
<td>MPO</td>
<td>PR3</td>
<td>PR3</td>
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<td>Renal Pulmonary Skin</td>
<td>ENT</td>
<td>Renal</td>
<td>Pulmonary ENT</td>
<td>ENT</td>
<td>Joints</td>
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<td><strong>Duration of vasculitis in months</strong></td>
<td>6</td>
<td>139</td>
<td>19</td>
<td>15</td>
<td>19</td>
<td>32</td>
<td>37</td>
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<tr>
<td><strong>Number of flares</strong></td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Number of induction therapies</strong></td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>Prior immunosuppressive medication</strong></td>
<td>-1m: CYC</td>
<td>-6m: MP, RTX</td>
<td>-4m: MP, PE, obinutuzumab</td>
<td>-5m: MP, PE, obinutuzumab</td>
<td>-1y: RTX, MP, CYC</td>
<td>-11.9/7y: MMF</td>
<td>-3m: MP, RTX</td>
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<tr>
<td></td>
<td>Anti-CD20 cumulative doses in mg</td>
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<td>4000</td>
<td>4000</td>
<td>2500</td>
<td>2000</td>
<td>6000</td>
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<td>1500</td>
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<td>17000</td>
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<td>Solumedrol cumulative doses in mg</td>
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<td>9000</td>
<td>6000</td>
<td>4500</td>
<td>3000</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indication to start</strong></td>
<td>Steroid resistance</td>
<td>Steroid resistance</td>
<td>Steroid resistance</td>
<td>Steroid resistance</td>
<td>Steroid dependence</td>
<td>Steroid dependence</td>
<td>Steroid-related toxicity</td>
</tr>
<tr>
<td><strong>Supply time (weeks)</strong></td>
<td>3.6</td>
<td>6.9</td>
<td>6.6</td>
<td>6.0</td>
<td>7.9</td>
<td>5.0</td>
<td>3.6</td>
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<tr>
<td><strong>Prednisone at start (mg/day)</strong></td>
<td>25</td>
<td>5</td>
<td>20</td>
<td>20</td>
<td>5</td>
<td>15</td>
<td>20</td>
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<tr>
<td><strong>BVAS at start</strong></td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>15</td>
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<tr>
<td><strong>Concomitant maintenance treatment</strong></td>
<td>Prednisone (5mg/day)</td>
<td>Prednisone (2.5mg/day)</td>
<td>-2m RTX (1000mg)</td>
<td>-8m RTX (500mg)</td>
<td>-1yr: RTX (1000mg)</td>
<td>Prednisone (7.5mg/day)</td>
<td>+1yr: RTX (1000mg)</td>
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<tr>
<td></td>
<td>Extra induction therapies</td>
<td></td>
<td>+8m RTX (2000mg)</td>
<td></td>
<td></td>
<td></td>
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</table>

N/A, not applicable; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3; MPO, myeloperoxidase; ENT, Ear Nose Throat; m, months; yr, year; CYC, cyclophosphamide; MP, methylprednisolone; RTX, rituximab; PE, plasma exchange, AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; BVAS, Birmingham vasculitis activity score; tot, total.
**a**

- **Case 8**
- **Case 7**
- **Case 6**
- **Case 5**
- **Case 4**
- **Case 3**
- **Case 2**
- **Case 1**

![Graph showing disease activity and treatment progress over time for cases 1 to 8.]

- Induction therapy
- Unknown disease activity
- Active disease
- Clinical remission

**b**

- **BVAS score**
- **Prednisone dosage (mg/day)**

![Graphs showing BVAS score and prednisone dosage over time for cases 1 to 8.]

**c**

- **BVAS score**
- **Prednisone dosage (mg/day)**

![Graphs showing BVAS score and prednisone dosage over time for cases 1 to 8.]

**d**

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
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<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
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<td>yes</td>
<td>yes</td>
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