Avacopan for the Treatment of ANCA-Associated Vasculitis


Journal Club by Alex Murphy
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an orphan disease that consists of a group of small vessel vasculitides

- Types: microscopic polyangiitis (MPA), granulomatosis polyangiitis (GPA), eosinophilic GPA (EGPA)

In AAV, autoantibodies called ANCAs are found at elevated levels and bind to neutrophils

- Most common autoantigens that ANCAs bind to are proteinase 3 (PR3) and myeloperoxidase (MPO)
- Activation of neutrophils within endothelial cells leads to vascular damage and tissue swelling

Patients with AAV may have severe complications such as renal impairment and organ damage

- AAV can result in decreased quality of life and medication-related toxic effects

Current standard of care therapy:

- induction with glucocorticoids combined with cyclophosphamide or rituximab
- maintenance with azathioprine, methotrexate, rituximab, or mycophenolate
Background and Overview

Introduction

- Activation of the alternative complement pathway results in terminal Complement 5a (C5a) production
- Avacopan is an oral C5a receptor antagonist that blocks the effects of C5a through the C5a receptor; it inhibits C5a-mediated neutrophil activation and migration
- Rationale for avacopan in AAV
  - Rapid achievement of response with reduce steroid use
  - Novel mechanism of action
  - Well tolerated, favorable safety profile, easily administered
Background and Overview

Funding Source and Objective

- ChemoCentryx sponsored the trial
  - First two authors had confidentiality agreements with the sponsor
  - All authors participated with sponsor in the design, analysis of data, and writing of the manuscript

- ADVOCATE Phase 3 Trial: Avacopan Development in Vasculitis to Obtain Corticosteroid elimination and Therapeutic Efficacy

- Objective: To evaluate whether avacopan could replace a glucocorticoid-tapering regimen used in the treatment of ANCA-associated vasculitis.
Methods

Study Design

• **Type**: international, multicenter, double-blind, double-dummy, randomized, controlled trial
  • Setting: 143 centers in North America, Europe, Australia, New Zealand, Japan
  • Enrollment: March 17, 2017, to November 1, 2019
  • Treatment: 52 weeks, with 8 weeks of follow-up
  • Approval from IRB
  • Analysis: intention-to-treat

• **Intervention**: avacopan 30mg twice daily plus prednisone-matching placebo vs. avacopan-matching placebo plus a tapering prednisone (60mg/day to discontinuation by week 20)

• **Ancillary treatments**:
  • All received either rituximab for 4 weeks or cyclophosphamide for 13 weeks followed by azathioprine
  • Either with worsening disease could get rescue IV and/or PO steroids
  • PJP prophylaxis required per protocol
Methods

Study Design

- **Primary Endpoints**: (1) remission at Week 26 and (2) sustained remission at Week 52
  - remission defined as BVAS of 0 and no glucocorticoid use 4 weeks prior to Week 26
  - sustained remission defined as remission at Week 26 without relapse to Week 52
    - relapse defined as return of vasculitis activity based on at least one major BVAS item, at least three minor BVAS items, or one or two minor BVAS items for at least two consecutive trial visits

- **Secondary Endpoints**: (1) adverse events over 60 weeks, (2) glucocorticoid-induced toxicity measured by GTI over 26 weeks, (3) response rapidity assessed by BVAS at Week 4, (4) change in health-related quality of life per SF-36 physical component and EQ-5D-5L visual-analogue scale, (5) change in eGFR, (6) change in UACR, (7) change in urinary MCP-1:creatine ratio, (8) change in VDI

- **Safety**
  - Serious adverse events
  - Adverse events of interest: Infections, LFTs, WBC count, Hypersensitivity
Methods

Study Design

Randomized 1:1

Avacopan Group (N=166)
- Avacopan, 30 mg twice daily
- ‘Dummy Prednisone’ (a prednisone matching placebo)
- CYC for 13 weeks followed by AZA, or RTX for 4 weeks

Prednisone Group (Active Control) (N=164)
- Avacopan-matching placebo twice daily
- Prednisone, 60 mg/day tapered to zero over 20 weeks
- CYC for 13 weeks followed by AZA, or RTX for 4 weeks

Primary Endpoint 1: Remission at 26 Weeks
Primary Endpoint 2: Sustained Remission at 52 Weeks
8-Week Follow up

AZA = azathioprine
CYC = cyclophosphamide
RTX = rituximab
## Methods

### Study Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>≥12yo, newly diagnosed or relapsing GPA or MPA</td>
<td>received &gt;3g of IV glucocorticoids within 4 weeks or &gt;10mg/day of oral prednisone continuously for &gt;6 weeks</td>
</tr>
<tr>
<td>positive test for anti-PR3 or anti-MPO</td>
<td>cyclophosphamide within 12 weeks or rituximab within 1 year</td>
</tr>
<tr>
<td>eGFR ≥15 ml/min/1.73m2</td>
<td>alveolar hemorrhage and invasive pulmonary ventilation</td>
</tr>
<tr>
<td>BVAS: at least 1 major item, 3 nonmajor items, or at least 2 renal items of hematuria and proteinuria</td>
<td>pregnant/breast-feeding, multi-system autoimmune disease</td>
</tr>
</tbody>
</table>

- Screening and randomization
  - 386 patients assessed for eligibility over screening period of 14 days (55 were excluded)
  - 331 underwent 1:1 randomization
  - 166 received avacopan and 164 received prednisone (1 did not receive prednisone)
  - 15 discontinued avacopan and 12 discontinued prednisone (majority before Week 26)
  - randomization stratified
    - vasculitis disease status (newly diagnosed or relapsing), ANCA status (anti-PR3 or anti-MPO), disease form (GPA or MPO), immunosuppressants (cyclophosphamide IV/PO or rituximab)
Methods

Statistical Analysis

• Sample size of 150 patients per arm would provide at least 90% power to show noninferiority
  • Assumes control/prednisone group remission rate was 60% (Week 26) and 45% (Week 52)
  • Estimates of the common difference in the incidences of remission were calculated using inverse-variance stratum weights

• Non-inferiority margin was -20%
  • Derived from the difference between the groups; one-sided alpha level of 0.025
  • Based on meta-analysis of previous clinical studies

• Secondary endpoints: mixed-effects models for repeated measures
  • Least square means for select secondary endpoints
  • Kaplan-Meier method used to estimate time to relapse of vasculitis
Results

Baseline Characteristics

- Avacopan (N=166) vs. prednisone (N=164)
- Well balanced demographics and disease characteristics
  - Mean age 60.9 years; Male (56%); White (84%)
  - Disease status: Newly diagnosed (69%), relapsed (31%)
  - Type of vasculitis: GPA (55%), MPA (45%)
  - ANCA status: anti-MPO positive (57%), anti-PR3 (43%)
  - Immunosuppressants: rituximab (65%), cyclophosphamide IV (31%) and PO (4%)
- Baseline mean BVAS of 16.2
- Baseline renal vasculitis in 81% of patients
- Baseline eGFR of 44.6 mL/min/1.73m² for avacopan and 45.6 prednisone
- Glucocorticoid doses during screening were similar in the two groups
Results

Primary Endpoints

(1) Remission at Week 26:
   Avacopan  120 (72.3%)
   Prednisone  115 (70.1%)

Est. common difference 3.4, 95% CI: -6.0 to 12.8
P<0.0001 (noninferiority); P=0.24 (superiority)

(2) Sustained remission at Week 52:
   Avacopan  109 (65.7%)
   Prednisone  90  (54.9%)

Est. common difference 12.5, 95% CI: 2.6 to 22.3
P<0.0001 (noninferiority); P=0.007 (superiority)

Efficacy observed was consistent across subgroups (newly diagnosed/relapsed, PR3/MPO, GPA/MPA, and cyclophosphamide/rituximab).
Results
Secondary Endpoints

- Greater incidence of glucocorticoid-induced toxic effects in prednisone group
  - GTI-CWS: 39.7 with avacopan vs. 56.6 with prednisone (Diff -18.6, 95% CI: -25.6 to -8.0)
  - GTI-AIS: 11.2 with avacopan vs. 23.4 with prednisone (Diff -12.1, 95% CI: -21.1 to -3.2)
  - Mean total prednisone 1349mg (4mg/day) with avacopan vs. 3655mg (12mg/day) prednisone
**Results**

**Secondary Endpoints**

- Beneficial effect of avacopan on eGFR and albuminuria at Week 26 and 52
  - eGFR increase: 7.3 ml/min/1.73m$^2$ (vs. 4.1) from baseline (Difference 3.2, 95% CI: 0.3 to 6.1)
  - eGFR increase in Stage IV CKD: 13.7 ml/min/1.73m$^2$ (vs. 8.2) (Difference 5.6, 95% CI, 1.7 to 9.5)
    - At Week 4, UACR decreased 40% in avacopan group vs. no change in prednisone group (P<0.0001)

![Figure S3. Estimated Glomerular Filtration Rate](image)
## Results

### Secondary Endpoints

- **Relapse**: 16 of 158 patients (10.1%) avacopan group and 33 of 157 patients (21.0%) in prednisone group
  - Hazard ratio for relapse after remission (avacopan vs. prednisone) was 0.46 (95% CI: 0.25 to 0.84)

- **Health-related quality of life (measured with SF-36 and EQ-5D-5L)**

- **Non-protocol immunosuppressant use for worsening disease** higher with prednisone (22.0% vs. 17.5%)

### Graphs

#### Probability of Freedom from Relapse

<table>
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<tr>
<th>Days to Relapse</th>
<th>Avacopan</th>
<th>Prednisone</th>
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<tr>
<td>0</td>
<td>1.00</td>
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<tr>
<td>10</td>
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<tr>
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#### No. at Risk

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<th>146</th>
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<td>119</td>
<td>111</td>
<td>90</td>
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Results

Safety

• Serious adverse events: 116 in the avacopan group vs. 166 in the prednisone group
  • Most common was worsening of vasculitis: 10.2% avacopan vs. 14.0% prednisone
  • Serious events (excluding vasculitis): 37.3% avacopan vs. 39.0% prednisone
  • Deaths: 2 with avacopan (worsening vasculitis and pneumonia) vs. 4 in prednisone group (fungal infection, infectious pleural effusion, acute MI, death of unknown cause)

• Serious infections: 13.3% in avacopan group vs. 15.2% in prednisone
  • Opportunistic infections: 3.6% vs. 6.7%
  • No herpes zoster infections with avacopan (2 in prednisone)
  • No *N. meningitidis* or *P. jirovecii* were observed

• ADE of an abnormal LFT in 5.4% with avacopan vs. 3.7% prednisone

• ADE related to glucocorticoids was 66.3% with avacopan vs. 80.5% prednisone group
Results

Authors’ Conclusion

• Avacopan, in the absence of daily prednisone, was noninferior, but not superior, to a prednisone taper in the proportion of patients achieving remission at Week 26 and was superior in sustained remission at Week 52.

• Comparison to previous trials
  • Beneficial effects of avacopan on eGFR and albuminuria
  • Quality of life improved in both groups; more benefit seen with avacopan at Week 52
  • Serious adverse events consistent with higher exposure to glucocorticoids

• Longer trials needed to determine the safety and durability of avacopan in patients with AAV.
Students’ Discussion
Strengths/Limitations

• Strengths
  • Good matching of baseline disease characteristics
  • Study design and generalizability
  • Excluded if non-protocol glucocorticoids used with standardized rescue therapy

• Limitations
  • Trial population was heterogenous
  • Secondary end points were not adjusted for multiplicity and should be interpreted with caution
  • Deviations from recommended guidelines for maintenance treatment
    • Rituximab usually repeated after 6 months (azathioprine inferior to rituximab)
    • Prednisone tapering schedule was short and may have led to flares of vasculitis
  • Glucocorticoids were used by patients in avacopan group
    • Although the mean daily dose in avacopan group was one third of that in the prednisone group
      and the incidence of additional glucocorticoid use was higher in the prednisone group
Students’ Discussion

Conclusion

• In patients with ANCA-associated vasculitis, avacopan was noninferior to a prednisone taper in inducing remission of vasculitis at Week 26 and was superior at Week 52, in addition to standard treatment.

• High doses and long-term of glucocorticoids carry well recognized morbidity. Avacopan offers an alternative induction regimen that aims to minimize steroid use and reduce relapse rates.

• Beneficial effects on renal response is seen early and continues for at least a year.

• Longer trials are needed to determine safety and duration of remission.
References