Inhibition du complément des vascularites à ANCA (avacopan)

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Disclosures

David Jayne has associations with Astra-Zeneca, Aurinia, Boehringer-Ingelheim, Chemocentryx, Chugai, GSK, InflaRx, Insmed, Lilly, Roche/Genentech, Sanofi-Genzyme and Takeda
ANCA vasculitis and survival

Heijl C et al, *RMD Open* 2017
## Serious infection in renal AAV, steroids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Reduced</th>
<th>Standard</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>46 (13)</td>
<td>53 (15)</td>
<td>0.78 (0.53 – 1.17)</td>
<td>0.23</td>
</tr>
<tr>
<td>ESRD, n (%)</td>
<td>70 (20)</td>
<td>68 (19)</td>
<td>0.96 (0.68 – 1.34)</td>
<td>0.65</td>
</tr>
<tr>
<td>Sustained Remission, n (%)</td>
<td>204 (58)</td>
<td>193 (55)</td>
<td>1.04 (0.92 – 1.19)</td>
<td>0.48</td>
</tr>
<tr>
<td>SAEs, n (%)</td>
<td>231 (65)</td>
<td>218 (62)</td>
<td>1.05 (0.94 – 1.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Incidence Rate Ratio (95% CI)

| Year 1 Serious Infections, n (%) | 96 (27) | 116 (33) | 0.70 (0.52 – 0.94) | 0.02    |
What is the evidence for complement in AAV?
What data is there from clinical trials?
Complement C5a

- **Neutrophil activation**
  - Chemoattractant, enzyme and O2 radical release

- **Organ dysfunction**
  - Myocardium, vascular permeability, cytokine action

- **Chronic inflammation**
  - T-cell dysregulation, T-reg ↓, Th-17 and Th-1 ↑

- **Auto-immune disease**
  - Associates with disease activity and adverse outcome
C5a signaling

- C5aR (CD88)
  - Pro-inflammatory

- C5L2 (C5aR2)
  - Anti-inflammatory
    - Suppression of pro-inflammatory mediators
    - Modulation of C5aR signaling
    - A decoy receptor
  - Pro-inflammatory
    - Mast cell activation
    - Increases ANCA induced neutrophil activation
The C5a Receptor (C5aR) C5L2 Is a Modulator of C5aR-mediated Signal Transduction*
What is the evidence for complement in AAV?
Chapel Hill Consensus 2012

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Large Vessel Vasculitis
- Takayasu Arteritis
- Giant Cell Arteritis

Small Vessel Vasculitis
- ANCA-Associated Vasculitis
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis
  - Eosinophilic Granulomatosis with Polyangiitis

Immune Complex SVV
- Anti-GBM Disease
- Cryoglobulinemic Vasculitis
- IgA Vasculitis (Henoch-Schönlein)
- Hypocomplementemic Urticarial Vasculitis
  (Anti-C1q Vasculitis)
Is renal AAV pauci-immune?
Complement deposition in ANCA Vasculitis

Circulating complement – patient/renal survival

C3

C4

Patient survival (%) vs. time from AAV diagnosis (months)

Renal Survival (%) vs. time from AAV diagnosis (months)

Augusto et al, Plos One 2016
Complement activation in AAV, lupus nephritis

C5b-9

Bb

Plasma Sc5b-9 levels (ng/ml)

Plasma Bb levels (μg/ml)

Active AAV
Active LN
AAV in remission
Normal

Active AAV
Active LN
AAV in remission
Normal

P<0.01
P<0.01
P>0.05
P<0.01

P<0.01
P>0.05

P<0.01
P>0.05

Kidney Int 2012
How does complement affect pathogenesis?
ANCA induced neutrophil activation is C5a dependent
Neutrophil extracellular traps (NETs)

ANCA induce NETS

NETs contain PR3/MPO

NETs co-localise with neutrophil injury
NETs, complement and endothelial injury

Schreiber A et al, PNAS 2017
Complement depletion abrogates vasculitis

Xiao et al, Am J Pathol 2007
Human C5a receptor blockade prevents experimental MPO-ANCA vasculitis

C5aR -/-  
C5L2 knock out exacerbated disease

C5aR +/+
C5a receptor 1 promotes autoimmunity, neutrophil dysfunction and injury in experimental anti-myeloperoxidase glomerulonephritis

- C5aR1
  - induced MPO-ANCA
  - Th1 responses
  - Neutrophil localization and activation

Dick J et al, *Kidney Int* 2018
Avacopan (C5aR inhibitor) in ANCA vasculitis
Avacopan
Targeting C5a

- **Avacopan → C5aR**
  - Leukocyte trafficking, migration, and activation

- **C5a**
  - **C5a Antibodies**
  - **Eculizumab (Soliris)**
  - **C5-convertase**

- **C5 (full length)**
  - **C5a (desArg)**
  - **C5L2**
  - **C5a internalization and destruction**

- **C3b**
  - **C3aR**
  - **Leukocyte migration and signaling**

- **C3b**
  - **C3a**
  - **C3b**
  - **iC3b**

- **Amplification Loop**
  - **Classical Pathway**
  - **Lectin Pathway**
  - **Alternative Pathway**

- **Reason for black box warning for eculizumab**
  - **Cell lysis** (i.e., *Neisseria* control)

- **Adaptive signaling**
- **Phagocytosis and clearance**
CCX168 (avacopan) dose selection

Becker et al., PLOS One 2016
How do you design a trial for a new drug in AAV?

Hypothesis from rituximab?

Hypothesis: Avacopan can replace cyclophosphamide.

Benefit: Spacing of cyclophosphamide.

Does spacing of cyclophosphamide toxicity?

Demonstrating additional efficacy is difficult?
## Avacopan (CCX168) AAV Phase II Trials

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>CLEAR</th>
<th>CLASSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Placebo + CYC/RTX + steroid</td>
<td>1. Placebo + CYC/RTX + steroid</td>
</tr>
<tr>
<td></td>
<td>2. Avacopan 30 + CYC/RTX + low steroid</td>
<td>2. Avacopan 10 mg + CYC/RTX + steroid</td>
</tr>
<tr>
<td></td>
<td>3. Avacopan 30 + CYC/RTX + no steroid</td>
<td>3. Avacopan 30mg + CYC/RTX + steroid</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>BVAS response at Week 12</td>
<td>BVAS response at Week 12</td>
</tr>
<tr>
<td></td>
<td>Safety</td>
<td></td>
</tr>
</tbody>
</table>
3 stage Phase II (CLEAR)

Stage 1
addition of avacopan to high dose GC
Data review

Stage 2 (randomized)
avacopan + low dose GC  placebo + high dose GC
Data review

Stage 3 (randomized)
avacopan alone  placebo + high dose GC

All received cyclophosphamide or rituximab; GC, glucocorticoid
Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

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Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶
Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,‡‡§§
Antonia Potarca,¶¶ Thomas J. Schall,¶¶ and Pirow Bekker,¶¶ for the CLEAR Study Group
Change in disease activity (BVAS)

- High Dose Steroids SOC (N=20)
- CCX168 with Low Dose Steroids (N=22)
- CCX168 with No Steroids (N=21)

BVAS % Change from Baseline

0%  -90%

-40% -61%

-64% -73%

-79% -57%

Time (weeks)

0  4  8  12
Change in GFR, proteinuria and MCP-1

** P < 0.01, * P < 0.05 for CCX168 vs. Control
Change in quality of life

Patient Reported Outcomes Statistically Significant at Week 12 in Avacopan Phase II CLEAR Trial

High-dose steroid\(^2\) group

All avacopan

Avacopan + no steroid vs. general population controls\(^2\)

\(^2\)Prednisone / Methylprednisone

* Significant improvement over 12 week dosing course

## Glucocorticoid adverse events

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>High Dose Steroids (N=23)</th>
<th>CCX168 + Low Dose Steroids (N=22)</th>
<th>CCX168 + No Steroids (N=22)</th>
<th>CCX168 Combined (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Any Event</td>
<td>15 (65.2%)</td>
<td>4 (18.2%)</td>
<td>11 (50.0%)</td>
<td>15 (34.1%) *</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>6 (26.1%)</td>
<td>2</td>
<td>1</td>
<td>3 (6.8%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1 (4.3%)</td>
<td>1</td>
<td>1</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (17.4%)</td>
<td>0</td>
<td>1</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (21.7%)</td>
<td>2</td>
<td>8</td>
<td>10 (22.7%)</td>
</tr>
<tr>
<td>Weight gain &gt;10 kg</td>
<td>2 (8.7%)</td>
<td>1</td>
<td>0</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Jayne D et al. *ERA-EDTA (abstract)* 2018
CLASSIC

- N=42
- 3 groups
  - Placebo
  - Avacopan 10mg
  - Avacopan 30mg vs placebo
- Background therapy
  - high dose steroid +
  - Cyclophosphamide or rituximab
- Serious adverse events:
  - 2, 3, 2
  - attributed to background therapy

**BVAS response week 12**

Phase III, ADVOCATE

Test Group (N = 150)
- CCX168, 30 mg twice daily
  - RTX, 4 weeks or CYC, 12 weeks followed by AZA
  - Placebo Prednisone

Control Group (N = 150)
- Placebo CCX168 twice daily
  - RTX, 4 weeks or CYC, 12 weeks followed by AZA
  - Prednisone, 60 mg/day tapered to 0 over 21 weeks.

Sustained remission rate at 12 months

1 year treatment period
IFX-1, anti-c5a monoclonal antibody

C5a
conformational change
new epitope

C5

C5b

C5b + C6 + C7 + C8 + C9x = MAC

bacteria

Bacterial / Meningococcal Lysis

Cleavage of C5 through:
• Complement pathway activation, or
• Directly through enzymes via “extrinsic” pathway

Phase IIs
IXCHANGE – EU
IXPLORE - US
Research agenda

➢ ADVOCATE
  – Avacopan exposure
  – Efficacy & safety
  – Personalisation ?

➢ Pathogenesis
  – Genetics ??
  – Better biomarkers for alternative complement activation
  – Role in granulomatous disease
Summary

- Complement as a therapeutic target
- Rationale for complement inhibition in vasculitis
  - Alternative complement pathway
- Avacopan development for ANCA vasculitis
## Acknowledgements

### Collaborative networks

- [European Vasculitis Society](https://www.euvas.org)
- [Vasculitis Clinical Research Consortium](https://www.vasculitis.org)

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