New Developments in ANCA-associated Vasculitis

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Ulrich Specks, M.D.
Connor Group Foundation Professor of Medicine
Mayo Clinic College of Medicine & Sciences
Chair, Division of Pulmonary & Critical Care Medicine
Mayo Clinic, Rochester, MN
Disclosures

• Research Grant Support to Mayo Clinic:
  • BMS, Roche, Chemocentryx, NIAMS

• Off-label use: all drugs used for AAV represent off-label use except rituximab
Learning Objectives

Attendees will be able to:

• Summarize the current state-of-the-art treatment for GPA and MPA.
• Recognize unmet needs in the management of GPA and MPA.
• Describe ongoing clinical trials addressing unmet needs in GPA and MPA.
• Understand the direction of future research efforts in the field of ANCA-associated vasculitis.
Outline

• Where do we stand in 2018?
• What are the unmet needs in the management of GPA and MPA?
  ➢ Remission induction
    ✓ Is plasma exchange beneficial?
    ✓ Can we get by without glucocorticoids?
    ✓ Anything else on the horizon?
  ➢ Remission maintenance
    ✓ How can we best maintain remission?
    ✓ Who needs remission maintenance?
Epidemiology of AAV in Olmsted County
A 20-Year Study

• 58 incident cases: 40% GPA, 48% MPA, 12% EGPA
• Annual incidence: 3.3/100,000 population (95% CI 2.4-4.1)
  ➢ Higher than reported from other regions in the world
• Prevalence: 42.1/100,000 (95% CI 29.6-54.6)
• Mortality of MPA and EGPA higher than general population
• Mortality of GPA not higher than general population

Therapeutic Targets in AAV

Innate Immunity

Adaptive Immunity

Neutrophils

B-Lymphocytes

T-Lymphocytes
Status of AAV Induction Therapy in 2018

- For non-severe GPA:
  - MTX remains the most widely accepted first-line agent
    A&R 2005; 52:2461-9

EULAR/ERA-EDTA Recommendations. Yates et al. ARD 2016
Status of AAV Induction Therapy in 2018

- For non-severe GPA:
  - MTX remains the most widely accepted first-line agent
    A&R 2005; 52:2461-9

- For severe GPA and MPA the RAVE trial showed:
  - RTX is non-inferior to CYC in severe AAV, including subsets with major renal involvement and alveolar hemorrhage
  - RTX is superior to CYC in relapsing and PR3-ANCA positive patients
    NEJM 2010; 363:221-32
    JASN 2015; 26:976-85
    NEJM 2013; 369:417-27
    JASN 2015; 26:976-85
    ARD 2016; 75:1166-9

EULAR/ERA-EDTA Recommendations. Yates et al. ARD 2016
Cost Considerations

- Drug cost
- Health care system
- Insurance environment
- Cost associated with overall treatment
- Economic cost beyond the insurance cost

**Rituximab in Combination with Corticosteroids for the Treatment of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A NICE Single Technology Appraisal**

- Conclusion: “Rituximab cost-effective but not for newly diagnosed patients”
- Caveat: Analysis was done “newly diagnosed” versus “relapse”, not PR3-ANCA versus MPO-ANCA
Status of AAV Induction Therapy in 2018

- **For non-severe GPA:**
  - MTX remains the most widely accepted first-line agent
    
  - **For severe GPA and MPA the RAVE trial showed:**
    - RTX is non-inferior to CYC in severe AAV, including subsets with major renal involvement and alveolar hemorrhage
    - RTX is superior to CYC in relapsing and PR3-ANCA positive patients

  - Other studies have shown that RTX is at least as good as CYC for patients with:
    - Severe renal disease
    - Alveolar hemorrhage requiring ventilatory support

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- Severe renal disease
- Alveolar hemorrhage requiring ventilatory support

- **EULAR/ERA-EDTA Recommendations. Yates et al. ARD 2016**
Status of AAV Maintenance Therapy in 2018

• Following induction with cyclophosphamide:
  ➢ AZA and MTX are equally effective
    Pagnoux et al. NEJM 2007; 359:2790-803
  ➢ MMF is considered second line agent
    Hiemstra et al. JAMA, 2010; 304:2381-8
  ➢ RTX is more effective than AZA
    Guillevin et al. NEJM 2014;371:1771-80

• Following induction with rituximab?

EULAR/ERA-EDTA Recommendations. Yates et al. ARD 2016
Therapeutic Targets in AAV

Innate Immunity

Adaptive Immunity

Glucocorticoids

Neutrophils

B-Lymphocytes

T-Lymphocytes

CYC  RTX  MMF

MTX  AZA
Survival of GPA
Population Based Study in UK

Fig. Survival according to the presence of granulomatosis with polyangiitis.

Wallace et al. Sem Arthritis Rheum 2016
Survival of GPA
Hospital Mortality for GPA in US

Wallace et al. Arthritis Care Res 2017
Mortality of GPA and MPA

48% of 1-yr mortality – infection
19% of 1-yr mortality – active vasculitis
Patient and Renal Survival in AAV
It’s All About Kidney Function

Determinants of long-term renal survival (MVA):
- Renal function at 6 months
- Renal relapse

De Joode et al. CJASN 2013; 8:1709-17
Unmet Need and Open Question in AAV in 2017

• **Opportunities for Remission Induction**
  - Improve early mortality
  - Minimize toxicity, particularly glucocorticoid toxicity
  - Minimize tissue damage, particularly renal damage
    - Role for Plasma Exchange?
    - Novel drugs?

• **Opportunities for Remission Maintenance**
  - Individualize treatment
    - Identify biomarkers for relapse risk
    - Target existing drugs selectively to patients at risk for relapse
  - Target the defect at the root of relapse risk
    - Novel drugs
QUESTION

• Plasma Exchange Should be Used in Which of the Following Patients?
  
A. Patients with severe renal disease (creatinine >5.6 mg/dL at presentation
B. Patients presenting with alveolar hemorrhage
C. Patients with serum ANCA and serum anti-GBM
D. In all of the above
E. In none of the above
## Results of the MEPEX Trial in AAV with Severe Renal Disease

### Significant Differences at 3 Months

<table>
<thead>
<tr>
<th></th>
<th>PLEX</th>
<th>IV MeP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In surviving patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis independent</td>
<td>81 %</td>
<td>59 %</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>In the cohort as a whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and off dialysis</td>
<td>69 %</td>
<td>49 %</td>
<td>0.02</td>
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</tbody>
</table>

Jayne et al. JASN 2007; 18:2180
Longterm Outcome of MEPEX Trial

Proportion free of ESRD or death

Time (years)

Patients at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>IV MeP</td>
<td>68</td>
<td>25</td>
<td>23</td>
<td>15</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>PLEX</td>
<td>69</td>
<td>32</td>
<td>26</td>
<td>13</td>
<td>6</td>
<td>0</td>
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</tbody>
</table>

Walsh et al. Kidney Int 2013
## PLEX in Alveolar Hemorrhage Caused by AAV

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N</th>
<th>PLEX</th>
<th>DAH resolution and hospital survival</th>
<th>No PLEX</th>
<th>DAH resolution and hospital survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartin-Ceba, 2015*</td>
<td>73</td>
<td>32</td>
<td>27</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Hruskova, 2013</td>
<td>53</td>
<td>40</td>
<td>18</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Ravindran, 2010</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Chen, 2009</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lin, 2009 (MPA only)</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Klemmer, 2003</td>
<td>20</td>
<td>20</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>169</td>
<td>104</td>
<td>69 (66%)</td>
<td>65</td>
<td>49 (75%)</td>
</tr>
</tbody>
</table>

Plasma exchange and glucocorticoid dosing in ANCA associated vasculitis: a randomized control trial (PEXIVAS)

Michael Walsh¹, Peter Merkel², and David Jayne³ for the PEXIVAS Study Group
¹McMaster University; ²University of Pennsylvania; ³Addenbrooke’s Hospital
PEXIVAS (N=700)
Factorial Design

Severe AAV

Cyclophosphamide Or Rituximab

Adjunctive Plasma Exchange

No Plasma Exchange

Standard-Dose GC

Reduced Dose GC

Standard-Dose GC

Reduced Dose GC

Follow-Up

ESRD or Death
QUESTION

Which of the following drugs are currently not under investigation in AAV?

A. Abatacept
B. Avacopan
C. Rituximab
D. Prednisone
E. A PAD4 inhibitor
Novel Drugs?

- Targeting the innate immunity – no glucocorticoids
- Lessons learned from understanding pathogenesis
  - Blocking C5a receptor – CCX168 = avacopan
  - Inhibiting NET formation?
  - Inhibiting ANCA target antigen activity
Lessons from the MPO-ANCA Transfer Mouse Model

Demonstrated role of complement system

- Lesions are complement dependent
- Intact alternative pathway is required AM J Pathol 2007; 170:52-64
- Mice lacking C5a receptor on neutrophils do not develop lesions JASN 2009; 20:289-98-31
- Anti-C5a monoclonal antibodies can be used therapeutically JASN 2014; 25:225-31

✓ Basis for CCX168 (anti-C5aR/CD88) phase II trials showing apparent steroid sparing potential Xiao JCI 2002;110:955-63
Management of ANCA-associated Vasculitis

What’s Hot of the Press?

Targeting the C5a receptor in severe GPA and MPA

Jayne et al. JASN 2017

** P < 0.01 for avacopan vs. steroid control group
Study Schema for ADVOCATE Trial

Two primary endpoints (analyzed after 12 months):
- Remission rate (based on BVAS) at 6 months
- Sustained remission rate (based on BVAS) at 12 months

1 year treatment period

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

Control Group (N = 150)
- Avacopan-matching placebo twice daily
  - CYC, 12 weeks followed by AZA, or RTX, 4 weeks
  - Prednisone, 60 mg/day tapered to 0 over 20 weeks.
Neutrophil Extracellular Traps Kill Bacteria

Volker Brinkmann, Ulrike Reichard, Christian Goosmann,
Beatriz Faurer, Yvonne Uhlemann, David S. Weiss,
Yvette Weinrauch, Arturo Zychlinsky

Neutrophils engulf and kill bacteria when their antimicrobial granules fuse with the phagosome. Here, we describe that, upon activation, neutrophils release granule proteins and chromatin that together form extracellular fibers that bind Gram-positive and -negative bacteria. These neutrophil extracellular traps (NETs) degrade virulence factors and kill bacteria. NETs are abundant in vivo in experimental dysentery and spontaneous human appendicitis, two examples of acute inflammation. NETs appear to be a form of innate response that binds microorganisms, prevents them from spreading, and ensures a high local concentration of antimicrobial agents to degrade virulence factors and kill bacteria.

- NET formation is a unique form of cell death distinct from apoptosis
- NET formation depends on NADPH oxidase mediated O2 radical species
ANCA Induces NET Formation and ANCA Target Antigens are Present on NETs

NETs in Glomerular Lesions of AAV

ANCA May Induce Vicious Cycle of Self-perpetuated NET Formation

- ANCA can induce NET formation
- NETs occur in AAV in the absence of infection
- NETs can activate plasmacytoid dendritic cells via LL37
- NETs contain PR3 & MPO where they are accessible to ANCA
- Chromatin-immunoglobulin complexes (NETs with bound ANCA) can induce loss of tolerance and autoantibody production in a TLR-9 dependent manner
- *S aureus* is a potent inducer of NET formation
  - NET formation also implicated in thrombosis
  - Therapeutic role for peptidyl-arginine-deiminidase 4 (PAD4) inhibition in AAV?

Therapeutic Targets in AAV

Innate Immunity

Adaptive Immunity

Glucocorticoids

Neutrophils

B-Lymphocytes

T-Lymphocytes

C5aR inhibitors
PAD 4 inhibitors

CYC  RTX  MMF
MTX  AZA
Ultimate Management Dilemma in ANCA-associated Vasculitis

Risk of Relapse
Cumulative Damage
Cumulative Steroid Exposure

Risk of Preventive Therapy
Efficacy of Maintenance
Toxicity of Maintenance
Cumulative Cyclophosphamide Dose

Ultimate Management Dilemma in ANCA-associated Vasculitis

What is the Balance Today? Rituximab

- Risk of Relapse
  - Cumulative Damage
  - Cumulative Steroid Exposure

- Risk of Preventive Therapy
  - Efficacy of Maintenance
  - Toxicity of Maintenance
Opportunities to Improve Remission Maintenance

Who needs remission maintenance?
Long-term RAVE data by Disease Phenotype

Probability of Remaining in Complete Remission

Time from Complete Remission to Relapse (days)

Number at risk

MPO/MPA/New Diagnosis (n=29)
PR3/GPA/Relapsing (n=52)

P < 0.01

Overall P < 0.01
PR3/GPA/Relapsing P = 0.47
MPO/MPA/New Diagnosis P = 0.97

Number at risk

CYC/AZA, MPO/MPA/New Diagnosis (n=14)
CYC/AZA, PR3/GPA/Relapsing (n=23)
RTX, MPO/MPA/New Diagnosis (n=15)
RTX, PR3/GPA/Relapsing (n=58)

NEJM 2013; 369:417-27 Supplement
Role of B- and T-Lymphocytes in Granulomatosis with Polyangiitis

• Correlation between frequency of activated peripheral blood B-cells and
  ➢ Disease activity of GPA (BVAS)
  ➢ Disease extent (generalized vs limited)

• Markers of T-cell activation were detectable during active disease and remission in GPA

Popa et al: J Allergy Clin Immunol 103:885, 1999
Inhibiting T-cell Activation: Key to Remission Maintenance in GPA?

Table 2  Summary of efficacy endpoints

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease improvement</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Remission (BVAS/WG=0)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Relapse</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Reached common closing</td>
<td>14 (70)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from entry to remission (months)</td>
<td>1.9</td>
<td>1–19</td>
</tr>
<tr>
<td>Time from remission to relapse (months)</td>
<td>6.7</td>
<td>5–9</td>
</tr>
<tr>
<td>Time on study before common closing/early termination</td>
<td>12.3</td>
<td>2–35</td>
</tr>
<tr>
<td>Remission duration before common closing (months)</td>
<td>14.4</td>
<td>4–20</td>
</tr>
<tr>
<td>VDI at common closing/early termination</td>
<td>3.0</td>
<td>0–7</td>
</tr>
</tbody>
</table>

BVAS/WG, Birmingham Vasculitis Activity Score for Wegener’s Granulomatosis; VDI, Vasculitis Damage Index.
RTX versus AZA for Remission Maintenance in AAV MAINRITSAN Trial

Induced with CYC (n=115)

Primary Endpoint:
Relapse rate at 28 mo

Results:
Pts (%) with major relapse
AZA: 17 (29%)
RTX: 3 (5%)
To avoid 1 event, 4 pts had
to be treated with RTX.

HR*: 6.61, 95%CI: 1.56 to 27.96, *P=0.002
AZA vs. RTX

RTX versus AZA for Remission Maintenance in AAV MAINRITSAN Trial
Economic Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD)</td>
<td>Median[IQR]</td>
</tr>
<tr>
<td>Inpatient stays, n</td>
<td>1.9(2.6)</td>
<td>1[0–2]</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>14.1(24.1)</td>
<td>7[1–16]</td>
</tr>
<tr>
<td>Outpatient visits, n</td>
<td>3.5(4.9)</td>
<td>1[0–5]</td>
</tr>
<tr>
<td>Cost (€/patient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol drug</td>
<td>313(130)</td>
<td>337[264–391]</td>
</tr>
<tr>
<td>Its administration</td>
<td>0</td>
<td>0[0–0]</td>
</tr>
<tr>
<td>Maintenance therapy</td>
<td>633(1,808)</td>
<td>0[0–0]</td>
</tr>
<tr>
<td>Relapses</td>
<td>2,547(4,748)</td>
<td>0[0–4,737]</td>
</tr>
<tr>
<td>Side effects</td>
<td>2,606(6,622)</td>
<td>0[0–2,523]</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2,954(5,611)</td>
<td>636[0–3,254]</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>993(407)</td>
<td>1,069[770–1,314]</td>
</tr>
<tr>
<td>Total cost</td>
<td>10,046(10,558)</td>
<td>6,049[2,140–14,501]</td>
</tr>
</tbody>
</table>

Rituximab was cost effective:
- Higher drug costs offset by higher relapse rate and renal damage
- Incremental cost effectiveness ratio: 259 Euro/avoided relapse

Montante et al. Rheumatology 2017;March:iii32-3.
RTX versus AZA for Remission Maintenance in AAV
RITAZAREM Trial (n=190)

Induction with RTX
  All Relapsers (severe or non-severe)
  Randomized at 4 mo (n=160)
  2 Glucocorticoid dosing options

Intervention:
  1g of RTX q 4 mo vs daily p.o. AZA

Primary Endpoint:
  Time to relapse at 24 mo

Results:
  Enrollment completed
  Primary outcome results pending

QUESTION

Which statement about serial PR3-ANCA testing is most appropriate?

A. It should not be done because it has no predictive value for relapse

B. It is most useful in patients who had remission induction with CYC followed by maintenance with AZA or MTX

C. It is most useful in a patient with GPA who had a relapse with lung nodules and ENT disease while on MTX maintenance

D. It is most useful in a patient who received RTX after presenting with alveolar hemorrhage and glomerulonephritis
Opportunities to Improve Remission Maintenance

Can retreatment be individualized?
The search for biomarkers

• Listen to the patient
• PR3-ANCA?
• PR3-ANCA expressing B-cells?
Can retreatment be individualized?
The PGA as a biomarker?

The Value of a Patient Global Assessment of Disease Activity in Granulomatosis With Polyangiitis (Wegener’s)

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (n = 885)‡</td>
<td>15.7</td>
<td>Referent</td>
</tr>
<tr>
<td>Two visits prior to relapse (n = 70)</td>
<td>17.7</td>
<td>0.41</td>
</tr>
<tr>
<td>One visit prior to relapse (n = 103)</td>
<td>20.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Relapse visit (n = 103)</td>
<td>28.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Values are the mean patient global assessment scores (n = number of study visits) during remission, at visits leading up to disease relapse, and at visits after disease relapse.
† Versus the referent group.
‡ Remission that is not followed by a relapse during the next 2 study visits.

Can retreatment be individualized?

Serial PR3-ANCA Testing

Factors determining clinical utility for relapse prediction analyzed in RAVE trial

Risk of relapse following PR3-ANCA rise depends on:

- Assay methodology: most sensitive not best
  - Know thy assay
  - Use same assay serially

- Disease phenotype at baseline:
  - Most useful in patients where disease manifestations attributable to capillaritis dominate the clinical presentation

- Patient’s treatment
  - More useful following rituximab therapy

Can retreatment be individualized?
Individualized RTX retreatment based on B-cells & PR3-ANCA

MAINRITSAN II Trial:
- same efficacy
- fewer RTX infusions
- same AEs
- ANCA not helpful

ANCA workshop Tokyo 3/17
Can retreatment be individualized?
PR3-ANCA expressing B-cells: Labelling


PR3-specific B cell
Other specificity B cell

Can retreatment be individualized?
PR3-ANCA expressing B-cells

Summary

• Glucocorticoid avoidance is primary focus of clinical research in GPA and MPA
  - Lower dosing regimens for induction (PEXIVAS, RITAZAREM)
  - (Almost) no glucocorticoids for induction (Phase III trial of avacopan)
  - More effective remission maintenance (RTX vs AZA)
  - Better targeted remission maintenance (Biomarkers)

• Innate immunity is target of new drugs for remission induction

• Adaptive immunity remains target of remission maintenance approaches
Acknowledgements

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  • Study Coordinators

• Patients

• Vasculitis Collaborators
  • RAVE Trial
  • VCRC
  • EUVAS

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