Vasculitis in 2021: New Medications Less Steroids Better Patient Outcomes

Not your Grandma’s vasculitis

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Disclosures

• I have no relevant disclosures
Agenda

Focus on two diseases: ANCA-associated vasculitis (AAV) & giant cell arteritis (GCA)

1. Blocking IL-6 (Tocilizumab) in GCA can reduce need for steroids
2. Plasma exchange may not be effective for AAV
3. Faster steroid taper in severe AAV
4. Blocking IL-5 (mepolizumab) in Churg Strauss (eGPA)
Giant Cell Arteritis

Immune complex small vessel vasculitis
- Cryoglobulinemic vasculitis
- IgA vasculitis (Henoch-Schönlein)
- Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Medium vessel vasculitis
- Polyarteritis nodosa
- Kawasaki disease

Anti-GBM disease

ANCA-associated small vessel vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (Wegener’s)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Large vessel vasculitis
- Takayasu arteritis
- Giant cell arteritis

Giant Cell Arteritis

❖ EXCLUSIVELY occurs in adults >=50; Lifetime risk of 1% in women, 0.5% in men

❖ Symptoms:
  ❖ New severe headache with tenderness over the temples
  ❖ Scalp tenderness
  ❖ Jaw claudication
  ❖ Sudden monocular vision loss, amaurosis fugax, diplopia
  ❖ Polymyalgia rheumatica

❖ Labs: ESR and CRP are elevated in ~95% of patients

GCA Treatment

- Steroids at first sign of disease
- Steroid tapers take 1-3 years, relapses are common
- Steroid side-effects are universal and can be severe in older patients

- Can we do better...?
Tocilizumab (IL-6 blockade) for GCA

Trial of Tocilizumab in Giant-Cell Arteritis

Randomization:
Tocilizumab + 6-month prednisone taper
Placebo + 6-month prednisone taper
Placebo + 12-month prednisone taper (typical tx)

• Primary outcome: steroid-free sustained remission at week 52
Figure 2. Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.
Tocilizumab for GCA

• FDA approved
• Can taper steroids significantly faster with fewer flares
• Cons:
  – IL-6 blockade obliterates CPR and ESR (lose a biomarker!)
  – IL-6 blockade can cause rare bowel perforation (avoid in patients with diverticulitis history)
  – $$$
ANCA-associated vasculitis

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ANCA-Associated Vasculitis: small to medium vessel disease

Granulomatosis with polyangiitis (GPA)
Formerly: Wegener’s granulomatosis
Systemic disease: 90% ANCA positive
“Limited disease: ~60% ANCA positive

Microscopic polyangiitis (MPA)
90% ANCA positive

Eosinophilic GPA (EGPA)
AKA: Churg-Strauss
30-50% ANCA positive

Scleritis & orbital inflammation

Necrotizing pauci-immune GN
Image courtesy of Cailin Sibley

Pulmonary capillaritis (DAH)

Palpable purpura and ulcers

Mononeuritis multiplex

Upper Airway Damage


Rheumatic Disease Clinics of North America Volume 41, Issue 1, February 2015, Pages 33-46
New ANCA Vasculitis

No

MTX + Steroids

Life or organ-threatening disease?

Yes

Steroids + Cyclophosphamide or Rituximab

Remission?

For how long..?

Maintain remission with Rituximab or Azathioprine

Treatment failure?
18-year-old with severe AAV

- 6-week history of red eye + photophobia. Recent otitis media. **Now with 1-2 days of cough with shortness of breath, no hemoptysis**
- Tender bumps/bruises on hands, feet, and lips.
- ROS: 2 weeks of malaise, generalized weakness, arthralgia, myalgia, sweats, 15 lb weight loss
- Track athlete, about to graduate high school
Pertinent exam findings

• VS: SpO2 85% on RA, HR 140
• Gen: Pale, ill-appearing
• HEENT: injected sclera, punctate erythematous lesions on the tongue and gingiva.
• CV/Pulm: Tachycardic, diffuse crackles
• Skin: nodular lesions on several fingertips and feet, palpable purpura on the legs and buttocks
• MSK: Synovitis of knees, wrists, elbows
Pertinent labs:

- Hgb 8.5 $\rightarrow$ 5.2 a few hours later (was 12.2 one week ago)
- UA: moderate blood, no protein
- C-ANCA 1:1280, PR3 1567
Bronchoalveolar lavage
Recap: 18-year-old with new ANCA vasculitis and brisk diffuse alveolar hemorrhage.

What do you do next?

✓ Admit to the ICU
✓ Transfusions
✓ Call everyone: rheum, derm, heme, etc.
✓ Send workup: echo, cultures, utox, etc. (all ok)
✓ Pulse methylprednisolone (1000mg daily)

...Increasing O2 requirements over several hours.

What else can we do? **Plasmapheresis?**
Rationale for plasmapheresis:

ANCA antibodies are *probably* pathogenic
PLEX removes antibodies...

Older data: PLEX reduces ESRD (but: no data for DAH, no difference in mortality, and not compared to modern standard of care)
Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

PEXIVAS methods

• Randomized, controlled
• **PLEX vs No PLEX** in ADDITION to standard care
• 6 years, 95 centers, 16 countries
• 704 patients with severe new or relapsing ANCA vasculitis (GFR <50 OR pulmonary hemorrhage)
• Primary outcome: composite death from any cause or ESRD
Built in a **low-dose** vs **standard dose** steroid study!

Clever 2x2 factorial design!

Severe AAV

Standard Therapy with Cyclophosphamide or Rituximab + Pulse Steroids

- Adjunctive Plasma Exchange
  - Standard-Dose Glucocorticoids
  - Reduced-Dose Glucocorticoids

- No Plasma Exchange
  - Standard-Dose Glucocorticoids
  - Reduced Dose Glucocorticoids
# Standard vs Reduced-Dose Steroids:

Table 1 **Dosing for oral Glucocorticoids in the standard and reduced-dose limbs from trial start**

<table>
<thead>
<tr>
<th>Week</th>
<th>Standard</th>
<th>Reduced-dose</th>
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<tbody>
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<td>1</td>
<td>60 50-75 kg pulse</td>
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By the end of 3 months, low dose group received 54% less steroid.

By the end of 6 months, low dose group received 61% less steroid.
NO DIFFERENCE IN DEATH or ESRD:

**PLEX vs no PLEX**

Primary outcome: 28.4% of PLEX group vs 31.0% of NoPLEX group

HR of PLEX 0.86 (95% CI 0.65-1.13; p=0.27)

**Standard vs Reduced-dose Steroids**

Fewer infections with reduced dose steroid (HR 0.69 (0.52-0.93))
No significant difference in death or ESRD:

- PLEX vs no PLEX
- Standard vs reduced steroids
- Subgroups: age, disease severity, induction therapy, or ANCA type

But—Powered for a moderate effect size
And—severe DAH was still a relatively small number (61)
So what did we do?

- Recap: 18-year-old with new severe ANCA vasculitis, brisk diffuse alveolar hemorrhage, rapidly declining oxygenation...
Hospital Course

• PLEX started hospital day #1
• Pulse methylpred → high dose steroids
• Rituximab induction
• Intubated on hospital day #3
• And (nearly) everything that could go wrong, went wrong.
Hospital Course

- 57 days in the hospital, 34 days in the ICU.
- Recurrent pulmonary hemorrhage, repeat pulse steroids, cryo, platelets, RBC
- Prolonged intubation, ARDS, proning, trach
- Large MCA infarct, non-infectious endocarditis with emboli → cortical blindness and hemiparesis
- Persistent/recurrent eosinophilia...
Eosinophilia

- Peripheral eosinophilia
- Bronchoalveolar lavage: 33% eosinophils (high)
- Responds to pulse steroids, recurs with taper...
- Hyper-eosinophilia workup unrevealing
What are these eosinophils?

• Normal eosinophils are very steroid-sensitive (even eGPA)
• One astute consultant: “I don’t know what is wrong with these eosinophils, but they aren’t normal.”
• What else can we do?
Anti-IL5 therapy for EGPA

- IL-5 regulates eosinophil proliferation, maturation and differentiation
- FDA approved for eosinophilic asthma and eGPA
Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis


• RCT mepolizumab vs placebo + standard of care

• Primary endpoint: total weeks in remission with <5mg/day prednisone AND proportion of patients in remission at week 36 and 48
Figure S1. Proportion of participants achieving remission (BVAS²=0, prednisolone/prednisone dose ≤7.5 mg/day), by visit.
Mepolizumab for eGPA

- Reduces peripheral eosinophilia, steroid-sparing benefit
- Quite safe (few more URIs in treatment group)
- However:
  - Very few severe end-organ involvement
  - Relapse rates high, 47% of mepolizumab group and 81% of placebo
  - Effect wears off quickly after stopping mepolizumab
  - Hefty price tag: $11K/month + “infusion” costs
Back to the case...

- 18-year-old, very severe ANCA vasculitis, now extubated, but ongoing active disease despite maximal therapy, and oddly persistent eosinophilia...
Post-hospital follow up:

- **Pulse**
  - 4/23/2019
  - 5/7/2019
  - 5/21/2019
  - 6/4/2019
  - 6/18/2019

- **Anti-IL5**
  - 4/23/2019
  - 5/7/2019
  - 5/21/2019
  - 6/4/2019
  - 6/18/2019

- **RITUXIMAB**
  - 4/23/2019
  - 5/7/2019
  - 5/21/2019
  - 6/4/2019
  - 6/18/2019

**Eosinophil Count**

- **Steroids:**
  - 4/23/2019
  - 5/7/2019
  - 5/21/2019
  - 6/4/2019
  - 6/18/2019

**Complications:**
- Pulmonary hemorrhage
- Strokes
- Endocarditis
- New skin vasculitis
- DVTS
- Flare of conjunctivitis
- Hospital discharge

**Hospital:** OHSU
Clinical Remission and gradual neurologic recovery

- Eosinophil Count
- Steroids:

- Anti-IL5 pulse
- RITUXIMAB
- Anti-IL5
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Follow up

• Remarkable neurologic recovery
• Substantial **steroids side effects:**
  – Weight gain
  – Acne
  – Hypertension
  – Skin infection
  – Difficulty sleeping, mood changes
  – Long term risk for osteoporosis
Could we have done better?

• Is it possible to treat severe ANCA associated vasculitis WITHOUT STEROIDS?
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*
Avacopan: C5A inhibition

Why? C5A is a neutrophil primer/attractor

Break the amplification loop of active disease!
RCT: Avacopan vs prednisone

- Placebo + Steroids vs Avacopan + No Steroids
- Patients with organ-threatening ANCA vasculitis
- ADDED to standard care
- Noninferiority study: Remission at week 26
- Good safety profile
- Currently under FDA review (controversy about study design and steroid use in the avacopan arm)
Avacopan is noninferior
Conclusions about ANCA vasculitis management

- New data is NOT supportive of PLEX in additional to standard therapy.
- We can taper steroids more rapidly!
- Maybe we won’t need steroid at all…? Avacopan
- Mepolizumab is a steroid-sparing anti-IL5 drug for eGPA

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OHSU
OHSU Vasculitis Center

- Rheumatologists: Drs. Marcia Friedman & Daniela Ghetie
- Dermatology: Drs. Nicole Fett and Lynne Morrison
- Ophthalmology: Drs. Jim Rosenbaum, Pheobe Lin, & Eric Suhler
- Nephrology: Dr. Rupali Avasare
- Pulmonary: Dr. Daniel Seifer
- ENT: Dr. Joshua Schindler
- Many more providers with a passion for vasculitis care.