Update and Review on Vasculitis

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Outline

• Classification and nomenclature updates
• Small vessel vasculitis
• Pathophysiology
• Diagnosis
• Management/therapeutic updates
Definition

• Vasculitis = inflammation of the blood vessel

v/s "Vasculopathy" = abnormalities of the blood vessels
First described case

• 1860s by Kussmaul and Maier

• 27 yo tailor died after 1 month hospitalization
• Finger numbness, muscle weakness
• Appearance of cutaneous nodules on his skin
• “Before our eyes, a young man developed a general paralysis of the voluntary muscles ... [He] had to be fed by attendants, and within a few weeks was robbed of the use of most of his muscles.”
First described case
Other forms of vasculitis can be differentiated from PAN by:

- The general confinement of the disease to medium-sized vessels as opposed to capillaries and postcapillary venules (small vessels) and the aorta and its major branches (large vessels)
- The exclusive involvement of arteries, with sparing of veins
- The tendency to form microaneurysms
- The absence of lung involvement
- The lack of granulomatous inflammation
- The absence of associated autoantibodies (e.g., antineutrophil cytoplasmic antibodies [ANCAs], anti–glomerular basement membrane [anti-GBM] antibodies, or rheumatoid factor)
- The association of some cases with hepatitis B virus (HBV) infection
2012 International Consensus

- Chapel Hill Consensus Conference on the Nomenclature of Vasculitis
  7 Categories

Size Matters

1. **Large Vessel Vasculitis (LVV)**
   - Giant cell arteritis
   - Takayasus arteritis

2. **Medium Vessel Vasculitis (MVV)**
   - Polyarteritis nodosa
   - Kawasaki disease

3. **Small Vessel Vasculitis (SVV)**
   - ANCA associated
   - Immune complex
Vessel size

- Aorta
- Giant cell arteritis
  - Takayasu's arteritis
- Large-to-medium-sized artery
- Polyarteritis nodosa
  - Kawasaki disease
- Small-sized artery
- Henoch-Schönlein purpura
  - Cryoglobulinemic vasculitis
- Arteriole
  - Anti-GBM
  - Leukocytoclastic vasculitis
- Capillary
- ANCA-associated vasculitis:
  - Microscopic polyangiitis
- Venule
- ANCA-associated vasculitis:
  - Granulomatosis with polyangiitis
  - Churg-Strauss syndrome
- Vein

Other categories

4. Variable Vessel Vasculitis (VVV)
   (behcets, cogan’s syndrome)

5. Single Organ Vasculitis (SOV)
   (PACNS, aortitis, cutaneous arteritis)

6. Vasculitis associated with systemic disease
   (lupus, rheumatoid or sarcoid vasculitis)

7. Vasculitis associated with probable etiology
   (Hep B, Hep C, syphillis, drug associated/cancer associated vasculitis)
Symptoms based on size

- **LVV**:  
  - Limb claudication  
  - Asymmetric blood pressures  
  - Absence of pulses  
  - Bruits  
  - Aortic dilation  
  - Renovascular HTN
Symptoms based on size

- **MVV:**
  - Cutaneous nodules
  - Ulcers
  - Livedo reticularis
  - Digital gangrene
  - Mononeuritis multiplex
  - Microaneurysms
  - Renovascular HTN
Symptoms based on size

- **SVV:**
  - Purpura
  - Vesiculobullous lesions
  - Urticaria
  - Glomerulonephritis
  - Alveolar hemorrhage
  - Cutaneous extravascular necrotizing granulomas
  - Splinter hemorrhages
  - Uveitis/scleritis/episcleritis
SVV

• Predominately affecting capillaries, venules, arterioles, and small arteries
• ANCA associated vasculitis (AAV)
  – pauci-immune
  – GPA, MPA, and EGPA (wegener's, CSS)
• Immune-complex deposition vasculitis
  – IgA vasculitis (HSP)
  – Anti-GBM vasculitis (goodpasture’s disease)
ANCA Associated Vasculitis (AAV)

- Granulomatosis polyangitis (GPA)
- Microscopic polyangitis (MPA)
- Eosinophilic granulomatosis with polyangitis (EGPA)
GPA: CHCC Definition

- Formerly known as Wegeners
- Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small or medium vessels
- Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract
- Necrotizing glomerulonephritis is common.
MPA: CHCC Definition

- Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels
- Granulomatous inflammation is absent
- Necrotizing glomerulonephritis is very common.
- Pulmonary capillaritis often occurs.
EGPA: CHCC definition

- Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract
- Associated with asthma and eosinophilia.
- ANCA is more frequent when glomerulonephritis is present.
Diagnostics

- CBC: anemia
- CMP: nephritis (RPGN, rising creat)
- UA: check for protein, rbc, cellular casts
- Uprot/creat ratio
- C3/C4
- ANA, RF, cryo
- ESR/CRP
- Hepatitis/HIV/quant tb
- ANCA
Antineutrophil cytoplasmic antibodies (ANCA)

C-ANCA=PR3-ANCA
- C=cytoplasmic
- PR3=proteinase 3

Granulomatosis with polyangiitis (Wegener’s granulomatosis)

P-ANCA=MPO-ANCA
- P=perinuclear
- MPO=myeloperoxidase

Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Are ANCAs pathogenic?

Clinical evidence

- Strong association with ANCA (MPA >90%, GPA >90%, EGPA >40% (>75% if w/ GN))

- Partial correlation of ANCA titers with disease activity

- Correlation of ANCA epitope specificity with disease activity (MPO-ANCA only)

- Disease induction by transplacental transfer of ANCA (one MPO-ANCA case report)

- Similar disease associated with drug-induced ANCA/microbial induced

- Response to immunosuppressive therapy that targets B cells

- HLA genetic associations with MPO-ANCA and PR3-ANCA-associated disease*
**AAV: GWAS**

*genetically distinct subsets*

### Table 3. Associations of SNPs and ANCA-Associated Vasculitis, According to Clinical Syndromes Stratified on the Basis of ANCA Specificity.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Locus</th>
<th>SNP</th>
<th>Granulomatosis with Polyangiitis</th>
<th>Microscopic Polyangiitis</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Proteinase 3 vs. Myeloperoxidase (N=1433 vs. 151)</td>
<td>Proteinase 3 vs. Control (N=1433 vs. 6858)</td>
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<tr>
<td>6</td>
<td>HLA–DP</td>
<td>rs3117242</td>
<td>5.24 (4.9x10^-24)</td>
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<td>6</td>
<td>HLA–DQ</td>
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<td>14</td>
<td>SERPINA1</td>
<td>rs7151526</td>
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<td>19</td>
<td>PRTN3</td>
<td>rs62132295</td>
<td>0.61 (2.3x10^-3)</td>
<td>0.73 (3.9x10^-7)</td>
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<tr>
<td>X</td>
<td>MOSPD2</td>
<td>rs6628825</td>
<td>0.77 (2.1x10^-1)</td>
<td>0.79 (1.4x10^-6)</td>
</tr>
</tbody>
</table>

1223 UK patients and 5884 control patients

**Associations of SNPs and ANCA-Associated Vasculitis, According to Clinical Syndromes Stratified on the Basis of ANCA Specificity**

NEJM 2012
AAV: Cluster analysis
Are ANCAs pathogenic?

In vitro evidence

• Activation of cytokine-primed neutrophils by ANCA IgG

• Endothelial injury by ANCA-activated neutrophils

• Alternative complement pathway activation by ANCA-activated neutrophils

Evidence from animal models

• Induction of pauci-immune vasculitis, glomerulonephritis and granulomatosis in mice and rats by anti-MPO IgG

• Prevention of murine anti-MPO IgG-induced disease by deficiency of neutrophils

• Prevention of murine anti-MPO IgG-induced disease by blockade of alternative complement pathway activation or blockade of C5a receptors
ANCA pathogenesis
ANCA pathogenesis
ANCA pathogenesis key points

• Emerging evidence suggests that epitope specificity may contribute to the pathogenicity of ANCAs
• Microbial factors, from S aureus and Gram-negative bacteria, could play a part in disease induction and expression
• Neutrophils remain central to the pathogenesis of AAV, with neutrophil extracellular traps playing an important role in initiating the immune response
• The alternative complement pathway is increasingly recognized as being important in mediating the pathogenicity of ANCA.
• anti-LAMP-2 antibodies may represent a novel form of ANCA (microbial molecular mimicry)
Promising biomarkers

- 479 samples from 174 patients (GCA, n = 66; TA, n = 35; PAN, n = 31; EGPA, n = 42) were tested, with one active visit sample and 1–3 remission visit samples per patient.

- Several cytokines: IL-15, IP-10, G-CSF, G-CMSF, BCA-1

- Soluble cytokine receptors: sIL-2Ra

- Enzymes: MMP-3, ACE

- Metalloproteinase inhibitor TIMP-1
<table>
<thead>
<tr>
<th></th>
<th>Serum protein</th>
<th>Odds ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>GCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCA-1</td>
<td>1.6</td>
<td>0.98–2.64</td>
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<tr>
<td>IP-10</td>
<td>0.55</td>
<td>0.32–0.93</td>
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<tr>
<td>sIL-2Ra</td>
<td>1.53</td>
<td>1.07–2.21</td>
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<tr>
<td>TIMP-1</td>
<td>4.24</td>
<td>1.19–15.04</td>
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<td><strong>PAN</strong></td>
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<tr>
<td>MMP-3</td>
<td>0.69</td>
<td>0.45–1.08</td>
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<tr>
<td><strong>CSS</strong></td>
<td></td>
<td></td>
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<tr>
<td>ACE</td>
<td>0.56</td>
<td>0.28–1.11</td>
<td></td>
</tr>
<tr>
<td>BCA-1</td>
<td>1.9</td>
<td>1.003–3.6</td>
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<tr>
<td>G-CSF</td>
<td>1.9</td>
<td>1.11–3.25</td>
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</tr>
<tr>
<td>GM-CSF</td>
<td>1.73</td>
<td>1.08–2.77</td>
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</tr>
<tr>
<td>IL-15</td>
<td>1.9</td>
<td>0.96–3.77</td>
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</table>

Cl = confidence interval; CSS = Churg-Strauss syndrome; GCA = giant cell arteritis; PAN = panarteritis nodosa
CONCLUSIONS:

• Effect sizes were modest in this partially treated cohort.

• TIMP-1 seems the most promising biomarker.

• Larger studies are needed to test the utility of these biomarkers for disease monitoring as well as confirmation in an independent cohort.
Imaging

- CT chest
- CT sinuses
- Renal U/S
Gold Standard

• Biopsy:
  – Renal
  – Lung
  – Nerve biopsy
  – Skin
  – Sinus
TREATMENTS...
LAUGHTER IS THE BEST MEDICINE

WELL, THEY SAY 'LAUGHTER IS THE BEST MEDICINE'...

...EXCEPT FOR TREATING DIARRHEA!
Treatment

ANCA-associated Vasculitis: Conventional Immunosuppression

• High dose corticosteroids
• Cyclophosphomide (CYC)
**CYC:**

**Good news**
- 91% marked improvement
- 75% complete remission

**Bad news**
- 42% permanent morbidity
- 46% serious infections
- 43% hemorrhagic cystitis
- 33x inc risk of bladder CA
- 11x inc risk of lymphoma
- 57% infertility

**Steroid-induced** damage:
Cushingoid features, weight gain, hypertension, cataracts, fractures
AAV-Conventional therapies

Research over the past decade has focused on answering two questions:

1. How can we minimize exposure to cyclophosphamide?
2. How can we avoid cyclophosphamide altogether?
AAV-Conventional therapies:
General concepts

• Treatment should be divided into 2 phases:
  – Induction therapy
  – Maintenance therapy

• Short courses of CYC may be as effective (CYCAZAREM)

• No difference in induction with IV or PO CYC (more CYC) (CYCLOPS)

• Elderly patients can benefit from less CYC/CS (CORTAGE study)
CYCAZAREM study

- 3 months of PO CYC/CS induction
- 71 pts AZA and 73 pts PO CYC
- At 12 months all switched to AZA until 18 months

*No diff in relapse rates - AZA v/s CYC
- shorter course of CYC

WEGNET study

- MTX v/s AZA:
- IV CYC/CS induction
- 63 pts MTX 20-25mg v/s
- 63 pts AZA 2.0mg/kg/d x12mo
- Primary end point= d/cing drug (SE) or death
- Secondary= relapse/SAE

*no difference in relapse rates

Pagnoux. NEJM 2008
MMF compared to AZA:
Induction: PO or IV CYC x6 months,
76 AZA 2mg/kg/d
80 MMF 2g/d
Tapered at 12mo, d/ced 42 mo

* higher relapse rates
WGET study

After induction (based on severity):
- 92 control arm
- 89 etanercept
- 27 month follow up

- Etanercept is NOT effective for the maintenance of remission
- only a minority of the patients achieved remission
- there was a high rate of treatment-related complications

Kaplan–Meier Estimates of the Time to Sustained Remission

NEJM 2005
MAINRITSAN study

- IV CYC/CS induction x4-6mo
- 57 RTX 500mg x18mo
- 58 AZA 2mg/kg/d x12mo, 1.5mg/kg/d until 18mo, 1mg/kg/d until 22 mo

- RTX superior to AZA in maintaining remission in AAV
- A 500-mg dose every 6 mo is sufficient to maintain remission
- Relapses are rare
- Treatment tolerance was good, limited number of side effects, mainly transient
CORTAGE study

- >65 yo induction regimen
- limiting CS exposure (9mo)
- fixed low-dose (500mg) IV CYC pulses q2-3 weeks x6 pulses
- reduce SAEs in comparison to conventional therapy
- does not affect the remission rate.
- 3-year relapse-free rates remain high for both arms

Pagnoux. Arthritis & Rheumatism. Apr 2015
Alternative Maintenance therapies

• Either Methotrexate (MTX) or Azathioprine (AZA) can be used for remission maintenance (CYCAZAREM and WEGENT)
• But Mycophenolate Mofetil (MMF) may be less effective than either (IMPROVE)
• etanercept is not effective (WGET)
• RTX for maintenance may be better than AZA (MAINRITSAN study)
RTX ongoing trials

• How long do we treat?
• Do we do fixed dosing or dose by CD19 levels?
  – REMAIN study—comparing 2 years v/s 4 year of maintenance therapy
  – RITAZAREM study—comparing 2 year fixed RTX dosing v/s AZA in relapsing disease
AAV-Conventional therapies

Research over the past decade has focused on answering two questions:

1. How can we minimize exposure to cyclophosphamide?

2. How can we avoid cyclophosphamide altogether?
RITUXVAS study

CONCLUSIONS:

- RTX (with cyc) therapy was not superior to standard IV CYC
- Sustained-remission rates were high in both groups
- The rituximab-based regimen was not associated with reductions in early severe adverse events

- New AAV with renal involvement:
  - 33 RTX arm 375mg/m2 x 4 weeks and 2 IV CYC
  - v/s 11 in IV CYC alone,
  - primary end point=sustained remission at 12 months and AE.
RAVE study

- 197 new (49%) or relapsing WG/MPA
- Randomized, double-blind
- rituximab 375mg/m²/wk x4 vs. oral CYC
- Primary end-point: remission and steroid withdrawal at 6 months

RTX therapy was not inferior to daily CYC treatment for induction of remission in severe AAV
RTX may be superior than CYC in relapsing disease

NEJM 2010
CONCLUSIONS:

- MTX can replace CYC for initial treatment of early AASV.
- The MTX regimen used in the present study was less effective for induction of remission in patients with extensive disease and pulmonary involvement.
- MTX was associated with more relapses than the CYC regimen after termination of rx.
MYCYC study

- Non-inferiority RCT: MMF v. CYC for remission induction
- 140 patients/25 centers (Europe, AUS/NZ)
- Treatment regimen: IV CYC v/s MMF 2-3 g/d
- Primary endpoint: Remission at 6 months for at least 1 month AND adherence to glucocorticoid taper
- Secondary endpoint: relapse rates at 18 mo

<table>
<thead>
<tr>
<th></th>
<th>MMF (%)</th>
<th>CYC (%)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Primary</td>
<td>67</td>
<td>69</td>
<td>0.05</td>
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<tr>
<td>Secondary</td>
<td>89</td>
<td>79</td>
<td>0.01</td>
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<tr>
<td>SAE</td>
<td>46</td>
<td>39</td>
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<tr>
<td>SAE-infection</td>
<td>26</td>
<td>16</td>
<td>0.14</td>
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</table>

CONCLUSIONS:
- 90% achieved remission at 6 months
- MMF arm less likely to stay in remission
Induction therapies

• RTX/CYC was not superior to CYC alone (RITUXVAS study)
• RTX alone was not inferior to PO CYC for induction (RAVE study)
• RTX was better than CYC for relapse/refractory disease (RAVE study)
• MMF for mild AAV induction therapy not inferior to CYC but increased relapse rates (MYCYC study)
• MTX was not inferior to CYC in induction, time to relapse was shorter (NORAM study)
Future therapies

• With RTX success, other B-cell targeted therapies:
  – Anti CD20/CD22: ocrelizumab, ofatumumab and epratuzumab
  – B-lymphocyte inhib: beliumumab
• Anti-costimulatory Tcell: abatacept-trial in GPA
• Anti IL-5: mepolizumab trial for EGPA
• IL-6/IL-17 inhib: toclizumab/secukinamb
• Tyrosine kinase inhib
Take home points

• Nomenclature/classification has been updated
• Size matters
• CHCC 2012 nosology moves us away from eponyms, and emphasizes pathology
• Promising biomarkers under research
• Diagnostics=tissue biopsy
Take home points

• **Treatment advances:**
  – Limiting CYC/steroids by:
    • Using short courses of CYC for induction followed by alternative maintenance agents: AZA, MTX, RTX, MMF, and LEF
    • Using RTX for refractory or relapsing disease
    • Using RTX for initial induction therapy
    • Using lower/shorter courses of CYC for >65yo
    • Adjunctive rx: PEX in severe cases, bactrim in mild resp
  – **Optimal amount and type** of maintenance still tbd (ongoing trials)
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15. Jones, R. A Randomized trial of MMV v/s CYC for remission induction of AAV. Presse Med. 42. 2013 (MYCYC)