An approach to vasculitis

Sept 2018
MSH
C Pagnoux

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Objectives

• Describe the clinical features typical for vasculitis involving small, medium or large vessels

• Describe the appropriate investigations to address the possibility of vasculitis

• Describe an approach to the initial management of the patient presenting with a vasculitic problem
What is vasculitis?
2012 revised Chapel hill nomenclature

- 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
2012 revised Chapel hill nomenclature

- **Variable Vessel Vasculitis (VVV):** Behçet's Disease (BD) and Cogan’s Syndrome (CS).

- **Single Organ Vasculitis (SOV):** Cutaneous Leukocytoclastic Angiitis, Cutaneous Arteritis, Primary CNS Vasculitis and Isolated Aortitis.

- **Vasculitis Associated with Systemic Disease:** Lupus Vasculitis, Rheumatoid Vasculitis and Sarcoid Vasculitis.

SPECIAL ARTICLE

Nomenclature of Cutaneous Vasculitis

Dermatologic Addendum to the 2012 Revised International Chapel Hill
Consensus Conference Nomenclature of Vasculitides
<table>
<thead>
<tr>
<th>CHCC2012 vasculitis category, name</th>
<th>Skin involvement status</th>
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<tbody>
<tr>
<td></td>
<td>Cutaneous component of systemic vasculitis</td>
</tr>
<tr>
<td>Large vessel vasculitis</td>
<td></td>
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<tr>
<td>Takayasu arteritis</td>
<td>No</td>
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<tr>
<td>Giant cell arteritis</td>
<td>Rare</td>
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<tr>
<td>Medium vessel vasculitis</td>
<td></td>
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<tr>
<td>Polyarteritis nodosa</td>
<td>Yes</td>
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<td>Kawasaki disease</td>
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<td>Small vessel vasculitis</td>
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<td>Granulomatosis with polyangiitis</td>
<td>Yes</td>
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<tr>
<td>Eosinophilic granulomatosis with polyangiitis</td>
<td>Yes</td>
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<tr>
<td>Anti–glomerular basement membrane disease</td>
<td>No</td>
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<tr>
<td>Cryoglobulinemic vasculitis</td>
<td>Yes</td>
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<td>IgA vasculitis (Henoch-Schönlein)</td>
<td>Yes</td>
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<td>Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)</td>
<td>Yes</td>
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<td>Variable vessel vasculitis</td>
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<tr>
<td>Behçet’s disease</td>
<td>Yes</td>
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<td>Cogan’s syndrome</td>
<td>Rare</td>
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<td>Vasculitis associated with systemic disease</td>
<td></td>
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<td>SLE, rheumatoid arthritis, sarcoidosis, etc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Vasculitis associated with probable etiology</td>
<td></td>
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<tr>
<td>Drugs, infections, sepsis, autoimmune diseases, etc.</td>
<td>Yes</td>
</tr>
<tr>
<td>Cutaneous SOV (not included in CHCC2012)</td>
<td>No (not observed yet)</td>
</tr>
<tr>
<td>IgM/IgG vasculitis</td>
<td></td>
</tr>
<tr>
<td>Nodular vasculitis (erythema induratum of Bazin)</td>
<td>No</td>
</tr>
<tr>
<td>Erythema elevatum et diutinum</td>
<td>No</td>
</tr>
<tr>
<td>Hypergammaglobulinemic macular vasculitis</td>
<td>No</td>
</tr>
<tr>
<td>Normocomplementemic urticarial vasculitis</td>
<td>No</td>
</tr>
</tbody>
</table>
Referrals for ?vasculitis
What is next?
What’s next?
Isolated? Not isolated?

CBC, lytes, LFT, CK
Creat, UA
CRP, ESR
SPEP, TSH
Serologies HBV HCV HIV (syphilis, Lyme)
ANA (ENA), ANCA, RF, C3 C4, cryog/cryof (cold agglu, APL/ACL)
CXR
If Bx → with IF

Primary vasculitis?
→ which one (what else)?
Secondary vasculitis?
→ drugs / allergy
→ neoplasm
→ infection
→ other systemic disease

Rx: colchicine, dapsone, HCQ, danazol, aza, lef, mmf, mtx… prednisone
2012 revised Chapel hill nomenclature

Large Vessel Vasculitis

TAKAYASU arteritis

- Pulseless women
- Women 15-25 years-old, Asians/Indians+
- Chronic disease
- Aorta and its first branches (arch++)
Limb artery stenosis → Claudication

Cervical-cerebral arteries → Strokes
Renal artery stenosis → High blood pressure
Giant cell arteritis

External carotid branches
Giant cell arteritis

Risk of occlusion +++

Denise Goodwin, Review of Optometry
Stroke 4%
Aortic involvement

- Aortitis in 3 to 18% of GCA patients
- FDG-TEP scanner → up to 50%

- predominant involvement of the thoracic aorta
- at diagnosis 85%, later 15%
- resolution or improvement under Rx 53% (back to normal 9%)
- increased risk of aneurysm (RR=17, women+, ascending ao+), even (mainly) after treatment discontinuation (5-11 years later)

→ chest X-ray, echocardiogram, abdomen Doppler-US
or → CT scan of the chest and abdomen

YEARLY??

Marie et al, Medicine (Baltimore) 2009;88:182-92
Referrals for ?vasculitis

- M 80 years old
- 2 months history of weakness, mild headaches
- Difficulty to walk

ESR 65

So, what is next?
Inflammation

- Increased C-reactive protein
- Increased Sedimentation rate
- Increased WBC (neutrophils)

.... SPEP
Giant cell arteritis

1. **First line**
   - Glucorticoids

2. **2nd line** (or if severe GC-side effects occur are expected)
   - Addition of: tocilizumab, MTX, abatacept

3. **3rd line**
   - Tocilizumab (++) abatacept

4. **4th line**
   - Ustekinumab, anakinra

Takayasu arteritis

1. **First line**
   - Glucorticoids

2. **2nd line**
   - Addition of: MTX, AZA, MMF, LEF

3. **3rd line**
   - Anti TNF-α agents (infliximab ++)

4. **4th line**
   - Tocilizumab, rituximab

Samson et al. European Journal Internal Medicine 2018
2012 revised Chapel hill nomenclature

Medium vessel

Polyarteritis nodosa

- Kussmaul 1866
- Necrotizing vasculitis → microaneurisms
PNS involvement
11-67% of the SNV patients
→ MONONEUritis MULTIPLEX
CNS involvement <10% of the GPA patients
- Stroke
- Hypersignals
Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2


Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padheh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcoglu, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc., Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elion Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.
<table>
<thead>
<tr>
<th>Classification criteria of Adult PAN</th>
<th>Clinical features of DADA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented vasculitis</td>
<td>Necrotizing vasculitis in medium arteries seen on biopsy Brain imaging showing stroke or aneurysm</td>
</tr>
<tr>
<td>Characteristic arteriographic abnormalities</td>
<td></td>
</tr>
<tr>
<td>A biopsy of small- or medium-sized artery</td>
<td></td>
</tr>
<tr>
<td>Weight loss &gt;4 kg</td>
<td></td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>Skin involvement: Livedo reticularis/racemosa, nodules, infarcts, purpura, Raynaud’s, erythema nodosum</td>
</tr>
<tr>
<td>Testicular pain or tenderness</td>
<td>Testicular pain</td>
</tr>
<tr>
<td>Myalgias, weakness of muscles</td>
<td>Myalgias, arthralgias, arthritis</td>
</tr>
<tr>
<td>Mononeuropathy or polyneuropathy</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>New-onset diastolic blood pressure &gt;90 mmHg</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Elevated levels of serum blood urea nitrogen or creatinine</td>
<td>Renal involvement Proteinuria, Hematuria</td>
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<tr>
<td>Evidence of hepatitis B virus infection</td>
<td></td>
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<tr>
<td>Central Nervous System involvement</td>
<td>CNS involvement: Stroke – ischemic or hemorrhagic</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
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</tr>
<tr>
<td>Fever</td>
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<tr>
<td>Eye involvement</td>
<td>Eye involvement</td>
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</table>

**Immune dysfunction**
- B cell abnormalities
- Common variable immunodeficiency
- Castleman-like disease
- Lymphoproliferative disease

**Bone marrow dysfunction**
- Pure red cell aplasia
- Hemolytic anemia
- Thrombocytopenia

*Human et al. Int J Rheum Dis 2018 Apr [Epub]*
Small vessel

Medium vessel
Alveolar hemorrhage
Necrotizing extracapillary GN
Rapidly progressive GN
Pauci-immune GN
Serous otitis media (bullaes)

Granulomatosis with polyangiitis (Wegener)
retiform purpura

Dual IIF and/or ELISA ANCA
Discordant antiPR3 P-ANCA
(anti-elastase)

Jenkins et al, J Am Acad Dermatol, July 2011
EGPA (or HES...???)
Referrals for ?vasculitis

• W 60 years old
• 2 months history of fatigue, anemia and weakness
• Rapid-onset SDRA with alveolar hemorrhage and AKI

• CRP 125, Creatinine 353
Referrals for ?vasculitis

- W 60 years old
- 2 months history of fatigue, anemia and weakness
- Rapid-onset SDRA with alveolar hemorrhage and AKI
- CRP 125, Creatinine 353
ANCA

C-ANCA: 90% PR3 proteinase 3

P-ANCA: MPO myeloperoxidase
Systemic GPA = 90%
Localized GPA = 50%
Microscopic polyangiitis >75%
Eosinophilic GPA <40%
cANCA antiPR3
pANCA antiMPO
Referrals for ?vasculitis

• W 60 years old
• 2 months history of fatigue, anemia and weakness
• Rapid-onset SDRA with alveolar hemorrhage and AKI

• CRP 125, Creatinine 353, cANCA+

What is next?
Biopsy
<table>
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<tr>
<th>Study name / acronym</th>
<th>Patient numbers</th>
<th>Inclusion criteria</th>
<th>Studied intervention</th>
<th>Primary end points</th>
<th>Main results/conclusions</th>
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<tr>
<td>CYCAZAREM (Jayne et al. EUVAS, 2003)</td>
<td>144</td>
<td>Newly-diagnosed GPA, MPA or renal-limited disease, with at least one major organ involved (but creatinine &lt;500 micromol/l)</td>
<td>All induced with oral CYC and GC until remission (3-6 months) then randomized for maintenance with oral azathioprine (2 mg/kg) or continuation of oral CYC (1.5 mg/kg) until month 12 (then azathioprine for all until month 18)</td>
<td>Relapse (major or minor) and adverse events at month 18</td>
<td>No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer-term (8.5 yr), 52% had relapse in the azathioprine group versus 36% in the CYC (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths</td>
</tr>
<tr>
<td>CYCLOPS (De Groot et al. EUVAS, 2009)</td>
<td>149</td>
<td>Newly-diagnosed GPA, MPA with renal disease (creatinine 150-500 micromol/l)</td>
<td>Pulse (IV mainly) CYC (15 mg/kg) vs oral CYC (2 mg/kg/day) until remission + (in both arms) GC and 3-month consolidation of CYC after remission, then azathioprine until month 18</td>
<td>Time to remission</td>
<td>Pulse IV CYC induces remission as well as daily oral CYC, at a reduced cumulative CYC dose (8.6 vs 18 g) and caused fewer leucopenia - At longer term (4.3-yr follow-up), no difference in survival but the rate relapse was lower in the daily oral group (HR 0.50, 95% CI 0.26–0.93)</td>
</tr>
<tr>
<td>RAVE (Stone et al. USA, 2010)</td>
<td>197</td>
<td>New or relapsing ANCA+ severe GPA or MPA (but creatinine &lt;354 micromol/l and no life-threatening manifestation)</td>
<td>RTX (375 mg/m² weekly x 4) vs oral CYC then azathioprine + (in both arms) GC (aiming to stop at month 6)</td>
<td>Complete remission off GC at 6 months</td>
<td>RTX is not inferior to CYC-azathioprine sequence at month 6 (and 18), and superior to CYC-azathioprine for relapsing OR PR3-ANCA+ patients at month 6 but only not inferior at month 18 (RTX is superior at 6 and 18 months for PR3-ANCA+ AND relapsing patients). Similar infection rates in both arms.</td>
</tr>
<tr>
<td>RITUXVAS (Jones et al. EUVAS, 2010)</td>
<td>44 (3:1 ratio)</td>
<td>Newly-diagnosed ANCA+ GPA, MPA or kidney-limited disease with renal disease</td>
<td>RTX (375 mg/m² weekly x 4) + 2 IV pulses of CYC (15 mg/kg at day 1 and 15) vs IV CYC pulses only (15 mg/kg) for 3-6 months, then azathioprine + (in both arms) GC</td>
<td>Sustained remission and rates of severe adverse events at 12 months</td>
<td>RTX is not superior to CYC-azathioprine sequence at 6 and 24 months. Sustained-remission rates were high in both groups. Similar rates of early severe adverse events in both groups</td>
</tr>
<tr>
<td>MEPEX (Jayne et al. EUVAS, 2007)</td>
<td>137</td>
<td>Newly-diagnosed GPA or MPA with renal disease and creatinine &gt;500 micromol/l</td>
<td>PLEX vs methylprednisolone pulses (IV 1 g for 3 days) + (in both arms) oral GC and oral CYC for 6 months, then azathioprine</td>
<td>Renal recovery at 3 months (dialysis independence)</td>
<td>24% reduction in risk of progression to ESRD with PLEX at 12 months - At longer term (4 yr): HR for PLEX compared to IV methylprednisolone for death or ESRD of 0.81 (95% CI 0.53–1.23) with a subHR for ESRD of 0.64 (95% CI 0.40–1.05)</td>
</tr>
<tr>
<td>CORTAGE Pagnoux et al, FVSG 2015)</td>
<td>108</td>
<td>Systemic necrotizing vasculitides (including 36 GPA and 44 MPA), patients’ age &gt;65 years</td>
<td>GC for 9 months and six 500-mg fixed-dose IV CYC pulses, every 2–3 weeks vs 26 months of GC and IV CYC 500 mg/m², then azathioprine or methotrexate in both groups</td>
<td>&gt;1 serious adverse event within 3 years of follow-up.</td>
<td>Less adverse events with the lower, fixed-dose CYC regimen (500 mg per pulse): 60% vs 78% (P=0.04). No significant difference in failure rates (11% with fixed-dose vs 14%), mortality (17% vs 24%) or relapses (44% with fixed-dose vs 29%; P=0.15.</td>
</tr>
<tr>
<td>NORAM (De Groot et al. EUVAS, 2005)</td>
<td>100</td>
<td>Newly diagnosed GPA or MPA, with creatinine level &lt;150 micromol/l and no major organ involvement</td>
<td>Methotrexate (15 initially increased to 25 mg/week) vs daily oral CYC + (in both arms) oral GC All treatments stopped at month 12</td>
<td>Remission at month 6</td>
<td>For limited GPA, remission rate is not inferior with methotrexate compared to oral CYC, but remission was delayed in patients with more extensive or pulmonary disease, and relapse rate at 18 months was higher in the methotrexate group. Adverse events were less frequent with methotrexate, but for liver dysfunction</td>
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<td>Relapse (major or minor) and adverse events at month 18</td>
<td>No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer-term (8.5 yr), 52% had relapse in the AZA group versus 36% in the CYC (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths</td>
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<td>WGET (WGET research group, 2005)</td>
<td>180</td>
<td>Newly-diagnosed (44%) or relapsing, limited (29%) or severe GPA</td>
<td>Standard therapy with GC and CYC (severe, then MTX or AZA for maintenance for 12 months) or MTX (limited, continued for 12 months after remission) with concurrent etanercept (25 mg subcutaneous, twice weekly) or placebo</td>
<td>Sustained remission (BVAS=0 for at least 6 months)</td>
<td>No significant differences between the etanercept and placebo groups (69.7% vs 75.3% sustained remission; P=0.39) – follow-up 27 months Solid cancers developed in 6 etanercept recipients (none in placebo group)</td>
</tr>
<tr>
<td>Metzler et al. (2007)</td>
<td>54</td>
<td>Generalized GPA</td>
<td>Induction with oral CYC and GC then maintenance with LEF (100 mg/day loading dose for 3 days, then 20 mg/day for 1 month, then 30mg/day) or MTX (7.5 mg/week oral for 1 month, then 15 mg/week for 1 month, then 20 mg/week)</td>
<td>Adverse events (severe and/or leading to study drug cessation) and relapse</td>
<td>Study terminated prematurely because of high rate of major relapses in the MTX group (13 vs 6 patients; P=0.037) – follow-up 21 months No MTX patient but 4 LEF patients had to discontinue the study because of LEF-attributable adverse events (2 hypertension, 1 peripheral neuropathy, 1 leucopenia)</td>
</tr>
<tr>
<td>WEGENT (Pagnoux et al, FVSG, 2008)</td>
<td>126</td>
<td>Newly-diagnosed systemic GPA or MPA</td>
<td>MTX (0.3 mg/kg/week, oral or subcutaneous if not tolerated orally) vs oral AZA (2 mg/kg/d) for 12-16 months + all induced with IV CYC pulses and prednisone until remission (3-6 months) then 3 consolidation pulses before randomization for maintenance</td>
<td>Adverse events (severe and/or leading to study drug cessation) and relapse</td>
<td>No difference between the groups in relapse and adverse event rates (results of longer term follow-up are under analysis)</td>
</tr>
<tr>
<td>IMPROVE (Hiemstra et al, EUVAS, 2010)</td>
<td>165</td>
<td>Newly-diagnosed systemic GPA or MPA</td>
<td>Oral MMF (2 g/d) vs oral AZA (2 mg/kg/d) until month 42 + all induced with IV or oral CYC pulses and prednisolone until remission (3-6 months) then randomization for maintenance</td>
<td>Relapse-free survival and adverse events</td>
<td>MMF was less effective than AZA for maintaining disease remission (HR of relapse 1.69 (95% CI 1.06-2.70; P=0.03). Severe adverse events did not differ significantly between groups</td>
</tr>
<tr>
<td>MAINRITSAN (Guilevin et al, FVSG, 2015)</td>
<td>115</td>
<td>Newly-diagnosed (80%) or relapsing, severe GPA (76%), MPA (20%) or renal limited disease, with (94%) or without ANCA</td>
<td>Induction with IV CYC and GC, then maintenance with RTX (500 mg on days 0 and 14, months 6, 12, and 18) or AZA (2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months)</td>
<td>Rate of major relapse (with BVAS&gt;0 and ≥1 major organ involvement and/or life-threatening disease) at month 28</td>
<td>Less major relapses with RTX (5%) vs AZA (29%; HR 6.61, 95% CI 1.56 to 27.96; P =0.002) at 28 months. - At 60 months, more major relapses in both arms, but still less in the RTX group</td>
</tr>
<tr>
<td>AZA-ANCA (Sanders et al., 2016)</td>
<td>131</td>
<td>Newly-diagnosed PR3-ANCA+ vasculitis</td>
<td>Oral CYC and GC for all then extended (1.5-2.0 mg/kg/day for 4 years after diagnosis then tapered by 25 mg every 3 months) or standard (1.5-2 mg/kg/day until 1 year after diagnosis then tapered by 25 mg every 3 months) azathioprine maintenance therapy if C-ANCA positive at remission (n=45/131)</td>
<td>Relapse-free survival at 4 years after diagnosis</td>
<td>No significant difference in relapse-free survival or relapse rates between study groups (and no difference between extended treatment in those ANCA-positive at remission and standard treatment in all patients, ANCA-positive or -negative at remission) – follow-up 45 months</td>
</tr>
</tbody>
</table>
Principles of treatment of severe, systemic GPA

**CYCLOPHOSPHAMIDE**

- **IV (pulse):** 15 mg/kg at D1, 15, 29 then /3 wk

- **Oral (continuous):** 2 mg/kg/day

**RITUXIMAB**

- 375 mg/m²/wk (or 1 g at D1 & 15)

- + Glucocorticoids

3 - 6 months

± Plasma exchange?

INDUCTION

MAINTENANCE
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

Death

700 patients
Up to 7 years f/u

PEXIVAS
Principles of treatment of severe, systemic GPA

**CYCLOPHOSPHAMIDE**

*IV (pulse):* 15 mg/kg at D1, 15, 29 then /3 wk

*Oral (continuous):* 2 mg/kg/day

**RITUXIMAB**

375 mg/m²/wk (or 1 g at D1 & 15)

* ± Glucocorticoids

± Plasma exchange?

**INDUCTION**

3 - 6 months

**MAINTENANCE**
Remission 80-90% percent
Principles of treatment of severe, systemic GPA

**CYCLOPHOSPHAMIDE**
- **IV (pulse):** 15 mg/kg at D1, 15, 29 then /3 wk
- **Oral (continuous):** 2 mg/kg/day

**AZATHIOPRINE** 2 mg/kg/day
**METHOTREXATE** 0.3 mg/kg/wk
**LEFLUNOMIDE** 20 mg/day
**MYCOPHENOLATE MOFETIL** 2 g/day

**RITUXIMAB**
- 375 mg/m²/wk (or 1 g at D1 & 15)

± Glucocorticoids

3 - 6 months

3 - 18 months

> 18 months

± Plasma exchange?
Frequent relapses...

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up from Dg</th>
<th>Relapse rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCAZAREM</td>
<td>WG, MPA</td>
<td>144</td>
<td>AZA 15.5% vs. CYC 13.7%</td>
<td>NS</td>
</tr>
<tr>
<td>NEJM, 2003</td>
<td></td>
<td></td>
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<td>WGET</td>
<td>WG</td>
<td>180</td>
<td>MTX 32.8% vs MTX/ETN 30.6%</td>
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<td>NEJM, 2005</td>
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<td></td>
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<tr>
<td>Langford</td>
<td>WG</td>
<td>42</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>WEGENT</td>
<td>WG, MPA</td>
<td>126</td>
<td>AZA 36.5% vs MTX 33.3%</td>
<td>NS</td>
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<tr>
<td>Pagnoux, NEJM, 2009</td>
<td></td>
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<tr>
<td>Sanders</td>
<td>WG, MPA</td>
<td>136</td>
<td>AZA 42.3% vs. CYC 57.4%</td>
<td>NS</td>
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<tr>
<td>NEJM, 2003</td>
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</tbody>
</table>

At 7 years, relapse rate 63.9% → 51.2% (445 patients)

Principles of treatment of severe, systemic GPA

**INDUCTION**

- **CYCLOPHOSPHAMIDE**
  - _IV (pulse)_: 15 mg/kg at D1, 15, 29 then /3 wk
  - _Oral (continuous)_: 2 mg/kg/day

- **AZATHIOPRINE** 2 mg/kg/day
- **METHOTREXATE** 0.3 mg/kg/wk
- **LEFLUNOMIDE** 20 mg/day
- **MYCOPHENOLATE MOFETIL** 2 g/day

- **RITUXIMAB** 375 mg/m²/wk (or 1 g at D1 & 15)
  - + Glucocorticoids

- 3 - 6 months

± Plasma exchange?

**MAINTENANCE**

- > 18 months
  - ± Plasma exchange?
**Induction**

- CS
- MP pulses D1-3
- ± Plasmapheresis
- RTX (375 mg x4)

**Maintenance**

- Azathioprine 2 mg/kg/d
- Rituximab 1000 mg m4, 8, 12, 16, 20

**RITAZAREM**

- Relapsers ANCA+

**ENDPOINT**

- 3-6 mo
- 18 mo
- 24
- 36-48
Can we do better?

• Individualized treatments?

• Other agents instead of or in addition to others?
Two CCX168 Phase 2 Trials in AAV

<table>
<thead>
<tr>
<th>CLEAR Trial (Steroid Elimination/Sparing Design)</th>
<th>CLASSIC Trial (Added to Standard of Care)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td><strong>US and Canada</strong></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Groups</strong></td>
<td></td>
</tr>
<tr>
<td>1. Placebo (of CCX168) + CYC/RTX + full Steroids</td>
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</tr>
<tr>
<td>2. CCX168 30 mg BID + CYC/RTX + Low Steroids</td>
<td>2. CCX168 10 mg BID + CYC/RTX + full Steroids</td>
</tr>
<tr>
<td>3. CCX168 30 mg BID + CYC/RTX  no Steroids</td>
<td>3. CCX168 30 mg BID + CYC/RTX + full Steroids</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
</tr>
<tr>
<td>ANCA-associated vasculitis with/without renal disease (Step 3)</td>
<td>ANCA-associated vasculitis with/without renal disease (from initiation)</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
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<tr>
<td>12 weeks with 12-week follow-up</td>
<td>12 weeks with 12-week follow-up</td>
</tr>
<tr>
<td><strong>Study Size</strong></td>
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<tr>
<td>60 patients</td>
<td>Up to ~45 patients</td>
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<tr>
<td><strong>Prim. Endpoint</strong></td>
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<tr>
<td>BVAS response at Week 12</td>
<td>BVAS response at Week 12</td>
</tr>
</tbody>
</table>

*Less is more.*

—Ludwig Mies van der Rohe