Rheumatologist

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CASE 1

- 55 year old Japanese-Canadian
- 09/2008 creatinine 169, 3 g/l protein, 3+ blood, 3 cellular casts, BP 160/100 - RF 28 (<20), CRP 0.5, ESR 14, ANA 1:80 homogeneous, ANCA negative, cryoglobulins negative
- Prednisone Jan 2009 → October 2009
- 09/2011, creatinine 302 → 800, 3+ blood, casts; C-ANCA at 1/10,000 in one lab then p-ANCA positive >8 and c-ANCA negative, anti-GBM Ab negative

- Not responsive to Solumedrol, Cyclophosphamide and plasmapheresis x 6
<table>
<thead>
<tr>
<th>ANCA as surrogate markers</th>
<th>PR3-ANCA</th>
<th>MPO-ANCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPA</strong></td>
<td>5-20%</td>
<td>&gt; 50% (75)</td>
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<tr>
<td><strong>GPA</strong></td>
<td>75-90%</td>
<td>5-15%</td>
</tr>
<tr>
<td><strong>EGPA</strong></td>
<td>&lt;5%</td>
<td>30-40%</td>
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**Sensitivity**

- The IIF assay is more sensitive than the ELISA
- A positive IIF assay should ALWAYS be confirmed by an ELISA
- The sensitivity of ANCA by IIF and/or ELISA is as high as 90% in active generalized GPA (Wegener’s) but as low as 60% in limited disease

**Specificity**

- Compared to disease controls, specificities are:
  - cANCA = 95%
  - pANCA = 81%
  - anti-PR3 = 87%
  - anti-MPO = 91%
- The specificity of the combination of pANCA + anti-PR3 OR pANCA + anti-MPO is as high as 99%

ANCA, anti-neutrophil cytoplasmic antibody; cANCA, cytoplasmic-ANCA; ELISA, Enzyme-linked immunoabsorbent assay; GPA (Wegener’s), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; pANCA, perinuclear-ANCA

**Conditions associated with ANCA**

<table>
<thead>
<tr>
<th>IIF</th>
<th>ELISA</th>
<th>Diseases/conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cANCA</strong></td>
<td>PR3</td>
<td>GPA (Wegener’s), MPA (CSS) Endocarditis, Tuberculosis, amoebiasis</td>
</tr>
<tr>
<td></td>
<td>BPI (bacterial permeability increasing protein)</td>
<td>Cystic fibrosis Infections</td>
</tr>
<tr>
<td><strong>pANCA</strong></td>
<td>MPO</td>
<td>MPA, GNRP, CSS (GPA (Wegener’s)) Felty’s syndrome (RA) Drugs (propylthiouracil +)</td>
</tr>
<tr>
<td><strong>pANCA or atypical ANCA</strong></td>
<td>Cathepsine G</td>
<td>Ulcerative colitis Primary sclerosing cholangitis</td>
</tr>
<tr>
<td></td>
<td>Lactoferrin</td>
<td>RA, ulcerative colitis</td>
</tr>
<tr>
<td></td>
<td>Elastase (or PR3)</td>
<td>Cocaine-induced vasculopathy</td>
</tr>
<tr>
<td><strong>Other or unidentified</strong></td>
<td></td>
<td>Infections RA, SLE Ulcerative colitis, AI Liver disease Drugs</td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasmic antibody; cANCA/pANCA, ANCA with cytoplasmic/perinuclear fluorescence labelling pattern in IIF; CSS, Churg-Strauss syndrome; ELISA, enzyme linked immunosorbent assay; GNRP, rapidly progressive glomerulonephritis; GPA (Wegener’s), granulomatosis with polyangiitis; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus
Case 2 - Diagnosis, 1998

- 1998 Wegener’s Granulomatosis (GPA)
- Manifestations:
  - C-ANCA positive
  - Crescentic GN, Creat 120-130 after treatment
  - Lung nodules, hemoptysis
  - Suprascapular mass -> Diabetes Insipidus
  - Recurrent otitis media, sinusitis and nasal ulcers
  - Purpuric rash
  - Constitutional symptoms
1990 ACR Classification criteria

- Nasal or oral inflammation: oral ulcers or purulent or bloody nasal discharge
- Abnormal chest radiograph: nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment: microhematuria (>5 RBC/HPF) or casts
- Granulomatous inflammation on biopsy: within the vessel wall or perivascular or extravascular

2 criteria → Sp 92% Se 88%
DCVAS
Diagnostic and Classification Criteria for Systemic Vasculitis
STUDY OVERVIEW
Classification of the Vasculitides

- Arteries
  - Large
  - Small
- Arterioles
- Capillaries
- Venules
- Veins

- Necrotizing glomerulonephritis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (Wegener's)
- Eosinophilic GPA (Churg Strauss syndrome)
- Polyarteritis nodosa
- Kawasaki disease
- Giant cell arteritis (Horton)
- Takayasu arteritis
- Henoch-Schoenlein purpura
- Cryoglobulinemia

References:

• **Granulomatous inflammation** involving the respiratory tract, and **necrotizing vasculitis** affecting small to medium-sized vessels, e.g. capillaries, venules, arterioles and arteries.

• **Necrotizing glomerulonephritis is common.**

• **Frequently associated with ANCA**
2012 revised Chapel hill nomenclature

- **Large Vessel Vasculitis (LVV):** Takayasu Arteritis (TAK) and Giant Cell Arteritis (GCA)
- **Medium Vessel Vasculitis (MVV):** Polyarteritis Nodosa (PAN) and Kawasaki Disease (KD)
- **Small Vessel Vasculitis (SVV):**
  - **ANCA-Associated Vasculitis (AAV)** including: Microscopic Polyangiitis (MPA), Granulomatosis with Polyangiitis (Wegener’s) (GPA) and Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss) (EGPA)
  - **Immune Complex SVV including:** Anti-GBM Disease, Cryoglobulinemic Vasculitis, IgA Vasculitis (Henoch-Schönlein) (IgAV) and Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis) (HUV).
- **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.
 Treatment and natural history

- Initial flare 1998
  - Cyclophosphamide for 3-6 months then
  - Azathioprine
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**

- 15 mg/kg (d1,14,28 then q3wk)
- 2 mg/kg/d
- + Corticosteroids
- 3 - 6 months

**INDUCTION**

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc
CYCLOPS

- Open label RCT
- 149 AASV (40% GPA)
- All with renal disease
- No Iº hypothesis
- Pulse (IV or oral) vs continuous oral CYC
- Remission at 9 mo
  - Pulse 88.1%
  - Continuous 87.7%
- DO = higher rate of leukopenia

- At 18 mo:
  - 14.5% relapsed
  - (18.8% IV vs. 9.4% PO)

DEATHS

12 patients in DO vs.
13 in IV pulse group (NS)

Median duration of follow-up of 4.3 yrs

RELAPSES

- 15 (20.8%) DO
- 30 (39.5%) pulse had ≥1 relapse

Total of 21 relapses (10 renal) in the DO vs. 54 (12 renal) in the pulse limb

Cox regression analysis
HR=0.50, 95% (CI, 0.26-0.93); p=0.029
RELAPSES

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Treatment and natural history

- Initial flare 1998
  - Cyclophosphamide for 3-6 months then
  - Azathioprine until 2002
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**
15 mg/kg (d1,14,28 then q3wk)
2 mg/kg/d

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

+ Corticosteroids

3 - 6 months

**INDUCTION**

> 18 months????

**MAINTENANCE**

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc
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 NEJM, 2003</td>
<td>WG, MPA</td>
<td>144</td>
<td>AZA 15,5% vs. CYC 13,7%</td>
<td>NS</td>
</tr>
<tr>
<td>WGET NEJM, 2005</td>
<td>WG</td>
<td>180</td>
<td>MTX 32,8% vs MTX/ETN 30,6%</td>
<td>NS</td>
</tr>
<tr>
<td>Langford Am J Med, 2003</td>
<td>WG</td>
<td>42</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>WEGENT Pagnoux, NEJM, 2009</td>
<td>WG, MPA</td>
<td>126</td>
<td>AZA 36,5% vs MTX 33,3%</td>
<td>NS</td>
</tr>
<tr>
<td>Sanders NEJM, 2003</td>
<td>WG, MPA</td>
<td>136</td>
<td>AZA 42,3% vs CYC 57,4%</td>
<td>NS</td>
</tr>
</tbody>
</table>

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

Mild relapses, 2007 and 2012...

- Mild flare, 2007
  - Treated with Azathioprine until 2009

- Mild flare, January 2012
  - Anorrhexia, malaise, chills, weight loss
  - Cough, hemoptysis
Optimal maintenance Rx?

- GPA
- antiPR3+
- ENT?
- Lung (nodules)??
- Low creatinine <100
- Cardiovascular?

Risk of relapse

MPA antiMPO+

High creatinine

REMAIN EUVAS trial (results June 2012?)
Walsh et al, Arthritis Care Res. 2010;62(8):1166-73

Duration of CS and IS
Mild relapses, 2007 and 2012...

- Mild flare, 2007
  - Treated with Azathioprine until 2009

- Mild flare, January 2012
  - Anorrexia, malaise, chills, weight loss
  - Cough, hemoptysis

- Started on methotrexate 15mg q week, Prednisone 40 mg OD, Septra DS 3X/week by rheum.
EARLY SYSTEMIC GPA (<150 µM)

NORAM

- Methotrexate vs oral Cyclophosphamide for induction
- Non-inferiority trial (d=15%) for remission at 6 months
- 95 p. with “early systemic” GPA for 12 months (6 MPA)

Remission at 6 mo
MTX 89.8%
CYC 93.5% (P=0.04)

Relapse at 18 mo
MTX 69.5%
CYC 46.5% (P=0.02)

CYC Leukopenia
MTX liver enzymes

CS at M18
8.8 g MTX vs 6.2 CYC
(P<0.01)

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CYC Leukopenia
MTX liver enzymes

CS at M18
8.8 g MTX vs 6.2 g CYC (P<0.01) and longer

NORAM long-term f/up

- Median f/up 6.0 (0.1-10.8) yrs
- N=72 with f/up >18 mo.
- 1 patient ESRD (MTX, NS)
- 11 died (NS)
- AES did not differ between groups
- MTX patients were exposed to CS, CYC, IS for longer periods than those CYC patients (p=0.004; p=0.037; and p=0.031, respectively)
- Cumulative relapse-free survival tended to be lower in the MTX groups (p=0.056)

Cumulative relapse-free survival from time of 1st remission: 69%, 32%, and 24% after 1, 3, and 5 years of f/up

Faurschou et al. Arthritis Rheum; E-pub May 2012
“the intensity of first-line immunosuppressive treatment is inversely related to the risk of relapsing disease in AAV”

Faurschou et al. Arthritis Rheum; E-pub May 2012
... to severe relapse, 2012

- c-ANCA > 8.0, p-ANCA <0.2, Anti-GBM negative
- Creat 467, 24-hour urine protein 6.3 g/day, RBC casts
- Popliteal DVT
- Hb 89, plt 342, WBC 13.8
- CXR small nodule RUL
RAVE

1 à 3 MP pulse(s)

CS + oral CYC * 3 to 6 mo
+ placebo RTX

Rituximab** + CS
+ placebo CYC

AZA → M18

Placebo AZA

* oral CYC 2 mg/kg/d
** RTX 375 mg/m2 x 4
Extended RAVE follow-up

- 197 patients ANCA+ (49% new, 51% relapsers)
- CR (NS)
  - At M6: 64% RTX vs 53% CYC/AZA
  - At M12: 47% RTX vs 39% CYC/AZA
  - At M18: 39% RTX vs 33% CYC/AZA
- Higher risk of relapse
  - Relapsers
  - No renal disease
  - PR3+
  - GPA
- Flares occurred only after B cell reconstitution in RTX arm

Stone JH et al. #2432 OP
Better response in relapsers (vs newly-diagnosed)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>New Dx (N=96)</th>
<th>Relapsers (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritualximab</td>
<td>60.4%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>42.0%</td>
<td>66.7%</td>
</tr>
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</table>

NS

$P = 0.013$

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:
   a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
   b) The patient has failed three months of oral cyclophosphamide therapy; OR
   c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
   d) Cyclophosphamide is contraindicated; OR
   e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
   f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m² x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient’s last treatment cycle with Rituxan.
Hazard ratio for ESRD or Death: 0.91 (95% CI 0.53 to 1.23; p=0.32)
Hazard ratio for ESRD: 0.64 (95% CI 0.40 to 1.05; p=0.08)
Hazard ratio for Death: 1.08 (95% CI 0.67 to 1.73; p=0.75)
PLEX for patients with Lung Hemorrhage?

- EUVAS data 108/535 patients had alveolar hemorrhage (ventilator dependent excluded)
  - AH associated with death in 3/4 trials (HR 1.6)

- 41 MEPEX patients (PLEX vs IV steroids) with hemorrhage (25 hemoptysis, 16 infiltrates only)
  - Treatment with PLEX did **not** improve outcome
    - 10/21 (47%) IV Mep vs 12/20 (60%) PLEX died in first year (p=0.56) (mostly sepsis)
    - Adjusted estimate HR=1.6 for PLEX (p=0.31)

PEXIVAS
a RCT of plasma exchange and glucocorticoid dosing in ANCA associated vasculitis

3 Co-PIs: Mike Walsh (Canada), David Jayne (UK) and Peter Merkel (USA)
PEXIVAS

Inclusion

- New or Previously diagnosed GPA or MPA
- ANCA + (by ELISA)
- Current “severe” manifestation
  - GN with eGFR <50 ml/min
  - Lung Haemorrhage
- Informed Consent or Deferred Consent

Exclusion

- <18 years old (<15 in peds centres)
- Concomitant anti-GBM or other non-AAV vasculitis
- Pregnant
- Received significant therapy for this presentation already
  - >1 IV dose or 2 weeks CYC
  - >1 dose RTX within 1 month
  - >21 days pred >30 mg/day
- Likely has ESRD already
- Physician feels PLEX mandated
Severe AAV

Cyclophosphamide
Or Rituximab

Adjunctive Plasma Exchange

Standard-Dose GC
Reduced Dose GC

No Plasma Exchange

Standard-Dose GC
Reduced Dose GC

Follow-Up

ESRD

Death
2nd annual CanVasc meeting

Montréal, QC
November 22nd, 2012

Registration and information on http://www.canvasc.ca
April 14 - 17 2013

16th International Vasculitis & ANCA Workshop

"Institut des Cordeliers"
Paris - France

Scientific committee:
Pr. Loïc Guillevin
(president)

Organisation:
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