An approach to vasculitis

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Disclosures

• Consulting and speaker fees
  – Hoffmann-La Roche
  – BMS

• Advisory boards
  – Hoffmann-La Roche
  – GSK

• Educational subventions (CanVasc)
  – Hoffmann-La Roche
  – Abbott Immunology
  – Pfizer-Amgen
  – Janssen-Cilag
  – Euroimmun
  – Terumo BCT
  – BMS
The questions

• Is it vasculitis?

• Can it be a secondary rather than a primary or idiopathic vasculitis?

• Are there / will there be any other major organ involvement?

• Who to treat? When to treat? With what?
Biopsy
What is vasculitis?
Limb artery stenosis \( \rightarrow \) Claudication

Cervical-cerebral arteries \( \rightarrow \) Strokes
Renal artery stenosis  →  High blood pressure
ANCA

C-ANCA: 90% PR3 proteinase 3

P-ANCA: MPO myeloperoxidase
ANCA

• Systemic GPA = 90%
• Localized GPA = 50%
• Microscopic polyangiitis >75%
• Eosinophilic GPA <40%
retiform purpura

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

Jenkins et al, J Am Acad Dermatol, July 2011
The questions

• Is it vasculitis?

• Can it be a secondary rather than a primary or idiopathic 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.
2012 revised Chapel hill nomenclature

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

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

CTDs (n = 35),
Major infections (n = 27),
Malignancies (n = 16),
Essential mixed cryo. (n = 13),
MPA (n = 4),
GPA (n = 3),
EGPA (n=3)
PAN (n = 3).

median f/up 4 months (IQR 213): relapses 8.3%

What is next?
What’s next? Isolated? Not isolated?

If Bx → with IF

CBC, lytes, LFT, CK
Creatinine, UA++
CRP, ESR, SPEP (IgA?)
TSH
Serologies: HBV, HCV, HIV  
(syphilis, Lyme)
ANA (ENA), ANCA, RF,  
C3-C4, cryogl/cryof  
(cold agglu, LAC/APL/ACL)

CXR
What’s next? Isolated? Not isolated?

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- CXR

**Primary vasculitis?**
- → which one (what else)?

**Secondary vasculitis?**
- → drugs / allergy
- → neoplasm
- → infection
- → other systemic disease
What’s next? Isolated? Not isolated?

If Bx → **with IF**

- CBC, lytes, LFT, CK
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**Primary vasculitis?**
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**Rx:** colchicine, dapsone, HCQ, danazol, pentox, aza, lef, mmf, mtx, ritux… prednisone
Treatment of severe GPA/MPA

**INDUCTION**

- AZATHIOPRINE 2 mg/kg/d
- METHOTREXATE 0.3 mg/kg/wk
- LEFLUNOMIDE 20 mg/d
- MYCOPHENOLATE MOFETIL 2 g/d
- + Corticosteroids

**MAINTENANCE**

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

> 3 - 6 months

> > 18 months????
Remission 80-90% percent
PROLONGED RISK OF SPECIFIC MALIGNANCIES FOLLOWING CYCLOPHOSPHAMIDE-THERAPY AMONG PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS (WEGENER’S).

- 293 GPA diagnosed between 1973-1999 and followed until 2010, Danish Cancer Registry general population
- Median follow-up = 9.7 years (0-36)
  - 73 cancers: 30 non-melanoma skin cancers, 11 bladder
    - SIR of NMSC from yr 2 onwards = 7.0 (95% CI: 2.3-16)
    - SIR of bladder cancer after 5-9, 10-14, and 15-19 yrs = 5.3 (95% CI: 1.1-15), 14.4 (95% CI: 5.3-31), and 10.5 (95% CI: 1.2-38)
    - SIR of myeloid leukemia during yr 5-9 = 23.9 (95% CI: 2.7-86)
- Increased incidence of NMSC, bladder cancer, and myeloid leukemia with cumulative CYC >36 grams
- Less than 36g CYC → “only” excess of NMSC
RAVE

1 à 3 MP pulse(s)

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

CS + oral CYC * 2 mg/kg/d

Rituximab** + CS
+ placebo CYC

Rituximab** + CS
+ placebo CYC

AZA → M18

Placebo AZA

(<350 µM)
(no severe AH)
ANCA+

** RTX 375 mg/m² x 4
76 in the rituximab group who had a CR
24 (32%) relapsed before M18

70 in the CYC had a CR
20 (29%) relapsed before M18

(P=0.16)
Maintenance of remission using RITuximab for Systemic ANCA-associated vasculitides

Systemic GPA or MPA or KLD with FFS ≥ 1
Newly diagnosed or after a relapse treated with CS–CYC
>18 and <75 years old at enrolment

Guillevin, Pagnoux et al. for the French Vasculitis Study Group
N Engl J Med, 6 Nov 2014
Induction

- **MP pulses d1–3**

Maintenance

- **CS**
  - 10 mg/d
  - 5 mo

- **± PE**

- **Rituximab 500 mg**
  - d1, 14, 6, 12, 18 mo

- **Azathioprine 2 mg/kg/d**
  - 18 mo

NEWLY DIAGNOSED RELAPSING (UP TO 1/3)

- 18-75 y.-o.
- GPA, MPA, KLD
- ANCA+ and/or Bx
115 patients
(65 M / 50 F; 55 ± 13 yr; 87 GPA, 23 MPA, 5 KLD; 92 new / 23 relapsing)

58 AZA
→ Major relapses

57 RTX
115 patients
(65 M / 50 F; 55 ± 13 yr; 87 GPA, 23 MPA, 5 KLD; 92 new / 23 relapsing)

58 AZA
Relapses
17 (29%)

57 RTX
Relapses
3 (5%)

No. at Risk
Rituximab: 57, 57, 57, 56, 56, 56, 56, 56, 56, 56, 54, 52, 39
Azathioprine: 58, 58, 55, 54, 53, 53, 50, 50, 48, 48, 47, 44, 41, 33

Months since Randomization:
0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28

Major relapses
Conclusions

• Various diseases, causes, manifestations, outcomes and risks

• Biopsy with IF

• Look for major organ involvement

• Stay tuned…
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
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<tr>
<td>Active GCA</td>
<td>GiACTA (&lt;6 wks CS)</td>
</tr>
<tr>
<td>GCA</td>
<td>Gevokizumab</td>
</tr>
<tr>
<td>Severe GPA/MPA with lung or kidney</td>
<td>PEXIVAS (&lt;2 wks CS)</td>
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<tr>
<td>Active GPA/MPA (not too severe)</td>
<td>CLASSIC</td>
</tr>
<tr>
<td>New GPA/MPA entering remission</td>
<td>BREVAS (&lt;6 wks remission)</td>
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<td>GPA at 6-12 remission on CS 6-10mg</td>
<td>TAPIR</td>
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<tr>
<td>Relapsing limited GPA</td>
<td>ABROGATE</td>
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<tr>
<td>Relapsing severe GPA/MPA</td>
<td>RITAZAREM (at relapse)</td>
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<tr>
<td>Refractory/relapsing EGPA</td>
<td>MIRRA</td>
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<tr>
<td>All</td>
<td>Genetic/cytoflux MSH</td>
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<tr>
<td></td>
<td>VCRC (any time)</td>
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<td>DCVAS (&lt;2 years)</td>
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References


