Vasculitis Workshop

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Disclosures (CPx)

• Speaker and consultant fees:
  – Roche (<10,000 CAD)
  – GSK (<10,000 CAD)

• Subventions for CanVasc
  – Roche
  – Euroimmun
  – AARC (grant)

Disclosures (LF)

• None
Objectives

• Review
  – some typical vasculitis cases
  – some challenging vasculitis cases

• Review
  – some therapeutic fundamentals in vasculitis
  – some of the unanswered questions…
Chapel Hill Nomenclature

Classification of the Vasculitides

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

Aorta

- Polyarteritis nodosa
- Kawasaki disease
- Giant cell arteritis (Horton)
- Takayasu arteritis
- Henoch-Schoenlein purpura
- Cryoglobulinemia

- Necrotizing glomerulonephritis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (Wegener’s)
- Eosinophilic GPA (Churg Strauss syndrome)

- + antiGBM
- + Behçet
- + CNS-V

Case #1

• 52M with recurrent lesions in both feet 20 -30 years (2-3X / year)
• 8 months – shins, buttocks, thighs, forearms, and abdomen
• Macular, red, pruritic that develop into purpuric lesions
• Lasts for a week then spontaneously resolves
Case #1

- Swelling in both arms with cold exposure
- Fever and joint pain in both knees
- No other systemic manifestation of a vasculitis

- Family History
  - Father was Hep C (+) / had similar lesions
Differentials?

A. Cutaneous PAN
B. ANCA associated vasculitis
C. Urticarial vasculitis
D. Cryoglobulinemic vasculitis
E. HCV/non HCV cutaneous porphyria tarda?
F. Other (allergy; T cell lymphoma; mastocytosis...)

[Image: it's Not Lupus.]
Case #1

• Past Medical History /Social History
  – Hypertension and Dyslipidemia
  – Previous smoker, non alcoholic beverage drinker
  – Previous use intranasal cocaine, marijuana no IV drug use, (+) tattoo
Cryoglobulinemic Vasculitis

- Cryoglobulin Syndrome*
- Hepatitis C virus related versus Non Hepatitis C virus related (infections, connective tissue diseases, malignancies)
Cryoglobulinemic Vasculitis

- Type I – Isolated monoclonal Ig*
- Type II — mixture of polyclonal Ig in association with a monoclonal Ig, typically IgM or IgA, with rheumatoid factor activity
- Type III — Mixed cryoglobulins consisting of polyclonal immunoglobulins*
Cryoglobulinemic Vasculitis
Preliminary Classification Criteria

> Fever (low grade), fatigue*
> Articular Involvement*
> Vascular Involvement (purpura, skin ulcers, necrotic skin lesions, Raynaud’s, hyperviscosity syndrome)
> Neurological Involvement
(3/4 items sens 70.2% spec 84.5%)

De Vita et al Ann Rheum 2011;70: 1183-90
Cryoglobulinemic Vasculitis
Preliminary Classification Criteria

Laboratory / Investigations

- Reduced C4
- M protein
- (+) RF Plus
- With (+) serum cryoglobulins

2/3 (sens 84.2% spec 79.6%)

De Vita et al Ann Rheum 2011;70: 1183-90
Cryoglobulinemic Vasculitis

<table>
<thead>
<tr>
<th></th>
<th>HCV</th>
<th>Non HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>63.5</td>
<td>58.7</td>
</tr>
<tr>
<td><strong>Liver involvement</strong></td>
<td>81% (188/230)</td>
<td>11%(5/42)</td>
</tr>
<tr>
<td><strong>Sicca syndrome</strong></td>
<td>24%(56/230)</td>
<td>71%(30/42)</td>
</tr>
<tr>
<td><strong>Malignant Lymphoproliferation</strong></td>
<td>18%(42/230)</td>
<td>35% (15/42)</td>
</tr>
</tbody>
</table>

De Vita et al Ann Rheum 2011;70: 1183-90
Case #1

- PE
- Stable vital signs
- No stigmata of liver disease
- Pupuric lesions on the extremities (shins, feet and forearms)
- No synovitis
Case #1

- Labs
- CBC, renal function INR, PTT normal
- ALT 59, AST 38, ALP 44, GGT 54, Albumin 43
- Cryoglobulin 4 degrees (+), RF (+), M protein (+), low C4
- antiCCP negative, ANA and ANCA negative
- CRP 0.6 ESR 24
- Biopsy: leukocytoclastic vasculitis
Therapeutic options?

A. Restart antiviral therapy
B. Corticosteroids
C. Cyclophosphamide
D. Rituximab
E. PLEX
F. IVIG
Cryoglobulinemic Vasculitis

Treatment

Non HCV related
Treatment of underlying disease
(lymphoproliferative disorder or connective tissue disease)
Cryoglobulinemic Vasculitis

Treatment

HCV related
Interferon alpha - relapses
Interferon alpha and Ribavarin – more efficacious
(?) non –responders vs intolerance*

St Clair et al Arthritis & Rheum 64(3)March 2012;604-608
Case #1

- Prednisone – lowest dose 20mg
- Rituximab 375 mg/m2 x 4 weeks
- Remission!
Cryoglobulinemic Vasculitis
Rituximab (RTX)

• Single center open label RCT
• RTX versus best available therapy
• Failed antiviral therapy
• 24 patients enrolled
• Primary endpoint: disease remission in 6 months (BVAS)
• Secondary endpoints: duration of remission & occurrence of severe adverse events

Sneller et al. Arthritis and Rheumatism; 64(3) March 2012: 835-842
Cryoglobulinemic Vasculitis
Rituximab (RTX)

Baseline characteristics – similar
- Remission RTX 83.3% vs 8.3% Control
  \( p = <0.001 \)*
- BVAS – comparable baseline > lower RTX group
  \( p=0.02 \)
- Median duration of remission 7 months
- RTX group: no increase or initiation of immunosuppressive therapy*

Sneller et al Arthritis and Rheumatism; 64(3) March 2012: 835-842
Cryoglobulinemic Vasculitis
Rituximab (RTX)

Labs…
• Peripheral blood B cell depletion* -11/12
RTX
• Cryoglobulins – lower in RTX group
\( p = \text{less than } 0.05 \)*
Complement levels – increased in RTX group*

HCV replication – not affected by RTX *

Sneller et al  Arthritis and Rheumatism; 64(3) March 2012: 835-842
Cryoglobulinemic Vasculitis
Rituximab (RTX)

Adverse events

- Infusion reaction (RTX group)
- No serious infection/ hospitalizations*
- Elevated hepatic transaminase levels: mild and similar in both groups
- No Hypogammaglobulinemia in RTX group
- GFR: Stable RTX group

* Sneller et al. Arthritis and Rheumatism; 64(3) March 2012: 835-842
Cryoglobulinemic Vasculitis

Rituximab

• RCT Rituximab for the treatment of severe Cryoglobulinemic Vasculitis.

• 59 patients *Randomized 1:1
• Non-Rituximab vs Rituximab
• Endpoints : survival of treatment

De Vita et al, Arthritis and Rheumatism 64(3) ; March 2012 ; 843-853
Cryoglobulinemic Vasculitis

Rituximab

- Superiority of Treatment
  RTX group 63.2% vs Non RTX 4.4%
  (p = <0.0001)

Survival Treatment
  RTX group 64.3% vs Non RTX 3.5%
  (p = <0.0001)

De Vita et al, Arthritis and Rheumatism 64(3); March 2012; 843-853
Cryoglobulinemic Vasculitis
Plasma Exchange

• Case Reports *
• Aim is to clear cryoglobulins and lower viral load
• Severe life threatening renal, neurological, cutaneous manifestations unresponsive to therapy

Mahr et al: Current Opinion 24(3) May 2012 ; 262 - 266
Cryoglobulinemic Vasculitis Interleukin 2

Single center open label prospective study 10 patients with chronic HCV infection with cryoglobulinemic vasculitis Resistance or intolerance to antiviral therapy Four courses of IL2 Primary endpoint: increase in, CD25, CD4, FOXP3+

Saadoun et al; NEJM 2011; 365;22 (2067-2077)
Cryoglobulinemic Vasculitis

Interleukin 2

Saadoun et al; NEJM 2011; 365;22 (2067-2077)
Case #2

Woman, 70 years-old
Lives alone, 4 healthy daughters & 2 sons

HTN
Otitis in childhood

Non smoker, non drinker
(no recreational drugs)
Case #2

For 1 month: R otitis
→ mastoiditis with R facial palsy
→ mastoidectomy + ceftriax + ciproflox

Creatinine 74 micmol/l, normal CBC
Case #2

1 week later: fever, SOB, then “septic shock”

Persistent purulent discharge from R ear

Creatinine 484 micmol/l, Hb 75 g/l
pO2 at 57, SatO2 at 87% under 4 l/min

→ Mechanical ventilation
Case #

Bronchoscopy with BALF = alveolar hemorrhage, no germ

Urine = protein 3+, hematuria +

→ Tazo + meropenem, dialysis
Case #

No skin or neurologic involvement

Normal echocardiography and brain CT scan

ICU? PLEX?
Case #

No skin or neurologic involvement

Normal echocardiography and brain CT scan

cANCA antiPR3 > 8 IU
(urine: red blood cell casts)

Biopsy?
Treatment of GPA and MPA

- **Non-severe MPA (FFS)** = CS alone
  
  Gayraud et al, Arthritis Rheum 2001;44:666-75

- **Limited/early systemic GPA** = CS + MTX
  

- **Severe/systemic GPA and severe MPA** = STAGED INDUCTION-MAINTENANCE STRATEGY
  
  Jayne et al, N Engl J Med 2003;349:36-44
  Hiemstra et al. 2010 Dec 1;304(21):2381-8.
Treatment of severe GPA/MPA

+ what?

+ Corticosteroids

3 - 6 months

*INDUCTION*

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**

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

+ **Corticosteroids**

**INDUCTION**

- 3 - 6 months

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

(<350 µM)
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.
Better response in relapsers (vs newly-diagnosed)

Rituximab is an alternative to CYC

YES but still in SPECIFIC PATIENTS/SETTINGS
Treatment of severe GPA/MPA

**CYCLOPHOSPHAMIDE**

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

- 2 mg/kg/d

+ Corticosteroids

**INDUCTION**

3 - 6 months

+ 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)

Median duration of follow-up of 4.3 yrs

DEATHS

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

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
  
  \[ HR = 0.50, \quad 95\% \text{ CI, 0.26-0.93}; \quad p = 0.029 \]
**RELAPSES**

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

- Cox regression analysis
  \[ HR = 0.50, \text{ 95\% (CI, 0.26-0.93)}; \text{ p=0.029} \]

Half the relapse rate,
Twice the CYC dose...
Make your choice...

**Table:**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO (n)</td>
<td>72</td>
<td>55</td>
<td>46</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Pulse (n)</td>
<td>76</td>
<td>64</td>
<td>54</td>
<td>24</td>
<td>3</td>
</tr>
</tbody>
</table>
Message #2

OK… daily oral CYC **MAY** be associated with a lower subsequent rate of relapse

But does it worth giving a double dose of CYC (as compared to IV)?
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
PLASMA EXCHANGE

- **MEPEX**
  - Design for renal recovery rate
  - 137 p. (WG 31%) with Cr ≥ 500 µmol/L (5.8 mg/dl)
  - 7 PE/14 days vs. daily 1g-MP pulses for 3 days

PEXIVAS

- WORLD WIDE TRIAL, NIH-VCRC sponsored
- 2*2 factorial open-label trial
- Aimed to enrol 500 patients → 150 in 2 years!
- GPA, MPA with AH and/or renal involvement (GFR <50 ml/min)
Message #3

Forget about your prejudices on PLEX in AAV

We DO NOT KNOW the precise place of PLEX and whether it is really beneficial at all!
AASV: INDUCTION-MAINTENANCE STRATEGY

- **CYCAZAREM**
  - Open label randomized trial
  - Superiority design
  - 155 patients (60% WG)
  - 144 Randomized at remission (after oral CYC)
  - **Relapses**
    - AZA 15.5%
    - CYC 13.7% (P=0.65)
  - Severe AE
    - AZA 11%
    - CYC 10% (P=0.94)

Message #4

REMEMBER

CYC = NEVER >6 months!
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

> 18 months????

**INDUCTION**

**MAINTENANCE**

+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc
We DO NOT KNOW the optimal duration of maintenance therapy

Is 4 better than 2 years? → REMAIN results, mid 2013
Imaging GPA melting pot...
Case #3

- Woman, 32 years-old
- Married, no children
- No past medical history
- Smoker (5 packs-years), occasional drinks
- No recreational drugs

- For 3 months, heavy legs, and recurrent purpuric and macular skin lesions on lower limbs
Case#3

- CBC, creatinine, LFT, CRP
- ANA, ANCA, cryoglobulin
- Serologies (HBV, HCV, HIV, TPHA-VDRL)
- Urine analysis
- Chest X-ray

- If nodular: Ca, CE… PPD, other serologies depending on the context (ricketssioses, yersiniosis…), IBD…
Case #3

- Skin biopsy = LCV
Case #3

- Colchicine 0.6 mg BID
- Dapsone 50 → 100 mg OD (clofazimine?)
- (Danazol, 100-300 mg OD, men, menopausal w)
- (Hydroxychloroquine)
- (Sulfasalazine)

- Prednisone
- Azathioprine
- Methotrexate
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)

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