Updates from the 15th ANCA workshop

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Chapel Hill Old Well
Updates from the 15\textsuperscript{th} ANCA workshop (part 1)

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Mount Sinai Hospital, Toronto, Canada
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Chapel Hill Nomenclature

- LVV: GCA and TA
- Medium-sized: PAN, KD

Charles Jennette
Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels:
  - GPA, MPA, EGPA = ANCA-ASV
  - HSP
  - + antiGBM (Goodpasture)
Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels
- CNS vasculitis, Cogan
- Vasculitis with systemic disease
  - Lupus, RA
  - Behçet
Chapel Hill Nomenclature

- LVV
- Medium-sized
- Small-sized vessels
- CNS vasculitis, Cogan
- Vasculitis with systemic disease
- Vasculitis associated with infection (HBV, HCV...)
- Other secondary vasculitis (drugs, toxics/cocaine...)
Classification

• International effort to devise
  – Classification criteria
  – Diagnostic criteria

→ DCVAS study
PR3 versus MPO AASV…

• Distinct clinical differences
• Granulomatous disease

• Animal model

• Different geographical distribution
  – PR3 Northern countries (EU, US)
  – MPO South, East Asia and Japan

Kallenberg, Groningen, NL
PR3 versus MPO AASV...

- Different time peak distribution
  - PR3 GPA peaks in 1996-98, 2005-07 (4.5 → 17.4/million/year)
  - No peak for MPO MPA (5.8/million/year)

- Relapse and mortality rates
  - PR3 = higher risk of relapse
  - MPO = higher mortality rate, higher risk of ESRD

Watts et al, Norwich UK
Pathological classification of AASV-glomerulonephritis

Th17 / IL17 in GCA

Weyand et al, *Circulation* 2010;121:906-915
Th17 vs Th1 in GCA

(A) Th17 (% of CD4 T cells), Con, No Tx, Tx

(B) Th1 (% of CD4 T cells), Con, No Tx, Tx

P<0.0001, P<0.0001

P<0.0001, P=ns
GCA and LVV

• Physiopathology
  – TH1, TH17
  → Differential TLR distribution and expression in normal human vessels

Cornelia Weyand
CSS / EGPA

- FVSG cohort
- Mepolizumab trial

Julia Holle, Germany
PACNS

• The difficulties to establish a definitive diagnosis remain…
• Biopsy is rarely performed

Leonard Calabrese, Cleveland US

• EPCs and CECs as potential surrogate markers of activity and/or diagnosis?

Deb et al, Hannover, Germany
Eleftheriou et al, London, UK
GPA and MPA

- antiLAMP2 controversy
- ANCA in tuberculosis
- antiPR3 mouse model
- Complement in AASV
Mouse model NOD

• NOD scid mice (lack B, T, NK)
• Irradiated at 8 weeks
• Injected with mobilized human hematopoietic stem cells
• At 6 weeks post-TBI: human CD45+ 18% chimerism
• Pre-treated with LPS IP
• Purified IgG from 3 antiPR3+ patients, healthy donors or subjects with other kidney disease

Little et al., Birmingham, UK
Complement in AASV

• Protection from disease in C5 and factor B K.-O. mice
  Xiao et al., Am J Pathol. 2007

• C5a primes neutrophils for ANCA-induced oxydative burst

• C5a-receptor deficient mice are protected for GN
C5aR antagonist CCX168

• Completely blocked anti-MPO induced GN in mice
• Orally administered
• Phase I = well tolerated, with excellent oral bioavailability (40 healthy subjects)
• 94% reduction in C5a-induced CD11b upregulation on neutrophils (ex vivo)

GPA and MPA

• antiLAMP2 controversy
• ANCA in tuberculosis
• antiPR3 mouse model
• Complement in AASV

• **Microparticles** (endothelial-, platelet-, neutrophil-MPs, MP tissue factor activity, MP-mediated thrombin generation)
• **cf-DNA/NETs** in active AASV (and DCs maturation)
• **Epigenetic** (silencing defects)
• Retinoic acid to block transcriptional activator of MPO and PR3
Therapeutic updates

- CYCLOPS
- CYCAZAREM
- MEPEX

Long term follow-up

- Duration of corticosteroid therapy

- Rituximab (results at 18 months)
  - RAVE
  - RITUXVAS