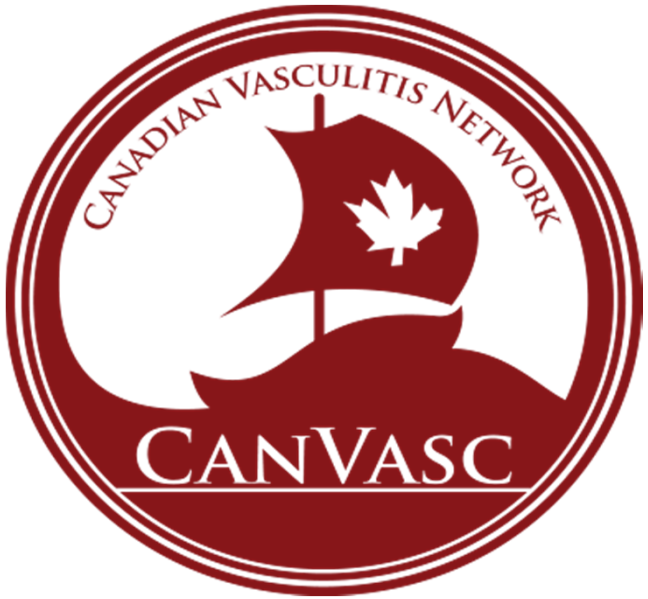
Update from the 2013 ANCA workshop

Dr. Christian Pagnoux
Mount Sinai Hospital
University Health Network
University of Toronto

Dr. Navjot Dhindsa
University of Manitoba
Arthritis Centre
Winnipeg



CPx



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CPx

~520 attendees

40 hours of oral sessions over 4 days

52 oral lectures, 68 oral abstract presentations, 231 posters

+ VCRC-EUVAS meeting 7 hours (April 14th)

+ EGPA task force 5 hours (April 13th)



The French FVSG attendees and Pr. Guillevin

Selection and plan

1. Pathogeny of vasculitis
   - ANCA epitope specificity
   - Treg, neutrophils, apoptosis
2. MPO/PR3 (Abs) versus phenotype
3. Therapeutic trials
   - MYCYC
   - MAINRITSAN (and RTX series)
   - CORTAGE
4. Late cardiovascular events
5. Miscellaneous

A31

Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis

Aleeza J. Roth,[1] Joshua D. Ooi,[2] Jacob J. Hess,[1] Mirjan M. van Timmeren,[3] Elisabeth A. Berg,[1] Caroline E. Poulton,[1] JulieAnne McGregor,[1] Madelyn Burkart,[1] Susan L. Hogan,[1] Yichun Hu,[1] Witold Winnik,[4] Patrick H. Nachman,[1] Coen A. Stegeman,[3] John Niles,[5] Peter Heeringa,[3] A. Richard Kitching,[2] Stephen Holdsworth,[2] J. Charles Jennette,[1] Gloria A. Preston,[1] and Ronald J. Falk[1]

[1]UNC Kidney Center, Department of Medicine, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [2]Department of Medicine, Monash University, Clayton, Victoria, Australia. [3]Department of Pathology and Medical Biology, University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands. [4]United States Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Research Triangle Park, North Carolina, USA. [5]Renal Division, Massachusetts General Hospital, Boston, Massachusetts, USA.

J Clin Invest 2013; 123:1773-1783

- Natural ANCA Abs exist

Cui et al. Kidney Intern 2010; 78:590-597

- ANCA negative patients exist also
- Unreliable correlation between ANCA & disease activity

Epitope specificity

- 45 MPO-ANCA+ from UNC
  - 40% MPA, 40% RLD, 20% GPA
  - 52 sera when active + 35 in remission
- 10 MPO-ANCA neg from UNC
- 20 MPO-ANCA+ from NL + 13 MPO-ANCA neg
- 10 UNC + 9 NL healthy controls

Total sera

→ **Purified Ig** from sera subjected to epitope excision MALDI-TOF / TOF-MS

J Clin Invest 2013; 123:1773-1783

Epitope specificity

- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry

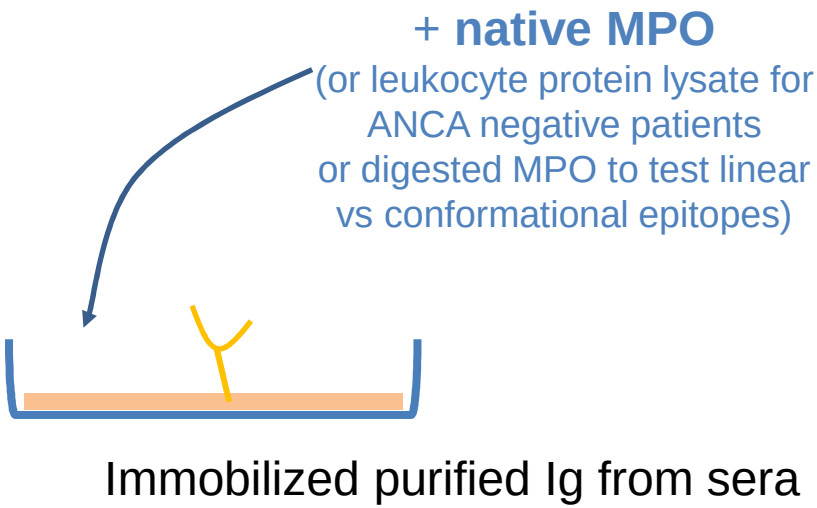


Immobilized purified Ig from sera

CPx

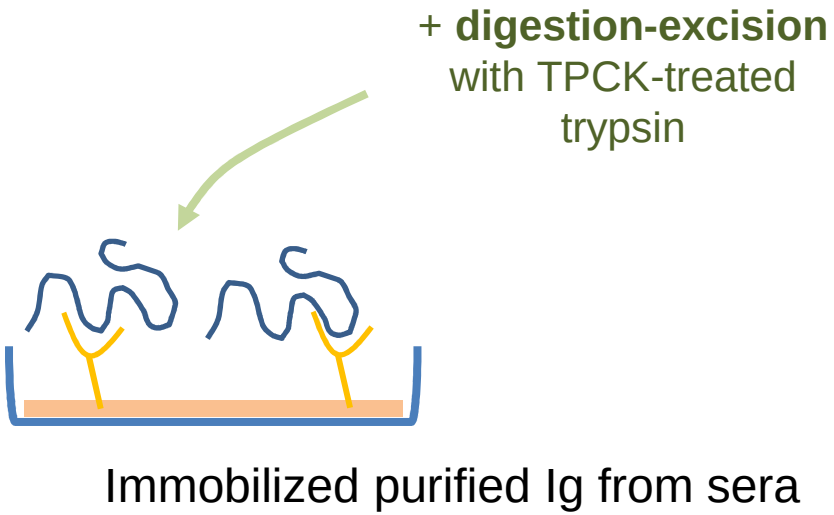
Epitope specificity

- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry



Epitope specificity

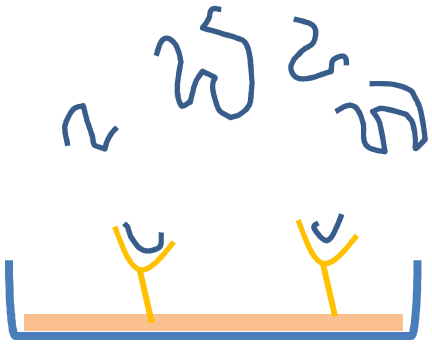
- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry



CPx

Epitope specificity

- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry



Immobilized purified Ig from sera

Highly sensitive epitope excision

CPx

Epitope specificity

- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry



Immobilized purified Ig from sera

Elution of bounded “cut” MPO peptides with 0.1% TFAA

Epitope specificity

- MALDI matrix-assisted laser desorption ionization
- TOF time of flight
- MS mass spectrometry



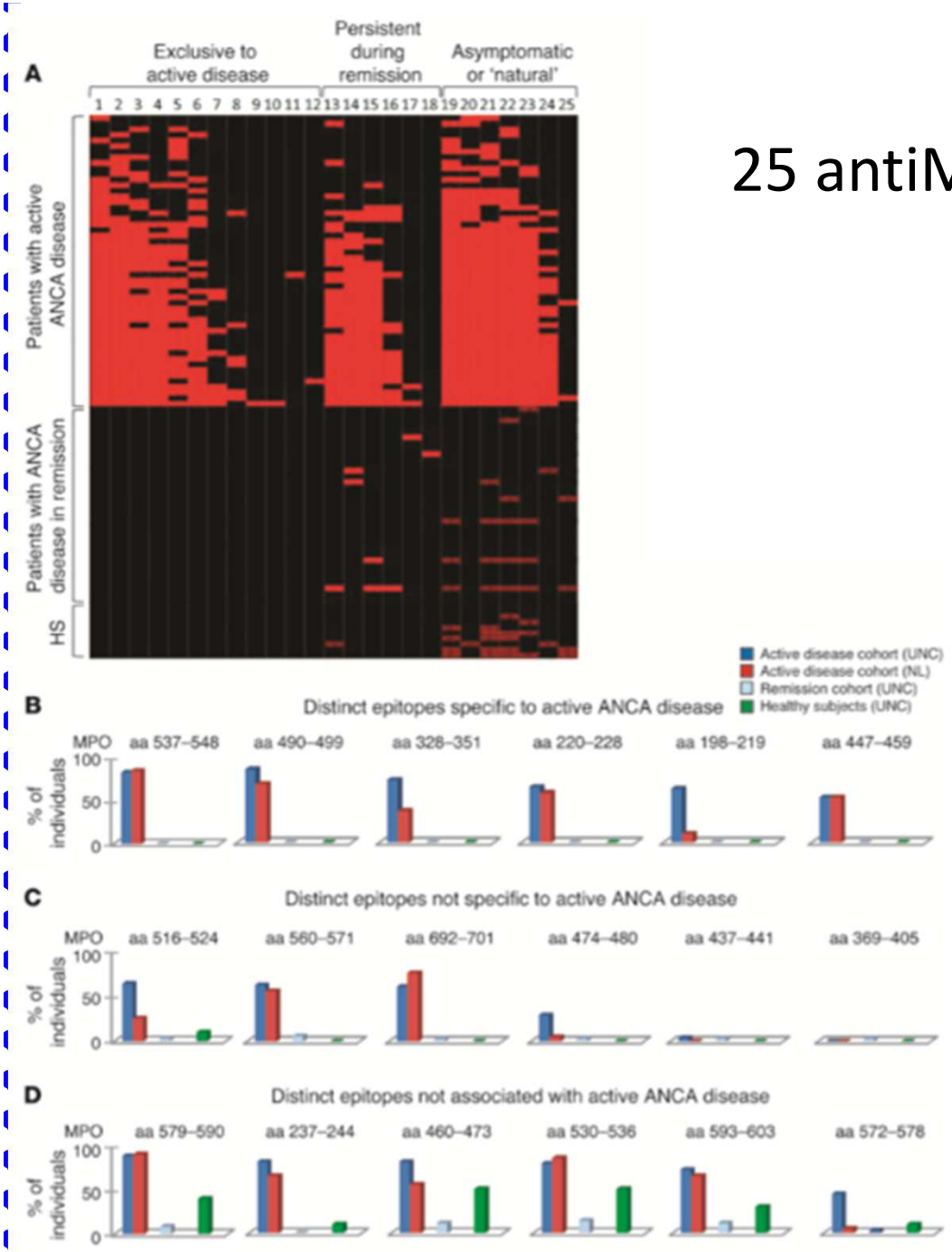


Immobilized purified Ig from sera

Elution of bounded “cut” MPO peptides with 0.1% TFAA

For healthy controls and patients in remission, with ^{16}O to ^{18}O exchange

CPx

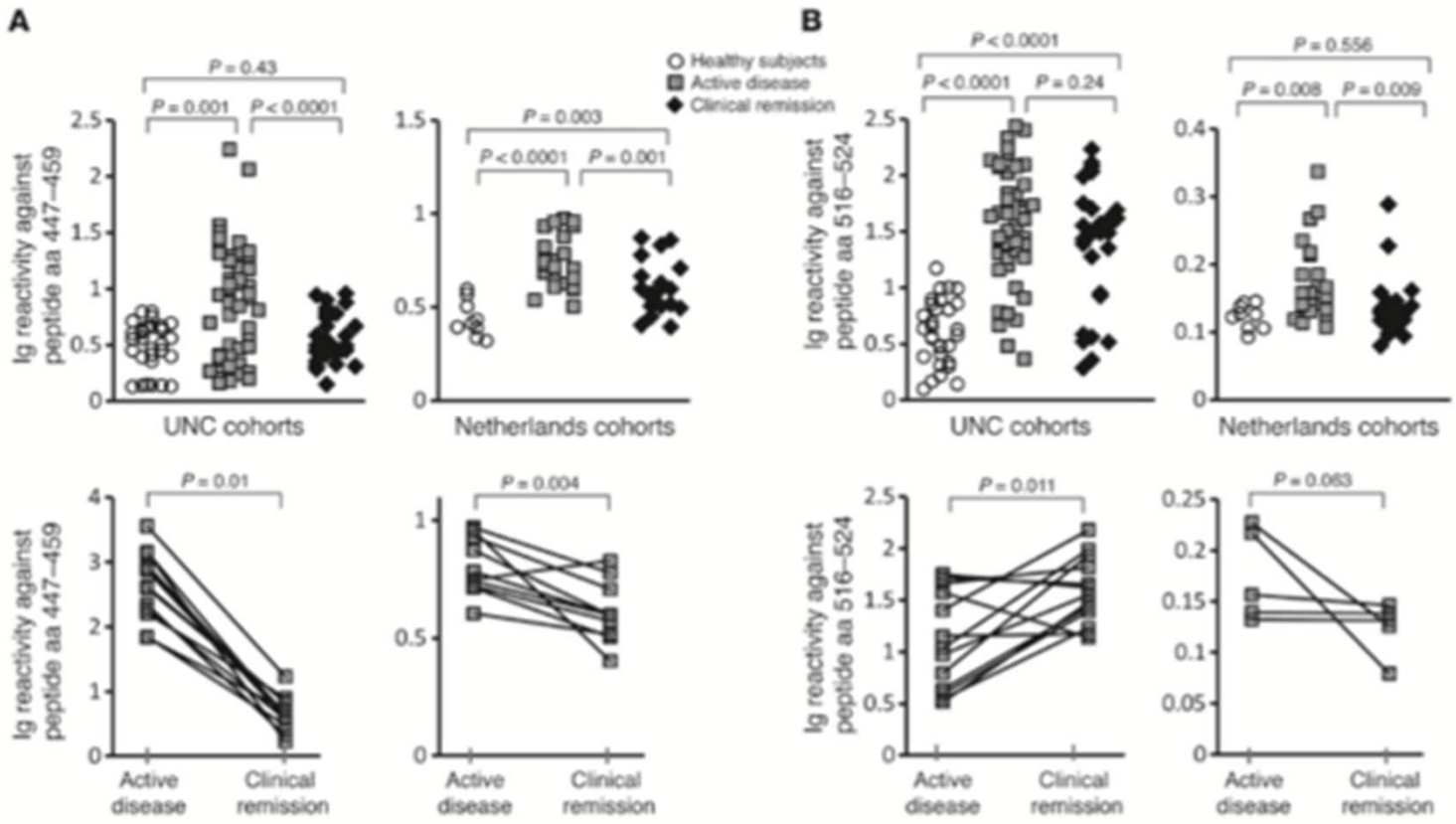


25 antiMPO epitopes identified

- 12 exclusive to active disease
- 5 during active disease and remission
- 8 natural, always present

20 conformational

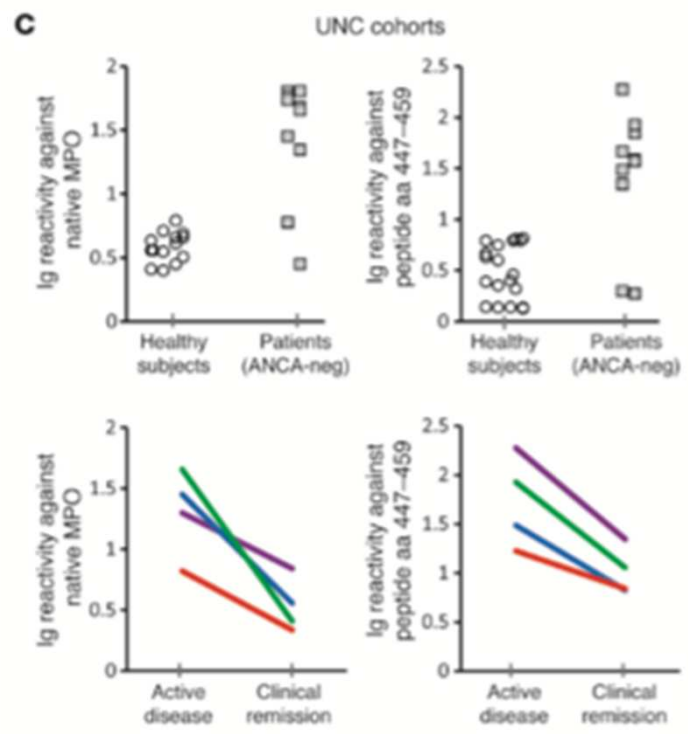
5 linear



By ELISA, one of these 5 linear epitopes showed to be associated exclusively with active disease in 43% of UNC and 52% of NL patients' samples

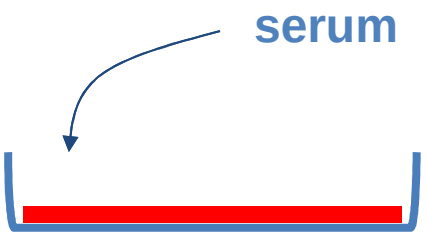
→ **aa 447-459**

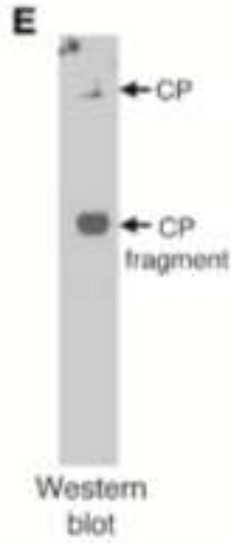
CPx

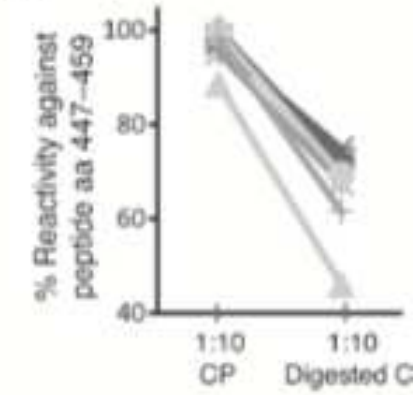


In MPO-ANCA neg (sera), purified Ig reacted in ELISA with both native MPO and aa 447-459 but no other MPO epitope, with similar correlation active disease / remission

→MPO-ANCA negative patients have MPO-ANCA+ towards aa 447-459 exclusively, detectable when using purified Ig



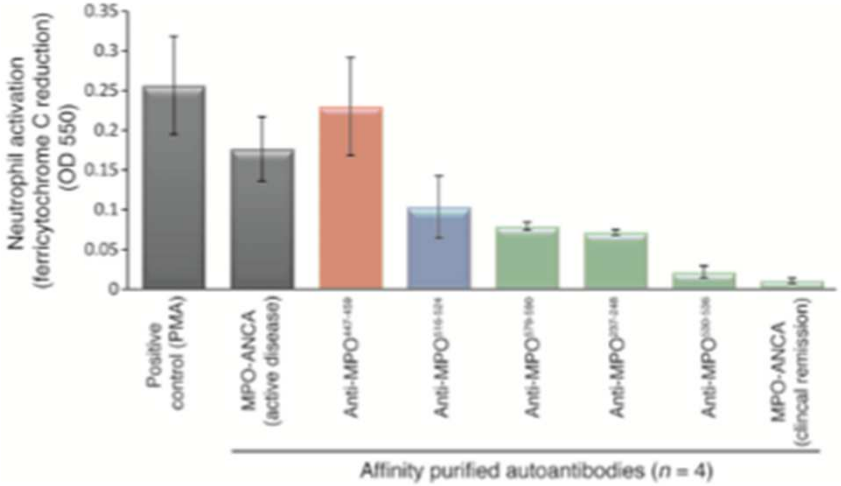




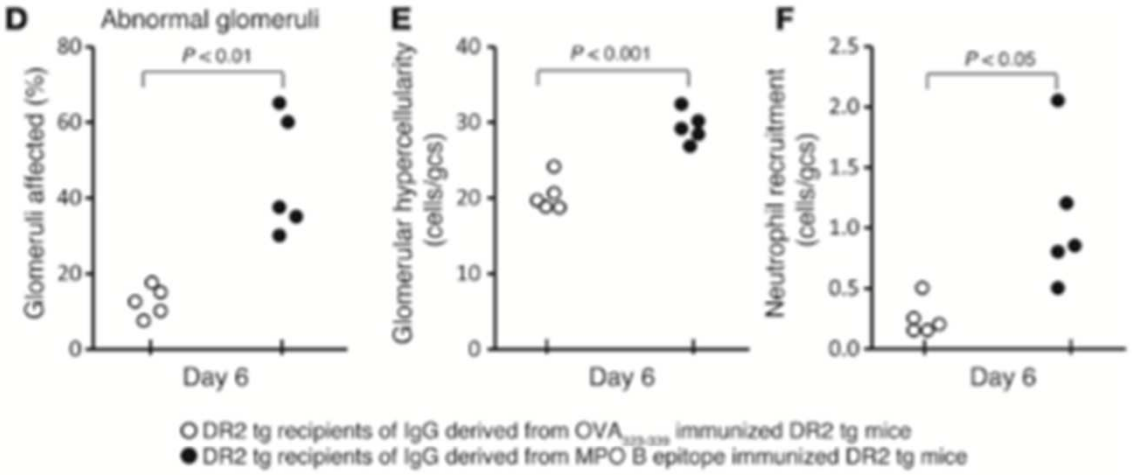
In MPO-ANCA neg sera, MPO aa 447-459 is complexed / bound with / covered by a enzymatically digested 50-kD fragment of ceruloplasmin

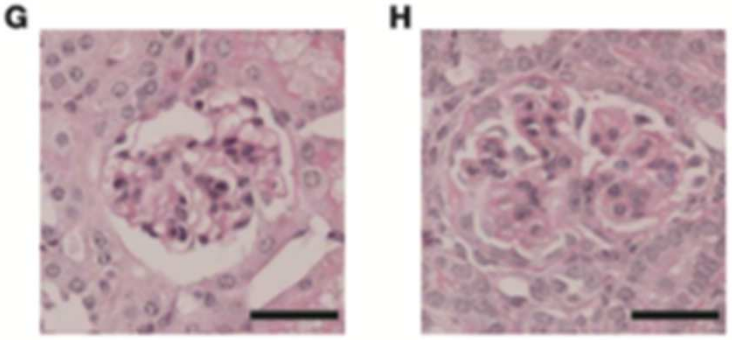
- selectively binding to aa 447-459
- only binds to the 50-kD CP (not the full-length 151-kD CP)

CPx



ANCA-MPO$^{447\text{-}459}$ induces neutrophil ROS release *in vitro*





Causes (<u>non necrotizing</u>) GN in DR2 Tg mice after passive IgG transfer (from mice immunized with MPO aa 442-460, that also develop a polyclonal response to the entire MPO molecule!)

- New ANCA test / purified Ig with $MPO^{447-459}$?
- New animal model to study?
- Epitope similarities with germs?



However…

- Only half the patients
- What about conformational epitopes?
- Mouse GN was proliferative (not necrotizing)

- What about PR3 / PR3-ANCA?

Free M et al – CH UNC – A13

CPx

Defective Treg function in AASV

- PBMCs from 63 AASV and 16 HC
- Flow cytometry for CD4+ subsets before and after stimulation with antiCD3/28
- Increased Tregs in active AASV but with decreased suppressive function
- Tregs from active AASV overutilize a FOXP3 isoform that lacks exon 2
- Increased CD4+ $CD127^{high}$ $CD25^{interm}$ that are more resistant to Treg suppression and produce pro-inflammatory cytokines

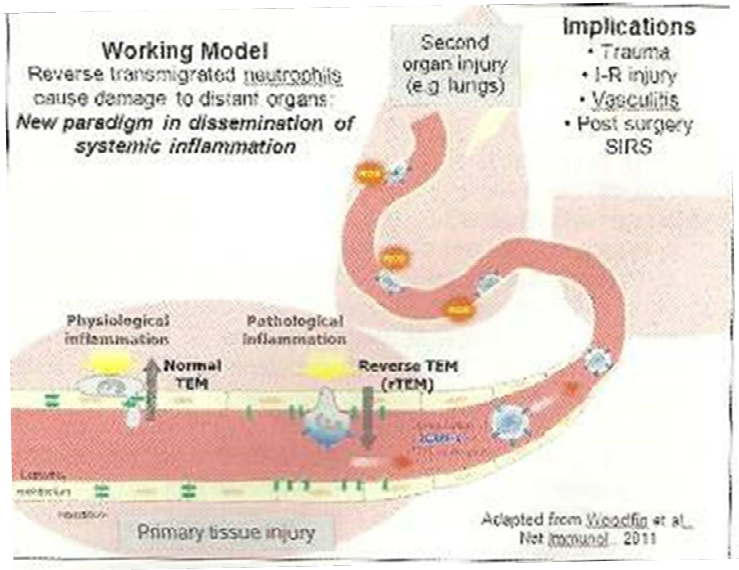
Cassatella M – Verona, Italy – L33
Witko-Sarsat V – Paris L34

Neutrophils

- MPO and PR3 (myeloblastin) in azurophilic granules (and mPR3)
- Role of NETs (extracellular traps)
- Neutrophil interactions with DCs, B, T and NK cells, through the production of several chemokines and cytokines, including pro-Th1 and Th17 ones and BLyS/BAFF, APRIL

Neutrophils

- Neutrophil (reverse) transendothelial cell migration
  - *in vivo* ischemia-reperfusion injury lung model
  - 3D direct observation
  - rTEM neutrophil are activated and can disseminate inflammation (local→systemic)



→ **Neutrophils as therapeutic targets?**

Nourshargh S – London UK – L2

CPx

Apoptosis

- Apoptosis implicated in the inflammation resolution process
  - apoptosis of inflammatory cells
  - phagocytosis of apoptotic cells (+ bodies) before they dislocate (necrosis → inflammation) = efferocytosis
  - switch in the profile of phagocytosing cells (MP, DC) to anti-inflammatory cells

→ Apoptotic cells have direct and indirect immunomodulatory effects

- Increased neutrophil survival and defects in clearance of apoptotic neutrophils in AASV

Rossi A – Edinburgh UK – L13
Perruche S – Besancon, Fr. – L14
Witko-Sarsat V – Paris L34

P188 – Morgan M et al. Birmingham, UK

CPx

Glycosylation of Asn297 ANCA IgG in GPA

- Purified antiPR3 IgG from sera of 49 GPA, 38 HC
- Mass spectrometry to study glycosylation
- Mainly IgG1 ANCA isotype
- Agalactosylated IgG1 more common in GPA (52% vs 29%)
- Lower sialylation
- Level of galactosylation (less for sialylation) correlated + with cytokines IL2, IL1, IL12, IL15 and time to remission
- But NOT correlated with BVAS

→ cytokine environment likely drives the level of galactosylation of antiPR3 ANCA

P127 – Lardinois O et al. Chapel Hill

CPx

Glycosylation of serum IgG antiMPO ANCA

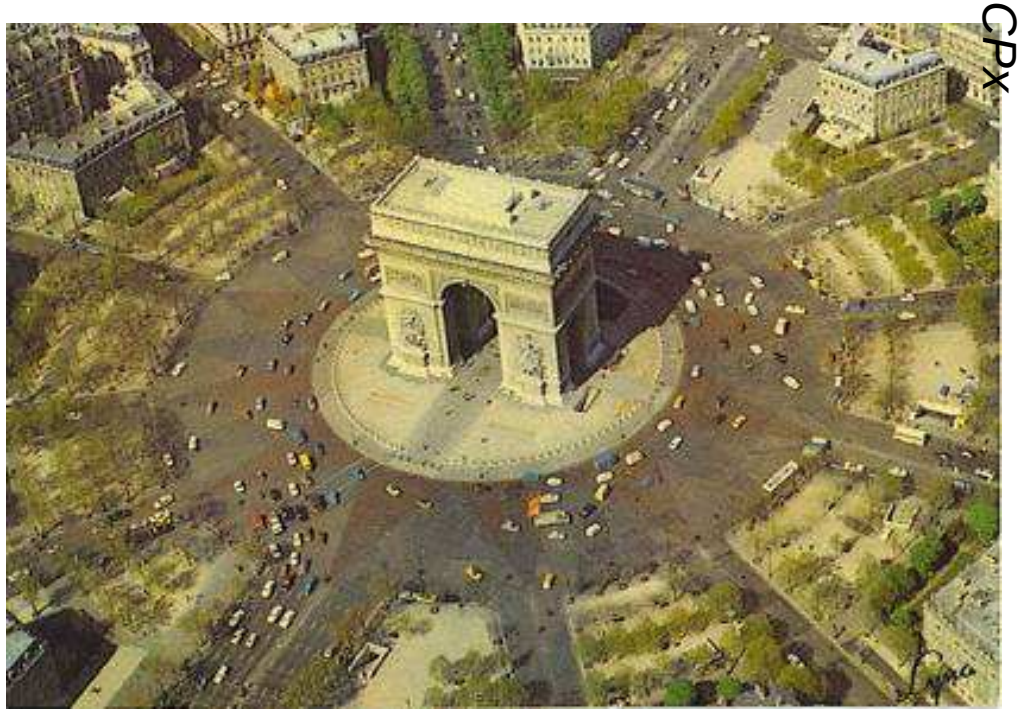
- 29 antiMPO, 21 antiPR3 patients, 30 healthy controls

  → IgG isolated from sera and digested to study glycosylation

- Level of glycosylation (sialic acid / galactose) correlated with disease activity in antiPR3 patients (*already known*)
- Level of glycosylation were elevated in antiMPO patients during both active disease or in remission

→ antiPR3 and antiMPO disease/pathogeny differs on this aspect…

GPA vs MPA
or PR3 vs MPO?



CPx

- Pathogeny and genetics
- Clinical presentation
- Outcomes

Antibodies versus phenotypes: L26 Falk R; L27 Jayne D; L32 Watts R; L43 Holle J

Flossman O et al. Ann Rheum Dis. 2011 Mar;70(3):488-94
Suppiah R et al. Arthritis Care Res (Hoboken). 2011 Apr;63(4):588-96

Original Article

Genetically Distinct Subsets within ANCA-Associated Vasculitis

Paul A. Lyons, Ph.D., Tim F. Rayner, Ph.D., Sapna Trivedi, M.R.C.P., M.Phil., Julia U. Holle, M.D., Ph.D., Richard A. Watts, D.M., F.R.C.P., David R.W. Jayne, M.D., F.R.C.P., Bo Baslund, M.D., Ph.D., Paul Brenchley, Ph.D., Annette Bruchfeld, M.D., Ph.D., Afzal N. Chaudhry, Ph.D., F.R.C.P., Jan Willem Cohen Tervaert, M.D., Ph.D., Panos Deloukas, Ph.D., Conleth Feighery, M.D., Wolfgang L. Gross, M.D., Ph.D., Loic Guillevin, M.D., Iva Gunnarsson, M.D., Ph.D., Lorraine Harper, M.R.C.P., Ph.D., Zdenka Hrušková, M.D., Mark A. Little, M.R.C.P.I., Ph.D., Davide Martorana, Ph.D., Thomas Neumann, M.D., Sophie Ohlsson, M.D., Ph.D., Sandosh Padmanabhan, M.D., Ph.D., Charles D. Pusey, D.Sc., F.Med.Sci., Alan D. Salama, F.R.C.P., Ph.D., Jan-Stephan F. Sanders, M.D., Ph.D., Caroline O. Savage, F.Med.Sci., Ph.D., Mårten Segelmark, M.D., Ph.D., Coen A. Stegeman, M.D., Ph.D., Vladimir Tesař, M.D., Ph.D., Augusto Vaglio, M.D., Ph.D., Stefan Wieczorek, M.D., Benjamin Wilde, M.D., Jochen Zwerina, M.D., Andrew J. Rees, M.B., F.Med.Sci., David G. Clayton, M.A., and Kenneth G.C. Smith, F.Med.Sci., Ph.D.

N Engl J Med
Volume 367(3):214-223
July 19, 2012

L31 Lyons P

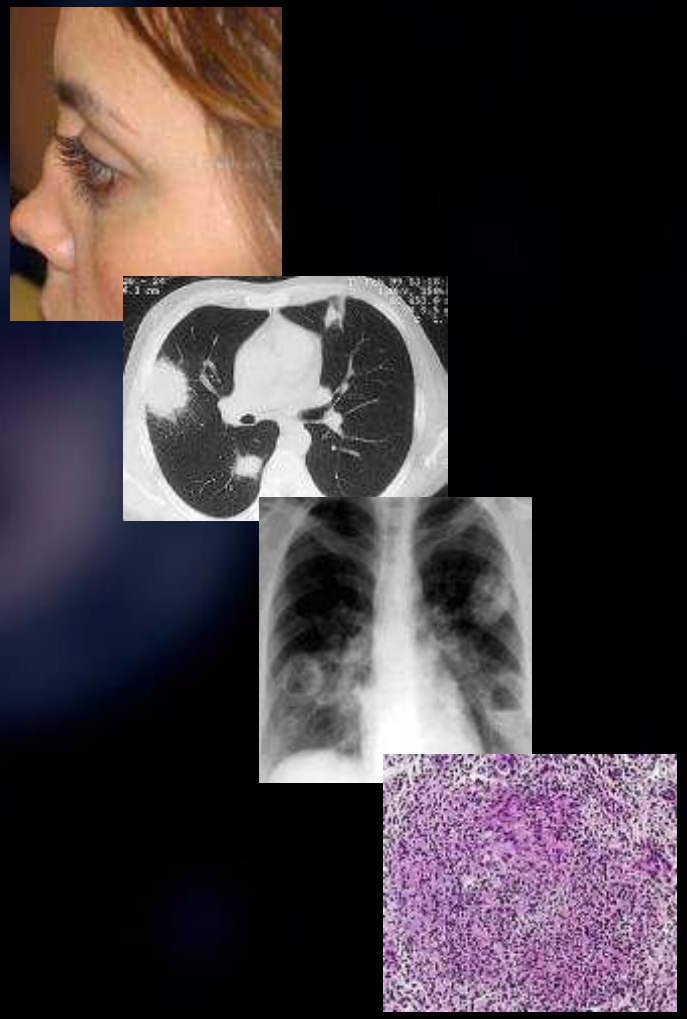
The NEW ENGLAND JOURNAL of MEDICINE

- antiPR3+ ANCA vasculitis is associated with *HLA-DP*, the genes encoding alpha1-antitrypsine (*SERPINA1*) and proteinase 3 (*PRTN3*) ($P = 6.2 \times 10^{-89}$, $P = 5.6 \times 10^{-12}$, and $P = 2.6 \times 10^{-7}$, respectively).

- antiMPO ANCA vasculitis is associated with *HLA-DQ* ($P = 2.1 \times 10^{-8}$).

L31 Lyons P

Canada-initiated study of GPA genetics

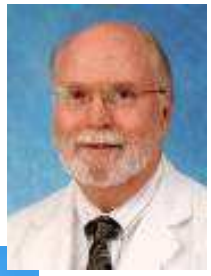


- Genotype 459 cases/1503 controls (Canadian)
- GWAS 700,000 markers
- Replicate 528 cases/1228 controls (WGGER, VCRC)

GENE	Proposed Function	P-value
HLA-DPB1	Immunoregulation	1.9×10^{-50}
HLA-DPA1	Immunoregulation	2.2×10^{-39}
SEMA6A	Immunoregulation	2.1×10^{-8}

Xie G et al. A40

2012 revised Chapel hill nomenclature

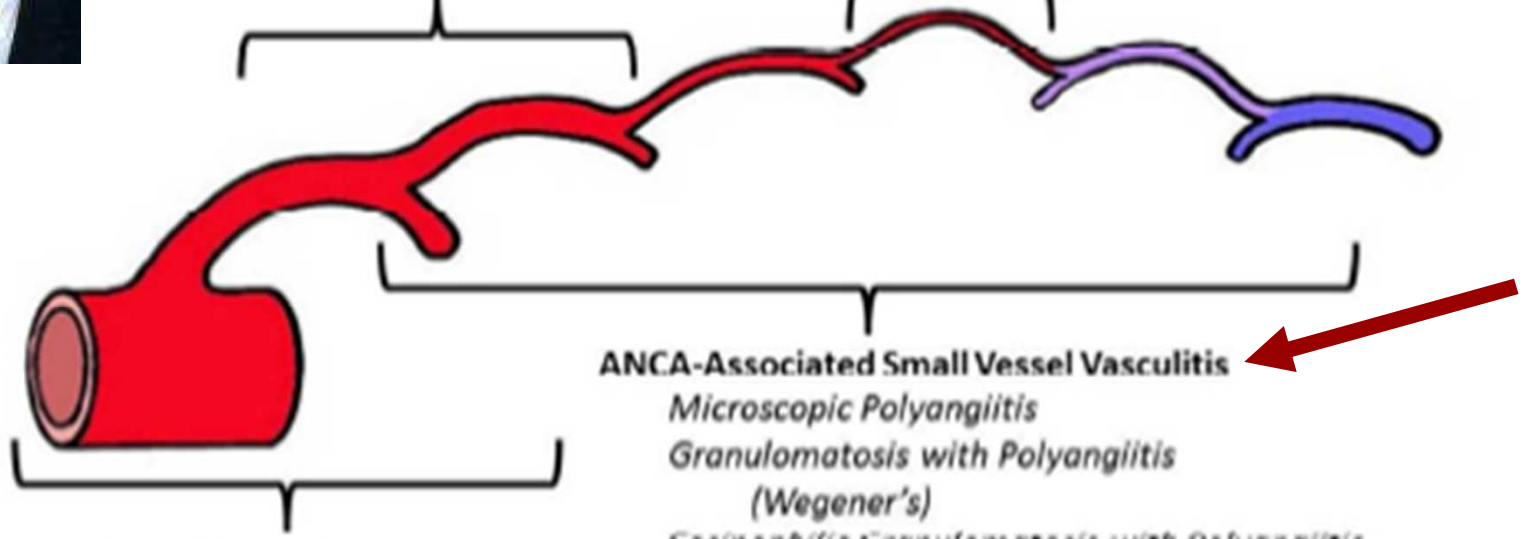




Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

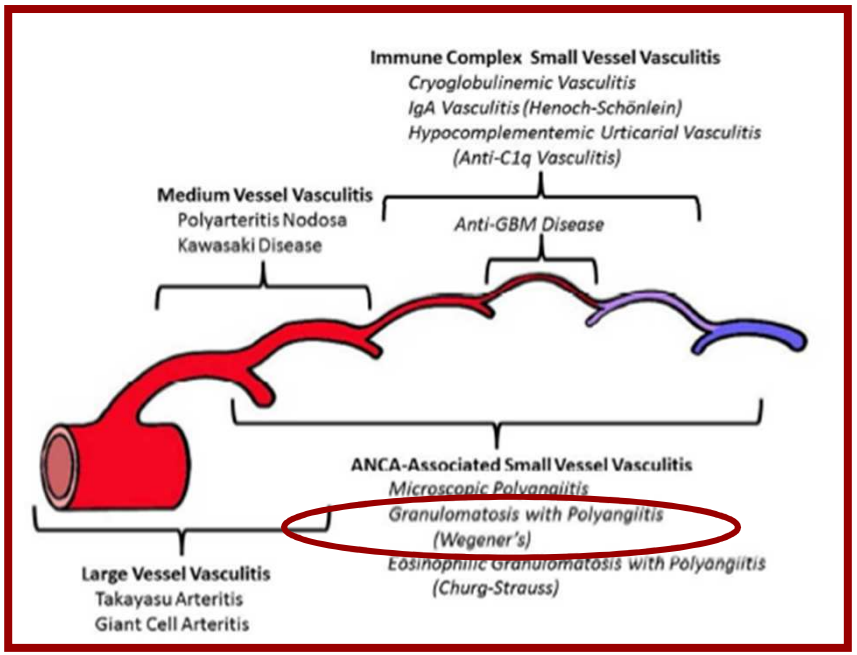
Anti-GBM Disease



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

Jennette et al. Arthritis Rheum. 2013



CPx

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO ANCA or PR3 ANCA. Not all patients have ANCA.

Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA negative.

Jennette et al., Arthritis Rheum 2013

- **Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins).**

- **Necrotizing glomerulonephritis is common.**

CPx

Treatments and trials



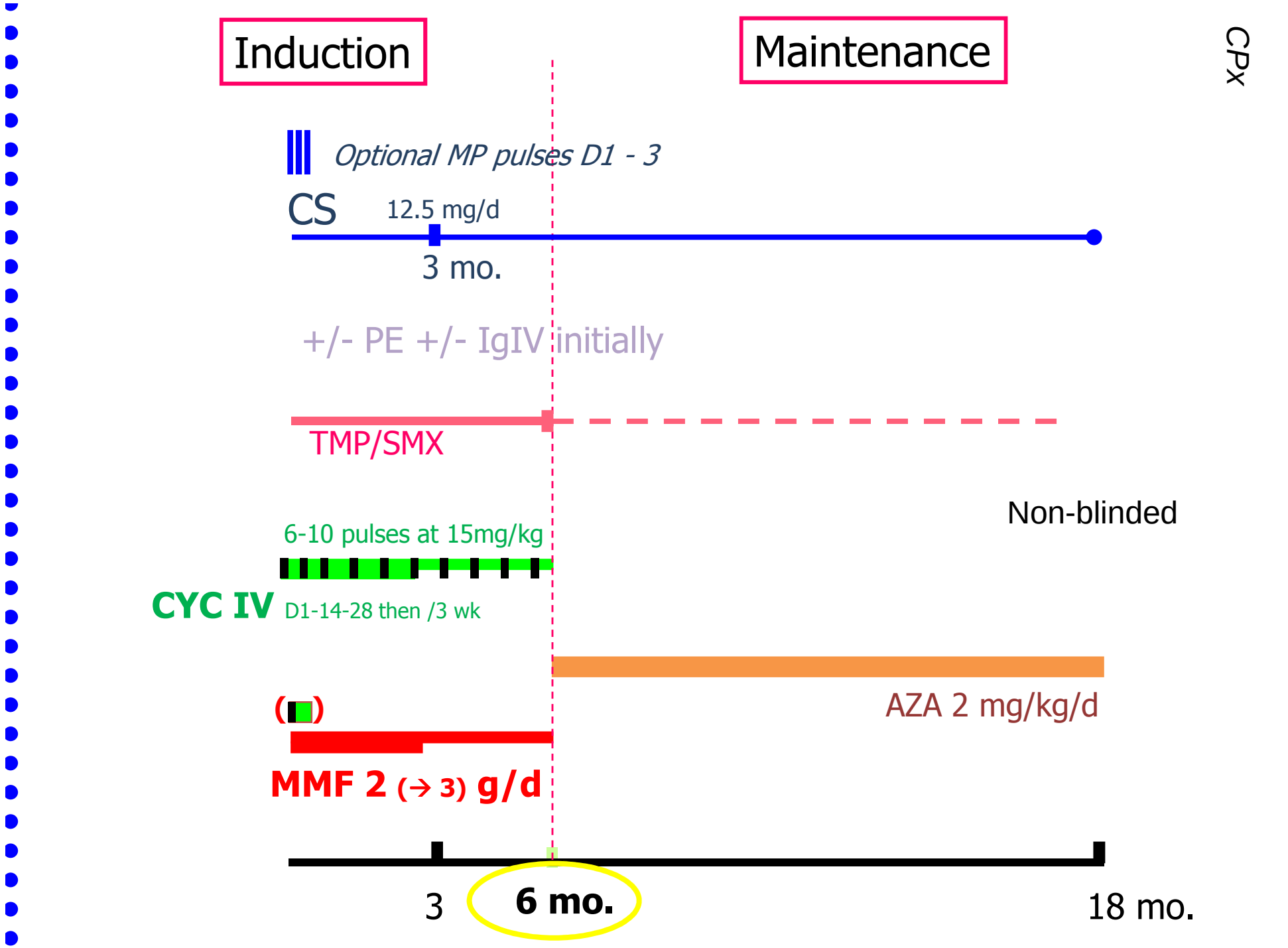
EUVAS - MYCYC

- Randomised non-blinded clinical trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitides

- GPA or MPA
  - newly diagnosed
  - active (≥ 1 major or 3 minor BVAS2003 items)
  - ANCA+ and/or histologically proven

- NO severe disease (such as life-threatening GI, AH, GFR <15ml/min or rapid decrease by >20%)

Jones R et al. A65, EUVAS – Cambridge UK


Induction
Maintenance
CPx
Optional MP pulses D1 - 3
CS
12.5 mg/d
3 mo.
+/- PE +/- IgIV initially
TMP/SMX
Non-blinded
6-10 pulses at 15mg/kg
CYC IV
D1-14-28 then /3 wk
AZA 2 mg/kg/d
(■)
MMF 2 (→ 3) g/d
3
6 mo.
18 mo.

MYCYC

Endpoint:

% of patients in sustained remission at M6

(BVAS=0, 2 times at >1 mo. Interval and CS ≤ 10 mg OD)

→ adherence to CS taper

Non-inferiority trial with Delta = 12%

80-90% IVCYC

MMF >73% (P 80%, α 5%)

140 patients enrolled from 33 sites (UK, Belgium, Italy, Spain, Austria, Germany, Czech Republic, Australia, NZ) → 25 centers enrolled patients

EUVAS – MYCYC at M6

	70 MMF	70 CYC	
Adults, n	66	66	
Age, years	58	60	
GPA, %	67%	64%	
PR3+, %	57%	60%	
GFR, ml/min	49	48	

EUVAS – MYCYC at M6

	70 MMF	70 CYC	
Adults, n	66	66	
Age, years	58	60	
GPA, %	67%	64%	
PR3+, %	57%	60%	
GFR, ml/min	49	48	
CR, %	67%	69%	0.05
PR, %	89%	79%	0.01
SAE, %	46%	39%	
SAE infections, %	26%	16%	0.14
Deaths	5 (7%)	4 (6%)	0.99
Rescue Rx	5	4	

Non-inferiority is NOT demonstrated for CR

→ -2% [IC; -14 to 10]

EUVAS – MYCYC at M18

	70 MMF	70 CYC
CR at any time, %	90%	91%
1st relapse	36%	20%
2nd relapse	52%	15%
SAE	50%	40%
SAE infections	28%	16%
Deaths	7%	6%

More relapse with MMF
P=0.02

Initial synergy MMF + high dose CS, then no longer, once CS dose is being decreased?

Single rituximab dose for induction

- 19 new or relapsing consecutive AASV with CI or ineffectiveness of conventional CS+IS (37%)
- 375mg/m^2 ONCE
- Median time to CR (BVAS=0, CS<10mg OD) 38 days
- 3-months probability of CR 80%
- Median time to B cell repopulation 9.5 mo.
- Median time to disease relapse 27 mo.

Chile experience with rituximab

- 13 consecutive AASV (8 GPA, 5 MPA) 2006-2012
- 10 M, age 47 [19-82]
- 500mg-1000mg x2 (D1-15) + MMF/AZA/MTX in 8; 4 given repeat courses
- CR in 6 months in 10 (77%), PR in 3
- 5 relapses (1st one after 9 months, 1 fatal Yr. 3)
- SAEs in 2 (PJP, RSV)

Repeat rituximab if flaring (1)

- 56 AASV
  - 38 GPA, 16 MPA, 2 EGPA
  - 17 new, 39 relapsers
- Induced with CS + RTX 375mg/m2 x 4 (or 1g x2) then CS + AZA/MTX
- f-up 30 mo., 2006-2013
- 17 (30%) relapsed (13 GPA, 4 MPA ; 2 new, 15 relapsers), after a mean of 22 [12-60] mo.

Repeat rituximab if flaring (2)

- 16 / 99 RTX RAVE patients received repeat open label RTX for relapsing AASV
- 15/16 achieved R (1 had a limited flare before reaching remission) → 7 achieved CR (PDN=0)
- 1 had severe flare (AH-died at week 7) + 4 patients suffered limited flares, after a mean of 244 days post-second RTX
- 3 SAEs: 1 death (AH), 1 colon cancer, severe sinusitis

A66 – Guillevin L, Pagnoux C et al. FVSG, Paris, France

CPx

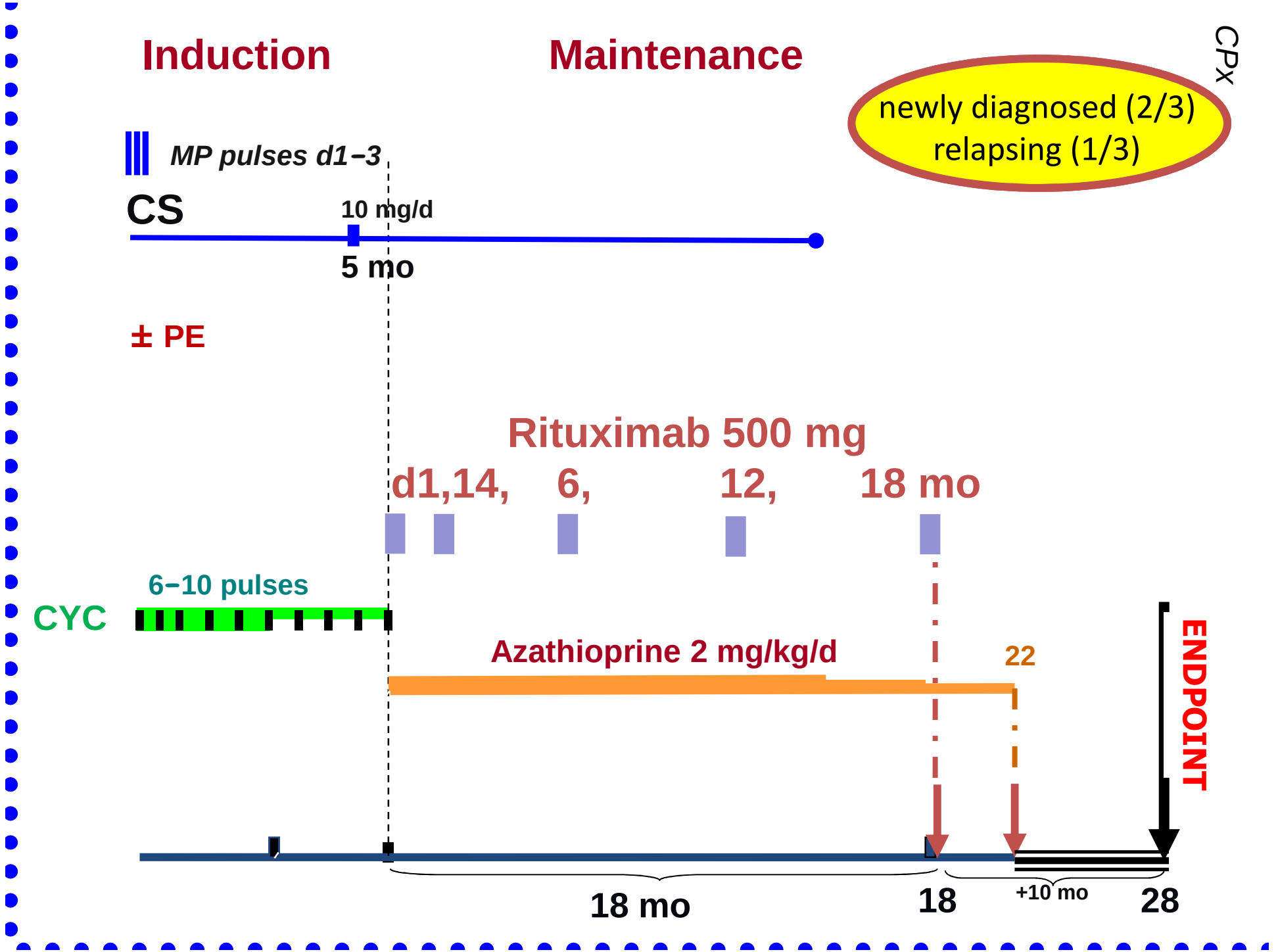
MAINRITSAN

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


Induction
Maintenance
CPx
newly diagnosed (2/3)
relapsing (1/3)
MP pulses d1–3
CS
10 mg/d
5 mo
± PE
Rituximab 500 mg
d1,14, 6, 12, 18 mo
6–10 pulses
CYC
Azathioprine 2 mg/kg/d
22
ENDPOINT
18 mo
18
+10 mo
28

Evaluation criteria

- **Primary criterion**
  - Number of major relapses 28 months after inclusion (18 mo rituximab or 22 mo azathioprine + 10 or 6 months)
- **Secondary criteria**
  - Number of side effects in each group
  - Number of minor relapses
  - Mortality in each group
  - Number of ANCA+ patients in each group

Hypothesis

- ✓ Relapse rate under azathioprine: **40%**
- ✓ Relapse rate under rituximab: **15%**

Results: demographics

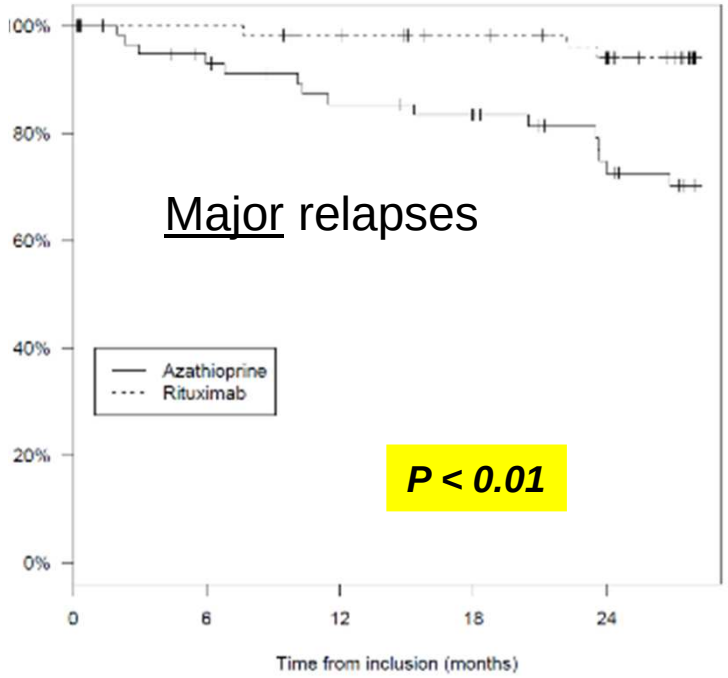
- ✓ 117 patients
- ✓ 66 men (56.4%) and 51 women (43.6%)
- ✓ 59 Azathioprine
  - ✓ 47 1st flares and 12 relapses
- ✓ 58 Rituximab
  - ✓ 46 1st flares and 12 relapses

117 patients analyzed

(66 M / 51 F; 55 ± 13 yr; 88 GPA, 24 MPA, 5 KLD; ***93 new / 24 relapsing***)

59 AZA

Relapses
17 (28.8%)



58 RTX

Relapses
3 (5.2%)

SAE 32% AZA vs 43% RTX
Deaths 2 AZA vs 0 RTX
Infections 12 AZA vs 11 RTX

Guillevin et al – FVSG, France

P221 – Pendergraft W et al. Boston, USA

CPx

Rituximab 1g / 4 months

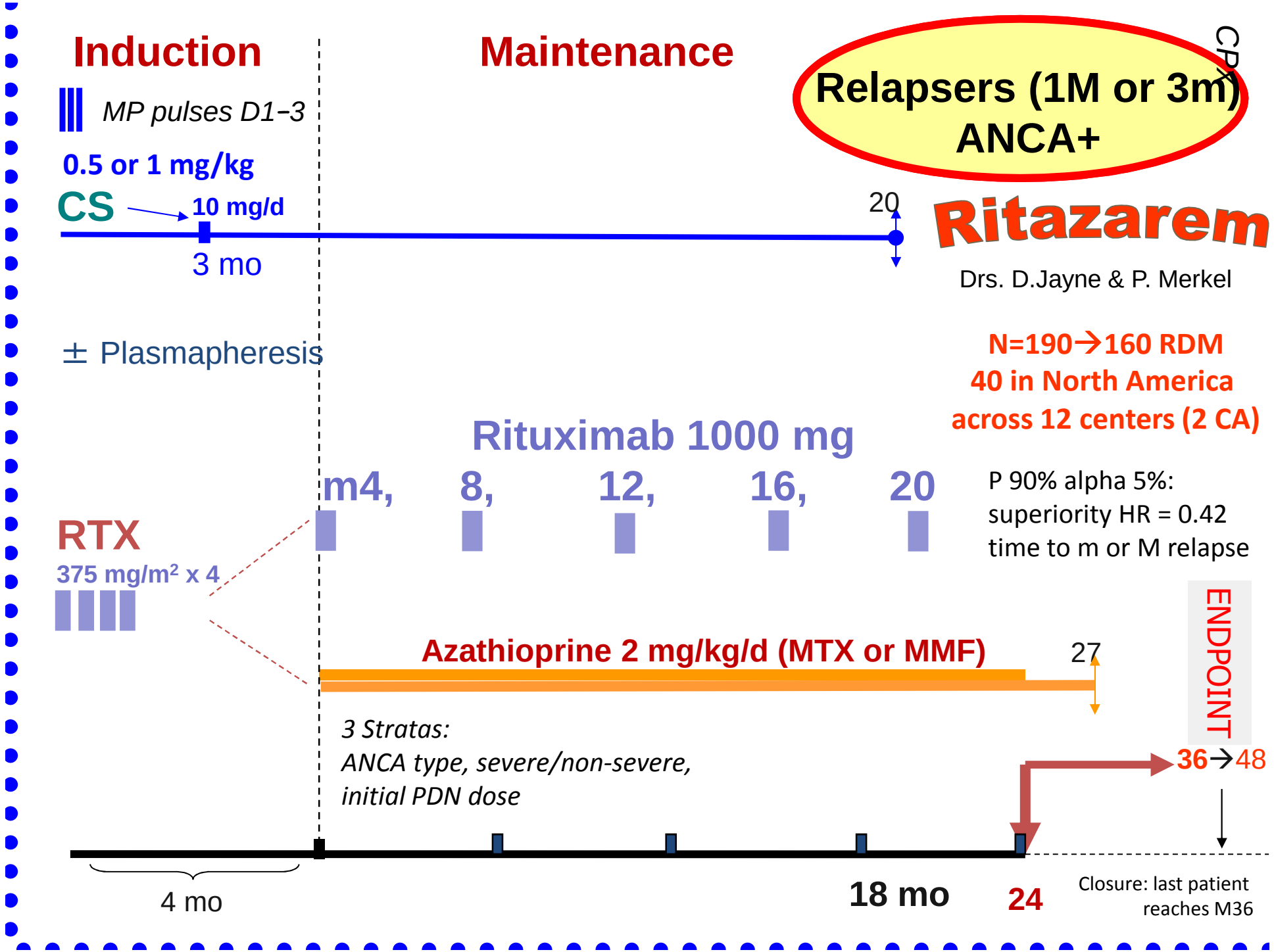
- 175 AASV, induced with CYC/RTX + CS ± PLEX then RTX 1g / 4mo. for maintenance
- med. 60 years-old, 56% F, 58% MPO, 2002-2012
- Major relapses (BVAS ≥3) in 5%
- Minor relapses in 19%
- Associated with decrease in associated CS/IS
- Easy to treat
- Survival mirrors that of USA general population

P227 – Besada E et al. Tromso, Norway

CPx

Rituximab 1g x 2 / year

- 35 GPA, induced with CS + RTX 1g x 2 then /yr
- f-up 47 mo., 2004-2011
- 9 (26%) relapses
- 13 (37%) had d/c RTX (hypogamma in 2/3)
- SAE infections in 9 (26%), mainly older, renal disease, high CYC exposure, high CS dose, drop in Ig, low CD4/CD8


Induction
Maintenance
MP pulses D1–3
0.5 or 1 mg/kg
CS
10 mg/d
3 mo
20
± Plasmapheresis
Relapsers (1M or 3m)
ANCA+
CPX
Ritazarem
Drs. D.Jayne & P. Merkel
N=190→160 RDM
40 in North America
across 12 centers (2 CA)
Rituximab 1000 mg
m4, 8, 12, 16, 20
RTX
375 mg/m² x 4
P 90% alpha 5%:
superiority HR = 0.42
time to m or M relapse
Azathioprine 2 mg/kg/d (MTX or MMF)
27
ENDPOINT
3 Stratas:
ANCA type, severe/non-severe,
initial PDN dose
36→48
4 mo
18 mo
24
Closure: last patient
reaches M36

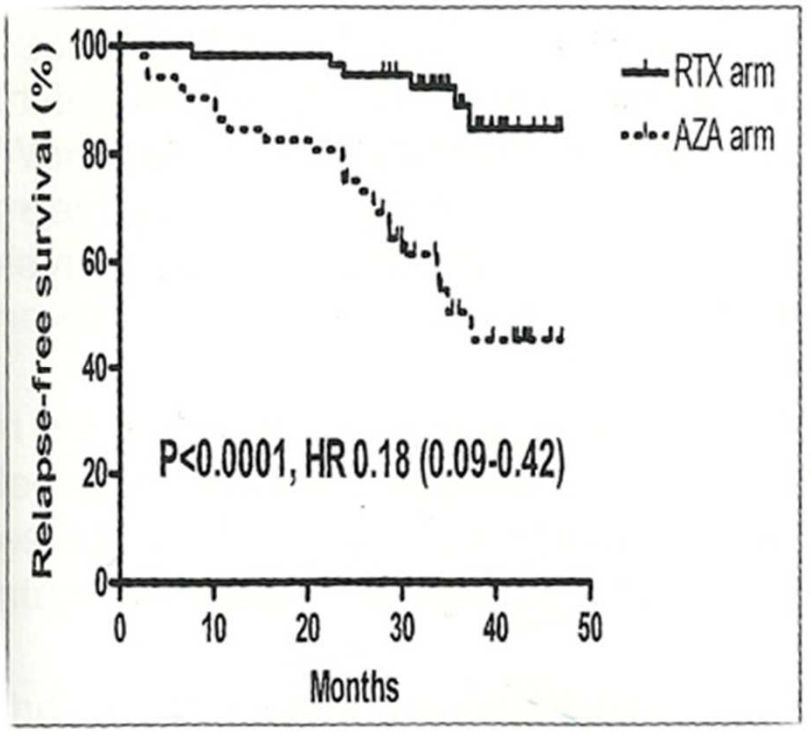
Follow-up at 34 months

Major relapses

10.7% RTX vs. 45.3% AZA (HR=0.18)

Deaths

4 AZA vs 0 RTX



P223 – Smith R et al. Cambridge, UK

CPx

Follow-up post-RTX maintenance

69 AASV induced with RTX 1g x2 then 1g / 6 mo. for 2 years then followed post-last RTX

- 90% GPA
- 13% relapsed under maintenance RTX

Median f-up post-RTX 23 mo. for 58 AASV >6 mo. f-up

- 25/58 **(43%) relapsed**
- After a median of 15.5 mo. after last RTX
- 12/54 ANCA neg at RTX end → ANCA+ → 9 (75%) relapsed after a median 1.6 mo. post ANCA+
- 15/54 ANCA+ at RTX end → 3 (20%) relapsed
- B cell returned after a median 11 mo.
- Detectable B cell in 68% and ANCA+ in 48% of the relapsers

CD5 B cells monitoring and RTX

- % of CD5 B cells is low in active AASV and normalizes in remission
- shorter time to relapse after RTX if this % is low at B cell repopulation (and low MMF dose)

Bunch et al. Clin J Am Soc Nephrol 2013

→ Validation cohort of 31 patients

→ those with <30% of CD5 B cells at repopulation post-TX relapse sooner than those with >30% of CD5 B (14±5 vs 26±12 months post-RTX)

RTX and IgG levels

- 64 patients with AASV or SLE (age 47, 42 F, 60% already had CYC). No other IS after RTX.
- Incidence of IgG<7 g/l higher post-RTX versus before, but not that of <5 or 3 g/l (=moderate)
- Decrease in IgG observed in 35% post RTX
- Increase in IgG observed in 14% post RTX!
- Not correlated with cumulative RTX dose (up to 20g)

CPx

Results of the Multicenter Randomized CORTAGE Trial

Treatment of Systemic Necrotizing Vasculitides in Patients ≥ 65 Years Old

Christian Pagnoux, Thomas Quéméneur, Jacques Ninet, Elodie Perrodeau, Elisabeth Diot, Xavier Kyndt, Benoît de Wazières, Jean-Luc Reny, Xavier Puéchal, Pierre-Yves Leberruyer, Olivier Lidove, Philippe Vanhille, Pascal Godmer, Albath-Aimé Sadiki, Boris Bienvenu, Pascal Cohen, Luc Mouthon, Philippe Ravaud, and **Loïc Guillevin for the French Vasculitis Study Group**



ARM A

Conventional treatment

According to { **diagnosis**; **FFS**

PAN/EGPA:

- **FFS = 0: CS alone**
- **FFS ≥ 1: CS + IV CYC 500 mg/m²/2–4 wk + 3 pulses then AZA/MTX 18 mo**

GPA/MPA:

- **CS + IV CYC 500 mg/m²/2–3 wk + 3 pulses then AZA/MTX/MMF 18 mo**

CPx

For a 60-kg patient

± 1–3 initial

MP pulse(s)

15 mg/kg/d

6 months

26 months

+ PE when indicated

Arm A

Jours *Days*	Durée *Duration*	Dose/jour (mg) *Dose/day (mg)*	Dose totale (mg) *Total dose (mg)*
1 à/*to* 21	3 sem/*week*	60	1260
22 à/*to* 42	3 sem/*week*	45	945
43 à/*to* 56	2 sem/*week*	30	420
57 à/*to* 84	4 sem/*week*	25	700
85 à/*to* 112	4 sem/*week*	20	560
13 à/*to* 140	4 sem/*week*	17.5	490
41 à/*to* 168	4 sem/*week*	15	420
69 à/*to* 253	12 sem/*week*	12.5	1050
54 à/*to* 308	12 sem/*week*	10	840
39 à/*to* 366	4 sem/*week*	9	252
67 à/*to* 394	4 sem/*week*	8	224
95 à/*to* 422	4 sem/*week*	7	196
43 à/*to* 470	4 sem/*week*	6	168
72 à/*to* 499	8 sem/*week*	5	280
00 à/*to* 565	8 sem/*week*	4	224
56 à/*to* 621	8 sem/*week*	3	168
12 à/*to* 667	8 sem/*week*	2	112
68 à/*to* 723	8 sem/*week*	1	56

ée Totale *al duration*		Dose totale *Total dose*
723 jours *723 days*	104 sem *104 weeks*	8305 mg
26 mois *26 months*		

Total dose
8305 mg

“Lighter” ARM B

CS: shorter duration

& lower cumulative dose

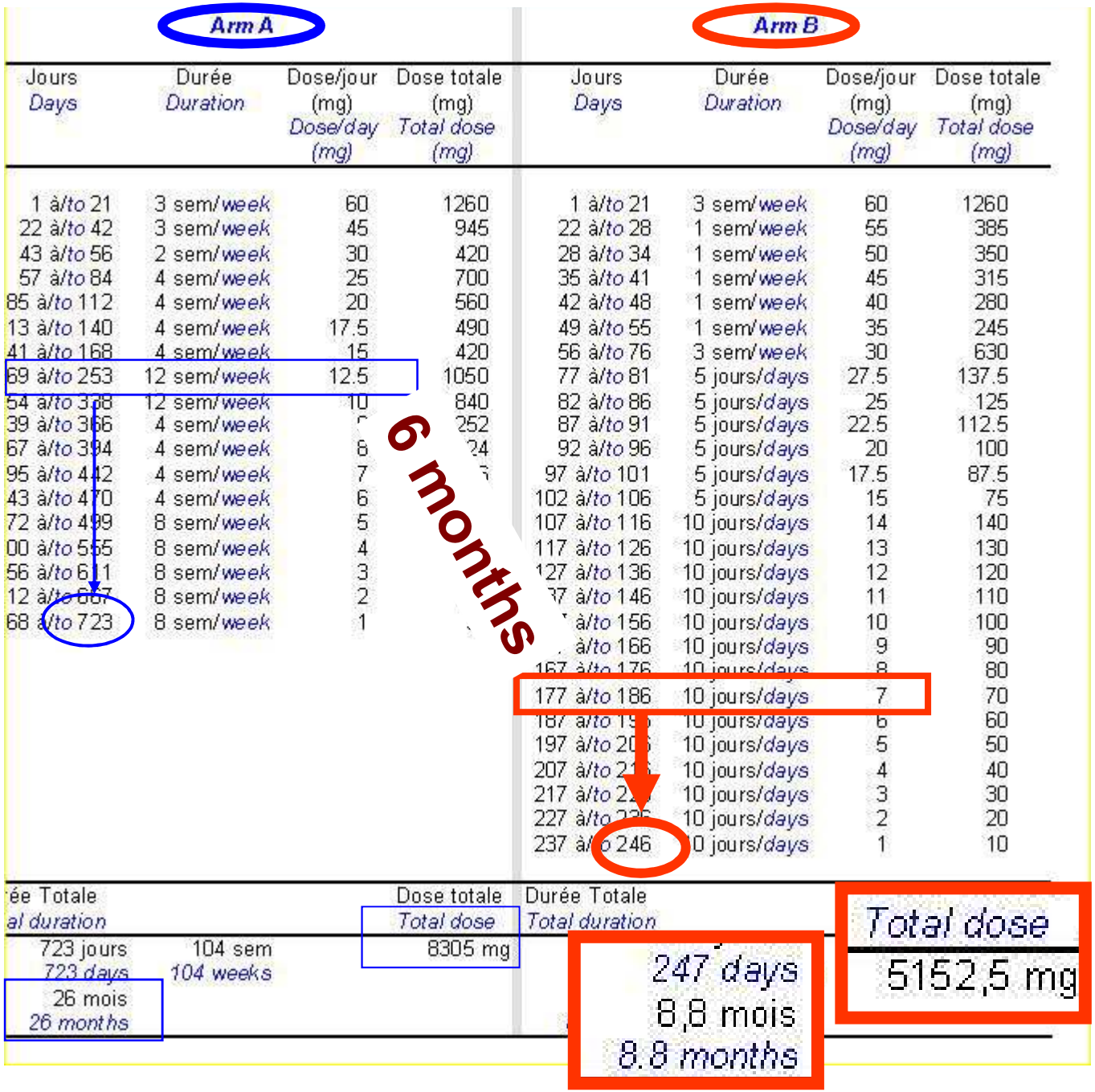
+

IV CYC for all

500 mg fixed dose d1, d15, d29,
then every 3 wk
→ remission, maximum of 6 pulses

then AZA/MTX for 18 mo

For a 60-kg patient



Arm A				Arm B			
Jours *Days*	Durée *Duration*	Dose/jour (mg) *Dose/day (mg)*	Dose totale (mg) *Total dose (mg)*	Jours *Days*	Durée *Duration*	Dose/jour (mg) *Dose/day (mg)*	Dose totale (mg) *Total dose (mg)*
1 à/*to* 21	3 sem/*week*	60	1260	1 à/*to* 21	3 sem/*week*	60	1260
22 à/*to* 42	3 sem/*week*	45	945	22 à/*to* 28	1 sem/*week*	55	385
43 à/*to* 56	2 sem/*week*	30	420	28 à/*to* 34	1 sem/*week*	50	350
57 à/*to* 84	4 sem/*week*	25	700	35 à/*to* 41	1 sem/*week*	45	315
85 à/*to* 112	4 sem/*week*	20	560	42 à/*to* 48	1 sem/*week*	40	280
13 à/*to* 140	4 sem/*week*	17.5	490	49 à/*to* 55	1 sem/*week*	35	245
41 à/*to* 168	4 sem/*week*	15	420	56 à/*to* 76	3 sem/*week*	30	630
69 à/*to* 253	12 sem/*week*	12.5	1050	77 à/*to* 81	5 jours/*days*	27.5	137.5
54 à/*to* 3?8	12 sem/*week*	10	840	82 à/*to* 86	5 jours/*days*	25	125
39 à/*to* 366	4 sem/*week*	?	252	87 à/*to* 91	5 jours/*days*	22.5	112.5
67 à/*to* 394	4 sem/*week*	8	?4	92 à/*to* 96	5 jours/*days*	20	100
95 à/*to* 442	4 sem/*week*	7	?	97 à/*to* 101	5 jours/*days*	17.5	87.5
43 à/*to* 470	4 sem/*week*	6		102 à/*to* 106	5 jours/*days*	15	75
72 à/*to* 499	8 sem/*week*	5		107 à/*to* 116	10 jours/*days*	14	140
00 à/*to* 565	8 sem/*week*	4		117 à/*to* 126	10 jours/*days*	13	130
56 à/*to* 611	8 sem/*week*	3		127 à/*to* 136	10 jours/*days*	12	120
12 à/*to* 667	8 sem/*week*	2		?7 à/*to* 146	10 jours/*days*	11	110
68 à/*to* 723	8 sem/*week*	1		à/*to* 156	10 jours/*days*	10	100
				à/*to* 166	10 jours/*days*	9	90
				167 à/*to* 176	10 jours/*days*	8	80
				177 à/*to* 186	10 jours/*days*	7	70
				187 à/*to* 19?	10 jours/*days*	6	60
				197 à/*to* 20?	10 jours/*days*	5	50
				207 à/*to* 21?	10 jours/*days*	4	40
				217 à/*to* 22?	10 jours/*days*	3	30
				227 à/*to* 23?	10 jours/*days*	2	20
				237 à/*to* 246	10 jours/*days*	1	10

6 months

ée Totale *al duration*		Dose totale *Total dose*	Durée Totale *Total duration*
723 jours *723 days*	104 sem *104 weeks*	8305 mg	247 days
26 mois *26 months*			8,8 mois *8.8 months*

Total dose 5152,5 mg

+ 1–3 initial MP pulse(s) 15 mg/kg/d

+ PE when indicated

Statistical hypothesis

- Reduction in treatment-related morbidity by 30% at 3 years

(70% → 40%)

Mouthon et al. Medicine 2002;81:27–40

- 1º criteria = time to 1st Severe Adverse Event

Alpha 5%, Power 80%

→ 44 patients per arm

→ 108 patients to enroll

Results (1)

Characteristic at diagnosis	Arm A Conventional N = 51	Arm B Lighter N = 53
Age, mean ± SD, yr	**75.3 ± 6.4**	**75.1 ± 6.2**
maximum	*91.7*	*90.3*
Male, n (%)	32 (63)	27 (51)
Diagnosis (n, [n with FFS = 0])	**[12]**	**[13]**
MPA	**23 [3]**	**21 [6]**
GPA	**15**	**22**
EGPA	**6 [5]**	**7 [4]**
PAN	**7 [4]**	**3 [3]**
ANCA positivity, n (%)	40 (80)	48 (92)

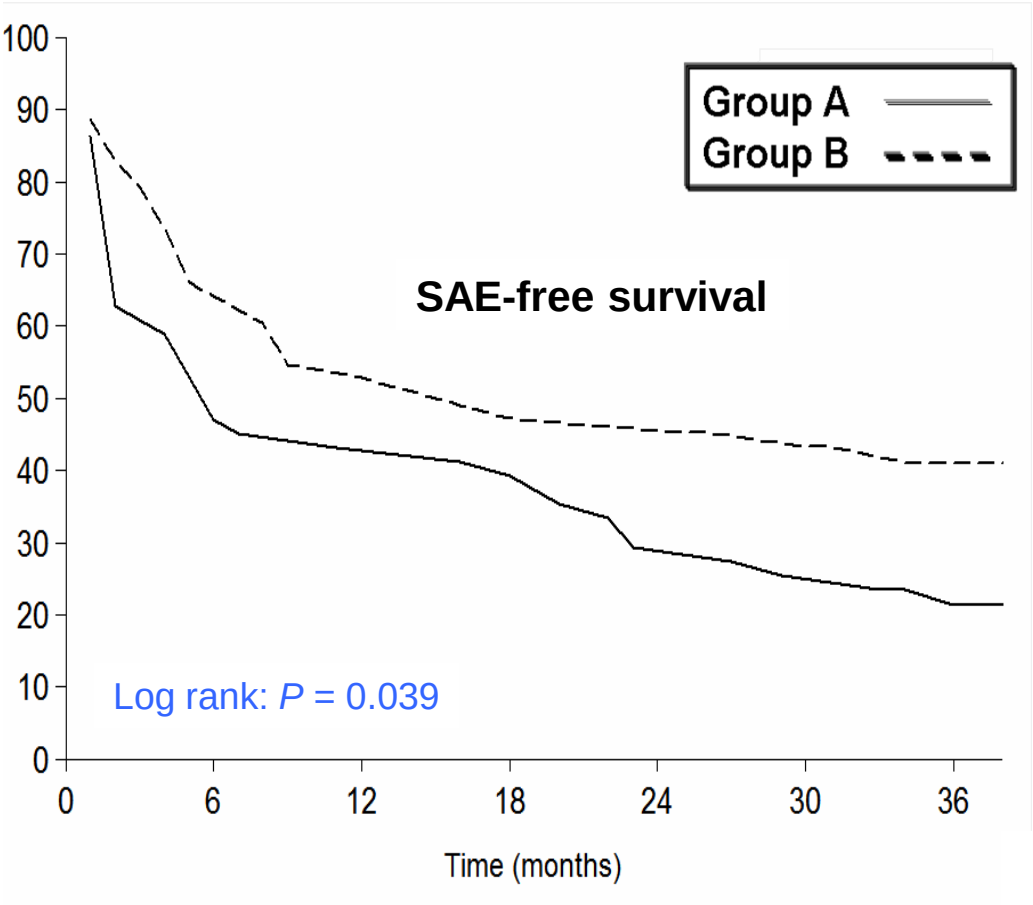
Results (2)

CPx

Characteristic at diagnosis	Arm A Conventional N = 51	Arm B Lighter N = 53
Renal involvement	**39 (76)**	**32 (60)**
Creatinine level (µmol/L) ± SD (GFR)	***260 ± 224 (34)***	***213 ± 170 (41)***
Creatinine >140 µmol/L (n)	*30 (65)*	*26 (52)*
Proteinuria >1 g/24 h (n)	*17 (37)*	*13 (30)*
Lung manifestations	32 (63)	35 (66)
Alveolar hemorrhage	*11 (22)*	*9 (17)*
GI tract involvement	**10 (20)**	**12 (23)**
Cardiomyopathy	**3 (6)**	**0**
Peripheral nervous system involvement	14 (27)	14 (26)
CNS involvement	**0**	**4 (8)**

Results (3): primary endpoint

CPx



≥ 1 SAE at 3 years

Arm A = 40 (78.4%) vs

Arm B = 32 (60.4%)

(*P* = 0.047)

Average SAE / patient with SAE

2.75 Arm A vs

2.28 Arm B

SAE-free survival

HR arm B/A = 0.61 [0.38–0.98]

	SAE-free survival
	3-yr survival [95% CI]
Group A, n = 51	**21.4% [11.4–33.5]**
Group B, n = 53	**41.1% [27.8–54.0]**

Results (4): primary endpoint

CPx

183 SAE in 72 patients

SAE, n / n of patients	Arm A	Arm B
Infections	**30 / 17**	**13 / 10**
Lung	*10 / 9*	*4 / 3*
Zona	*5 / 5*	*0*
Cardiovascular	**12 / 10**	**3 / 3**
Cytopenia(s)	**10 / 8**	**5 / 3**
Fractures	**4 / 4**	**8 / 6**
Miscellaneous	**46 / 28**	**35 / 21**
Deaths	**12**	**9**
Total	**110 / 40**	**73 / 32**

ANCA WS #228 (poster) – Salama et al. London, UK

CPx

Empirically derived CYC dosing normogram

Pulsed CYC dose reductions for renal function and age		
	Creatinine (μmol/L)	
Age (years)	**< 300**	**300-500**
<60	**15 mg/kg/pulse**	**12.5 mg/kg/pulse**
60-70	**12.5 mg/kg/pulse**	**10 mg/kg/pulse**
>70	**10 mg/kg/pulse**	**7.5 mg/kg/pulse**

- AEs in EUVAS trials to model the optimal dose of CYC for age and kidney (eGFR)
- Best-fit line ($Y=Bmax \times X / Kd + X$)
- Normogram used to treat 22 patients

ANCA WS #228 (poster) – Salama et al. London, UK

CPx

Empirically derived CYC dosing normogram

- Age 57.3 +/- 3 yrs
- eGFR 32.2 +/- 3.8 ml/min
- Mean dose 817mg/pulse
- Pulse dose 73mg less on average than table
- 73% received lower dose
- Same remission probability at 1 year
- Lower/same AE scores (not powered)

ACR 2012 + ANCA WS poster 209 – Langford et al. VCRC

CPX

An Open-Label Trial of Abatacept in Mild Relapsing GPA

Mild relapsing: confined to ≥1 sites, with Rx being the reinstitution or increase in CS to ≤30mg OD and/or an increase or addition of a 2nd immunosuppressant but not CYC (no AH, no renal)

CTLA4-Ig, abatacept
10 mg/kg IV D1, 14, 28 then monthly
On top of ongoing Rx with CS (15), AZA (3), MTX (7), MMF (4)

→ 20 patients

Variable	Value at Study Entry	
Age (range)	45 years (17-73)	
Female/Male	9/11	
PR3-cANCA	80%	
MPO-pANCA	10%	
GPA duration mean (range)	100 months (5-326)	
BVAS/WG mean (range)	3.1 (1-6)	
VDI mean (range)	2.5 (0-7)	
Organ Involvement	Before Study Entry (Ever)	Active Disease at Study Entry
Constitutional	85%	30%
ENT	100%	90%
Musculoskeletal	75%	50%
Cutaneous	60%	40%
Mucous membranes	25%	5%
Lung	70%	30%
Kidney	40%	-
Eye	30%	-
Nerve	20%	-

Langford C et al – Cleveland Clinic Foundation / VCRC

ACR 2012 + ANCA WS poster 209 – Langford et al. VCRC

CPX

An Open-Label Trial of Abatacept in Mild Relapsing GPA

- **18 (90%) had disease improvement**
- **16 (80%) achieved remission with BVAS/WG=0 (median duration of remission before study closure was 12 months [4-21])**
- **11/15 on PDN were able to stop PDN**

- **3 relapses (19% of those who achieved remission), at a median of 8.3 months**
- **6 (30%) dropped out because active disease, not severe (3 relapsers + 3 failures)**

- **9 SAEs in 7 patients, including 7 infections, none severe**

→ Phase III STUDY IN MILD GPA RELAPSE "ABROGATE"

ANCA WS – A68 (oral) – De Joode AAE et al. Netherlands

CPx

RCT extended vs standard maintenance AZA in new antiPR3+ AASV

- RCT in newly-diagnosed PR3+ AASV, ANCA+ at switch (= at remission after CYC)
- N=126 from 12 centers, 2003-2011
- Standard AZA 2mg/kg/d for 1 yr, then tapered by 25mg every month
- Extended AZA for 4 yrs then tapered down
- F-up 48 mo (11-53)
- No difference in ANCA-neg (not randomized) and ANCA+ at switch in relapse-free survival

ANCA WS – A68 (oral) – De Joode AAE et al. Netherlands

CPx

RCT extended vs standard maintenance AZA in new antiPR3+ AASV

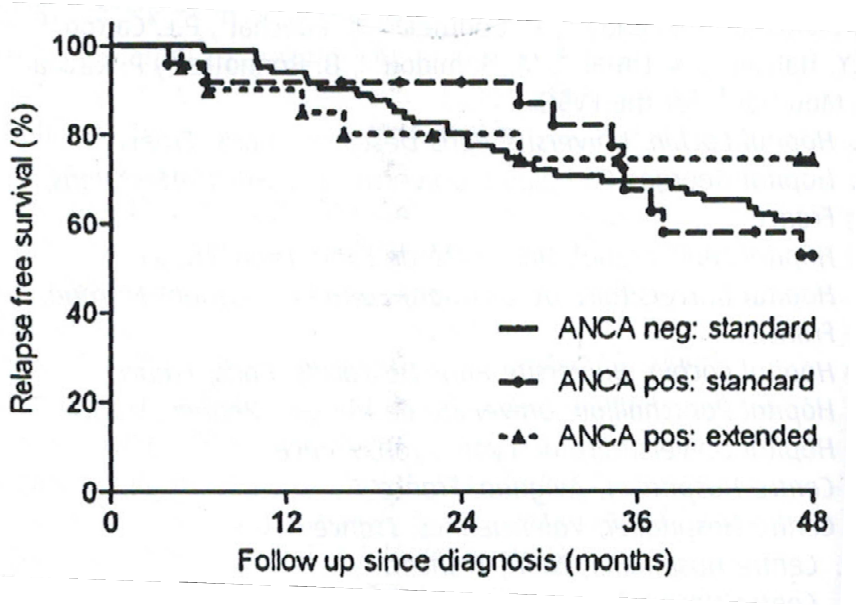
- 44 randomized at remission (ANCA+)

→ no difference between arms (p=0.36)

At 4 yrs

relapse-free survival was:

- 60% in ANCA-neg at switch
- 52% in ANCA+ standard arm
- 74% in ANCA+ extended arm



→ ***Limited power***

→ ***Wait for the EUVAS REMAIN trial results… next year?***

Late cardiovascular events



Morbidity in AASV

- Infection accounts for most of the deaths in the 1st year
- Malignancies and CV disease beyond 1 year
- Risk factors for CV disease include
  - antiMPO ANCA+
  - Hypertension
  - Renal disease
  - Traditional risk factors
  - Endothelial dysfunction (demonstrated in AASV)
  - Likely (prolonged) corticosteroid treatment

CanVasc addendum:

→ + chronic inflammation?

→ Role for immunosuppressants such as MTX to limit this?

→ FVSG-STATVAS trial on statins started (rosuva → IMT)

P157 – Yuste et al. Cambridge, UK

CPx

CV outcomes and predictors in AASV

- Retrospective single center review of 307 AASV (173 GPA, 47% M, age 53, f-up 6 yrs)

→ 51 CVE in 42 (13.6%) patients (acute coronary sd, new angina, symptomatic peripheral vasc disease, stroke or TIA) with 28 (9%) deaths

→ 28% of these events occurred >1 year post diagnosis

- Predictors of CVE:
  - maintenance prednisone dose, HR = 169!!
  - Cumulative CYC dose, HR = 16
  - Hb level at last follow up, HR = 0.6 (low level = worse)
  - PR3 levels at onset, HR = 0.97 (low level = worse)

CPx, ND

Other





& miscellaneous

Large vessel vasculitides



Anti-ferritin Ab and GCA

- 122 subjects with suspected GCA + 40 healthy controls
- Sera tested for Ig anti-19-45 FTH1 in ELISA

Group	TAB+ GCA	TAB- GCA	Not GCA	Healthy
Anti-FTH Ab With threshold at 2 DS	72.5%	41.3%	31.9%	2.5%
Anti-FTH Ab With threshold at 3 DS	60%	34.5%	21.2%	0%

- At 2 DS: NPV 57% and PPV 72%
- Titer correlated with CRP (but not visual or aortic pb)

→ Good but not as much as in the study from Baerlecken *et al.*
(who found 92% in TAB+ and 1% in healthy controls)

P96 – Kermani T et al. Mayo, US

CPx

GCA with upper extremity large vessel disease

- 120 patients with UE LV-GCA (1999-2008)
- 80% F, age 68 yrs (all >50), TAB+ in 52%
- Abnormal pulse 60%, UE claudication 52%, bruits 38%, Raynaud's 11%; cranial GCA signs 41%, vision pb 4%
- Dx made by angio 29%, CTA 49%, MRA 20%, PET 1%, US 1%
- S./clav stenosis 56%, throacic aorta disease 56%
- Patients with dilated s/clav more often had thoracic aortic aneurysm
- F-up 3.7 yr (for 102 pts): relapse 76%, IS needed in 50%, revascularisation 13%, resolution of vessel changes 29% (unchanged or worse 16%)

Risk of aortic aneursym in GCA

- Parallele cohort study on 6,999 GCA vs 6:1 matched non-GCA population (GP pratice, age, sex)
- Competing risk model on AA, competing with death, after ajdustment for other CV risk factors
- Sub HR for AA= 1.92 (95% CI, 1.52-2.41) in GCA patients
- Predictors of AA: smoker (3.37), CV disease (1.98), diabetes (0.32)
- In GCA cohort alone: male (2.10), smoking (3.79), diabetes (0.19)

P106 – Hetland H et al. Norway

CPx

Leflunomide for GCA (and PMR?)

- 20 consecutive GCA (10) or PMR (10) patients from 1 center
- 1 discontinued LEF before M3 because of mild AE
- In GCA:
  - CRP → decreased by 14 mg/dl at month 3 (initial 17mg/dl)
  - PDN daily dose reduced by 4mg at month 3
- In PMR:
  - CRP → NO decrease at month 3 (initial 22mg/dl)
  - PDN daily dose reduced by 4mg at month 3

→ Think of LEF for GCA, asides MTX (& AZA)? RCT needed?

Tocilizumab for GCA: long-term data

- Retrospective single center study with f-up 37 mo [17-70]
- 12 patients with relapsing GCA (8 failed to other IS, 4 with contra-indication to steroids)
- IV TCZ 4mg/kg for 3 and 8mg/kg for 9, every mo. for 16 mo. [6-27]
- Before TCZ = 2.7 flares per year, on average
- During TCZ = 0.6 flare per year, on average (5 flared after a mean of 11 mo. [2-25])
- One relapsed after the cessation of TCZ, 3 are off CS
- 5 leukopenia, 8 transaminitis, 1 pneumonia

ITAS.A for TAK

- ITAS 2010 developed to assess disease activity
- ITAS.A now includes 0-3 scores for ESR and CRP separately from the clinical data
- 178 patients tested with this score at d0, M3 and M6, in 2 sites
- ITAS.A more often showed persistent disease activity despite a good clinical response on ITAS 2010

ITAS2010 – IndianTakayasu's Arteritis Activity Score

Tick Box only if abnormality is present and new or worse within the past 3/12.

Tick box only if abnormality is ascribed to current, active vasculitis.

Name:
Unit Number: Visit Date:
Investigator:

CPX

PRESENT

1. SYSTEMIC
None ☐
Malaise/Wt. Loss>2Kg ○
Myalgia/Arthralgia/Arthritis. ○
Headache ○

2. ABDOMEN
None ☐
Severe Abdominal Pain ○

3. Genitourinary System
None ☐
Abortions ○

PRESENT

4. RENAL
None ☐

Hypertension (Diastole >90)
"" Systolic >140 ◎

5. Nervous System
None ☐

Stroke ○
Seizures (not hypertensive) ◎
Syncope ○
Vertigo/dizzyness ○

6. CARDIOVASCULAR SYSTEM

none ☐

Bruits (see 6a)
Pulse Inequality (See 6 b) ◎
New Loss of Pulses (See 6c) ◎
Claudication (See 6d) ◎
Carotidodynia ◎

Aortic Incompetence ○
Myocardial Infarct/Angina ○
Cardiomyopathy/cardiac failure ○

6a. Bruits

	R	L
Carotid	○	○
Subclavian	○	○
Renal	○	○

6b. Pulse and BP Inequality
Present ○

6c. Pulse Loss

Carotid	○	○
Subclavian	○	○
Brachial	○	○
Radial	○	○
Femoral	○	○
Popliteal	○	○
Posterior Tibial	○	○
Dorsalis Pedis	○	○

6d. Claudication
Arm ○
Leg ○

Other Vasculitis items:

ESR **CRP**

Item scores ☐ **= 0** ○ **= 1** ◎ **= 2**

Scoring ITAS2010 : Add all scores in CVS , if both boxed circle and circle are ticked, add both (see glossary) **.**

Scoring ITAS.A including acute phase response

- for ESR, score ITAS plus: 0 for <20; 1 for ESR 21-39; 2 for ESR 40- 59; and 3 for >60 mm ESR /hr
- for CRP score ITAS plus: 0 for CRP <5; 1 for CRP 6-10; 2 for CRP 11-20; and 3 for >20 mg/dl

Physician Global Assessment

Active / Grumbling or persistent / Inactive

New Imaging Y / N? If Y - specify _____

ITAS2010 form. M.R Sivakumar, R.Misra, D.Danda & P.A.Bacon - Mar'10
ITAS.A form – ibid Oct 2012

P109 – Comarmond C et al. Paris

CPx

Asymptomatic myocardial disease in TAK by MRI

- Retrospective single center study
- 27 TAK, 80 age- and sex-matched controls with no known CV disease
- Late gado-enhancement in 8 (22.2%) TAK, suggestive of myocardial ischemia in 5 of them (18.5%)
- Similar Framingham between TAK and matched controls but TAK had an OR=4 of myocardial ischemia
- Trends for association with older age, renovascular features/HTN, male, aneurysmal dilation, Numano type V

T. Youngstein, J Mason Abstract A62

ND

Takayasu arteritis-outcome study in a UK cohort

- N 98 mean age at diagnosis 31.5 yrs.
- Mean delay in diagnosis 3 years
- FDG-CT-PET proved most useful for diagnosis
- Treatment included Methylprednisolone +Azathioprine (37%)/MTX (43%)/MMF (7%); Cyclophosphamide (10%)
- Annual MRA and US monitored outcome

T. Youngstein, J Mason Abstract A62

ND

Takayasu arteritis-outcome study in a UK cohort

- Stable disease 81.5%
- Progression 9.8%;
- Improvement in lesions 8.7%

A63 – Youngstein T et al. UK

GPX ND

Biologics for refractory TAKAYASU

- Retrospective single center study
- 9/98 TAK patients received biologics (5 failed to CYC, 3 received ≥2 biologics, 8 remain on biologics)
- Mean duration of biologics Rx, 2.6 yrs (1 had SAE)
- 8 received antiTNF-alpha: one had new stenoses → switched and responded to antiIL6-R blockade
- 3 received antiIL6-R blockade (2 as first line biologics)

- Significant fall in CRP and ITAS, and decrease in prednisone dose

Tocilizumab for refractory TAKAYASU (2)

- 10 patients
- Retrospective single center study (5 pts) + literature (9 pts)
- aged 24.5 [13-23], TAK duration 25 mo, ITAS 4.5 [0-13]
- TCZ every 4 weeks for 6 cures [5-6]
- Clinical response with ITAS 0 and decreased CRP in 100% by 4 infusions, decrease in PDN 24 → 5mg OD
- 60% had sustained responses with stable imaging
- 3 had active disease at last infusion + 1 flared 1 month after his last infusion
- AE: 1 skin rash, 1 transaminitis, 1 UTI, 1 URTI

Tocilizumab for refractory TAKAYASU (3)

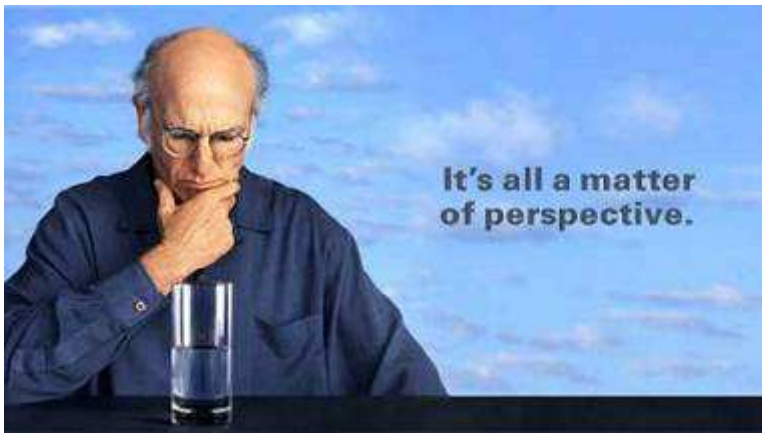
- 14 patients
- Retrospective single center study (5 pts) + literature (9 pts)
- aged 40, 12 F, 12 under CS, 9 MTX, 6 AZA, 5 IFL
- TCZ: 8mg/kg every 4 weeks with 6 cures [5-8]
- F/up 9 mo [7-14]:
  - Sustained response: 100% at M3; 82% at M6; 67% at last visit
  - PET-FDG positive in 9/9 before → positive at M6 in 2/9
  - Prednisone: 7 CS-dependent before → none at M12
  - **1 stopped TCZ because of a relapse**

P108 – Gunnarson R et al. Oslo

CPx

TAK relapse UNDER tocilizumab

- One single case
- F aged 14 at TAK diagnosis, refractory to all IS… dependent to prednisone >12.5mg OD
- IV TCZ 8mg/kg/mo.
- At 4th infusion, relapse, carotidynia, CRP 124, abnormal PET scan (widespread disease)
- Improved after IV M-prednisolone pulses…



Small vessel vasculitides



Anti-LAMP2: why the controversy?

- LAMP2 is an heavily glycosylated membrane protein, trafficking between membrane and lysosomes
- Role in autophagy, cholesterol transport and Ag presentation
- On (glomerular) endothelial cells, neutrophils and monocytes +
- Most common epitopes recognized by antiLAMP2 Abs are P41-49 (100% homologous to a FimH sequence from fimbriated bacteria such as *E. coli*) and P331-341
- No standardized test yet → IIF assay developed, WB, ELISA

Anti-LAMP2: why the controversy?

- antiLAMP2 IgG in 78-93% of AASV patients with active untreated GN
- BUT only 7% of AASV patients in remission (0 in healthy)
- antiLAMP2 become negative within 1 month of starting treatment and remains so in the absence of relapse
- In relapsing patients: 57-81% are again antiLAMP2+

→ INTRICATE study to further determine the value of antiLAMP2

- Animal model
- Infection and antiLAMP2: perhaps but only transient

Thyroid diseases and AASV

- Retrospective single center study
- Thyroid disease found in 44/181 (24.3%) AASV patients versus 7.4% in age- and sex-matched controls
- 79.5% of them had HYPO; 11.4% had HYPER; 9.1% had transient abnormal tests
- More female 72.7% (in AASV and 67% controls)
- More often antiMPO+ AASV (57% of those with thyroid were antiMPO+ vs. 40% of those without thyroid problem)
- AntiTPO Abs + in 5/19 (26%) AASV tested (vs 0/3 controls)

F. Rees et al. Poster P59, UK

ND

Long term follow up of 96 GPA patients at a single centre

	Pre 2003	2003-2012
n	52	44
Follow up (yrs)	14.1	3.9
n receiving Cyc	49	39
Mean life time Cyc (g)	37.1	10.6
Mean n of IV Cyc cycles	1.5	1.1
% relapses at 2 yrs*	48%	58%
Neutropenia<2 (%)	44	7
Non-severe infection	21	18
Severe infection (hospitalization) %	4	11

F. Rees et al. Poster P59, UK

ND

Long term follow up of 96 GPA patients at a single centre

Disease complications	Pre 2003	2003-2012
Death (%)	25	7
Dialysis (%)	15	0
Renal transplant (%)	6	0
Subglottic stenosis (%)	17	14

P120 – Schinke S et al. Lubeck

CPx

German MPA cohort (n=123)

- Retrospective single center study with f-up 22 mo [0-180]
- 102 generalized disease, 14 severe at diagnosis (1990-2012)
- CS+CYC for induction 83%
- CR in 80%, refractory 14%
- Relapses in 41% of the patients
- 42% retained ESRD and 30% PNS disease symptoms
- No difference in term of CR or survival between those treated before 2002 and who had received mean CY 16g vs. those treated after and who had received mean CY 8g

  → one can limit the exposure to CY

- Only 1 death

P64 – Nelson D et et al. Mayo USA

CPx

PET-CT in GPA

- Single center retrospective study on F18-DG-PET
- 10 GPA (2005-2012)
- 8/10 had uptake in lungs
- 4/10 had uptake in sinuses
- 8/10 had uptake in vessels
- Uptake level is similar to that observed in malignancies
- 2 had follow-up PET, which showed decreased uptake after Rx

Kidneys in AAV: What to learn from biopsies?

- Berden classification:
  - Focal 50% normal glomeruli
  - Crescentic ≥ 50% glomeruli
  - Mixed
  - Sclerotic ≥ 50% glomeruli glbally sclerotic

Association with renal and patient survival at 1 and 5 years

C Levi et al. Abstract A37

ND

Computerized Interstitial Fibrosis quantification is the most powerful histological predictor of renal outcome in AAV

- N=65 AAV; biopsy proven renal involvement
- Computerized interstitial fibrosis (IF) analyzed with specific software
- Serum creatinine 433+/-265 mmol/l
- Anti-MPO 65%
- Focal 405; crescentic 30%; mixed 25%; sclerotic 5%

C Levi et al. Abstract A37

Computerized Interstitial Fibrosis quantification is the most powerful histological predictor of renal outcome in AAV

- There was no correlation between IF score and glomerular classification
- Sclerotic GN was associated with poorer outcome
- No significant difference among other categories
- IF score was significantly associated with renal prognosis $p<0.01$

E. Muso et al. Abstract A38

ND

The necessity of the addition of interstitial pathological parameters on the glomerular histological classification to predict long-term outcome in MPO-AASV RPGN cohort in Japan

- N 87 with AAV GN
- Berden categories + interstitial fibrosis (IF) + tubular atrophy (TA) scored
- IF and TA categorized into 3 grades: <50%, 50-74%, ≥75%
- eGFR and renal survival analyzed at onset, 6 months, 1 and 5 years after renal bipsy

E. Muso et al. Abstract A38

ND

The necessity of the addition of interstitial pathological parameters on the glomerular histological classification to predict long-term outcome in MPO-AASV RPGN cohort in Japan

- MPA 100%
- In mixed and focal groups: those with high IF had poorer 5 year outcome
- Sclerotic group had severe IF with very low eGFR at entry

Conclusion: evaluation based only on glomerular lesions not enough for long term renal prognosis in MPA in Japan

Proteinuria and hematuria in AASV

- Single center retrospective study
- 28 AASV with GN, age 68 at Dx, MPO+ in 17, P3+ in 12 (1dble +)
- Creatinine 240 micmol/l at Dx
- Time to resolution of hematuria 104 days
- Time to resolution proteinuria 238 days
- Faster in PR3+ than MPO+ (for both)
- No correlated to age, each other, initial creatinine
- 0/9 pts. with no hematuria at M3 developed ESRD
- 5/18 pts. with hematuria at M3 developed ESRD (NS)

A47 – Lee T et al. UNC, US

CPx

Prognosis of severe AASV-GN

- Single center retrospective study
- 155 AASV with eGFR<15
- Age 67 yr, 56% M, 88% white, 56% MPO+, eGFR 7 [5-9]
- 87% received CYC, 28% PLEX
- Renal and patient survival at 1 year = 74% and 81%
- Renal and patient survival at 5 yrs = 68% and 67%
- Treatment response at M4 + CYC use were predictive of long-term renal / patient survival
- Frequency of response beyond month 4: only 3.6%

→ Treat patients with very low eGFR! *(perhaps useless to continue if not respsonsive at month 4)*

Renal transplantation in AASV

- Around 20% of AASV patients develop ESRD at long term
- >1/3 of them receive renal transplant (= 1 to 3% of all transplant recipients) – most are “too old” to receive
- Patient survival similar to non-AASV patients: 86-93% at 5 years, not influence by ANCA or disease types
- Renal survival similar to non-AASV patients: 80-97% at 10 years, not influence by ANCA or disease types (nor clearly by ANCA status at the time of transplant)
- Better (?) if in remission >12 months (perhaps before)
- AASV relapse risk lower than under dialysis, between 0.01 to 0.07 per year (total <17% at 3 years)

Renal transplantation in AASV - DUTRAVAS

- Dutch study on 113 AASV patients with 1st renal graft
- From 6 centers
- At 5 years:
  - 19 grafts lost due to disease relapse (4), infarction (4), acute rejection (4), interstitial fibrosis and tubular atrophy (3), sepsis (2), acute ciclosporin toxicity (1), Post-transplant lymphoproliferative disorder (1)
  - Renal-graft survival = 83% (excluding 3 immediate infarctions)
  - 14 patients had vasculitis relapse (intra+ extra-renal 7, renal 4, extra-renal 3) → 4/11 with renal disease led to graft loss
  - ASV relapse rate = 3.6% per year within 5 years
  - Renal disease recurrence rate = 2.8% per year within 5 years

Maintenance Rx in children with GPA

- Single center retrospective study, 01/2000-2013
- 32 children, 21 F, age 13.7 yrs, 26 cANCA, 4 pANCA
- 8 limited GPA: CS + MTX 7, AZA 1
- 24 systemic GPA: CS + IV CYC (mean 7 pulses) then MTX 7, AZA 14, MMF 3
- Relapses in 14 (43%) children
  - half of them within year 1 (22% had a relapse at M12)
  - 2/8 (25%) with limited disease, under MTX
  - 11/24 (50%) with systemic GPA

    under 4/7 MTX, 5/14 AZA, 2/3 MMF

P165 – Hruskova et al, Prague + Cambridge, UK

CPx

Long-term outcome of severe AH

- Retrospective case review
- 53 pts. (in a 824 AASV cohort), 20 F, age 59, 70% GPA
- AH first manifestation of AASV in 87%
- Mechanical ventilation needed in 68%
- Renal disease in 98%, requiring dialysis in 53%
- 76% received PLEX → at M3, 83% alive
- F-up 49 months → 59% alive, 45% dialysis-free
- Higher mortality in those >65 yrs and/or requiring dialysis

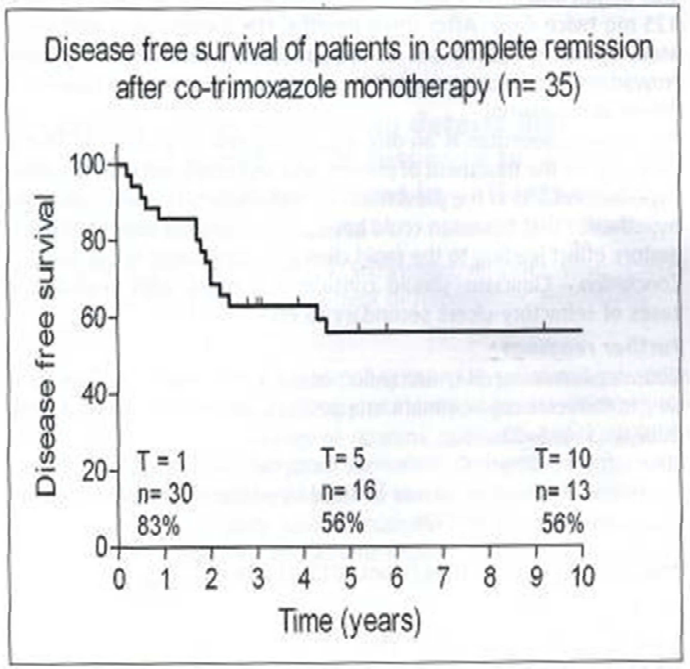
SGS and bronchial stenoses (BS) in GPA

- Retrospective case review from 2 French centers
- 19 GPA patients (7 BS + 12 SGS), 13 F, age at onset 29 yrs
- 15 antiPR3+, 2 antiMPO+, 2 ANCA negative
- 11 biopsied, but all Bx negative
- "Local outcomes" independent of GPA course
- SGS: relapses ++ [1-8 times]
- Good but transient efficacy of local treatments
- CYC never effective on SGS but prevented BS (57% only)
- RTX prevented relapses in the 3 patients treated with it
- 1 died of SGS complication; none required tracheostomy

P212 – Tuin J. et al. Groningen, NL

CTX alone for localized GPA

- Retrospective report of the center's 49 localized GPA treated with CTX alone 1989-2012
- 20 M, age 49, 40 new + 9 relapsing, 40 ANCA+
- 35 achieved remission + 10 progressed + 4 stopped/AEs
- 20 did not relapse (DFS 146 mo.)
- 12 had localized relapses, 3 had systemic relapses after DFS 22 mo.
- S. aureus carriers (n=19) had shorter DFS



P206 – Bruchfeld et al. Sweden (+UK + CCX)

CPx

C5aR-inhib. CCX168 (CLEAR)

- Phase 2 safety study in 40 centers
- GPA, MPA, KLD, all ANCA+ and renal disease
- 1:2, blinded, placebo:oral 30mg CCX68 BID for 3 mo then 3 mo f/up

+ CYC + CS 20mg OD in CCX arm / 60mg OD for placebo (step 1)

+ CYC + NO CS in CCX arm / 60mg OD for placebo (step 2)

→ 12 patients per step

→ Step 1 completed (6M, age 59, 7MPO, creat 119)

no SAE, no flare under Rx, 1 flare in f/up (blinded)

→ Step 2 almost completed

1 flare under Rx (blinded)

A7 – McAdoo et al. UK

CPx

SYK-inhibitor in experimental auto-immune GN

- Fostamatinib (SYK inhibitor)
- EAG: rats immunized with rat GBM Ag (alpha 3) at d0

→ Develop Ab to alpha 3 and crescentic GN by d18 + lung AH by d36

- N=8x2, given FOS d0 to d18 40mg/kg BID or vehicle only (study 1)
- N=8x2, given FOS d18 to d36 40mg/kg BID or vehicle only (study 2)

→ Reduction by 58% in the number of specific alpha 3-B cells in FOS treated rats

→ Reduced MCP1 *ex vivo* production

→ Reverses GN and prevents lung hemorrhage

A7 – McAdoo et al. UK

CPx

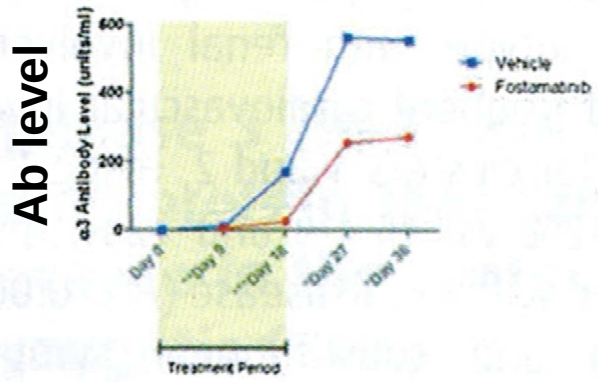
SYK-inhibitor in experimental auto-immune GN

	STUDY 1			STUDY 2		
	VEH	FOS	Reduction	VEH	FOS	Reduction
Proteinuria (mg/day)	172	96	41%*	118	2	98%**
Haematuria (cell/ul)	139	34	75%*	200	0	100%**
Crescentic Glom (%)	74	41	45%**	70.5	1.5	98%**
Macrophage/Glom (Score)	10.5	12.6	NS	9.8	0.2	99%**
LH (Score)	2	0.85	58%*	1.75	0	100%**

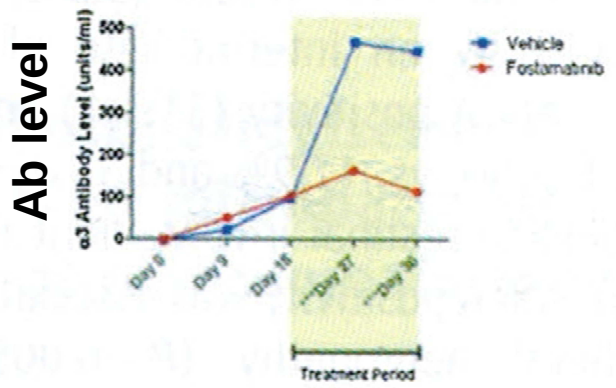
Results expressed as mean/group at Day 36. *=p<0.05;** =p<0.01; NS=not significant

!!!

STUDY 1



STUDY 2



P135 – Casian A et al. Cambridge UK

CPx

RTX and vascular function in GPA

11 active GPA: 9 under RTX, 2 under CYC

Mean age 59 yrs, 8 M, BP 145/84 mmHg, CT 5 mM

→ Endothelial study pre- (all) & 6 mo. post-Rx (3R + 1 CY)

→ AcCh endothelium-dependent flow vasodilation (EDFV), sodium nitroprusside and NG-MMLA by venous plethysmography, pulse wave velocity (stiffness)

→ Baseline PWV increased at baseline in all patients

(vs. normal value for age)

→ EDFV improved at M6 in 3/3 RTX vs. worse in 0/1 CYC

Preliminary data… waiting for full report on more patients

ANCA WS 2013 #38 (poster)

CPx

"UK-VCRC-FVSG" EGPA patients with RTX

Retrospective from 4 centers: 30 EGPA refractory or relapsing

- Median follow-up: 40 months

→ 26 (87%) achieved remission at M6 (+ no response in 2 + PR in 2)

→ 8 relapsed after a median of 18 months (+ 18 pre-emptive RTX)

→ 28/30 (93%) continued to require CS for asthma

Hot A et al – Lyon, Lille, Paris, Cambridge,Pennsylvania

R. Hajja-Ali et al. Abstract A44

ND

Long-term outcomes of patients with reversible vascoconstriction syndrome (RCVS)

- Prospective cohort (Cleveland) N 50; Follow up 10-254 months
- Mailed in validated questionnaires
- 20/50 available for analysis (26 lost to f/u; 8 did not reply; 3 refused)
- F 90%; 95% presented with thunderclap headache
- Ischemic stroke 50%; SAH 45%; ICH 15%

R. Hajja-Ali et al. Abstract A44

ND

Long-term outcomes of patients with reversible vascoconstriction syndrome (RCVS)

- 55% continued to have headache with 91% of these stating improvement in character
- Almost all were independent with little disability

P27, 28 – Hajj-Ali R. et al. Cleveland

HR-3T MRI in RCVS

- Retrospective single center study on 13 RCVS versus 13 CNS vasculitis (12 PACNS + 1 VZV)
- Age RCVS 52 years (F 85%), PACNS 42 years (F 15%)

- RCVS
  - 77% had vessel wall thickening
  - 31% had minimal wall enhancement → *"minimal" but still…*

- CNS-V: 92% had wall enhancement and/or thickening

L38 C. Pagnoux.

ND

How to treat primary vasculitis of the central nervous system (PACNS)?

- No prospective therapeutic trial
- Few retrospective studies with small number
- Current practice recommendation (especially biopsy proven and severe disease) is to treat as severe forms of systemic vasculitides
- IV pulse CS and Cyclophosphamide for induction and maintenance with Azathioprine/methotrexate/ MMF
- Some date in children with MMF as a better remission maintenance agent





Conclusions

CONCLUSIONS (1)

- Most important presentations were on fundamental studies and perspectives
  - Epitope specificity for MPO-ANCA… and PR3?
  - Place of neutrophils, apoptosis, Treg… vs B cells…
- Ongoing and new debates on classification (PR3 vs MPO, EGPA vs HASM) and increasing place of other unique vasculitides (EGPA, PACNS, SOV, HCV-AV) … and *pediatrics*?

CONCLUSIONS (2)

- Confirmatory studies and series on MMF, rituximab/AASV, CYC dose adjustment, and few on tocilizumab/LVV with mitigated results…

… awaiting results from studies

closed (REMAIN, CHUSPAN 2, *AGATA-GPA*),

ongoing (PEXIVAS, DCVAS, ABAVAS LVV, CLEAR, MAINRITSAN 2)

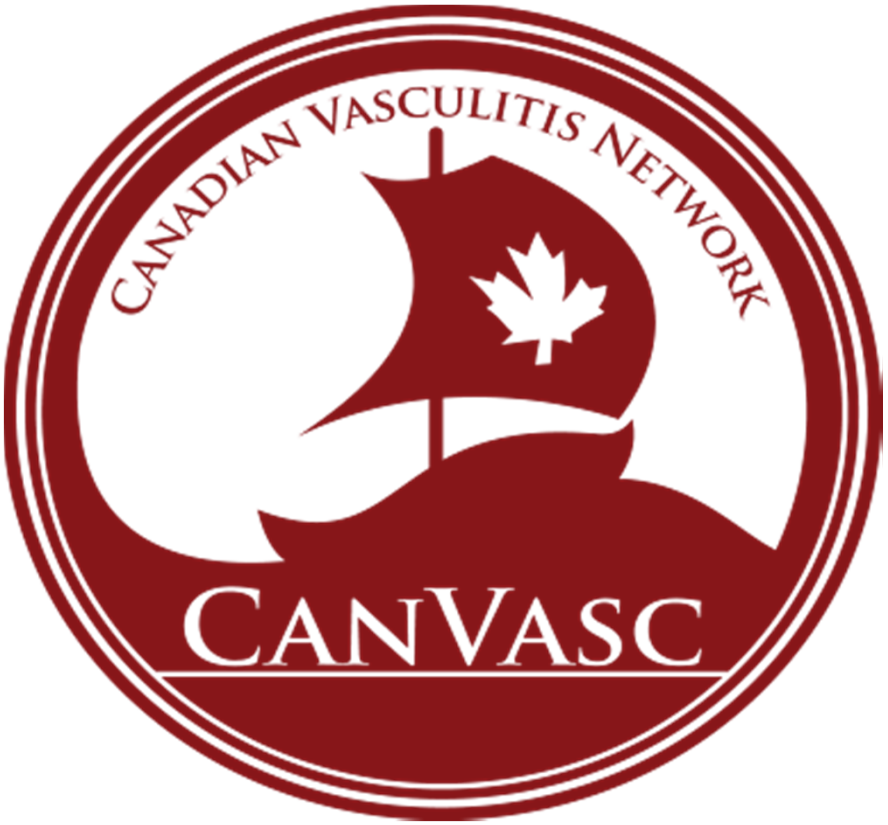
and to start (RITAZAREM, BREVAS, MEPOLI-EGPA, GiACTA, SPARROW, TAPIR, ABROGATE)

CPx

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