Vascularites rénales associées aux ANCA

Société Médicale des Hôpitaux de Paris

16 Mars 2012

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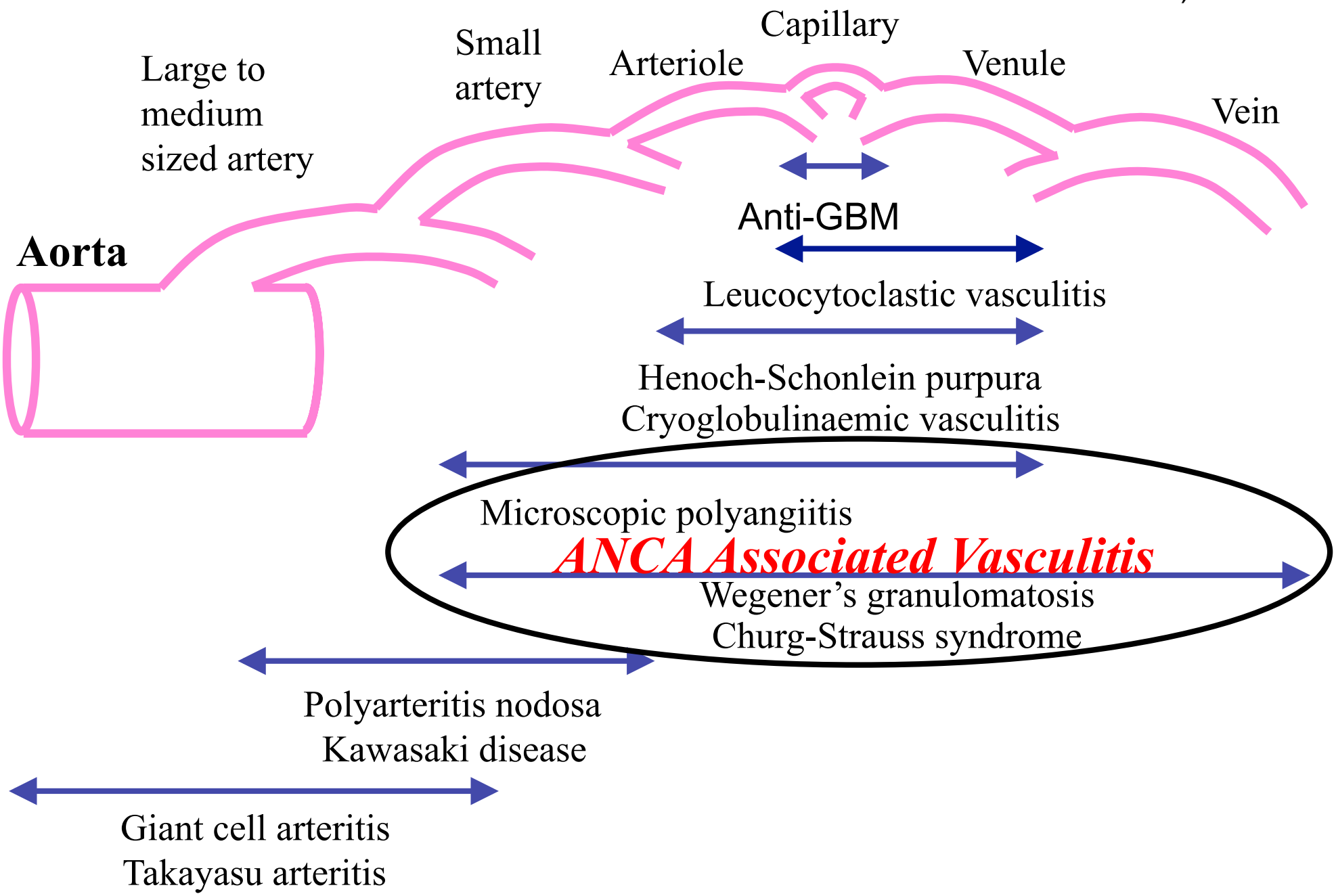
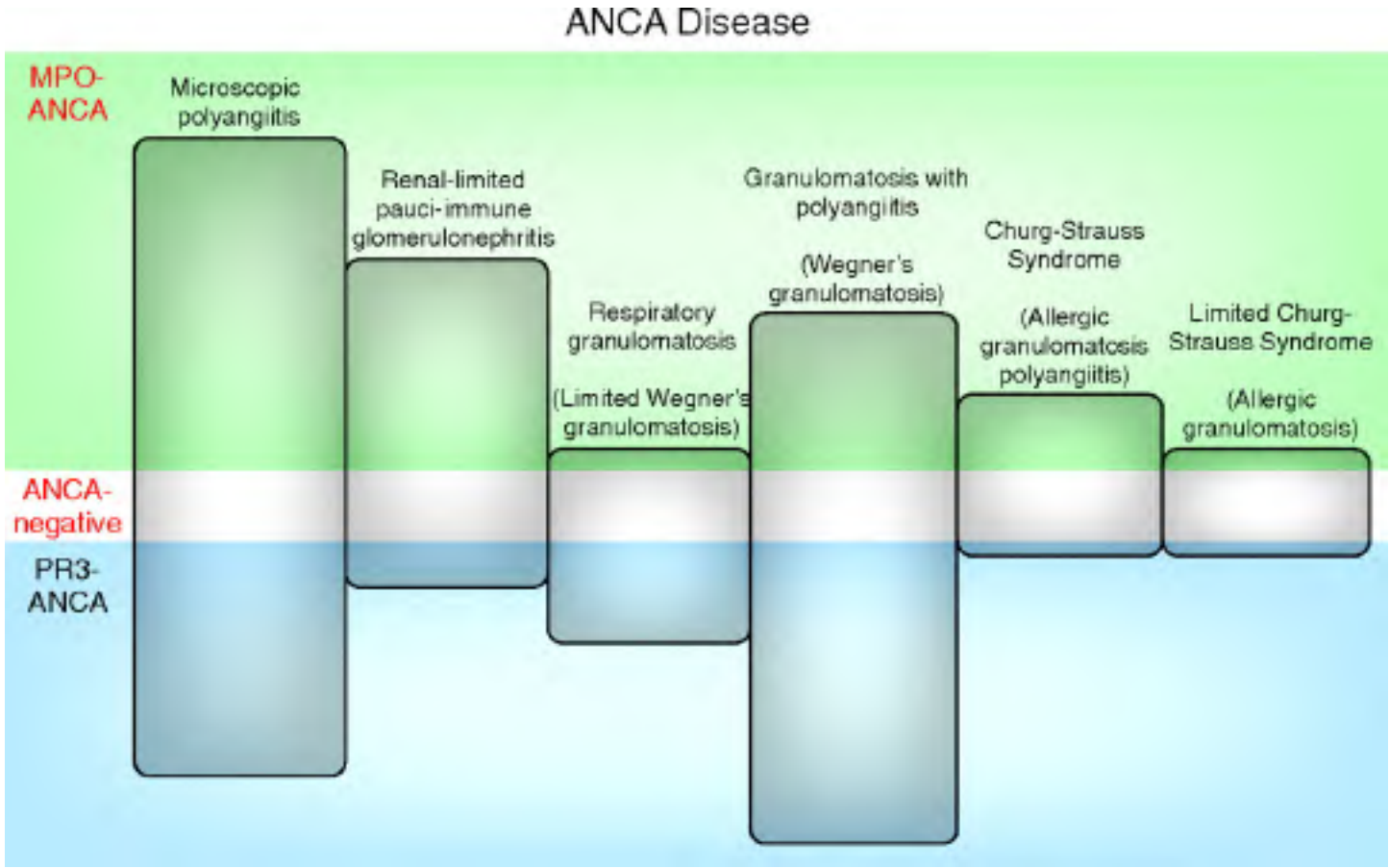
Classification of systemic vasculitis: Chapel Hill Nomenclature

Arthritis Rheum, 1994

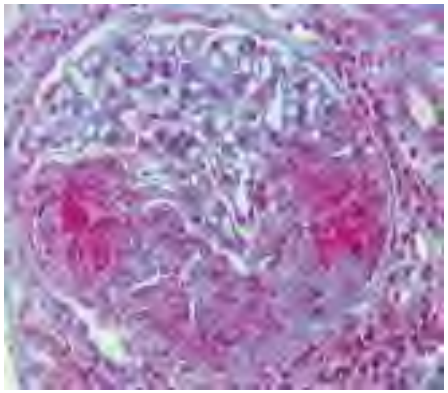


A proposed nomenclature for ANCA disease

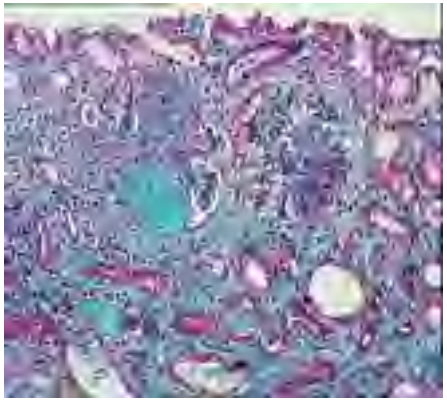


Falk RJ, JASN 2010
ANCA and Vasc.meeting,Chapel Hill 2011

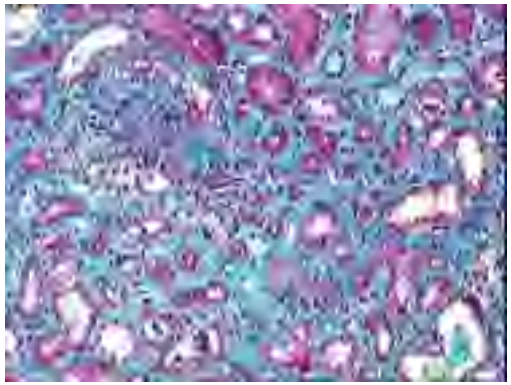
Histopathologic classification



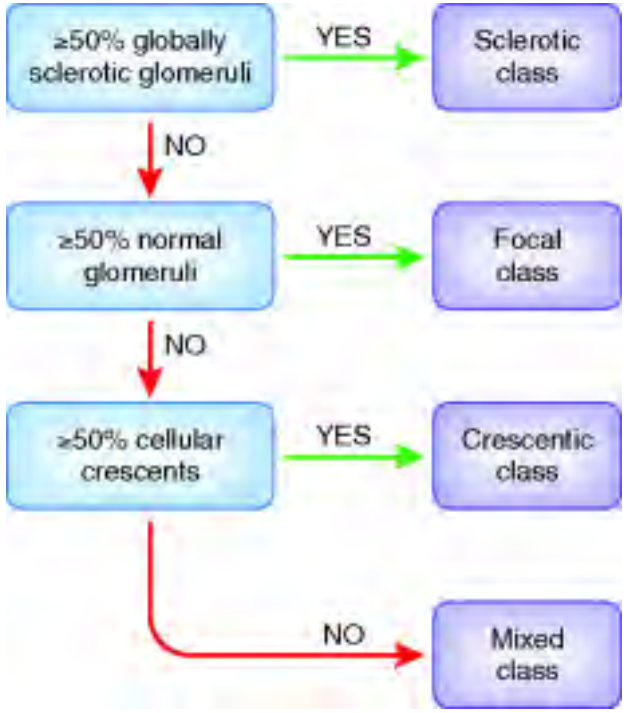
active

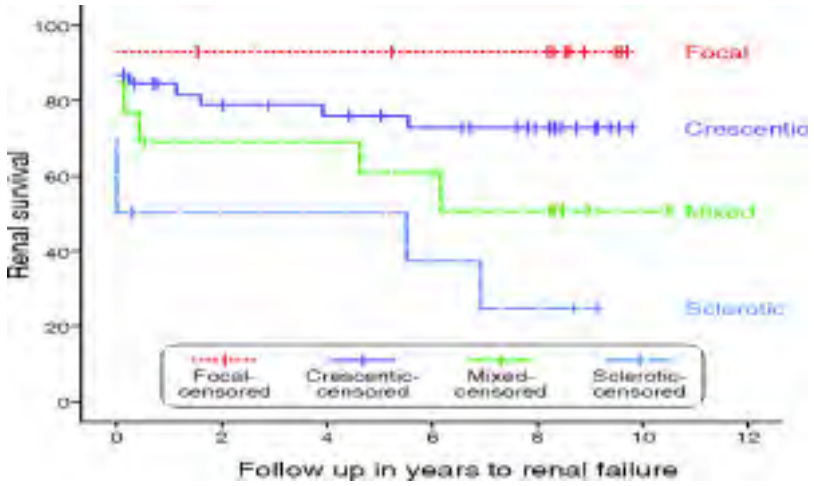


mixed



sclerotic

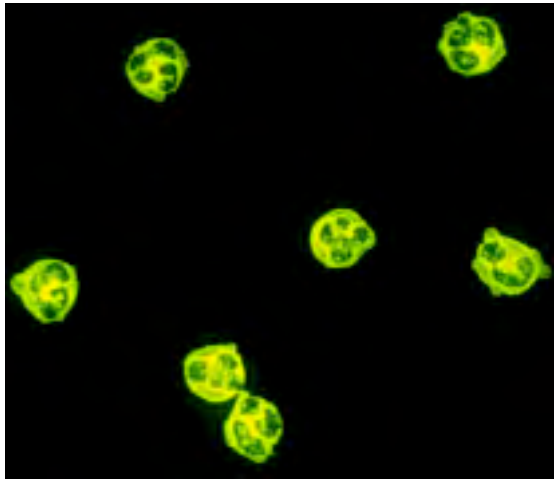




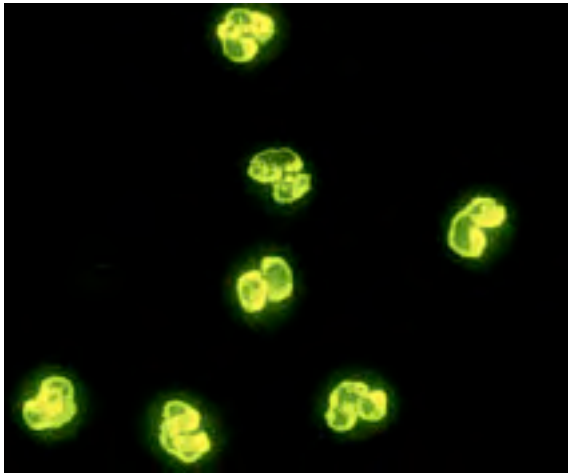
Berden A, JASN 2010

ANCA in Systemic Vasculitis

- Recognise neutrophil enzymes proteinase-3 or myeloperoxydase
- Identified by immunofluorescence and specific ELISA for PR3 or MPO



C/PR3 ANCA

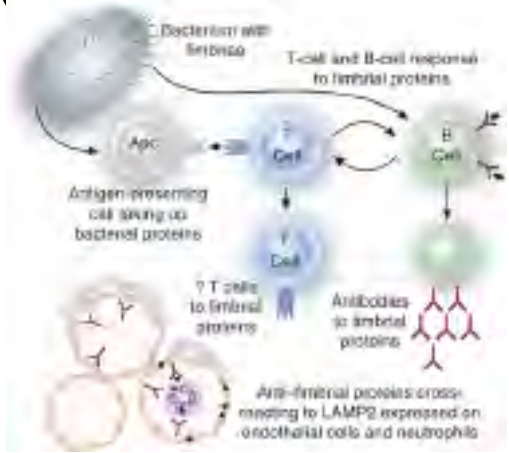


P/MPO ANCA

LAMP-2 a target for ANCA

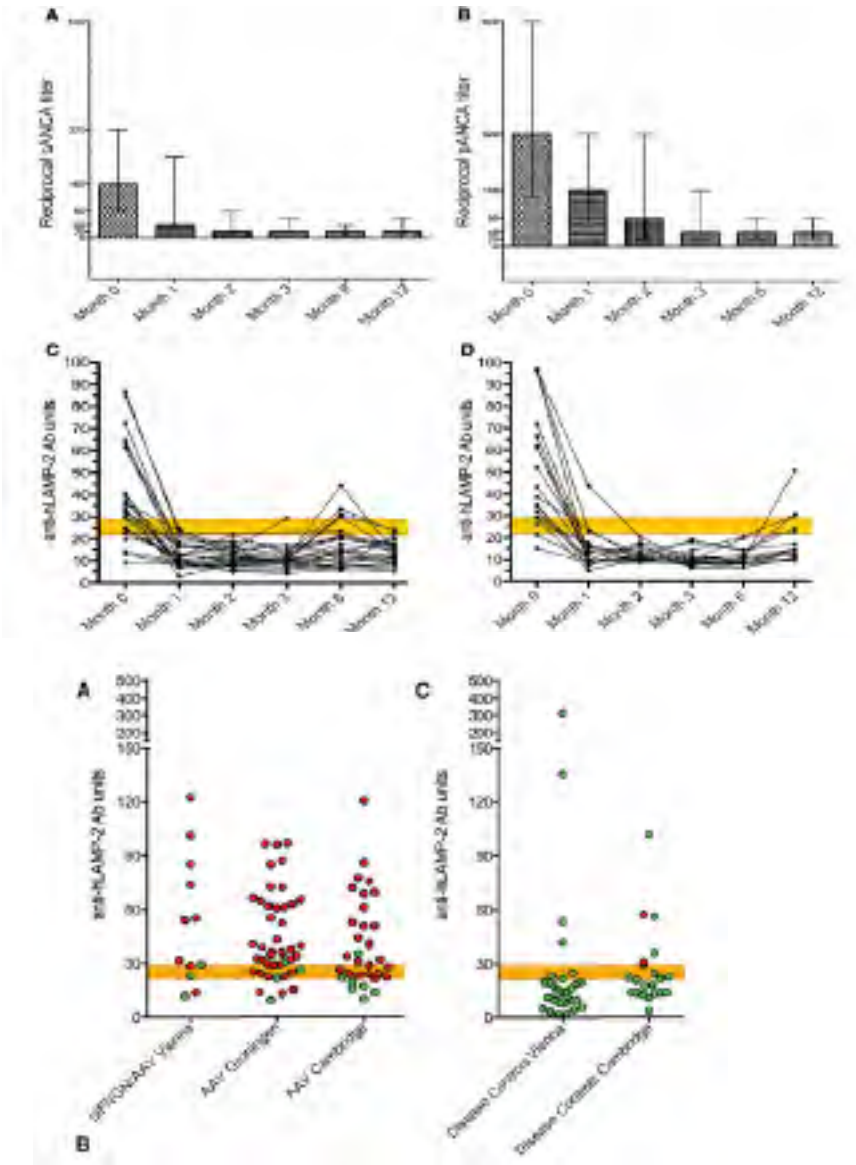
Shining a LAMP on pauci-immune focal segmental glomerulonephrits

- LAMP-2:lysosomal-associated membrane protein 2 = ANCA Ag
- anti-LAMP-2 Ab in pts with Nec GN: 14/16 pts (Kain 1995), 78/84 pts (Kain 2008)
- ANCA anti-LAMP-2 are pathogenic :
  - activate neutrophils and cause endothelial cell injury
  - induce FS Nec GN in susceptible rats
- Anti-LAMP-2 Ab recognize a 9 AA-epitope (P41-49) with significant homology to Fim H, a bacterial fimbrial protein, found in various Gram-bacteria
- WKY rats immunized with recombinant Fim H protéin (or P41-49) showed:
  - ANCA reactivity
  - anti-LAMP-2 Ab
  - pauci-immune focal Nec GN

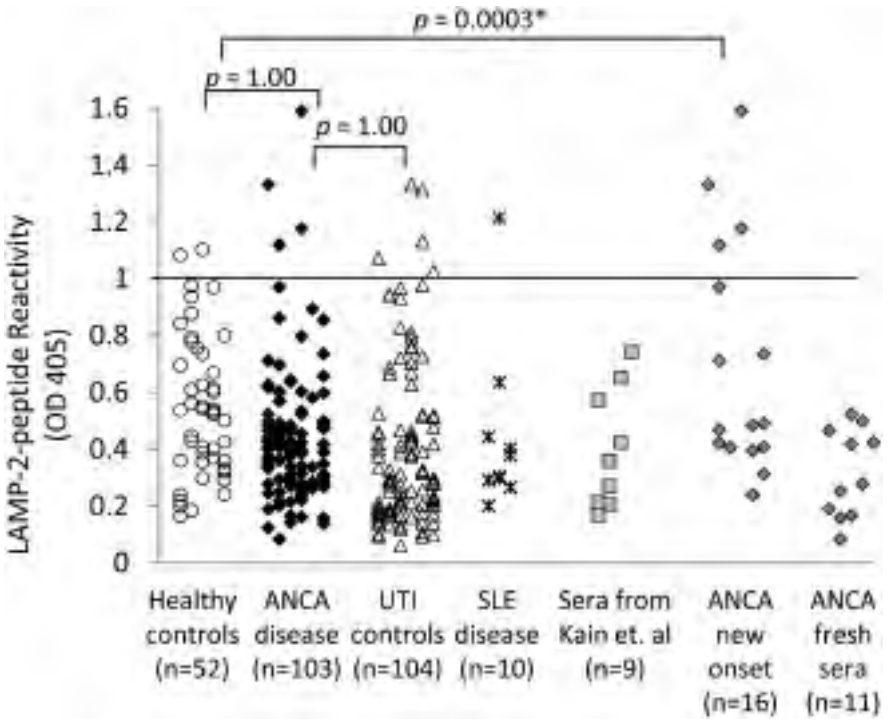


Kain R, Nat Med 2008

Anti-LAMP-2 Ab in ANCA-associated SV



Kain R, JASN 2012



Group	Positive/Total (n/n)	Proportion (%)
North Carolina	22/103	21.36%
Massachusetts	48/226	21.24%

Roth AJ, JASN 2012

Update on Therapy in AASV

- Remission induction

  Remission maintenance

- The evidence : randomized controlled trials from GFEV and EUVAS:

  - Survival
  - Relapses
  - Drug toxicity
  - Organ damage (ESRD)

Treatment limitations

158 patients

- relapses 50% (5 yrs)
- mortality 22%
- ESRF 11%
- toxicity 42%

- infertility	57%	- myelodysplasia	2%
- hem. cystitis	43%	- lymphoma	1%
- bladder cancer	3%	- cataract	21%
- opportunistic inf.	46%	- diabetes	8%

OR for tumours:

. 2,4 for cancer

. 33 for bladder carcinoma

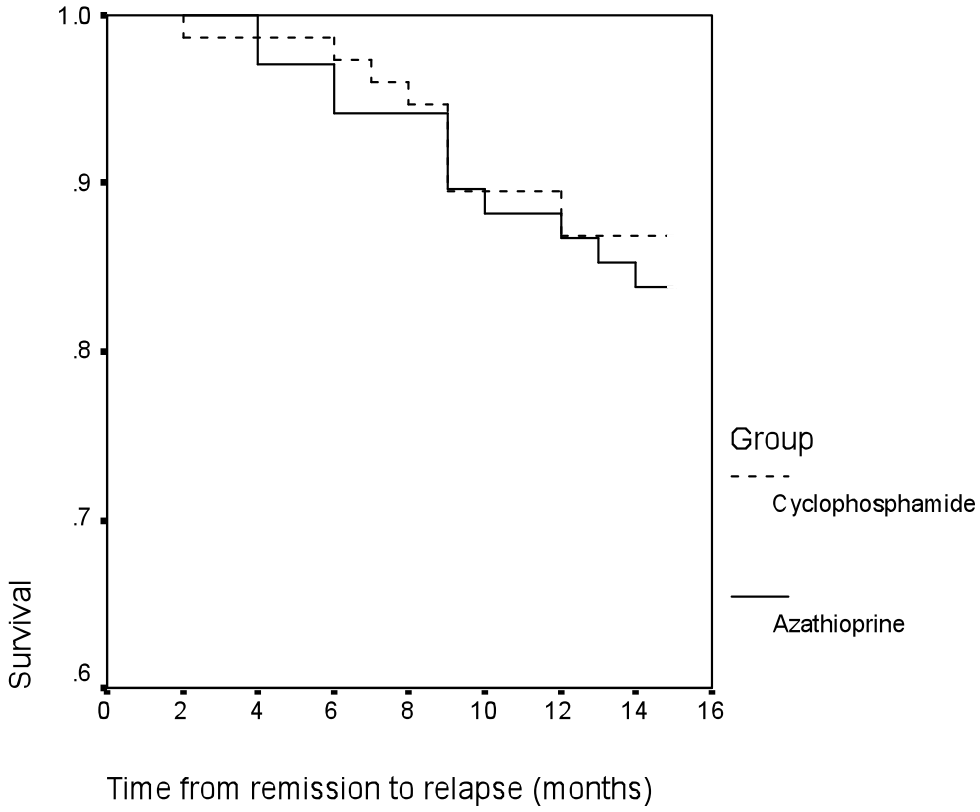
. 11 for lymphoma

Hoffman G, AIM 1992

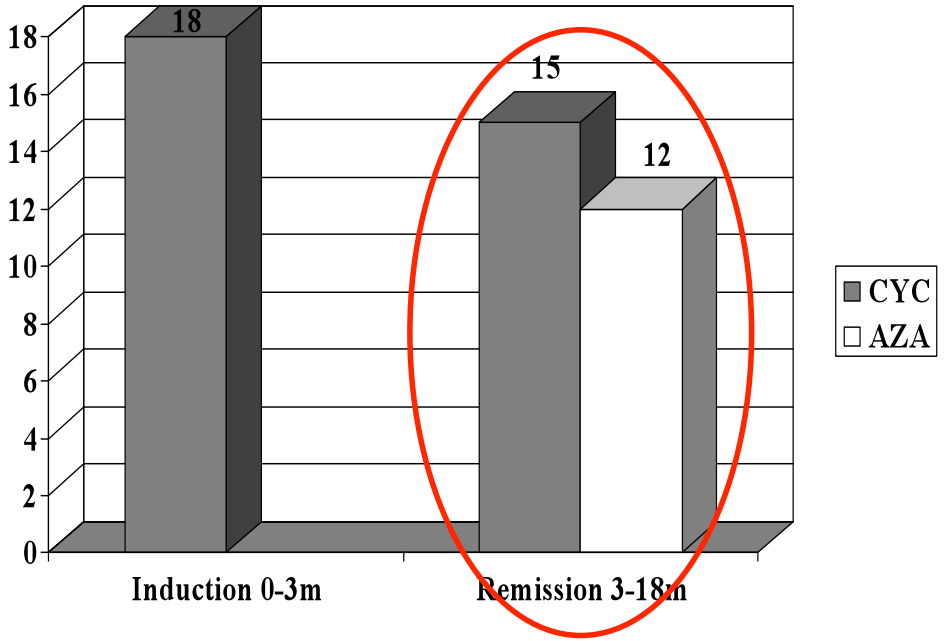
AAV: Cyclophosphamide reduction

Generalised- CYCAZAREM n=155/144

Relapses



Severe and life-threatening adverse-effects



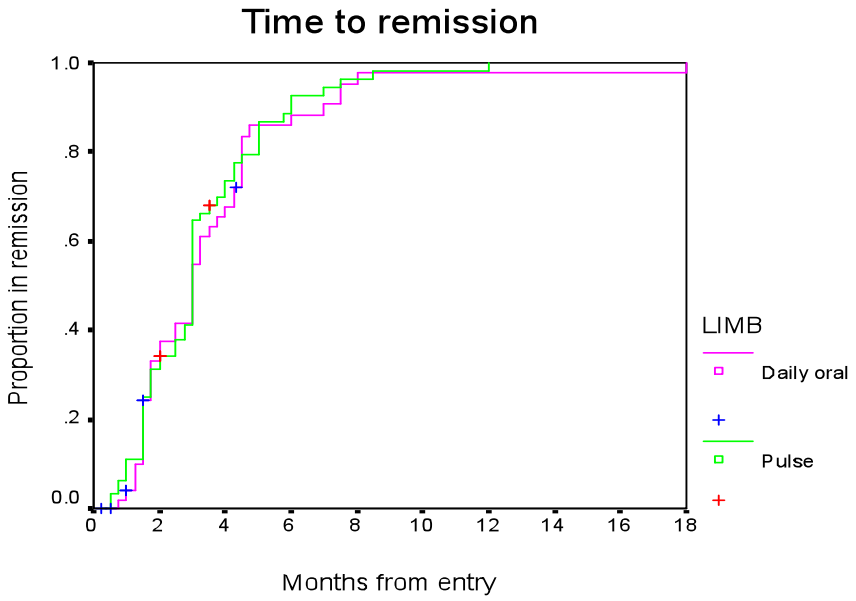
Jayne D, NEJM 2003

AAV: Cyclophosphamide reduction

ARTICLE | Annals of Internal Medicine

Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial



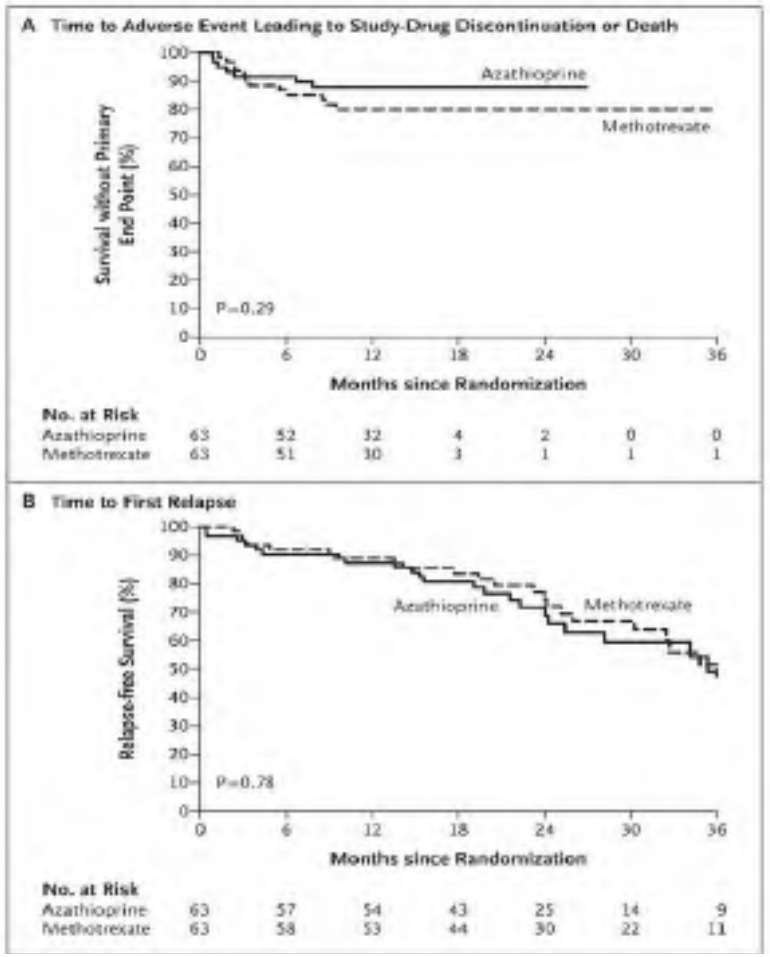
n: 160/149

- Fewer episodes of leukopenia with pulse (26% *vs* 45%)
- SAE: 19 pulse, 31 oral
  severe infection: 7 pulse, 10 oral
- Death: 14 pts
  -5 pulse; 3 active disease
  -9 oral; 7 active disease

de Groot K, Ann Intern Med 2009

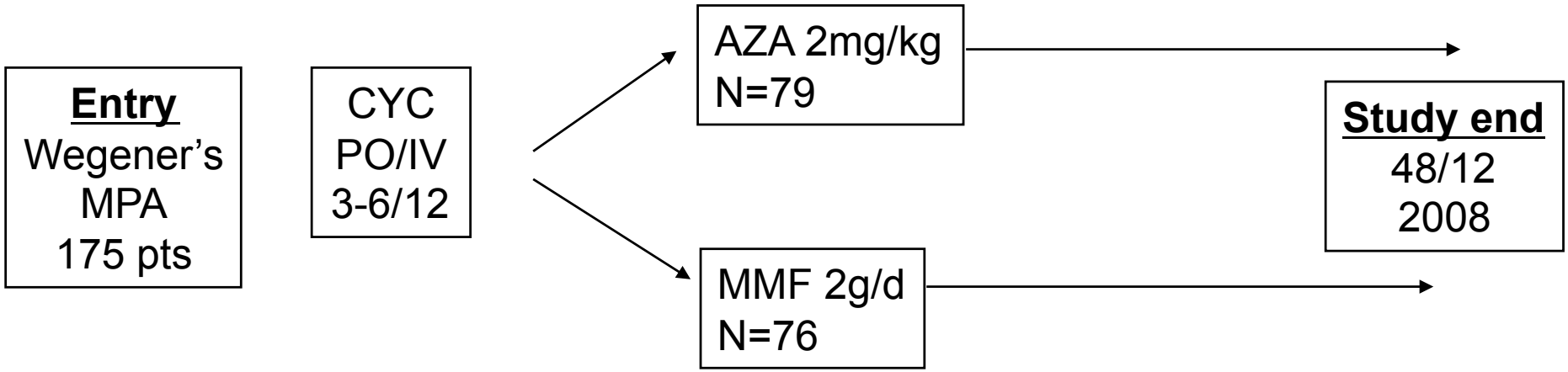
Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

- 159/126 pts
- Relapses (%) at 18m/36m:
  - Aza: 17.8/50.1
  - Mtx: 13.7/46.7
- Drug discontinuation or death
  - Aza: 7 pts
  - Mtx: 12 pts
- SAE:
  - Aza: 5 pts
  - Mtx: 11 pts



Pagnoux C, NEJM 2008

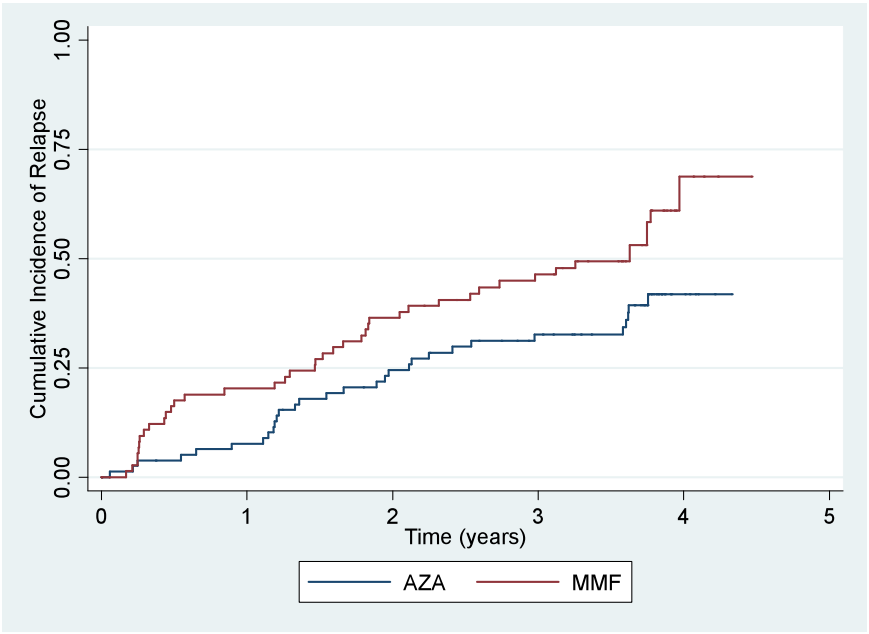
MMF vs AZA for remission - IMPROVE trial



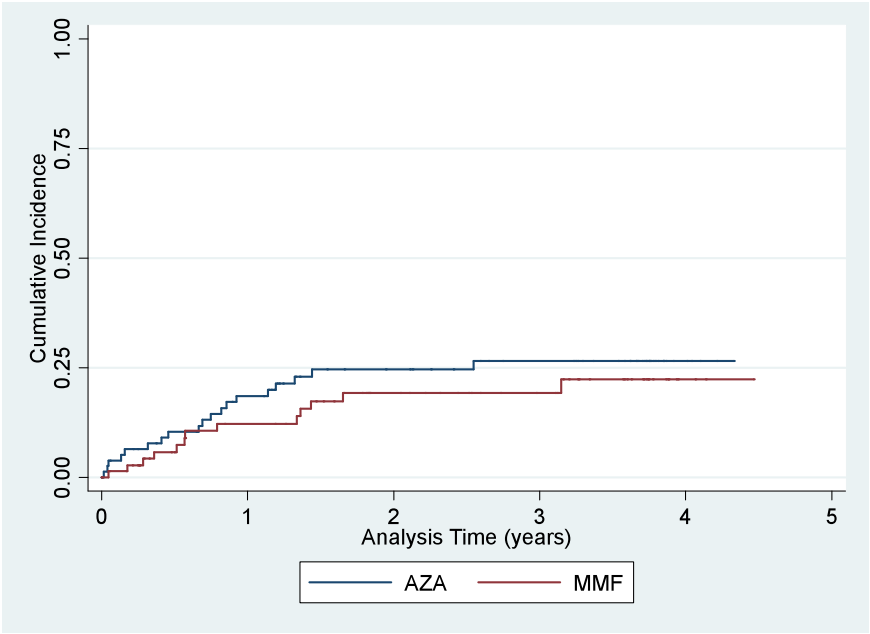
- WG 100, MPA 56
- AZA 80, MMF 76
- BVAS: 16/14 (6-25)
- Creat 178 (103-310)

TF Hiemstra JAMA 2010

MMF vs AZA for remission - IMPROVE trial



Cumulative Incidence of Relapses

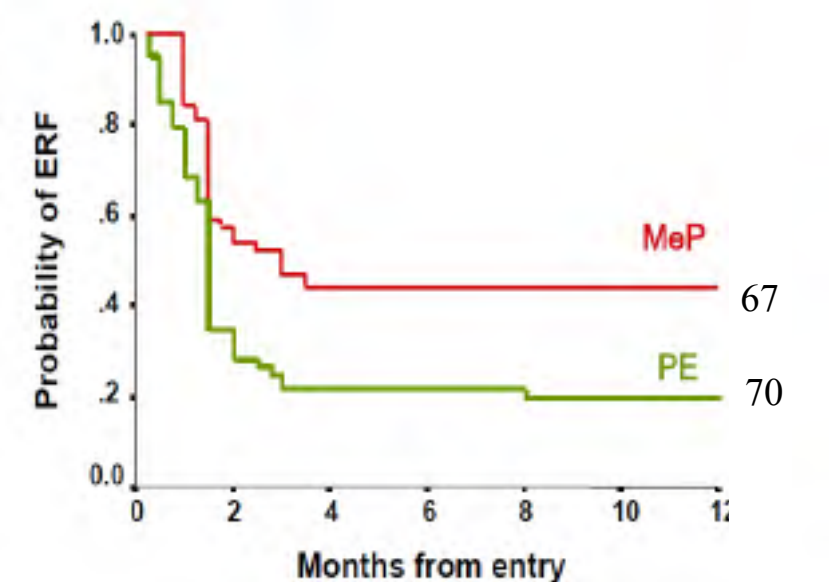


Cumulative Incidence of Severe Adverse Events

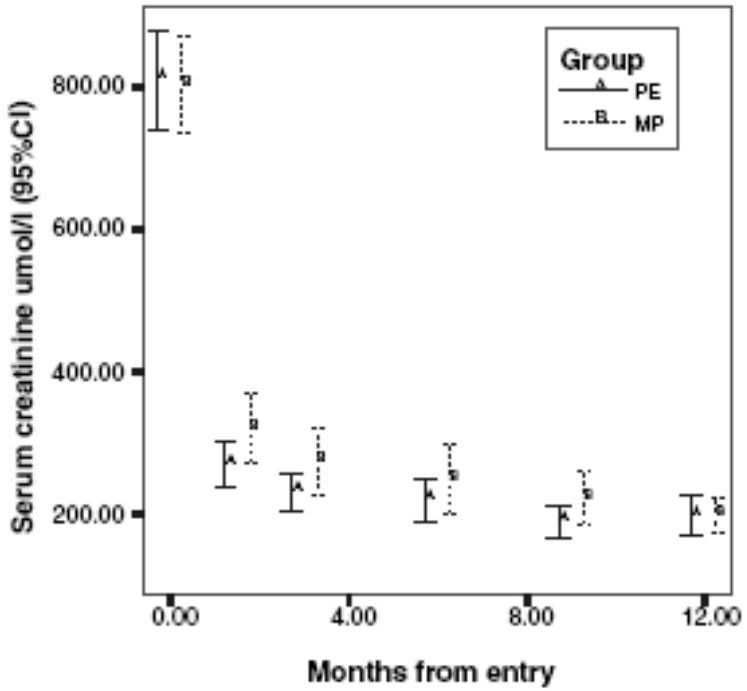
TF Hiemstra JAMA 2010

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

MEPEX



151 pts

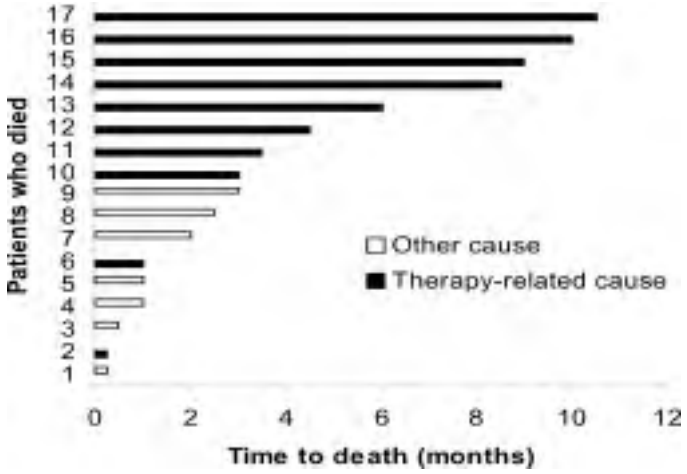


Jayne D, JASN 2007

MEPEX trial

Adverse events according to type, severity (mild/moderate or severe/life threatening), and treatment group

Adverse Event	Study Groups				Total
	Intravenous Methylprednisolone		Plasma Exchange		
	Mild/ Moderate	Severe/Life Threatening	Mild/ Moderate	Severe/Life Threatening	
Leukopenia (at least 1 episode)	35	7	35	8	85
Recurrent leukopenia (>1 episode)	13	2	11	4	30
Infection	13	17	11	20	61
Thrombocytopenia	2	0	3	5	10
Allergy	4	0	6	0	10
Cardiovascular	2	3	1	3	9
Diabetes	3	2	2	1	8
Gastrointestinal	0	1	3	2	6
Bone fracture	0	2	1	2	5
Thrombosis	1	0	1	3	5
Hemorrhage	0	1	1	1	3
Alopecia	0	0	2	0	2
Vascular access complication	0	1	0	1	2
Other	1	3	2	2	8
Totals	74	39	79	52	244
No.(%) of patients with ≥1 event	59 (87)	32 (48)	63 (91)	35 (50)	122 (89)

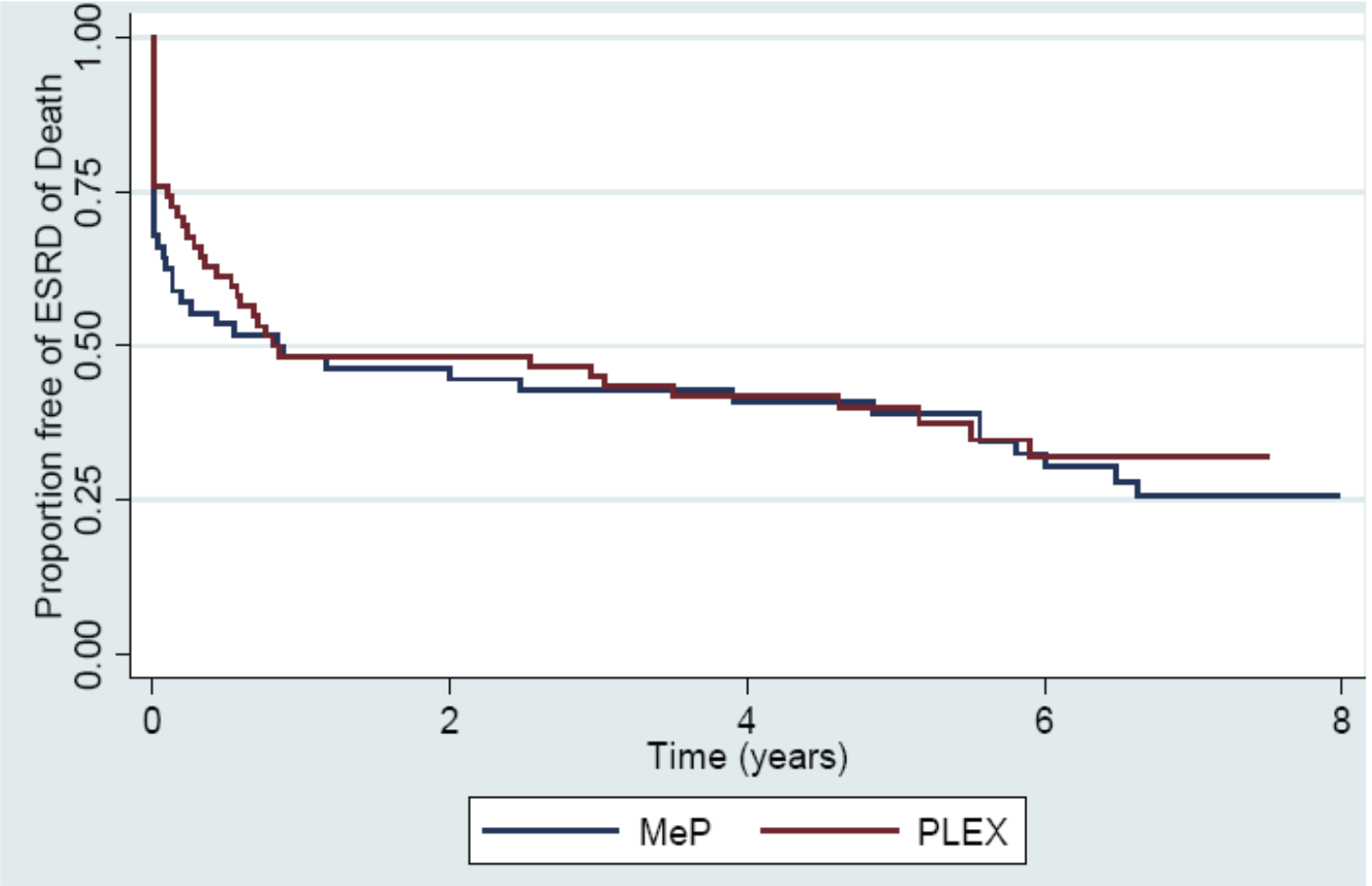


High mortality in both arms: 25%:

infection 19, pulm. hemorrhage 6, CVD 4.

Jayne D, JASN 2007

MEPEX trial: Long-Term Follow-up

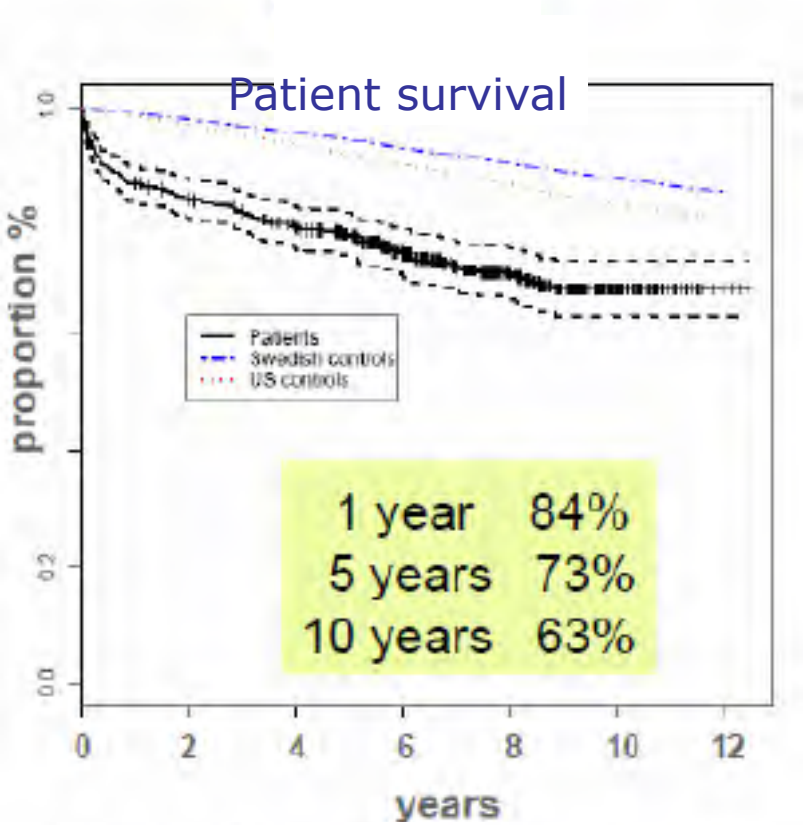


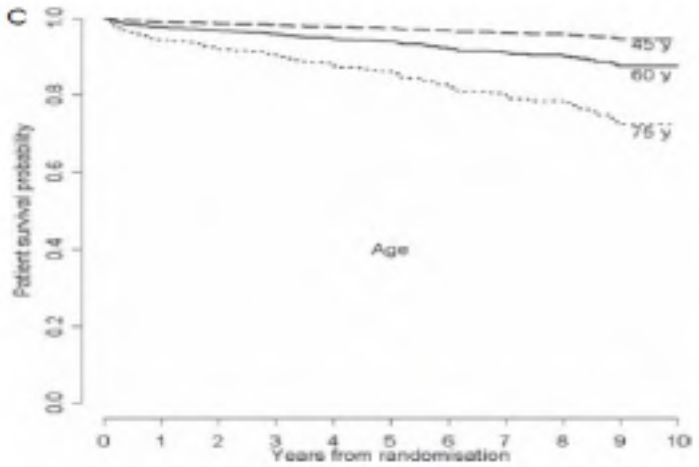
ESRD or Death

Casian A, Chapel Hill 2011

Mortality and Adverse effects: EUVAS cohort

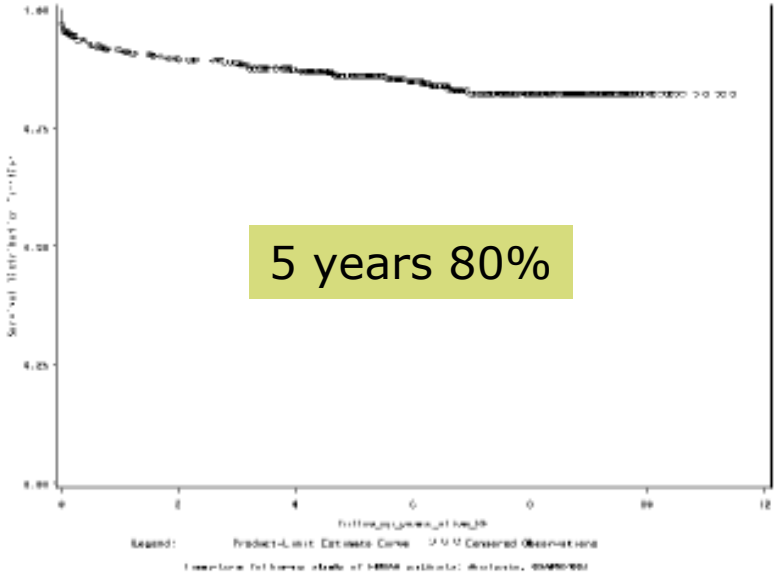
Flossman O, ARD 2011



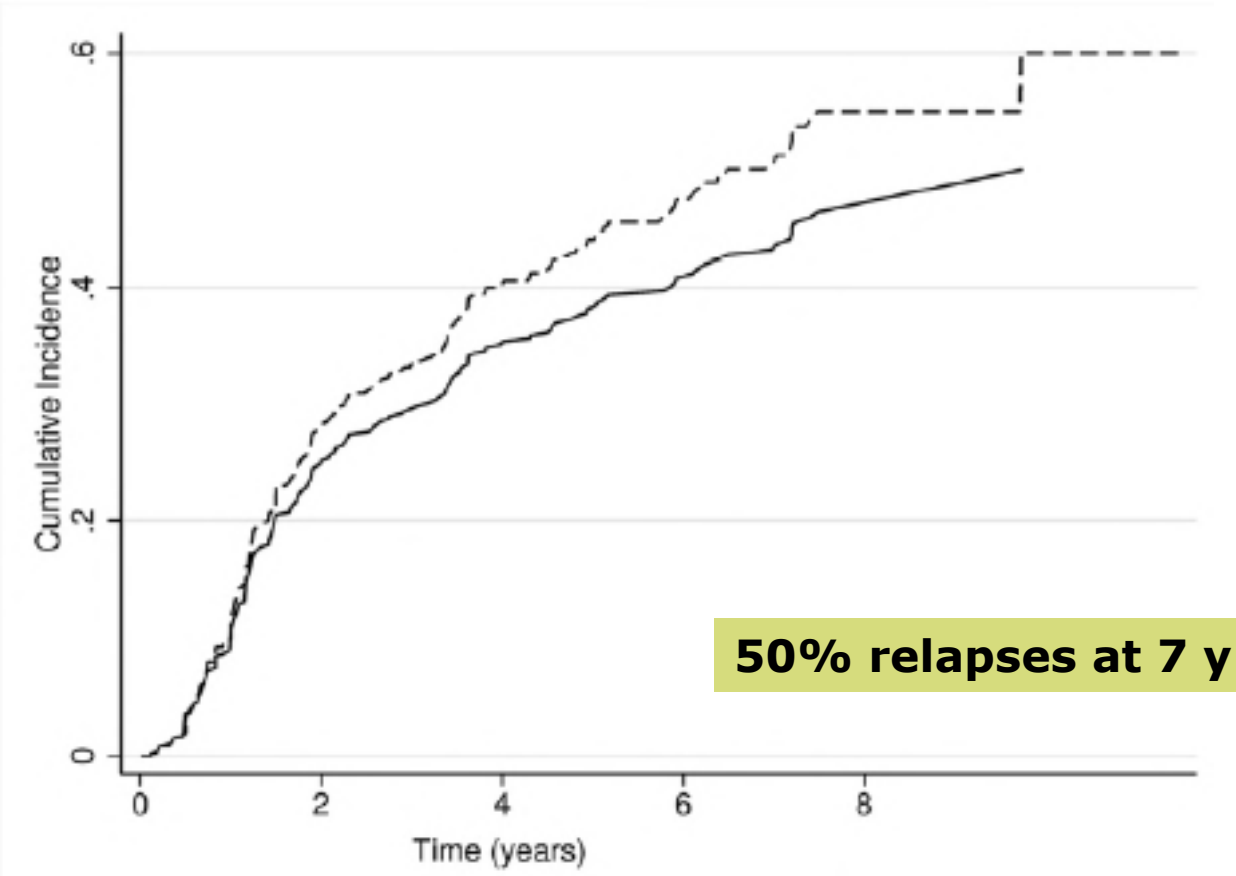


- 535 pts
- 133 deaths at 5.2 y
- 1st year mortality 11%
  - Active vasculitis 19%
  - Infections 48%
- After 1st year
  - CV disease 26%
  - malignancy 22%
  - infection 20%
- Prognostic factors: eGFR <15, age, BVAS, Hb & WBC

Renal survival



Relapses: EUVAS cohort



50% relapses at 7 y

Walsh M, AR 2012

Early mortality predictors

Multivariable analysis

- Infection 1.2
- Leucopenia 1.2
- GFR 0.7
- Cumulative Cyc dose 1.2

Little M, ARD 2009

Malignancy

Table 2 Calculated age, sex and area SIR for observed cancers at all sites, at all sites excluding NMSC and by site ordered by decreasing numbers of observed cancer cases

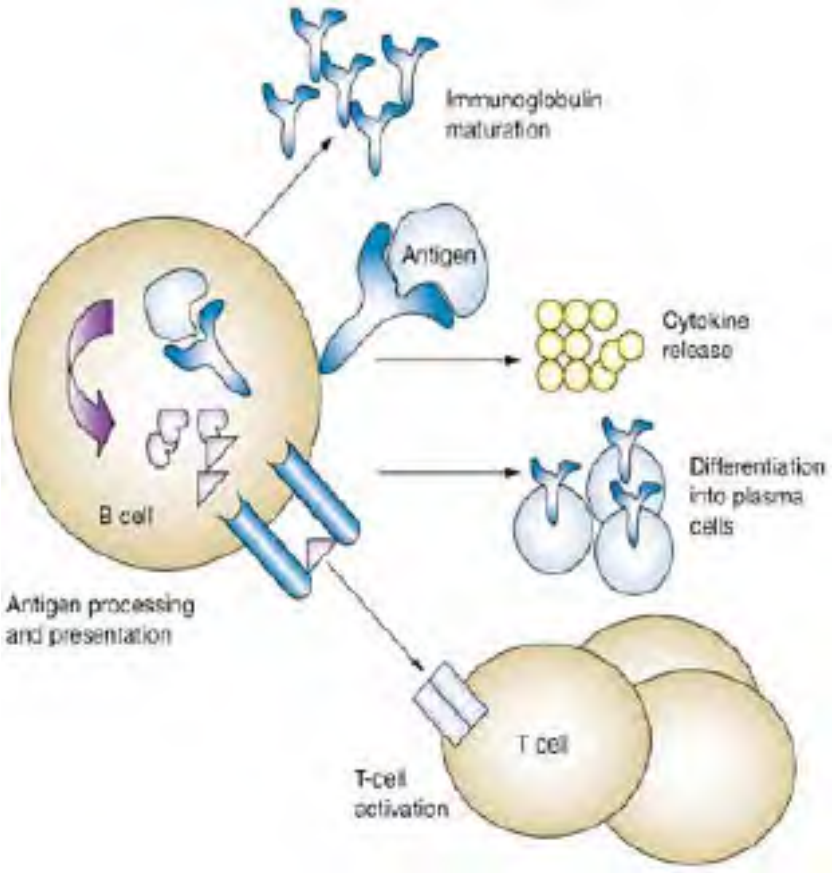
Cancer site	PY	No. of cancers		SIR (95% CI)	p Value
		Observed	Expected		
All sites	2553	50	31.71	1.58 (1.17 to 2.08)	0.003
All non-NMSC sites	2580	35	27.00	1.30 (0.90 to 1.80)	0.16

Heijil C, ARD 2011

Other adverse outcomes

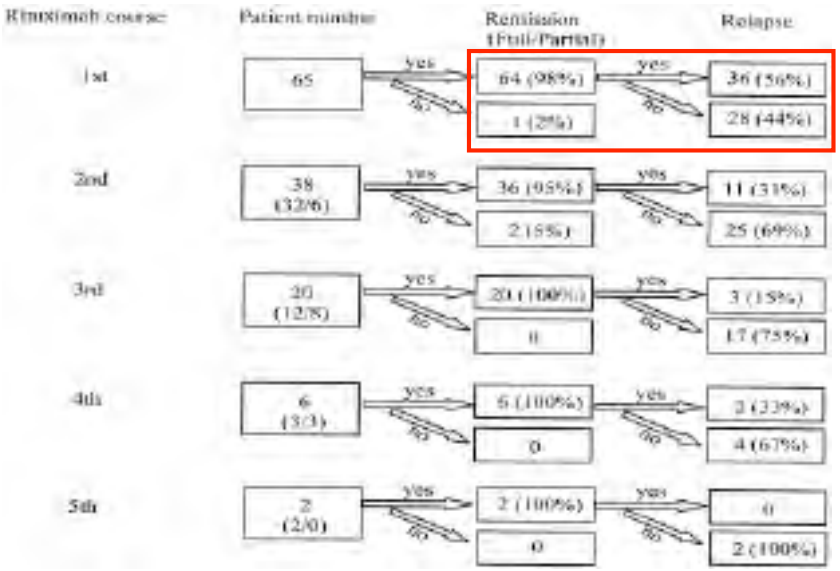
- Cumulative steroid exposure
- Damage: 95%-irreversible disease scars
- Depressed QOL

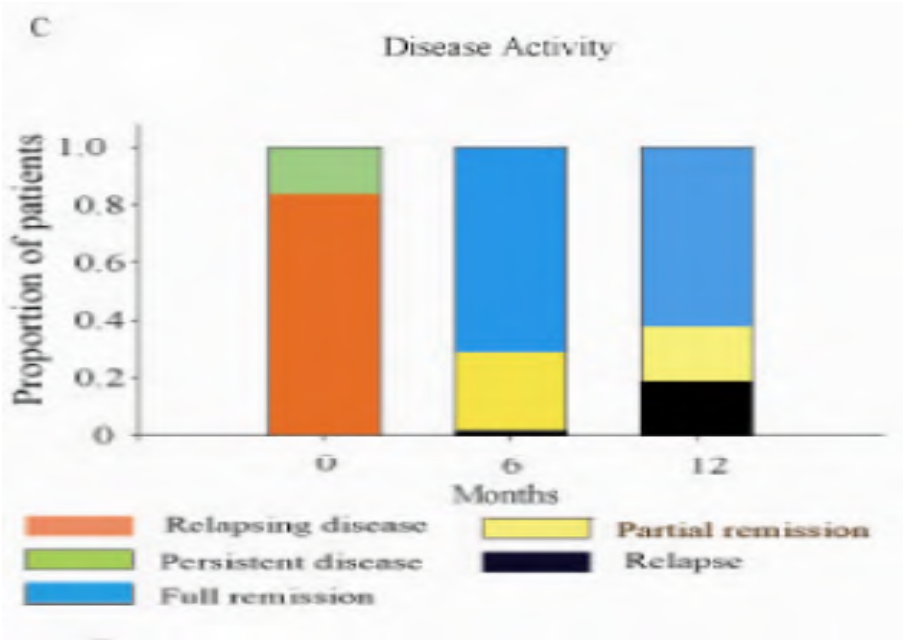
Role of B-cells



- Cytokines
- Ig production
- Presentation to T-cells
- Plasma cells

A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis





- Retrospective, standardized data collection from 65 sequential pts
- B cell depletion: 100%
- Complete remission: 49 (75%)

  Partial remission: 15 (23%)
- Median time to remission: 2 m (1-5)
- Relapse: 57% (28 pts) after CR

  median time to relapse: 11.5 m
- $\geq$ 2 courses of Rtx in 38 pts

  CR in 32 pts (84%)

Jones R, Arthritis Rheum 2009

Rituximab for remission induction

NEJM 2010

Hypothesis: Rituximab is not inferior to cyclophosphamide for remission induction

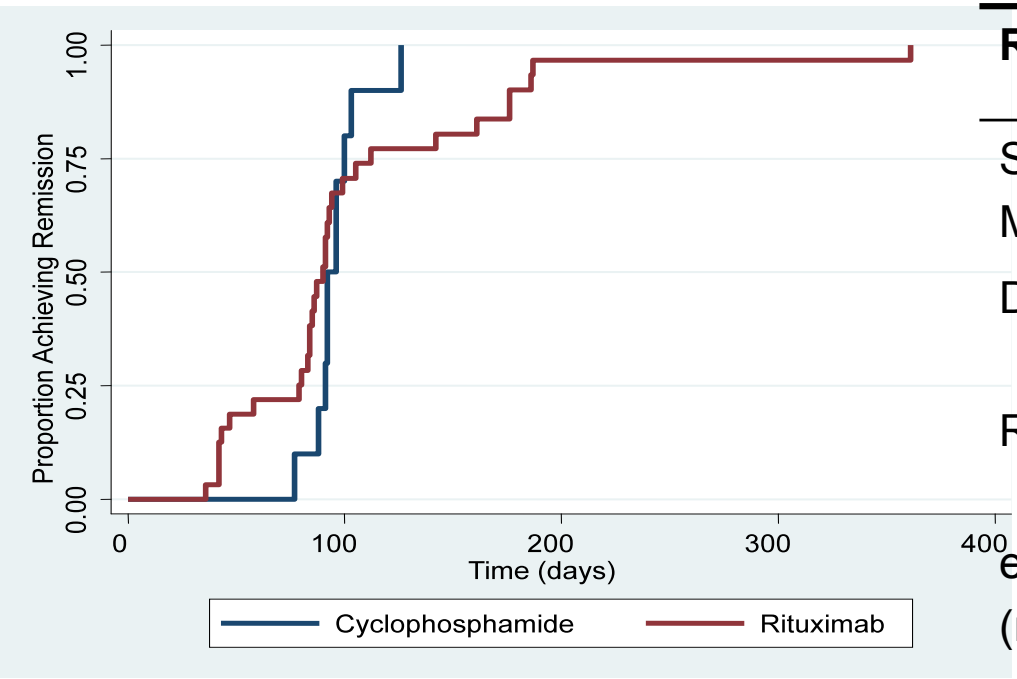
RAVE

- 197 pts
- 53 y
- GFR 61
- vs oral Cyc
- New or relapsing AAV

RITUXVAS

- 44 pts (33:11)
- 68 y
- GFR 17
- vs IV Cyc
- New severe renal AAV

RITUXVAS: End points



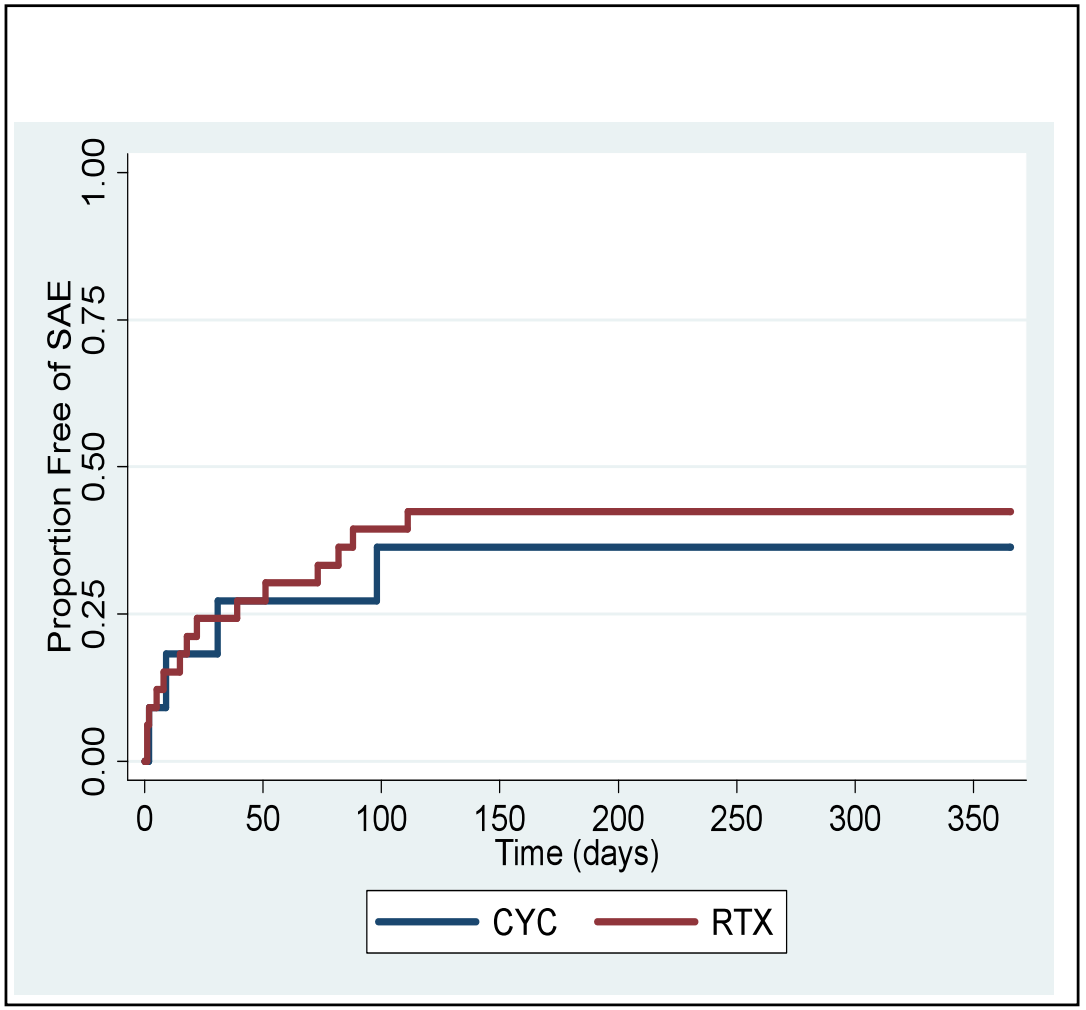
time to remission

Results	**RTX N=33**	**CYC N=11**
Sustained remission at M12 (BVAS0x2 at 6m)	76%	82%
Deaths	6 (18%)	2 (18%)
Remission	82%	91%
eGFR at M 12 (recovery from dialysis)	51 (5/8)	33 (1/1)
ANCA neg by 6 months	89%	81%

R Jones, NEJM 2010

RITUXVAS: Primary Safety End Point

	RTX	CYC
Severe Adverse Events	31 (42%) 1.0 /pt/y	12 (36%) 1.1 /pt/y
Infections	21 (39%) 0.66 /pt/y	7 (21%) 0.60 /pt/y
Death	6 (18%)	2 (18%)



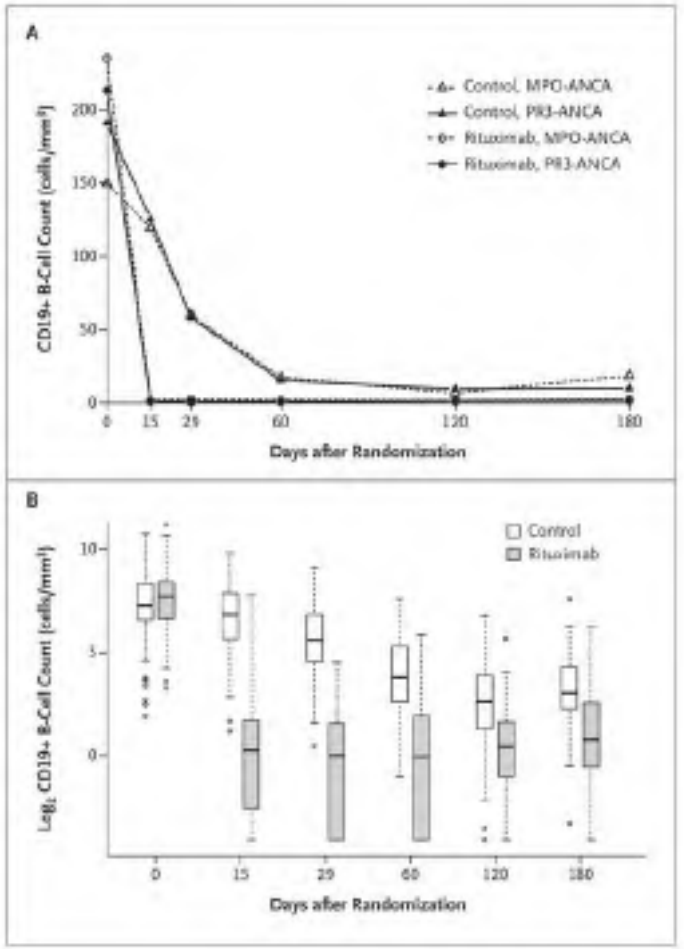
R Jones, NEJM 2010

RAVE trial

- Primary outcome is remission at 6 months: BVAS-WG=0 and w/o Pred. at M 6
  - RTX: 64%
  - CyP: 53%

- RTX superior in achieving remission in pts (n=101) with severe flares at baseline (67% *vs* 42%)

- Similar number of selected AE: RTX 31%, CyP 33%, with no difference in rate of infection (severe inf.7%)



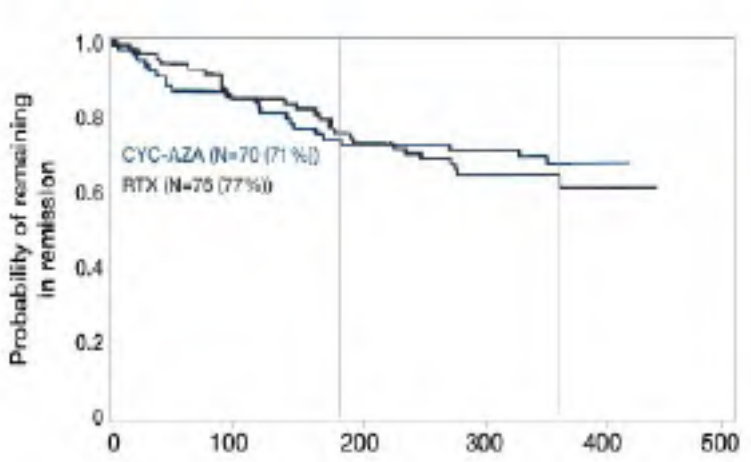
JH Stone NEJM 2010

RAVE: 18 months FU

	RTX(99)	Cyc-Aza(98)
success	39	32
Severe flares	38	30
Still in remission	36%	31%

No difference between 2 arms:

- rate of CR
- time to CR and 1st flare
- rate of flares
- rate or severity of AE



Severe flares are rare in the absence of B lymphocytes

RITUXVAS: 2 year follow-up results

	Ritux N=33	Cyc N=11
1ry composite outcome (relapse, death, ESRF)	14 (42%)	4 (36%)
• Relapse	7/27 (26%)	2/10 (20%)
• Death	6 (18%)	3 (27%)
• ESRF	2 (6%)	0 p 0.57
Rise in GFR	20	16
SAE	61%*	36% p 0.64

* 3 cancers : breast, melanoma, basal cell carcinoma

Jones R, Chapel Hill 2011

Questions

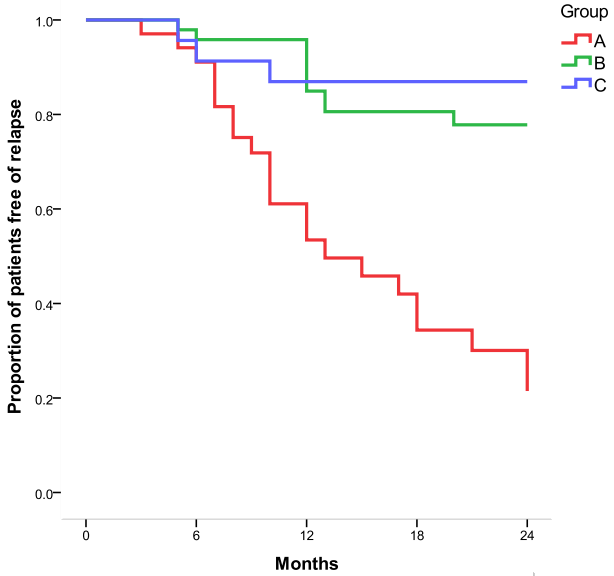
Maintenance therapy?

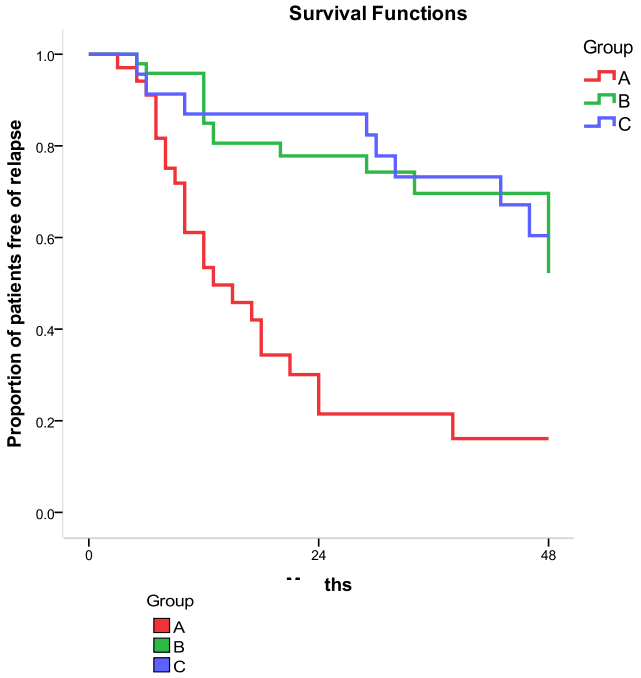
- Conventional Aza/MTX +/- steroids
- Repeat rituximab:

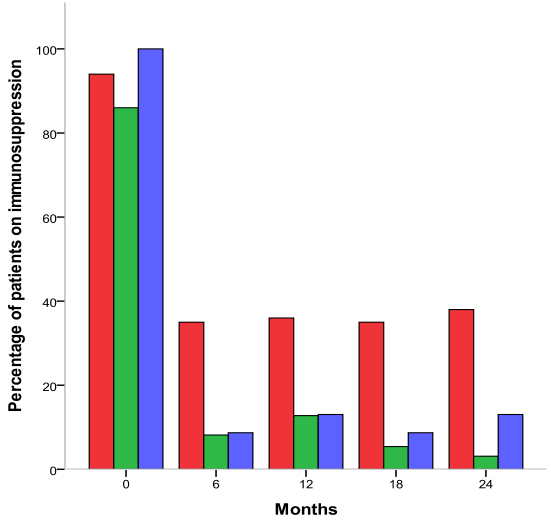
  - at time of relapse
  - guided by B cells/ANCA
  - routine time-based Ritux dosing

- Can Rituximab "cure" relapsing/refractory AAV?

Time based routine rituximab re-treatment for relapsing ANCA-associated Vasculitis







Smith R, submitted

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

MAINRITSAN

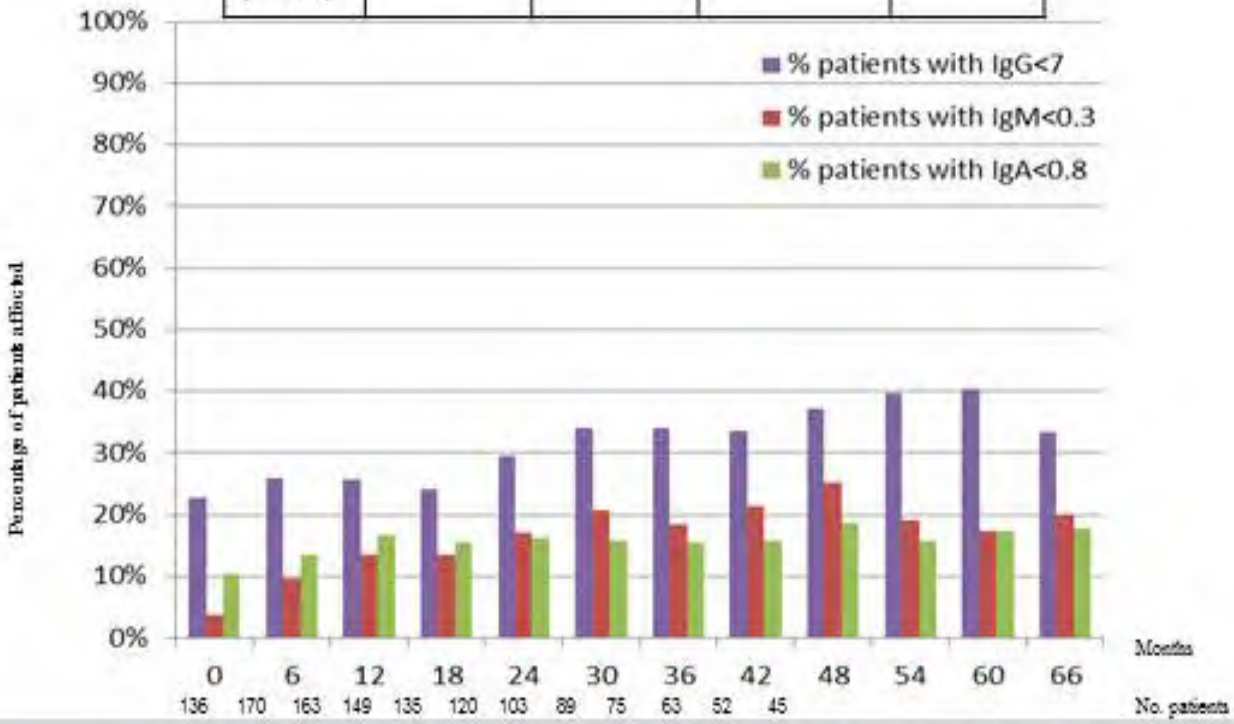
Etude de l'efficacité du Rituximab versus Azathioprine en traitement d'entretien au cours des vascularites associées aux ANCA

Investigateur coordonnateur :
Pr Loïc Guillevin

Centre de Gestion :
URC Paris Centre
Hôpital Cochin
ARC : Laurence Lecomte

Hypogammaglobulinemia post rituximab

	IgG <7 g/L	MILD	MODERATE	SEVERE
		5-7 g/L	3-4.9 g/L	< 3 g/L
% patients (N=177)	91 (51%)	48 (27%)	36 (20%)	7 (4%)



Marco H et al. *ERA/EDTA (abstract)* 2011

Rituximab in AAV

- Same rate of adverse events as conventional immunosuppressive therapy
- Effective treatment of relapsing/refractory AAV
- Reduced diagnostic and treatment delay
- As effective as CYC for remission induction
- Allow reduction of steroids and discontinuation of immunosuppressants in maintenance phase
- Long term efficacy and safety remain to be determined

Remerciements

- Équipe de Tenon: de Gabriel Richet et Liliane Morel-Maroger….. à celles/ceux d'aujourd'hui- Pierre Ronco
- GFEV, Loïc Guillevin
- EUVAS, David Jayne, Niels Rasmussen
- Service de Valenciennes