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Treatment of ANCA-associated vasculitides

Certainties and controversies

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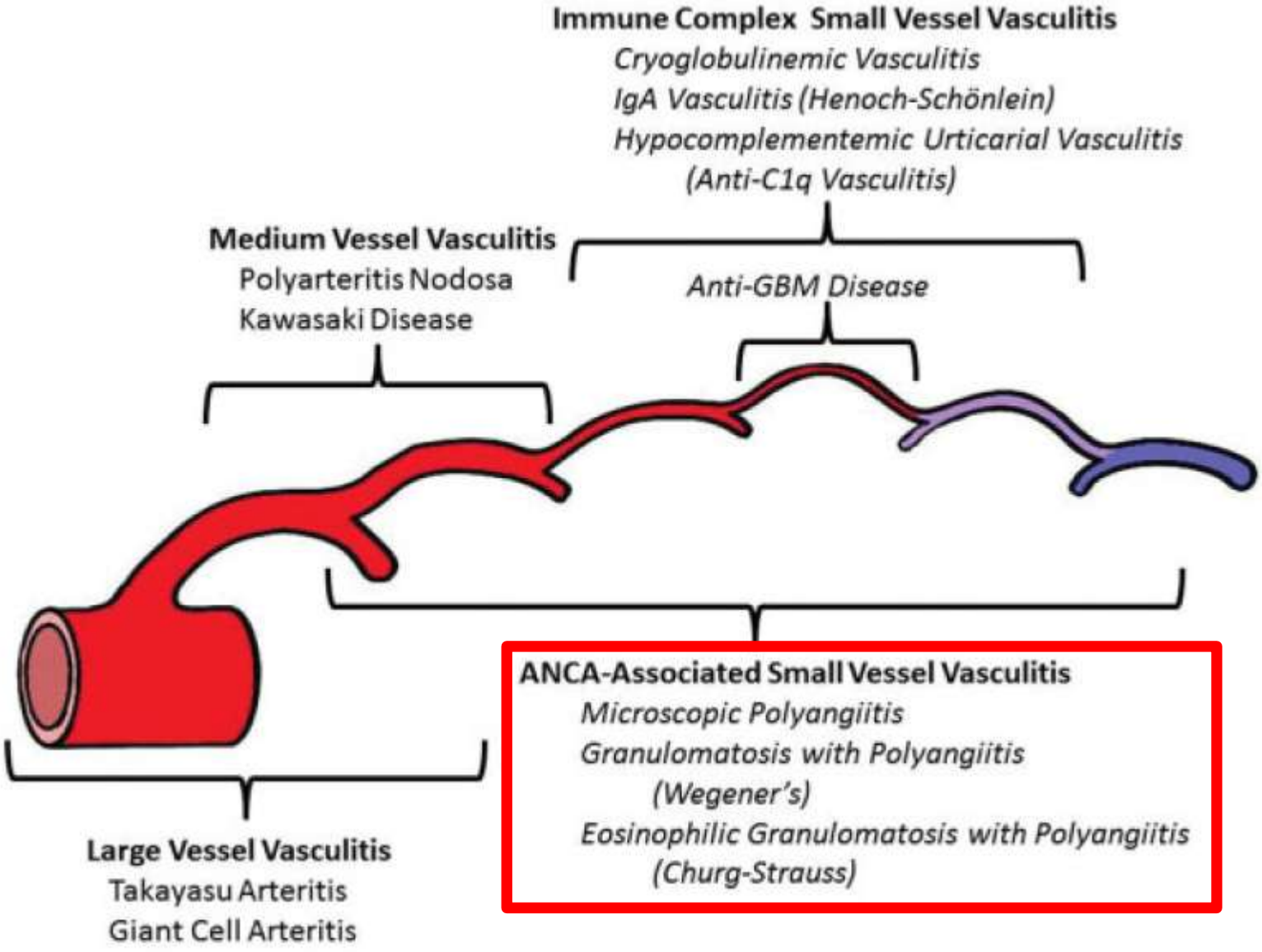
FVSG FRENCH VASCULITIS STUDY GROUP

Conflict of interest

- **Advisory board : Roche, Chugaï, Vifor, LFB, Grifols, AstraZeneca**
- **Consulting fees : Roche, Chugaï, LFB, Grifols, GSK, AstraZeneca**
- **Travel expenses : Roche, LFB, Grifols, Octapharma, GSK, Janssen**

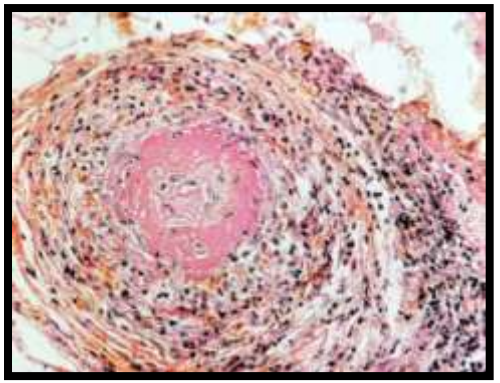
Chapel Hill 2012 Consensus conference



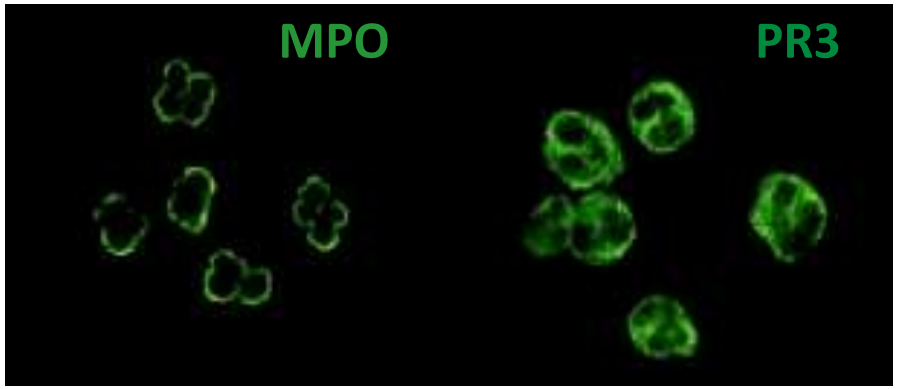
Jennette, Arthritis Rheum, 2013

ANCA-associated vasculitis

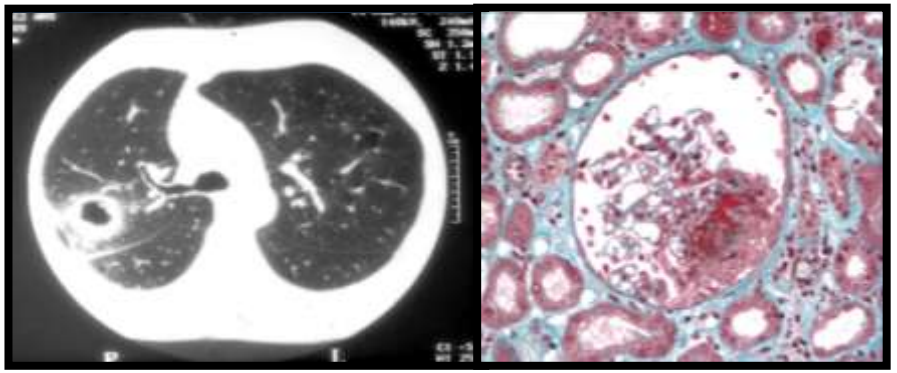
Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries)



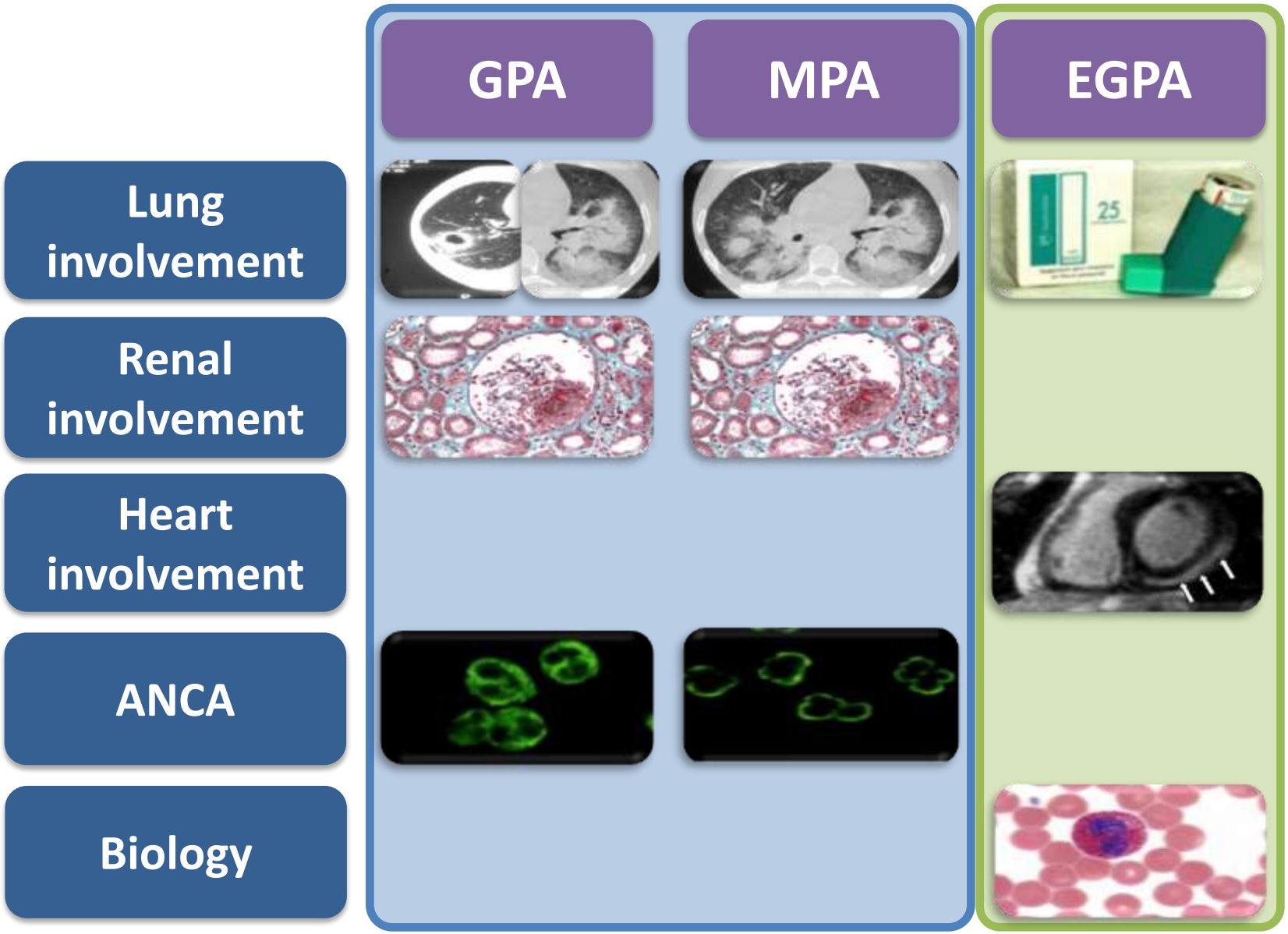
Associated with ANCA targeting myeloperoxidase or proteinase 3



Systemic disease with pulmonary, ENT and renal involvement



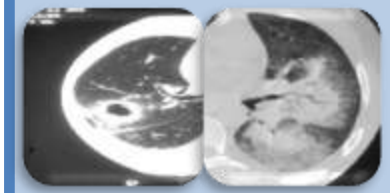
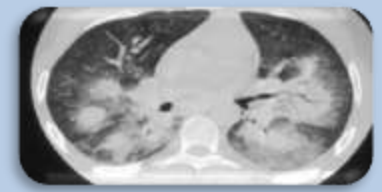
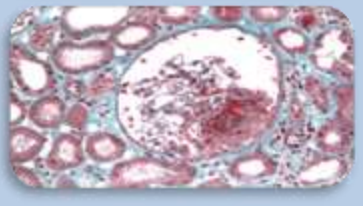
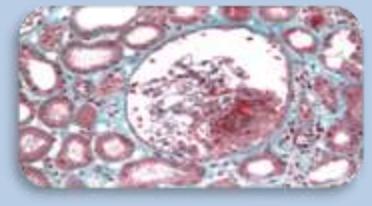
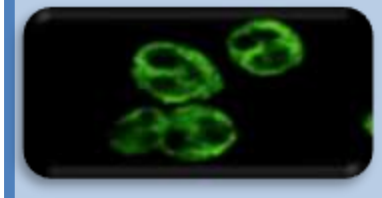
GPA/MPA vs. EGPA : Distinct phenotypes



GPA/MPA vs. EGPA : Distinct trials

RAVE, MAINRITSAN, RITAZAREM, …

MIRRA, REOVAS, …

	GPA	MPA	EGPA
Lung involvement			
Renal involvement			
Heart involvement			
ANCA			
Biology			

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

Stone JH et al, N Engl J Med, 2010;363:221-32

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Specks U et al, N Engl J Med, 2013;369:417-27

Hypothesis
RTX = CYC

Double-blind RCT
197 patients

99 patients — **98 patients**

INDUCTION

Prednisone + oral CYC 3-6 mo. + placebo-RTX

Prednisone + RTX 375 mg/m²/wk x 4 + placebo-CYC

ENTRETIEN

AZA 12-15 mo.

Nothing

	RTX (n=99)	CYC (n=98)
GPA (%)	75	76
MPA (%)	24	24
1st flare (%)	48	49
ENT (%)	61	56
Pulmonary (%)	52	54
AH	27	24
Renal (%)	66	66
eGFR (ml/min)	54	69

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

Stone JH et al, N Engl J Med, 2010;363:221-32

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

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Primary outcome : BVAS = 0 at 6 months and no steroids

RTX arm 63/99 (64%)

CYC arm 53/99 (54%)

Excluded ...

CONCLUSIONS

Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease. (Funded by the National Institutes of Allergy and Infectious Diseases, Genentech, and Biogen; ClinicalTrials.gov number, NCT00104299.)

Relapsing patients subgroup

RTX arm 67% vs. CYC arm 42%

P=0.01 for superiority

Rapidly progressive enal failure with serum creatinin >350 μmol/L

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Jones RB et al, N Engl J Med, 2010;363:211-20

Phase 2, open-label
44 patients

11 patients — **33 patients**

INDUCTION

Prednisone + CYC IV 3-6 mo.

Prednisone + RTX 375 mg/m²/wk x 4 + CYC IV day 1/15

ENTRETIEN

AZA

Nothing

Hypothesis
RTX/CYC > CYC

	RTX /CYC (n=33)	CYC (n=11)
Median age	68	67
GPA (%)	55	36
MPA (%)	36	36
Renal-limited	9	27
Renal (%)	100	100
eGFR (ml/min)	20	12
Dialysis (%)	24	9
PLEX (%)	24	27

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Jones RB et al, N Engl J Med, 2010;363:211-20

Primary endpoints

Sustained remission rates at 12 month

Severe adv

1

2

9

Se

14 [illegible]ximab group (42%)

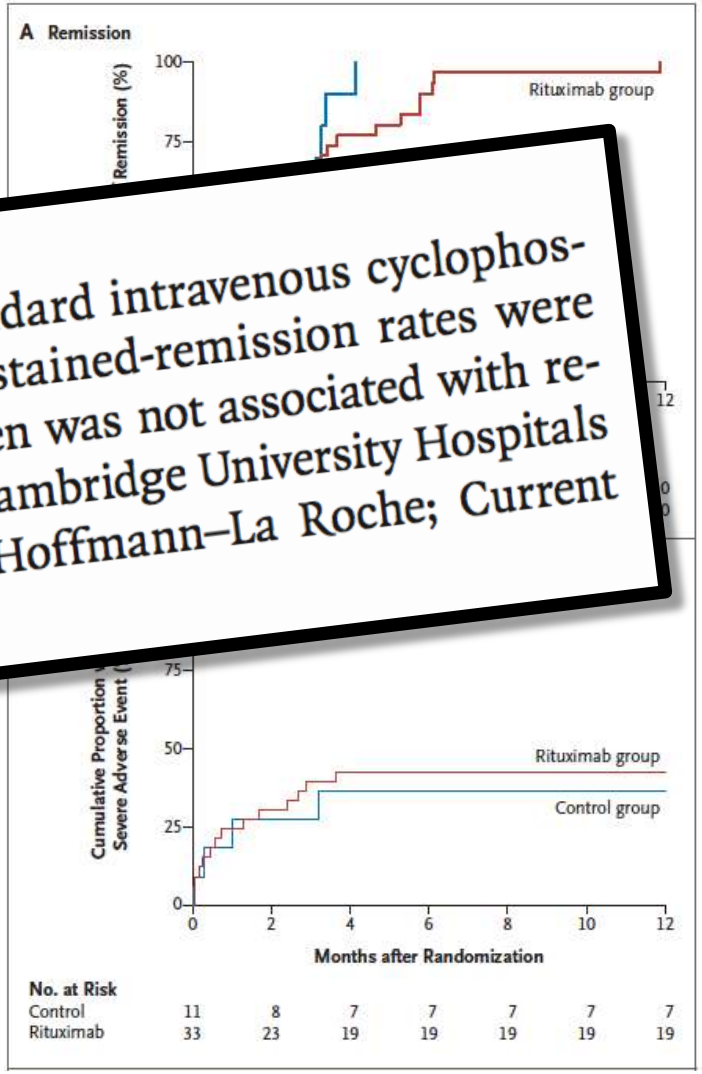
4/11 (36%) in the control group **(P=0.77)**

Death: 6/33 (18%) in the RTX/CYC group

vs. 1/11 (9%) in the control group

CONCLUSIONS

A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events. (Funded by Cambridge University Hospitals National Health Service Foundation Trust and F. Hoffmann–La Roche; Current Controlled Trials number, ISRCTN28528813.)



Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

Guillevin L et al, N Engl J Med, 2014;371:1771-80

Hypothesis
RTX > AZA

Induction phase

1 g x 3 i.v. méthylprednisolone

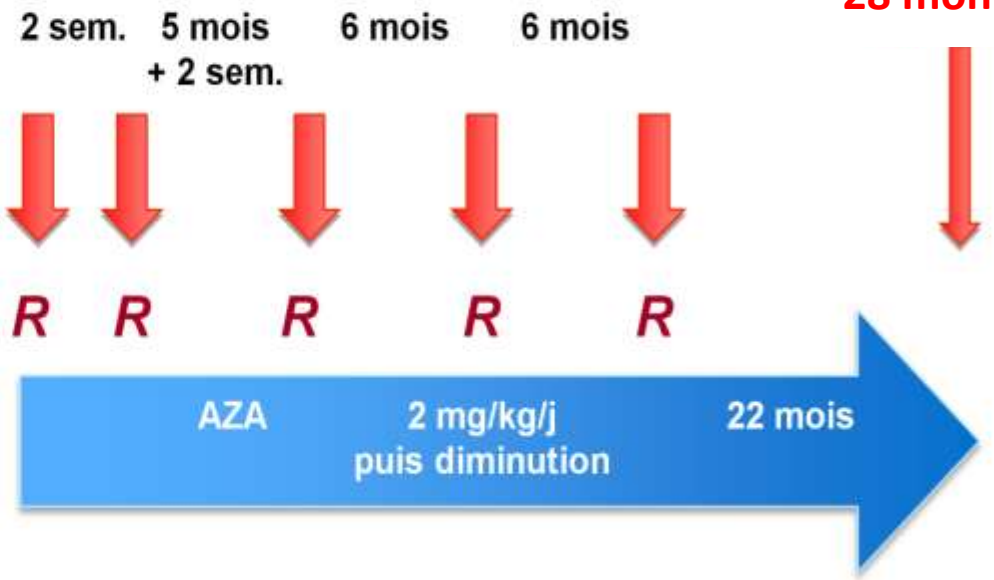
Prednisone (1mg/kg/j)
puis 20 mg à 3 mois
puis 10 mg à 6 mois

CYC i.v.
(0,6 g/m² x 3 puis 0,7 g/m² x 3)

Maintenance phase

R = 500 mg RTX-fixed dose

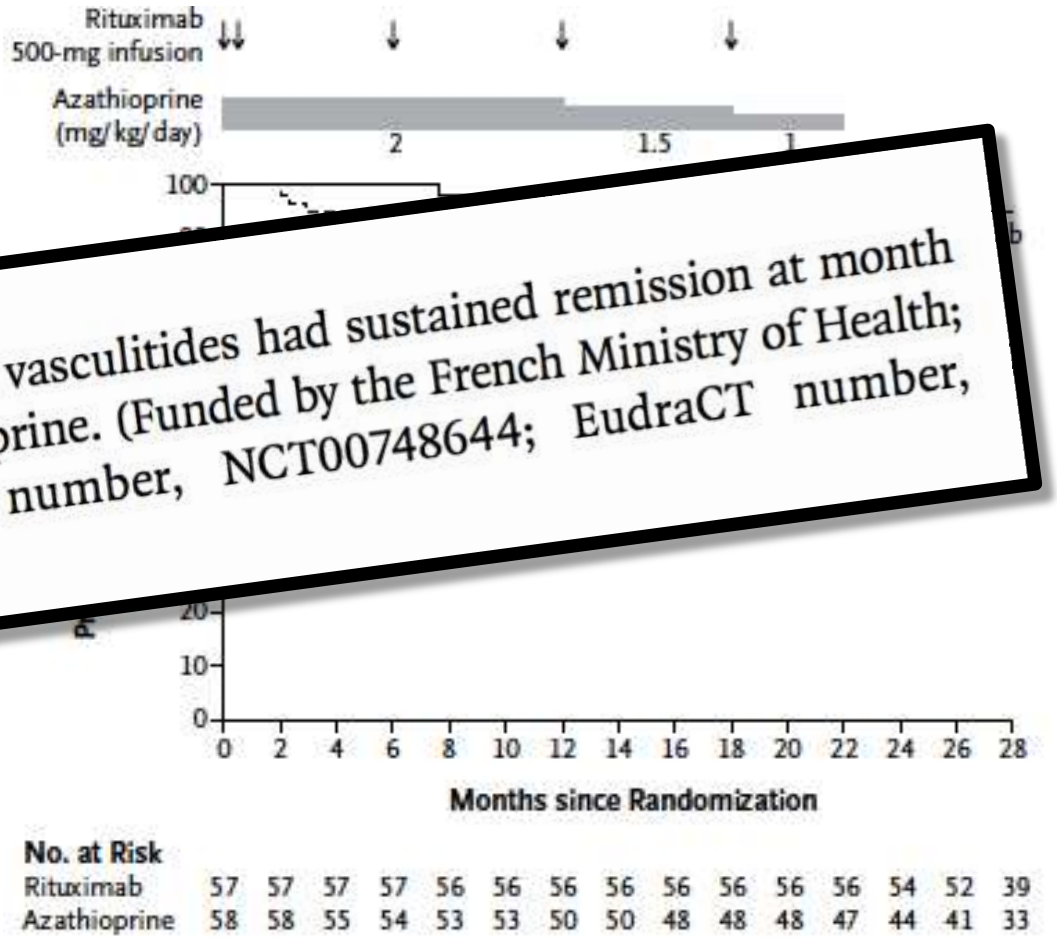
Evaluation at 28 months



Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

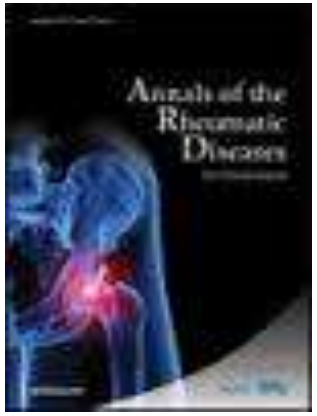
Guillevin L et al, N Engl J Med, 2014;371:1771-80

	AZA (n=58)	RTX (n=57)
GPA (%)	69	82
MPA (%)	21	
R	71	70
eGFR (ml/min)	58	68
Nervous system	33	40



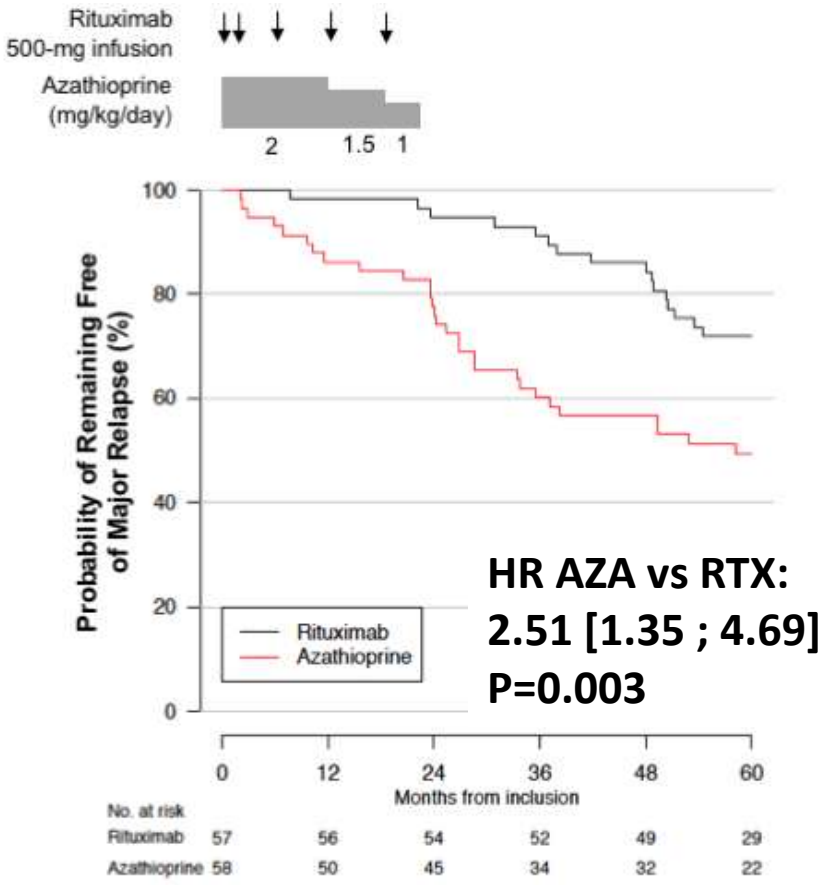
CONCLUSIONS

More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine. (Funded by the French Ministry of Health; MAINRITSAN ClinicalTrials.gov number, NCT00748644; EudraCT number, 2008-002846-51.)

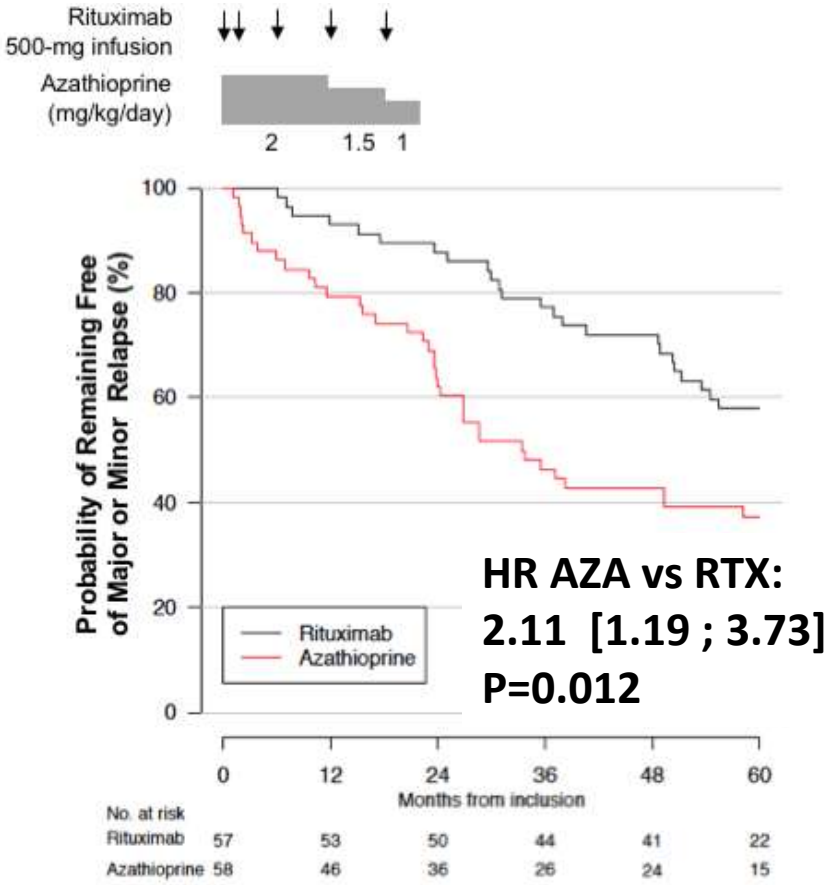


Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

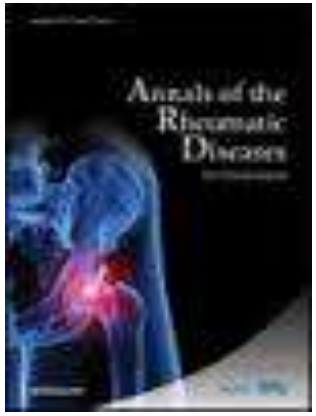
Terrier B et al, Ann Rheum Dis, 2018



HR AZA vs RTX:
2.51 [1.35 ; 4.69]
P=0.003



HR AZA vs RTX:
2.11 [1.19 ; 3.73]
P=0.012



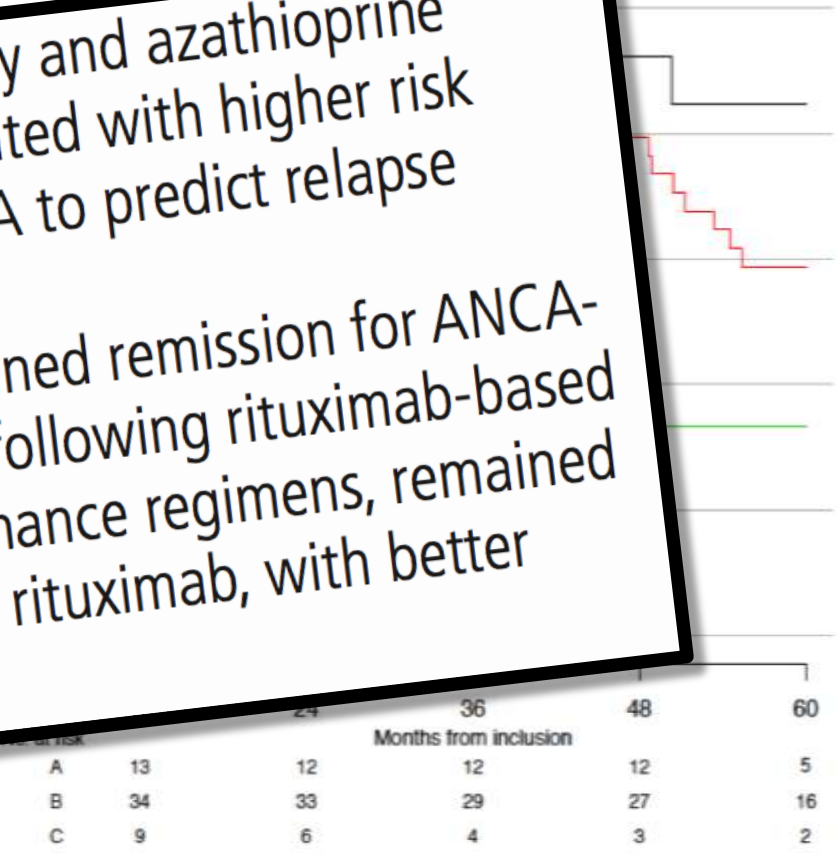
Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

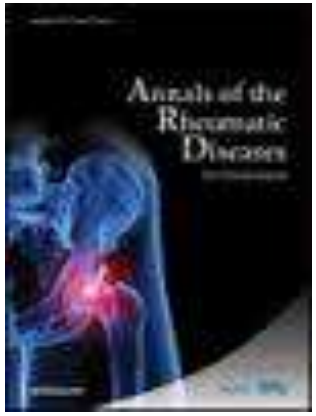
Terrier B et al, Ann Rheum Dis, 2018

Antiproteinase-3-ANCA positivity and azathioprine arm were independently associated with higher risk of relapse. HRs of positive ANCA to predict relapse increased over time.

Conclusion The rate of sustained remission for ANCA-associated vasculitis patients, following rituximab-based or azathioprine-based maintenance regimens, remained superior over 60 months with rituximab, with better overall survival.

Variables		
Univariate analy		
Age (years)		
Male (vs fema		
GPA (vs MPA c		
PR3-ANCA (vs		
Serum creatinin		
Ear, nose and th		
Pulmonary invol		
Cardiovascular in		
Induction to remi (persistence vs dis		
Multivariate analysis		
PR3-ANCA (vs MP		
Serum creatinine >		
Ear, nose and throat		
Arm (AZA vs RTX)	(1.55 to 4.76)	<0.001





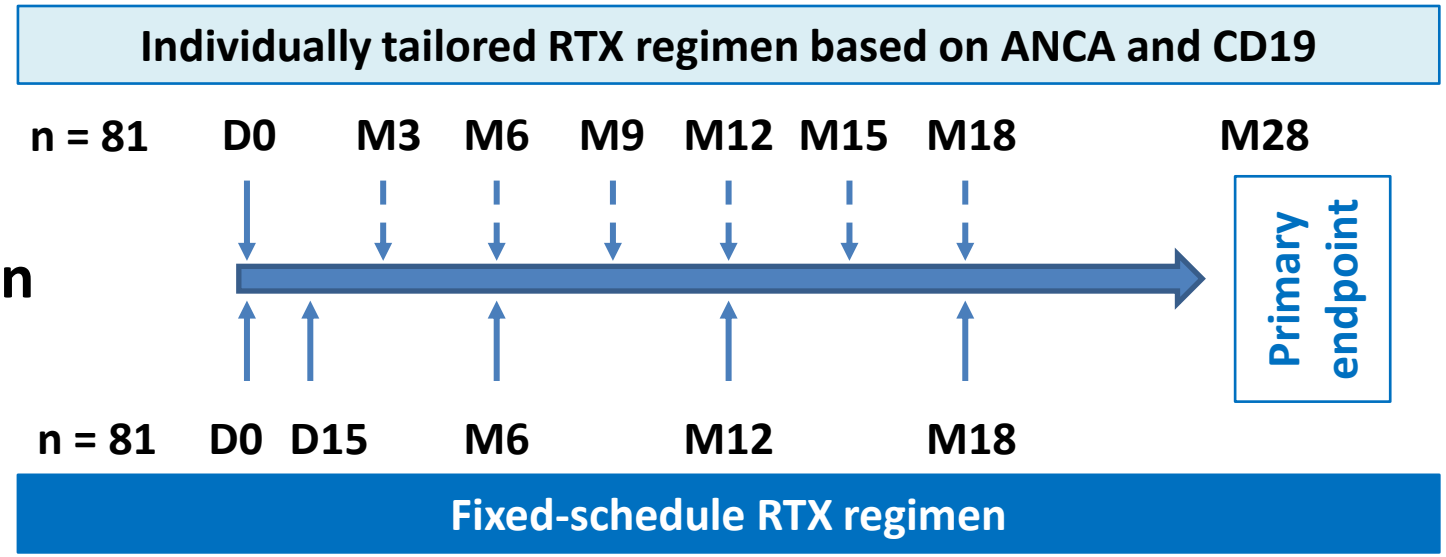
Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

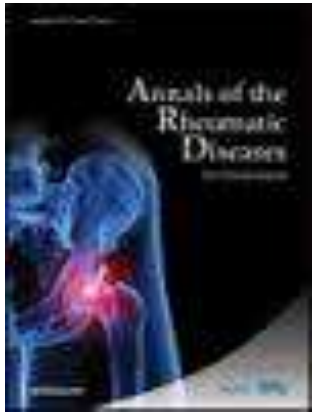
Charles P, Terrier B et al, Ann Rheum Dis, 2018

Open-label, multicenter, randomized controlled trial

Patients in complete remission after induction therapy with glucocorticoids plus RTX or CYC

Randomization





Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

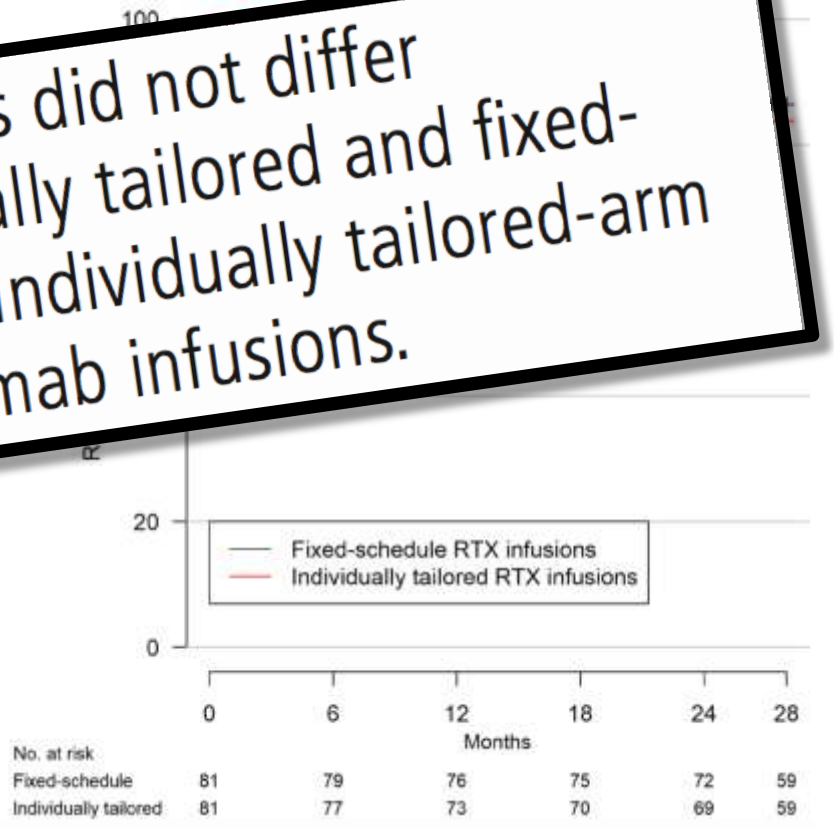
Charles P, Terrier B et al, Ann Rheum Dis, 2018

Number of relapses at month 28

14 relapses (17.3%) in 13 tailored-infusion recipients

Conclusion AAV relapse rates did not differ significantly between individually tailored and fixed-schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab infusions.

Relapse-free surviv



Safety

85% in the tailored-arm vs. 91% in the fixed-arm with at least one AE (P=0.33)

Should rituximab be used in very severe vasculitis forms (alveolar hemorrhage, renal failure) ?

Recommendations of the French Vasculitis Study Group on the use of rituximab in AAV

Charles, Presse Med, 2013

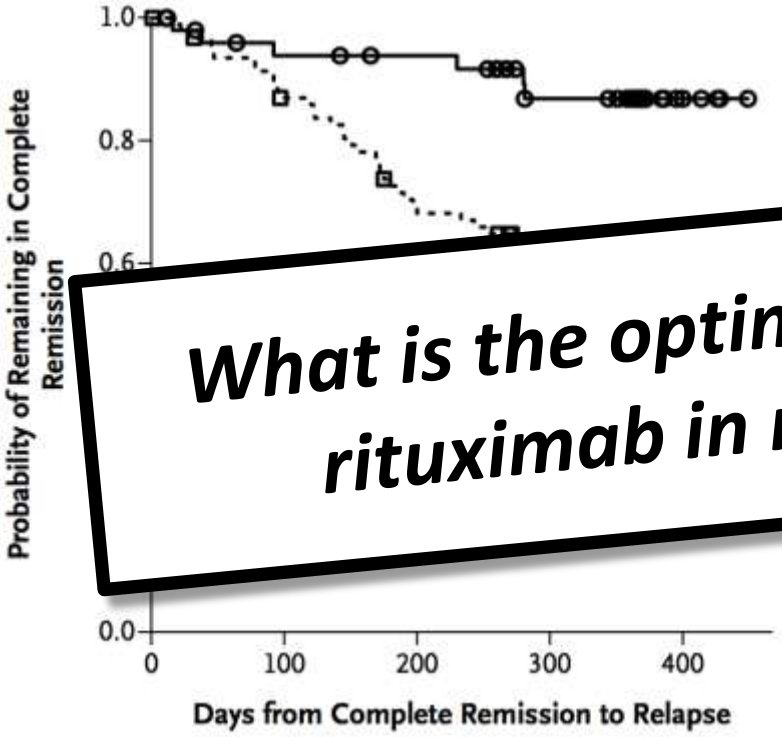
Should rituximab be used in very severe vasculitis forms (alveolar hemorrhage, renal failure) ?

What is the optimal dose and duration in maintenance phase ?

Charles, Ann Rheum Dis, 2018
Guillevin, N Engl J Med, 2014

PR3 vs. MPO-ANCA : Distinct prognosis at the rituximab era

Rituximab as induction therapy



Rituximab as maintenance therapy

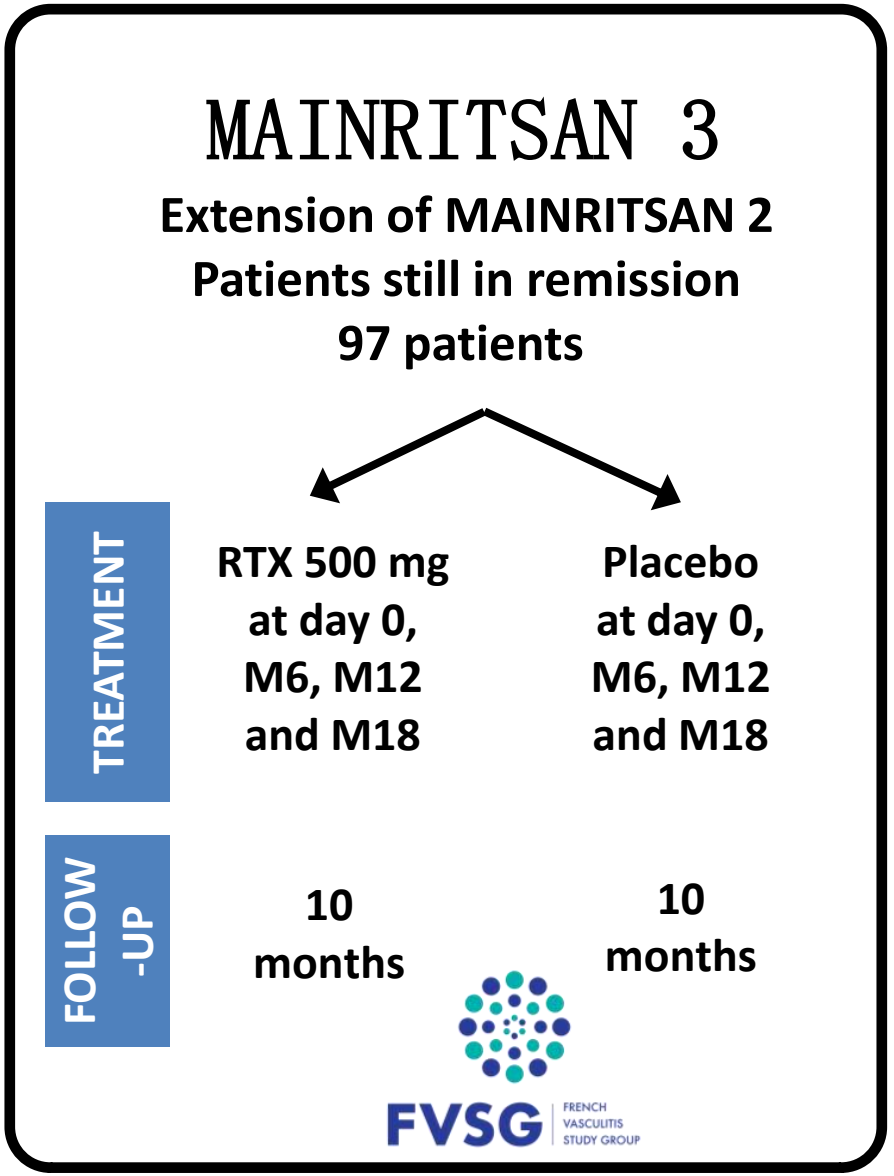
Variables	HR (95% CI)	P values
Univariate analysis		
Age (years)	1.00 (0.98 to 1.02)	0.984
Male (vs female)	1.00 (0.59 to 1.68)	.997
GPA (vs MPA or renal limited)		.030
		.012
		.093
		.61
		.84
		.64
		0.756
Multivariate analysis		
PR3-ANCA (vs MPO-ANCA or no ANCA)	2.04 (1.06 to 3.91)	0.032
Serum creatinine >2.27 mg/dL	0.58 (0.31 to 1.11)	0.100
Ear, nose and throat involvement	1.18 (0.59 to 2.35)	0.634
Arm (AZA vs RTX)	2.72 (1.55 to 4.76)	<0.001

What is the optimal dose and duration of rituximab in maintenance phase ?

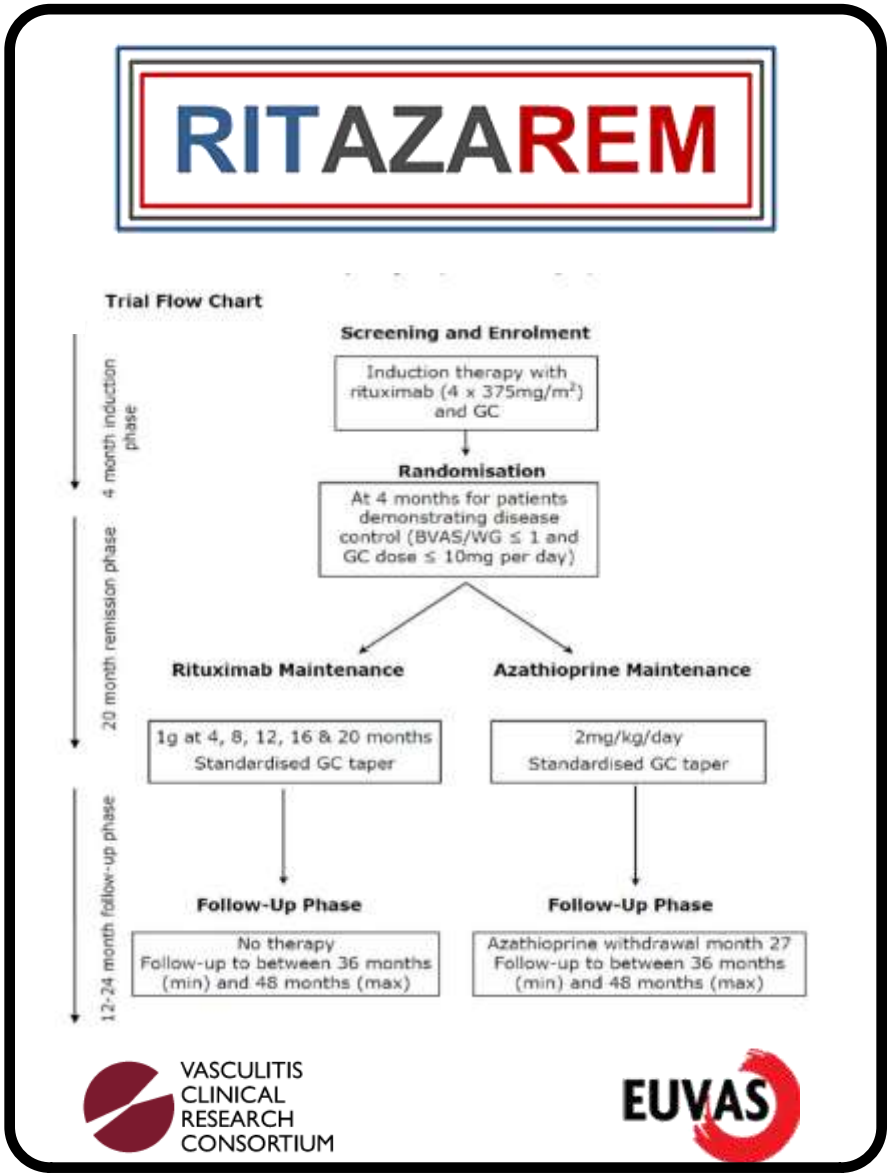
Terrier, Ann Rheum Dis, 2018
Specks, N Engl J Med, 2013
Stone, N Engl J Med, 2010

What is the optimal duration in maintenance phase ?

- Comparison of 18 months vs. 46 months
- Primary endpoint : relapse free survival
- Results probably presented at ACR 2019
- Will statistical power be enough for subgroup analyses ?



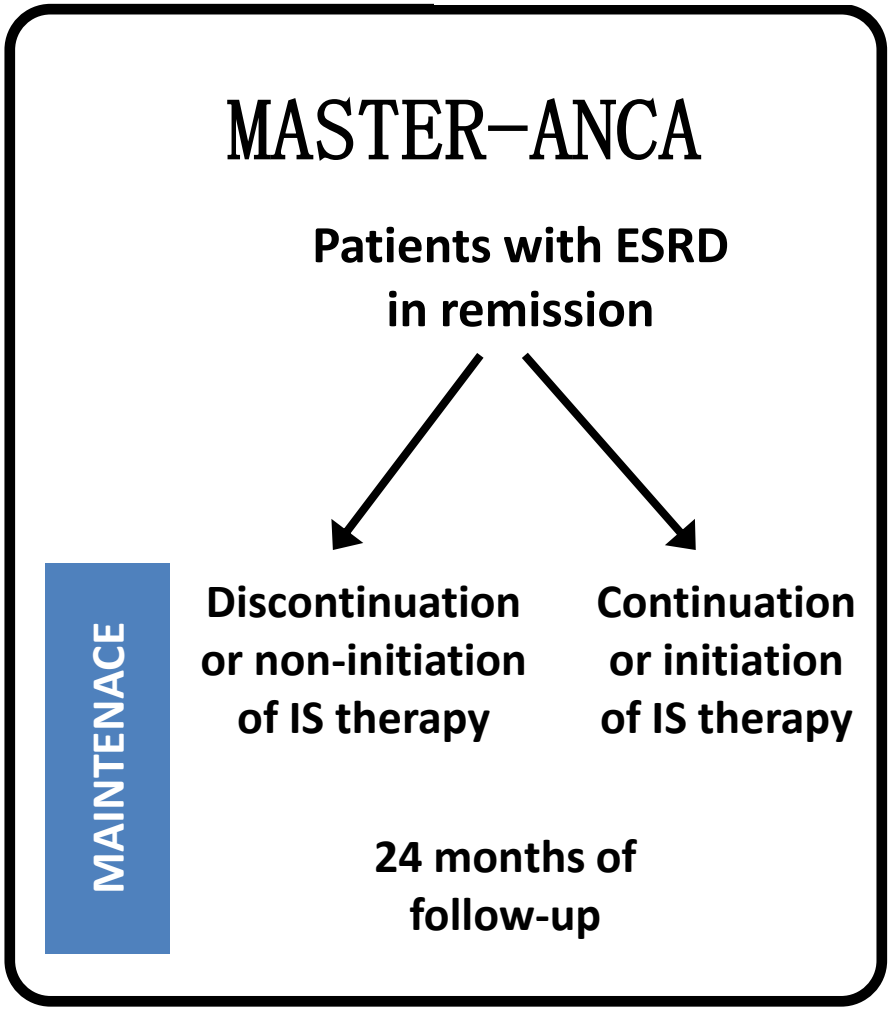
What is the optimal dose in maintenance phase ?



- **RTX 1 g every 4 months (total 5 g) vs. 500 mg every 6 months (total 2.5 g)**
- **Primary endpoint : relapse free survival**
- **Concerns about using such dose of RTX on the risk of severe infections**

Do all patients require a maintenance treatment ?

- Morbidity and mortality of immunosuppressive agents
- Significant predictors of mortality: advancing age, eGFR <15 mL/min
- Patients with higher creatinine levels have a lower risk of relapse (sHR 0.39 [95% CI 0.22-0.69] for a creatinine level >200 µmol/L)
- **Could patients with ESRD benefit from the absence of maintenance treatment ?**



Flossman, Ann Rheum Dis, 2011
Walsh, Arthritis Rheum, 2012

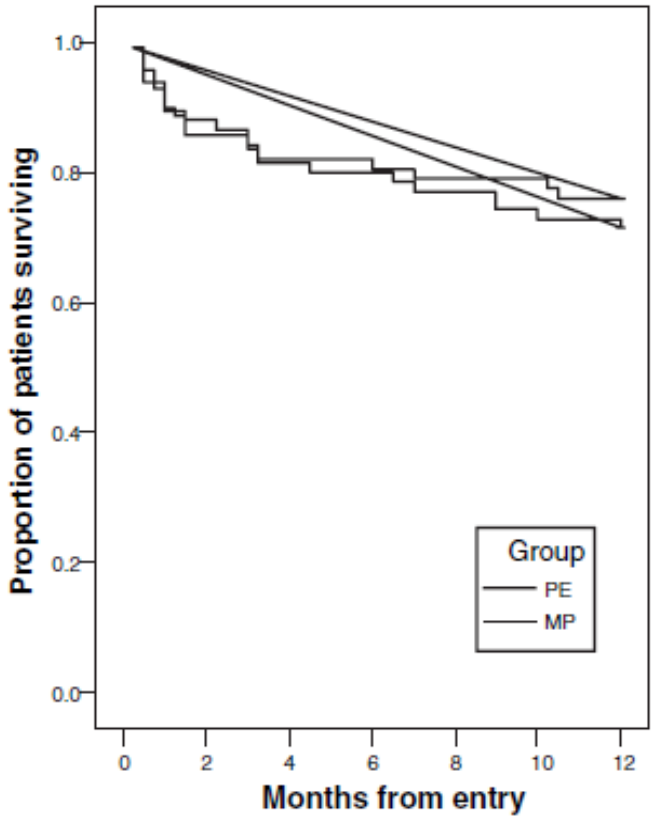
What place for plasma exchanges before 2018 ?

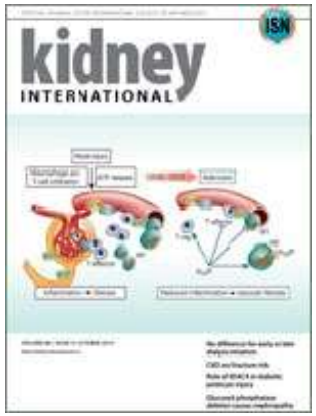
Indications of plasma exchanges in combination with glucocorticoids and cyclophosphamide/rituximab
Rapidly progressive glomerulonephritis with serum creatinin >500 µmol/L
Rapidly progressive glomerulonephritis with serum creatinin between 150 and 500 µmol/L **BUT** rapid progression of renal failure
Severe alveolar hemorrhage (massive hemoptysis, acute respiratory distress syndrome)
Rapidly extensive mononeuritis multiplex *Refractory vasculitis despite optimal treatment*

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

Jayne DR et al, J Am Soc Nephrol, 2007;18:2180-88

- Treatment of severe renal vasculitis with serum creatinin >500 µmol/L
- Comparison between pulses of MP vs. PLEX, in combination with oral CYC
- Primary endpoint : dialysis independence at 3 months (49% with MP vs. 69% with PLEX, P=0.02)
- Secondary endpoints : renal survival at 12 months (57% with MP vs. 81% with PLEX, P=0.008)

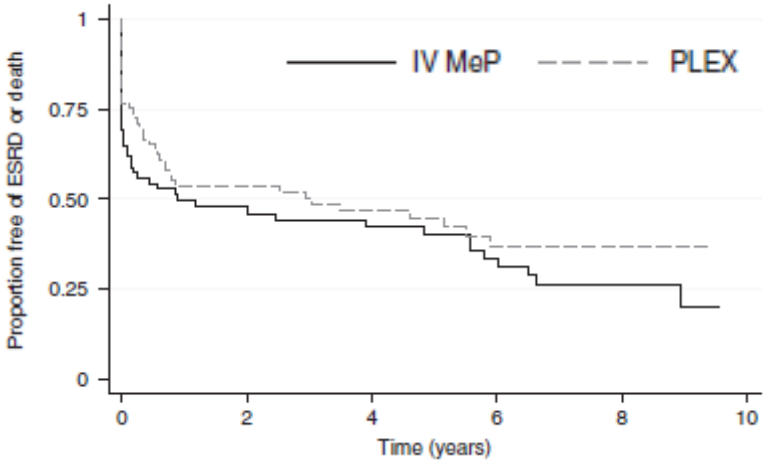


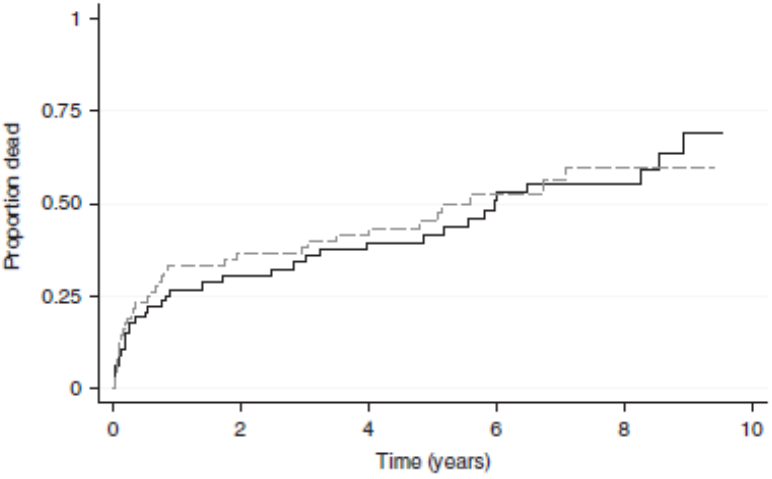


Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear

Walsh M et al, Kidney Int, 2013;84:397-402

- HR for death/ESRD for PLEX vs. MP: 0.81 (IC 95% 0.53-1.23)
- HR for death for PLEX vs. MP: 1.08 (IC 95% 0.67-1.73)
- HR for ESRD for PLEX vs. MP: 0.64 (IC 0.40-1.05, P=0.08)
- **No long-term benefit of PLEX**

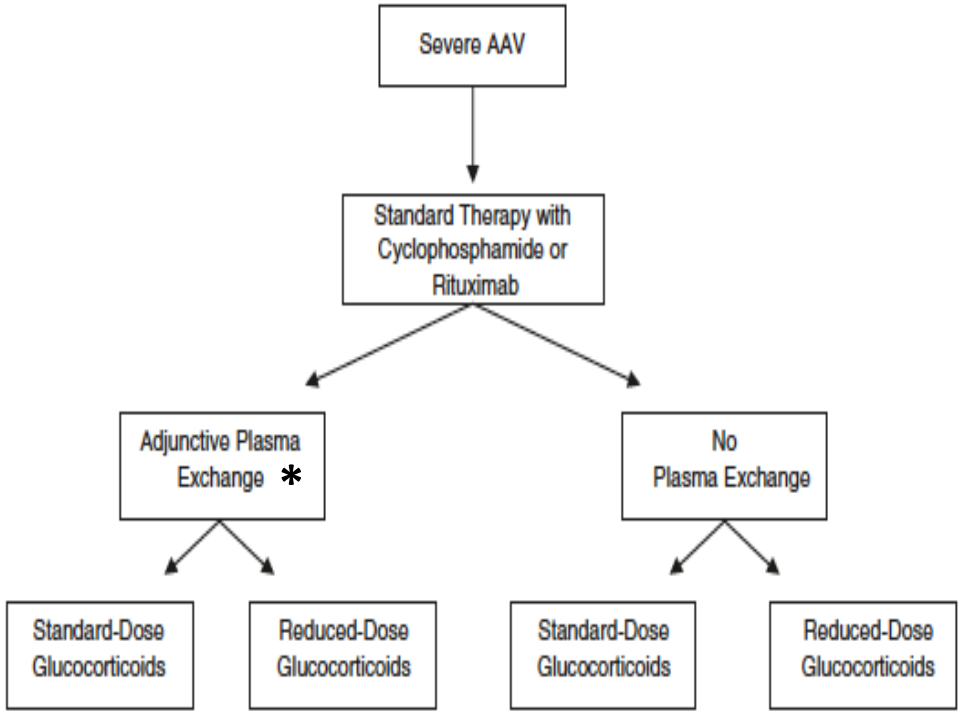




Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

PEXIVAS

- 704 patients with severe ANCA-associated vasculitis:
  - Renal failure with eGFR <50 mL/min
  - Alveolar hemorrhage
- Composite primary endpoint : time to death/ESRD (= dialysis for >12 weeks)

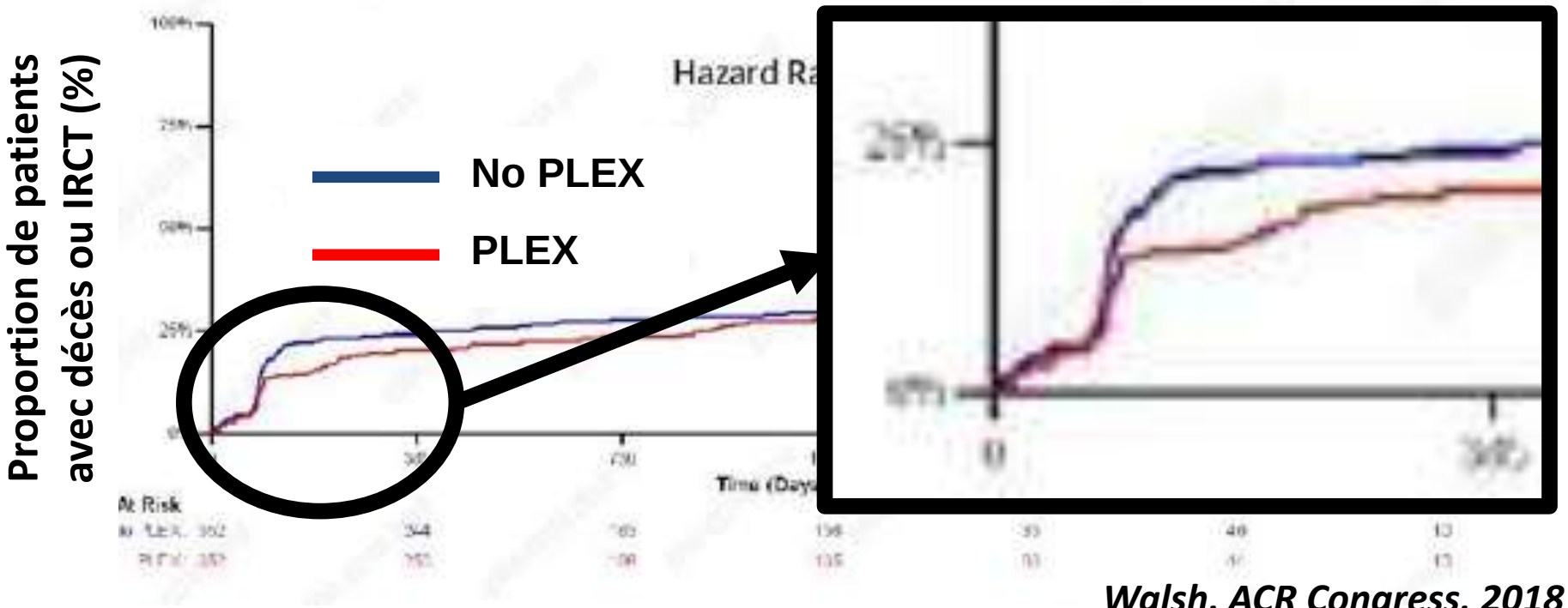


PLEX Arm : 7 PLEX over 14 days

Walsh, Trials, 2013

Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Primary outcome occurred in 28% of patients allocated to PLEX compared to 31% in the no PLEX group (HR 0.86, 95% CI 0.65 to 1.13; P=0.27)



Walsh, ACR Congress, 2018

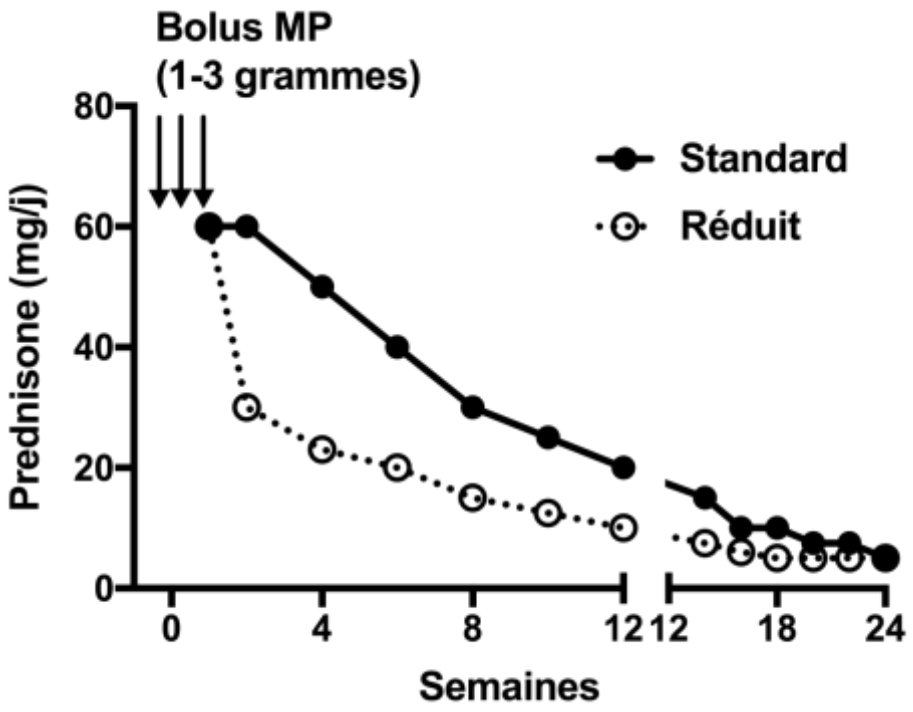
Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial

Analysis of patients with AH suggesting a signal in favor of PLEX, with a relative risk of achieving the composite primary endpoint of 0.95 in the absence of AH, **0.65 in the presence of moderate AH and 0.67 in the presence of a severe AH** (P=NS)

Possible benefit at 1 year and in severe alveolar hemorrhage ?

Walsh, ACR Congress, 2018

Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial



- Primary outcome occurred in 28% in the reduced GCs group and 26% in the standard GCs group (absolute risk difference 2.3%, 90% CI -3.4% to 8.0%; **non-inferiority hypothesis met**)

- **Serious infections in the first year occurred less often in the reduced GCs group** compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52 to 0.94; P=0.02)

Walsh, ERA EDTA Congress, 2018

What place for plasma exchanges after 2018 ?

Recommendations of the French Vasculitis Study Group on the use of PLEX in AAV

What place for plasma exchanges after 2018 ?

Recommendations of the French Vasculitis Study Group on the use of PLEX in AAV

Take home messages

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