Recent advances in management of Pulmonary Vasculitis

Dr Nita MB

23-01-2015

Overview of the seminar

- Recent classification of Vasculitis
- What is new in present classification?
- Trials on remission induction
- Trials on remission maintenance
- Ongoing trials

2012 Revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides

Large vessel vasculitis (LVV)
- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel vasculitis (SVV)
- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener's) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - Anti–glomerular basement membrane (anti-GBM) disease
  - Cryoglobulinemic vasculitis (CV)
  - IgA vasculitis (Henoch-Schönlein) (IgAV)
  - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

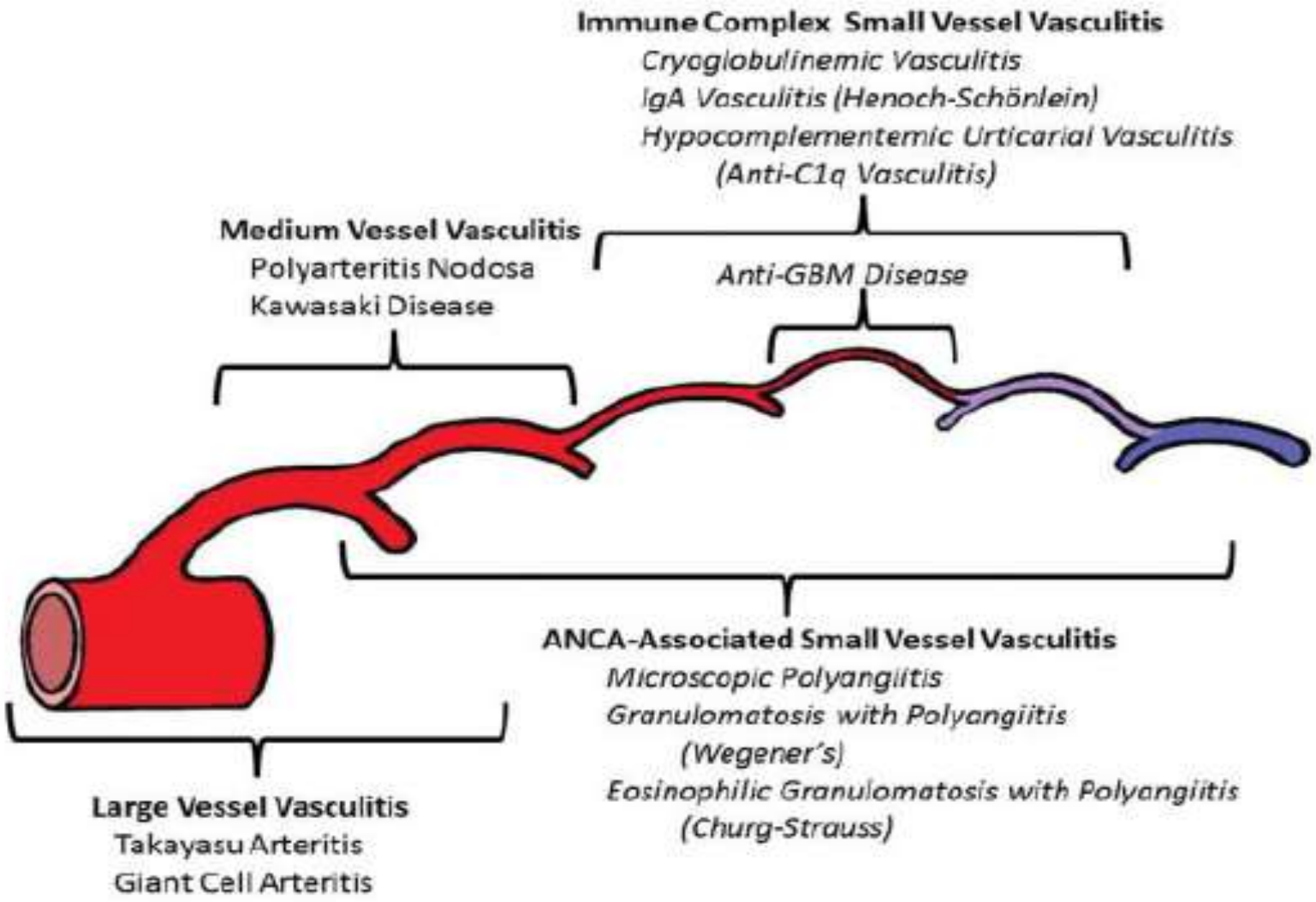
Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

- Four new primary categories included
- Replaced some eponyms with descriptive terms
- Focuses on aetiology, pathogenesis, pathology, and clinical characteristics as the basis for categorization

Jennette JC et al. Arthritis and Rheumatism. Vol.65, No.1, January 2013, pp 1-11

Distribution of vessel involvement by the major categories of vasculitis



Jennette JC et al. Arthritis and Rheumatism. Vol.65, No.1, January 2013, pp 1-11

Disease stages in ANCA-associated vasculitis (AAV)

Disease stage	EUVAS and EULAR definition[53,61]	Systemic vasculitis outside ENT or lung	Threatened vital organ function	Serum creatinine (μmol/l)
Localized	Upper and/or lower respiratory tract disease without further systemic involvement or constitutional symptoms	No	No	<120
Early systemic	Any disease without organ-threatening or life-threatening involvement	Yes	No	<120
Generalized	Renal or other organ-threatening disease	Yes	Yes	<500
Severe	Renal or other vital organ failure	Yes	Organ failure	>500
Refractory	Progressive disease unresponsive to standard therapy	Yes	Yes	Any

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibody; ENT, ear, nose, throat; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group.

Schönermarck U et al. Nat. Rev. Nephrol. 2014;10:25-36

Management of Pulmonary Vasculitis
Old vs Newer Agents

Induction of remission

CYCLOPS Trial

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

A Randomized Trial

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD; Wolfgang L. Gross, MD; Rashid Luqmani, MD; Charles D. Pusey, MD, PhD; Niels Rasmussen, MD; Renato A. Sinico, MD; Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin Westman, MD, PhD; and Caroline O.S. Savage, MD, PhD, for the EUVAS (European Vasculitis Study Group)

Initial Results (9 mths)

Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up

Lorraine Harper,[1] Matthew D Morgan,[1] Michael Walsh,[2] Peter Hoglund,[3] Kerstin Westman,[4] Oliver Flossmann,[5] Vladimir Tesar,[6] Phillipe Vanhille,[7] Kirsten de Groot,[8] Raashid Luqmani,[9] Luis Felipe Flores-Suarez,[10] Richard Watts,[11] Charles Pusey,[12] Annette Bruchfeld,[13] Niels Rasmussen,[14] Daniel Blockmans,[15] Caroline O Savage,[1] David Jayne[1] on behalf of EUVAS investigators

Long-term F/U Results (18 mths)

de Groot K et al. Ann Intern Med 2009;150:670-680
Harper L et al. Ann Rheum Dis 2012;71:955-960

CYCLOPS : Methodology

- Multicenter, open-label, RCT
- 149 patients with newly diagnosed generalized AAV (GPA or MPA) with renal involvement but not immediately life-threatening disease (76 patients in the pulse group and 73 patients in the daily oral group)
- 56 patients had GPA, 71 had MPA, and 22 had renal-limited vasculitis
- 76 patients (pulse CYC 15mg/kg every 2-3 weeks plus prednisolone) and 73 patients (daily oral CYC 2mg/kg/day plus prednisolone)

Baseline patient characteristics

Characteristic	Pulse Cyclophosphamide Group (n = 76)	Daily Oral Cyclophosphamide Group (n = 73)
Mean age (SD), *y*	56.5 (15.3)	58.2 (13.7)
Men, *n (%)*	41 (54)	47 (64)
Diagnosis, *n (%)*		
Wegener granulomatosis	25 (33)	31 (42)
Microscopic polyangiitis	38 (50)	33 (45)
Renal limited vasculitis	13 (17)	9 (12)
Confirmatory renal biopsy, *n (%)*	60 (79)	57 (78)
Positive biopsy result and ANCA-positive, *n (%)*	60 (79)	56 (77)
Positive biopsy result and ANCA-negative, *n (%)*	0	1 (1)
Negative biopsy result and ANCA-positive, *n (%)*	16 (21)	16 (22)
PR3-ANCA–positive, *n (%)*	30 (39)	30 (41)
MPO-ANCA–positive, *n (%)*	38 (50)	37 (51)
PR3- and MPO-ANCA–positive, *n (%)*	4 (5)	2 (3)
PR3- and MPO-ANCA–negative, *n (%)*	4 (5)	4 (5)
Mean BVAS for new or worse disease (SD)*	20 (6.8)	21 (6.7)
Mean disease extension index (SD)†	4.2 (2.2)	4.5 (2.2)
Mean serum creatinine level (SD)		
μmol/L	225 (128)	222 (120)
mg/dL	2.55 (1.45)	2.51 (1.36)
Mean estimated GFR (SD), *mL/min per 1.73 m²*‡	38 (27)	35 (21)
Mean C-reactive protein level, *nmol/L*	523.82 (542.87)	838.11 (847.64)
Vasculitis Damage Index Score (range)	0 (0–5)	0 (0–3)

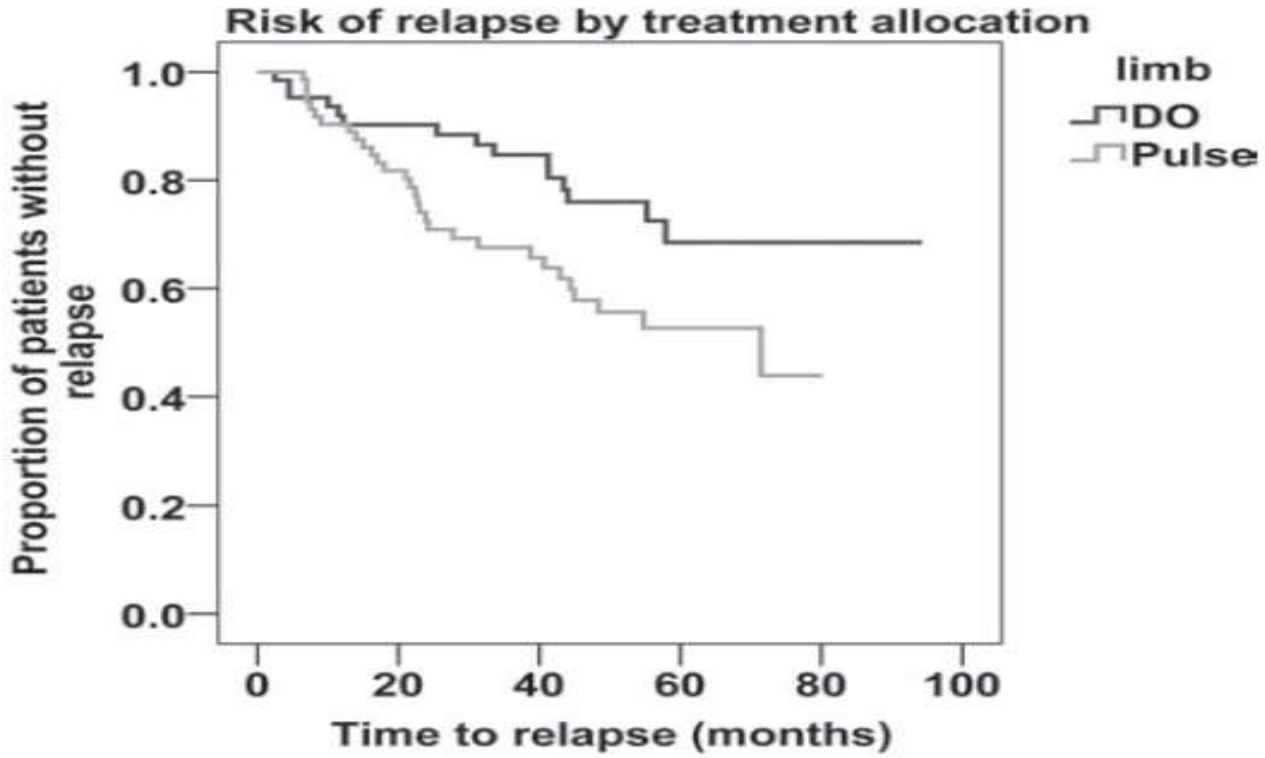
Results (short-term)

- Both the groups did not differ in time to remission (p=0.59) or proportion of patients who achieved remission at 9 months (88.1% vs 87.7%)
- 13 patients in the pulse group and 6 patients in the daily oral group achieved remission by 9 months and subsequently had relapse
- Absolute cumulative cyclophosphamide dose in the daily oral group was greater than that in the pulse group (15.9g vs 8.2g; $p<0.001$)
- The pulse group had a lower rate of leukopenia (HR 0.41, CI: 0.23-0.71)

Long-term outcomes

Parameter	9 Months		12 Months		15 Months		18 Months	
	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group	Pulse Group	Daily Oral Group
Total patients, *n*	63	58	62	55	62	54	62	54
Disease status, *n*								
Active disease	2	0	1	0	1	0	1	0
Achieved remission	61	58	61	55	61	54	61	54
Censored (in remission), *n*								
Died	4 (1)	8 (3)	5 (2)	9 (4)	5 (2)	9 (4)	5 (2)	9 (4)
Lost to follow-up	2 (1)	1 (1)	2 (1)	1 (1)	2 (1)	1 (1)	2 (1)	1 (1)
Withdrew	7 (4)	6 (2)	7 (4)	8 (4)	7 (4)	9 (5)	7 (4)	9 (5)
Relapse after initial remission, *n*	7	3	7	6	10	6	13	6
Renal outcomes								
End-stage renal disease, *n*	4	0	4	1	4	1	5	1
Median estimated glomerular filtration rate (IQR), *mL/min per 1.73 m²*†	44 (29–62)	52 (38–66)	45 (32–65)	50 (37–69)	47 (29–68)	53 (41–69)	50 (30–70)	48 (36–69)
Cumulative cyclophosphamide dose								
Median dose for patients still in study (IQR), *g*	8.28 (6.55–10.68)	17.5 (13.8–24.75)	8.5 (6.74–10.93)	18 (13.49–26.31)	8.58 (6.76–11.9)	18.05 (13.48–26.77)	8.58 (6.76–11.9)	18.05 (13.5–27)

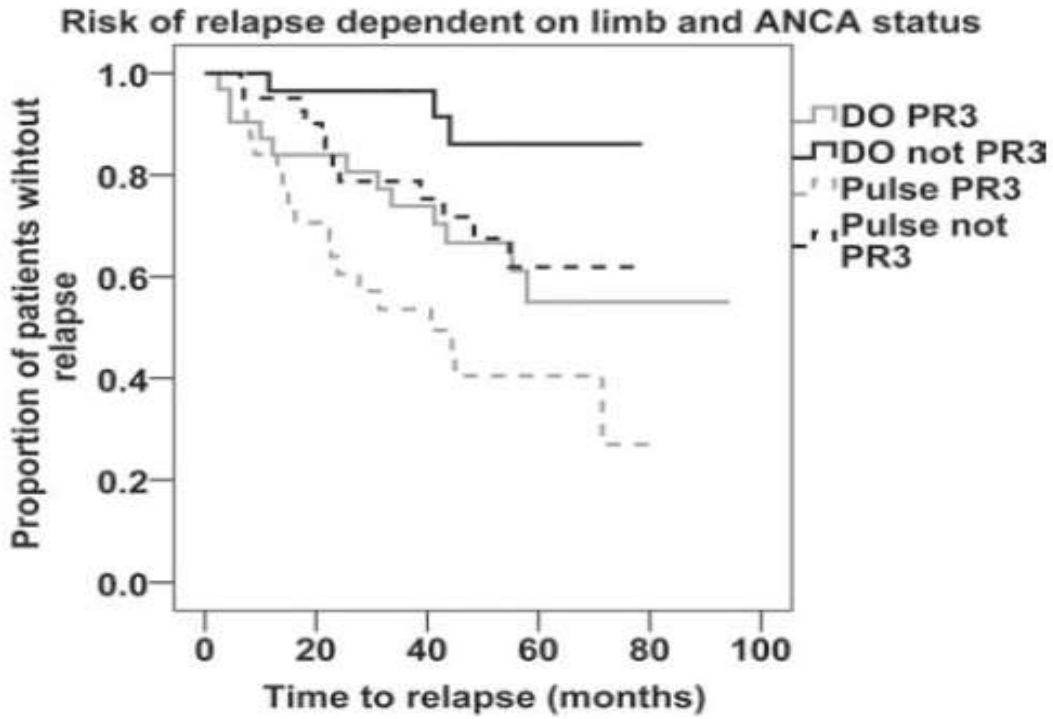
Relapse-free survival in the treatment arms



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

Significantly increased risk of relapse during F/U in patients randomized to pulse CYC than daily oral CYC (p=0.029)

Risk of relapse defined by PR-3 ANCA status and trial treatment limb



Time (months)	0	20	40	60	80
DO not PR3-ANCA (n)	39	24	20	8	0
Pulse not PR3-ANCA (n)	43	32	22	9	0
DO PR3-ANCA (n)	33	25	21	9	2
Pulse PR3-ANCA (n)	33	21	13	5	1

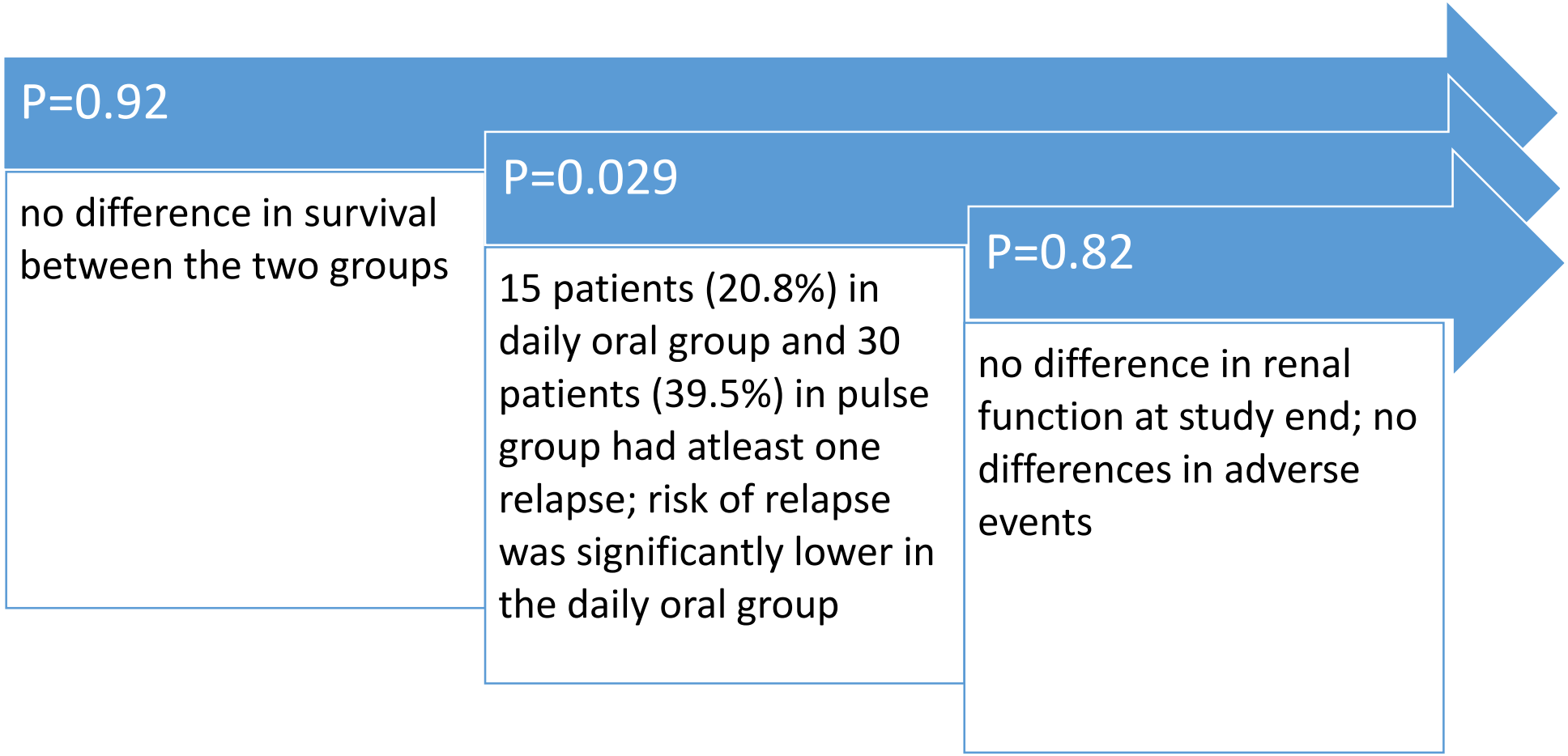
PR-3 ANCA positive patients receiving pulse treatment had the highest risk of relapse, and DO treated patients who were not PR-3 ANCA had the lowest risk of relapse; patients who were not PR-3 ANCA and treated with pulse treatment and DO treated patients who were PR-3 ANCA positive had an intermediate risk of relapse

Factors associated with relapse

		95.0% CI		
	HR	Lower	Upper	p Value
DO vs pulse	0.46	0.25	0.86	0.015
PR3-ANCA positive vs negative	2.47	1.32	4.59	0.004

ANCA, antineutrophil cytoplasm autoantibodies; PR3-ANCA, antiproteinase 3 antibodies; DO, daily oral.

Long-term outcomes (retrospective analysis) median duration of F/U 4.3 yrs



NORAM Trial

Randomized Trial of Cyclophosphamide Versus Methotrexate for Induction of Remission in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Kirsten de Groot,[1] Niels Rasmussen,[2] Paul A. Bacon,[3] Jan Willem Cohen Tervaert,[4] Conleth Feighery,[5] Gina Gregorini,[6] Wolfgang L. Gross,[7] Raashid Luqmani,[8] and David R. W. Jayne,[9] for the European Vasculitis Study Group

Initial Results (6 mths)

Long-Term Outcome of a Randomized Clinical Trial Comparing Methotrexate to Cyclophosphamide for Remission Induction in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Mikkel Faurschou,[1] Kerstin Westman,[2] Niels Rasmussen,[3] Kirsten de Groot,[4] Oliver Flossmann,[5] Peter Höglund,[6] and David R. W. Jayne,[7] on behalf of the European Vasculitis Study Group

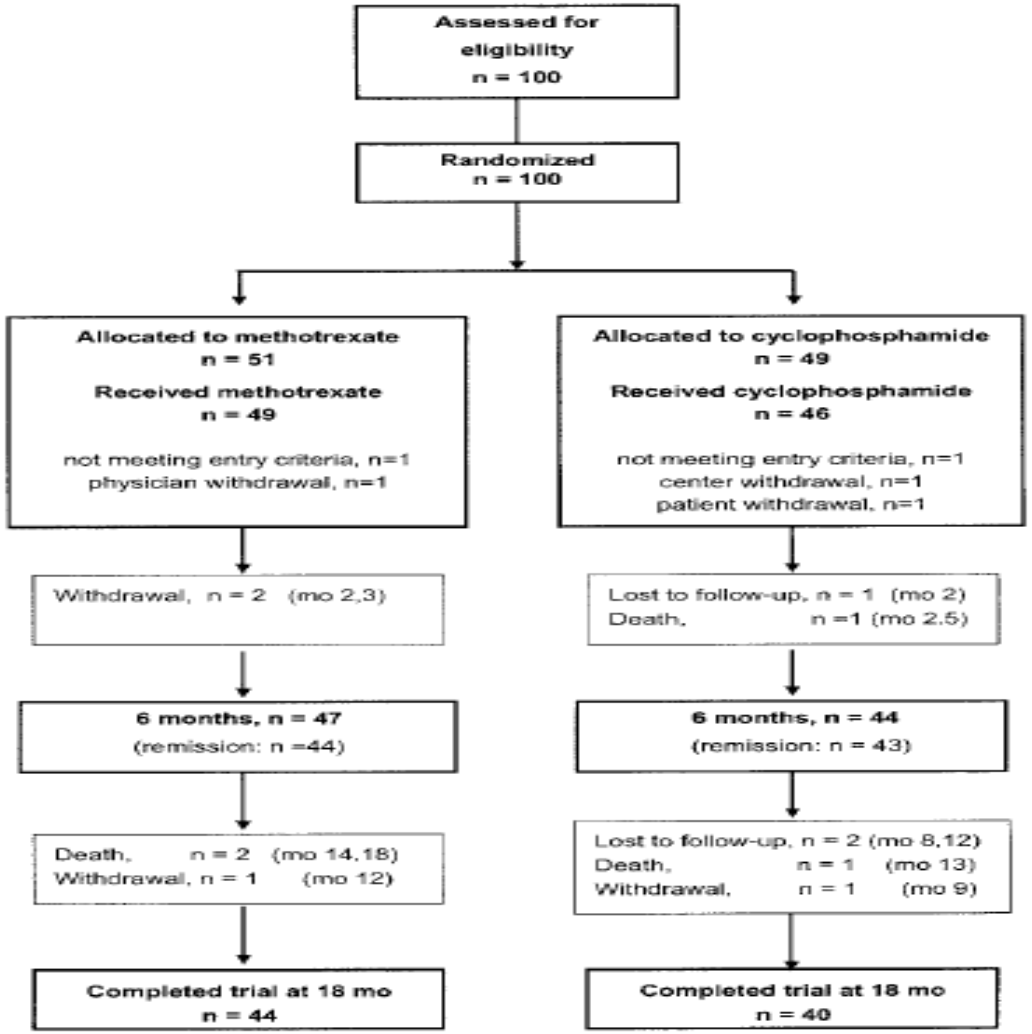
Long-term Results (18 mths)

de Groot K et al. Arthritis and Rheumatism 2005, Vol.52, No.8, pp 2461-2469
Faurschou M et al. Arthritis and Rheumatism 2012, Vol.64, No.10, pp 3472-3477

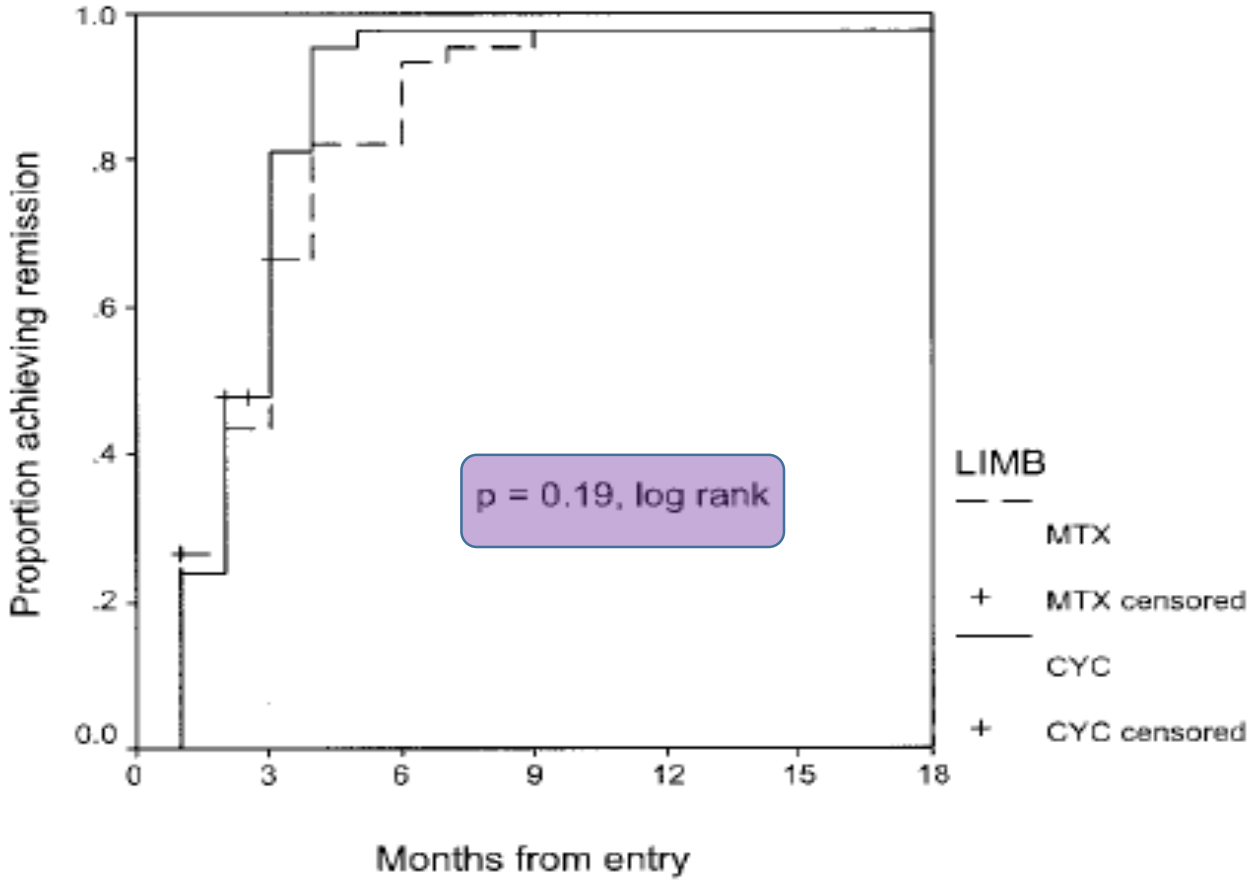
NORAM : Methodology

- Multicenter, unblinded, prospective, RCT
- 100 patients with newly diagnosed AAV (GPA or MPA) with manifestations of vasculitis in ≥ 1 organ system in combination with constitutional symptoms, serum creatinine levels < 150µmol/L, and without critical organ manifestations of disease
- 51 patients (oral MTX 20-25 mg/week plus prednisolone), 49 patients (oral CYC 2 mg/kg/day)

Distribution of patients in the 18 mth trial



Primary outcome



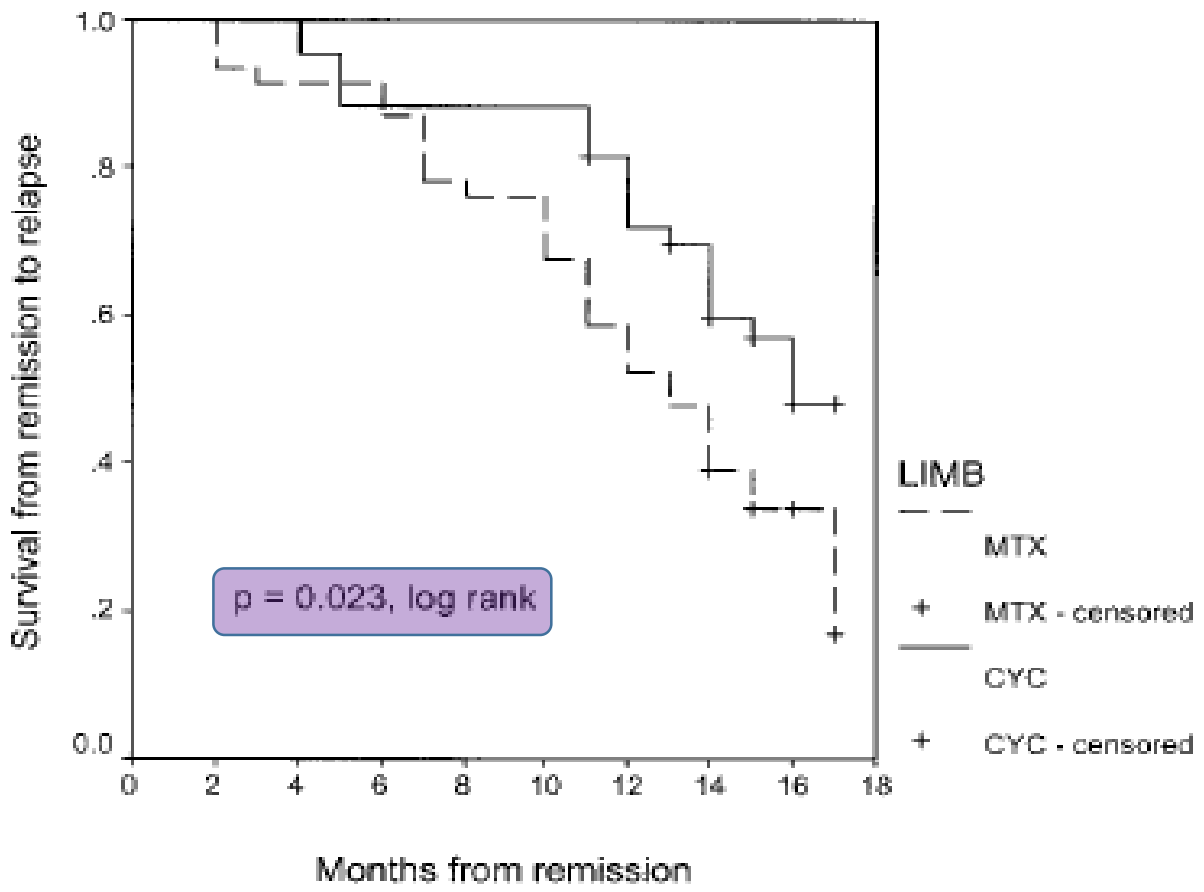
Remission rate at 6 mths

(noninferiority testing)

MTX (89.8%), CYC (93.5%)

p=0.041

Time from remission to relapse (long-term outcome)



Relapse rates at 18 mths

MTX (69.5%), CYC (46.5%)

Time from remission to relapse

MTX (13mo), CYC (15mo)

Adverse events

Type of adverse event	Mild/moderate		Drug cessation, MTX/CYC	Severe/ life-threatening		Drug cessation, MTX/CYC
	MTX	CYC		MTX	CYC	
Allergy	–	–		1	–	
Thrombocytopenia	–	1		–	–	
Infection	5	5	1/0	4	4	0/1
Leukopenia	3	14	0/1	1	–	1/0
Multiple leukopenia	–	6		–	–	
Alopecia	–	1		–	–	
Cataract	–	1		–	–	
Osteoporosis	–	–		–	1	
Avascular necrosis	–	–		1	–	
Diabetes	–	3		–	–	
Infertility	–	–		1	–	
Hypertension	3	1		–	–	
Liver dysfunction	7	1	2/0	–	–	
Nausea/vomiting	1	–		–	–	
Hypersensitivity reaction	–	1	0/1	–	–	
Other	10	5		1	1	
Total	29	39	3/2	9	6	1/1

* MTX = methotrexate; CYC = cyclophosphamide.

Mean 0.87 episodes/patient; leukopenia more common in the CYC group (p=0.012), and liver dysfunction more common in the MTX group (p=0.036)

MEPEX Trial

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

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

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

Michael Walsh[1], Alina Casian[2], Oliver Flossmann[3], Kerstin Westman[4], Peter Höglund[5], Charles Pusey[6] and David R.W. Jayne[2] on behalf of the European Vasculitis Study Group (EUVAS)

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Jayne DRW et al. J Am Soc Nephrol 2007;18: 2180-2188
Walsh M et al. Kidney International 2013;84: 397-402

MEPEX : Methodology

- Long-term RCT involving 137 patients with newly diagnosed AAV and serum creatinine > 500µmol/L or requiring dialysis
- 69 patients received PLEX and 68 received IV MeP in addition to CYC and oral glucocorticoids
- 42 patients (30.65%) had GPA
- 31 patients (22.6%) had alveolar haemorrhage at presentation

Baseline characteristics of patients

	IV MeP ($n=68$)	PLEX ($n=69$)
Age, median (IQR)	66 (59–71)	67 (60–70)
Female, *n* (%)	24 (35)	28 (49)
Granulomatosis with polyangiitis, *n* (%)	25 (37)	17 (25)
Anti-PR3 positive, *n* (%)	31 (46)	27 (39)
Creatinine at entry, median (IQR)	732 (611–918)	701 (583–896)
BVAS at entry, median (IQR)	19.5 (14.5–27.0)	19 (15–23)
Alveolar hemorrhage present, *n* (%)	18 (26.5)	13 (18.8)

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; IQR, 25th to 75th percentile interquartile range; IV MeP, intravenous methylprednisolone; PLEX, plasma exchange; PR3, proteinase 3.

Long-term primary and secondary outcomes

Outcome	IV MeP, $n=68$ (%)	PLEX, $n=69$ (%)	HR (95% CI)	*P*-value
Death or ESRD	46 (68)	40 (58)	0.81 (0.53–1.23)	0.32
Death	35 (51)	35 (51)	1.08 (0.67–1.73)	0.75
ESRD[a]	33 (49)	23 (33)	0.64 (0.40–1.05)	0.08
Relapse[a]	16 (21)	10 (14)	0.56 (0.26–1.21)	0.14

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; IV MeP, intravenous methylprednisolone; PLEX, plasma exchange group.

[a]Subhazard ratio presented.

P-value based on Cox regression or competing risk regression model.

Short-term outcome : at 3 mths, proportion of dialysis-independent patients was significantly higher in the PLEX group (69%) than in the IV MeP group (49%), p=0.02

Long-term outcome : at 12 mths, PLEX was associated with decreased risk of ESRD (43% vs 19%)

Causes of death over long-term F/U

Primary cause of death, *n* (%)	IV MeP (*n* = 35)	PLEX (*n* = 35)
Vasculitis (%)	1 (2.9)	1 (2.9)
Pulmonary hemorrhage (%)	3 (8.6)	1 (2.9)
Infection (%)	9 (25.7)	15 (42.9)
Cardiovascular (%)	6 (17.1)	4 (11.4)
ESRD (%)	1 (2.9)	1 (2.9)
Cancer (%)	3 (8.6)	2 (5.7)
Other	12 (34.3%)	11 (31.4%)

Abbreviations: ESRD, end-stage renal disease; IV MeP, intravenous methylprednisolone; PLEX, plasma exchange.

There was no difference in the overall distribution of cause of death ($P = 0.80$).

- Mycophenolate mofetil (MMF)

➢ Comparison between MMF and CYC for remission induction in AAV

ongoing trial MYCYC

➢ Preliminary results suggest MMF is noninferior to pulse CYC for remission induction at 6 mths, but subsequently risk of relapse seems to be substantially higher with MMF

Rituximab in remission induction

RAVE trial

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Initial results (6 months)

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Barri J. Fessler, M.D., Linna Ding, M.D., Ph.D., Lisa Viviano, R.N., Nadia K. Tchao, M.D., Deborah J. Phippard, Ph.D., Adam L. Asare, Ph.D., Noha Lim, Ph.D., David Ikle, Ph.D., Brett Jepson, M.S., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina Keogh, M.B., B.Ch., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., Mark Mueller, B.S., C.C.R.P., Lourdes P. Sejismundo, R.N., Kathleen Mieras, C.C.R.P., and John H. Stone, M.D., M.P.H., for the RAVE-ITN Research Group*

Long-term follow-up results (18 months)

N Engl J Med 2010;363:221-32
N Engl J Med 2013;369:417-27

Methodology in RAVE trial

- Multicenter, randomized, double-blind, double-dummy, non-inferiority trial of rituximab (RTX)
- 197 patients with ANCA-associated vasculitis (99 patients in rituximab group, 98 patients in control group)
- 48 patients (24%) had MPA, 148 patients (75%) had GPA, 1 indeterminate
- Approx. 49% of patients in both groups had a new diagnosis
- 54% had pulmonary involvement and 66% had renal involvement at baseline

Outcomes

- The primary comparison at 6, 12 and 18 months was the percentage of patients who :

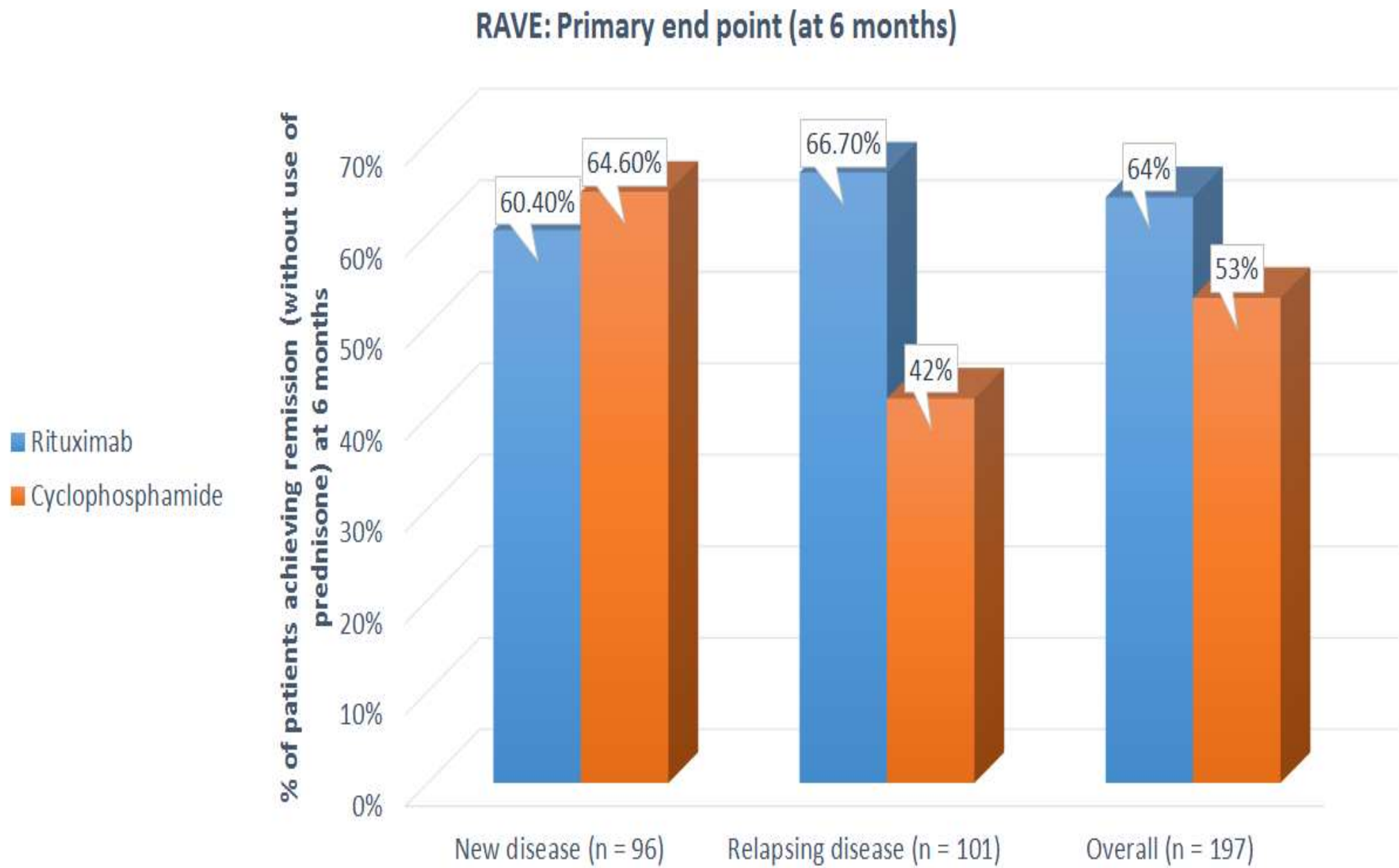
  1). attained a score of 0 on the BVAS/WG disease severity index

  2). had completed the glucocorticoid-tapering regimen

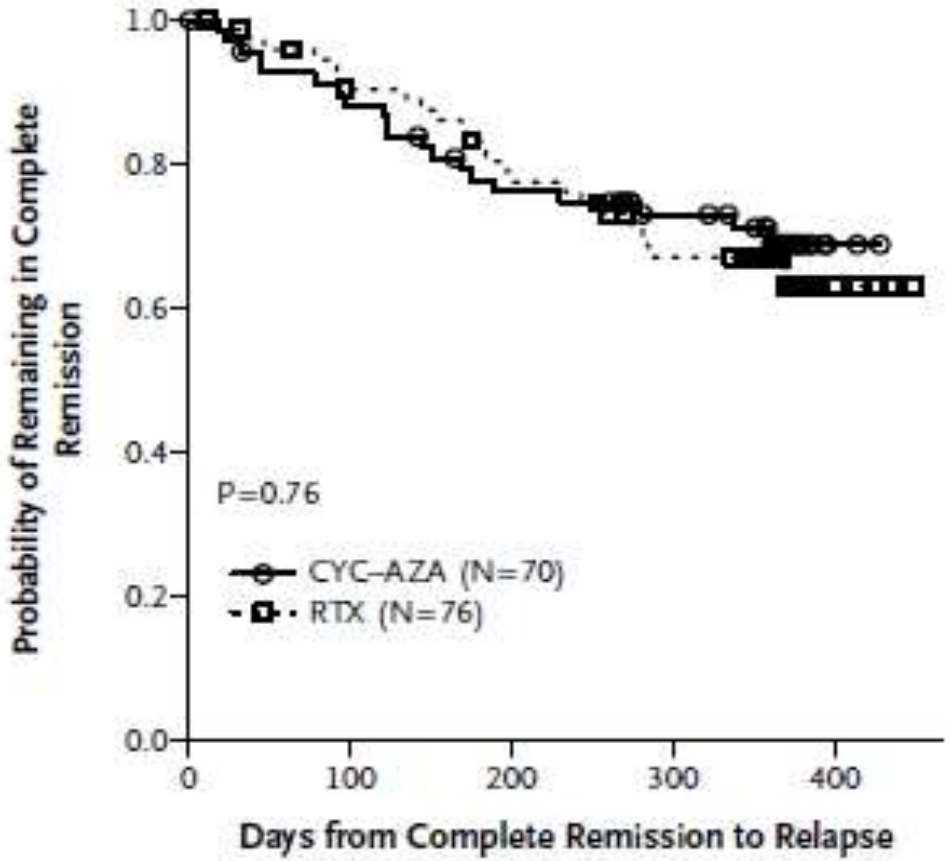
  3). had not had a relapse or any other reason for treatment failure before the time point of interest

Efficacy outcomes at 6, 12, and 18 months

Efficacy Measure	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Difference	P Value
	number (percent)		*percentage points (95% CI)*	
Complete remission				
6 mo	63 (64)	52 (53)	11 (–3 to 24)	0.13
12 mo	47 (47)	38 (39)	9 (–5 to 22)	0.22
18 mo	39 (39)	32 (33)	7 (–7 to 20)	0.32
Remission and <10 mg/day of prednisone				
6 mo	70 (71)	60 (61)	10 (–4 to 23)	0.16
12 mo	59 (60)	60 (61)	–2 (–15 to 12)	0.82
18 mo	54 (55)	52 (53)	2 (–12 to 15)	0.84
Complete remission at any time†	76 (77)	70 (71)		0.15
Remission and <10 mg/day of prednisone at any time‡	82 (83)	84 (86)		0.91
Remission at any time‡	89 (90)	89 (91)		0.50
Complete remission in patients with relapsing disease at baseline†				
6 mo	34/51 (67)	21/50 (42)	25 (6 to 44)	0.01
12 mo	25/51 (49)	12/50 (24)	25 (7 to 43)	0.009
18 mo	19/51 (37)	10/50 (20)	17 (0 to 34)	0.06
	milliliters per minute			

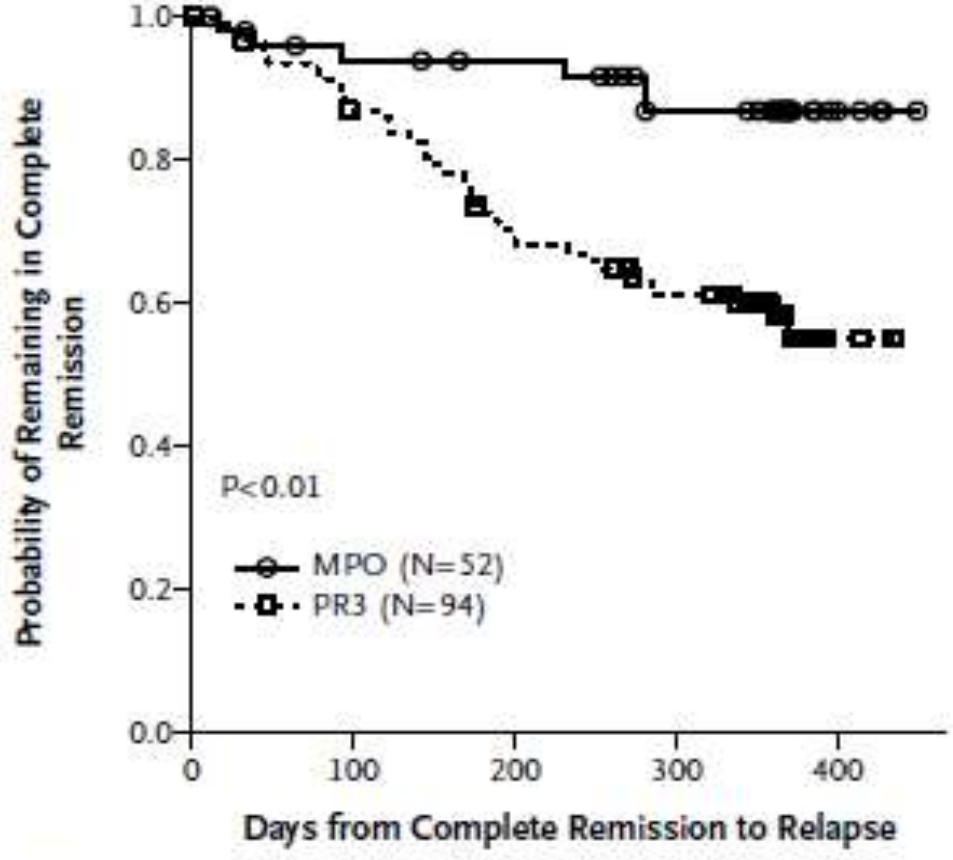

RAVE: Primary end point (at 6 months)
% of patients achieving remission (without use of prednisone) at 6 months
70%
60%
50%
40%
30%
20%
10%
0%
60.40%
64.60%
66.70%
42%
64%
53%
Rituximab
Cyclophosphamide
New disease (n = 96)
Relapsing disease (n = 101)
Overall (n = 197)

A Time to First Relapse after Complete Remission, According to Treatment



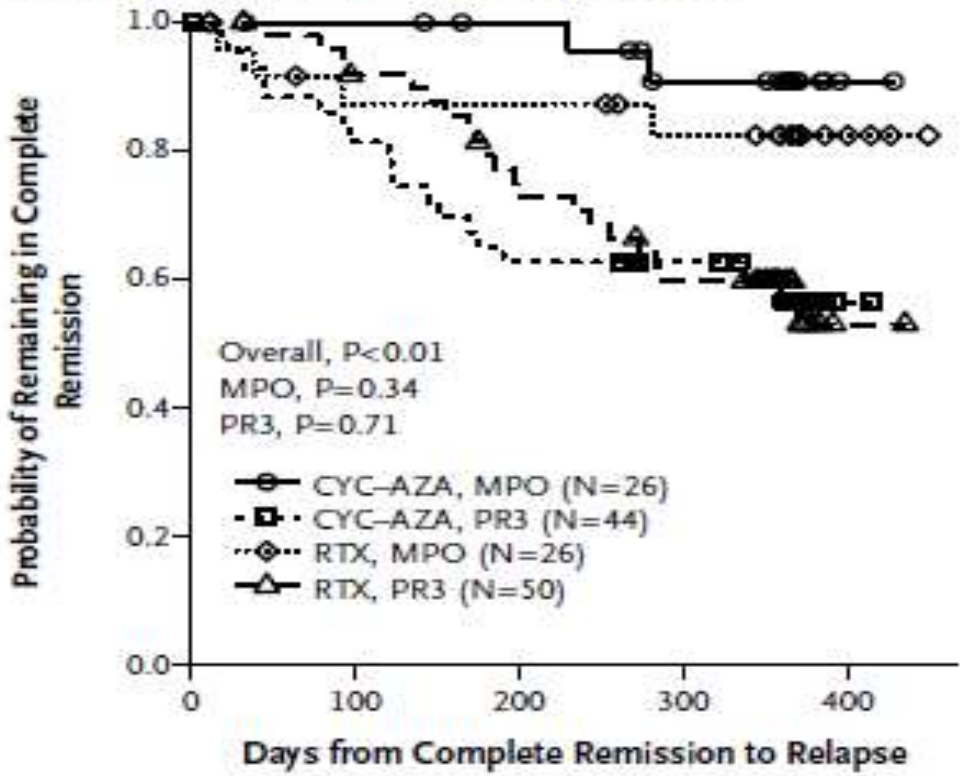
No. at Risk					
CYC–AZA	70	61	51	43	3
RTX	76	65	55	45	5

B Time to First Relapse after Complete Remission, According to Baseline Type of ANCA



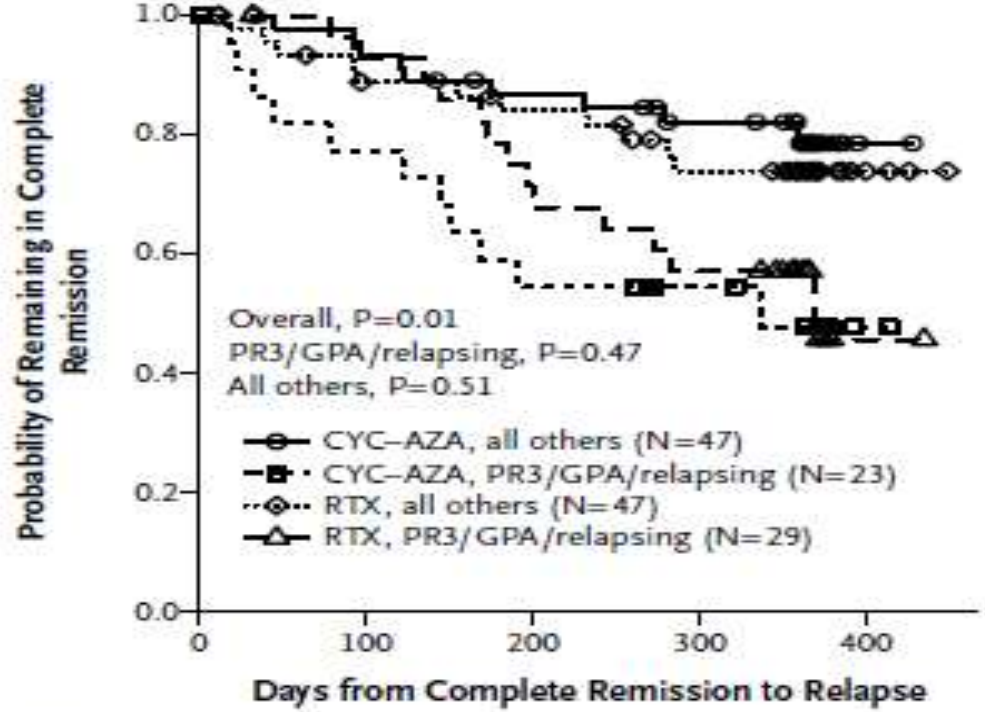
No. at Risk					
MPO	52	46	44	37	5
PR3	94	80	62	52	3

C Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA

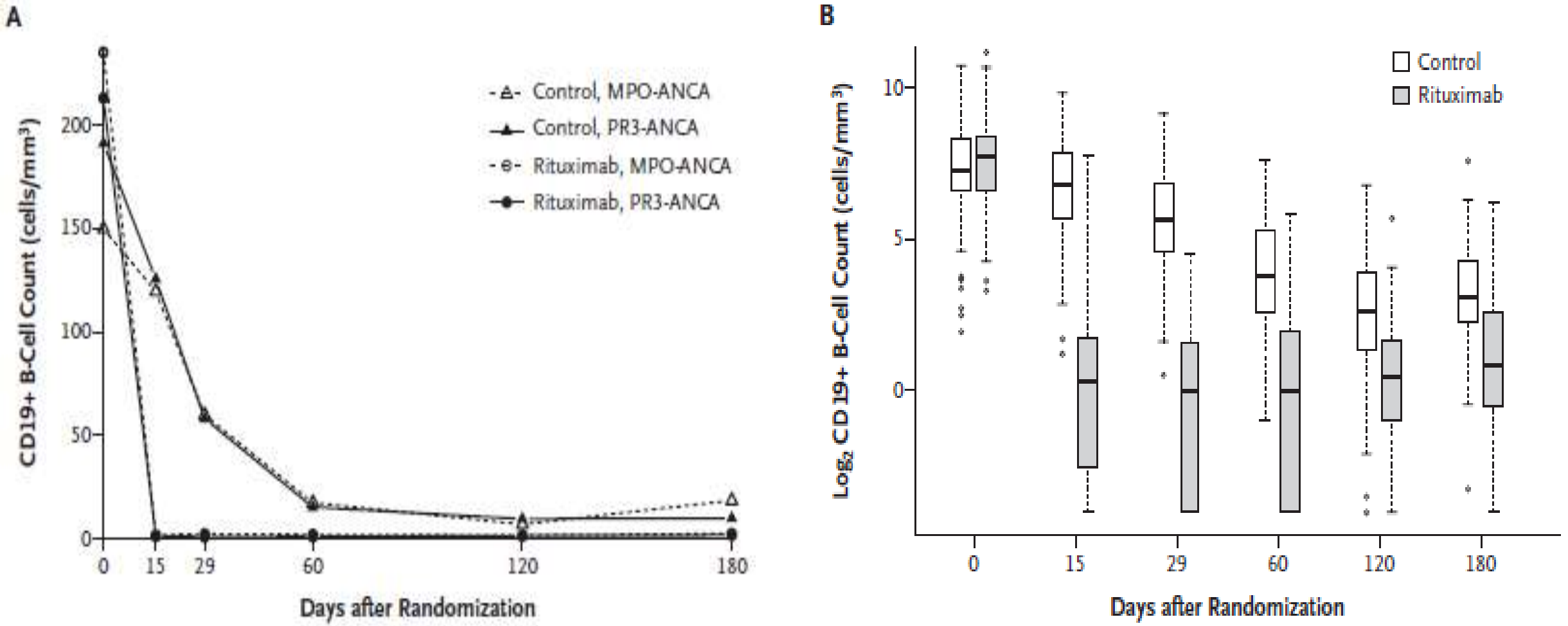


No. at Risk					
CYC–AZA, MPO	26	26	24	19	2
CYC–AZA, PR3	44	36	28	25	2
RTX, MPO	26	21	21	18	4
RTX, PR3	50	45	35	28	2

D Time to First Relapse after Complete Remission, According to Presence of Three Risk Factors



No. at Risk					
CYC–AZA, all others	47	44	39	34	2
CYC–AZA, PR3/GPA/relapsing	23	18	13	10	2
RTX, all others	47	39	36	29	4
RTX, PR3/GPA/relapsing	29	27	20	17	2



- **B-cell count in RTX group decreased to <10/mm³ after 2 infusions in 96% of cases and remained so until 6mths. Most RTX-treated patients fully reconstituted their B-cells between 9 and 12mths**
- **87.5% of the relapses in RTX group occurred after B-cells became redetectable**
- **However, 2/3rd of the RTX-treated patients who had reconstituted their B-cells did not have a relapse**
- **Relationship between relapse risk and B-cells in control arm was less clear**

RITUXVAS trial

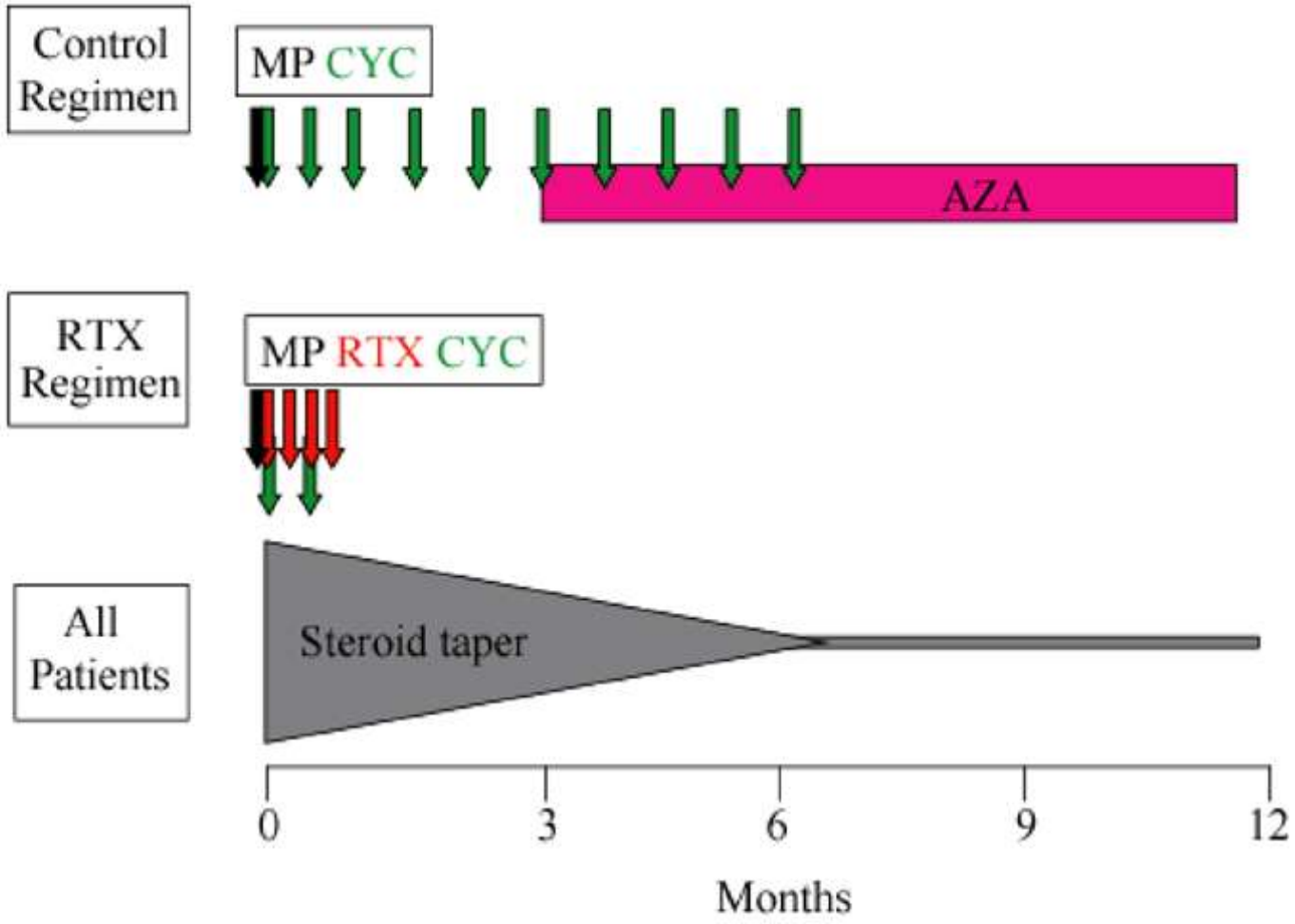
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

N Engl J Med 2010;363:211-20

Methodology in RITUXVAS trial

- Multicenter, open-label, two-group, parallel-design, randomized trial
- 44 patients with newly diagnosed ANCA-associated vasculitis and renal involvement
- Randomly assigned in 3:1 ratio (33 patients in rituximab group, 11 patients in control group)
- Primary end points : sustained remission rates at 12 months and severe adverse events

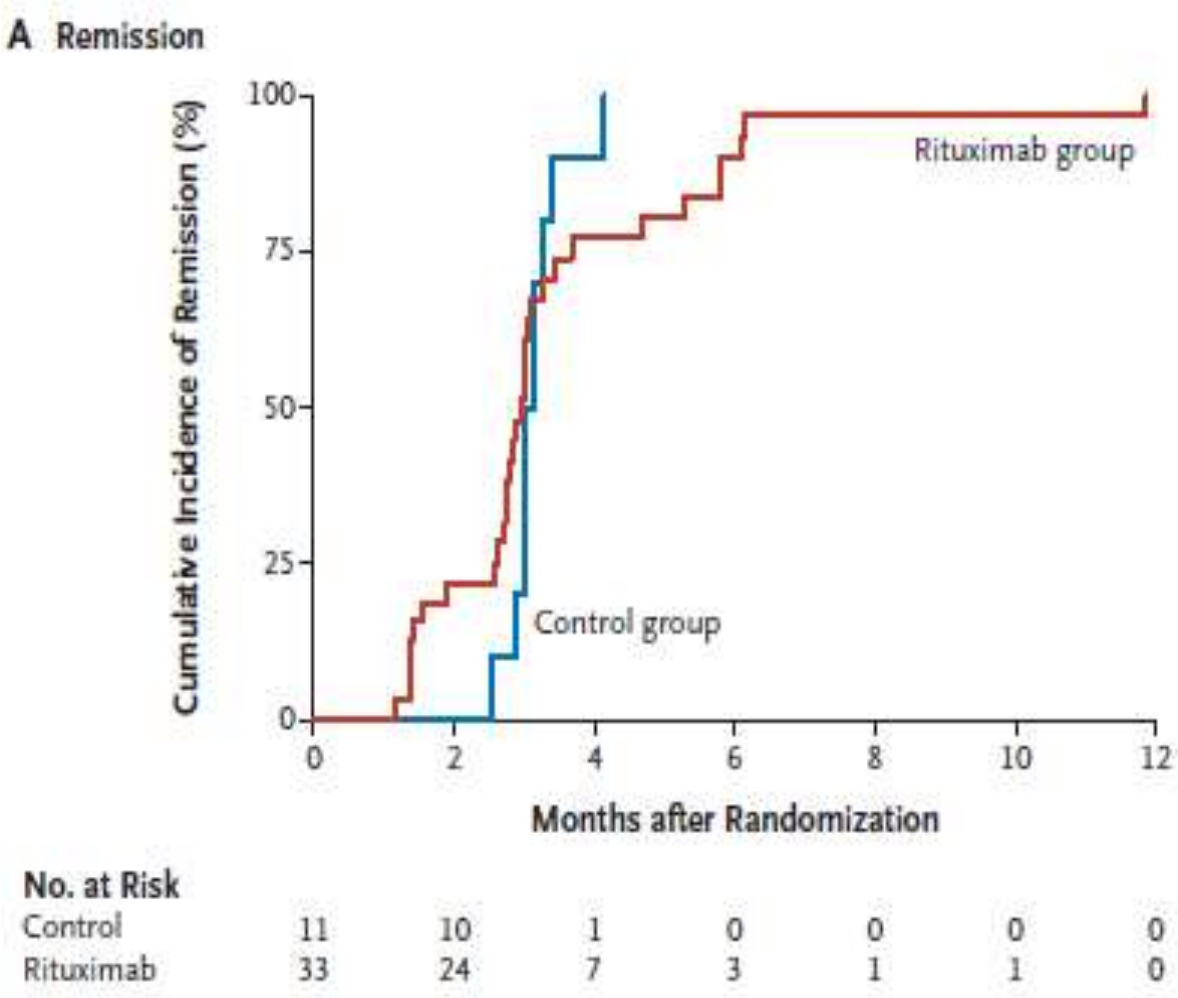


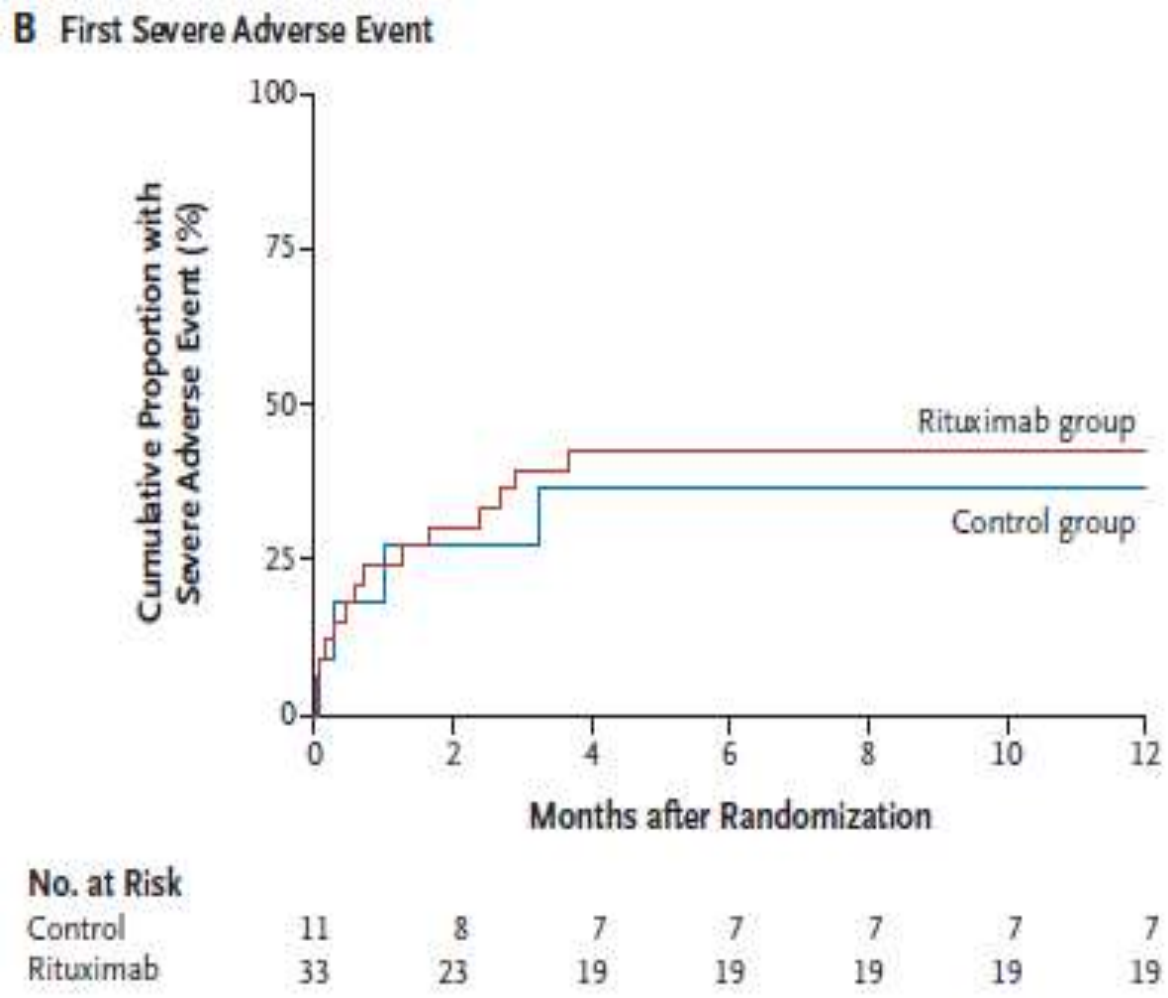
Black arrows indicate intravenous methylprednisolone (MP), 1 gram. Red arrows indicate intravenous rituximab (RTX), 375mg/m^2. Green arrows indicate intravenous cyclophosphamide (CYC), 15mg/kg with dose adjustments for age and renal function. AZA=azathioprine.

- **CYC every 2 weeks for the first 3 doses, then every three weeks thereafter until stable remission was achieved (minimum 6, maximum 10 doses)**
- **AZA for remission maintenance after CYC withdrawal**

- **Rituximab weekly for 4 consecutive weeks, and CYC with the first and third rituximab infusions**
- **Did not receive azathioprine for remission maintenance**

- **Steroid 1mg/kg/d initially, reduced to 5mg/d by 6mths**





- **RTX-based regimen was not superior to standard IV CYC. 25 patients in the RTX group (76%) and 9 patients in the control group (82%) had a sustained remission (p=0.68).**
- **Median time to remission was 90 days (IQR, 79 to 112) in the RTX group and 94 days (IQR, 91 to 100) in the control group (p=0.87)**
- **RTX-based regimen was not associated with reductions in early severe adverse events**

Maintenance of remission

MAINRITSAN trial

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

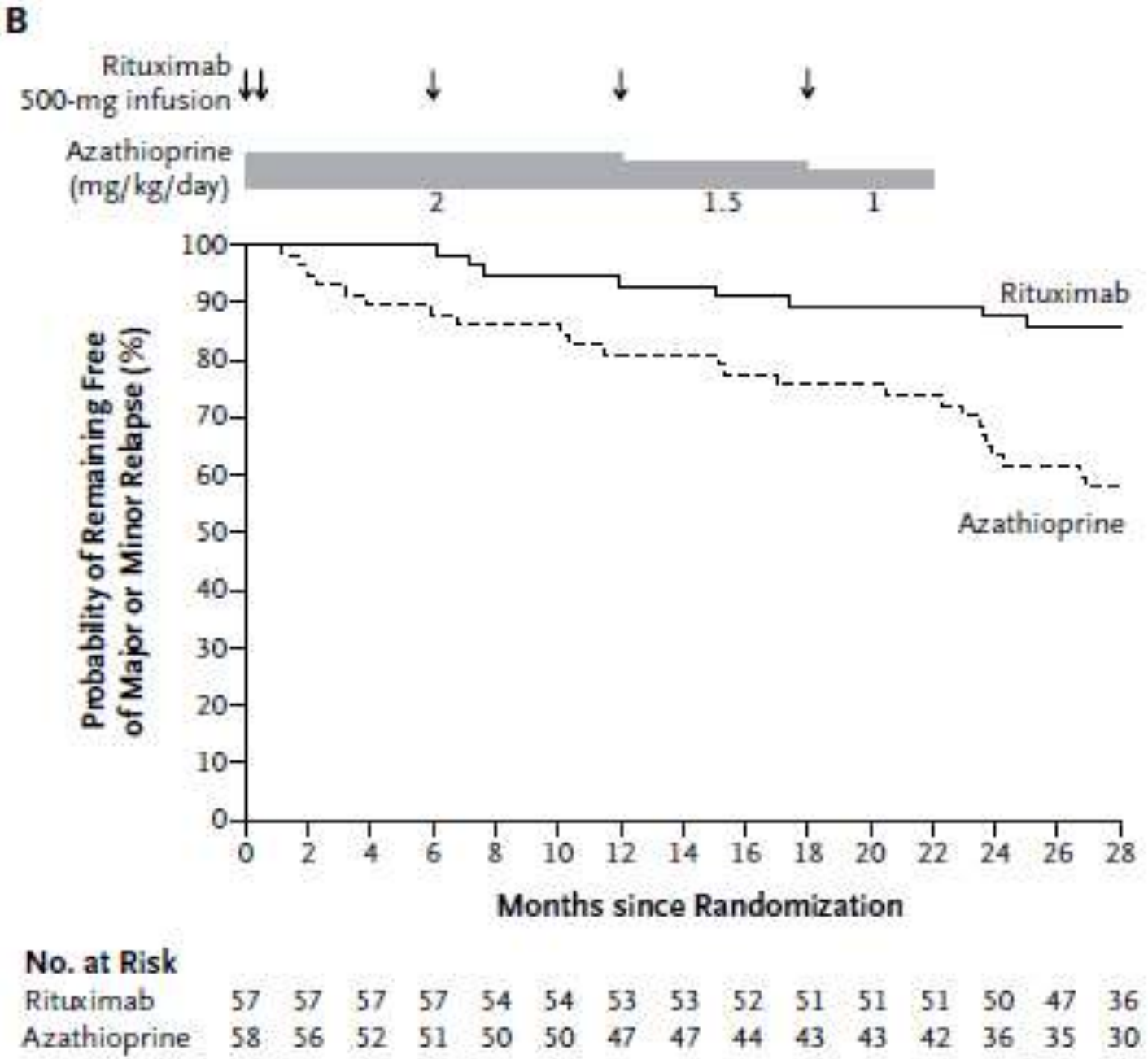
N Engl J Med 2014;371:1771-80

Methodology

- Nonblinded, randomized, controlled trial involving 115 patients with newly diagnosed or relapsing disease
- 87 patients had GPA, 23 patients had MPA, and 5 patients had renal-limited AAV
- 58 patients in azathioprine group and 57 patients in rituximab group
- Primary end point at month 28 : the rate of major relapse (the reappearance of disease activity or worsening, with a BVAS score > 0, and involvement of ≥ 1 major organ, disease-related life-threatening events, or both)

Intervention

- Patients were randomly assigned to receive maintenance therapy with RTX (500 mg on days 0 and 14, thereafter at mths 6, 12, and 18 after the first infusion) or azathioprine (AZA) (2 mg/kg/day from mth 0-12, 1.5 mg/kg/day until mth 18, then 1 mg/kg/day until the last day of mth 22)



- **Relapse rates were 3.6% in the RTX group and 27% in the AZA group**
- **Hazard ratio for major or minor relapse in the AZA group was 3.53 (95% CI, 1.49-8.40; p=0.01)**

Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis

Federico Alberici[1,2,3], Rona M. Smith[1,2], Rachel B. Jones[1,2], Darren M. Roberts[1,2], Lisa C. Willcocks[1,2], Afzal Chaudhry[1,2], Kenneth G. C. Smith[1,2,4] and David R. W. Jayne[1,2]

- **69 AAV patients receiving RTX treatment protocol consisting of induction and maintenance phases were included (67 were failing other therapies)**
- **For initial remission induction, RTX was dosed at 1g every 2 weeks or 375 mg/m^2 weekly for 4 consecutive weeks**
- **For remission maintenance, RTX was dosed at 1g every 6 mths for 24 mths**
- **At the first RTX administration, ongoing immunosuppressives were withdrawn**

www.ncbi.nlm.nih.gov/pubmed/25477054

Results

- 69 patients were in remission at the end of maintenance phase on a median prednisolone dose of 2.5 mg/day and 9% were receiving additional immunosuppression
- 9 patients relapsed during the RTX treatment protocol
- 28 patients relapsed a median of 34.4 mths after the last RTX infusion
- Risk factors for relapse were PR3-associated disease (p=0.039), B cell return within 12 mths of the last RTX infusion (p=0.0038), and switch from ANCA negativity to positivity (p=0.0046)

PEXIVAS Trial

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

Michael Walsh[1*], Peter A Merkel[2], Chen Au Peh[3], Wladimir Szpirt[4], Loïc Guillevin[5], Charles D Pusey[6], Janak de Zoysa[7], Natalie Ives[8], William F Clark[9], Karen Quillen[10], Jeffrey L Winters[11], Keith Wheatley[12], David Jayne[13] and on behalf of the PEXIVAS Investigators

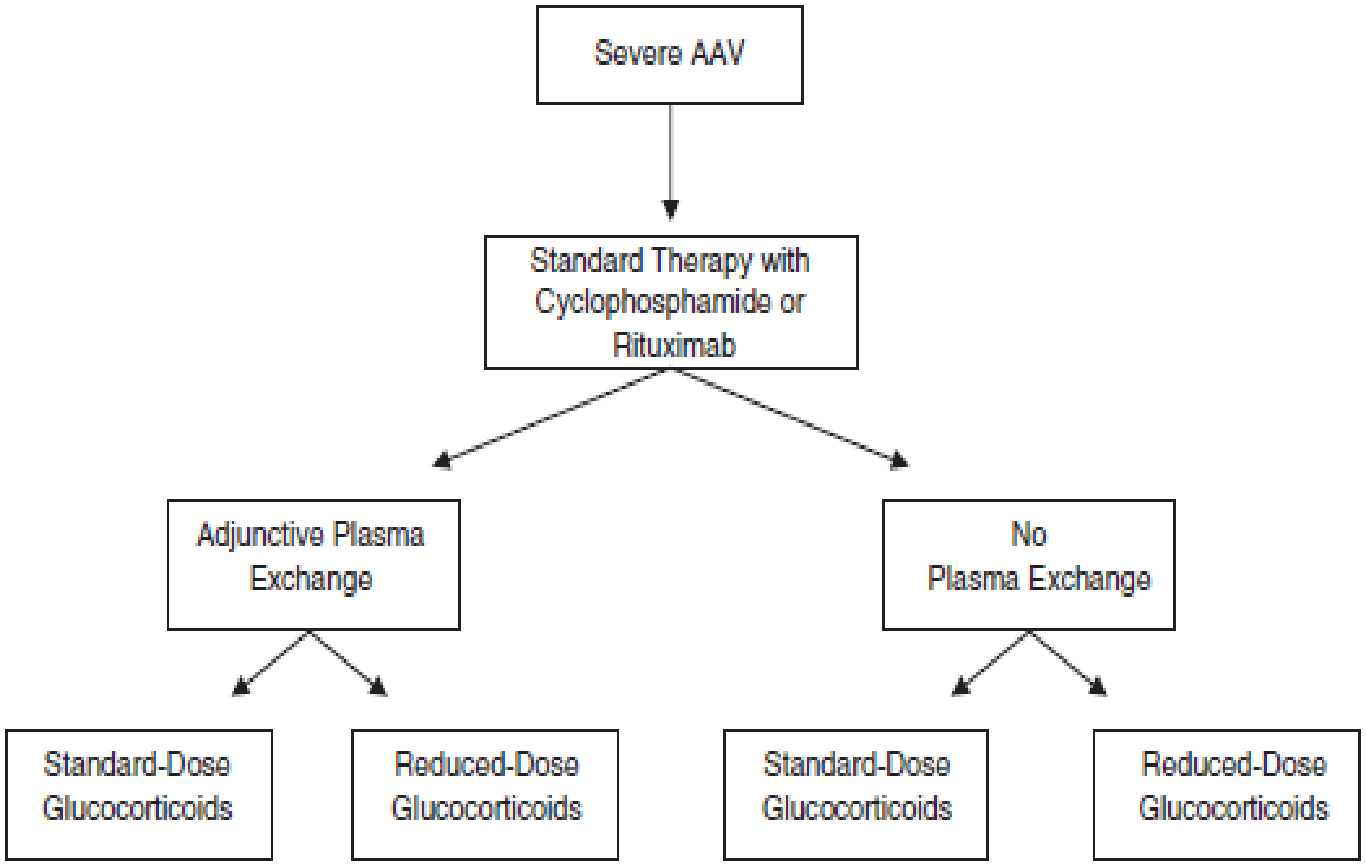
Walsh M et al. Trials 2013; 14:73

Methodology

- International, multicenter, open-label, two-b-two factorial, RCT involving 500 patients with severe AAV
- Eligible patients enrolled will receive one of 4 regimens :

1. PLEX and standard dose GC
2. PLEX and reduced dose GC
3. No PLEX and standard dose GC
4. No PLEX and reduced dose GC

Schema of treatment allocation



Glucocorticoid dosing in the standard and reduced dose groups

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Outcome measures

- Primary : the time to the composite of death from any cause and ESRD
- ESRD : requirement for atleast 12 consecutive weeks of renal replacement therapy (hemodialysis, peritoneal dialysis, and/or continuous renal replacement therapy) or renal transplantation
- Secondary : death from any cause and ESRD separately, health-related quality of life, serious infections, number of serious adverse events, and proportion with a sustained remission

RCTs for maintenance of remission in AAV

Trial (number of patients)	Inclusion criteria	Treatment groups (dose)	Primary end points	Outcome
CYCAZAREM[63] (144)	GPA, MPA or relapse and renal or vital organ involvement	Oral azathioprine (2 mg/kg) versus oral cyclophosphamide (1.5 mg/kg daily)	Relapse Adverse events	No difference in relapse
IMPROVE[65] (165)	New diagnosis of GPA or MPA	Oral mycophenolate mofetil (2 g daily) versus oral azathioprine (2 mg/kg)	Time without relapse Adverse events	More relapses with mycophenolate mofetil than azathioprine, trend towards more adverse events with azathioprine
WEGENT[64] (126)	GPA or MPA and renal or multiorgan involvement	Methotrexate (0.3 mg/kg once weekly) versus azathioprine (2 mg/kg)	Adverse events with consecutive treatment cessation or death	No difference between groups in primary end point and relapses
LEM[67] (54)	Generalized GPA and creatinine <1.3 mg/dl	Leflunomide (30 mg daily) versus methotrexate (up to 20 mg per week)	Relapse	More relapses with methotrexate than leflunomide, trend towards more adverse events with leflunomide
WGET[66] (174)	GPA and BVAS >3	Etanercept and methotrexate or cyclophosphamide versus placebo and methotrexate or cyclophosphamide	Sustained remission for >6 months	No benefit with etanercept, more cancers in etanercept group

Abbreviations: AAV, antineutrophil cytoplasmic antibody-associated vasculitis; BVAS, Birmingham vasculitis activity score for GPA; GPA, granulomatosis with polyangiitis (formerly Wegener's granulomatosis); MPA, microscopic polyangiitis.

Schönermarck U et al. Nat. Rev. Nephrol. 2014;10: 25-36

Treatment options for refractory AAV

Refractory	Rituximab	Four infusions of 375 mg/m², once a week	Holle et al.[55]
Refractory	Intravenous immunoglobulin	2 g/kg or 0.5 g/kg/d for 4 days	Jayne et al.[56]
Refractory	Infliximab	3–5 mg/kg infusions, once or twice monthly	Lamprecht et al.[88]
Refractory	Mycophenolate mofetil	2 g daily	Joy et al.[89]
Refractory	15-deoxyspergualin	0.5 mg/kg daily for six cycles (adjusted to leucocyte count)	Birck et al.[90]
Refractory	Antithymocyte globulin	Intravenous 2.5 mg/kg daily for 10 days (adjusted to leucocyte count)	Schmitt et al.[91]

Schönermarck U et al. Nat. Rev. Nephrol. 2014;10:25-36

Ongoing RCTs

- MYCYC (140 patients) : MMF (2-3g daily) vs IV pulse CYC (15mg/kg) for remission induction in newly diagnosed AAV (GPA or MPA) and major organ involvement
- CORTAGE (104 patients) : Rapid glucocorticoid tapering and reduced dose IV pulse CYC (500mg) vs standard IV pulse CYC (500mg/$m^{2)}$ for remission induction in newly diagnosed AAV (MPA, GPA, EGPA, PAN) and age > 65 yrs
- PEXIVAS : For remission induction
- RITAZAREM : RTX and AZA for remission maintenance
- REMAIN : For optimal duration of maintenance therapy

Take home message

- For induction of disease remission, rituximab is not inferior to cyclophosphamide
- For maintenance of remission, rituximab is superior to azathioprine
- For duration of induction and maintenance of disease remission, till date different trials have used different periods with no final clear cut definition of a specified period