ANCA-Associated Vasculitis: A Guide to Modern Management

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Disclosures

- Novartis Advisory Board

Objectives

- To describe the induction therapy for ANCA associated vasculitis (AAV)
- To discuss the role of plasmapheresis in severe AAV
- To describe the preferred maintenance therapy for AAV
- To examine the new therapeutic options for AAV


Herr Wegener-Breslau:

Über generalisierte, septische Gefäßerkrankungen.

"On Generalized Septic Vessel Diseases”

- Granulomatosis with polyangiitis (GPA) was first described in 1937 as a necrotizing granulomatous disorder of the respiratory tract
- Multisystem autoimmune syndrome
  - Vasculitis predominantly affecting microscopic vessels with a predilection for the respiratory tract and the kidneys
  - Associated with circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA) in most of the cases

Wegener, F., 1987. On generalised septic vessel diseases. By Friedrich Wegener, 1937 (translation). Thorax 42, 918–919.

ANCA Vasculitis mortality is high if not treated

- The average survival of 5 months from the time of diagnosis *(Godman and Churg, 1954)*
- In about 4/5 of the cases the cause of death was renal failure *(Walton, 1958)*
- Cyclophosphamide (CYC) was effective for disease control in 4 patients with GPA *(Novack and Pearson, 1971)*
- Oral CYC became the mainstay of therapy with dramatic improvement in disease control and survival

Case No.	Age (Yr)	Sex	Upper Air Passages	Pulmonary	Central Nervous System	Renal	Other	Comment
1	52	F	+	++++	+	++		Marked clinical improvement after 2 mo of cyclophosphamide therapy; no recurrence after 16 mo; patient off all therapy for 12 mo.

Data in 1/4 cases of GPA
(Modified from Novack et al)

Assessing disease burden

- Disease activity can be assessed by **Birmingham Vasculitis Activity Score** (BVAS): http://bit.ly/2hP0kBW
  - Comprises of elements pertaining to 9 organs
  - **Major symptoms** are the organ threatening signs and symptoms
    - **Kidneys, Lungs, Brain, Gut, Motor neurons, and Eyes**

Remission:

- BVAS=0 on < 10 mg of Prednisone (PRED)
- Sustained remission: BVAS 0 while off PRED for at least 6 mo

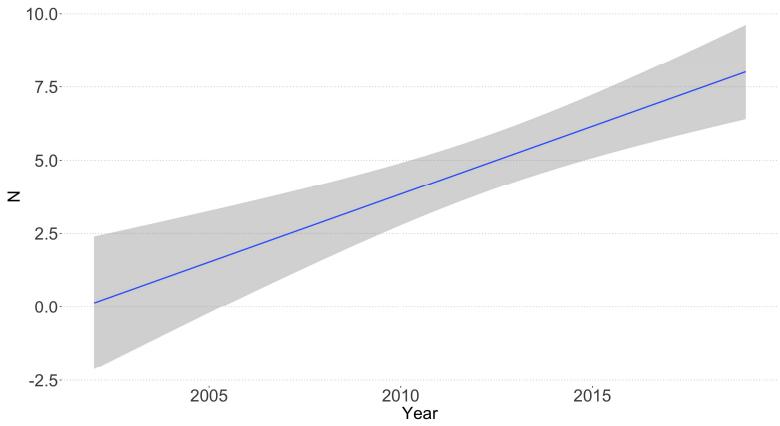
Relapse:

- Minor relapse: $\leq$ 2 new BVAS features – none major
- Major relapse: 1 new major or $\geq$ 3 minor features

ANCA associated vasculitis in New Mexico

Rank	Diagnosis	N (%)
1	Diabetic glomerulosclerosis	212 (20.4)
2	Lupus nephritis	152 (14.6)
3	IgAN/HSP	116 (11.2)
4	Secondary glomerulosclerosis	91 (8.8)
5	ATN	87 (8.4)
6	ANCA associated GN	69 (6.6)

Age of Diagnosis Median- Years (IQR)	
ANCA associated GN	59.2 (44.3-67.7)



Diagnoses encountered on Native kidney biopsies; 2002 – 2019. Data from the University of New Mexico Kidney biopsy registry. Shaffi (unpublished data)

1. To describe the induction therapy for ANCA associated vasculitis (AAV)

Pulse vs. Daily Cyclophosphamide for remission induction
CYCLOPS Trial

de Groot, K. *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann. Intern. Med.* **150,** 670–680 (2009).

Harper, L. *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann. Rheum. Dis.* **71,** 955–960 (2012).

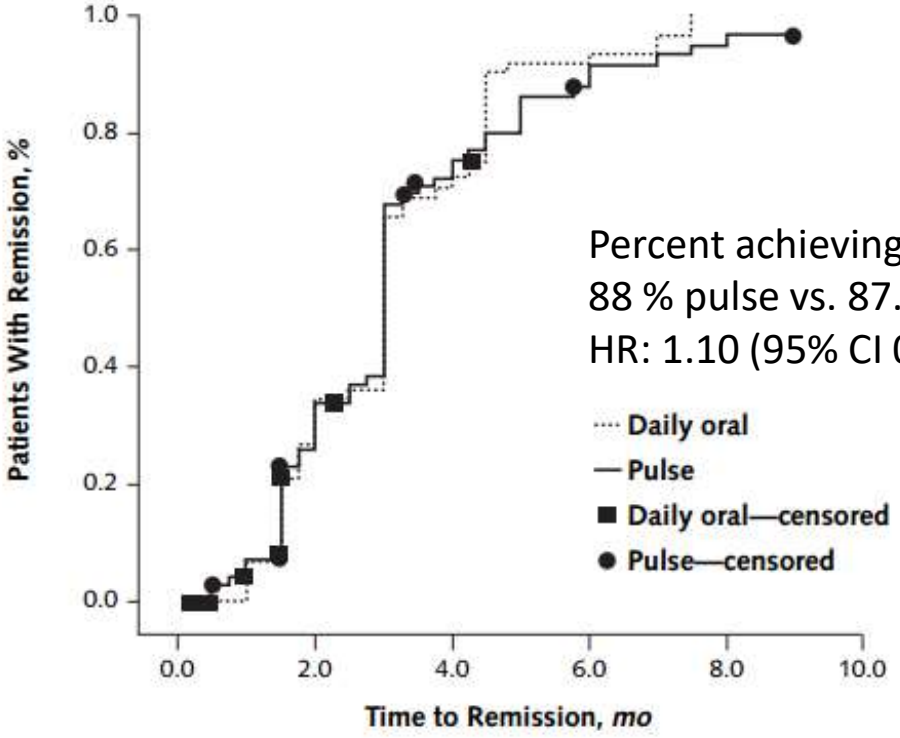
CYCLOPS – Oral vs. Pulse CYC for induction

<table>
<tr><td>Design</td><td colspan="2">Open label, multicenter, RCT, n=149</td></tr>
<tr><td>Patients</td><td colspan="2">Newly diagnosed Europeans and Mexicans with GPA or MPA with renal involvement</td></tr>
<tr><td>Intervention</td><td>CYC pulses q 3 weeks until remission followed by q 3-week pulses for 3 months</td><td rowspan="2">Remission maintenance:
Both groups received:
AZA 2 mg/kg 3 → 18 mo
PRED I mg/kg; Tapered 12.5 mg at 3 mo; 5 mg at 18 mo</td></tr>
<tr><td>Control</td><td>Oral CYC of 2 mg/kg till remission followed by 1.5 mg/kg for 3 months</td></tr>
<tr><td>Outcomes</td><td colspan="2">Primary
• Time to remission (BVAS ≤1)
Secondary
• % in remission; % with major and minor relapses at 6 and 9 months; Death; Change in renal function; Infections</td></tr>
</table>

CYCLOPS – Population characteristics

Characteristic	Pulse CYC Group (n = 76)	Daily Oral CYC Group (n = 73)
Mean age (SD), y	56.5(15.3)	58.2(13.7)
Men, n (%)	41(54)	47(64)
Diagnosis, n (%)		
GPA	25(33)	31(42)
Microscopic polyangiitis	38(50)	33(45)
Renal limited vasculitis	13(17)	9(12)
Mean serum creatinine level (SD) mg/dl	2.55(1.45)	2.51(1.36)
Mean BVAS for new or worse disease (SD)	20(6.8)	21(6.7)

CYCLOPS – Outcomes: Time to remission



Daily oral	73	43	18	4	0
Pulse	76	46	15	4	2

Percent achieving remission:
88 % pulse vs. 87.7 in daily group
HR: 1.10 (95% CI 0.78 to 1.55)

CYCLOPS – Outcomes

Parameter	Baseline		18 Months	
	Pulse	Daily Oral	Pulse	Daily Oral
Total patients, n	76	73	62	54
Active disease, n	76	73	1	0
Achieved remission, n	0	0	61	54
Died, n(%)	0	0	5 (2)	9 (4)
Relapse after initial remission, n	0	0	13	6
End-stage renal disease, n	0	0	5	1
Median eGFR (IQR), ml/min/1.73m^2	32 (15-52)	29 (18-48)	50(30-70)	48(36-69)
Cumulative cyclophosphamide median dose for patients still in study (IQR), g	0	0	8.58 (6.76-11.9)	18.05 (13.5-27)

CYCLOPS – Outcomes: Adverse events

Events	Pulse CYC Group (n = 76)	Daily Oral CYC Group (n = 73)
Any adverse event		
Patients, n (%)	58 (77)	56 (77)
Episodes, n		
Mild or moderate	77	101
Severe or life-threatening	19	31
Leukopenia - Episodes, n	28	59
Liver dysfunction, n	2	3
Osteoporosis, n	2	0
Cancer, n	1	0
Hemorrhagic cystitis, n	2	1
Amenorrhea, n	1	0

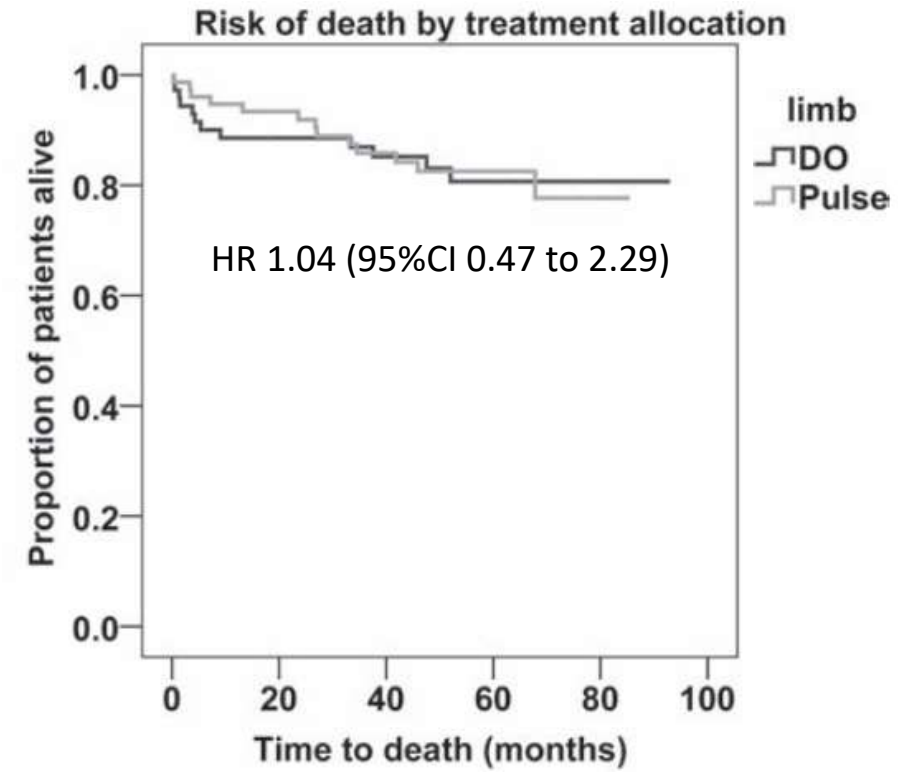
CYCLOPS 18 months – Summary

- **Remission**
  - No difference between time to or proportion who achieved remission
- **Relapse**
  - Non-statistically significant trend of greater relapse in the pulse group (HR, 2.01 [95 % CI 0.77 - 5.3])
- **Death**
  - No difference
- **Renal function improvement**
  - No difference (Median improvement in GFR between pulse and daily groups was 5 and 8 ml/min/1.73m^2, respectively)
- **Adverse events**
  - Leukopenia lower in pulse than in daily oral group (26 vs 45%, P =0.016)

CYCLOPS – Long-term follow-up

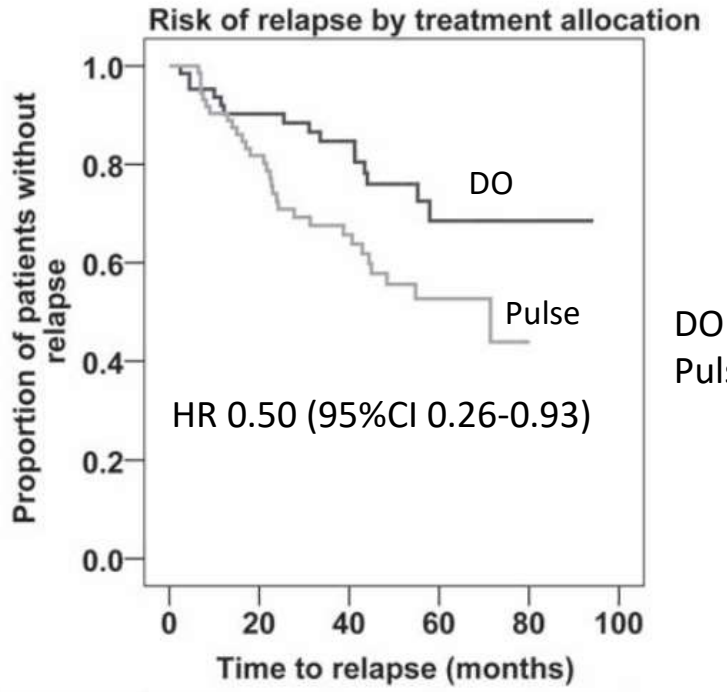
- Retrospective follow-up of the 148 patients enrolled in the CYCLOPS trial
- Median follow up duration **4.3 years (IQR 3 - 5.4)**
- Outcomes:
  - Survival
  - Relapse in the whole population as well as stratified according to the ANCA status
  - Immunosuppressive regimens used

CYCLOPS – Long-term follow-up: Patient Survival

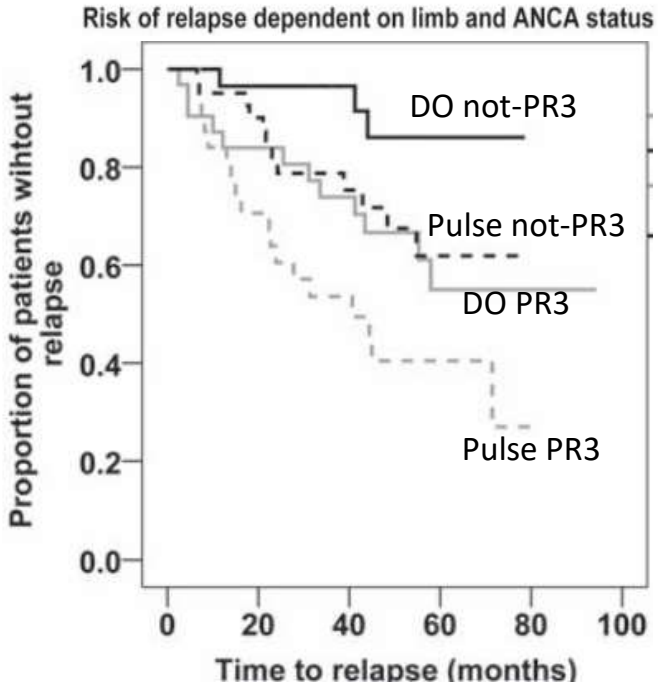


No difference in survival between the daily oral vs. pulse CYC

CYCLOPS – Long-term follow-up: Relapse



DO: Daily oral CYC
Pulse: Pulse CYC



The risk of relapse was lower in the patients who received daily oral CYC

PR3 status and pulse CYC use were independently associated with the risk of relapse

CYCLOPS – Long-term follow-up: Renal function

- Despite high relapse rate in the pulse group, there was no significant difference in renal function and risk of ESRD

Risk of ESRD :

- Pulse group: 13%
- DO group:11 %

Median serum Cr at last follow-up visit :

- Pulse group: 1.32 mg/dL (IQR 1.07-2.06)
- DO group: 1.32 mg/dL(IQR 1.18-1.62)

CYCLOPS – Long-term follow-up: Summary

- Higher risk of relapse in the pulse group
  - Highest risk of relapse in the **PR3 +** ANCA who **received pulse CYC** induction
- No difference in renal function, risk of ESRD or survival
- No significant difference in duration of immunosuppressive use and adverse events

RTX+CYC vs. IV CYC for remission induction
RITUXVAS

Jones, R. B. et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. New England Journal of Medicine 363, 211–220 (2010).

Jones, R. B. et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann. Rheum. Dis. 74, 1178–1182 (2015).

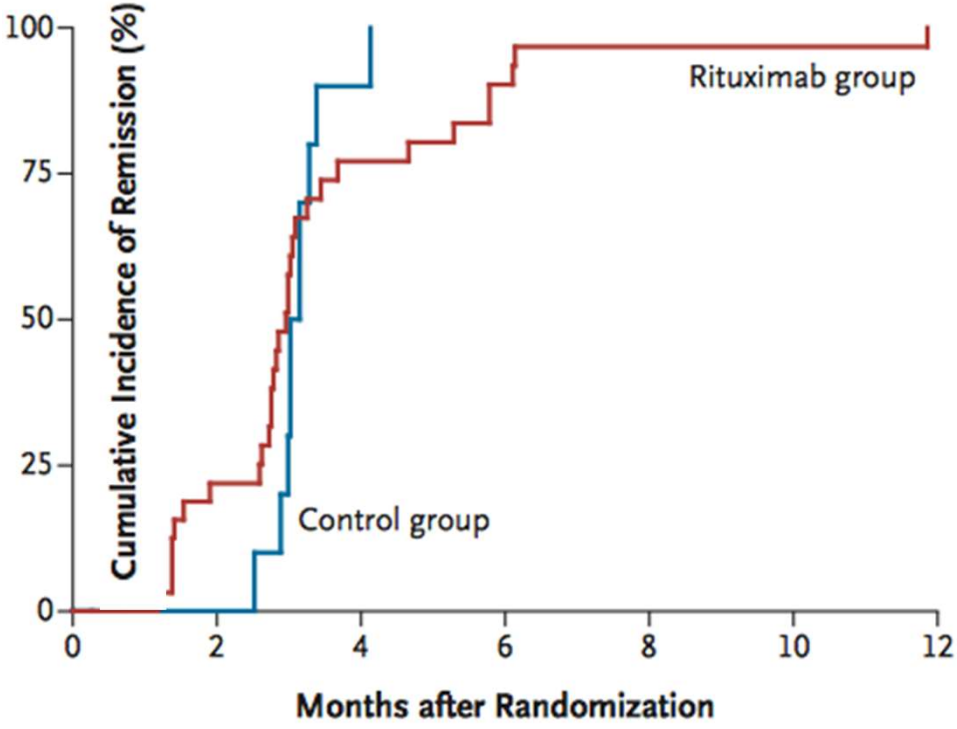
RITUXVAS – 12 months

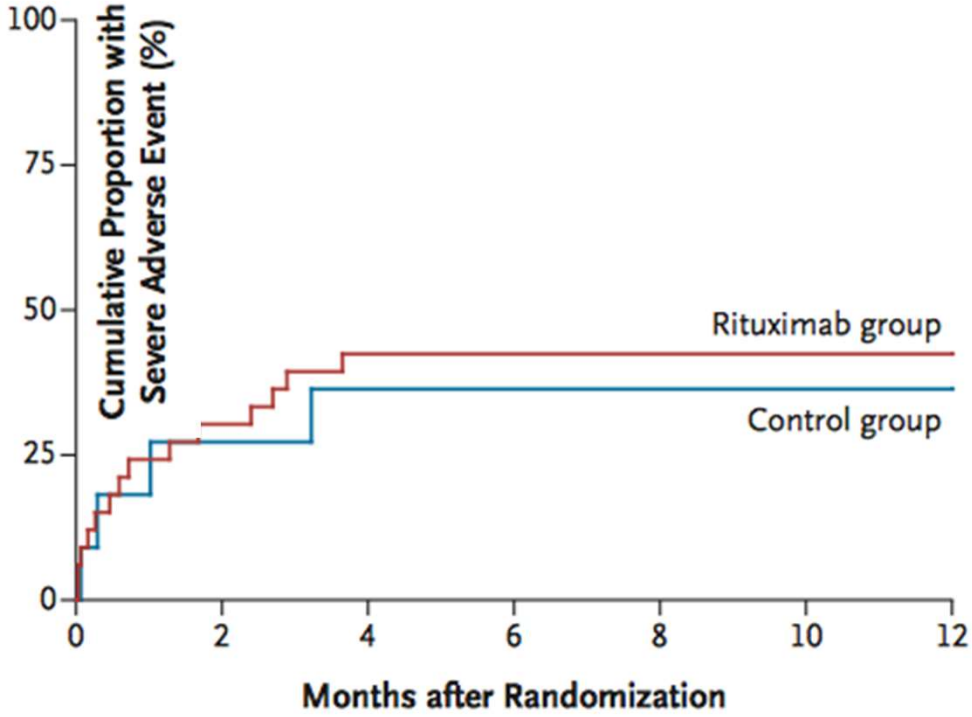
Design	Open label RCT (n=44)	
Patients	Patients with treatment naïve ANCA vasculitis	
Intervention	RTX 375 mg/m^2 – 4 doses 1 week apart + CYC 15 mg/kg with the 1st and 3rd RTX dose	**Before randomization:** Plasmapheresis and 2 g of solumedrol pulses allowed **After randomization:** 1 solumedrol pulse followed by PRED 1mg/kg→ Tapered to 5mg at 6 months **Remission maintenance:** Only the control group received AZA
Control	IV CYC pulses for 3 – 6 months	
Outcomes	Sustained remission and serious adverse events at 12 months	

RITUXIVAS – Patient Characteristics

	Rituximab (n =33)	Control (n=11)
Age (Median)	68	67
Male sex, n (%)	17 (52)	6 (55)
Glomerular filtration rate, Median (ml/min/1.73m^2)	20	12
Dialysis required at entry, n(%)	8 (24)	1 (9)
Intravenous methyl prednisolone, Median(IQR), g (Range)	1 (1-1)	1 (1-1)
Use of plasma exchange, n(%)	8 (24)	3 (27)

RITUXIVAS – Outcomes at 12 months





RITUXIVAS – 12-month Results

- RTX/CYC based regimen was not superior to CYC induction and AZA remission maintenance at 12 months of follow up in patients with severe AAV
- High remission rates were achieved with both regimens
- No difference in serious adverse events between RTX and CYC based regimens
- Cumulative CYC dose was less in the RTX based regimen

RITUXVAS – 24 months

	Rituximab group (n=33) N(%)	Control group (n=11) N(%)	RR (95% CI)
Sustained remission at 6 months	25 (76)	9 (82)	
Remission maintained at 24 months	20 (61)	7 (64)	
Recovery if eGFR <15 ml/min/1.73m^2	7/13 (54)	2/6 (33)	
ESRD	2 (6)	0	1.11 (0.12 – 9.77)
Death	6 (18)	3 (27)	0.66 (0.20 - 2.22)
Composite of death, ESRD and relapse	14 (42)	4 (36)	1.16 (0.48 -2.80)

RITUXIVAS – 24 month: Summary

- No difference in outcomes (relapse free survival, patient, and renal survival) at 24 months
- Rapid improvement in GFR
  - Approx. 1/3 of the pts were dialysis dependent or had eGFR of <15 at randomization
  - 54% vs. 33% recovered renal function in the RTX and CYC/AZA groups, respectively
- B cell depletion ($<0.01 \times 10^9$ / L)
  - All in the RTX group and 1 in the CYC group achieved complete B cell depletion
  - B cells returned after a median of 12.6 months
  - B cell return was associated with relapse in the RTX group (30 % in the return vs. 0 % in the no-return group)

RTX vs. Oral CYC for remission induction
RAVE Trial

Stone, J. H. *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N. Engl. J. Med.* **363,** 221–232 (2010).

Specks, U. *et al.* Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. *New England Journal of Medicine* **369,** 417–427 (2013).

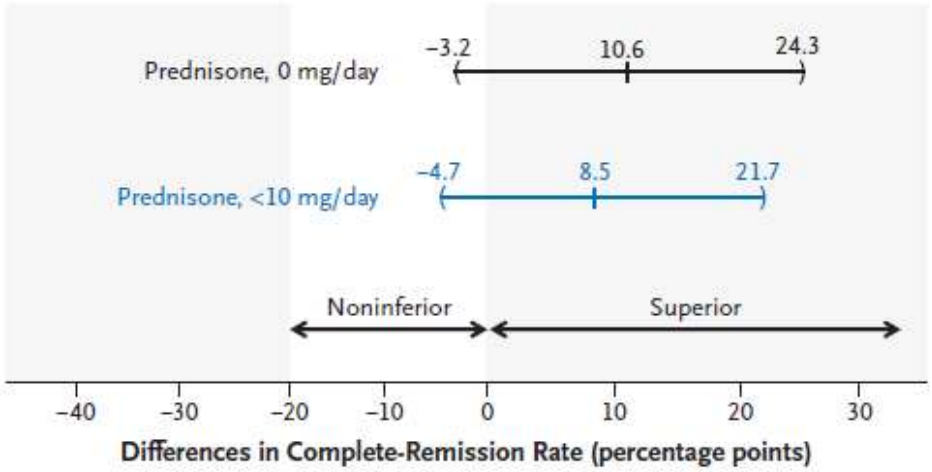
RAVE – RTX vs. Oral CYC for remission induction

<table>
<tr><td>Design</td><td colspan="2">Multi center, RCT, double-blinded, non-inferiority trial</td></tr>
<tr><td>Patients</td><td colspan="2">Newly diagnosed or relapsing patients with ANCA vasculitis with severe disease and BVAS ≥3 followed for 6 months</td></tr>
<tr><td>Intervention</td><td>RTX 375 mg/m^2 q week for 4 doses</td><td rowspan="2">Both groups received:
PRED: I mg/kg → tapered off in 5 months if remission achieved with no disease activity
Remission maintenance:
AZA 2 mg/kg for 6 months only in the control group</td></tr>
<tr><td>Control</td><td>Oral CYC of 2 mg/kg (renally adjusted) till remission</td></tr>
<tr><td>Outcomes</td><td colspan="2">Primary:
• BVAS/WG of 0 with successful PRED taper at 6 months
Secondary:
• Rates of disease flare; BVAS/WG 0 with PRED of < 10 mg/day at 6 months; Cumulative steroid dose</td></tr>
</table>

RAVE – Patient characteristics

Variable	Rituximab (N=99)	Control (N=98)	P Value
Age at onset of symptoms (yr), SD	54±16.8	51.5±14.1	0.26
BVAS/WG	8.5±3.2	8.2±3.2	0.38
Renal involvement (%)	66	66	0.92
Creatinine clearance (ml/min)	54±3	69±4	0.04
Pulmonary involvement (%)	52	54	0.83
Alveolar hemorrhage (%)	27	24	0.54

RAVE – Results



Difference between the proportion of patients who achieved the primary endpoint between the RTX and the CYC arms

- The lower margin of the CI **does not** cross the lower non-inferiority limit; therefore, RTX is not inferior to CYC
- The lower margin of the CI **does** cross the upper non-inferiority limit; therefore, RTX is not superior to CYC

RAVE – Results

	RTX (%)	CYC (%)	Comments
Complete remission and off PRED at 6 months	64	53	
Complete remission and receiving < 10 mg of PRED at 6 mo	71	62	
Patients with relapsing disease at time 0 who reached primary end point	67	42	OR: 1.4 (95% CI 1.03-1.91)
Primary end point achievement by sub-groups			
PR3 –ANCA associated vasculitis (AAV)	65	48	0.04
MPO- AAV	61	64	0.80
Major renal disease	61	63	0.92
Alveolar hemorrhage	57	11	0.48
ANCA Negativity at 6 months	47	24	
PR3 Negative	50	17	<0.001
MPO Negative	40	41	0.95

RAVE – Summary

- RTX/PRED was **not inferior** to CYC/PRED/AZA
- RTX/PRED was **superior** to CYC/AZA/PRED regimen in patients with **relapsing** and **PR3** ANCA Vasculitis
- RTX/PRED was **more effective in causing B cell** depletion than the CYC/PRED/AZA regimen
- The RTX and PRED based regimen resulted in **higher PR3 negativity**
- A total of 66% patients had renal involvement
  - CrCl was relatively high in both groups
  - Patients with Sr Cr > 4 mg/dL were excluded from the study

RAVE – 18 MO follow-up

- Patients included in the original RAVE trial who were in complete remission and were off PRED were followed for 18 months
  - RTX group received placebo
  - CYC group received AZA 2mg/kg
- Primary outcome:
  - Complete remission at 12 and 18 months without relapse
- Secondary outcomes:
  - CD 19 positive B Cells
    - Depleted:<10 /uL
    - Reduction:10-<69/uL
    - Reconstitution:≥69/uL

RAVE – 18 MO follow-up: Whole cohort

Efficacy Measure	**Rituximab** %	**CYC/AZA** %	**Difference % (95% CI)**	**P Value**
Complete remission (Months)				
6	64	53	11 (-3 to 24)	0.13
12	47	39	9 (-5 to 22)	0.22
18	39	33	7 (-7 to 20)	0.32
Remission and <10 mg/day of Prednisone (Months)				
6	71	61	10 (-4 to 23)	0.16
12	60	61	-2 (-15 to 12)	0.82
18	55	53	2 (-12 to 15)	0.84
Estimated creatinine clearance				
Baseline	76.83±3.77	91.56±3.75	-14.74	0.01
18 mo	82.12±4.12	96.30±4.12	-14. 18	0.02

RAVE – 18 MO outcomes: Relapsing disease at baseline

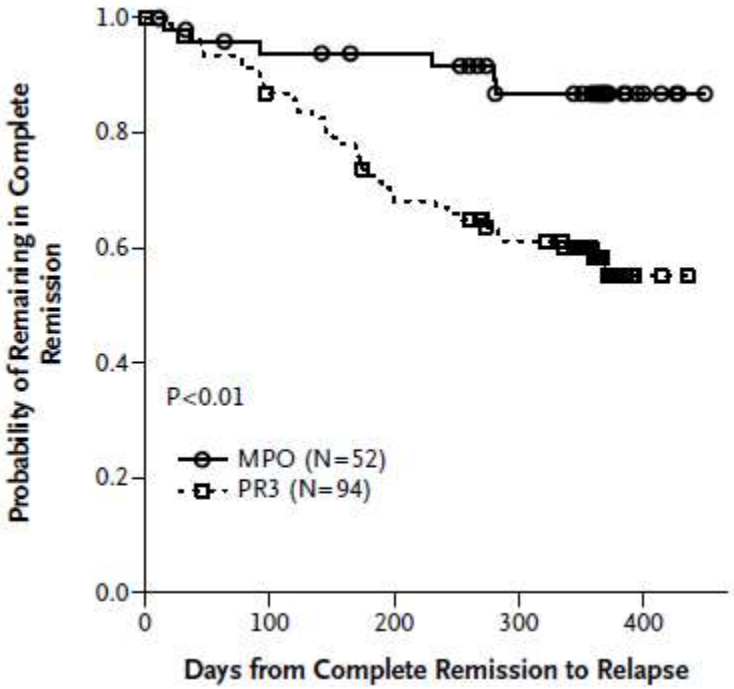
Efficacy Measure	Rituximab	CYC/AZA	Difference (%)	P Value
Complete remission in patients with relapsing disease at baseline (%) (Months)				
6	67	42	25 (6 to 44)	0.01
12	49	24	25 (7 to 43)	0.009
18	37	20	17 (0 to 34)	0.06
Estimated creatinine clearance, mean (SD) (ml/min)				
Baseline	53.54±4.63	70.52±14.64	-16.97	0.01
18 mo	64.08±5.21	80.10±15.10	-16.02	0.03

RAVE – 18 MO outcomes: Stratified on serology

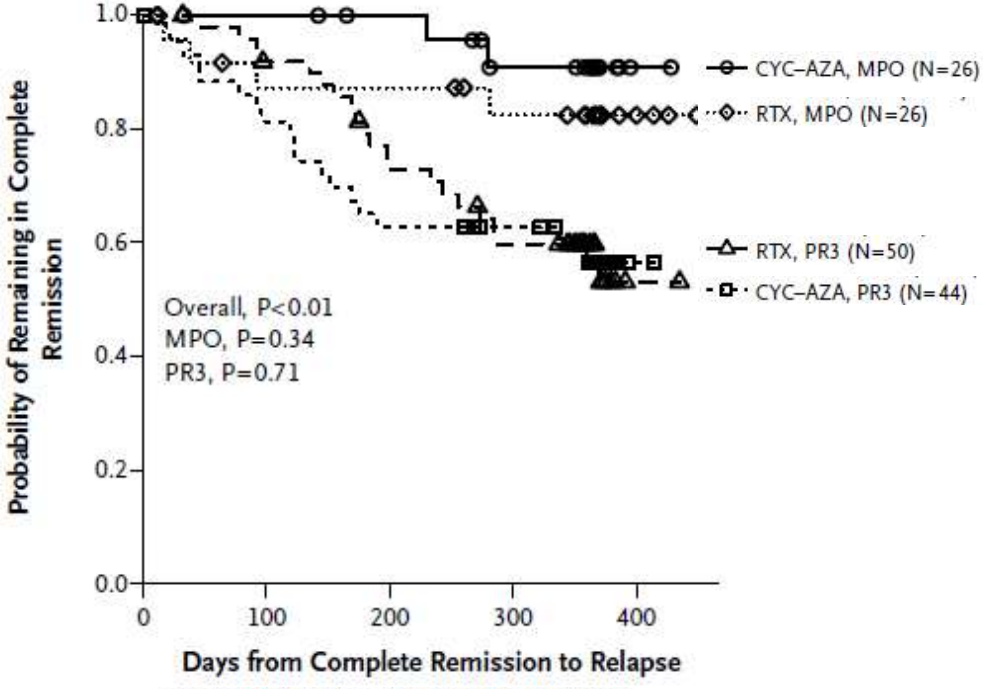
	PR3-AAV			MPO-AAV		
	RTX (n=66)	**CYC/AZA (n=65)**	p Value	**RTX (n=33)**	**CYC/AZA (n=33)**	p Value
CR at 6 months (%)	65	48	0.04	61	64	0.80
CR at 12 months (%)	47	32	0.09	49	52	0.81
CR at 18 months (%)	36	29	0.39	46	39	0.62

Unizony, S. *et al.* Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann. Rheum. Dis.* **75,** 1166–1169 (2016).

RAVE – 18 MO outcomes: Factors associated with relapse

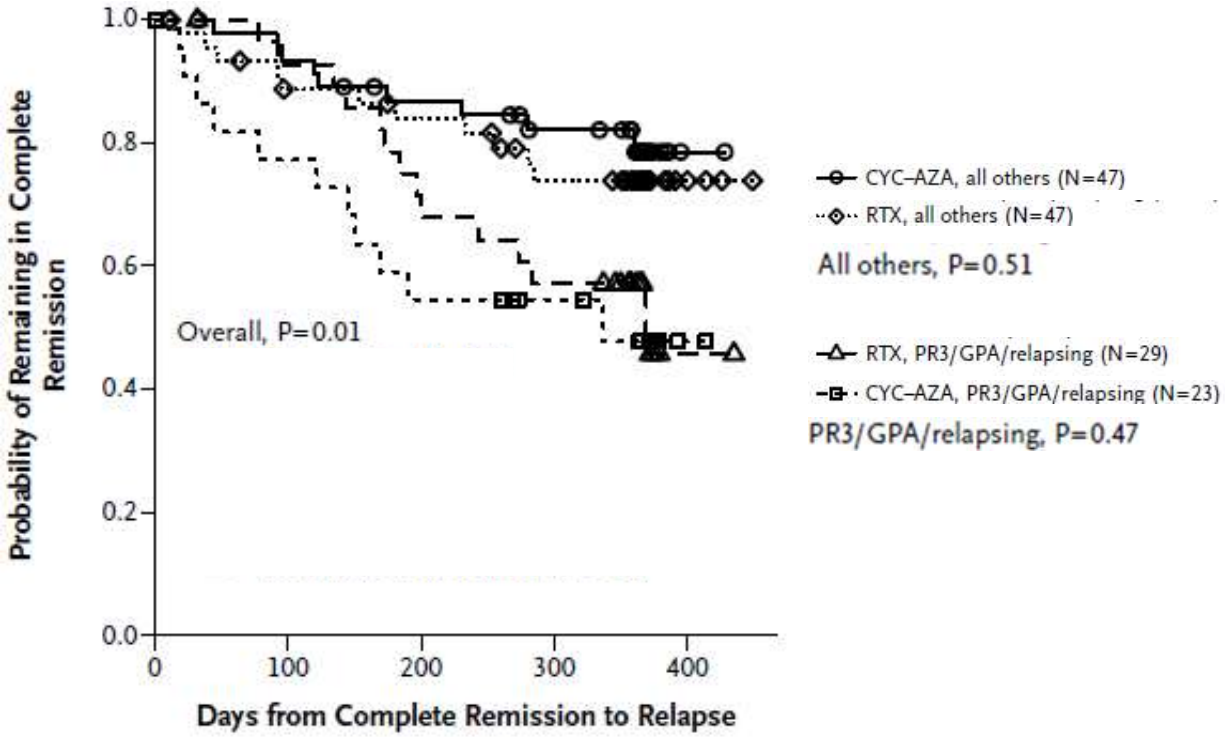


Time to First Relapse after Complete Remission, According to Baseline Type of ANCA



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

RAVE – 18 MO outcomes: Factors associated with relapse



Time to first relapse after complete remission according to presence of three risk factors (**Diagnosis of GPA with PR3 positivity and severe relapse at baseline**)

RAVE 18 MO outcomes – Adverse events

- Severe leukopenia (WBC < 3000) more frequent in the CYC/AZA vs. RTX (23 vs. 5; P <0.001)
- Pneumonia more frequent in the CYC/AZA than the RTX group (11 vs. 4; P <0.03)
- No other significant differences between the groups in rates of other adverse events including death

RAVE- 18 MO follow-up: Summary

- **RTX** continued to be **more effective** than CYC in **inducing remission** at **6** and **12** months in patients with **relapsing disease**
- **RTX** was **more effective** than CYC in inducing remission at **6** months in patients with **PR3 AAV**
- **Relapse rate** was **high** in **both groups** at 18 months (RTX 32 vs. CYC 29%)
- **GPA, PR3 positivity and relapsing disease at baseline** were associated with relapse
- Increasing **ANCA titers** or **B Cell reconstitution** did not predict relapses
  - However, relapses were rare in the absence of ANCA and B cells

Rituximab as an induction agent for severe renal disease?

Design	Retrospective cohort –March 2014 to April 2015	
n	37; 33 patients with follow-up >6 mo	
Baseline	**RTX/GLUC (n 12)**	**RTX/GLUC/CYC (n 25)**
ANCA type (n)		
PR3	4	9
MPO	6	16
Negative	2	0
eGFR (ml/min) median IQR	12 (6-16)	13 (7-16)
Dialysis dependence	7 (58)	8 (32)
Alveolar hemorrhage	3 (25)	8 (32)
Analysis		
Remission, n (%)	12 (100)	21/22 (95)
Renal recovery, n (%)	5 (72)	5(62)
ESRD, n(%)	4(33)	8(32)
Death in the first 6 months, n(%)	0 (0)	3 (12)
Infections, n (%)	2 (17)	8 (32)

Geetha D, et al. Rituximab for treatment of severe renal disease in ANCA associated vasculitis. J Nephrol. 2016 Apr;29(2):195–201.

2. To discuss the role of plasmapheresis in severe AAV
MEPEX and PEXIVAS trials

Jayne, D. R. W. *et al.* Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. *JASN* **18,** 2180–2188 (2007).

Walsh M, Merkel PA, Peh C-A, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. New England Journal of Medicine. 2020;382(7):622-631.

Remission induction - MEPEX

Design	Open label RCT	
Patients	Biopsy proven, treatment naïve Europeans with renal ANCA vasculitis with serum Cr > 5.8 mg/dL	
Intervention	A total of 7 cycles of plasma exchange (PLEX) in 14 days	**Both groups received:** • Oral prednisolone 1 mg/kg/day tapered over 6 months • Oral CYC 2.5 mg/kg/day for 3 months • AZA (2 mg/kg) maintenance
Control	1 gm IV Solumedrol q day (3 doses)	
Outcomes	**Primary:** • Renal recovery (Pt survival, dialysis independence and Cr <5.8 mg/dL) **Secondary:** • Renal and patient survival at 1 year • Severe adverse event rate	

MEPEX – Population characteristics

Clinical and laboratory features	Intravenous Solumedrol (n=67)	Plasma exchange (n=70)	p
Age- yr; median (range)	66 (27 to 81)	67 (28 to 79)	0.93
Female gender N (%)	24 (36)	29 (41)	0.50
Dialysis requiring N (%)	48 (71.6)	47 (67.1)	0.57
PR3 ANCA, N (%)	31 (46.3)	26 (37.1)	0.35
MPO ANCA, N (%)	31 (46.3)	40 (57.1)	
BVAS median (range)	21 (12 to 41)	21 (12 to 39)	0.69
Cr - mg/dL median (range)	8.12 (5.16 -17.71)	8.52 (5.65 -19.21)	0.96

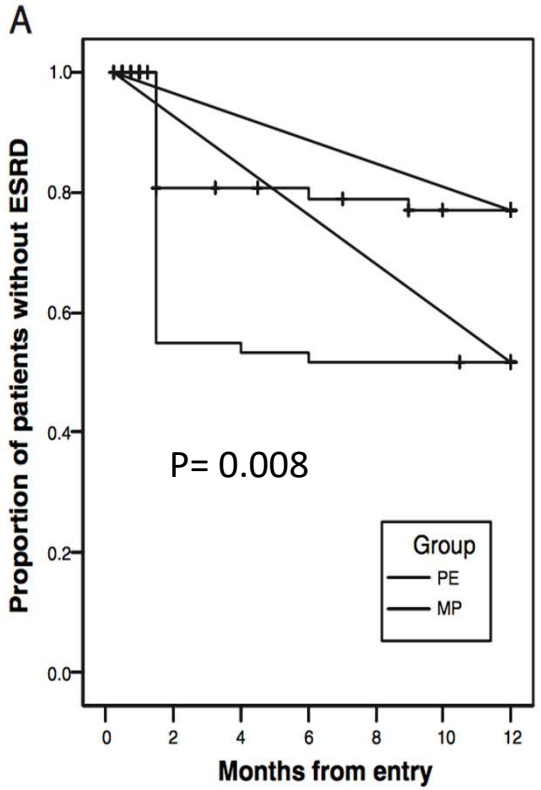
MPEX – Kidney biopsy findings

Histologic Lesion	Intravenous Methylprednisolone (n = 49)	Plasma Exchange (n = 51)	Total Group (n = 100)
Glomerular			
% normal glomeruli	13.6 ± 18.2	12.1 ± 12.1	12.8 ± 15.3
% fibrinoid necrosis	28.9 ± 25.3	22.2 ± 24.9	25.5 ± 25.2
% crescents	59.2 ± 28.6	53.0 ± 28.9	56.0 ± 28.8
segmental	23.1 ± 23.4	28.9 ± 31.3	25.9 ± 27.3
circumferential	76.9 ± 44.3	71.1 ± 54.3	74.1 ± 49.5
cellular	90.4 ± 49.1	90.8 ± 57.2	90.6 ± 53.0
fibrous	9.6 ± 12.6	9.2 ± 18.0	9.4 ± 15.3
% global sclerosis	24.6 ± 26.9	28.2 ± 24.6	26.4 ± 25.7
Tubulointerstitial and vascular interstitial fibrosis (0/1/2)	1.2 ± 0.6	1.3 ± 0.6	1.2 ± 0.6

MEPEX – RESULTS: PLEX → Improved renal recovery

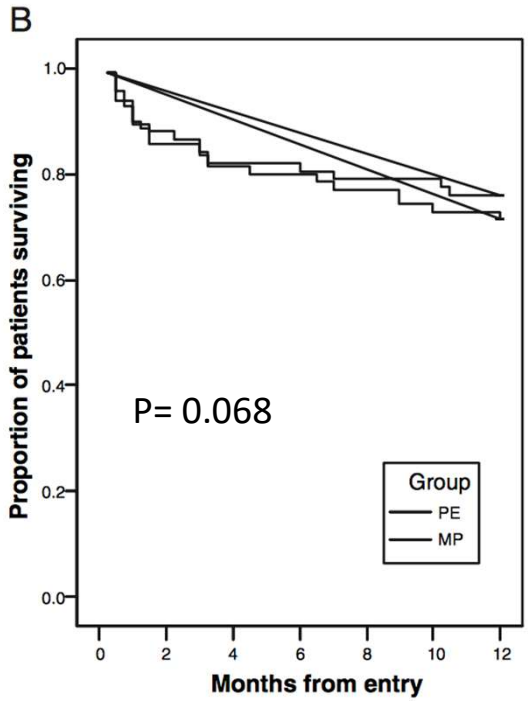
	Solumedrol n=67 n(%)	Plasma Exchange n=70 n(%)	95% CI of the difference (%)
Renal recovery at 3 months	33 (49)	48 (69)	18-35
Independence from dialysis at 12 months	29 (43)	41(59)	4-40

The association of renal recovery and treatment with plasma exchange remained in the multivariate analysis (p=0.04)



MEPEX – RESULTS: PLEX →Similar patient survival

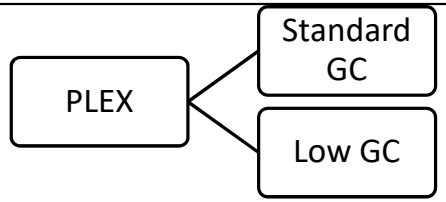
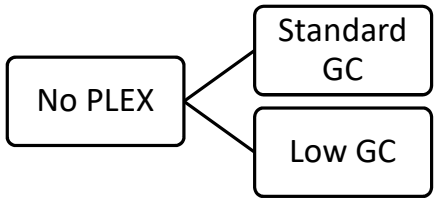
	Solumedrol N=67 n(%)	PLEX N=70 n(%)
Survival at 3 months	56 (84)	59 (84)
Survival at 12 months	51 (76)	51(73)



MEPEX: Summary

- In patients with severe ANCA associated renal disease, PLEX improved **renal survival** but **not patient survival**
- MEPEX raised questions:
  - Does PLEX decrease ESRD in long term?
  - Does PLEX increase patient survival in long term?
  - Should PLEX performed if renal biopsy shows extensive fibrosis?
  - Should pulse solumedrol and PLEX be used concurrently?

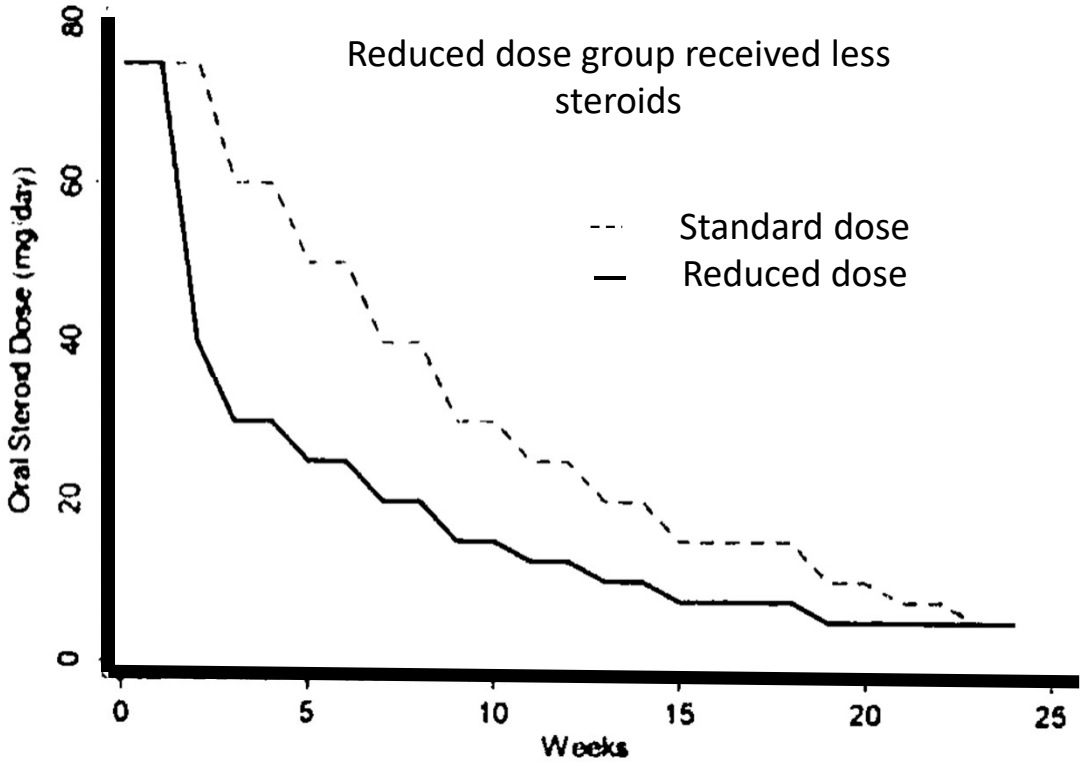
PEXIVAS

Design	Open label RCT (n=704)	
Patients	Patients with severe ANCA (eGFR <50 ml/min/1.73m^2) with crescentic GN and/or pulmonary hemorrhage	
Intervention	Both groups received Pulse steroids and Either CYC or RTX	
Control		
Outcomes	**Primary Outcomes**: Composite of 1)all-cause mortality or 2) ESRD two years after the final subject is enrolled **Secondary Outcomes**: Death from any cause, ESKD, Sustained Remission (2 y after the final subject is enrolled), Rate of serious infections, Health-related quality of life using SF-36	

PEXIVAS: Population Characteristics

	PLEX (n=352)	Control (n=352)	Reduced Dose (n=353)	Standard Dose (n=351)
Mean age, years (SD)	62.8 (14.4)	63.5 (13.7)	63.3 (14.2)	63.1 (13.9)
Female, n (%)	149 (41.3)	158 (44.9)	156 (44.2)	151 (43)
Dominant ANCA, n (%)				
PR3	143 (40.6)	143(40.6)	143 (40.5)	143 (40.7)
MPO	209(59.4)	209(59.4)	210 (59.5)	208 (59.3)
Lung Hemorrhage, n (%)				
Any	95 (27)	96 (27.3)	96.2 (27.2)	95 (27)
Severe	31 (8.8)	30 (8.5)	31 (8.8)	30 (8.5)
Creatinine				
Median (25th -75th) mg/dL	3.69 (2.33 - 5.55)	5.55 (2.36 - 5.59)	3.61 (2.14 - 5.42)	3.78 (2.47-5.67)
>5.65 mg/dL, n (%)	101 (28.7)	104 (29.5)	102 (28.9)	103 (29.3)
On Dialysis, n (%)	66 (18.8)	74 (21.0)	67 (19.0)	73(20.8)
Immunosuppression, n(%)				
IV CYC	177 (50.3)	177 (50.3)	179 (50.7)	175 (49.9)
Oral CYC	120 (34.1)	121 (34.3)	120 (34)	121 (34.5)
Rituximab	55 (15.6)	54 (15.4)	54 (15.3)	55 (15.6)

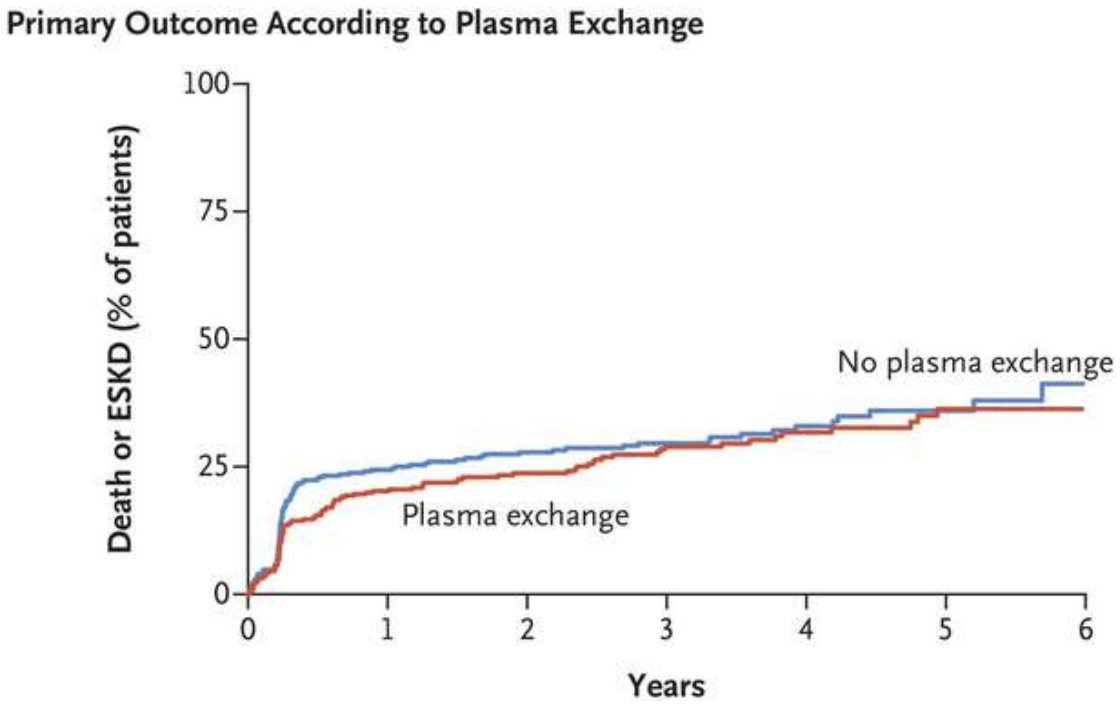
Reduced dose group received less steroids



Tapering protocol in patients weighing >75 kg

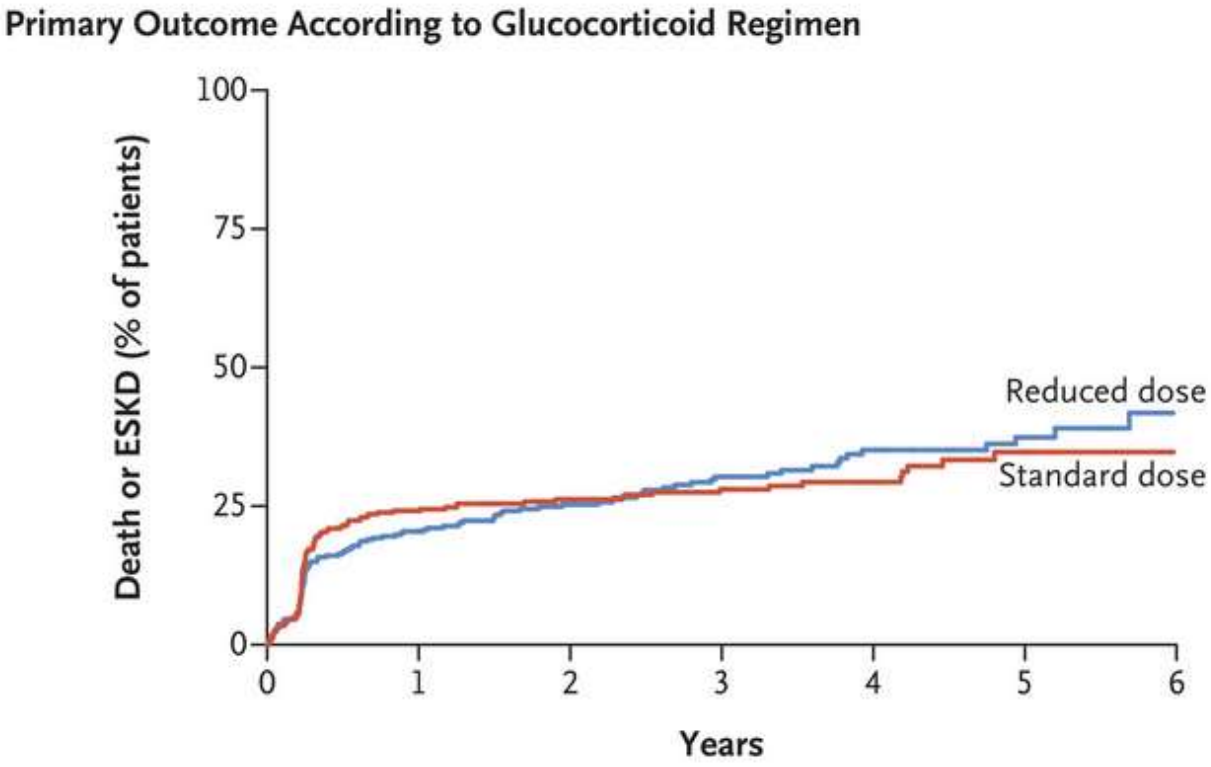
Week(s)	Standard Dose Pulse	Reduced Dose Pulse
1	75	75
2	75	40
3-4	60	30
5-6	50	25
7-8	40	20
9-10	30	15
11-12	25	12.5
13-14	20	10
15-16	15	7.5
17-18	15	7.5
19-20	10	5
21-22	7.5	5
23-52	5	5
>52	Local Practice	

Results: PLEX – Primary Composite Outcome



At Risk							
No PLEX	352	244	183	136	83	46	10
PLEX	352	253	186	135	83	44	10

Results: Low Vs. High Dose Steroids – Primary Composite Outcome



Results: Secondary Outcomes

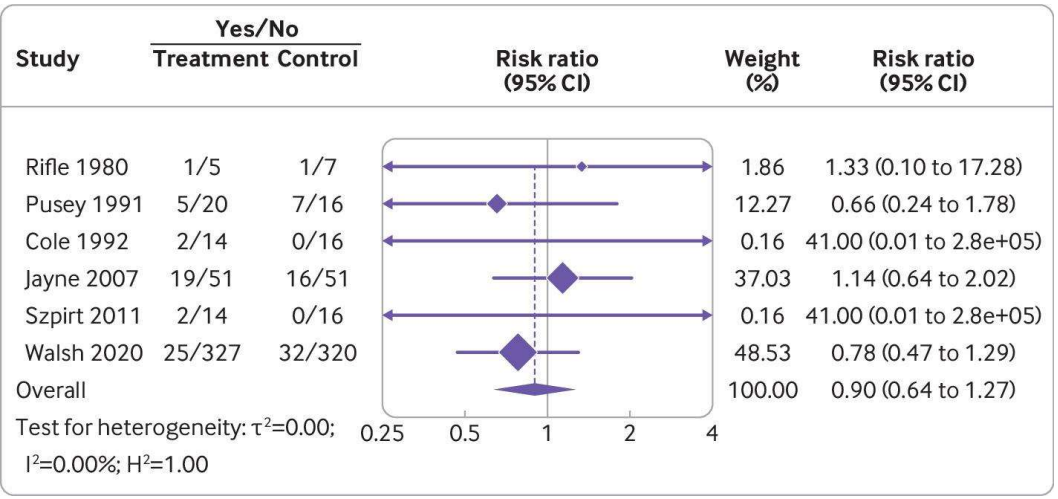
Outcome	PLEX	Control	Hazard Ratio (95% CI)
Death, n (%)	46 (13)	53 (15)	0.87 (0.58 – 1.29)
ESRD, n (%)	67 (19)	71 (20)	0.81 (0.57 – 1.13)
Sustained Remission, n (%)	200 (57)	197 (56)	1.01 (0.89 - 1.15)
SAE s, n (%)	224 (64)	225 (64)	1.21 (0.96 – 1.52)
Year 1 Serious Infections, n (%)	**119 (34)**	**93 (26)**	**1.16* (0.86 –1.56)**

*Incidence Rate Ratio (95% CI)

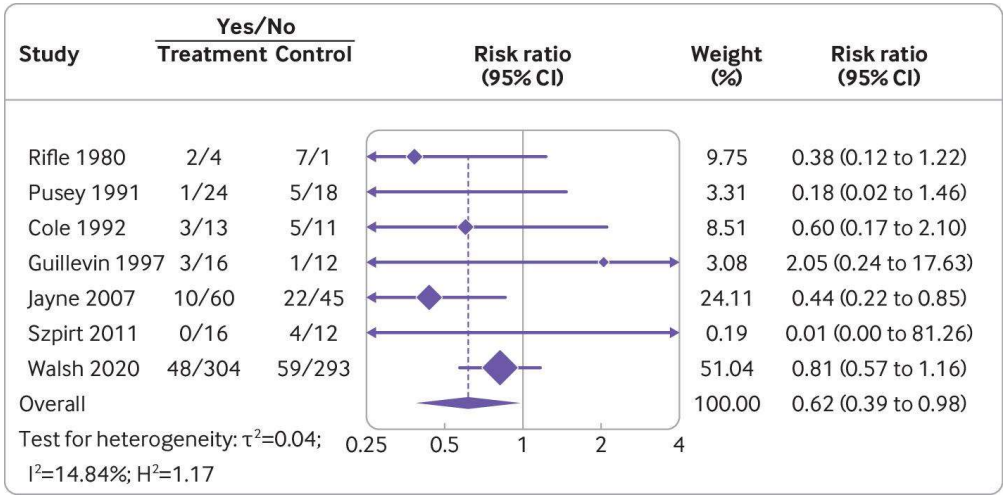
PEXIVAS - Conclusions

- PLEX did not significantly reduce mortality or ESRD in patients with sever ANCA associated vasculitis
  - Kidney biopsy results not known
- A reduced dose of glucocorticoids was non-inferior to a “standard” dose
  - **Fewer serious infections**

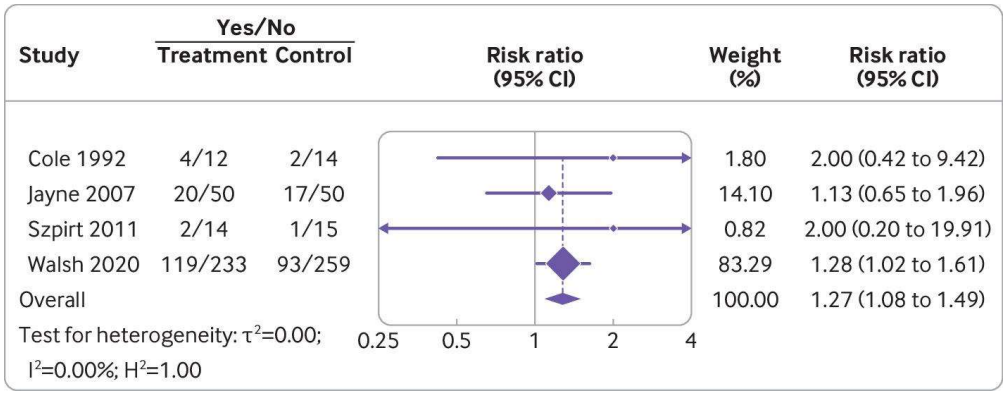
All-cause mortality



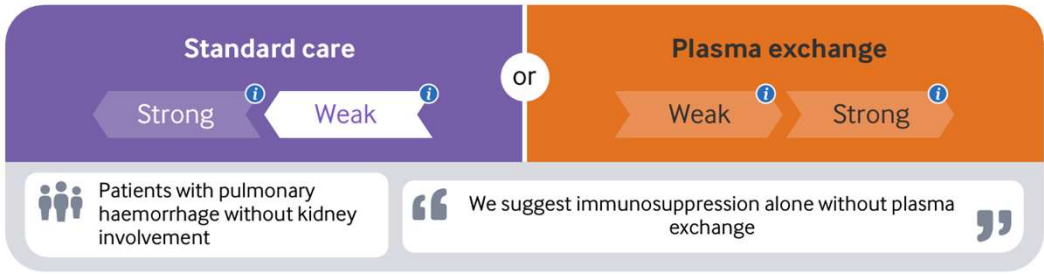
ESKD

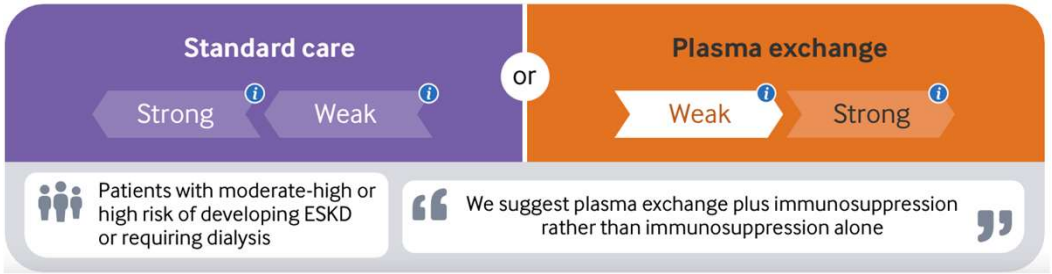


Infection



Walsh M, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ*. 2022;





Zeng L, Walsh M, Guyatt GH, et al. Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline. *BMJ*. 2022;376:e064597

3. To describe the preferred maintenance therapy for AAV RTX vs. AZA

GUILLEVIN, L. ET AL. RITUXIMAB VERSUS AZATHIOPRINE FOR MAINTENANCE IN ANCA-ASSOCIATED VASCULITIS. NEW ENGLAND JOURNAL OF MEDICINE **371,** 1771–1780 (2014).

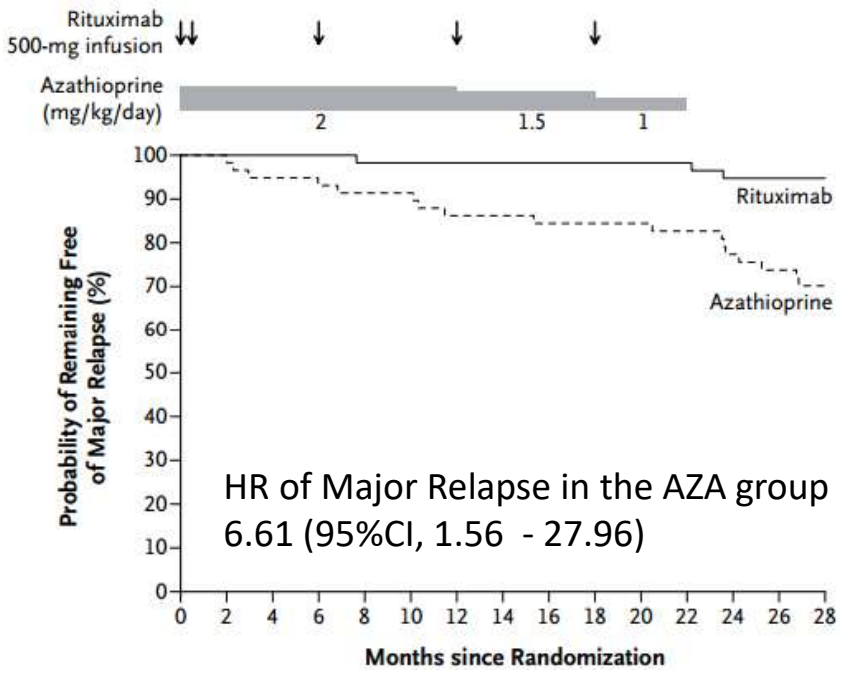
Charles P, Terrier B, Perrodeau É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77(8):1143-1149.

Charles P, et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. *Ann Intern Med*. 2020;173(3):179-187.

RTX for remission maintenance in ANCA vasculitis (MAINRITSAN1)

Design	Open label RCT (n=115) followed for 28 months	
Patients	Newly diagnosed or relapsing ANCA vasculitis patients in complete remission	
Intervention	**Remission induction:** PRED: • I mg/kg → Taper • In some pts, pulse solumedrol: 1-3 gm CYC pulses: • 0.6 g/m^2: 0, 2 & 4 wk • 0.7 g/m^2: q 3 wk x 6 doses	**Remission maintenance:** RTX: • 500 mg on 0 and 14 days & • 6, 12 and 18 mo PRED: • Tapered to 5 mg at 18 mo
Control		**Remission maintenance:** AZA: • 0-12 mo: 2 mg/kg • 13-18 mo: 1.5 mg/kg • 19-22 mo: 1 mg/kg → No AZA from 22 mo onwards PRED: • Tapered to 5 mg at 18 mo
Outcomes	**Primary:** Major relapse (%); **Secondary:** Minor relapses, rates of adverse events, mortality	

Results



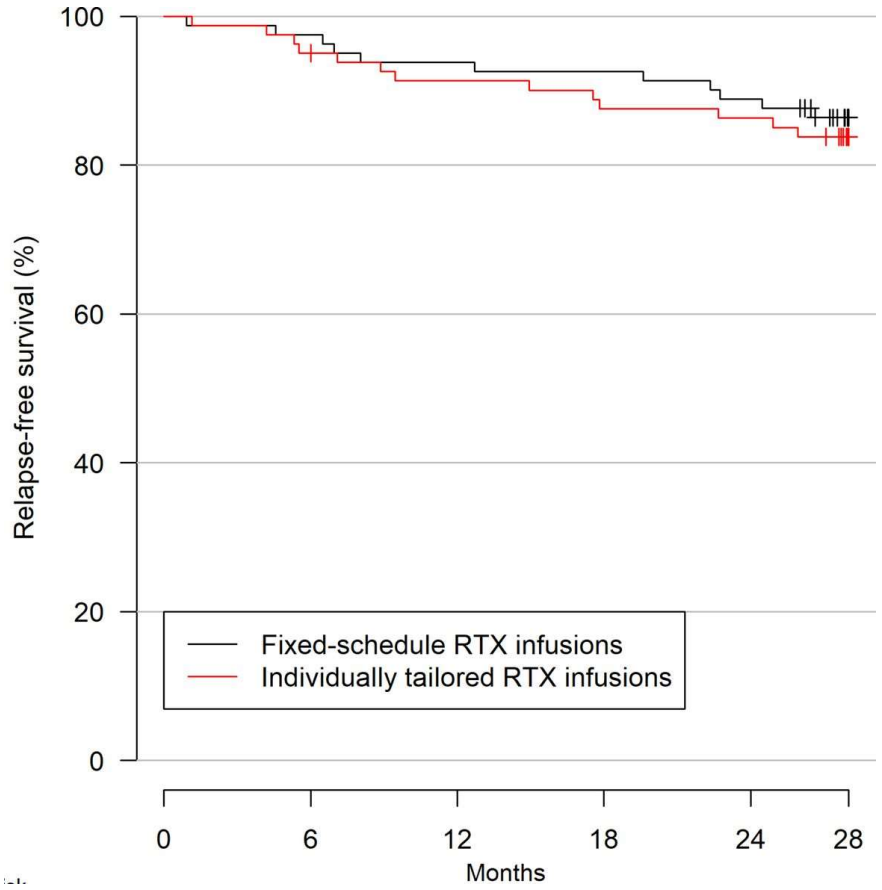
Relapses	Total	0-12	13-18	19-22	23-28
AZA (n)	17	8	2		7
RTX (n)	3	1	0	0	2

Kaplan–Meier Curves for the probability of remaining free of relapse according to treatment group

MAINRITSAN-2

Premise	For maintenance, should RTX be administered on a fixed or a tailored schedule?	
Design	Open label RCT (n=115) followed for 28 months	
Patients	Newly diagnosed AAV pts in complete remission	
Intervention	RTX 500 mg at randomization	CD19 and ANCA q 3 mo RTX 500 mg only if: CD19+B lymphocytes (>0/mm3) or ANCA reappeared or ANCA titer rose rapidly (>2 dilution increase on IFA or doubling of PR3/MPO ELISA)
Control		RTX 500 mg on d 0 and 14, and mo 6,12,and 18
Outcomes	**Primary: Number of new relapses or worsening BVAS > 0**	

Charles P, Terrier B, Perrodeau É, et al. 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). *Ann Rheum Dis*. 2018;77(8):1143-1149.



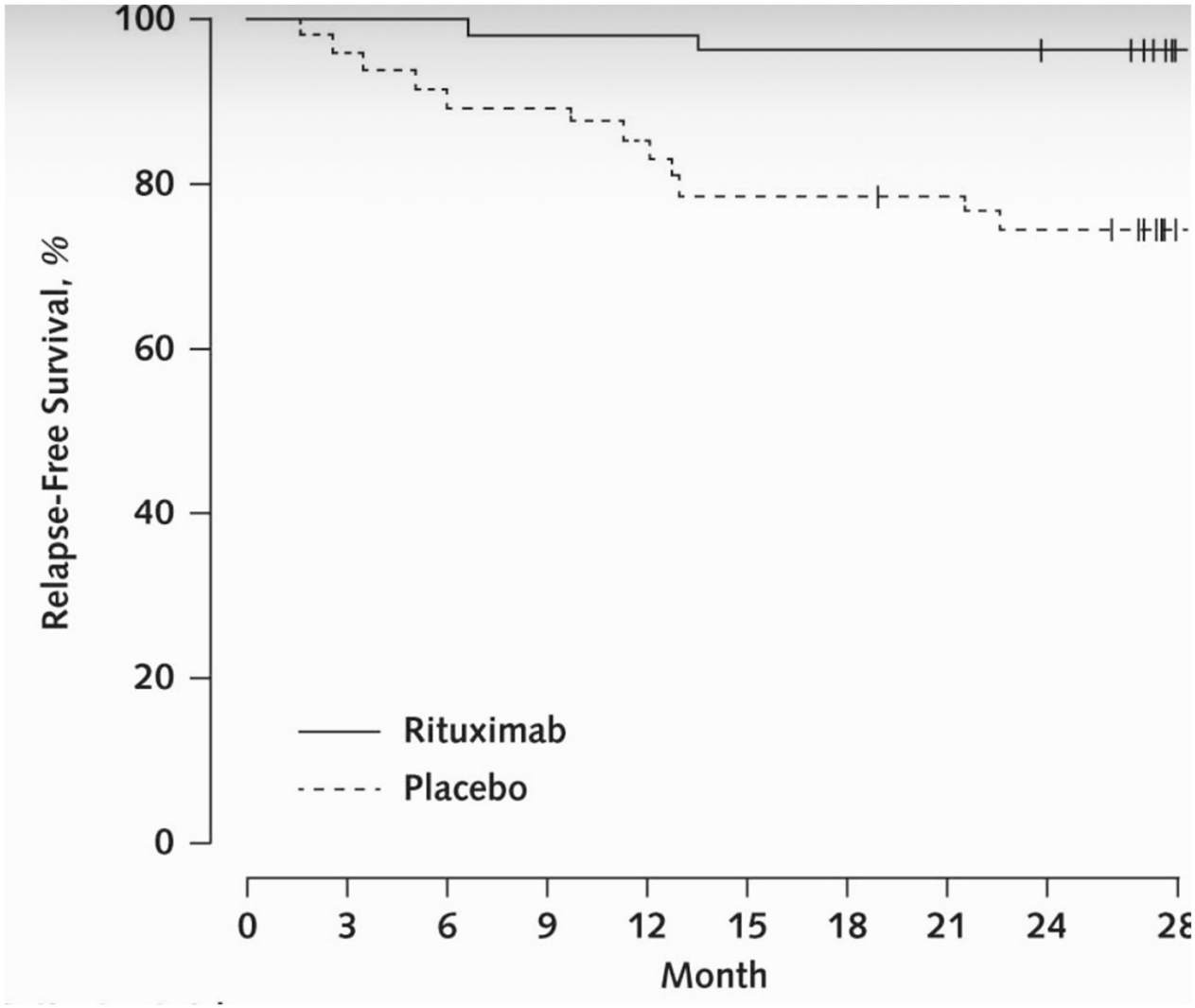
ANCA evolution and B-cell detection patterns throughout follow-up for patients with ≥1 relapses or none

	Patients with	
	≥1 relapse(s) (n=22)*	No relapse (n=139)
ANCA evolution (%)		
Always negative	7 (31.8)	33 (23.7)
Negative at inclusion and became positive	3 (13.6)	14 (10.1)
Positive at inclusion and became negative	2 (9.1)	51 (36.7)
Positive at inclusion and titres rose	1 (4.5)	10 (7.2)
Positive at inclusion and remained stable	9 (40.9)	29 (20.9)
Circulating CD19+ B cell evolution (%)		
Always negative	11 (50)	8 (5.8)
Detected at least once	11 (50)	131 (94.2)
ANCA and circulating CD19+ B cell evolutions (%)		
ANCA-negative and no circulating B cells detected	4 (18.2)	5 (3.6)
Other	18 (81.8)	134 (96.4)

MAINRITSAN-3

Premise	How effective RTX is in maintaining remission in patients with AAV who received 18-mo of rituximab therapy?
Design	RCT; N 97; GPA 68, MPO 29
Population	Pts who AAV who are in CR after 18 mo of maintenance therapy
Control	Placebo q 6 mo x 4
Intervention	RTX q 6 mo x 4
Primary outcome	Relapse free survival at 28 mo

Charles P, et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. *Ann Intern Med*. 2020;173(3):179-187.


100
80
60
40
20
0
Relapse-Free Survival, %
Rituximab
Placebo
0
3
6
9
12
15
18
21
24
28
Month

4. To examine the new therapeutic options for AAV
Use of C5a antagonists to limit PRED exposure

Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. JASN. 2017 Sep 1;28(9):2756–67.

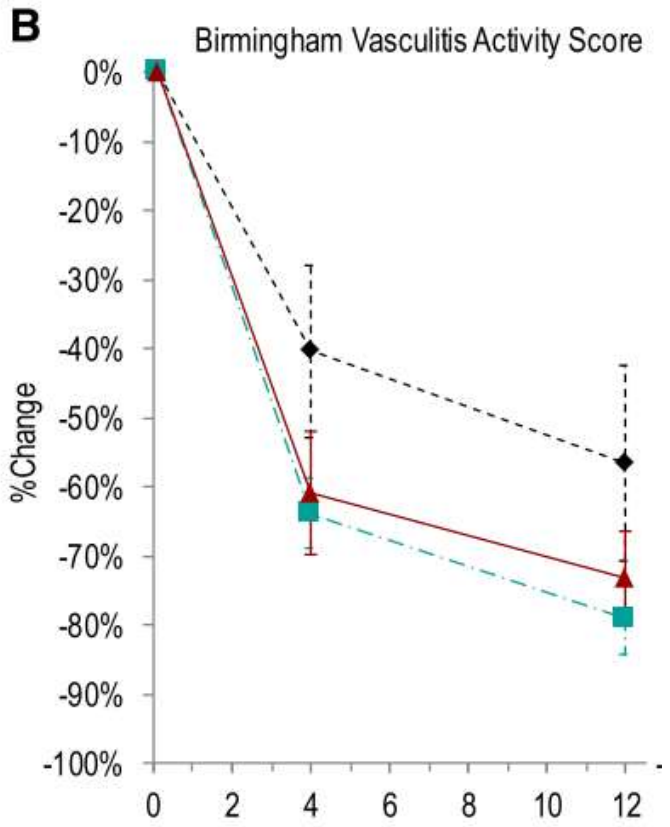
C5A Receptor Inhibitor Avacopan in AAV

Design	RCT non-inferiority trial	
Patients	Newly diagnosed or relapsing ANCA associated vasculitis (AAV)	
Intervention and control groups	**Induction and Maintenance:** IV CYC Pulses followed by Azathioprine 2 mg/kg → 12 to 24 mo	**Step 1: n 12** Avacopan 30 mg BID + PRED 20 Or Placebo + PRED 60 **Step 2: n 12** Avacopan 30 mg BID Or Placebo + PRED 60 mg
	CYC IV followed by AZA or Rituximab (375 mg m^2 q week x 4)	**Step 3: N 41** Avacopan 30 mg BID + Placebo Or Avacopan 30 mg BID + PRED 20 mg Or Placebo + PRED 60 mg
Outcomes	Primary: % with $\geq$50% BVAS ↓ from baseline with no worsening in any organ	

Population

Category	Placebo + 60 mg PRED n=23	Avacopan + 20 mg PRED n=22	Avacopan without PRED n=22
Age, y	59.1±14.0	57.0±14.2	57.4±14.0
Anti MPO-positive, n(%)	10 (43)	12 (55)	13 (59)
Anti PR3-positive, n(%)	11 (48)	10 (45)	8 (36)
Renal involvement, n(%)	23 (100)	21 (95)	21 (95)
Pulmonary involvement, n(%)	9 (39)	8 (36)	7 (32)
eGFR, m/min per 1.73 m^2, mean(SD)	47.6±15.1	52.5±26.7	54.7±19.6

Results – Primary end-point



(B) BVAS mean ± SEM % change from baseline for:

(◆) Placebo plus high-dose prednisone, n=20
(▲) Avacopan without prednisone, n=21
(■) Avacopan plus reduced-dose prednisone, n=22

Results – Primary end-point

Category	Placebo + 60 mg PRED n=23→20	Avacopan plus 20 mg PRED n=22→22	Avacopan without PRED n=22→21
Primary end-point at 12 weeks	14(70)	19(86.4)**	17(81)*

**** p 0.002 for non-inferiority**

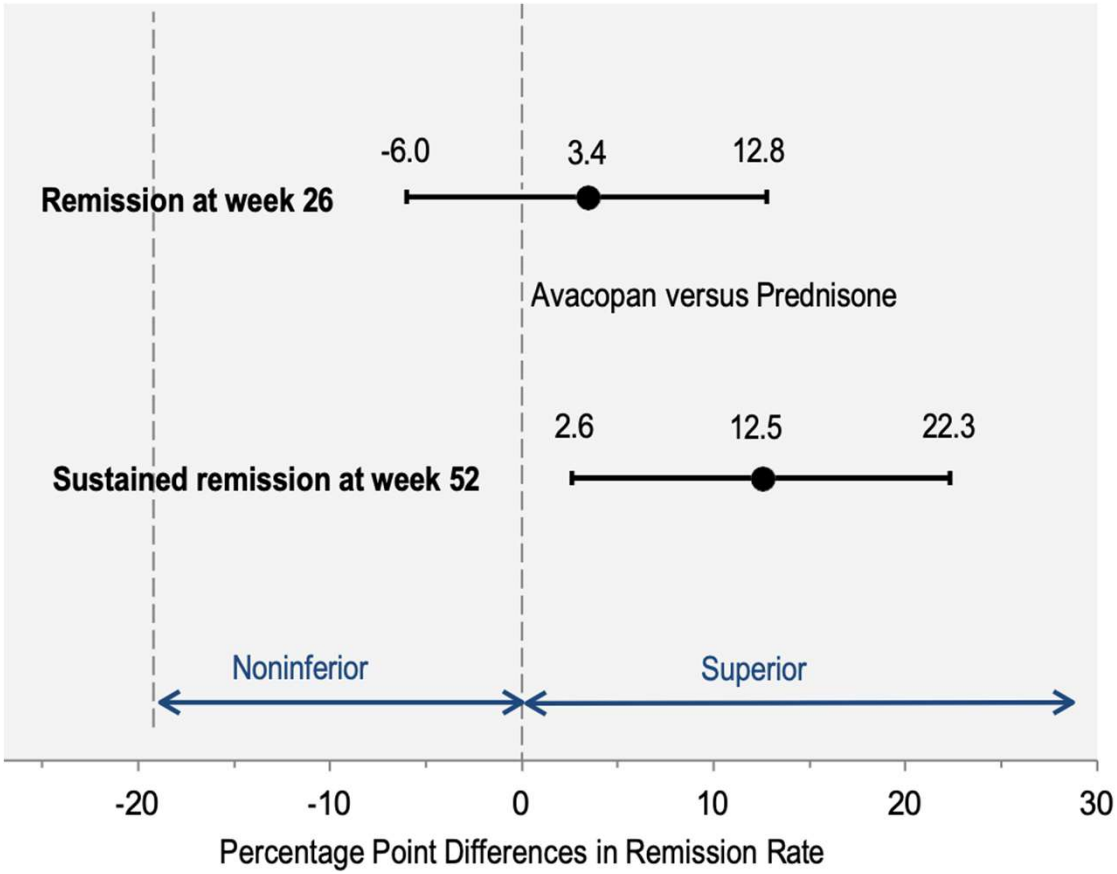
***p 0.01 for non-inferiority**

AVACOPAN – TIME TO REPLACE GLUCOCORTICOIDS?

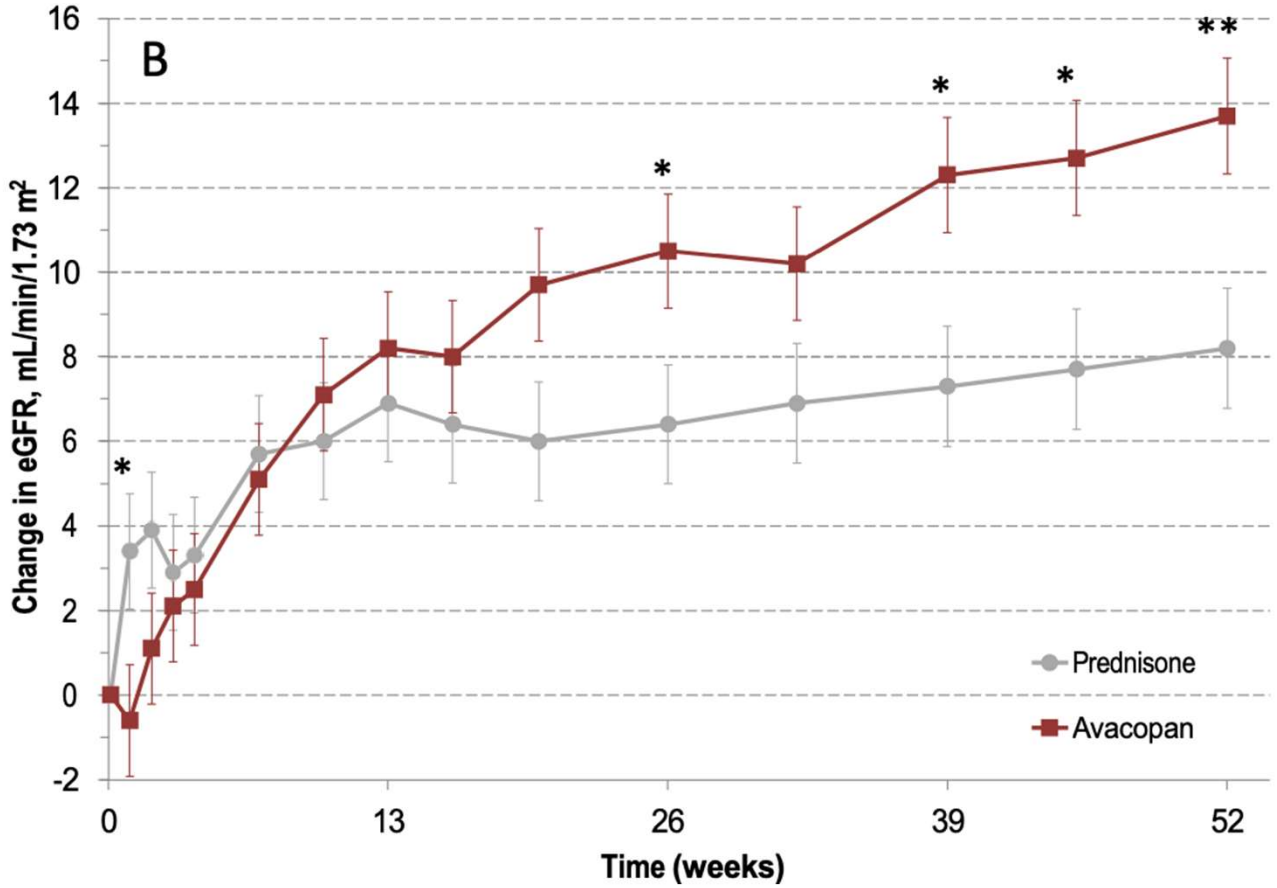
Design	International, multicenter, double-blinded RCT non-inferiority trial	
Premise	Can Avacopan replace glucocorticoids in AAV?	
Patients	Newly diagnosed or relapsing ANCA associated vasculitis (AAV)	
Intervention	Cyclophosphamide with Azathioprine Rituximab (4 WKs)	Avacopan 30 mg po BID
Control		Prednisone taper (WK 1: 60 mg → WK: 4-6 25 mg → WK 21: 0mg)
Outcomes	1st outcome: BVAS of 0 @ with 26 WK with no GLUC use in the previous 4 weeks 2nd outcome: Primary outcome + BVAS of 0 @ 52 WK with no GLUC use	

Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. *New England Journal of Medicine*. 2021;384(7):599-609.

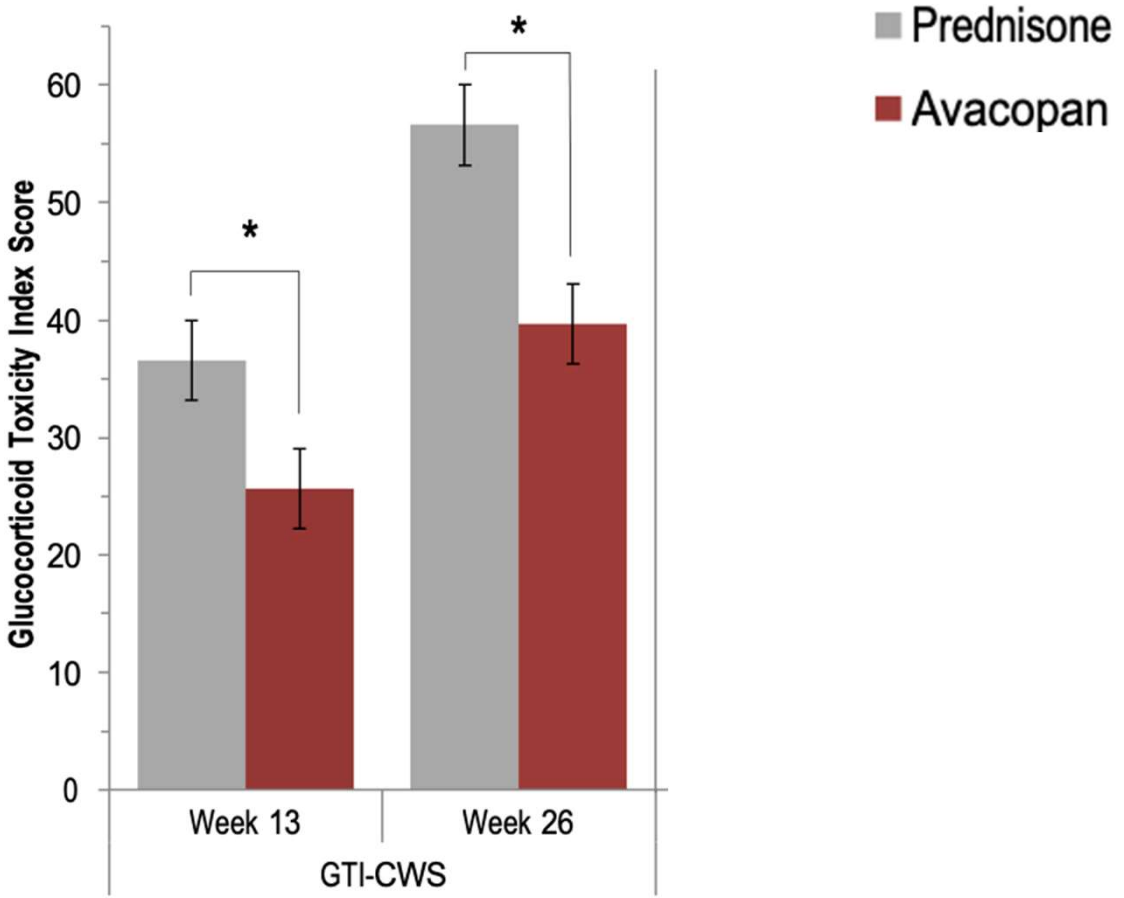
First and Second outcomes



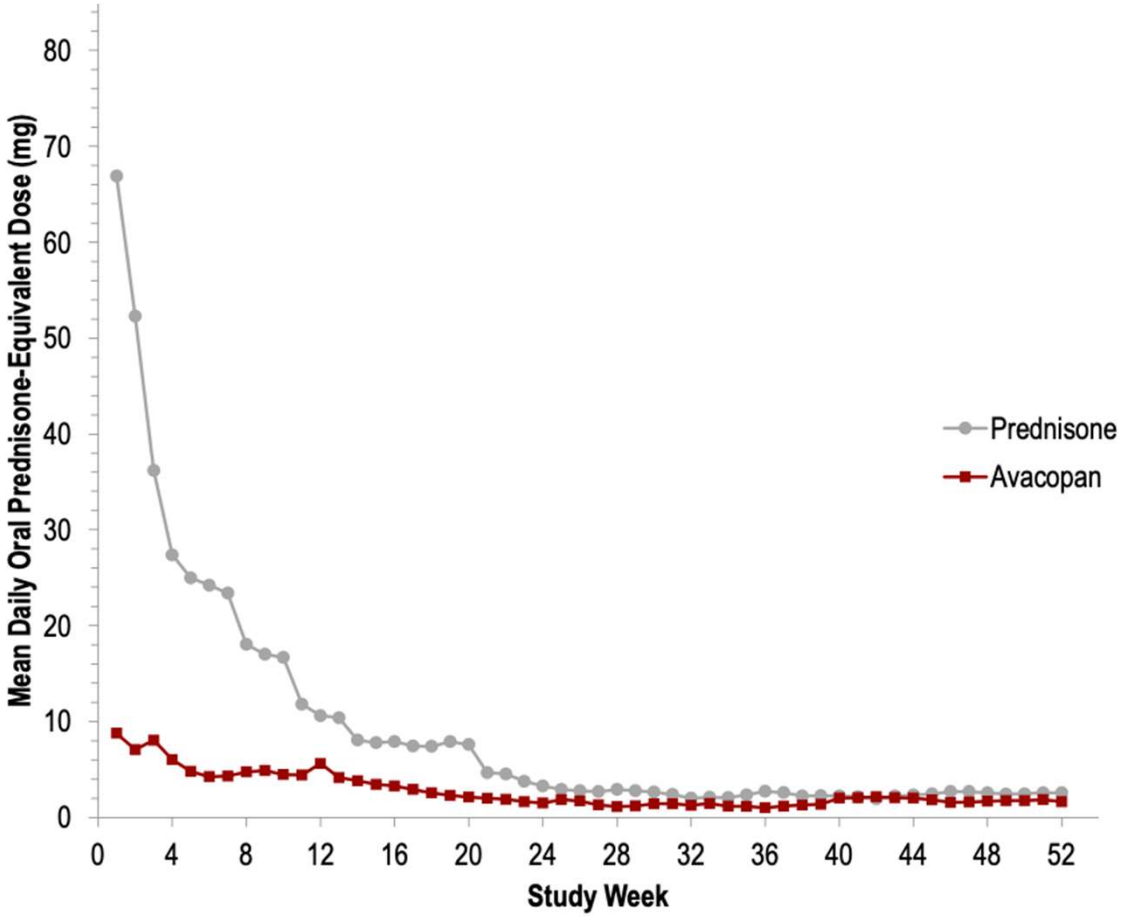
Change in eGFR in patients with renal disease



Glucocorticoid Toxicity Index Cumulative Worsening Score



Oral Prednisone – Equivalent GLUC dose (mg)



Summary 1 – Remission induction

- Rituximab is non-inferior to CYC for remission induction in patients with SCr <4 mg/dl
  - Observational data suggests that RTX may be an effective induction agent in patients with severe renal disease

- IV pulse CYC with or without RTX is used for remission induction in severe renal AAV

Summary 1 – Remission induction

- Rituximab is superior to CYC in patients with relapsing disease and/or PR3 positivity

- PEXIVAS trial showed no benefit of addition of PLEX for outcomes of ESRD and/or Death in patients with severe ANCA associated vasculitis

Summary 2 – Remission maintenance

- Rituximab can be used for remission maintenance
  - B Cell activity returns 4-6 months after RTX administration
- Two approaches used for maintenance RTX dosing:
  - Scheduled doses every 4 to 6 months
  - Patient specific approach → Clinical course, ANCA negativity, CD19 levels

Summary 3 – Remission maintenance

- Efforts to limit steroid exposure in patients with AAV
  - Outcomes for the reduced dose and high dose prednisone were similar during remission induction and maintenance phases in the PEXIVAS trial
  - Novel agents (C5a) receptor antagonists reduce prednisone exposure in the maintenance phase

Summary 4 – Risk of relapse

- Relapse rates remain high in patients with PR3- ANCA vasculitis
- **GPA, presence of PR3** and **previous episodes of severe relapse** are associated with increased risk of relapse
- The role of ANCA or CD 19 counts in predicting a relapse is not clear

Questions?