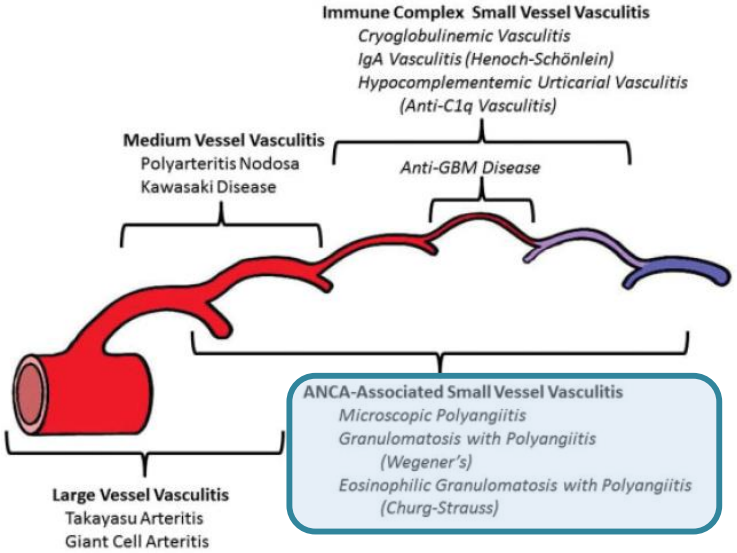
Treatment of Renal ANCA-Associated Vasculitis

Pr Alexandros Karras
Nephrology Dpt
HEGP Hospital, Paris, France
Université Paris Cité

Disclosures

- Vifor
- GSK
- Novartis
- Otsuka
- Astra-Zeneca
- Bohringer-Ingelheim

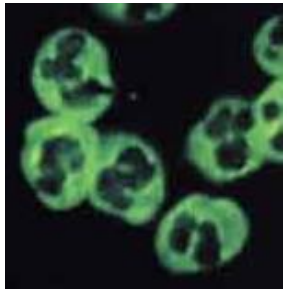
ANCA-Associated vasculitis



2012 Chapel Hill Consensus Conference

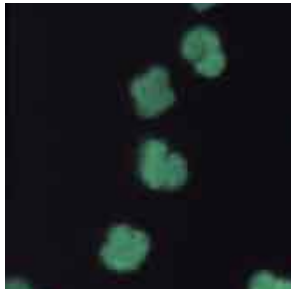
ANCA = Anti-Neutrophil Cytoplasmic Antibodies

cANCA



Immunofluorescence

pANCA



Proteinase 3 (PR3)

ELISA

Myeloperoxydase (MPO)

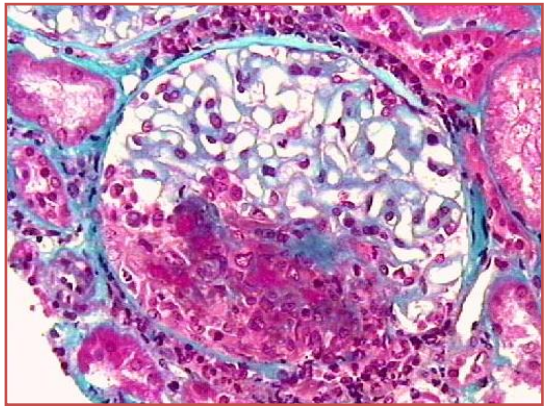
Granulomatosis with Poly-Angiitis **(GPA)** (ex Wegener)

Micro-Polyagiitis **(MPA)**

Renal involvement in AAV

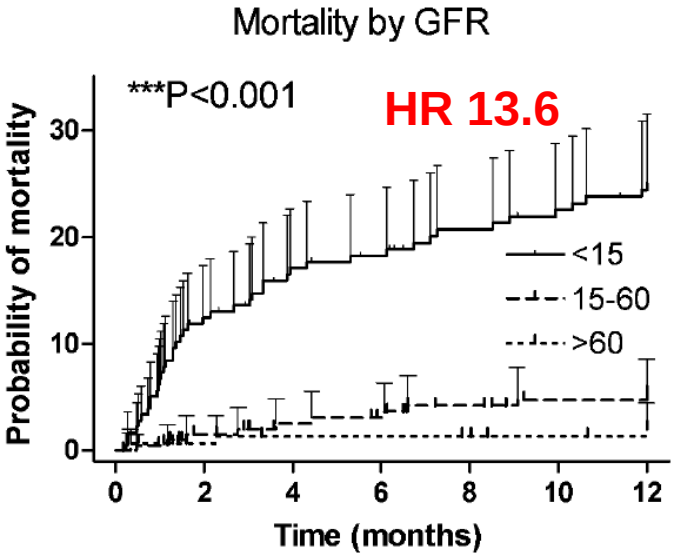
Rapidly Progressive GN

Necrotizing crescentic glomerulonephritis



Frequent : 58-80% of GPA
80-100% of MPA
<20% in EGPA

Associated with increased mortality

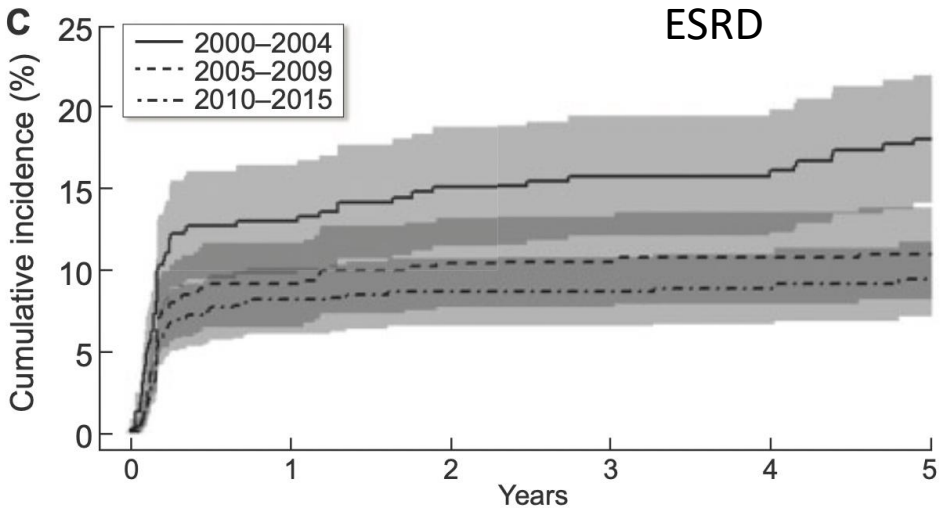


Little M, Ann Rheum Dis, 2009

Renal prognosis in AAV

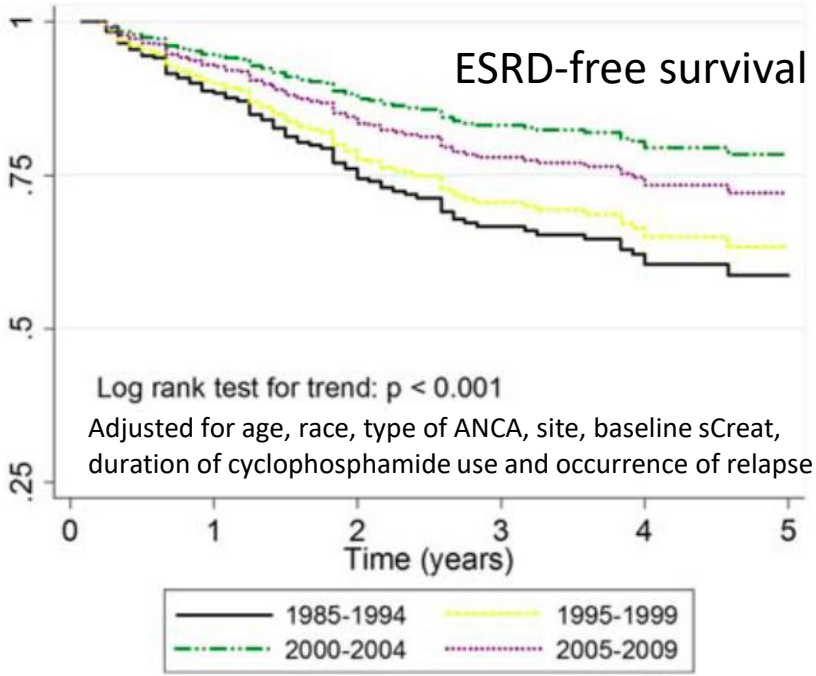
Nelveg-Kristensen, NDT 2022

n=1631 with AAV



Rhee, Arthritis & Rheum 2016

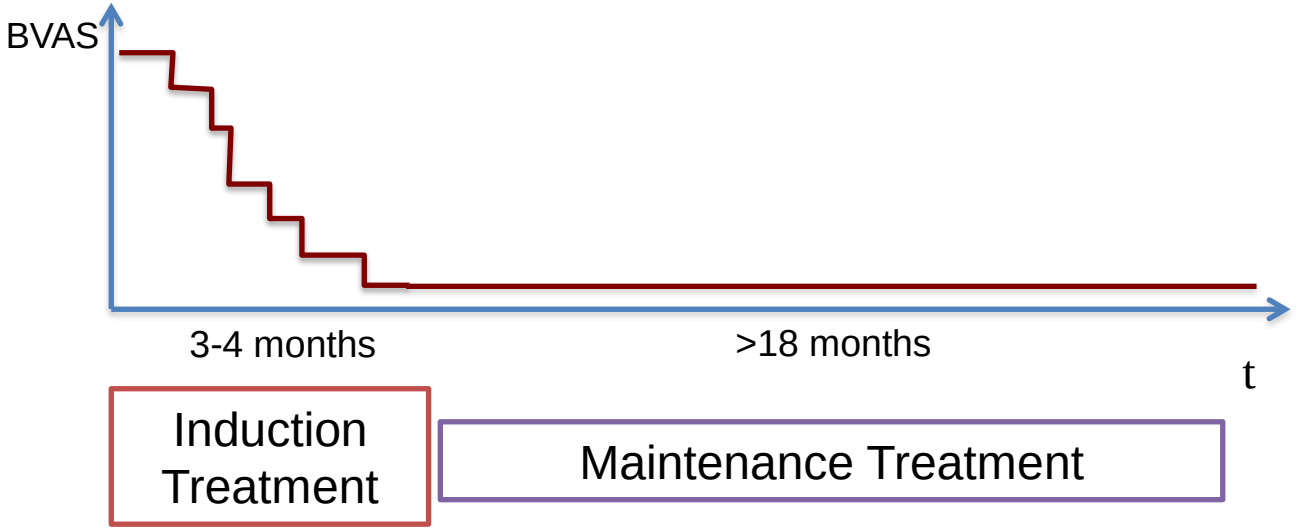
n=554 with renal AAV



Actual 5-year ESRD risk :
10-15% of all AAV patients
20-25% of renal AAV patients

PRINCIPLES OF TREATMENT IN ANCA-ASSOCIATED VASCULITIS (AAV)

Birmingham Vasculitis Activity Score



EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

	LoE	SoR	FV (%)	LoA (0–10)
For induction of remission in patients with new-onset or relapsing GPA or MPA with organ-threatening or life-threatening disease, we recommend treatment with a combination of glucocorticoids and either rituximab or cyclophosphamide.* Rituximab is preferred in relapsing disease.†	1a* 2b†	A* B†	100	9.6±0.8

LoE : Level of evidence, SoR : Strenght of Recommendation, FV : Final vote, LoA : Level of Agreement

Hellmich, Ann Rheum Dis 2024

RTX vs CYC for induction : the RAVE study

- Prospective multicenter north-american trial
- 197 pts with GPA/MPA (de novo or relapse)
- Renal involvement : 66%
- Randomization (1:1)
  - RTX (375mg/m² x4) +CS, no maintenance IS
  - CYC oral (3 months)+ CS, maintenance with AZA
- Rapid CS tapering (targetting withdrawal at M5)
- Primary endpoint : remission without CS at M6

BUT

Patients with severe RF (creat>40 mg/L) or severe pulm. involvement were not included

No difference in terms of infectious complications

	RTX (n=99)	CYC (n=98)	
Primary Endpoint	64%	53%	Non inferiority No superioriy
Early relapses	11	14	
ANCA negativity M6	47%	24%	P<0.05
Primary Endpoint (Subgroup of Relapse Pts)	67%	42%	P<0.05

Stone, NEJM 2010

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV *(1B)*.

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Kidney International 2024

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Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l])*

Figure 7 | Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. *A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

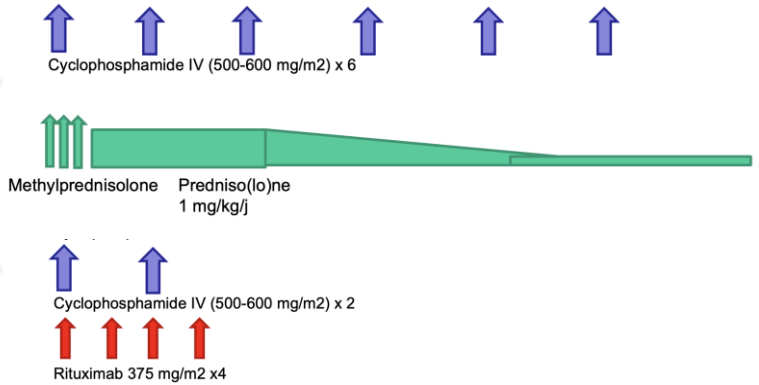
Combination of RTX+CYC in severe renal AAV ?

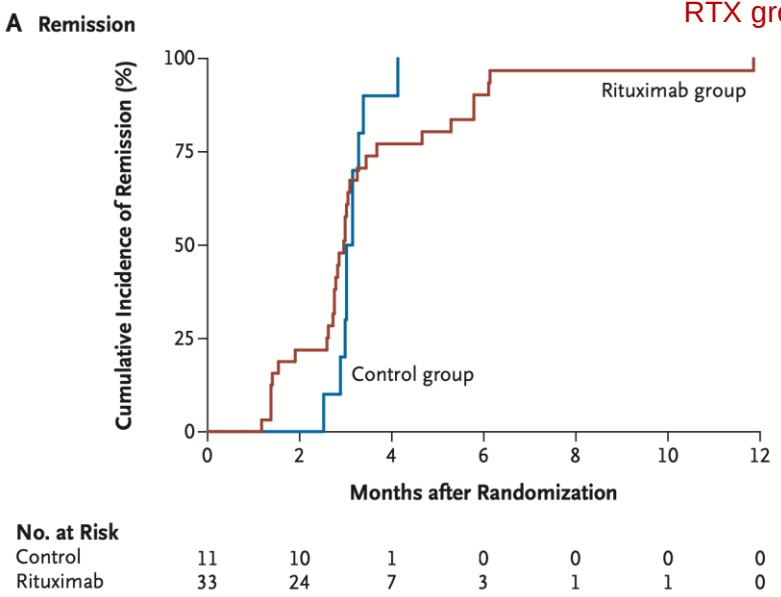
The RITUXVAS trial

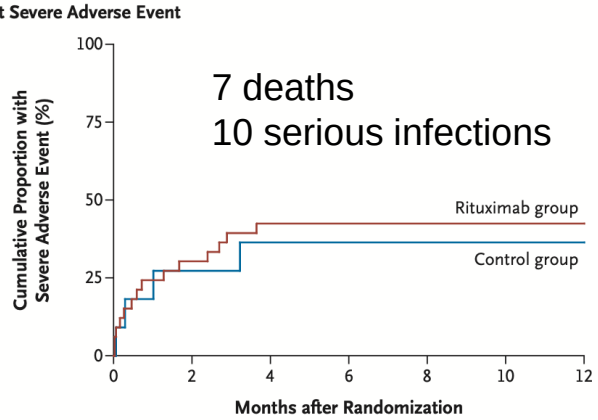
44 pts with severe renal AAV
mean eGFR 16 ml/min

Control group

RTX group







7 deaths
10 serious infections

EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

	LoE	SoR	FV (%)	LoA (0–10)
As part of regimens for induction of remission in GPA or MPA, we recommend treatment with oral glucocorticoids at a starting dose of 50–75 mg prednisolone equivalent/day, depending on body weight. We recommend stepwise reduction in glucocorticoids according to table 4 and achieving a dose of 5 mg prednisolone equivalent per day by 4–5 months.	1b	A	100	9.4±0.8

Table 4 Glucocorticoid dosing (mg/day, prednisolone equivalent) with rituximab or cyclophosphamide-based regimens for remission induction in GPA or MPA according to the PEXIVAS Study[93]

	Body weight (kg)		
Weeks	<50	50–75	>75
1*	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–18	5	5	7.5
19–52	5	5	5
>52	Individual taper	Individual taper	Individual taper

*Consider use of intravenous methylprednisolone at a cumulative dose of 1–3 g on days 1–3 in patients with severely active disease, including but not limited to renal involvement with a documented estimated glomerular filtration rate <50 mL/min/1.73 m^2 and/or diffuse alveolar haemorrhage.

LoE : Level of evidence, SoR : Strenght of Recommendation, FV : Final vote, LoA : Level of Agreement

Hellmich, Ann Rheum Dis 2024

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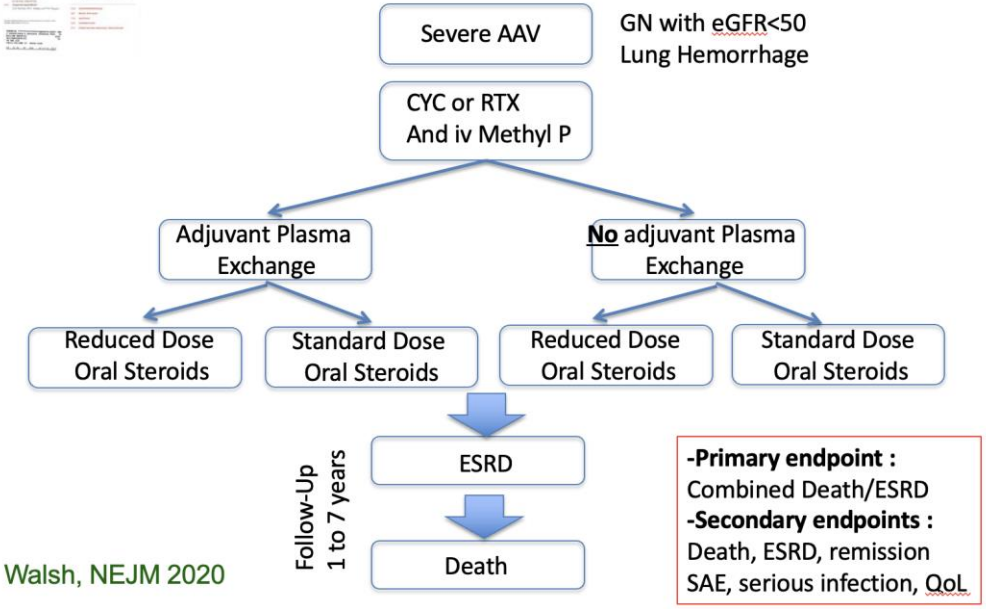
Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 9.

	'Reduced-corticosteroid dose' in PEXIVAS trial		
Week	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

Reduction of corticosteroid doses in AAV

PEXIVAS Trial



-**Primary endpoint :**
Combined Death/ESRD
-**Secondary endpoints :**
Death, ESRD, remission
SAE, serious infection, QoL

Walsh, NEJM 2020

All patients in the PEXIVAS trial received an initial dose of i.v. methylprednisolone of 1–3 g

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		

= **54%** reduction at M3
= **61%** reduction at M6

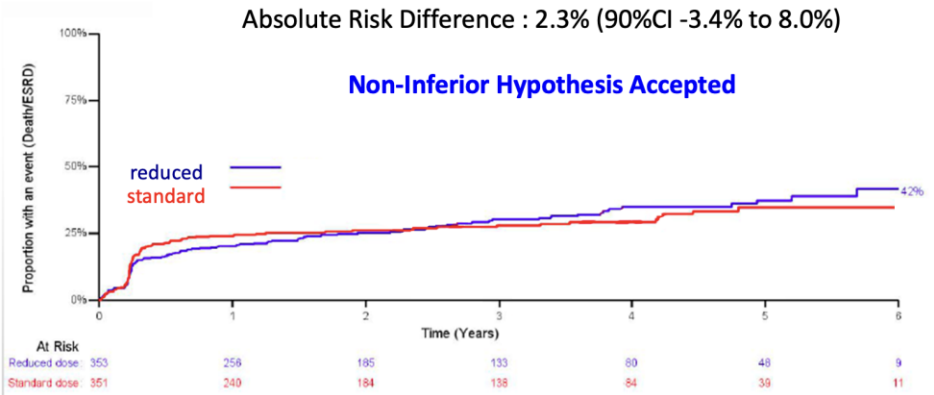
Reduction of corticosteroid doses in AAV

PEXIVAS : Results

Primary endpoint (ESRD or Death) / steroids

Reduced Dose : 92 (28%) vs Standard Dose : 83 (26%)
Absolute Risk Difference : 2.3% (90%CI -3.4% to 8.0%)

Non-Inferior Hypothesis Accepted



PEXIVAS : Results

Secondary endpoints / Steroids

SECONDARY ENDPOINTS	Reduced	Standard	Hazard Ratio (95%CI)	P-value
Death, n (%)	46 (13)	53 (15)	0.78 (0.53-1.17)	0.23
ESRD, n (%)	70 (20)	68 (19)	0.96 (0.68-1.34)	0.65
Sust. remission, n (%)	204 (58)	193 (55)	1.04 (0.92-1.19)	0.48
SAEs, n(%)	231 (65)	218 (62)	1.05 (0.94-1.17)	0.20
			Incidence ratio (95%CI)	
Serious infections n (%) during year 1	96 (27)	116 (33)	0.69 (0.52-0.93)	0.02

A reduced dose of GC was non-inferior to a standard dose and was associated with fewer serious infectious complications

Beware of rapid steroid tappering ?

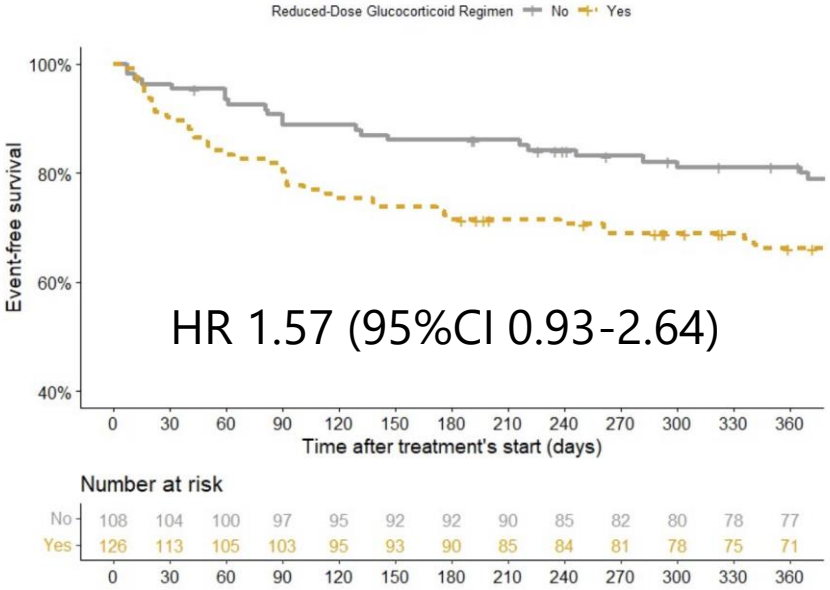
AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

2023

ABSTRACT NUMBER: 0725

Real-life Use of the PEXIVAS Reduced-dose Glucocorticoid Regimen in Granulomatosis with Polyangiitis and Microscopic Polyangiitis

<u>Composite endpoint :</u>
-Death,
-ESKD,
-Refractory disease
-Relapse



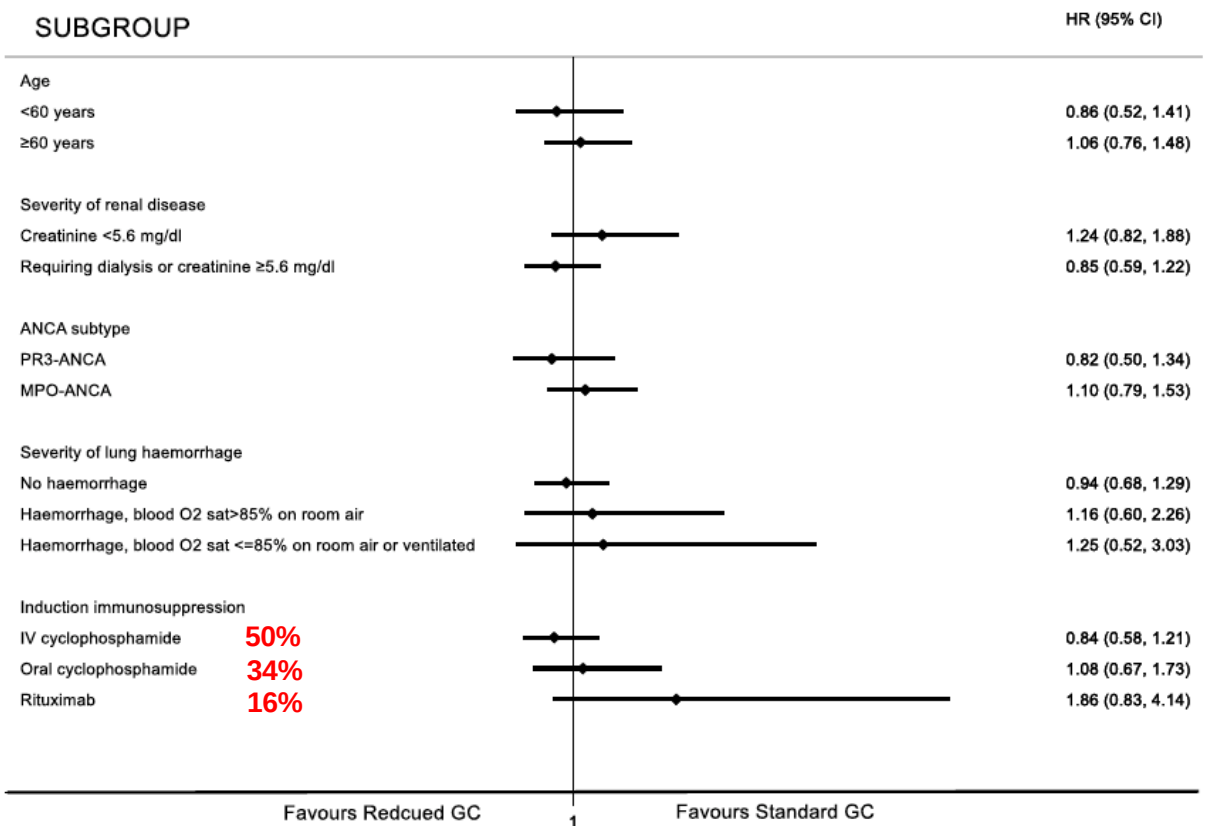
<u>Subgroup analysis :</u>
Increased risk in patients with
-sCreat >300 µmol/l
RR 2.14; 95% CI 1.14-4.03
-RTX induction
RR 1.61; 95% CI 0.94-2.77

Initial treatment :
-75% IV CS pulses
-71% RTX induction

Beware of rapid steroid tappering ?

PEXIVAS

Primary endpoint / steroids : subgroup analysis



Walsh, NEJM 2020

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

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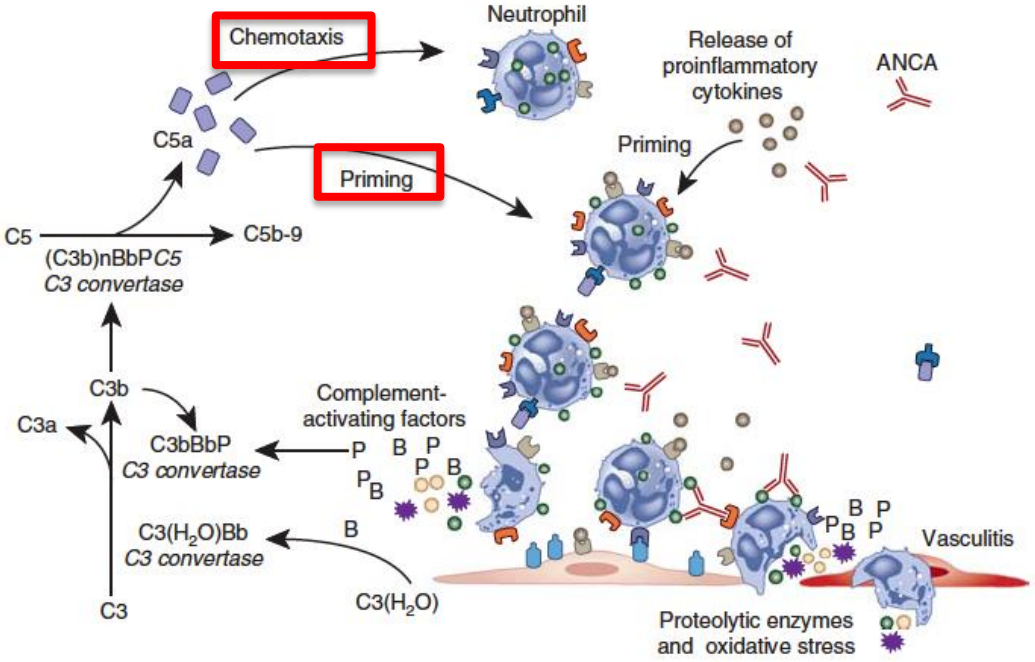
Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 9.

'Reduced-corticosteroid dose' in PEXIVAS trial

Practice Point 9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.

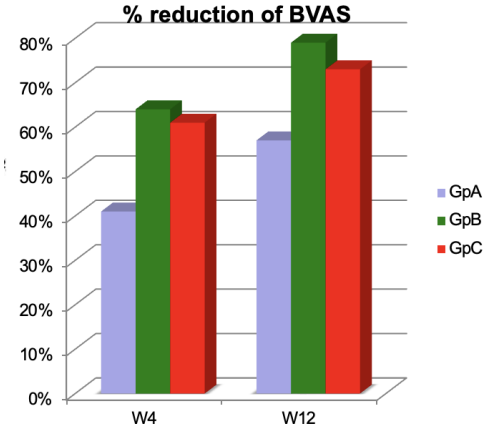
Complement blockade :
a new way to reduce glucocorticoids ?



CLINICAL RESEARCH www.jasn.org

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group



Jayne, JASN 2017

Induction therapy in renal AAV : Avacopan

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

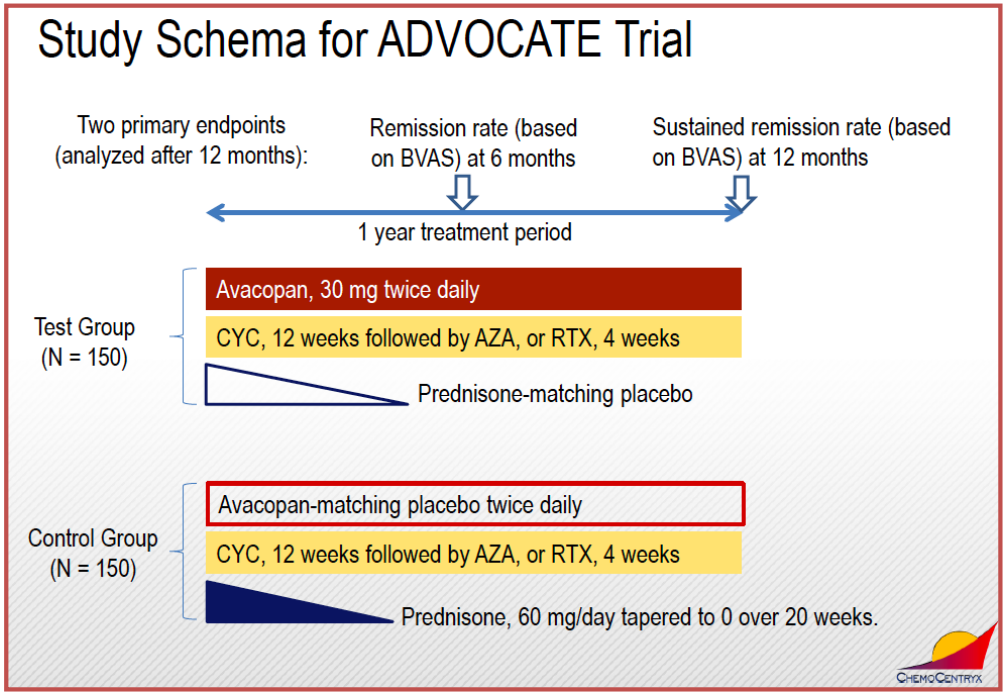
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

International, double blinded controlled non-inferiority trial

- 331 patients
- MPO vs PR3 : 57% / 43%
- Median eGFR at inclusion : 51 ml/min

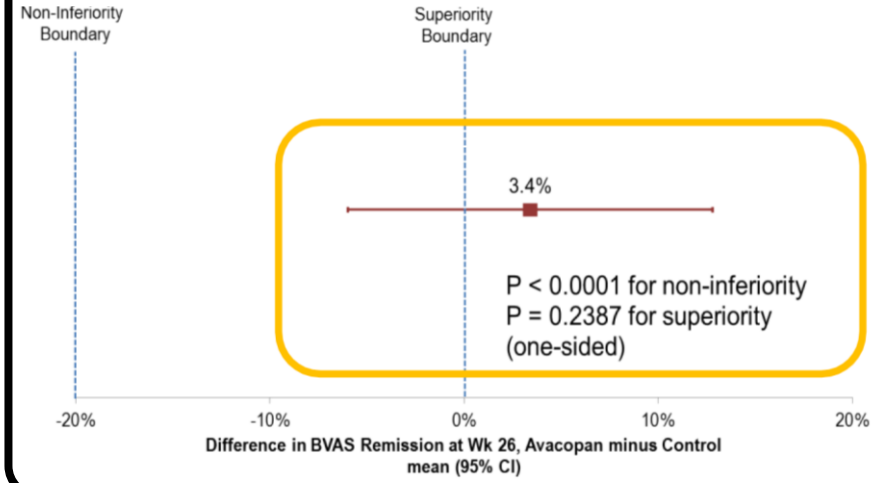
Non-inclusion criteria :
- -eGFR <15 ml/min
- -severe IAH



Jayne, NEJM 2021

Induction therapy in renal AAV : Avacopan

Remission at 6 months
70% in GC group vs. 72% in Avacopan group

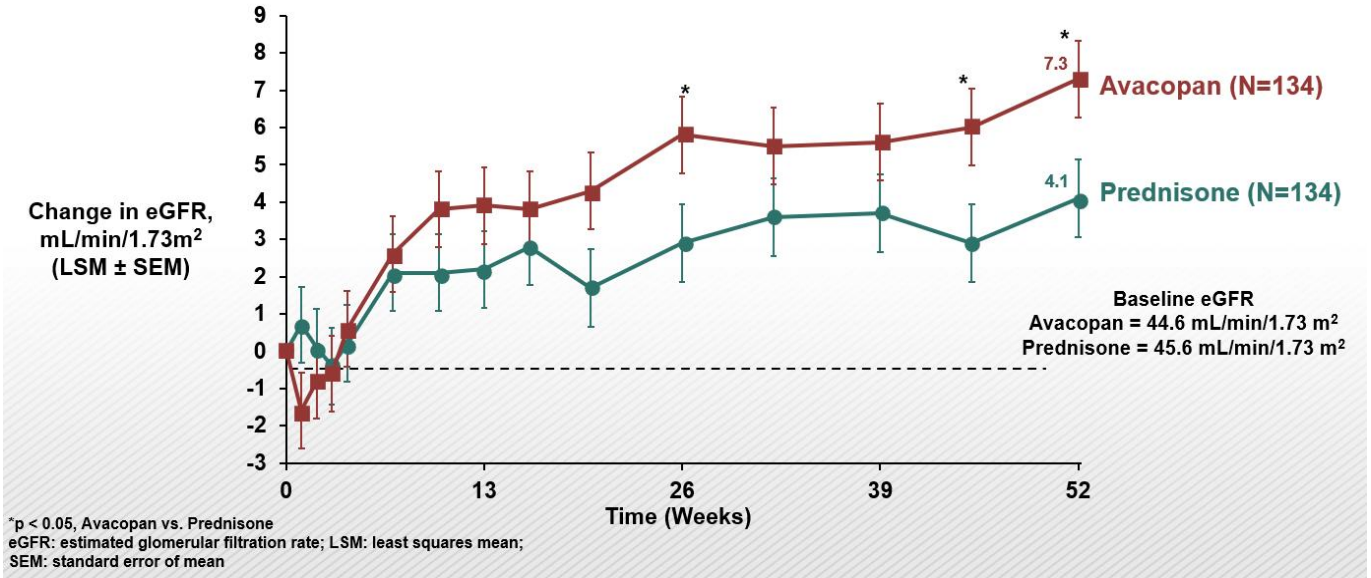


Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event potentially related to glucocorticoids — no. (%)**	110 (66.3)	132 (80.5)
Cardiovascular	72 (43.4)	85 (51.8)
Infectious	22 (13.3)	25 (15.2)
Gastrointestinal	3 (1.8)	4 (2.4)
Psychological	27 (16.3)	39 (23.8)
Endocrine or metabolic	23 (13.9)	48 (29.3)
Dermatologic	14 (8.4)	28 (17.1)
Musculoskeletal	19 (11.4)	21 (12.8)
Ophthalmologic	7 (4.2)	12 (7.3)
Any adverse event potentially related to glucocorticoids as assessed by the investigators — no. (%)	107 (64.5)	131 (79.9)
Any serious adverse event potentially related to prednisone as assessed by the investigators — no. (%)	11 (6.6)	24 (14.6)

Jayne, NEJM 2021

Induction therapy in renal AAV : Avacopan

Change from Baseline to Week 52 in Estimated Glomerular Filtration Rate among patients with Renal involvement at Baseline (n=268/330)



+7.3 ml/min/1.73 m2

Delta = 3.2 ml/min

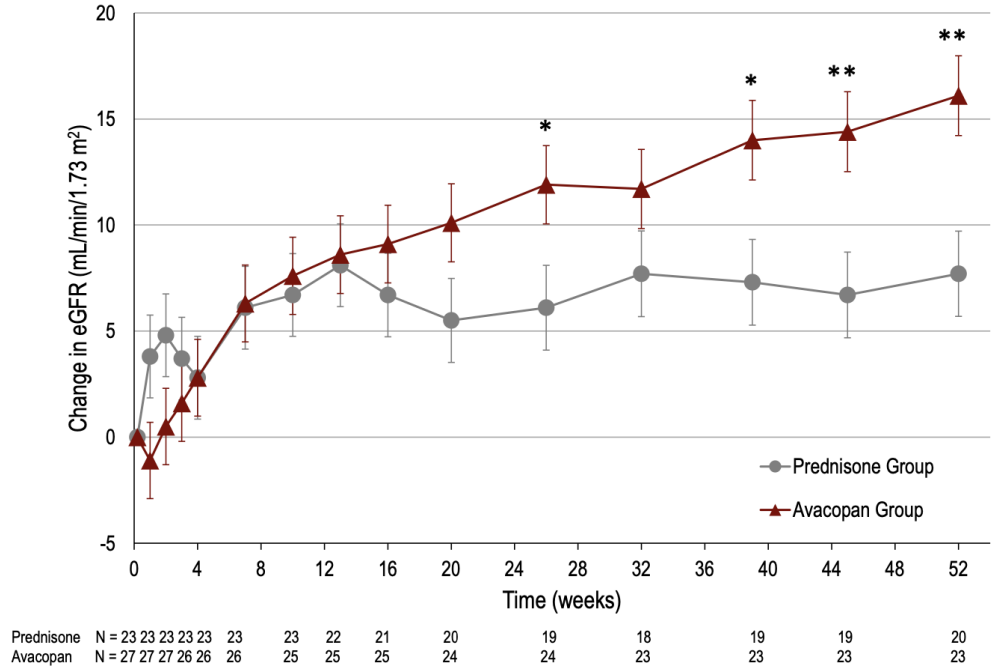
+4.1 ml/min/1.73 m2

p<0.01

Jayne, NEJM 2021

Induction therapy in renal AAV : Avacopan

Change from Baseline to Week 52 in Estimated Glomerular Filtration Rate among patients with eGFR <20 ml/min/1.73m^2 at Baseline (n=50/330)



+16.1 ml/min/1.73 m2

Delta = 8.4 ml/min

+7.7 ml/min/1.73 m2

*Patients with lower GFR **may** benefit from greater GFR recovery (KDIGO 2024)*

Cortazar, Kidney Int Reports 2023

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Kidney International 2024

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'Reduced-corticosteroid dose' in PEXIVAS trial

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Practice Point 9.3.1.9: Consider plasma exchange for patients with SCr >3.4 mg/dl (>300 µmol/l), patients requiring dialysis or with rapidly increasing SCr, and patients with diffuse alveolar hemorrhage who have hypoxemia.

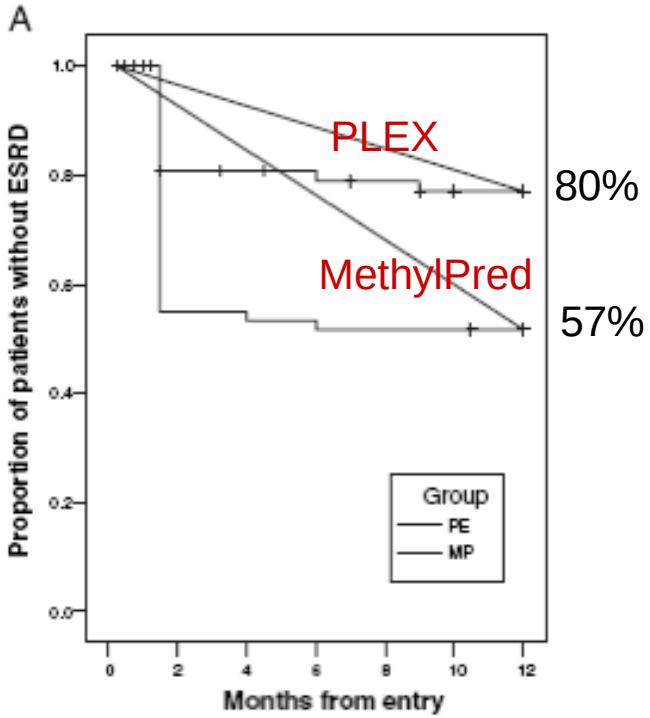
Induction therapy in renal AAV : Plasma Exchange

The MEPEX study Jayne, JASN 2007

- 137 patients GPA/MPA with **Severe renal disease (Screat>500)**
- The two groups of patients receive :
  - CYC PO 2.5 mg/kg/d
  - Cort : 1 mg/kg/d from D1
- Randomization :

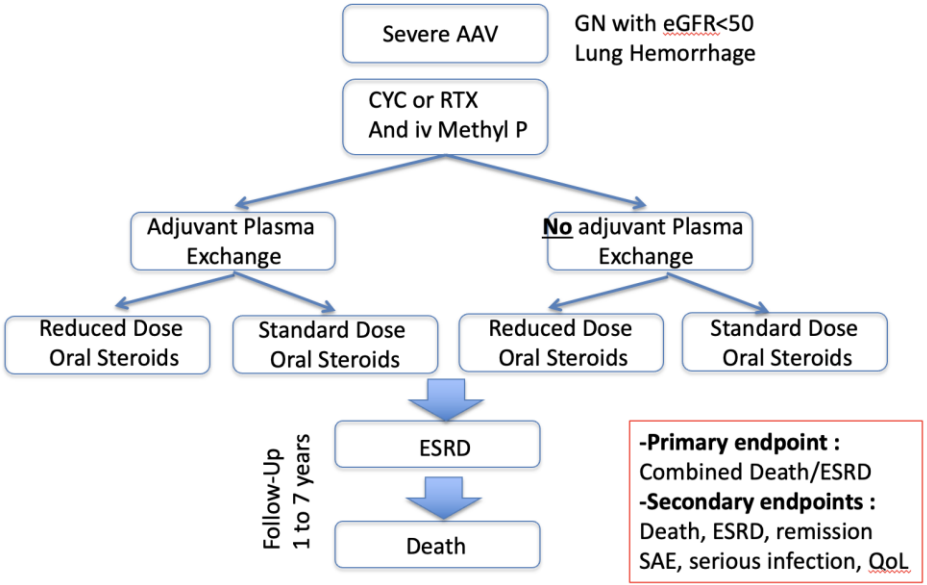
vs
- **Plasma exchange**
- **i.v. Methylprednisolone**

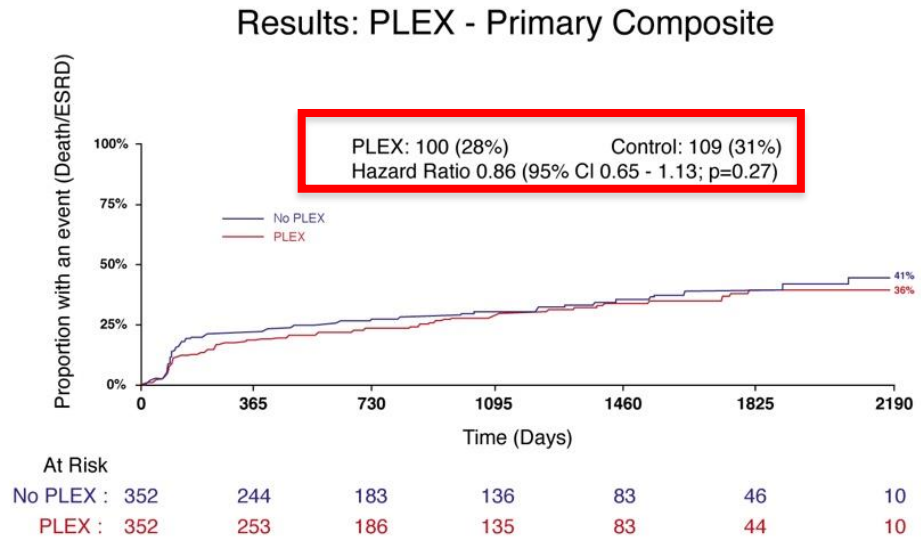
ESRD risk among survivors
is reduced by **24%**
(95% CI 6.1-41)
in the PLEX arm



Induction therapy in renal AAV : Plasma Exchange

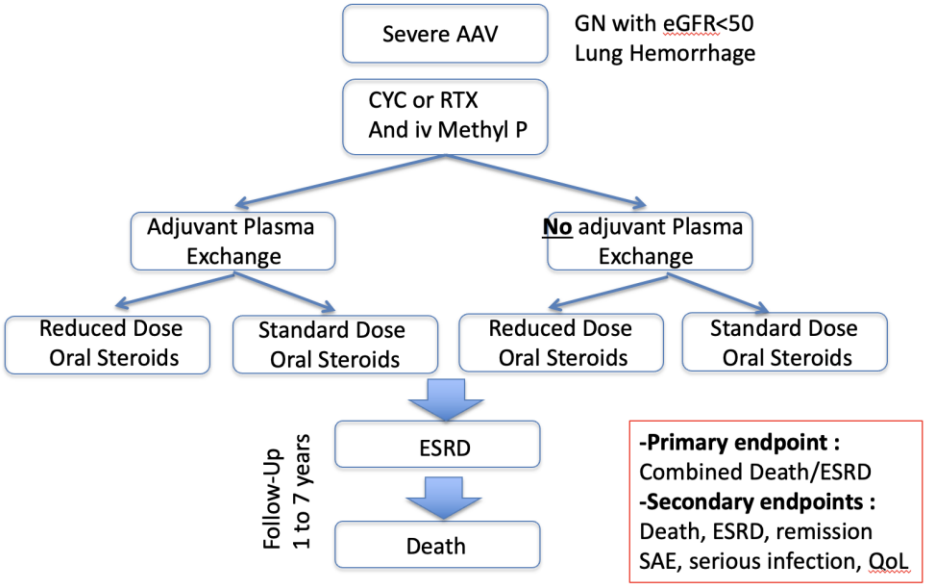
The PEXIVAS trial Walsh, NEJM 2020





Induction therapy in renal AAV : Plasma Exchange

The PEXIVAS trial Walsh, NEJM 2020



PRIMARY COMPOSITE ENDPOINT	Hazard Ratio (95%CI)	P-value
Unadjusted	0.89 (0.68-1.17)	0.42
Per-protocol population	0.85 (0.66-1.16)	0.35
Censored at M12	0.77 (0.56-1.06)	0.11
Subgroups		
< 60 years > 60 years	1.20 (0.73-1.97) 0.75 (0.54-1.04)	0.13
Creat >500 Creat <500	0.98 (0.65-1.48) 0.77 (0.53-1.11)	0.38
PR3-ANCA MPO-ANCA	0.84 (0.51-1.36) 0.84 (0.62-1.21)	0.91
No lung hemorrhage Mild lung hemorrhage Severe lung hemorrhage	0.95 (0.69-1.31) 0.64 (0.33-1.24) 0.67 (0.28-1.64)	0.49
IV CYC Oral CYC RTX	0.79 (0.55-1.14) 0.98 (0.61-1.57) 0.87 (0.38-1.96)	0.79

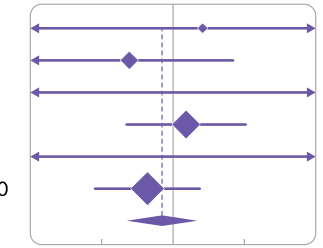
Induction therapy in renal AAV : Plasma Exchange

The BMJ Metanalysis

Walsh M, BMJ 2022

MORTALITY

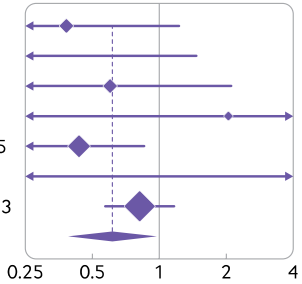
Study	Yes/No Treatment	Yes/No Control	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Rifle 1980	1/5	1/7		1.86	1.33 (0.10 to 17.28)
Pusey 1991	5/20	7/16		12.27	0.66 (0.24 to 1.78)
Cole 1992	2/14	0/16		0.16	41.00 (0.01 to 2.8e+05)
Jayne 2007	19/51	16/51		37.03	1.14 (0.64 to 2.02)
Szpirt 2011	2/14	0/16		0.16	41.00 (0.01 to 2.8e+05)
Walsh 2020	25/327	32/320		48.53	0.78 (0.47 to 1.29)
Overall				100.00	0.90 (0.64 to 1.27)



Test for heterogeneity: τ^2=0.00; I^2=0.00%; H^2=1.00

ESKD M12

Study	Yes/No Treatment	Yes/No Control	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Rifle 1980	2/4	7/1		9.75	0.38 (0.12 to 1.22)
Pusey 1991	1/24	5/18		3.31	0.18 (0.02 to 1.46)
Cole 1992	3/13	5/11		8.51	0.60 (0.17 to 2.10)
Guillevin 1997	3/16	1/12		3.08	2.05 (0.24 to 17.63)
Jayne 2007	10/60	22/45		24.11	0.44 (0.22 to 0.85)
Szpirt 2011	0/16	4/12		0.19	0.01 (0.00 to 81.26)
Walsh 2020	48/304	59/293		51.04	0.81 (0.57 to 1.16)
Overall				100.00	0.62 (0.39 to 0.98)



Test for heterogeneity: τ^2=0.04; I^2=14.84%; H^2=1.17

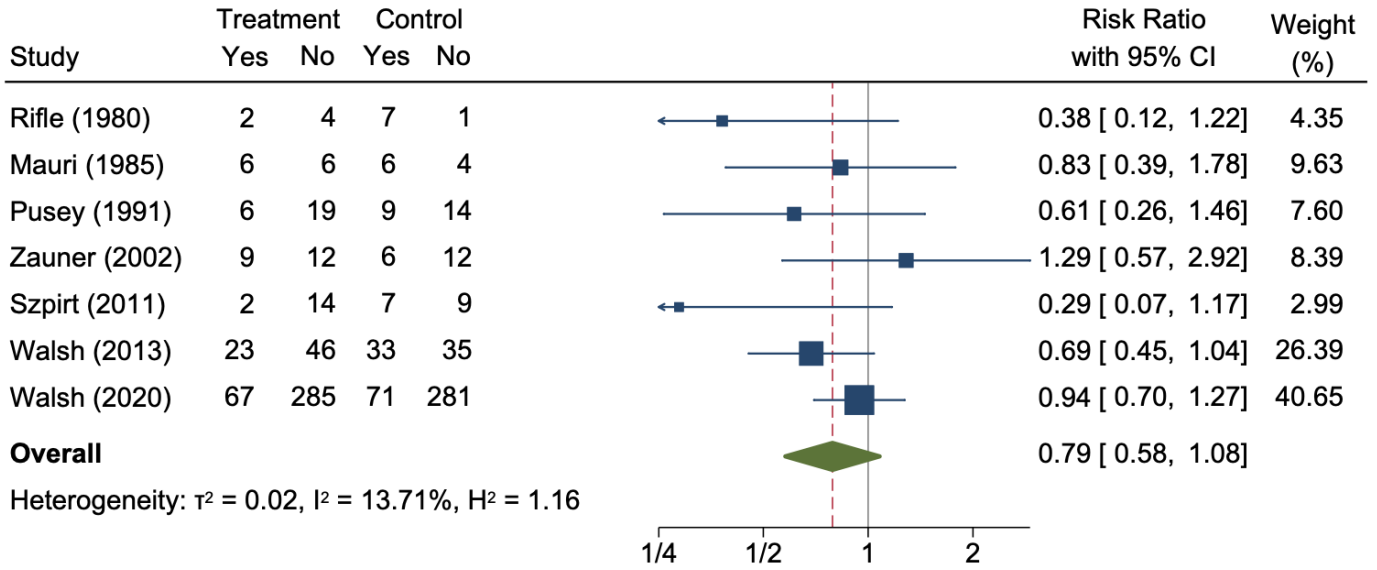
No effect on mortality, but improvement of kidney prognosis at M12

Induction therapy in renal AAV : Plasma Exchange

The BMJ Metanalysis

Walsh M, BMJ 2022

No clear effect on long-term kidney prognosis



Supplemental Figure 3. Effect of plasma exchange on the outcome of end-stage kidney disease at longer term follow-up (median 3 years) in patients with anti-neutrophil cytoplasm antibody-associated vasculitis using the DerSimmonian and Laird random effects model.

Induction therapy in renal AAV : Plasma Exchange

The BMJ Metanalysis

Walsh M, BMJ 2022

Risk group for end stage kidney disease (ESKD)	LOW	Low to moderate	Moderate to high	High
Baseline serum creatinine level	≤ 200 µmol/L	>200-300 µmol/L	>300-500 µmol/L	> 500 µmol/L
Baseline risk of developing ESKD at 1 year	≤ 2.5%	>2.5-7.5%	>7.5-25.0%	>25.0%
Absolute risk reduction of ESKD at 1 year	0.1%	2.1%	4.6%	16.0%
Absolute risk increase of serious infection	2.7%	4.9%	8.5%	13.5%

We suggest IS alone without plasma exchange

We suggest IS with plasma exchange

Points to consider when PLEX are discussed

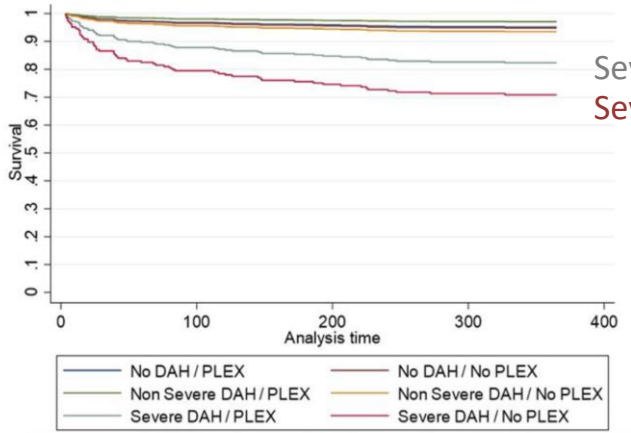
- Presence of anti-GBM antibodies ?
- Kinetics of sCreat ?
- Extra-renal manifestations of AAV ?

PEXIVAS :

191 DAH

61 severe DAH
(SaO2 <85% or mechanical support)

Figure 1: One year survival in PEXIVAS by plasma exchange (PLEX) and severity of diffuse alveolar hemorrhage (DAH), adjusted for age, sex, ANCA type, kidney function, and initial treatments



Severe DAH with PLEX

Severe DAH without PLEX

Group	Died 3 months		Died 1 year		Effect of PLEX	
	PLEX	No PLEX	PLEX	No PLEX	HR (95% CI)	Interaction p value
Overall	18 (5.1)	21 (6.0)	25 (7.1)	32 (9.1)	0.74 (0.44 to 1.26)	
No DAH	12 (4.7)	9 (3.5)	17 (6.6)	17 (6.6)	0.86 (0.43 to 1.71)	
Any DAH	6 (6.3)	12 (12.5)	8 (8.4)	15 (15.6)	0.52 (0.21 to 1.24)	0.37
Non-severe DAH	1 (1.6)	3 (4.6)	2 (3.1)	5 (7.6)	0.43 (0.08 to 2.31)	0.42
Severe DAH	5 (16.1)	9 (30.0)	6 (19.4)	10 (33.3)	0.45 (0.14 to 1.40)	0.44

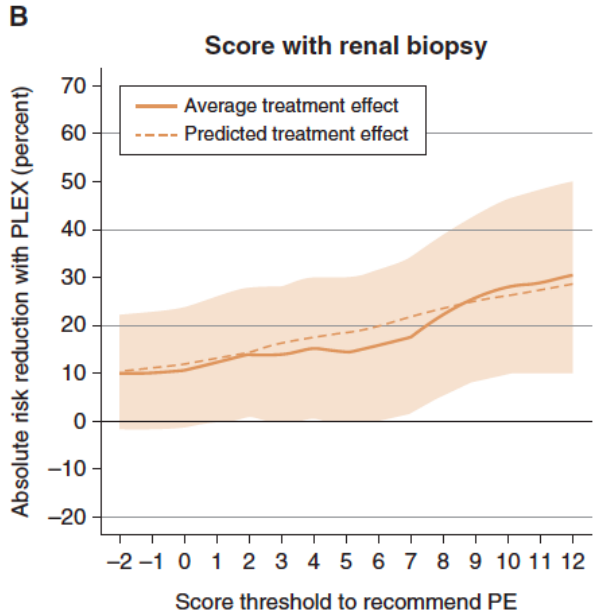
Fussner, Am J Resp Crit Care Med 2024

Points to consider when PLEX are discussed

- Presence of anti-GBM antibodies ?
- Kinetics of sCreat ?
- Extra-renal manifestations of AAV ?
- Refractory AAV despite initiation of IS ?
- Frailty/infectious risk of the patient ?
- Result of kidney biopsy ?

Kidney Histopathology Can Predict Kidney Function in ANCA-Associated Vasculitides with Acute Kidney Injury Treated with Plasma Exchanges

Retrospective study of the FVSG
187 pts treated with PLEX
233 pts without PLEX

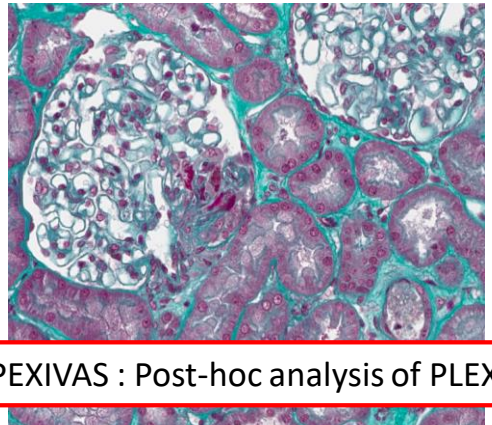


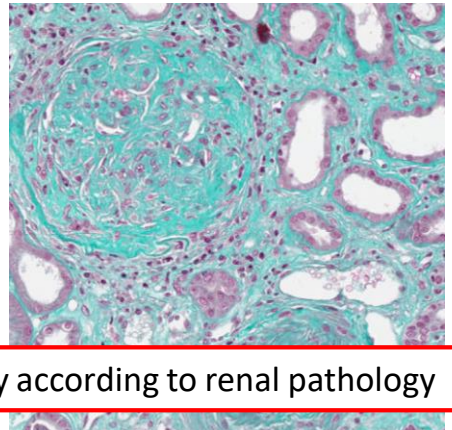
Variable	Score points
Male sex	1
MPA	5
RLV	3
PR3 positive	−10
MPO positive	−3
Serum creatinine	
251...400 μmol/L	5
401...600 μmol/L	8
>600 μmol/L	16
Brix score ≥ 7	1
Berden score	
Crescentic	6
Mixed	−8

Nezam, JASN 2022

Points to consider when PLEX are discussed

- Presence of anti-GBM antibodies ?
- Kinetics of sCreat ?
- Extra-renal manifestations of AAV ?
- Refractory AAV despite initiation of IS ?
- Frailty/infectious risk of the patient ?
- Result of kidney biopsy ?





PEXIVAS : Post-hoc analysis of PLEX efficacy according to renal pathology

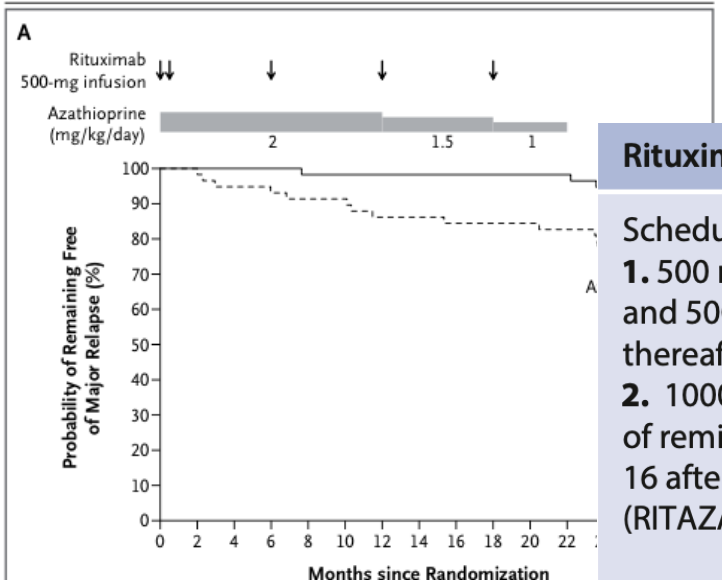
KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

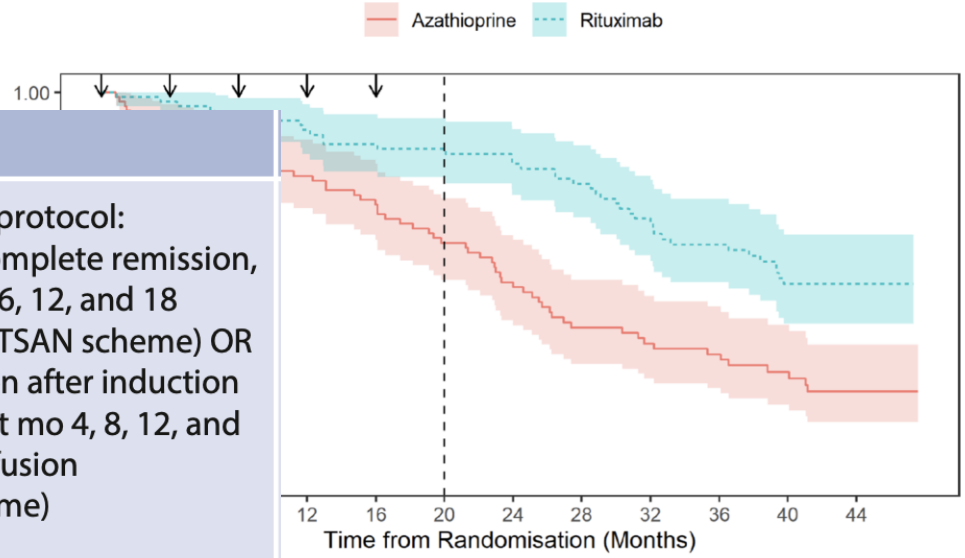
MAINRITSAN Trial

Guillevin, NEJM 2014



RITAZAREM Trial

Smith, Ann Rheum Dis 2023



Rituximab

Scheduled dosing protocol:
1. 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR
2. 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)

Using CD19+ count and ANCA titer to re-inject RTX ?

MAINRITSAN 2 – study design

Groupe Français d'Etude des Vascularites

Induction

Iv CYC or RTX

REMISSION

D0 D15 M6 M12 M18

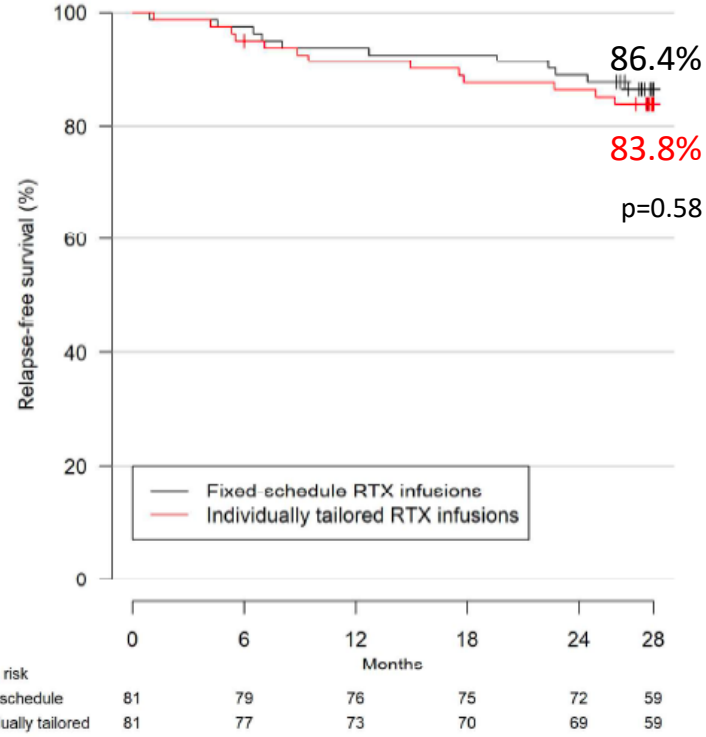
"Fixed dose" arm

D0 M3 M6 M9 M12 M15 M18

"On demand" arm

= RTX 500 mg

Re-infusion only if
ANCA titer x 2 on ELISA
or CD19+>0/mm3



Charles P, ARD 2018

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

Practice Point 9.3.2.2: The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

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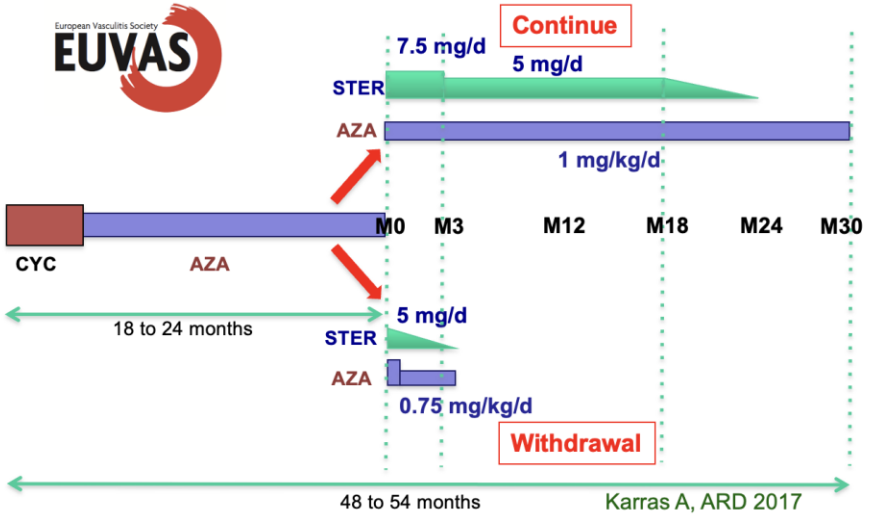
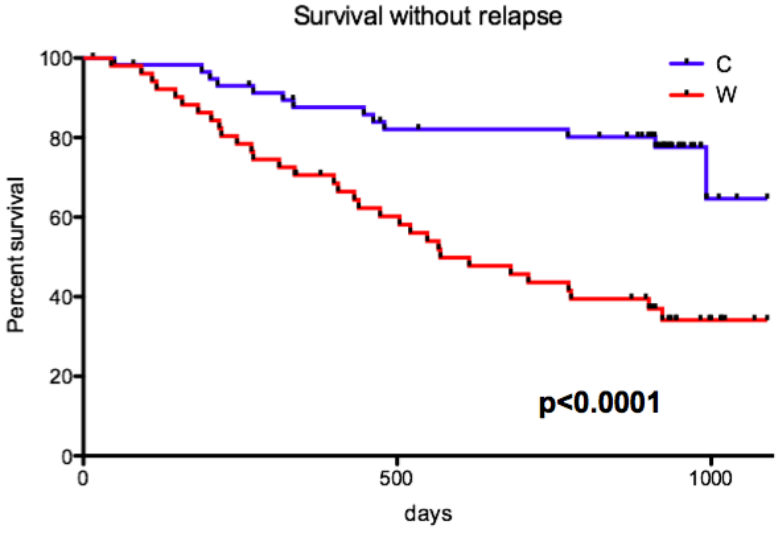
REMAIN Trial

Karras A, Ann Rheum Dis 2017





KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

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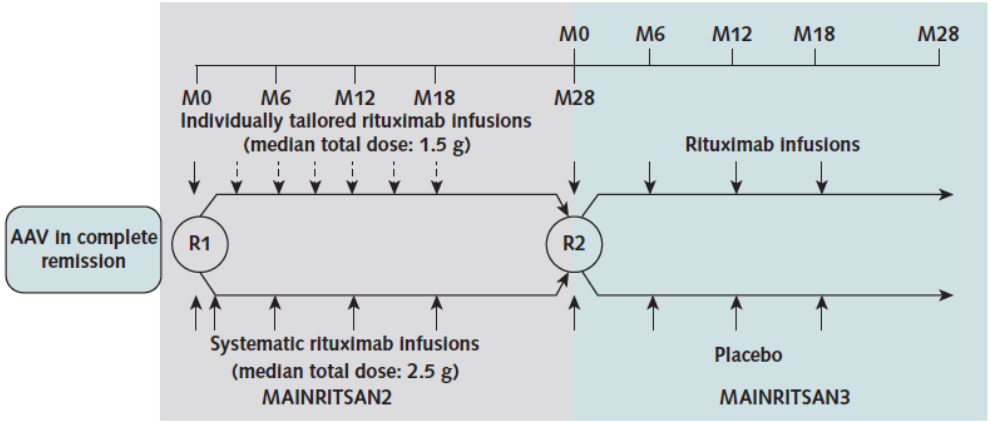
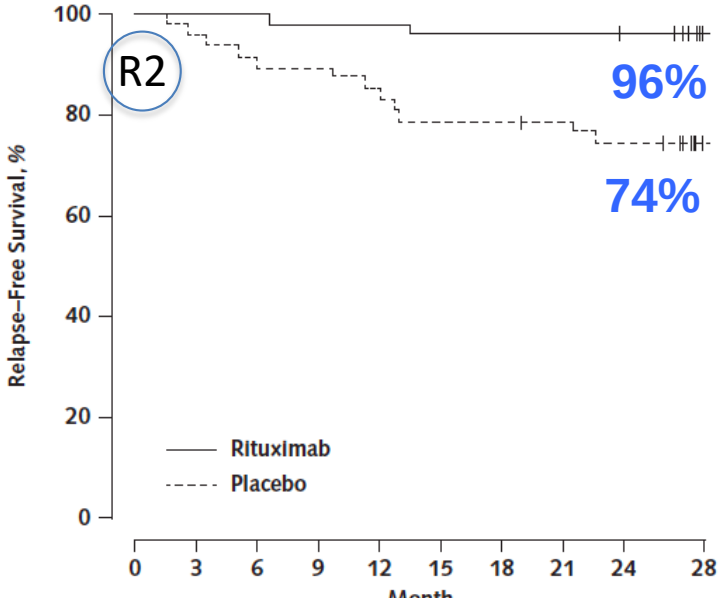
MAINRITSAN 3 Trial Charles P, Ann Int Med 2020

18 vs (18+18) months maintenance treatment





KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Kidney International 2024

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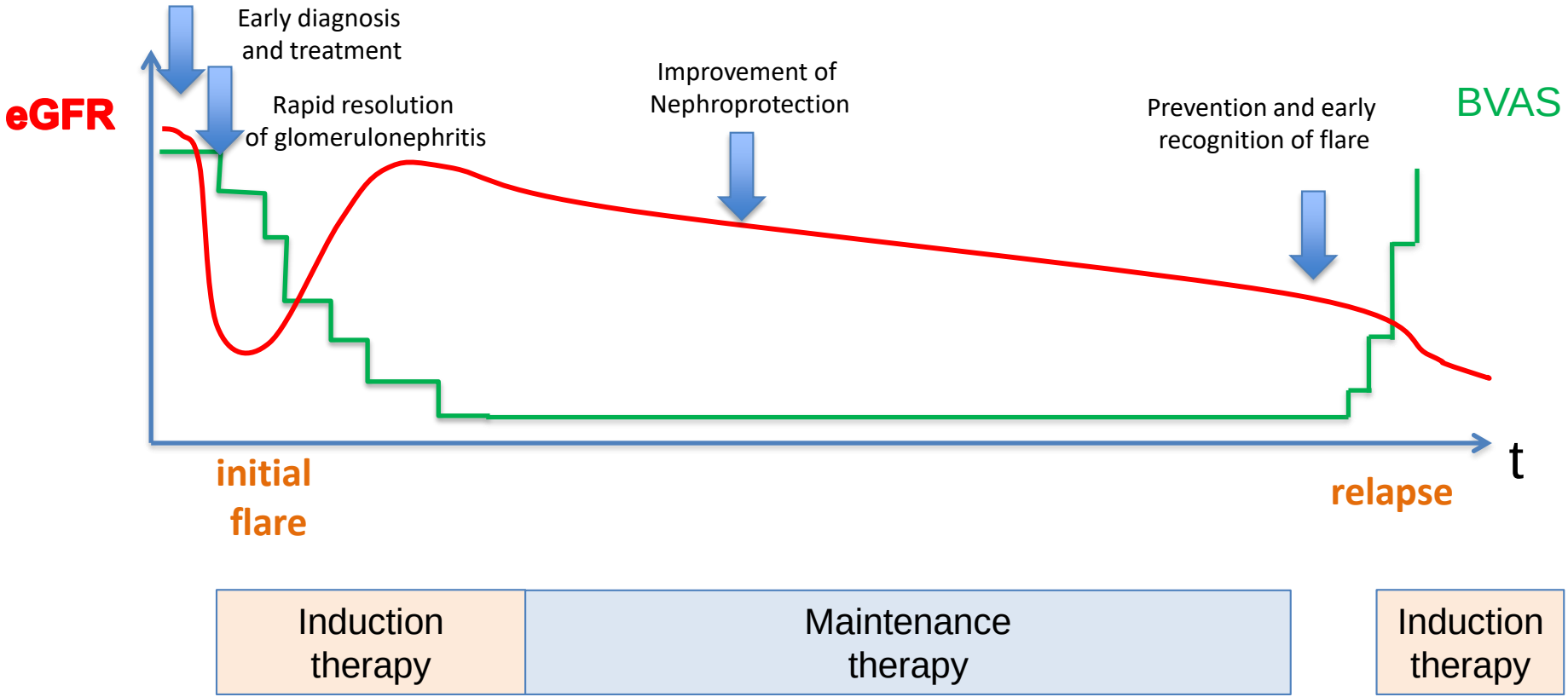
Practice Point 9.3.2.2: The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

Practice Point 9.3.2.3: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 12).

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Figure 12| Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

Renal prognosis in AAV : when can we save nephrons ?



Nephroprotection in AAV-associated nephropathy

Occurrence of ESKD is not always associated with active glomerulonephritis but with slow progression of chronic damage

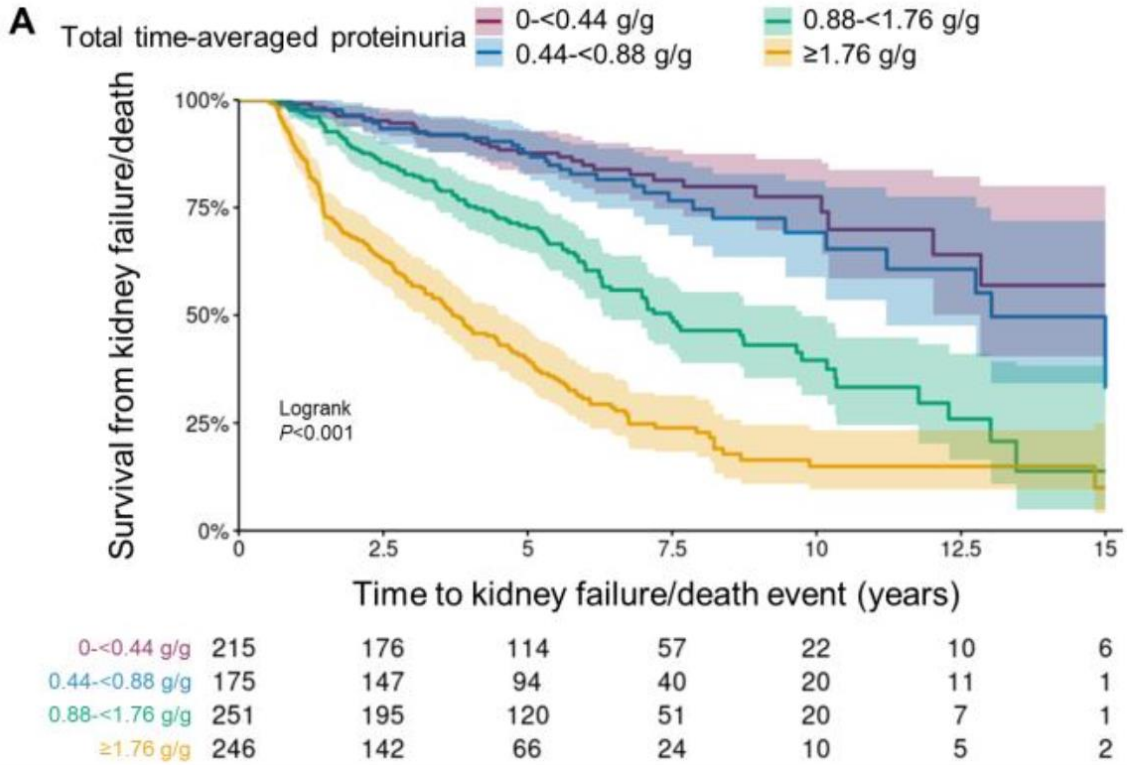
Table 2 | Summary of cause and disease activity among patients reaching ESRD

ESRD subgroup	*n* (%)	% With active disease	BVAS (mean ± s.d.)
ESRD group[a]	136	51.5	7.75 ± 8.05
New-onset GN	69 (51%)	100	13.76 ± 5.98
Relapsing GN	8 (6%)	100	7.50 ± 5.92
Progressive CKD without active vasculitis	58 (43%)	0	0

Lionaki et al, Kidney Int 2009

Nephroprotection in AAV-associated nephropathy

Proteinuria in chronic glomerular diseases is associated with initial damage but also with renal outcome



Renal prognosis in IgA nephropathy

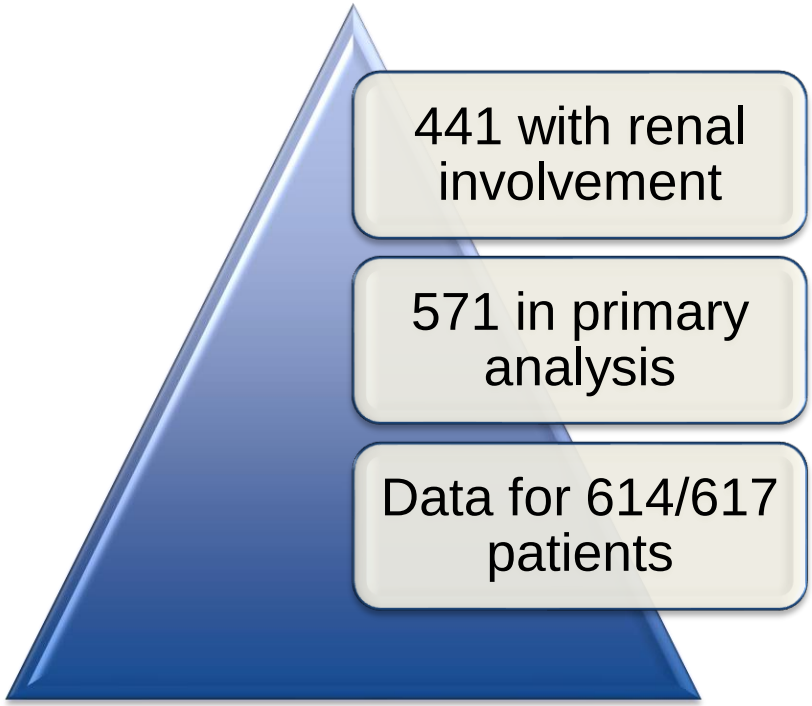
Pitcher, CJASN 2023

Nephroprotection in AAV-associated nephropathy

Is **persistent proteinuria** (after induction of remission) predictive in AAV ?

Metanalysis of 5 EUVAS and FVSG RCTs

IMPROVE (Hiemstra 2010)	156 new AAV	Induction CYC	Maintenance AZA vs MMF
MYCYC (Jones 2019)	140 new AAV	CYC vs MMF	AZA
RITUXVAS (Jones 2010)	44 new AAV	CYC vs RTX	+/- AZA
MAINRITSAN (Guillevin 2014)	115 new or relapsing AAV	CYC	RTX vs AZA
MAINRITSAN 2 (Charles 2018)	162 new or relapsing AAV	CYC, RTX or MTX	Fixed vs tailored RTX



Benichou N, Karras A, Kidney Int 2023

Nephroprotection in AAV-associated nephropathy

Is **persistent proteinuria** (after induction of remission) predictive in AAV ?

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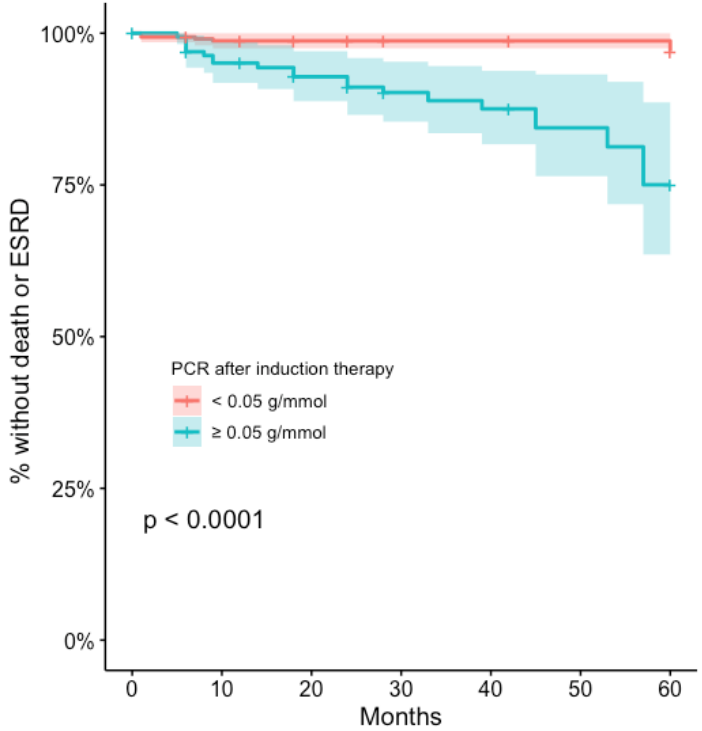


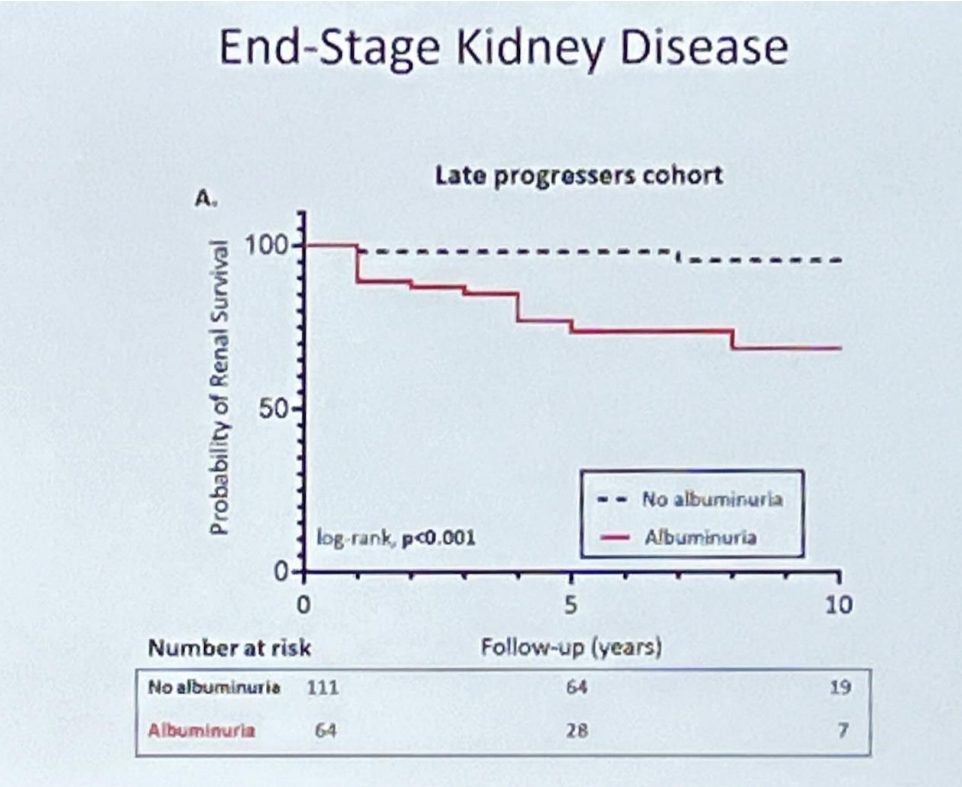
Multivariate Cox regression analysis of factors associated with death or ESKD

Variables	Adjusted HR	95% CI	p value
Age (per 1-year increase)	1.04	1.00 - 1.07	0.056
Anti-MPO specificity	1.09	0.42 – 2.86	0.107
Maintenance therapy: other than RTX	0.79	0.32 – 1.97	0.611
Serum creatinine after induction therapy (per 1 µmol/L)	1.01	1.01 – 1.02	< 0.001
Hematuria after induction therapy	1.50	0.62 – 3.62	0.369
UPCR after induction therapy ≥ 0.5 g/g	3.06	1.09 – 8.59	0.034

Benichou N, Karras A, Kidney Int 2023

Nephroprotection in AAV-associated nephropathy

Is **persistent proteinuria** (after induction of remission) predictive in AAV ?



Kaplan Meier analysis of ESKD in the late progressors cohort according to the presence or absence of albuminuria at 6 months (< or > 300 mg/g)

Chalkia A, Vasculitis Workshop 2024

Nephroprotection in AAV-associated nephropathy

Is **persistent proteinuria** a target for nephroprotection in AAV?

-No data available concerning the benefits of usual antiproteinuric therapy (ACEi / ARB) or nephroprotective measures (glycemic control, tobacco, salt restriction) in AAV nephropathy

-What about new drugs with renoprotective properties ?

- SGLT2 inhibitors (SGLT2i) – dapagliflozin, empagliflozin…
- Mineralosteroid Receptor Antagonists (MRA) - finerenone
- GLP1R agonists - semaglutide, liraglutide…
- Endothelin receptor antagonists (ERA) – sparsentan

Role of nephrologists for prevention of CKD progression in AAV patients

Conclusions : AAV treatment

- Rituximab can replace Cyclophosphamide for induction, except in patients with severe kidney or pulmonary involvement.
- Rituximab + Low-dose Cyclophosphamide can be used in patients with GFR <15

- Doses of corticosteroids can be rapidly taperred (in most cases)
- Avacopan can be used instead of steroids in patients with high risk of CS toxicity (and possibly to improve renal recovery ?)

- Plasma exchange can be discussed in patients with initial sCreat >300, but are associated with important infectious risk

- Rituximab must be prefered for maintenance therapy, when available
- The duration of maintenance therapy (2 to 4 years) depends on relapse risk

- Nephroprotective antiproteinuric treatments are important for delaying ESKD

Acknowledgments

Loic Guillevin, Luc Mouthon, Xavier Puechal, Benjamin Terrier (Cochin - Paris)
Nicolas Benichou, Jean-Paul Duong (HEGP- Paris)
D. Jayne (Cambridge), I Bajema (Leiden)

Evaluating and reducing relapse risk in AAV

- Every renal relapse is associated with a decrease in eGFR of 8-12 ml/min
- Associated with an increased risk of ESRD

Table 3. Relative risk for renal failure for CKD stage and renal relapse in multivariate analysis

CKD Stage	Relative Risk (95% Confidence Interval)	*P* Value
3	Reference	
4	16.4 (4.5 to 59.7)	<0.001[a]
5	43.1 (11.7 to 158.6)	<0.001[a]
Renal relapse	3.27 (1.24 to 8.63)	0.01[a]
Mean arterial pressure (per mmHg)	0.99 (0.96 to 1.01)	0.29
Proteinuria (per g/24 h)	1.14 (0.62 to 2.1)	0.62

de Joode, CJASN 2013

Table 4 Independent baseline predictors for ESRF with renal relapse as time-varying covariate

Competing risk	sHR	95% CI		*P*-value
Age, year	0.99	0.97	1.01	0.38
Female	0.84	0.43	1.64	0.61
Anti-PR3+	0.94	0.32	2.79	0.92
Anti-MPO+	1.40	0.47	4.15	0.54
Serum creatinine, μmol/l				
100–150	Referent	NA	NA	NA
151–275	2.03	0.40	10.34	0.40
276–500	6.63	1.63	27.00	0.01
>500	13.82	3.12	61.18	<0.001
BVAS				
Cutaneous	0.50	0.20	1.25	0.14
Mucous membranes	1.59	0.77	3.29	0.21
ENT	0.54	0.27	1.09	0.09
Chest	1.70	0.85	3.40	0.13
Cardiovascular	1.36	0.45	4.05	0.59
Abdominal	2.35	0.90	6.16	0.08
Nervous	0.57	0.20	1.61	0.29
Induction therapy				
Oral CYC	Referent	NA	NA	NA
i.v. CYC	1.97	0.18	21.20	0.58
MTX	1.52	0.66	3.50	0.33
Adjunctive therapy				
PLEX	0.37	0.15	0.88	0.03
Renal relapse	8.86	4.19	18.72	<0.001

Wester Trejo, Rheumatology 2019

Evaluating and reducing relapse risk in AAV

initial patient/disease characteristics

Predicting relapse in anti-neutrophil cytoplasmic antibody-associated vasculitis: a Systematic review and meta-analysis

Catherine King [1,2], Katie L. Druce[3,4], Peter Nightingale[1], Ellen Kay[2], Neil Basu[5], Alan D. Salama[6] and Lorraine Harper[1,2]

TABLE 1 All risk factors remaining in the meta-analysis

Risk factor	Number of studies	Effect size [HR (fixed, 95% CI)]	*P*-value	I^2 (%)
Anti-PR3 ANCA positive at diagnosis	4	1.69 (1.46, 1.94)	<0.00001	7
Lung involvement at diagnosis	3	1.18 (0.90, 1.86)	0.24	0
Age at diagnosis (per year)	3	1.00 (0.99, 1.01)	0.79	84
Cardiovascular system involvement at diagnosis	2	1.78 (1.26, 2.53)	0.001	43
Upper respiratory tract involvement at diagnosis	2	1.39 (0.91, 2.13)	0.13	0
Creatinine at diagnosis >200 μmol/l (relative to creatinine ≤100 μmol/l)	2*	0.39 (0.22, 0.69)	0.001	n/a
Creatinine at diagnosis 100–200 μmol/l (relative to creatinine ≤100 μmol/l)		0.81 (0.77, 0.85)	<0.001	n/a

King, Rheumatology Advances in Practice 2021

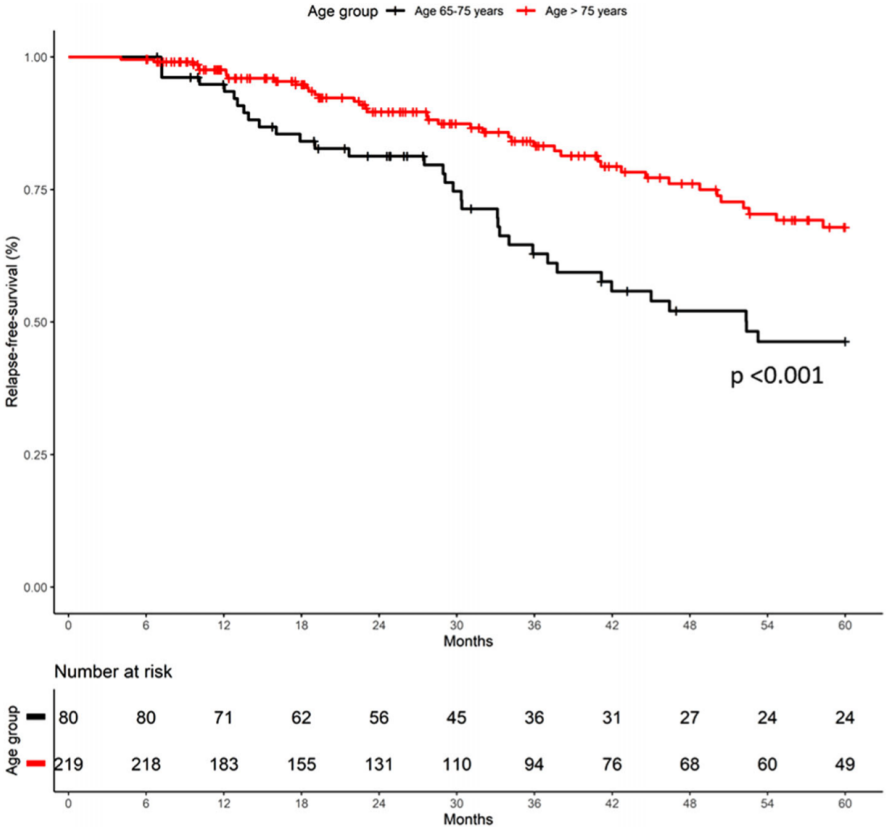
Evaluating and reducing relapse risk in AAV

initial patient/disease characteristics

Patients of 75 years and over with ANCA-associated vasculitis have a lower relapse risk than younger patients: A multicentre cohort study

Sara Thietart[1,2], Guillaume Beinse[3], Perrine Smets[4], Alexandre Karras[5], Carole Philipponnet[6], Jean-François Augusto[7], Khalil El Karoui[8], Rafik Mesbah[9], Dimitri Titeca-Beauport[10], Mohamed Hamidou[11], Pierre-Louis Carron[12], François Maurier[13], Karim Sacre[14], Pascal Cohen[1,2], Eric Liozon[15], Claire Blanchard-Delaunay[16], Alex Kostianovsky[1], Christian Pagnoux[1], Luc Mouthon[1,2], Loïc Guillevin[1,2], Benjamin Terrier[1,2], Xavier Puéchal[1,2,*] & for the French Vasculitis Study Group[1]

Thietart, J Int Med 2022



Evaluating and reducing relapse risk in AAV

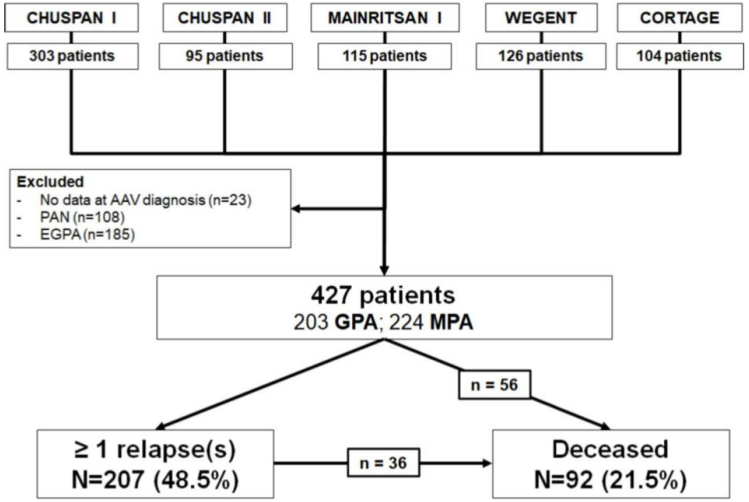
initial patient/disease characteristics

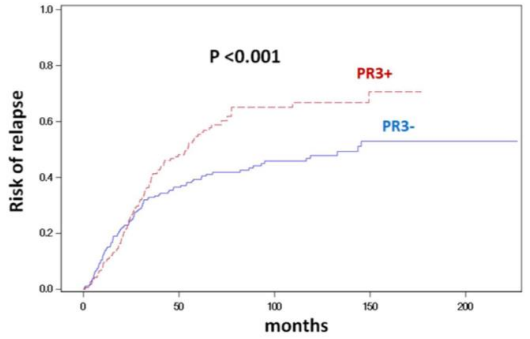
RMD Open
Rheumatic & Musculoskeletal Diseases

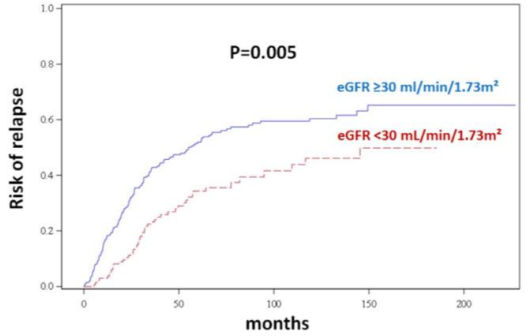
ORIGINAL RESEARCH

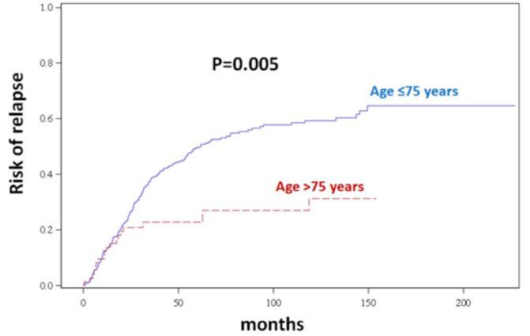
Score to assess the probability of relapse in granulomatosis with polyangiitis and microscopic polyangiitis

Maxime Samson ,[1] Hervé Devilliers,[2] Sara Thietart,[3] Pierre Charles,[4] Christian Pagnoux,[5] Pascal Cohen,[6] Alexandre Karras,[7,8] Luc Mouthon,[6] Benjamin Terrier ,[6] Xavier Puéchal ,[6] Loic Guillevin[6]









Evaluating and reducing relapse risk in AAV

initial patient/disease characteristics

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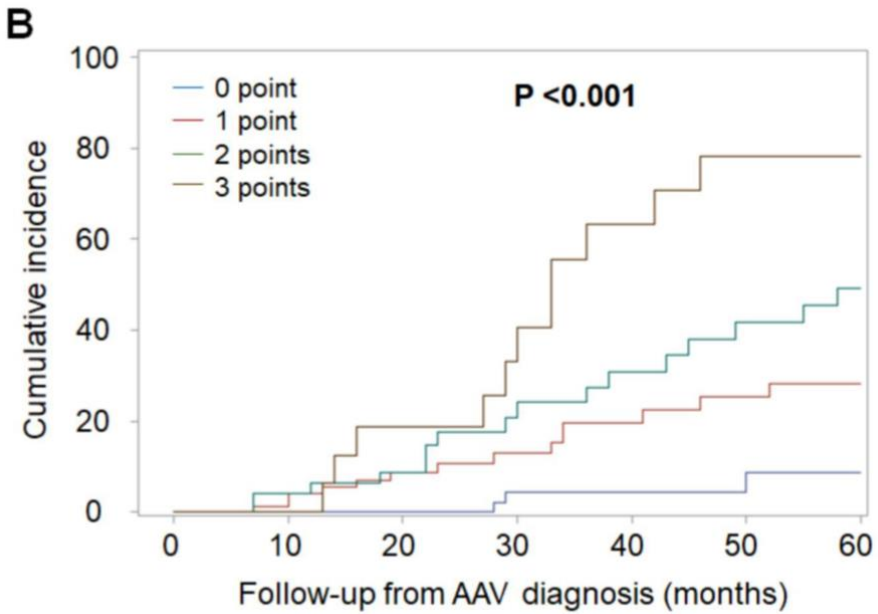
FVSG Relapse Score (FRS) :
1 point for PR3-ANCA,
1 point for eGFR ≥30
1 point for age ≤75 years
at AAV diagnosis



Evaluating and reducing relapse risk in AAV

During or after maintenance therapy

1. B-cell depletion and repopulation

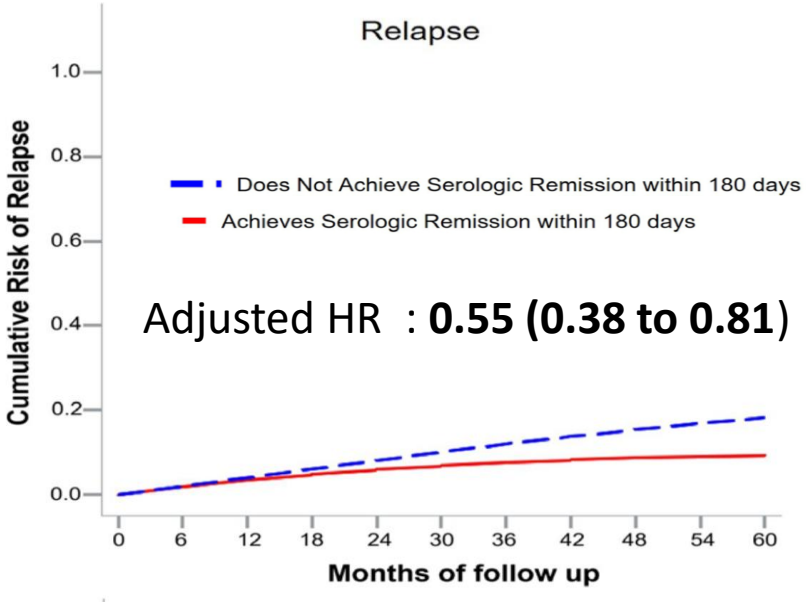
Most (>80%) relapses occur after B-cell repopulation
Early (<12mo) B-cell repopulation is associated with relapse

2. ANCA titer

Persistence of ANCA despite treatment is associated with increased relapse risk

The effect of achieving serological remission on subsequent risk of relapse, end-stage renal disease and mortality in ANCA-associated vasculitis: a target trial emulation study

Gregory McDermott ,[1] Xiaoqing Fu,[2] Claire Cook,[2] Catherine Ahola,[2] Brett Doliner,[3] Jennifer Hanberg,[3] John H Stone ,[4] Hyon K Choi ,[2] Yuqing Zhang ,[2] Zachary S Wallace [2]

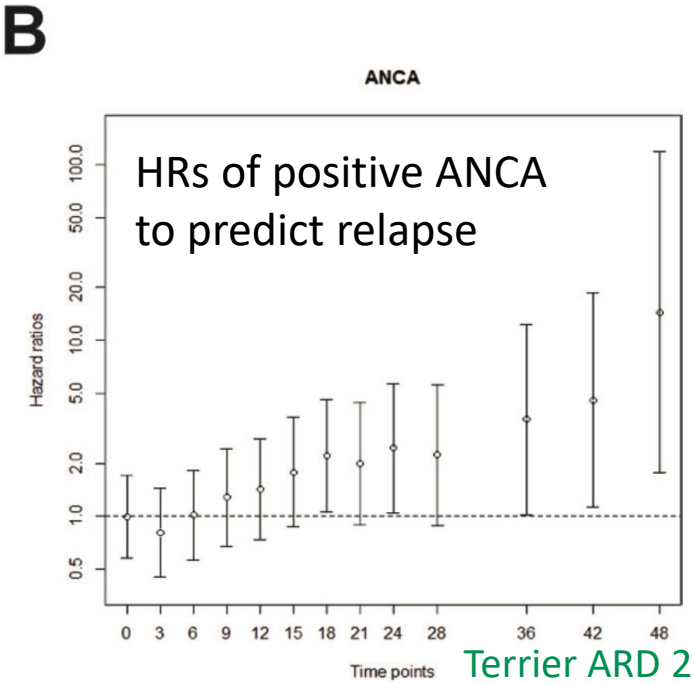


Adjusted HR : **0.55 (0.38 to 0.81)**

McDermott ARD 2022

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

Benjamin Terrier,[1] Christian Pagnoux,[1,2] Élodie Perrodeau,[3] Adexandre Karras,[4] Chahera Khouatra,[5] Olivier Aumaître,[6] Pascal Cohen,[1] Olivier Decaux,[7] Hélène Desmurs-Clavel,[8] François Maurier,[9] Pierre Gobert,[10] Thomas Quémeneur,[11] Claire Blanchard-Delaunay,[12] Bernard Bonnotte,[13] Pierre-Louis Carron,[14] Eric Daugas,[15] Marize Ducret,[16] Pascal Godmer,[17] Mohamed Hamidou,[18] Olivier Lidove,[19] Nicolas Limal,[20] Xavier Puéchal,[1] Luc Mouthon,[1] Philippe Ravaud,[3] Loïc Guillevin,[1,21] on behalf of the French Vasculitis Study Group



Terrier ARD 2018

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Doubling of ANCA titer (ELISA) has been associated with increased risk for relapse

Evaluating and reducing relapse risk in AAV

The prognostic value of ANCA titer

ANCA as a Predictor of Relapse: Useful in Patients with Renal Involvement But Not in Patients with Nonrenal Disease

Michael J. Kemna,
Paassen,* and Jan

PR3-ANCAs predict relapses in ANCA-associated vasculitis patients after rituximab

Laura S. van Dam
Cees van Kooten[1], T

ial
bodies

es are a useful marker
trophil cytoplasmic
des

B Terrier,[1] D Saadc
J-C Piette,[1,5] P Cac

Doubling of ANCA titer (ELISA)

has been associated with a

8- to 23- fold increased risk for relapse

Association Between Reappearance of Myeloperoxidase–Antineutrophil Cytoplasmic Antibody and Relapse in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Subgroup Analysis of Nationwide Prospective Cohort Studies

Haruki Watanabe,[1] Ken-Ei Sada,[1] Yoshinori Matsumoto,[1] Masayoshi Harigai,[2] Koichi Amano,[3] Hiroaki Dobashi,[4] Shouichi Fujimoto,[5] Joichi Usui,[6] Kunihiro Yamagata,[6] Tatsuya Atsumi,[7]

Evaluating and reducing relapse risk in AAV

The clinical use of ANCA titer and CD19+ count

MAINRITSAN 2 – study design

Groupe Français d'Etude des Vascularites

Induction

Iv CYC or RTX

REMISSION

D0 D15 M6 M12 M18

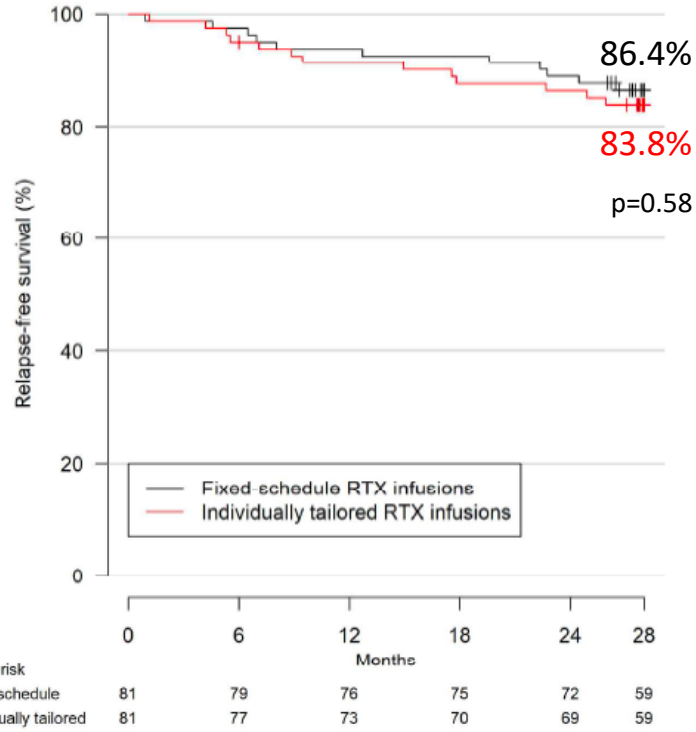
"Fixed dose" arm

D0 M3 M6 M9 M12 M15 M18

"On demand" arm

= RTX 500 mg

Re-infusion only if
ANCA titer x 2 on ELISA
or CD19+>0/mm3



Charles P, ARD 2018

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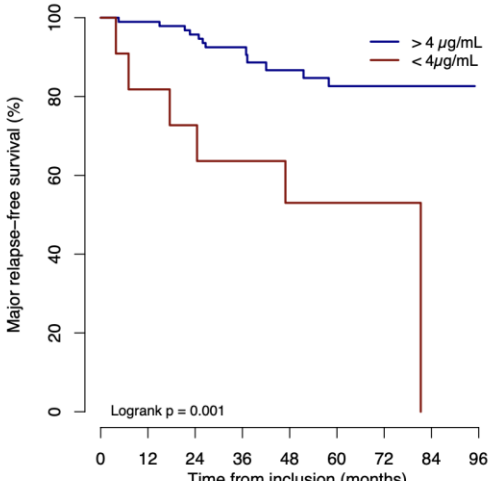
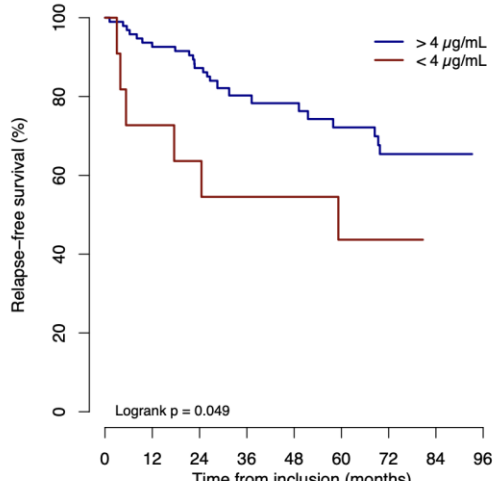
3. Plasma rituximab concentration

Low trough levels of RTX at M3 are associated with relapse

Khoudour, A&R 2023





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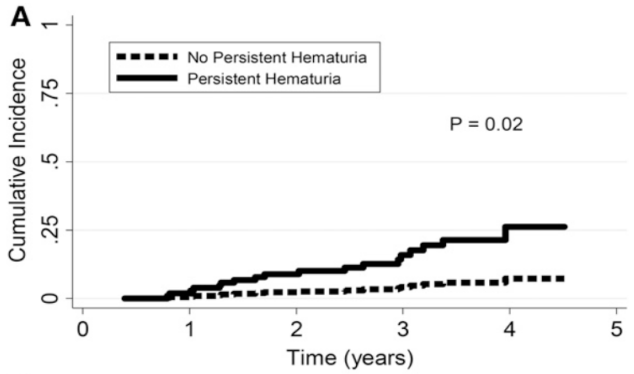
Khoudour, A&R 2023

4. Hematuria

Persistent hematuria is associated with relapse risk

Rhee, CJASN 2018



Evaluating and reducing relapse risk in AAV

Back to « old-fashion » and simple urine biomarkers ?

The Utility of Urinalysis in Determining the Risk of Renal Relapse in ANCA-Associated Vasculitis

Rennie L. Rhee, John C. Davis, Linna Ding, Fernando C. Fervenza, Gary S. Hoffman, Cees G.M. Kallenberg, Carol A. Langford, W. Joseph McCune, Paul A. Monach, Philip Seo, Robert Spiera, E. William St. Clair, Ulrich Specks, John H. Stone, and Peter A. Merkel

Characteristic	All, *n*=149	Persistent Hematuria beyond 6 mo	
		Yes, *n*=63	No, *n*=86
Age, yr	55 (44–66)	54 (43–68)	55 (44–63)
Women, %	41	56	30
Achieved menopause (if a woman), %	62	51	77
Race, %			
White	93	92	94
Black	3	3	2
Other	4	5	3
ANCA-associated vasculitis type, %			
Granulomatosis with polyangiitis	81	71	87
Microscopic polyangiitis	19	29	13
ANCA type by ELISA, %			
Anti-PR3	68	65	71
Anti-MPO	32	35	29
Duration of trial enrollment, mo	36 (24–43)	36 (25–46)	36 (24–42)
Newly diagnosed, %	59	57	60
BVAS/GPA	7 (5–10)	8 (6–10)	7 (4–9)

Table 2. Outcomes in patients with ANCA-associated vasculitis with and without persistent hematuria

First Event after Enrollment	Persistent Hematuria beyond 6 mo		*P* Value
	Yes, *n*=63	No, *n*=86	
Any relapse (%)	24 (38)	33 (38)	0.97
Renal relapse	14 (22)	4 (5)	<0.01
Nonrenal relapse	10 (16)	29 (34)	0.01
ESRD (%)	5 (8)	3 (3)	0.23
Time to any relapse,[a] mo	17 (11–31)	13 (11–20)	0.92
Time to renal relapse,[a] mo	22 (12–36)	26 (15–36)	0.37

Rhee, CJASN 2018

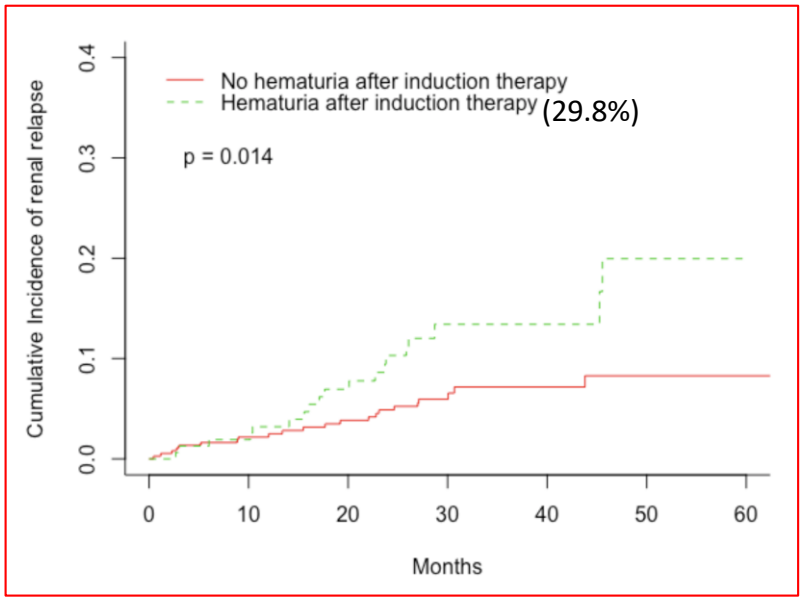
Evaluating and reducing relapse risk in AAV

Back to « old-fashion » and simple urine biomarkers ?

Post hoc study pooling 5 RCT trials (MAINRITSAN1 and 2, RITUXVAS, MYCYC, IMPROVE), evaluating the association of persistant hematuria, with the occurrence of relapse

n=571, median FU : 28months

Variables	Any Relapse			Renal Relapse		
	Adjusted sHR	95% CI	p value	Adjusted sHR	95% CI	p value
Male sex	1.00	0.70 - 1.42	0.980	0.70	0.36 - 1.36	0.290
Age (per 1-year increase)	0.99	0.98 - 1.00	0.054	1.01	0.99 - 1.04	0.350
ANCA type (ref: MPO)						
Negative	1.60	0.80 - 3.20	0.180	1.68	0.44 - 6.40	0.450
PR3	**1.61**	**1.09 - 2.38**	**0.017**	1.57	0.77 - 3.21	0.220
eGFR at flare diagnosis (per 1 ml/mn/1.73m2)[a]	**1.05**	**1.00 - 1.01**	**0.044**	1.00	0.99 - 1.01	0.650
Hematuria after induction therapy	1.10	0.78 - 1.56	0.590	**2.18**	**1.14 - 4.18**	**0.019**



Benichou N, Kidney Int 2023

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Khoudour, A&R 2023

4. Hematuria

Persistent hematuria is associated with relapse risk

4. New biomarkers ?

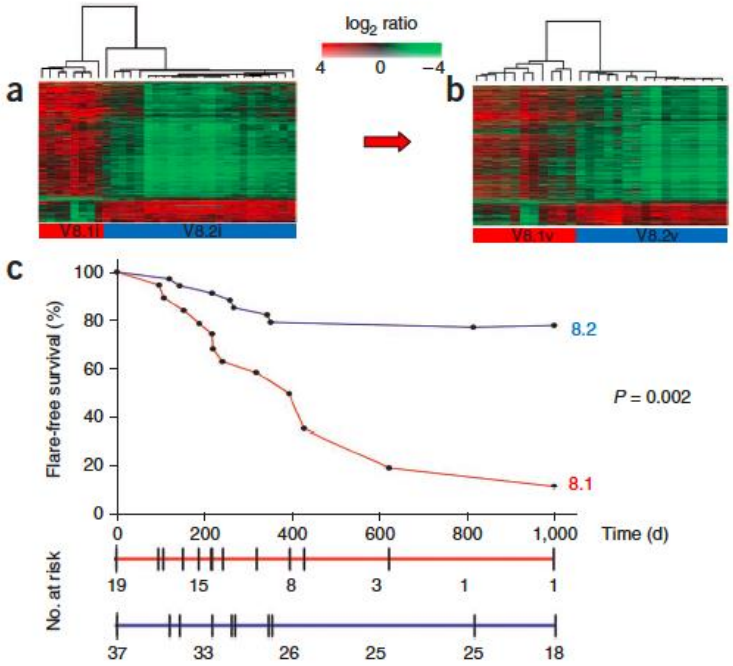
Evaluating and reducing relapse risk in AAV

Prognostic value of lymphocyte subpopulations ?

A CD8$^+$ T cell transcription signature predicts prognosis in autoimmune disease

Eoin F McKinney[1,2], Paul A Lyons[1,2], Edward J Carr[1,2], Jane L Hollis[2], David R W Jayne[2], Lisa C Willcocks[1,2], Maria Koukoulaki[1,2], Alvis Brazma[3], Vojislav Jovanovic[4], D Michael Kemeny[4], Andrew J Pollard[5], Paul A MacAry[4], Afzal N Chaudhry[2] & Kenneth G C Smith[1,2]

Memory T-cells
(+transcription of genes involved in IL-7R pathway and TCR signaling)
-Presence associated with relapse in SLE, AAV, Crohn disease



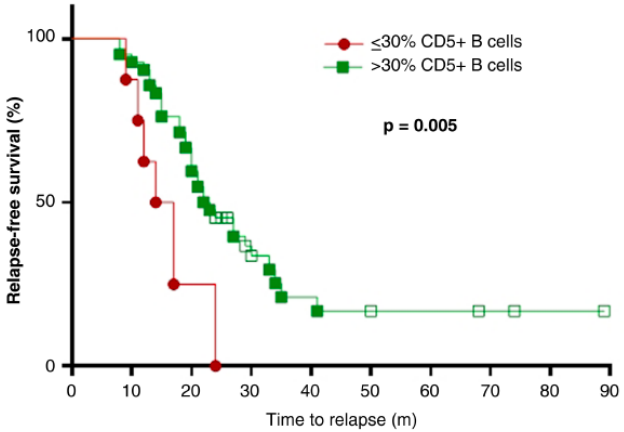
McKinney, Nat Med 2010

Evaluating and reducing relapse risk in AAV

Prognostic value of lymphocyte subpopulations ?

Regulatory B-cells (CD19+CD5+)

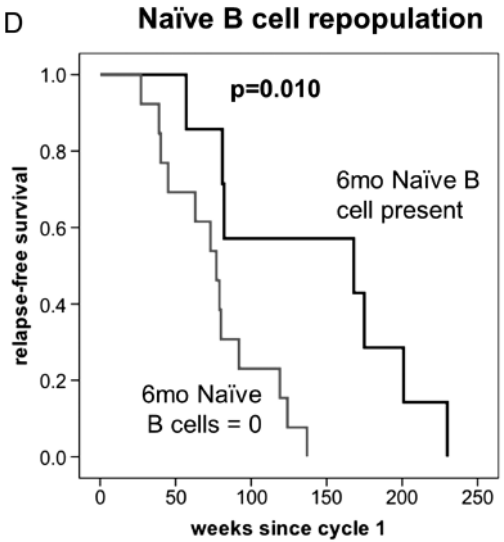
-Decreased in active vasculitis
-Low B reg count at M6 is associated with relapse



Bunch, ARD 2015

Naive B-cells (CD19+CD27-)

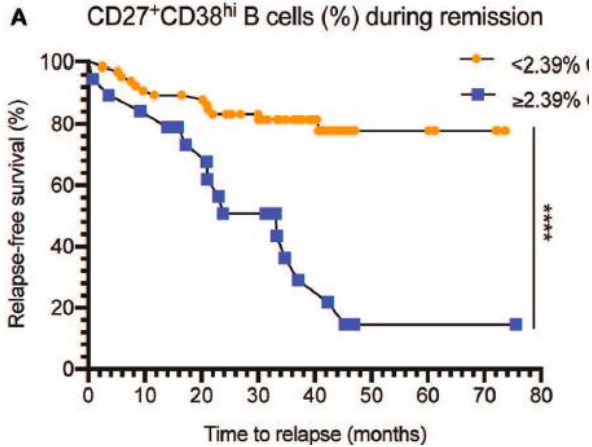
-Decreased in active vasculitis
-Their absence at M6 is associated with relapse



Md Yusof, ARD 2015

Plasmablasts (CD27+CD38 Hi)

-High frequency during remission predicts relapse in GPA



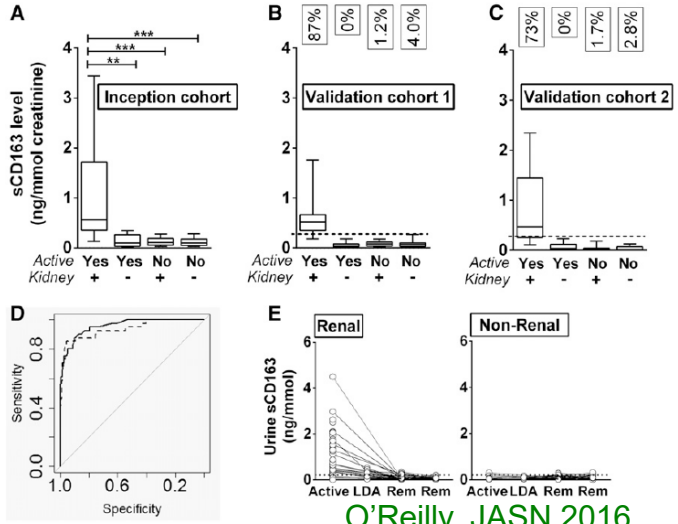
Von Borstel, Front Immunol 2019

Evaluating and reducing relapse risk in AAV

CLINICAL RESEARCH www.jasn.org

Urinary Soluble CD163 in Active Renal Vasculitis

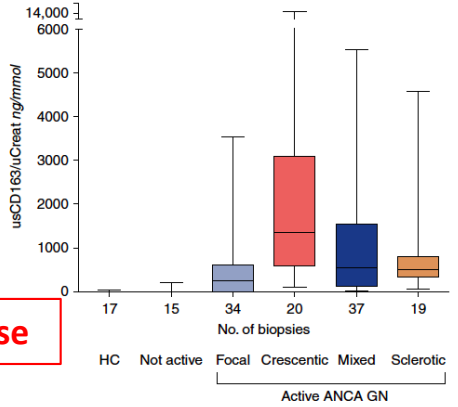
Vincent P. O'Reilly,* Limy Wong,* Claire Kennedy,* Louise A. Elliot,† Shane O'Meachair,‡ Alice Marie Coughlan,* Eoin C. O'Brien,* Michelle M. Ryan,* Diego Sandoval,* Emma Connolly,* Gerjan J. Dekkema,§ Jiaying Lau,* Wayel H. Abdulahad,¶ Jan-Stephan F. Sanders,§ Peter Heeringa,¶ Colm Buckley,** Cathal O'Brien,†‡‡ Stephen Finn,†‡‡ Clemens D. Cohen,§§ Maja T. Lindemeyer,§§ Fionnuala B. Hickey,* Paul V. O'Hara,* Conleth Feighery,† Sarah M. Moran,* George Mellotte,* Michael R. Clarkson,‖ Anthony J. Dorman,** Patrick T. Murray,¶¶ and Mark A. Little*



O'Reilly, JASN 2016

Urinary Soluble CD163 and Disease Activity in Biopsy-Proven ANCA-Associated Glomerulonephritis

Joop P. Aendekerk,[1] Sjoerd A.M.E.G. Timmermans,[1] Matthias H. Busch,[1] Judith Potjewijd Peter Heeringa,[2] Jan G.M.C. Damoiseaux,[3] Chris P. Reutelingsperger,[4] and Pieter van Paassen,[1] for the Limburg Renal Registry*



Late (but non-invasive) diagnosis of renal relapse

Table 3. Diagnostic performance of urinary soluble CD163, serum and urinary soluble CD25, and conventional markers for detecting relapsi

Markers	Cutoff	Samples: Active ANCA-Associated GN/All Available	Area under the Curve [95% Confidence Interval]	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
AKI		47/57	0.66 [0.48 to 0.83]	0.51	0.80	0.92	0.26
New-onset hematuria		45/55	0.58 [0.38 to 0.78]	0.67	0.50	0.86	0.25
Proteinuria	0.60 g/d	47/58	0.78 [0.64 to 0.91]	0.68	0.82	0.94	0.38
AKI with hematuria and/or proteinuria		47/57	0.75 [0.59 to 0.92]	0.70	0.80	0.94	0.36
C-reactive protein		47/57	0.62 [0.43 to 0.81]	0.64	0.60	0.88	0.26
[illegible]							
Urinary soluble CD163	30 ng/mmol	47/58	0.94 [0.88 to 1.00]	0.94	0.91	0.98	0.78
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Urinary soluble CD25	210 ng/mmol	47/58	0.50 [0.31 to 0.69]	0.32	0.82	0.88	0.22

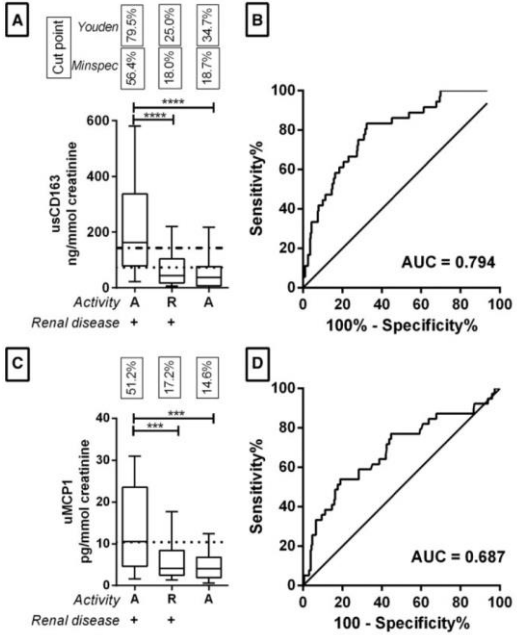
Aendekerk CJASN 2016

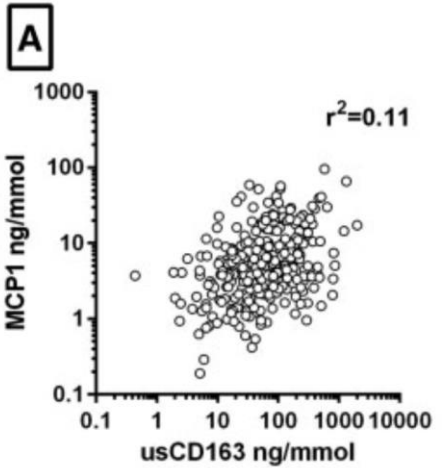
Evaluating and reducing relapse risk in AAV

Nephrol Dial Transplant (2020) 35: 283–291
doi: 10.1093/ndt/gfy300
Advance Access publication 31 October 2018

Urinary soluble CD163 and monocyte chemoattractant protein-1 in the identification of subtle renal flare in anti-neutrophil cytoplasmic antibody-associated vasculitis

Sarah M. Moran[1], Paul A. Monach[2,3], Lina Zgaga[4], David Cuthbertson[5], Simon Carette[6], Nader A. Khalidi[7], Curry L. Koening[8], Carol A. Langford[9], Carol A. McAlear[10], Larry Moreland[11], Christian Pagnoux[6], Philip Seo[12], Ulrich Specks[13], Antoine Sreih[10], Jason Wyse[14], Steven R. Ytterberg[15], Peter A. Merkel[10,11] and Mark A. Little[1,16] for the Vasculitis Clinical Research Consortium





Combination of urine biomarkers ?

usCD163 : released from activated glomerular macrophages

MCP-1 : produced from renal cells to recruit macrophages