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CMR CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

Hôpital Cochin
Port-Royal
AP-HP

ANCA-associated vasculitis

Treatment guidelines and emerging therapies

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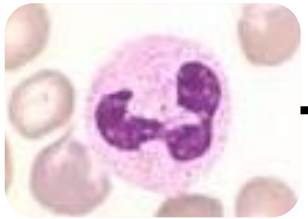
GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES

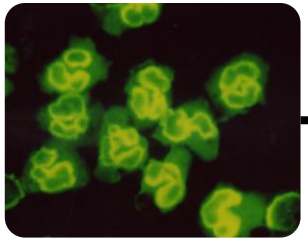
Disclosures

- **Boards:** AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, CSL Vifor
- **Conference:** AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Pfizer, CSL Vifor
- **Travel grants:** AstraZeneca, GlaxoSmithKline, CSL Vifor

Which mechanisms are involved?

Neutrophils

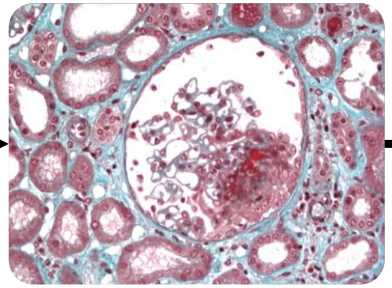




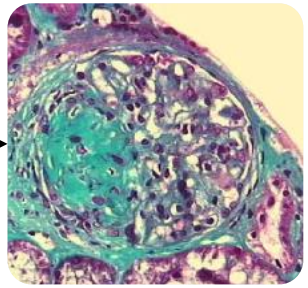
MPO-ANCA

C5a

Alternative complement pathway activation



Influx of inflammatory cells Vasculitis



Scarring Damage

Glucocorticoids

Cyclophosphamide/Rituximab

Anti-claudine 1

PLEX

Pioglitazone

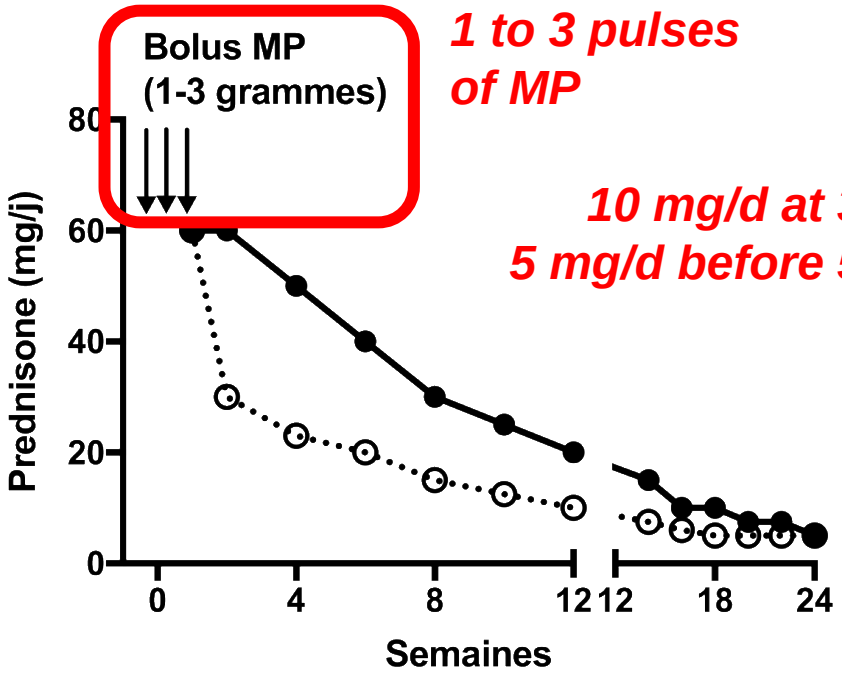
Avacopan/Iptacopan

What are the therapeutic issues in practice?

1. **What dosage of glucocorticoids?**
2. **Which immunosuppressant?**
3. **What is the role of plasma exchange?**
4. **What place for avacopan?**
5. **What are the therapeutic perspectives?**

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

Walsh M et al, N Engl J Med, 2020



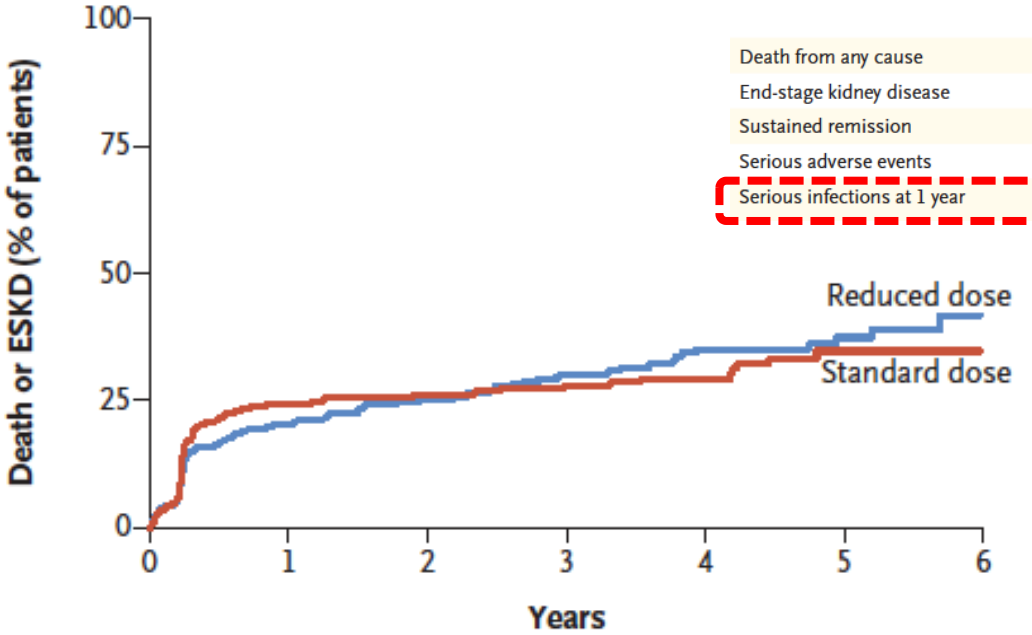
Targets:
10 mg/d at 3 months
5 mg/d before 5 months

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<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		

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

Walsh M et al, N Engl J Med, 2020

Secondary Outcome	Plasma Exchange vs. No Plasma Exchange	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)



Death and/or ESKD in 26% of the standard group vs. 28% of the reduced group (non-inferiority hypothesis demonstrated).

Recommendations for glucocorticoids

ACR 2021	For patients with active, severe GPA/MPA, either IV pulse GCs or high-dose oral GCs may be prescribed as part of initial therapy **We conditionally recommend a reduced-dose GC regimen over a standard-dose GC regimen for remission induction**
EULAR 2022	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 achieving a dose of 5 mg prednisolone equivalent per day by 4–5 months**
KDIGO 2024	We recommend that GCs in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV **Oral glucocorticoids with rapid tapering are preferred over slower tapering**

Chung, Arthritis Rheumatol, 2021 ***Hellmich, Ann Rheum Dis, 2023*** ***Floege, Kindey Int, 2024***

French recommendations 2024

What induction glucocorticoid regimen?

Recommendation	**% agreement**	**LoA**
A rapid GC tapering regimen is recommended, in association with RTX or CYC treatment, as induction therapy for severe GPA or MPA, aiming for 10 mg/d at 3 months and 5 mg/d from months 5 to 12.	98,2	9,3 ± 1,0
Pulses of methylprednisolone may be considered initially in cases of life-threatening or organ-threatening disease.	100	9,6 ± 0,7
In patients at high risk of relapse, long-term GCs maintenance therapy at a dose of 5 mg/d may be considered.	94,5	8,6 ± 1,4

Real-life use of the PEXIVAS reduced-dose GCs regimen in the rituximab era

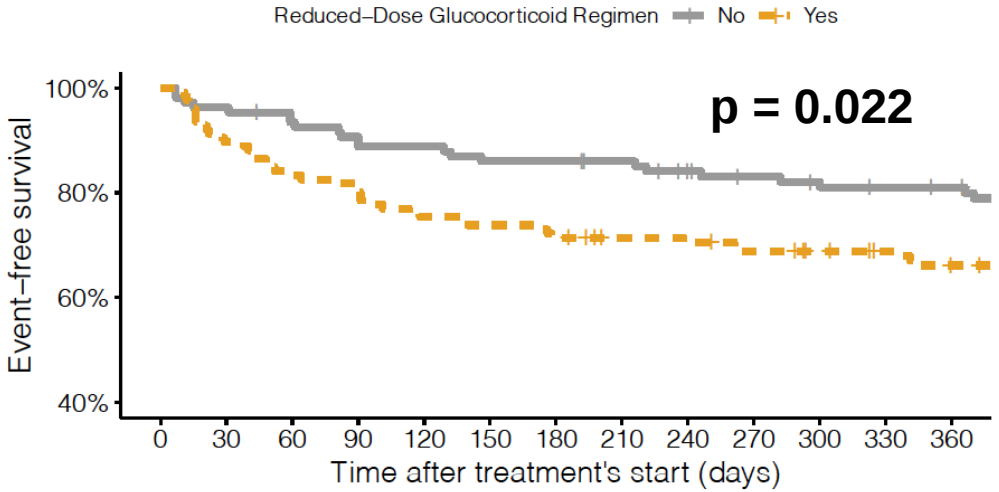
Composite criterion

PEXIVAS criterion (death and ESKD)

+ Impossibility of lowering GCs

+ Minor relapse

+ Major relapse



Composite criterion associated with:

Reduced dose of GCs

Creatinine >300 µmol/L

Induction treatment with rituximab

Nagle, Ann Rheum Dis, 2024

What are the therapeutic issues in practice?

1 What dosage of glucocorticoids?

2 **Which immunosuppressant?**

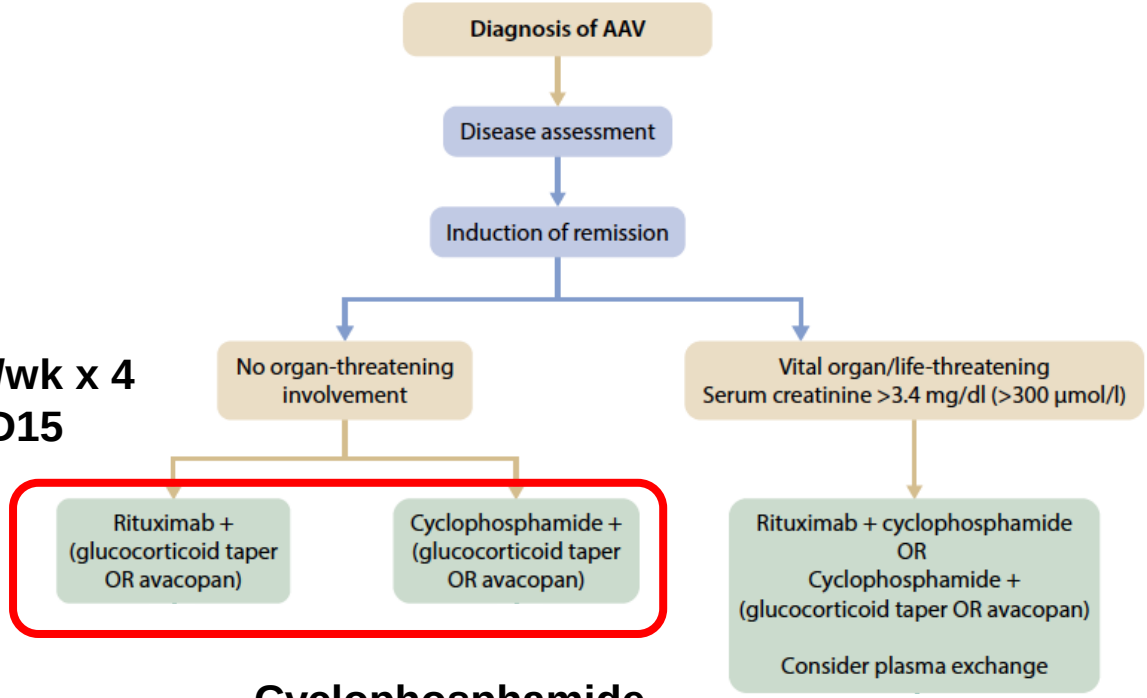
3 What is the role of plasma exchange?

4 What place for avacopan?

5 What are the therapeutic perspectives?

Recommendations KDIGO 2024

Immunosuppressive agents



Rituximab
375 mg/m²/wk x 4
ou 1 g D1 D15

Cyclophosphamide
0.6 g/m² x 3 then 0.7 g/m² x3

Floege, Kindey Int, 2024

Recommendations KDIGO 2024

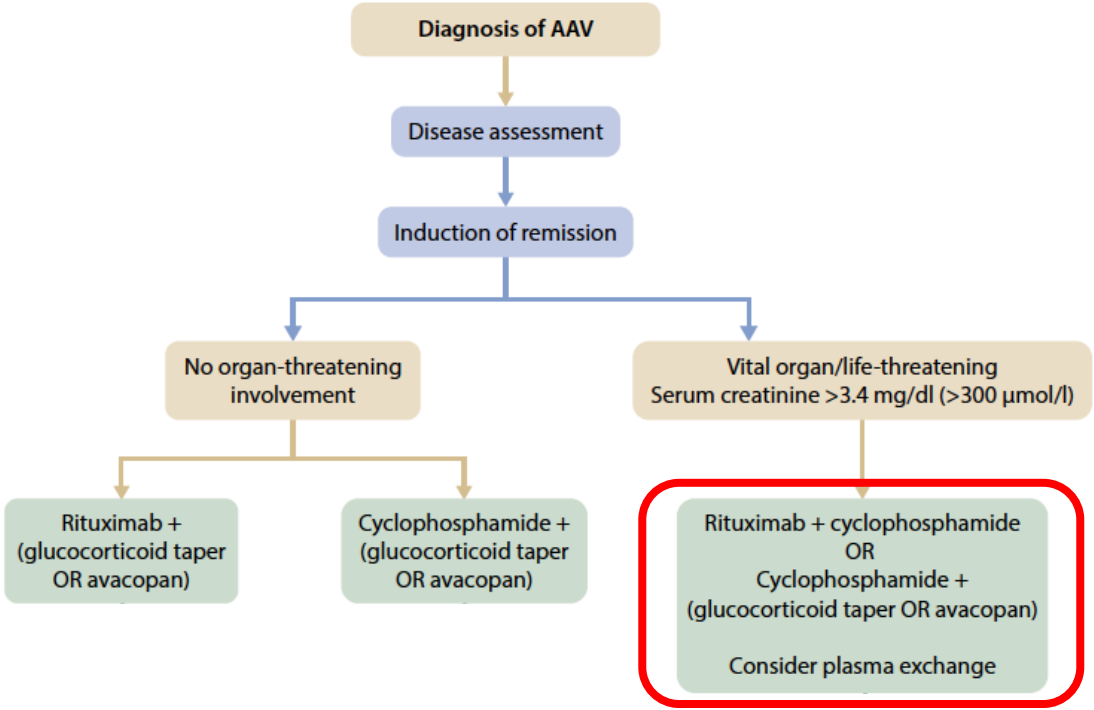
Immunosuppressive agents

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal 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]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

Floege, Kindey Int, 2024

Recommendations KDIGO 2024

Immunosuppressive agents



Cyclophosphamide
15 mg/kg D1 D15
+ Rituximab
375 mg/m^2/wk x 4
ou 1 g D1 D15

Floege, Kindey Int, 2024

French recommendations 2024

Which immunosuppressant to use for induction?

Recommendation	**% agreement**	**LoA**
RTX is recommended over CYC : • in patients with relapsing AAV, • in women of childbearing age, children, adolescents or the elderly, • in cases of PR3-ANCA positivity or GPA, or when GCs sparing is required.	86,3	8,8 ± 1,5

French recommendations 2024

Which immunosuppressant to use for induction?

Recommendation	**% agreement**	**LoA**
It is recommended to use CYC rather than RTX in the case of life-threatening events: • alveolar hemorrhage under mechanical ventilation, • severe renal impairment at diagnosis with creatinine > 354 µmol/L A combination of CYC and RTX may also be considered in these patients, to limit CYC doses.	96,2	8,8 ± 1,4

What are the therapeutic issues in practice?

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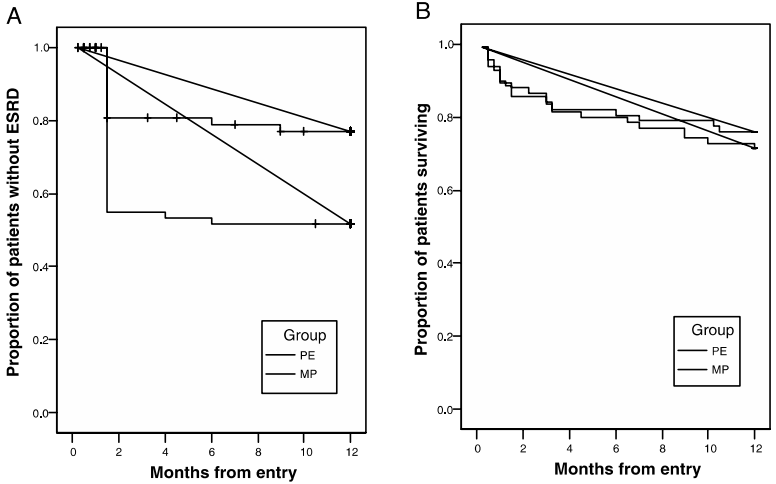
MEPEX trial

PLEX versus IV pulses of MP IV (in addition to oral CYP and GCs)
1st flare of AAV, creatinine level ≥ 500 μmol/L or dialysis

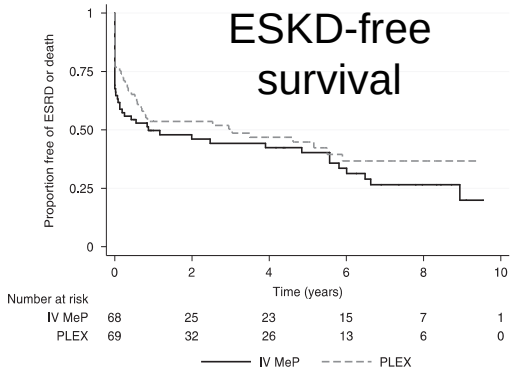
Primary objective: renal recovery at M12
Creatininemia < 500 μmol/L or weaned off dialysis

MEPEX 2007
PLEX: -50% dialysis at 1 year
No survival benefit



MEPEX 2013

PLEX: No long-term benefit on ESKD-free survival



Jayne, JASN, 2007
Walsh, Kidney Int, 2013

PEXIVAS trial

704 GPA/PAM patients with AKI (eGFR < 50 ml/min) or DAH
Double randomized, open-label, randomized controlled trial

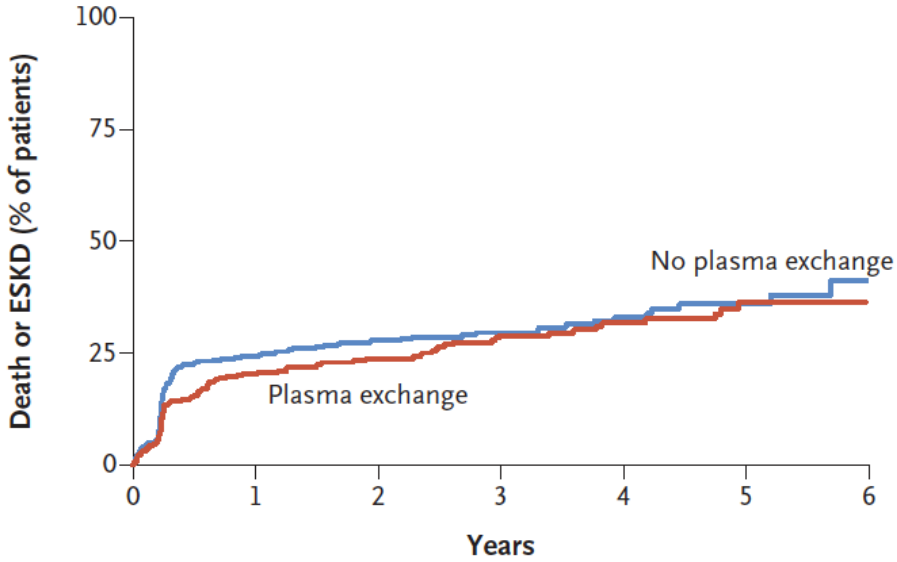
- PLEX vs no PLEX
- Standard/reduced dose GCs

63 years old, 66% male

90% 1st flare of AAV
60% MPO-ANCA, 40% PR3-ANCA
85% CYC (50% IV, 35% oral)/15% RTX

Median serum creatinine 330 μmol/L
Creatininemia ≥ 500 μM or dialysis (29%)
DAH in 27% (severe in 8.5%)

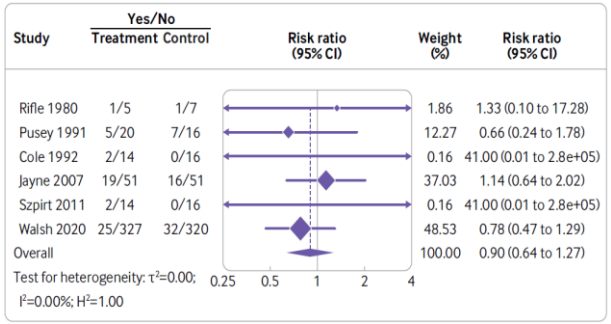
No benefit from PLEX (ESKD or death)
Whatever the analysis subgroup



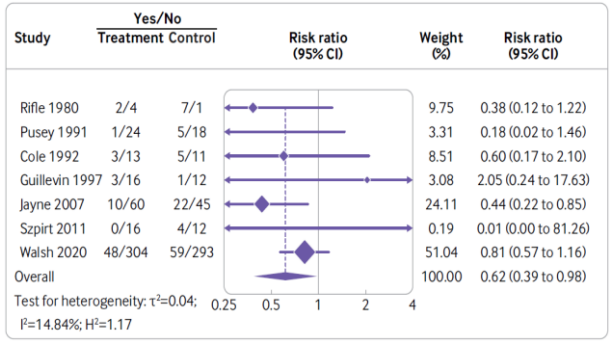
Walsh, NEJM, 2020

What is the role of plasma exchange?

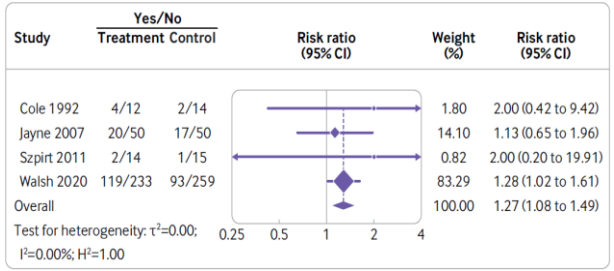
Similar mortality at M12

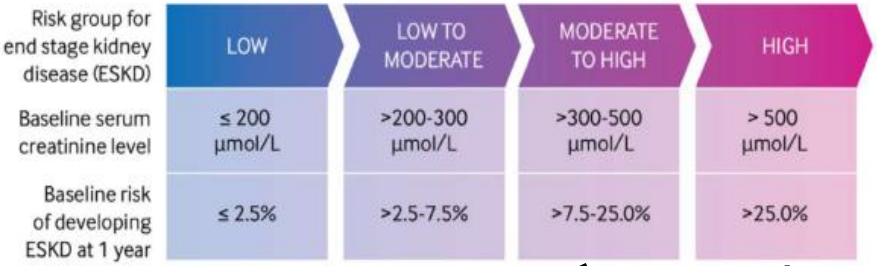


ESKD at M12 Benefits of PLEX?



Serious infections at M12 Risk of PLEX





PLEX: 4.6% reduction in risk of ESKD at M12 (21.7 patients to be treated)

PLEX: 16% reduction in risk of ESKD at M12 (6.25 patients to be treated)

+1 severe infection for 14 patients treated with PLEX

Walsh, BMJ, 2022
Zeng, BMJ, 2022

Recommendations EULAR 2022

Plasma exchanges

PLEX **may be considered** as part of the induction treatment of GPA and PAM in patients with creatinine levels > 300 µmol/L associated with active glomerulonephritis

PLEX is **recommended** for patients who also have anti-GBM+ antibodies

Routine use of PLEX for the treatment of **alveolar hemorrhage is not recommended**

Hellmich, Ann Rheum Dis, 2022

Recommendations KDIGO 2024

Plasma exchanges

PLEX considered if :

- **Serum creatininémi >300 µmol/L**
- **Diffuse alveolar hemorrhage with hypoxemia**
- **Overlap between AAV and anti-GBM vasculitis**

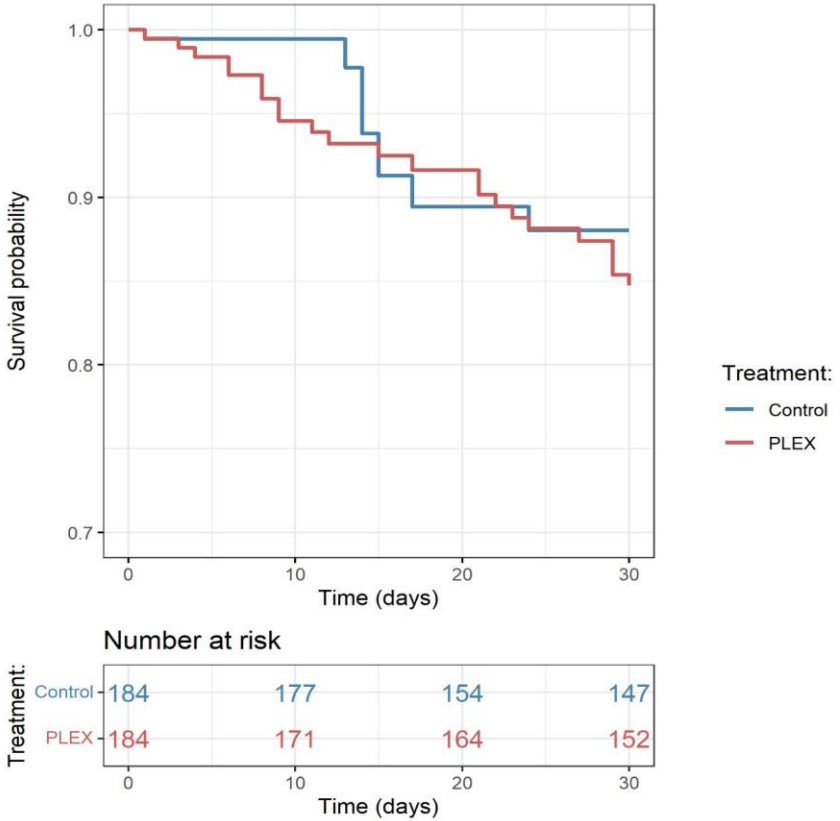
Floege, Kindey Int, 2024

French recommendations 2024

Recommendation	**% agreement**	**LoA**
PLEX is not routinely recommended for induction treatment of AAV, **even in severe cases**	98,2	9,5 ± 0,9
PLEX is indicated in patients with **anti-GBM antibodies** (with or without ANCA) and discussed on a case-by-case basis in patients with AAV and **severe renal impairment** (serum creatinin >300 µmol/L or rapidly worsening despite initiation of treatment)	100	9,4 ± 0,8
PLEX is not indicated for non-severe DAH, **but can be discussed for severe DAH**	98,1	9,2 ± 0,9

What is the role of plasma exchange in DAH?

Retrospective multicenter study analyzing the impact of PLEX on 30-day mortality after ICU admission for severe AAV-associated DAH
Emulation of a target trial
184 patients enrolled (median age 66 years, 53.3% MPO-ANCA), PLEX in 78.3%.
At 30 days, survival was 85% in the PLEX group and 88% in the non-PLEX group, with no difference in mortality (HR 1.23; 95% CI 0.57-3.89).



Sanna, submitted

What are the therapeutic issues in practice?

1. What dosage of glucocorticoids?
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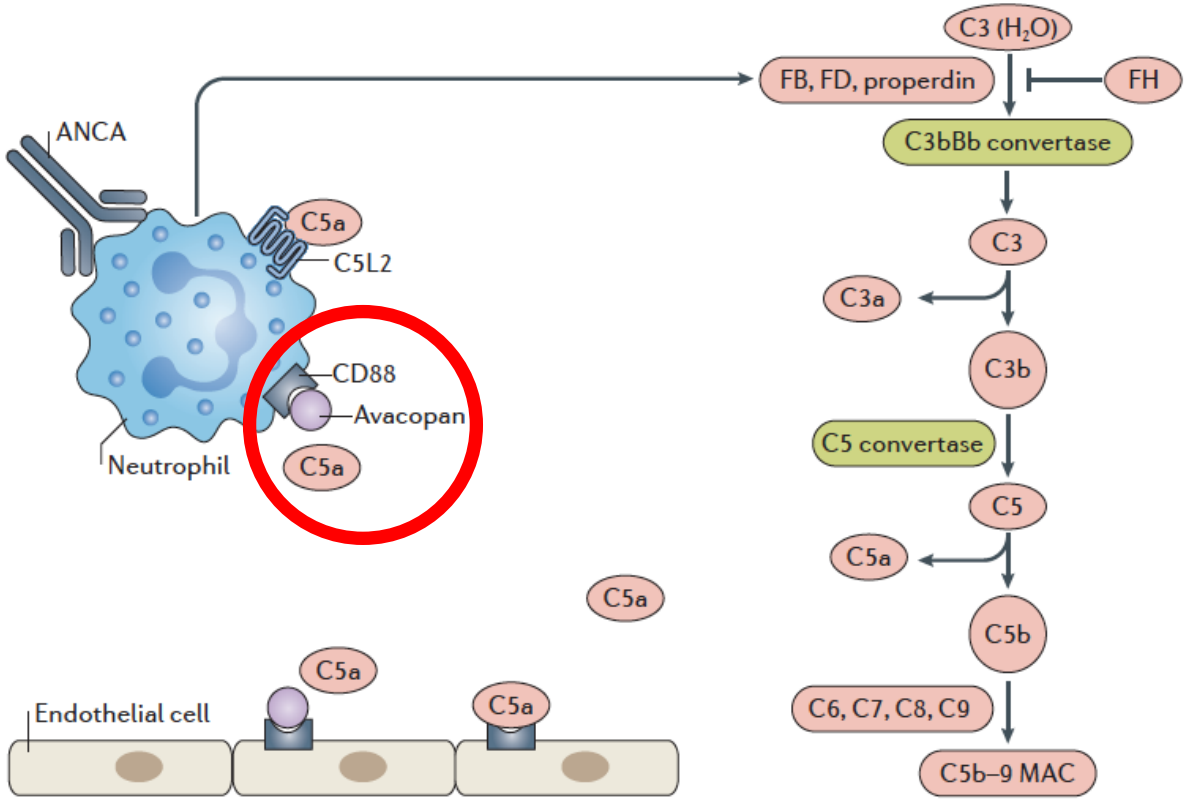
Targeting the alternative complement pathway



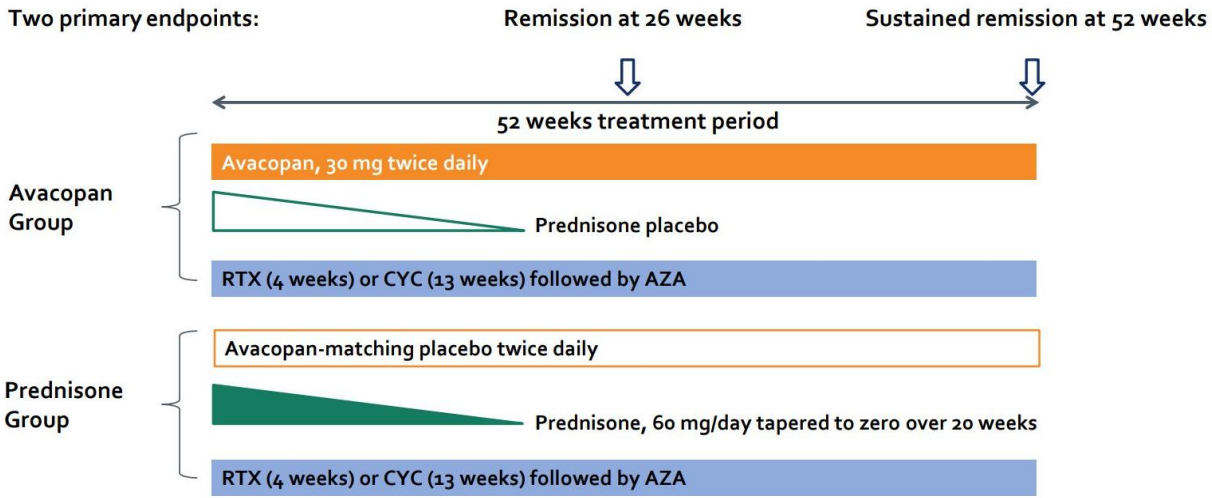
Kettritz, Nat Rev Nephrol, 2017

ADVOCATE trial

Phase 3, international, placebo-controlled, double-blind, noninferiority trial evaluating avacopan compared to glucocorticoids
Patients randomized in a 1:1 ratio to receive oral avacopan at a dose of 30 mg twice daily or oral prednisone on a tapering schedule

331 patients enrolled

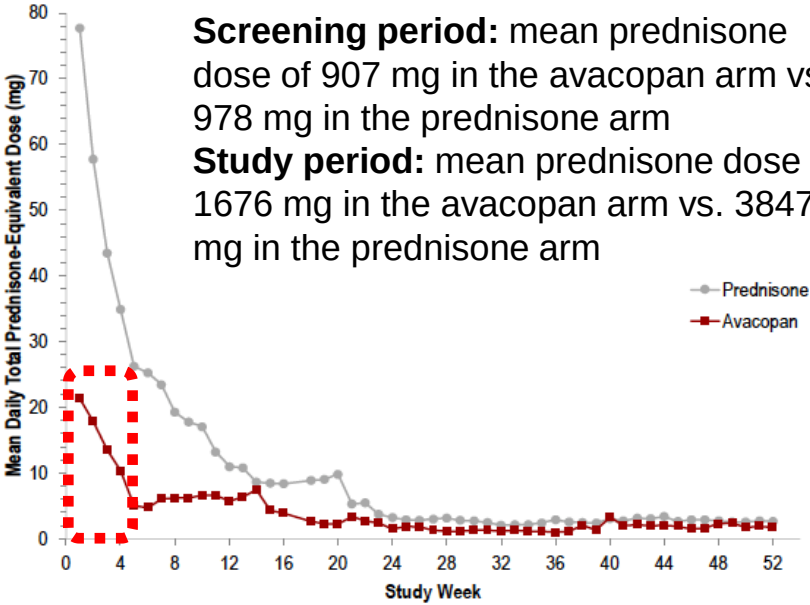
1st primary endpoint:
BVAS of 0 at week 26 and no GCs use in the previous 4 weeks
2nd primary endpoint:
Remission at both weeks 26 and 52



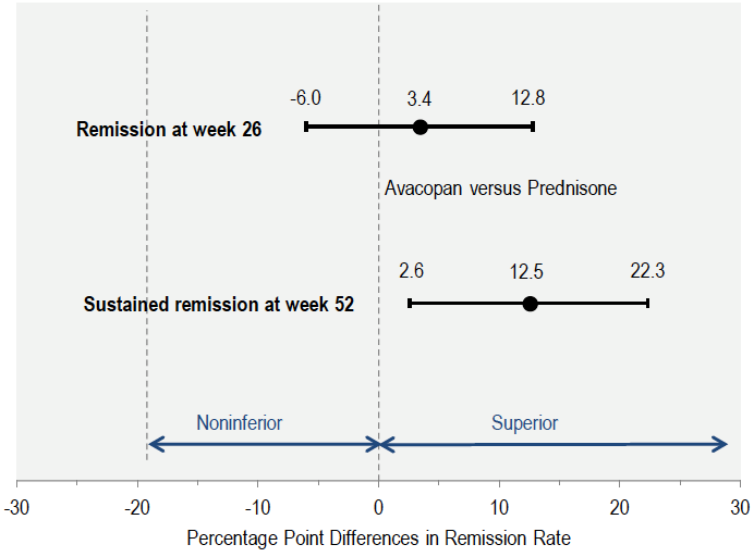
Jayne, NEJM, 2021

Primary endpoints

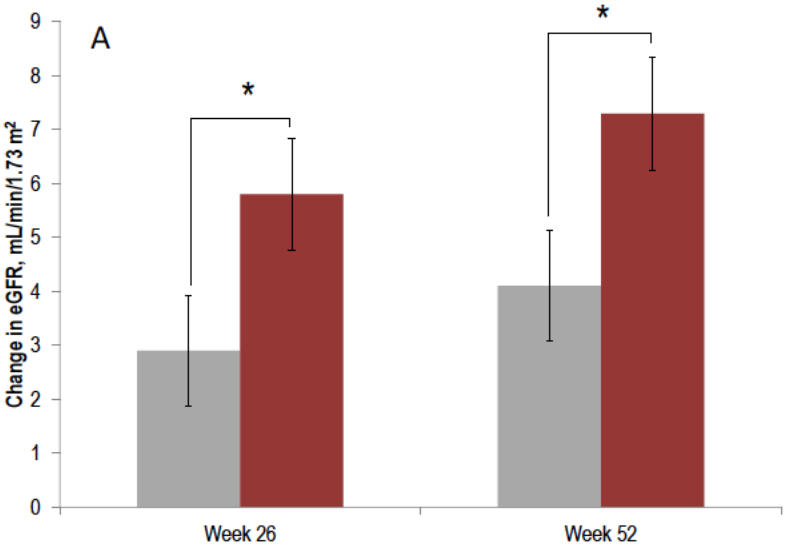
End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖

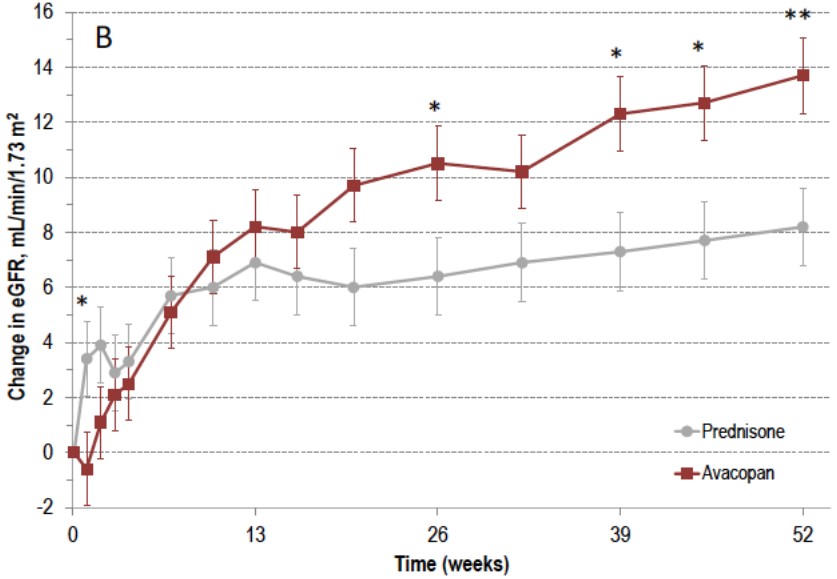


Screening period: mean prednisone dose of 907 mg in the avacopan arm vs. 978 mg in the prednisone arm
Study period: mean prednisone dose of 1676 mg in the avacopan arm vs. 3847 mg in the prednisone arm



Evolution of eGFR at 6 and 12 months

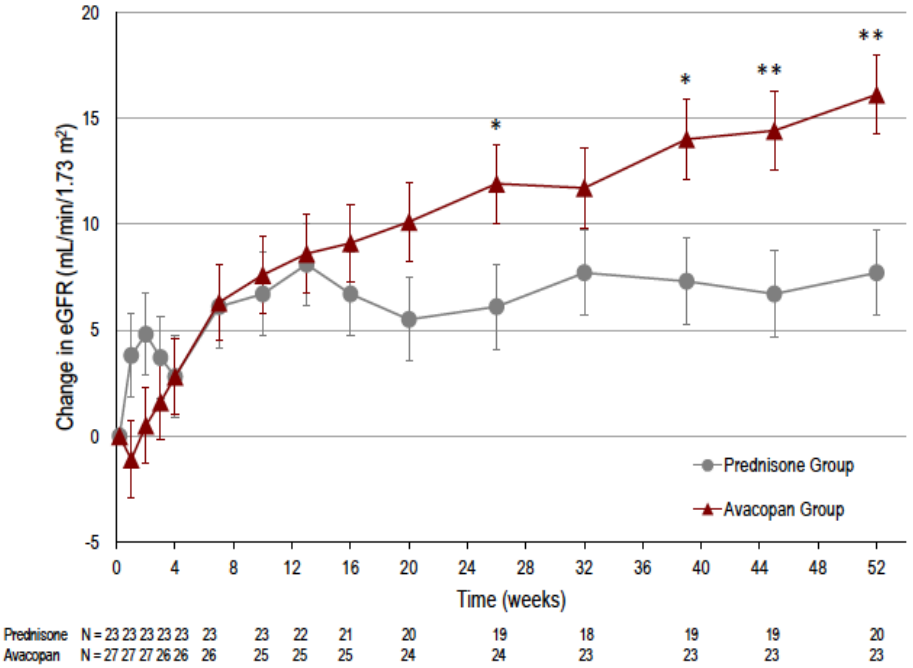




Subgroup of most severe patients

27/166 (16%) in the avacopan group and 23/164 (14%) in the prednisone group had an initial eGFR <20 ml/min/1.73 m2

At week 52, mean increase in eGFR was 16.1 and 7.7 ml/min/1.73 m2 in the avacopan and prednisone groups, respectively (P=0.003)



Cortazar, KI Reports, 2023

Recommendations for the use of avacopan

EULAR 2022

Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA/MPA as part of a **strategy to substantially reduce glucocorticoid exposure**

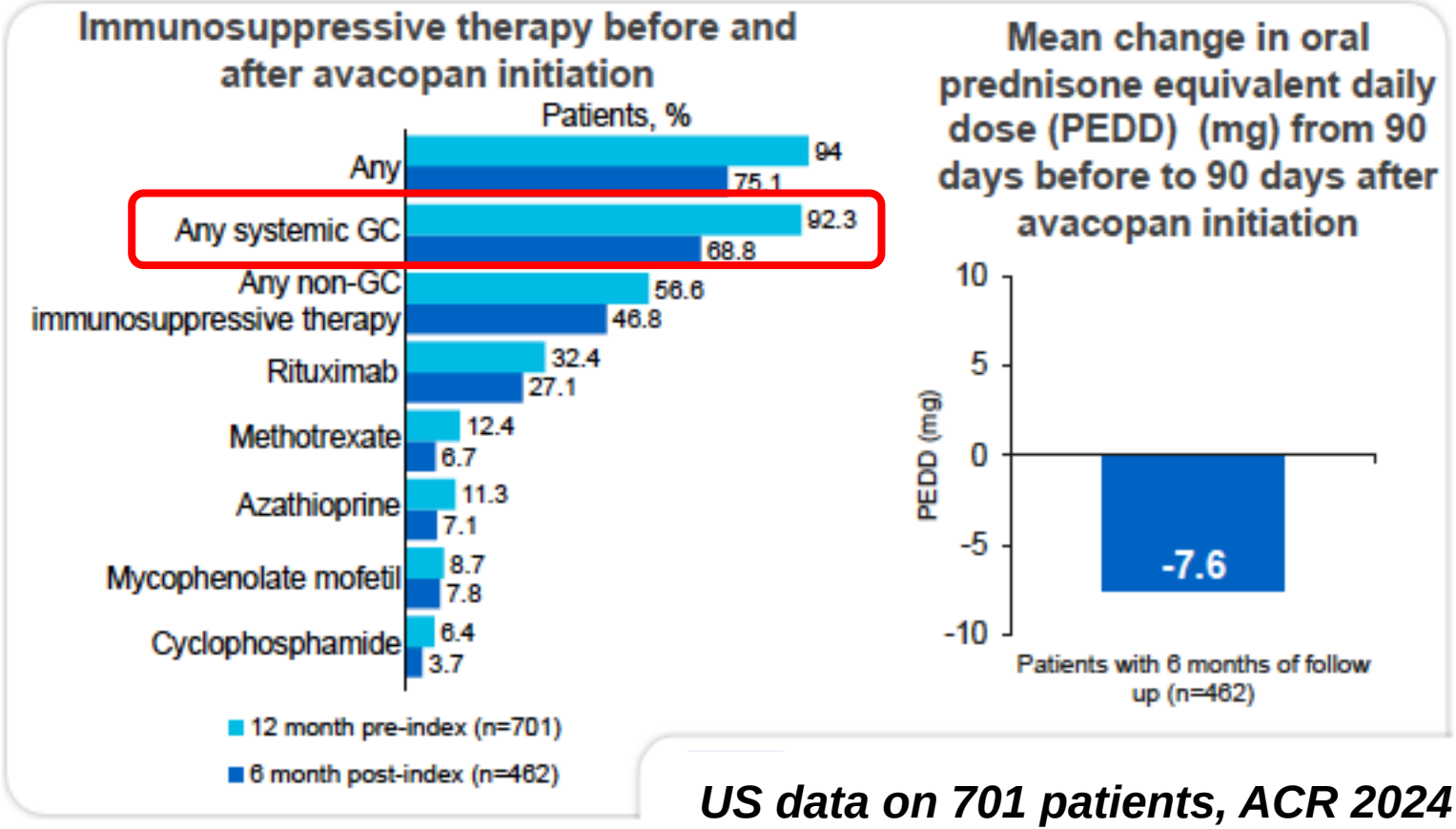
KDIGO 2024

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

Hellmich, Ann Rheum Dis, 2023

Floege, Kindey Int, 2024

Proper use of avacopan is still being determined



US data on 701 patients, ACR 2024

French recommendations 2024

Recommendation	**% agreement**	**LoA**
Avacopan can be used in patients with GPA or PAM treated with RTX or CYC to achieve **rapid GCs weaning**	100	8,9 ± 1,1
The efficacy of avacopan has not been evaluated in the most severe forms (DAH requiring mechanical ventilation or renal impairment with eGFR <15 ml/min/1.73m2)	98,2	9,4 ± 1,2
Avacopan should be prescribed at a **dosage of 30 mg twice daily for one year**. If avacopan is initially combined with GCs, it is suggested that prednisone be rapidly reduced to 20 mg/d, with the aim of weaning patients off the drug within 4 weeks	96,4	9,3 ± 1,0

What are the therapeutic issues in practice?

1. What dosage of glucocorticoids?
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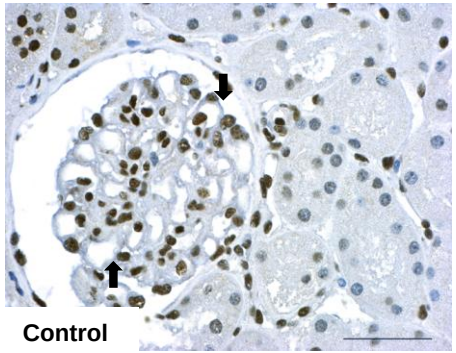
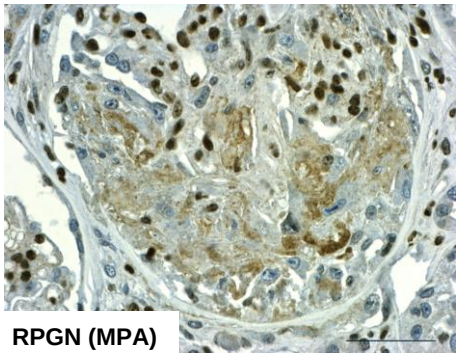
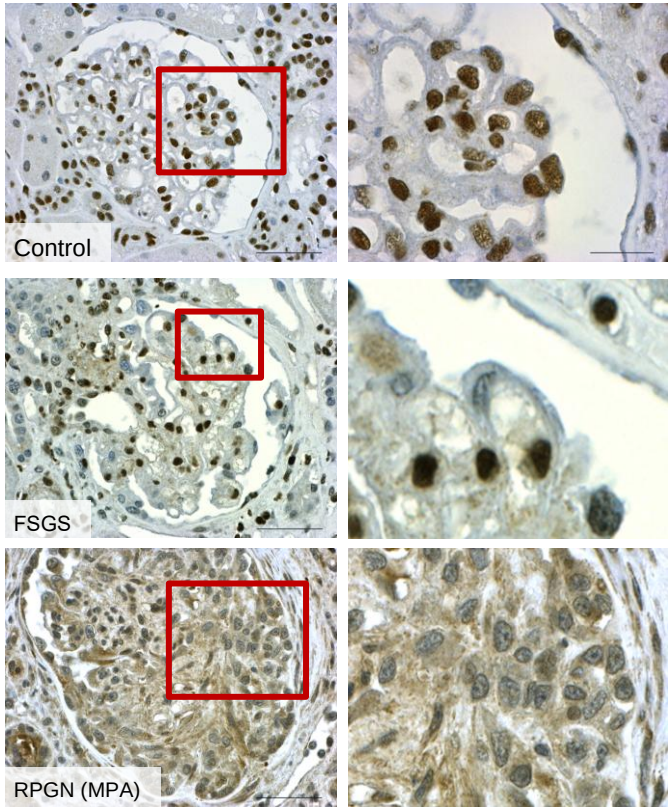
PPARγ expression in glomerular diseases

Healthy glomerular epithelial cells constitutively express PPARγ



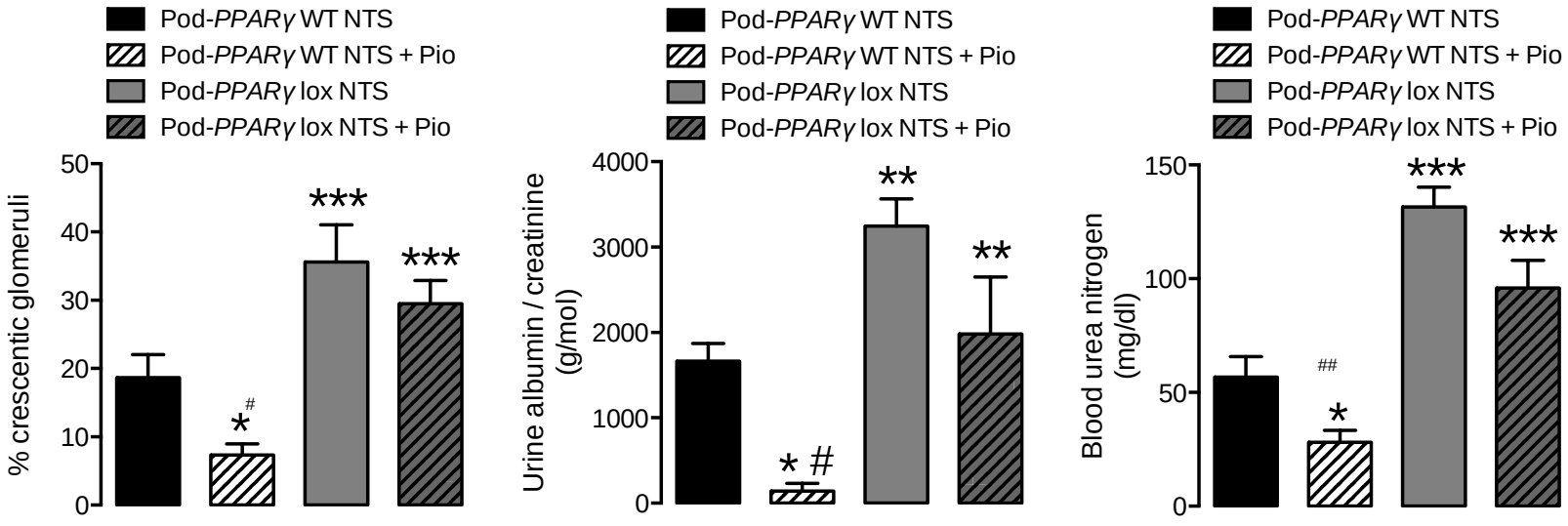




The nuclear PPARγ expression is lost in AAV-related crescentic RPGN

Henique, JASN, 2016

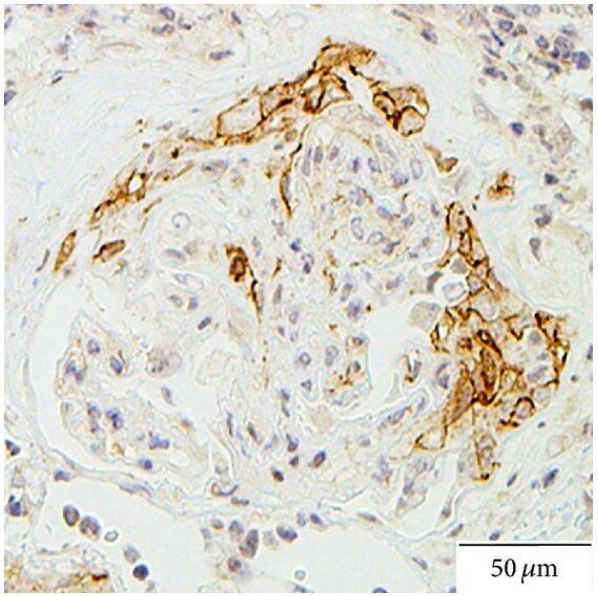
Podocyte deficiency of PPARγ worsens RPGN and pioglitazone improves renal damage

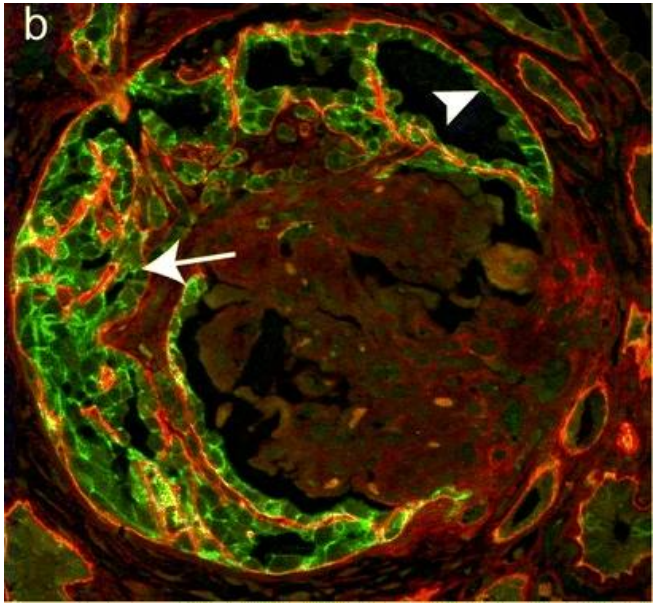


Academic RCT in France
A Trial to Evaluate the Efficacy of Pioglitazone to Promote Renal Tolerance in AAV (RENATO trial)
NCT05946564

Henique, JASN, 2016

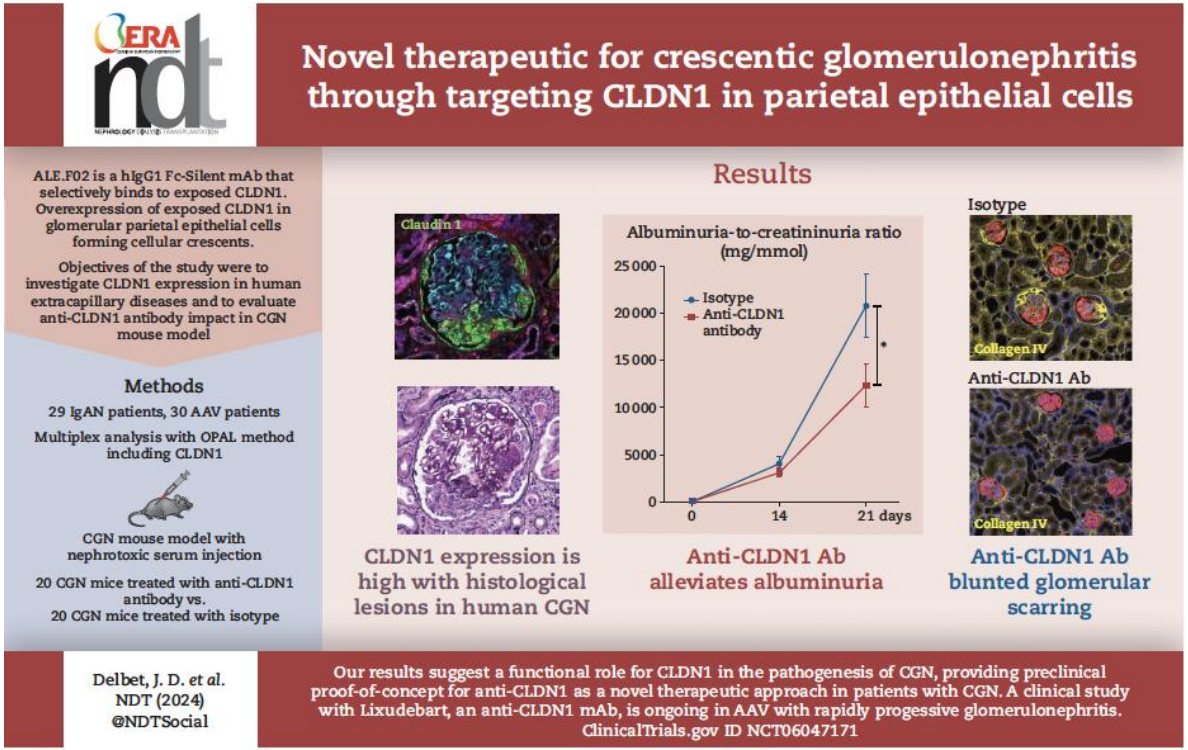
Claudin-1 is expressed by activated glomerular parietal epithelial cells in AAV-related RPGN





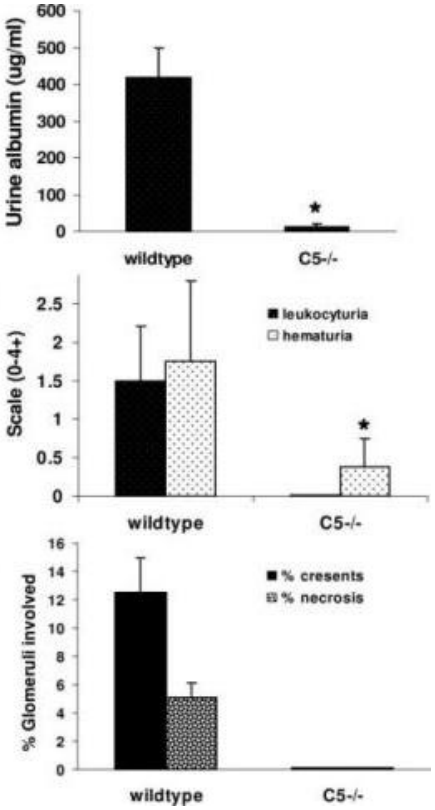
Miesen, Cell Tissue Research, 2017

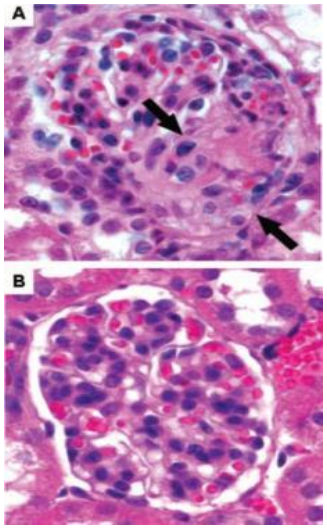
Claudin-1 is a potential target for AAV-related crescentic RPGN



RCT RENAL-F02 (Lixudebart, anti-claudin-1 mAb) Alentis Therapeutics NCT06047171

Inhibition of the alternative complement pathway activation





Wild-type mice (ou C4-/-)

C5-/- mice (ou FB-/-)

Release of complement-activating factors by ANCA-activated neutrophils

CLNP023R12201 Trial
Laboratoire Novartis

Xiao, Am J Pathol, 2007

Maintenance therapy

Rituximab
500 mg/6 months

RTX administration consists of a 500 mg infusion every 6 months (4 infusions over 18 months)

Extension of RTX treatment beyond 18 months may be discussed on a case-by-case basis, depending on the patient's profile, benefit/risk balance and preference

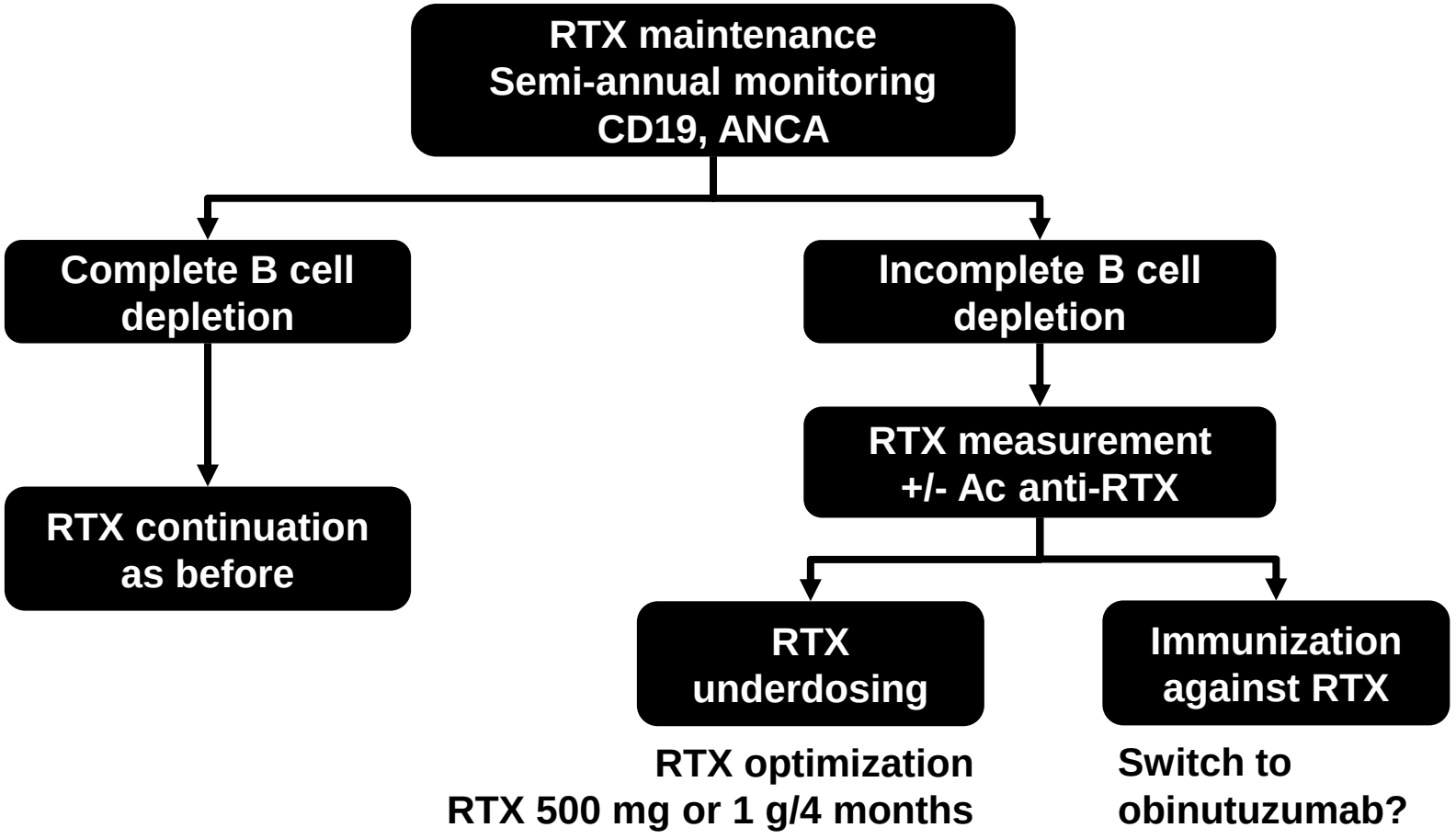
Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide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

French recommendations 2024

Maintenance treatment modalities

Recommendation	**% agreement**	**LoA**
RTX should be used as a remission maintenance treatment for systemic GPA and severe MPA	100	9,9 ± 0,4
The RTX maintenance regimen consists of an IV infusion of 500 mg every 6 months (4 infusions over 18 months)	100	9,6 ± 1,1
Extending RTX treatment beyond 18 months can be discussed on a case-by-case basis, depending on the patient's profile, benefit/risk balance and preference.	100	9,5 ± 1,0

What to do in the event of poor B depletion?



Take home messages

Major reduction in cumulative dose of induction GCs in latest therapeutic trials

Place of plasma exchange still unclear, but repositioned in RPGN

Avacopan represents an important therapeutic option in this quest for maximum reduction of GC therapy

Therapeutic perspectives aimed at reducing renal damage

Rituximab maintenance for 18 months or longer

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