# Avacopan en vie réelle au cours des vascularites à ANCA

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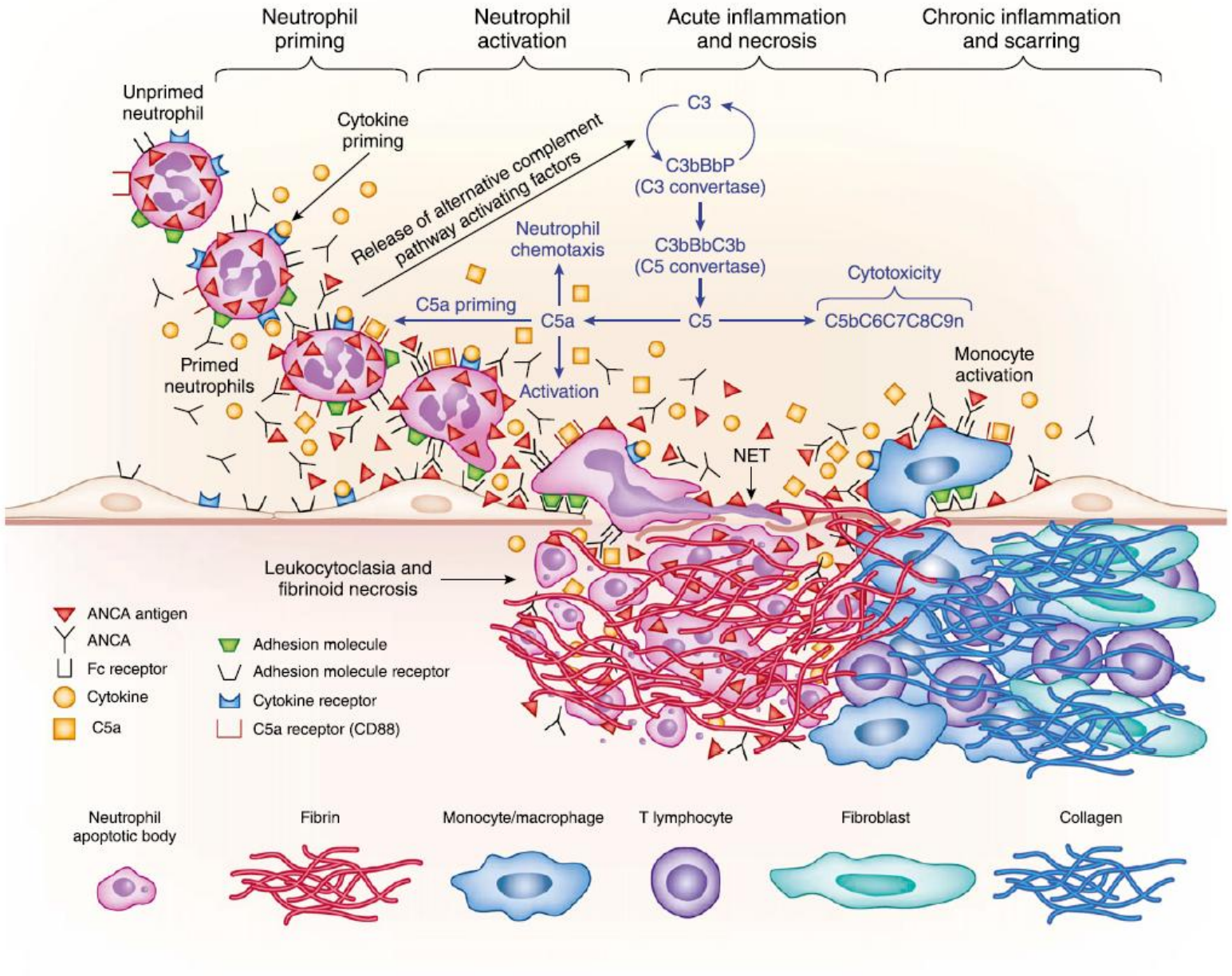
# Conflicts of interest

- Consulting – SAB : Novartis, Abionyx Pharma, CSL-Vifor
- Boards: GSK, Alexion, AZ, CSL-VIfor

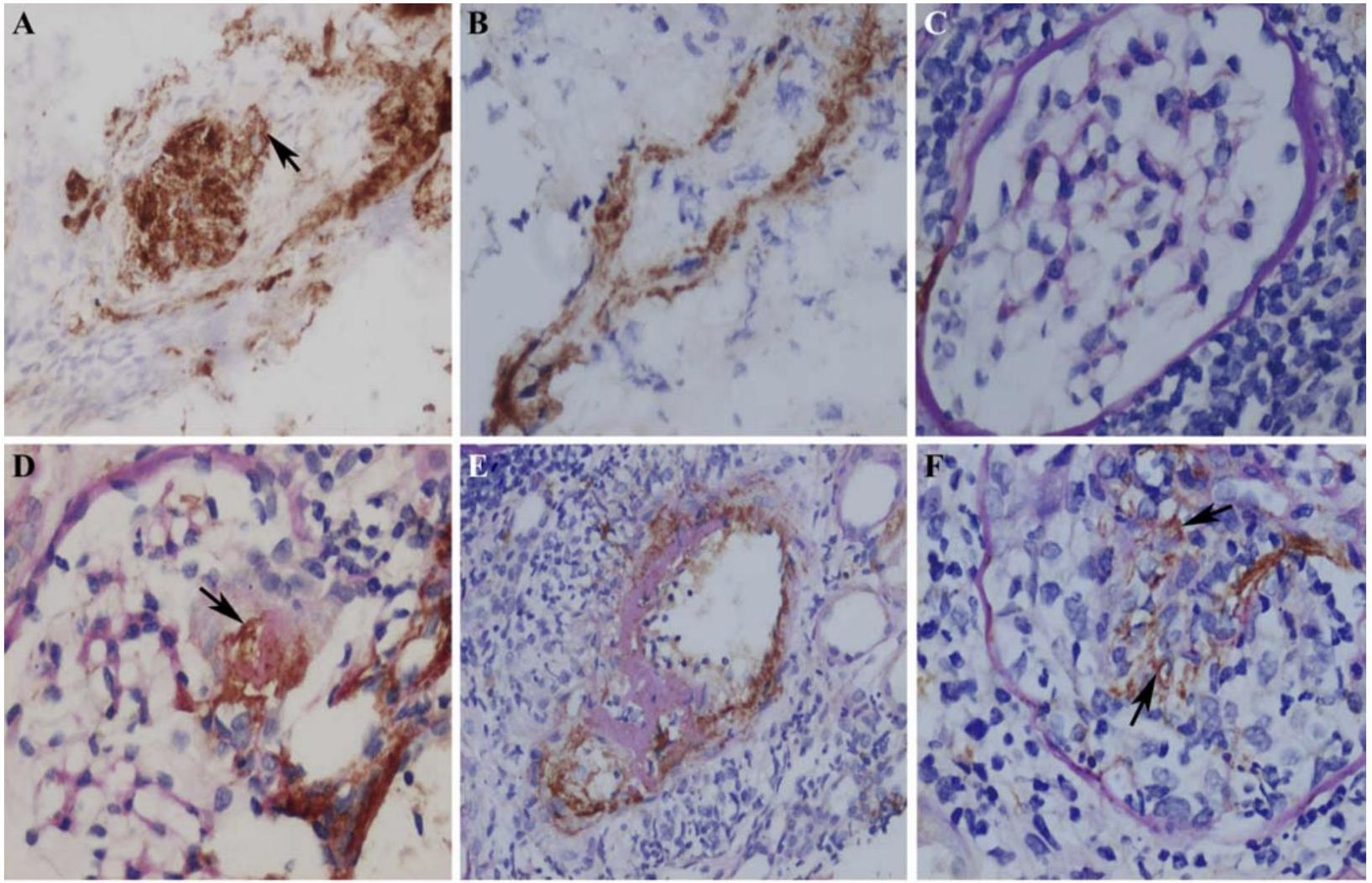
# What are the unmet needs in AAV?

- To prevent or reduce short and long term glucocorticoids toxicity
- To improve end-organ outcomes
    - Prevent  end-stage kidney disease
    - Optimize the renal response (final eGFR)
- To reduce chronic activity of AAV
- To control refractory AAV

# Why targeting the complement pathway in AAV?

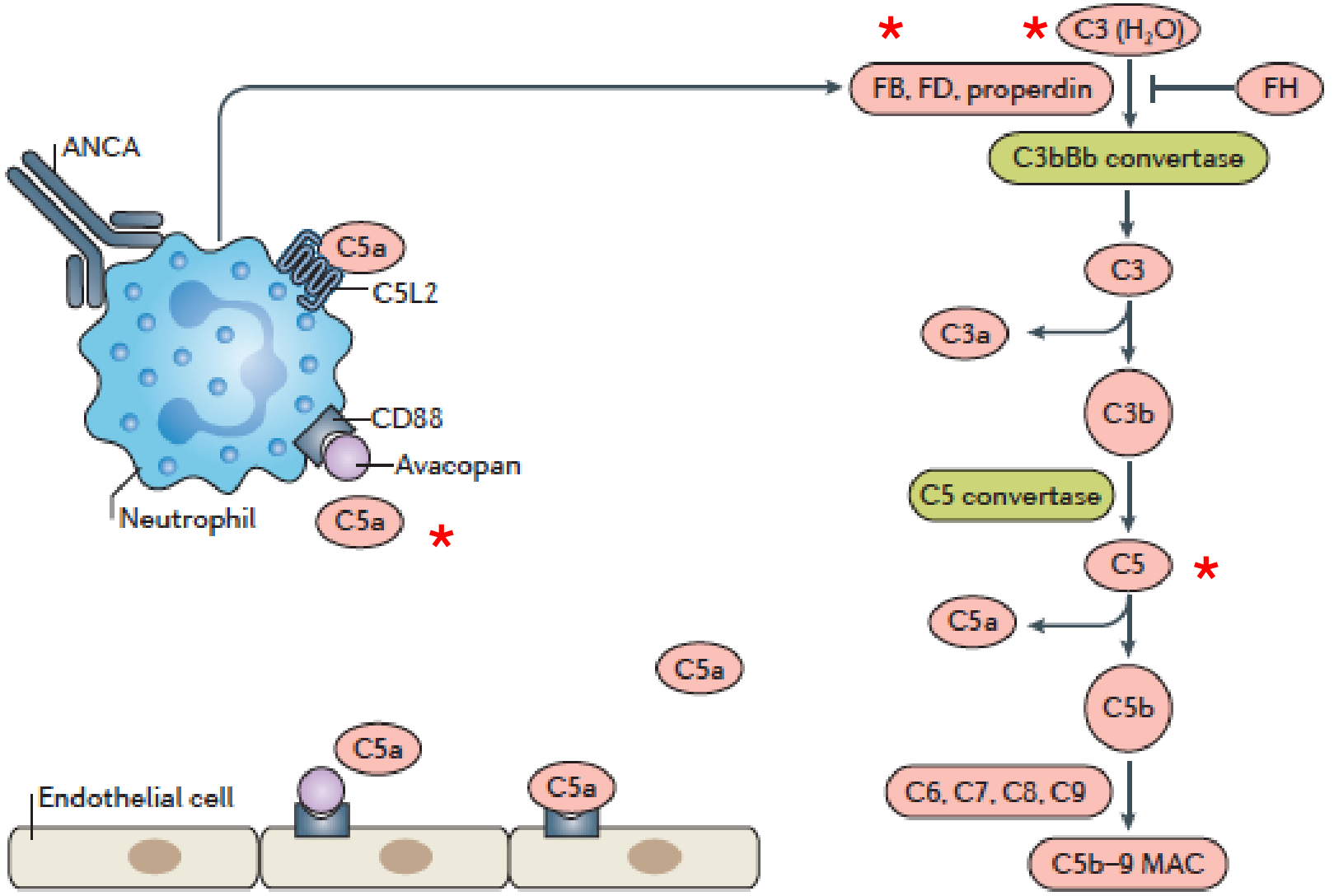


# Alternative complement pathway in ANCA - RPGN




*Xing et al. J Clin Immunol 2009*

# Why targeting the complement pathway in AAV?



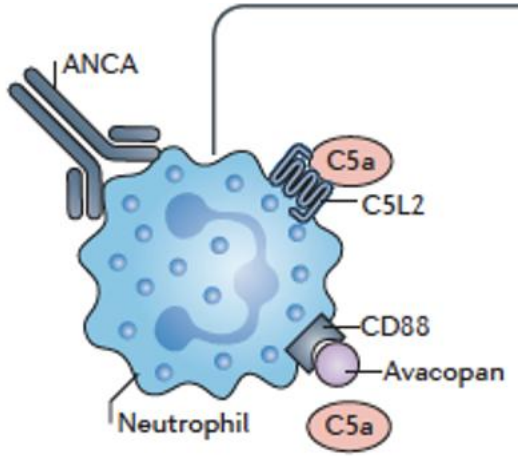

*Gou et al. Kidney Int 2013*

# Pre-clinical proof of concept for C5a receptor inhibition

- **Activation of the alternative complement pathway** was demonstrated in animal models of AAV and in humans
    - High circulating levels of Factor B, C3a, C5a and sC5b9

- Neutrophils and Monocytes are highly **activated and amplified** by C5a-C5aR1 axis but **inhibited** by the C5a-C5L2 axis

- **Gene invalidation of**
    - C5aR1 protects mice from MPO-RPGN
    - C5L2 sensitizes mice from MPO-RPGN



# Avacopan - clinical evidences

## Phase 2 - CLEAR

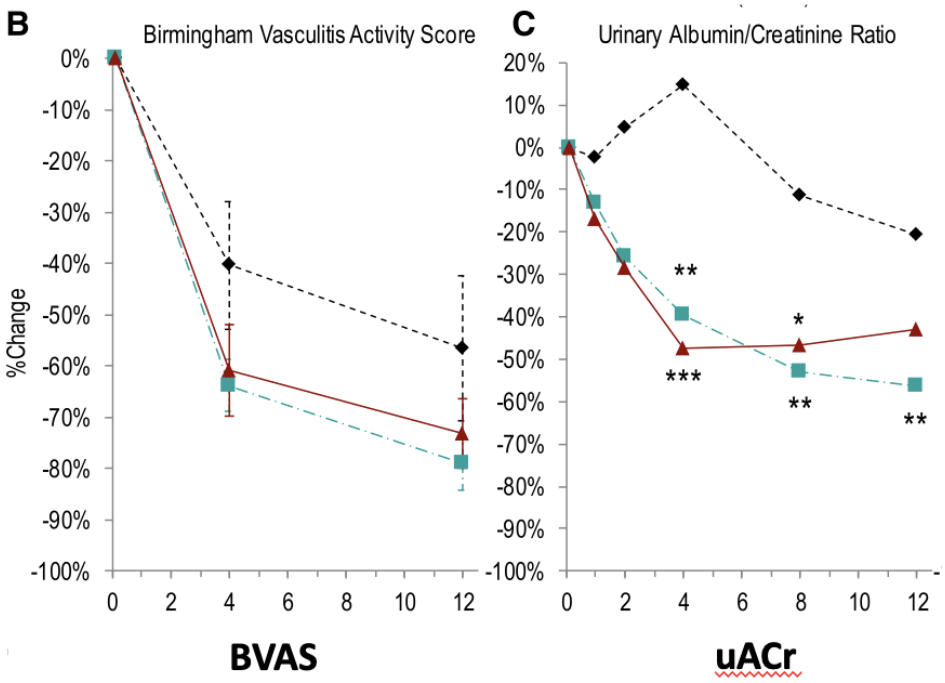
- 12 weeks
- N = 67
- AAV – RPGN
- RTX or CYC plus
    - GCs
    - GCs low dose + avacopan
    - avacopan
- Renal endpoint & BVAS

## Phase 3 - ADVOCATE

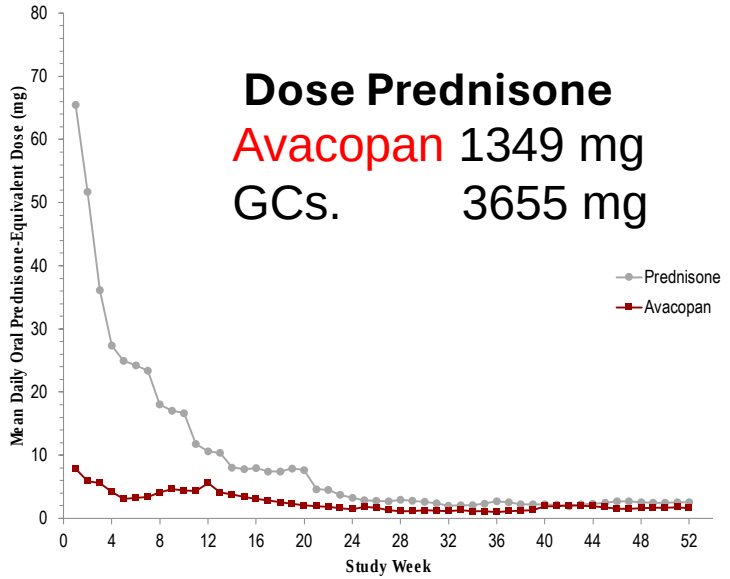
- 52 weeks
- N = 331
- AAV – eGFR 15 – 60 mL/min
- RTX or CYC plus
    - GCs low dose
    - Avacopan (stop GCs <4wk)
    - No standard maintenance
- Renal endpoint & BVAS & safety

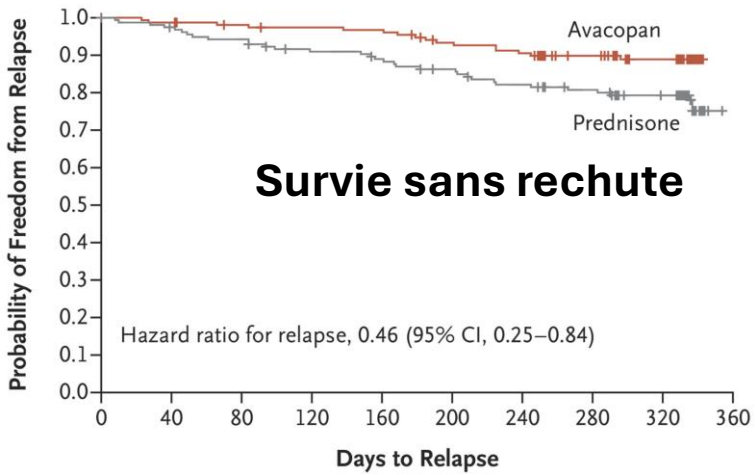
# Avacopan - clinical evidences

## Phase 2 - CLEAR



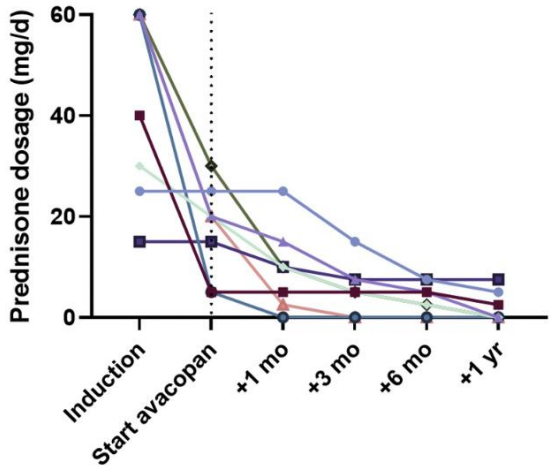

## Phase 3 - ADVOCATE

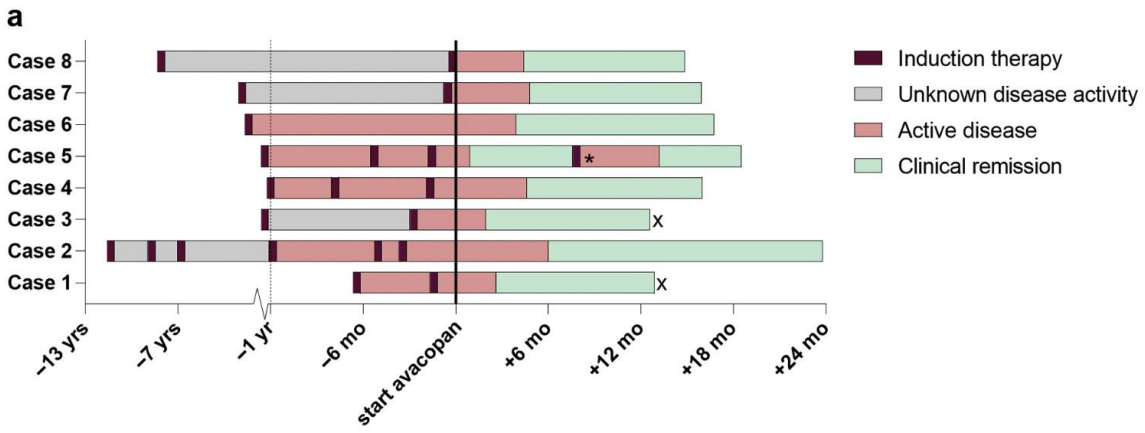


# Avacopan - clinical evidences

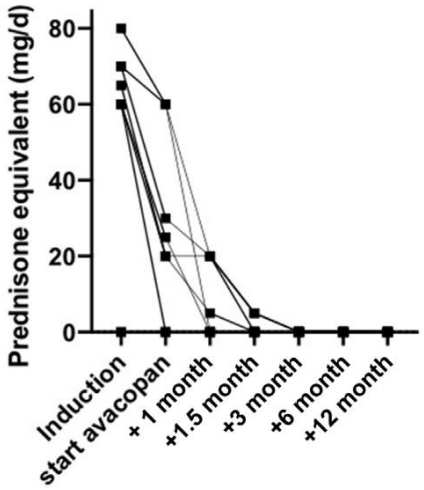
## Difficult to treat patients (Nth). N = 8

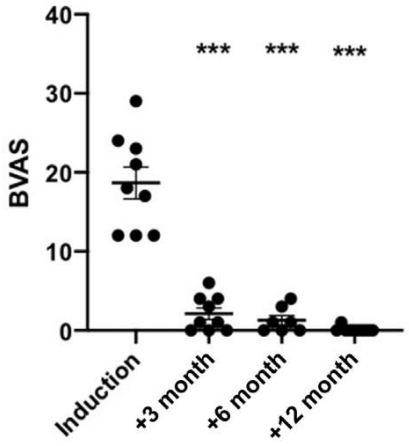



*Van Leeuwen et al. KI reports 2023*

## Real life – frontline (Fr.) N=9

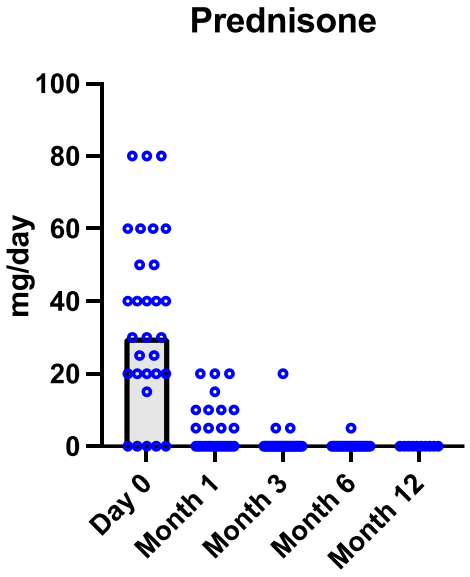


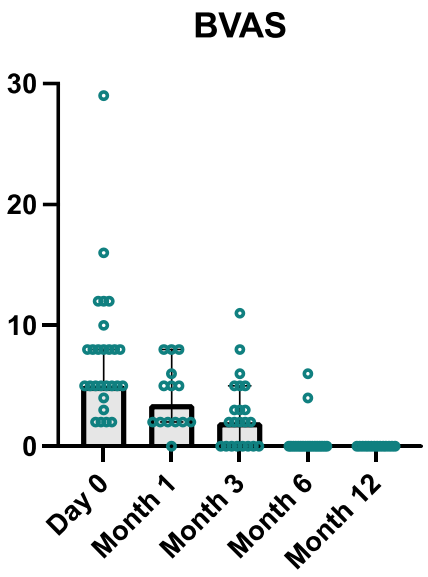



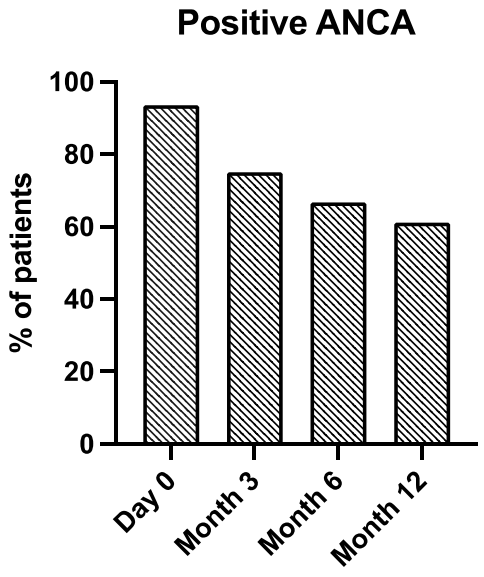

*Gabilan et al. KI reports 2023*

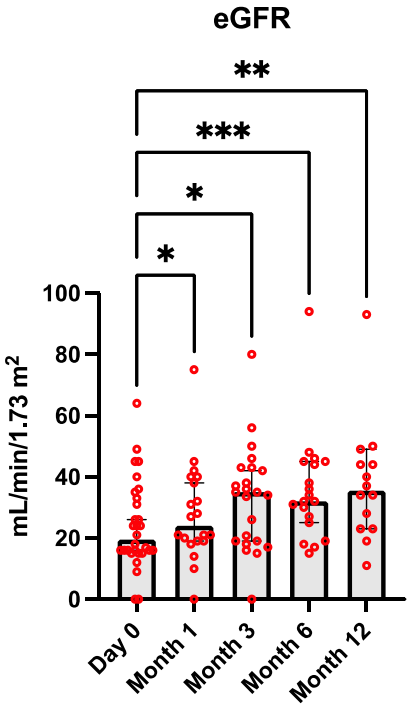
# Avacopan - clinical evidences

## Early access program – frontline (Fr.) N=31




| | |
|---|---|
| **GC withdrawal < 3 months** | 90% |
| **AAV control** | 97% |
| **Relapse** | 6% (n=2) |
| **Avacopan withdrawal** | 20% |

**Cumulative GCs dose after avacopan** 700 mg

*Gabilan et al. Rheumatology 2024*

# Avacopan - clinical evidences

## Real life – frontline (US.) N=92

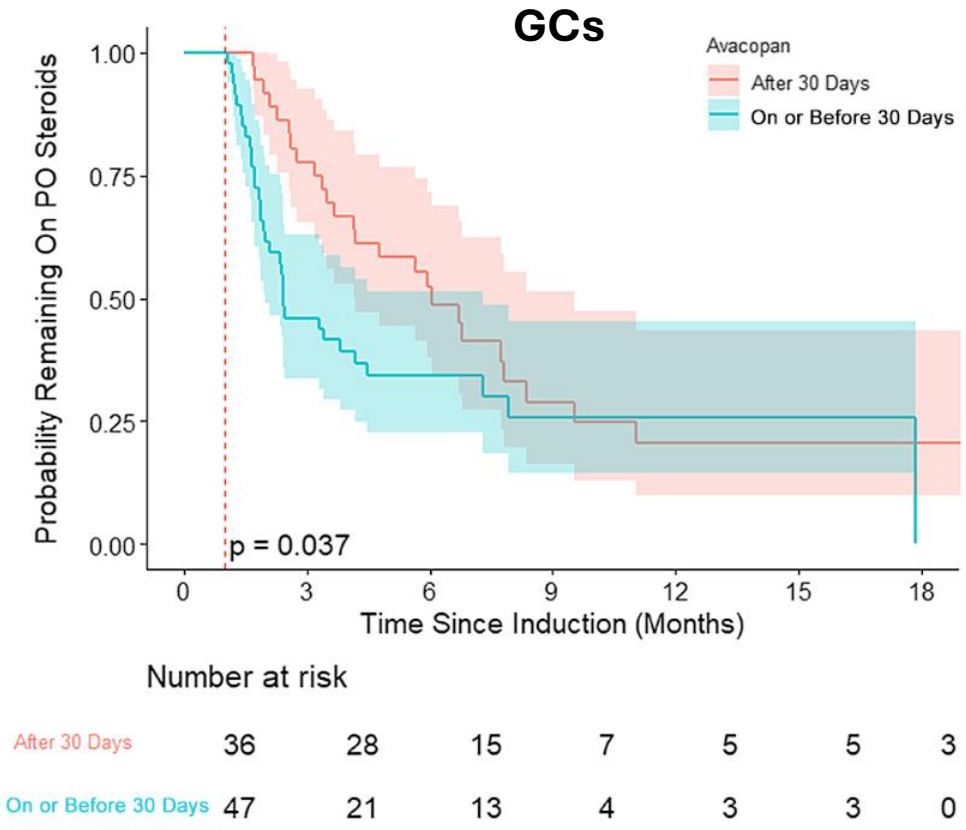
**eGFR<15mL/min** 23%
**HD** 10%

| | |
|---|---|
| Primary outcome | |
| Clinical remission at wk 26 | 61/68 (90%) |
| Clinical remission at wk 52 | 32/38 (84%) |
| Secondary outcomes | |
| Change in eGFR (baseline to wk 26 ($n = 48$) | +12.2 (25.4) |
| Change in eGFR (baseline to wk 52) ($n = 22$) | +19.8 (23.1) |
| Duration of hematuria, wk | 14.4 (9.1–20.6) |
| Resolution of hematuria | 42 (68%) |
| Proteinuria at wk 26, mg/g Cr | 454 (154–1163) |
| Proteinuria at wk 52, mg/g Cr | 290 (143–742) |
| Proteinuria, nadir, mg/g Cr | 397 (150–896) |
| Time to nadir proteinuria, wk | 15.4 (8.6–29.2) |
| Clinical relapse | 3 (3%) |
| Infections requiring hospitalization | 12 (13%) |
| Dialysis dependence[a] | 6 (9%) |
| Death | 4 (4%) |

*Zonozi et al. KI reports 2023*

# Avacopan - clinical evidences

## Real life – frontline (US.) N=92



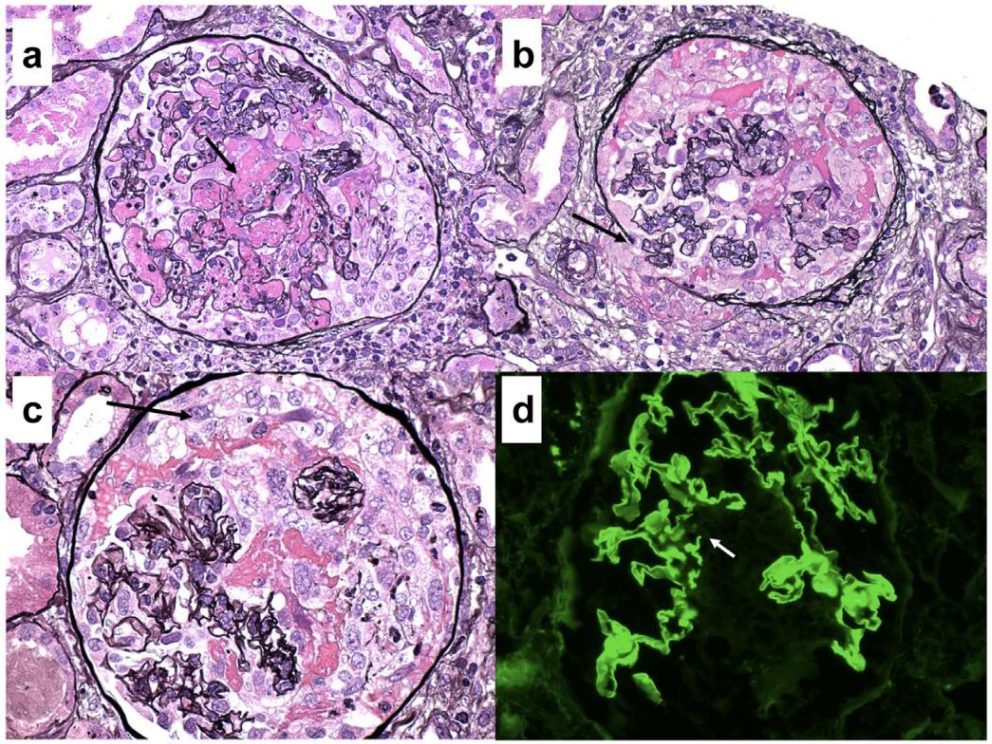

**RTX** 48%
**RTC+CYCld** 46%
**Mean GC** (Wk 52). 2.2 grams

Reduction of GCs doses

*Zonozi et al. KI reports 2023*

# Avacopan for severe ANCA - RPGN

| Patient | Cr at presentation (Day 0) | Cr at HD initiation (Day) | Day of steroid initiation | Day of avacopan initiation | Prednisone (mg) at avacopan initiation | Remission (BVAS = 0) | Resolution of hematuria (Day) | Serologic remission (Day) | Day of last HD | Cr at last follow-up (Day) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2.3 | 4.9 (10) | 4 | 15 | 40 | Yes | 155 | Y (113) | 125 | 2.2 (265) |
| 2 | 5.54 | 5.6 (2) | 2 | 49 | 15 | Yes | 150 | Y (68) | 192 | 2.0 (224) |
| 3 | 4.8 | 6.9 (4) | 1 | 9 | 60 | Yes | 124 | Y (60) | 14 | 1.4 (269) |



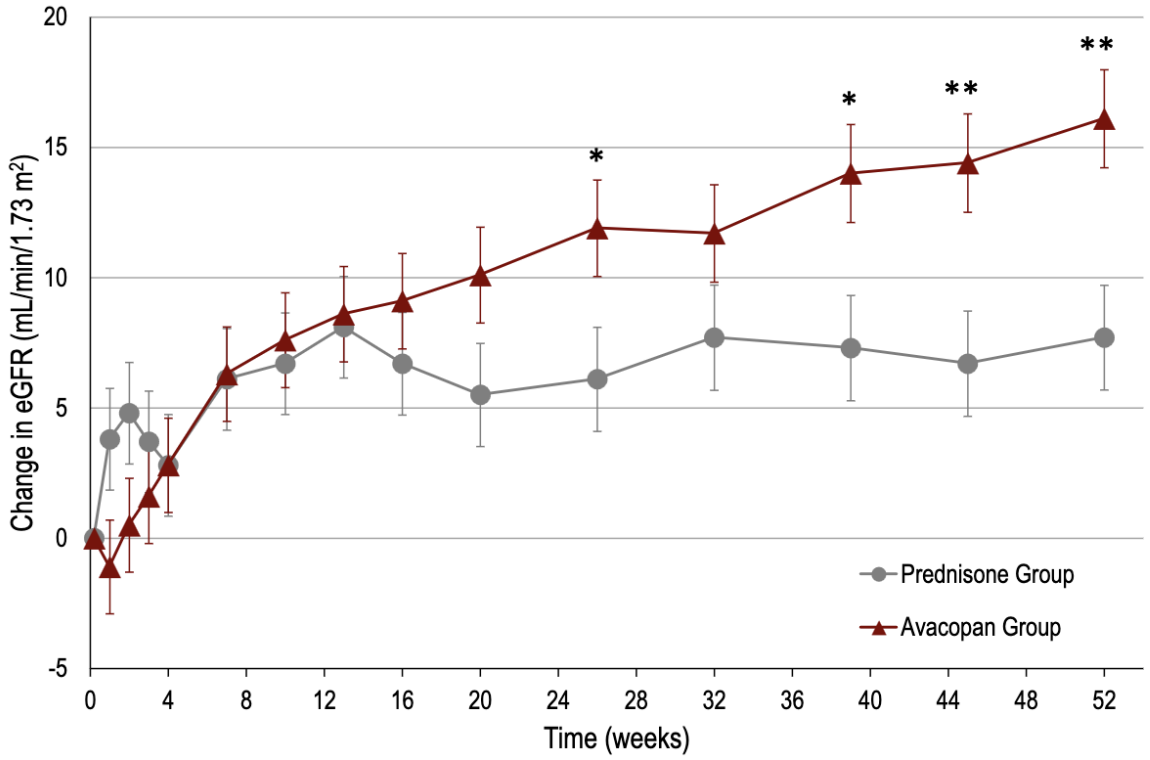

- No warnings about tolerance (10-15 cases)
- ANCA and anti-GBM positivity is not a contraindication

*Gabilan et al. KI reports 2022*
*Cortazar et al. KI reports 2023*

# ADVOCATE – severe forms

**50 patients**

DFGe < 20 mL/min/1.73m2 à l'admission




**eGFR**

| Event | Prednisone group (*N* = 23) | Avacopan group (*N* = 27) |
|---|---|---|
| Any adverse event, *n* (%) | 23 (100%) | 27 (100%) |
| Number of events | 405 | 332 |
| Any serious adverse event,[a] *n* (%) | 16 (69.6%) | 13 (48.1%) |
| Number of events | 45 | 25 |
| Any infection, *n* (%) | 21 (91.3%) | 21 (77.8%) |
| Number of events | 63 | 41 |
| Any serious infection, *n* (%) | 7 (30.4%) | 6 (22.2%) |
| Number of events | 10 | 6 |

**Safety**

*Cortazar et al. KI reports 2023*

# Avacopan for severe ANCA - RPGN

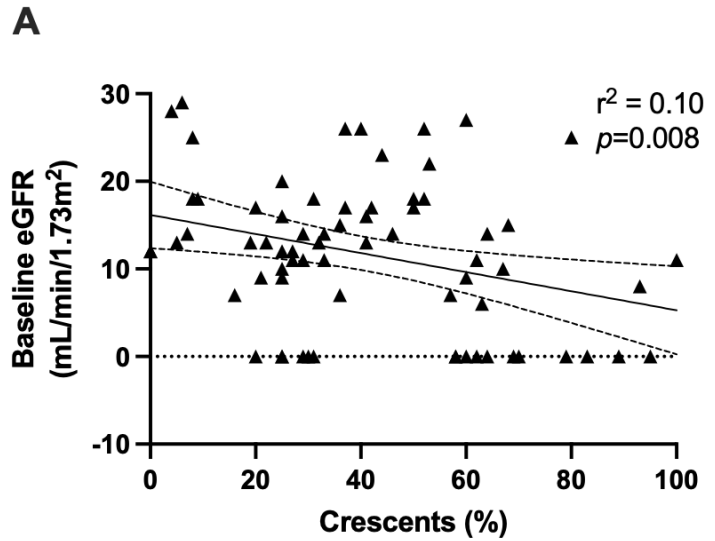
**70 AAV patients (avacopan n=20) with**

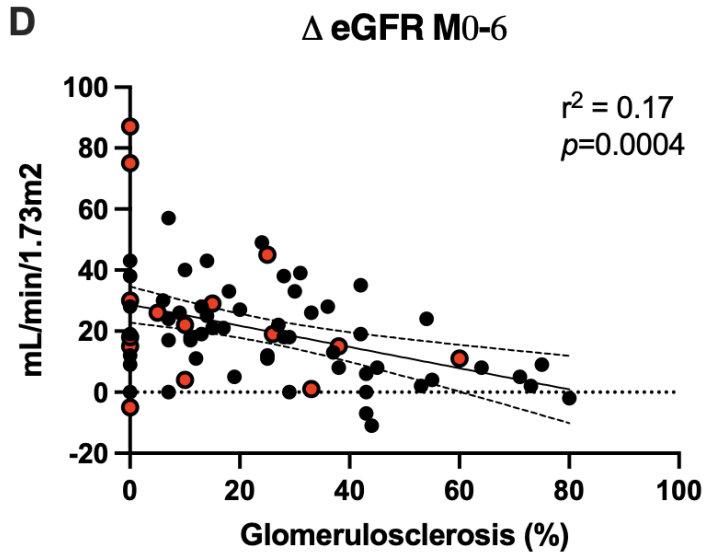
- eGFR 0 – 30 mL/min/1.73m2 at diagnosis
- 6 months of follow-up
- kidney biopsy at diagnosis

**At baseline**

- Number of crescentic glomeruli correlated with eGFR at the time of the biopsy but not with eGFR gain at M6

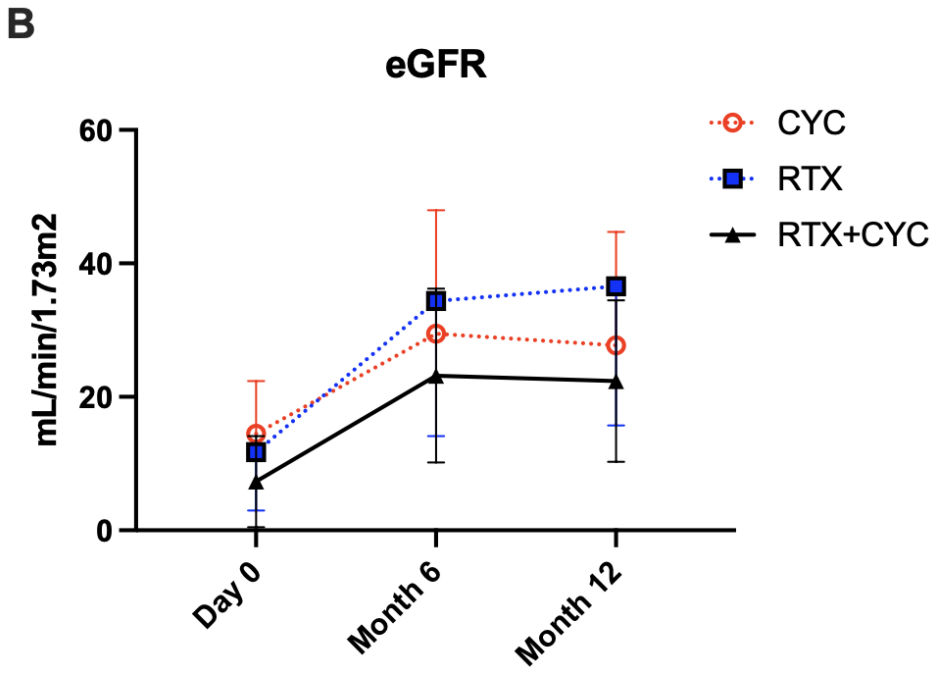
- Glomerulosclerosis inversely correlated with eGFR gain at M 6 but not with eGFR at the time of the biopsy

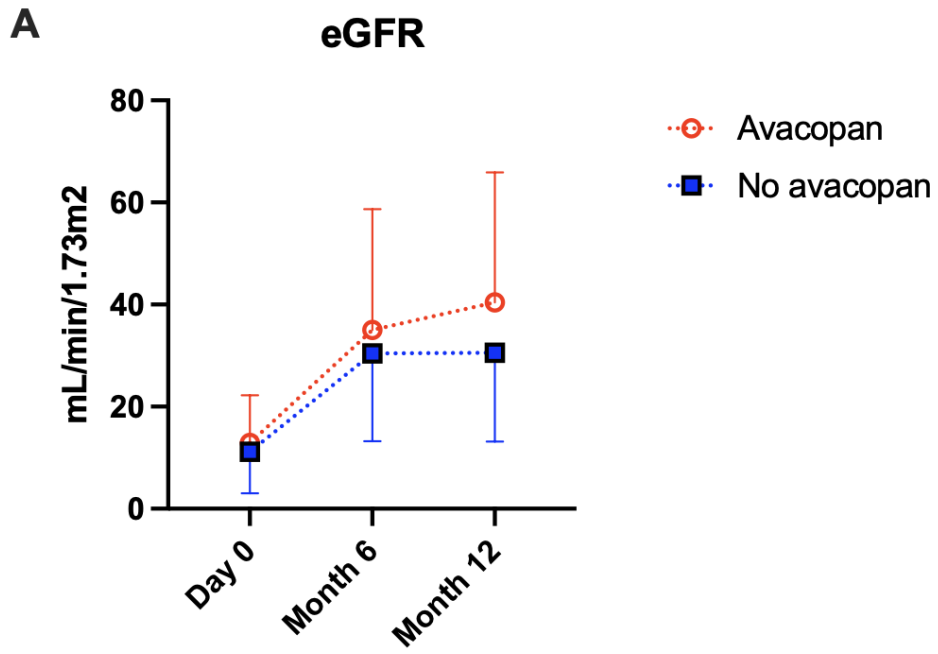



*Faguer et al. In revision*

# Avacopan for severe ANCA - RPGN




| Cortisone HD N = 50 | Avacopan N = 20 |
|---|---|
| RTX 54%<br>CYC 30%<br>RTX+CYC 16% | RTX 90%<br>RTX+CYC 10% |
| Prednisone 15±12 months | Prednisone 1.9±1.8 months |
| EP 50% | EP 50% |

- Kidney outcomes are similar in patients receiving GCs (high-doses) and avacopan-based IS regimen
- Early avacopan withdrawal (15 – 20%) : liver cholestasis

*Faguer et al. In revision*

# How and when to prescribe avacopan?

## Approval / Reimbursement inFrance (August 2023)

‘**Active and severe AAV in combination with RTX or CYC**’

GCs « according to clinical conditions »

## French recommendations (PNDS 2025)

Contraindication to high-dose GCs (cardiovascular diseases, osteoporosis, psychiatric conditions)

**Modalities**

30 mg b.i.d for 12 months

Monitor liver tests

**Prescription with uncertainty**

- Severe RPGN (eGFR 15-30 mL/min): avacopan first?
- Dose and duration of GCs?
- Granulomatous manifestations
- Most severe forms of IAH & RPGN (eGFR <15mL/min)

# How to stop avacopan?

***Most patients***

- Stop at month 12 (no gradual decrease – RITUXIMAB maintenance)

***Early stop***

- *Patient « wish »*
  - M6-12 and vasculitis remission : closed monitoring (RITUXIMAB maintenance)
- *Adverse event*
  - Vasculitis remission : closed monitoring or low-dose GCs if early withdrawal (RITUXIMAB maintenance)
- *AAV relapse*
  - Resume GCs (regimen according to response) – new induction in severe cases

***Hepatitis***

- If ASAT/ALAT > 5N, immediate withdrawal and search for alternative diagnosis
- If ASAT/ALAT >8N, definitive withdrawal
- Incidence 4 -15% – normalization after withdrawal (Japan 41% - 'vanishing bile duct syndrome')

***Specific infections ? (candidiasis – fungal infections)***

- Stop if uncontrolled infection, remission of the vasculitis, and potential alternatives

*Jayne et al. NEJM 2021; Gabilan et al. KI Report 2024; Mori et al. Rheumatology 2025*

# In summary

- AVACOPAN is (can be) now routinely used in patients with AAV, especially in those with contraindications to high-dose GCs
- AVACOPAN allows to dramatically reduce the exposure to GCs and can help improve organ prognosis
- There are still unmet needs (duration, dose, most severe forms)
- The development of new therapies targeting immune cells (B lymphocytes or plasma cells), complement pathways, crescent formation… is transforming the AAV treatment landscape. New multitargets and individualized combination will emerge in coming years.

# Acknowledgments

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