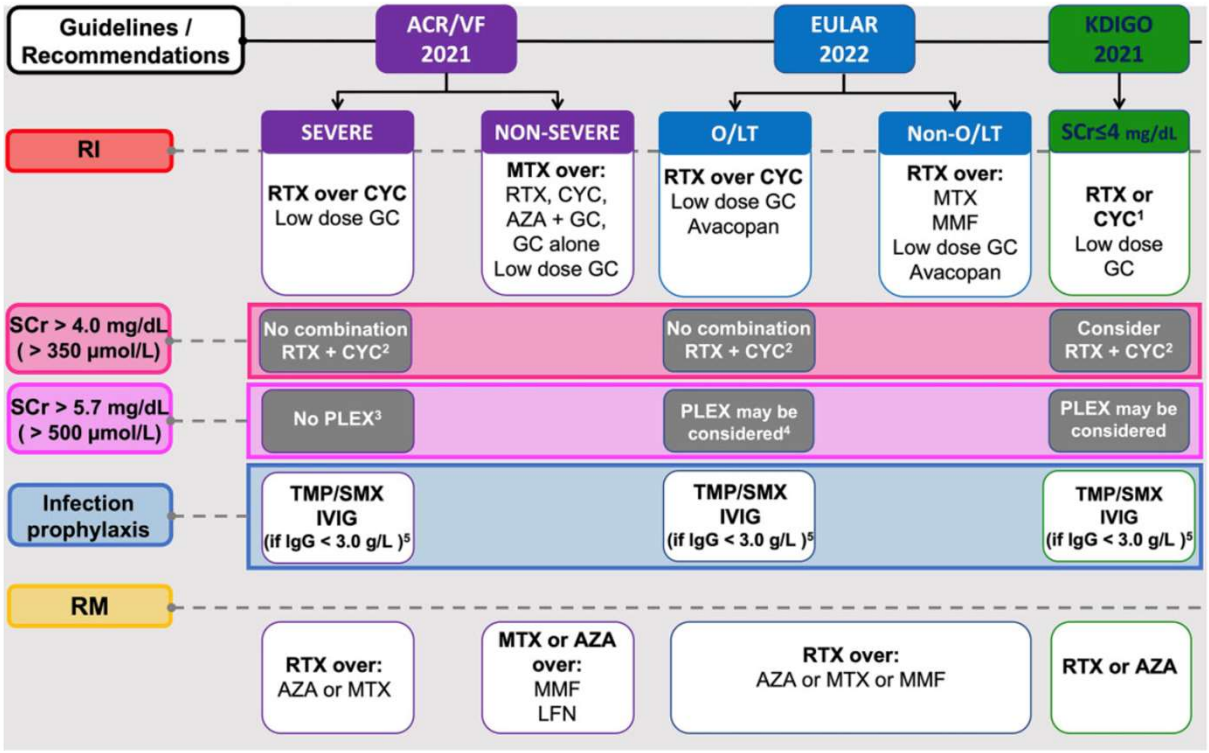
Avacopan added to standard-of-care therapy in ANCA-associated vasculitis with severe kidney involvement: a randomized, placebo-controlled, double-blinded multicenter superiority study

REVERSE

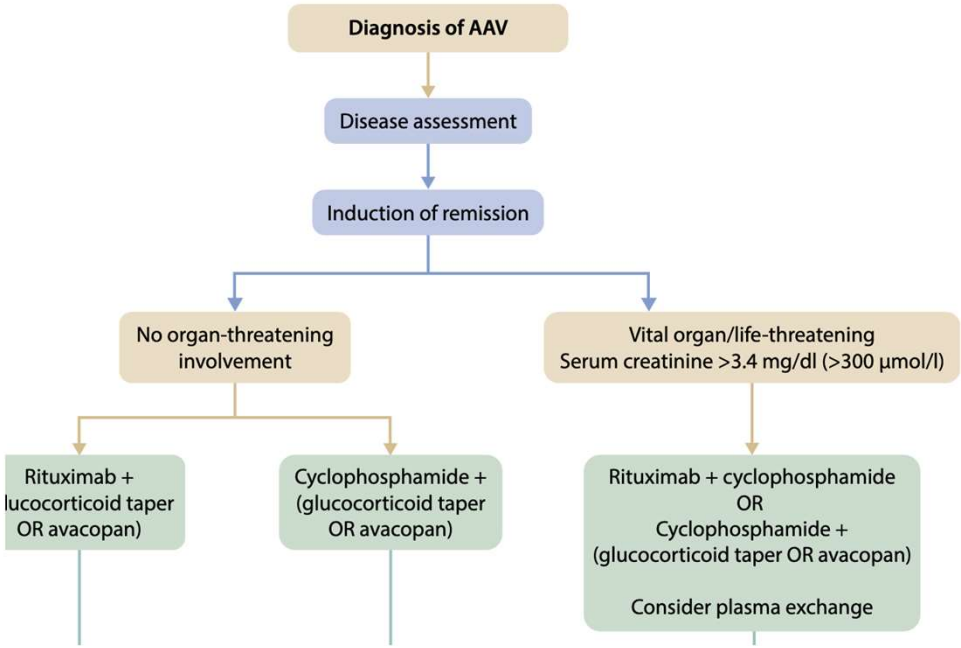
PHRC 2024 (…?)

VAA sévère – recommandation « d'experts »

Casal-Moura et al. NDT 2023



KDIGO 2024



Données de vraie vie (FR, US): arrêt GCs 5-6 semaines mais arrêt de l'avacopan dans 20-25% des cas (hépatites, rechute, VAA réfractaire). US: dose GCs 1.6 g à M6, 2.2 g à M12 (et RTX+CYC dans 50% des cas)

Avacopan – anti-C5aR

HAUTE AUTORITÉ DE SANTÉ

GPA ou PAM
ACTIVE et SEVERE

La dose recommandée de Tavneos est de 30 mg (3 gélules de 10 mg chacune) par voie orale deux fois par jour, matin et soir, avec de la nourriture.

Tavneos doit être administré en association avec du rituximab ou du cyclophosphamide comme suit :

- rituximab à raison de 4 doses hebdomadaires par voie intraveineuse ou,
- cyclophosphamide par voie intraveineuse ou orale pendant 13 ou 14 semaines, suivi d'azathioprine ou de mycophénolate mofétil par voie orale et,
- glucocorticoïdes si cliniquement indiqué.

Organ-/life-threatening manifestations[a]	Not organ-/life-threatening manifestations[b]
GN ←	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary hemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	
+ Limb/digit ischemia (ACR/VF)	

- Les formes « sévères » étaient exclues de l'étude ADVOCATE

Jayne et al. ARD 2023

Hypothèse

Plutôt qu'opposer GCs et avacopan, la combinaison de GCs (schéma PEXIVAS low-dose) et d'avacopan au cours des atteintes rénales sévères des VAA pourraient être synergique et améliorer le pronostic rénal des patients ainsi qu'optimiser le contrôle de la vascularite systémique.

Objectifs

Main objective

To demonstrate an improvement in kidney function at week 52 (eGFR ≥ 30 mL/min/1.7m2; i.e. CKD stage 1-3) in patients with severe forms of AAV-associated RPGN (eGFR 0-29 mL/min/1.7m2 at inclusion) when avacopan is added to GCs-based SOC.

Main evaluation criterion

Proportion of patients reaching an estimated glomerular filtration rate ≥30 mL/min/1.7m² (CKD-EPI formula applied to the measure of standardized serum creatinine) at week 52.

Objectifs

Secondary objectives:

- To assess survival in both groups up to week 64
- To assess in both groups the vasculitis activity: Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) at weeks 24, 52 and 64
- To assess in both groups the incidence of treatment-related adverse events
- To assess in both groups the kidney function (eGFR and proteinuria) at weeks 24, 52 and 64
- To assess in both groups the proportion of end-stage kidney disease (chronic dialysis) at weeks 24, 52 and 64
- To assess in both groups the intensity of kidney inflammation (usCD163 and uMCP1; urinary and serum levels of C3a, C5a and factor Bb) at inclusion and at weeks 4, 12, 24 and 52
- Changes in quality of life from baseline to week 64
- To assess the ability of kidney biopsy to predict the renal response to avacopan, in those receiving avacopan (per-protocol analysis)
- Medico- economic analyses
- Biobanking (plasma and urines) and peptidomic analyses

Critères d'inclusion

- Are male or female, 18 to 85 years of age
- Kidney biopsy before inclusion available (up to 6 weeks before inclusion) or patients agreeing to have a renal biopsy procedure performed no later than prior the visit at week 4
- Have been **newly diagnosed or relapsing active AAV-related RPGN at the time of inclusion** (either granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), with or without positive ANCA testing)
- Have an active disease (BVAS ≥ 3, with at least one of the 2 renal items of proteinuria (urinary proteinuria/creatininuria > 300 mg/g) and haematuria (>10 RBC/hpf) within the BVAS), and **eGFR 0-29 mL/min/1.7 m2 at inclusion**
- Be planned to receive a SOC induction regimen by rituximab or cyclophosphamide plus glucocorticoids (± plasma exchanges) for the current AAV flare (rituximab or cyclophosphamide may have been started before the inclusion in the study, maximum 2 weeks before the inclusion)

Critères d'exclusion (principaux)

- Treatment by >3000 mg methylprednisolone or equivalent within the 3 weeks preceding the screening visit
- Known eGFR before the AAV flare already <35 mL/min/1.7m^2
- Glomerulosclerosis >50% or kidney interstitial fibrosis >50%, if results of a kidney biopsy are available. If kidney biopsy is performed after inclusion in the study, the patients will continue the study according to the protocol.
- …

Stratification

DFG <15 mL/min/1.7m2 vs. ≥ 15 mL/min/1.7m2

Nombre de patients

- **Durée de l'étude**: 15 mois (12 sous avacopan / placebo + 3 mois de suivi/washout)
- **Durée du recrutement**: 36 mois
- Hypothèse principale

We hypothesized that the incidence of patients reaching an eGFR ≥30mL/min/1.73m2 at week 52 (estimated at 45% in previous multicenter observational cohort) could reach 70% in the experimental group. Thus, a 25% absolute difference between groups in the primary endpoint incidence (45% in the control versus 70% in the experimental group) seems to be a reasonable hypothesis. ***In addition, given the cost of avacopan (around 71 k€ per 52 weeks of treatment and per patient), a 25% absolute difference between groups was considered as a minimal requirement.***

- **Nombre de sujets nécessaire** (avec 10% de perdus de vue)

➢ **130 patients soit 65 par bras**

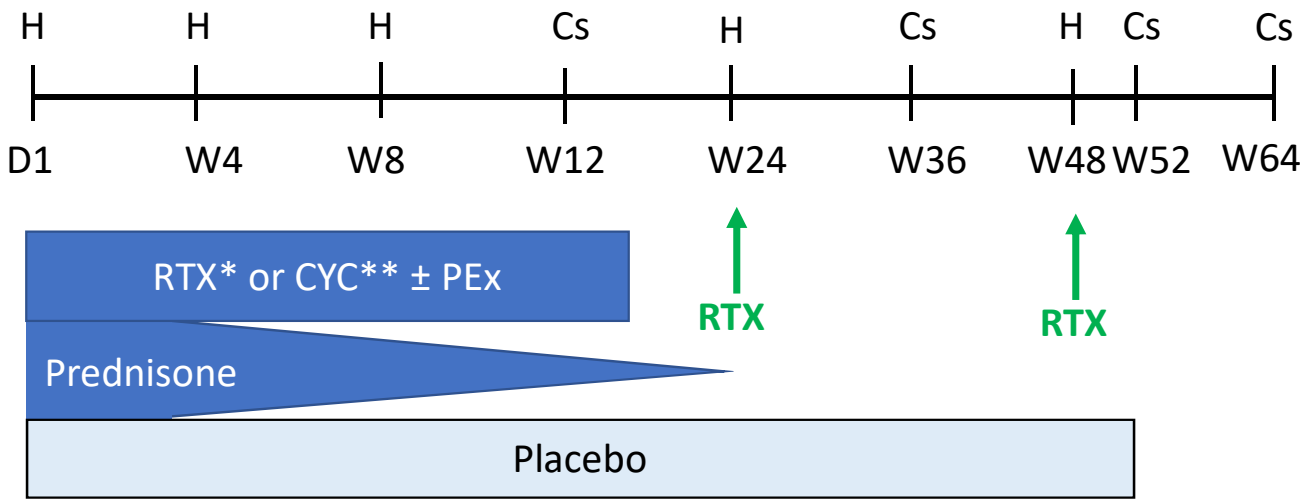
Newly diagnosed or relapsing active AAV (BVAS≥3) with eGFR 0-29 mL/min/1.7m2 at inclusion

Randomization with stratification on:

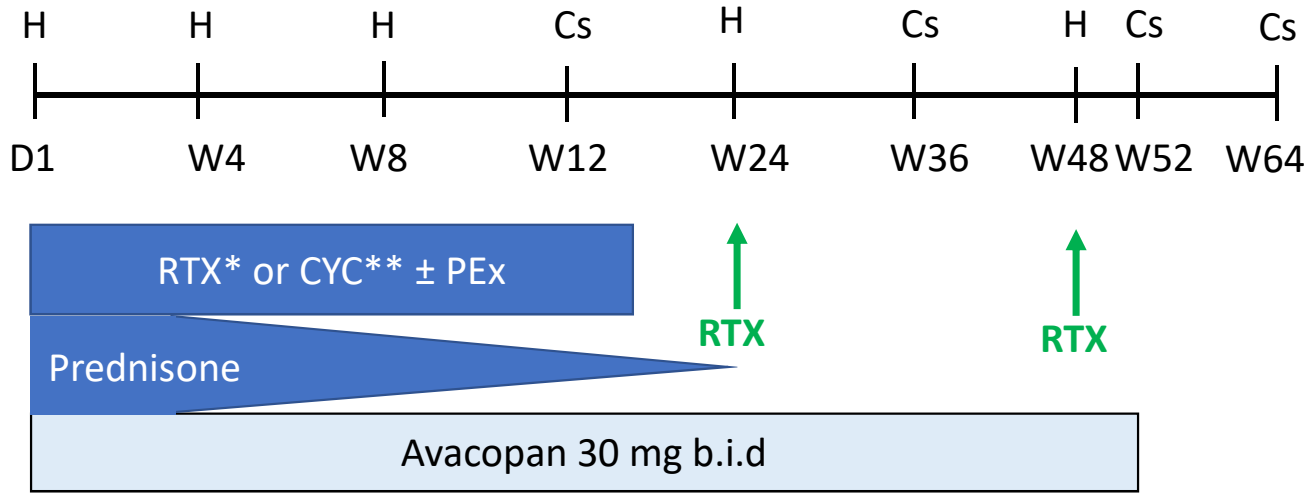
- eGFR (< 15 or ≥ 15 mL/min/1.7m^2)

Randomization

Control group



Experimental group



*RTX: 375 mg/m2 weekly for 4 weeks
**CYC: 0.5 g/m2 at D0 and weeks 2, 4, 7, 10 and 13 (reduced to 0.5 g according to kidney function)

Remerciements: CSL-VIFOR / AMGEN

- Fourniture de l'avacopan et de son placebo (65 patients / 52 semaines)
- … 4.3 millions d'euros

- Sans intervention sur le protocole

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- **Soutiens** (++): Julie Bellière, David Ribes

- **Accord**: 25 centres (Néphrologie / Médecine Interne)