Essai RENATO

MULTICENTER **R**ANDOMIZED TRIAL TO **E**VALUATE THE EFFICACY OF PIOGLITAZONE TO PROMOTE RE**NA**L **TO**LERANCE IN ANCA-ASSOCIATED VASCULITIS

Rationnel :

Limiter les séquelles rénales d'une poussée de VAA, en améliorant la « cicatrisation » rénale ?

Crescentic Rapidly Progressive Glomerulonephritis (RPGN)

Pauci-immunes

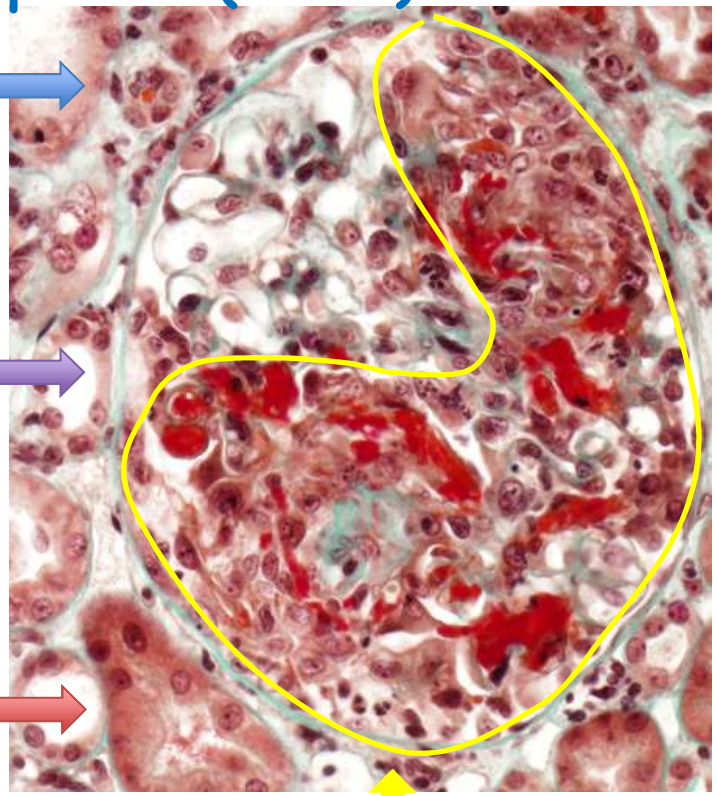
ANCA
Activated neutrophils

anti-GBM Abs

anti-α3NC1 / α5NC1
Autoreactive T Lymphocytes

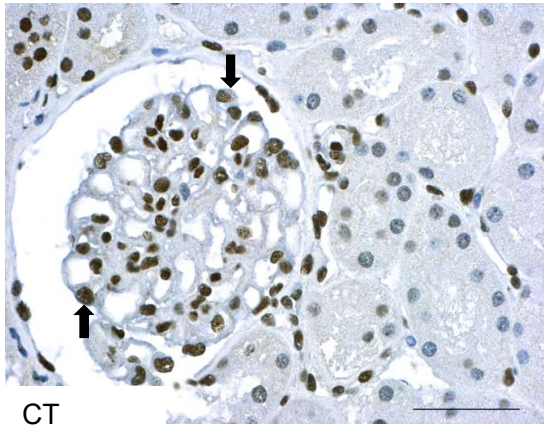
Immune complexes

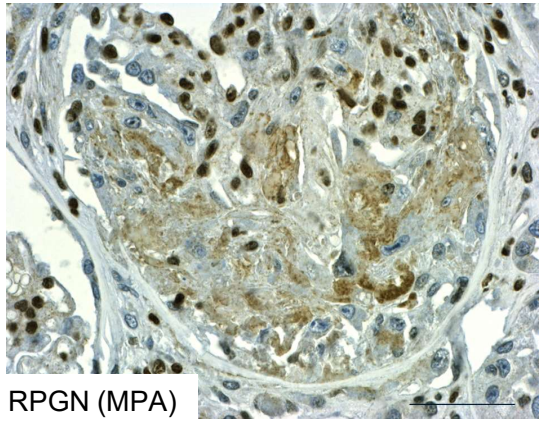
Auto-antibodies
Complement activation
Various Mechanisms (Lupus, IgA Nephropathy, infections…)

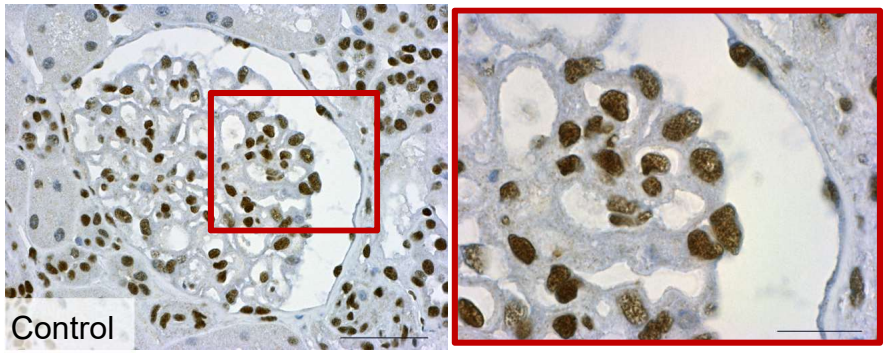


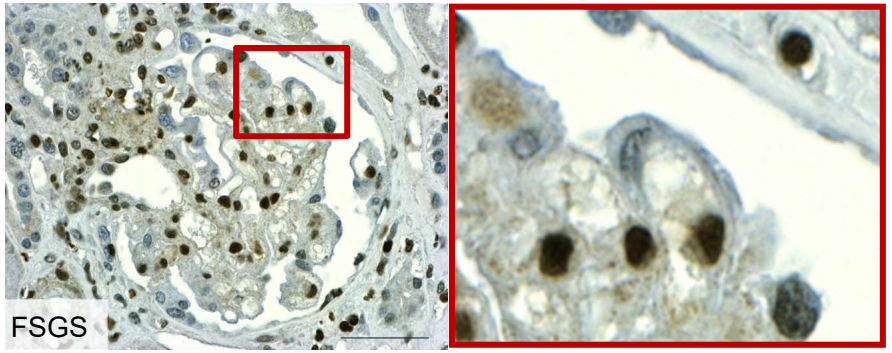
Common mechanisms causing loss of tolerance of glomerular epithelial cells to vasculitides?

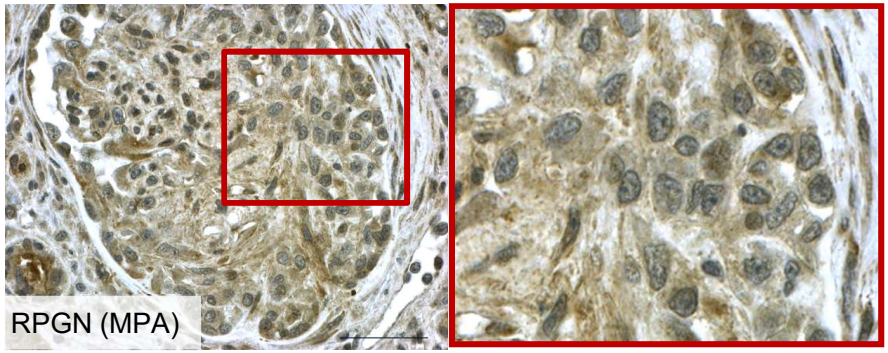
Healthy Glomerular Epithelial Cells express PPARγ constitutively







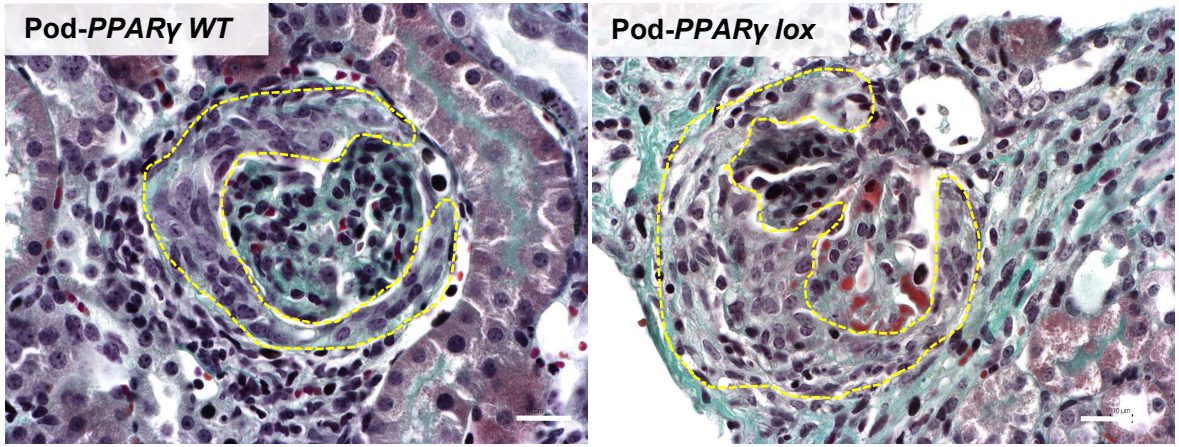


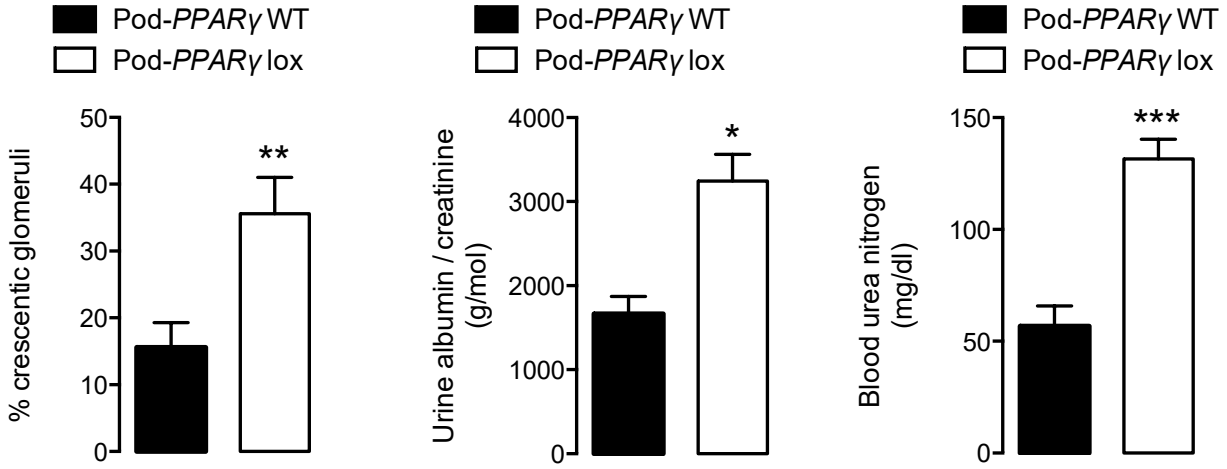


Henique et al.
J Am Soc Nephrol. 2016

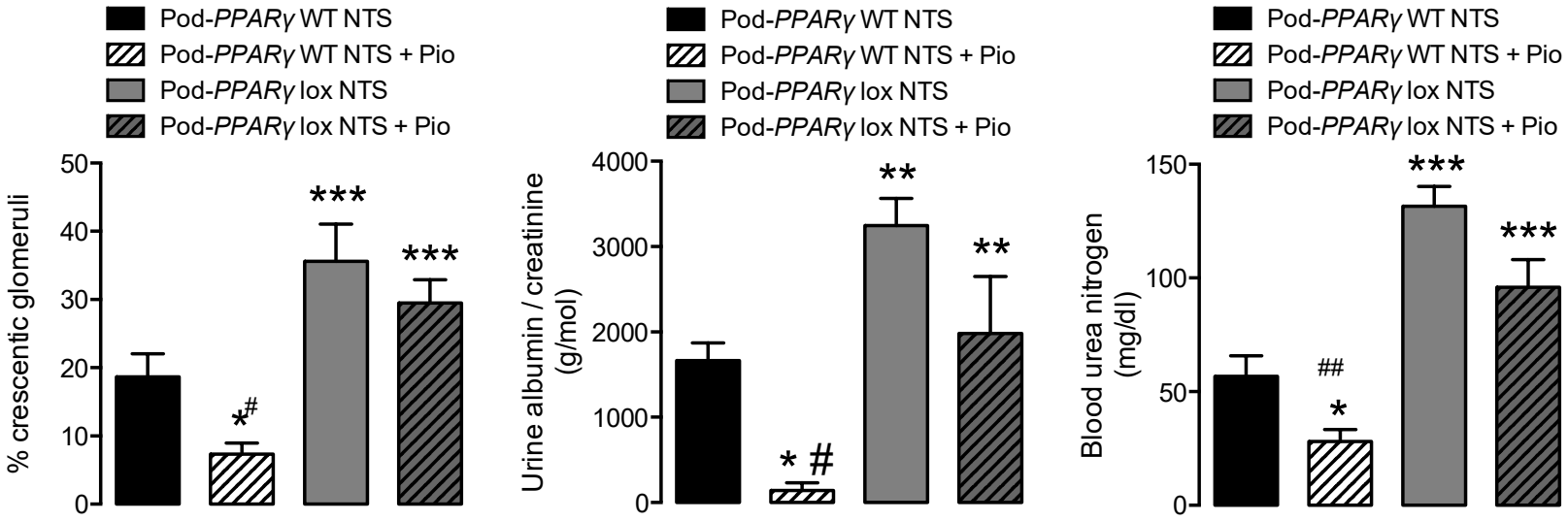
The nuclear PPARγ expression is lost in MPA- and GPA-associated crescentic RPGN

Podocyte Selective PPARγ Deficiency Aggravates Crescentic RPGN



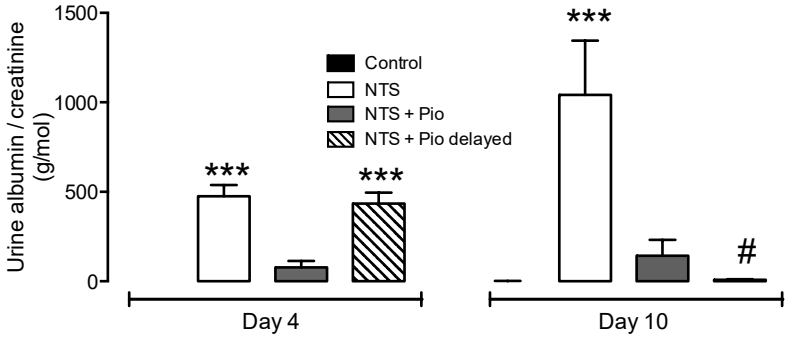


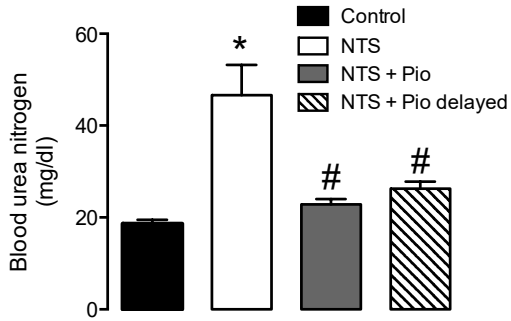
Pioglitazone Alleviates RPGN in WT mice BUT NOT in Podocyte Selective PPARγ Deficiency

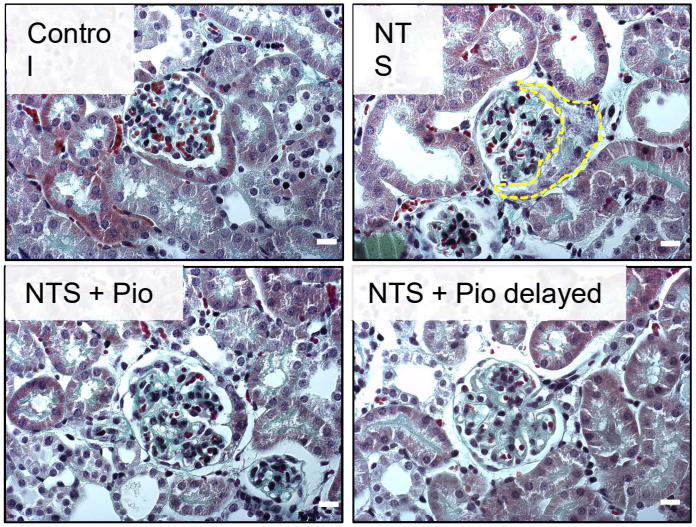


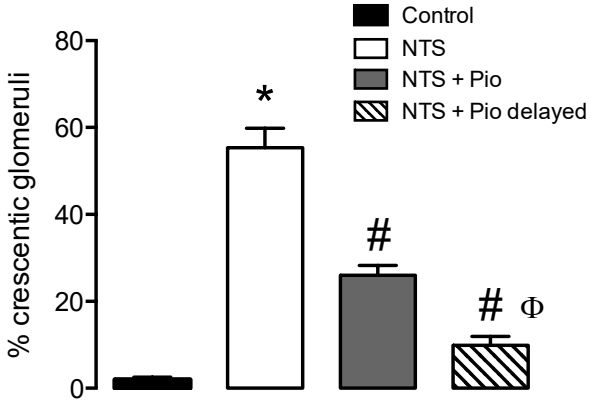
Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

Delayed PPARγ Agonism Halts Crescentic RPGN









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- Primary objective : to demonstrate a reduction of renal damage in ANCA-associated renal vasculitis, by pioglitazone add-on treatment on top of SOC standardized immunosuppressive regimen with glucocorticoids and rituximab.
- Secondary objectives :
  - To evaluate the efficacy of pioglitazone on long-term preservation of renal function,
  - To assess the efficacy of pioglitazone on the reduction of hypertension and metabolic side effects of glucocorticoids.
  - To describe the clinical and biological tolerance of pioglitazone in this population,
  - To measure the impact of this drug on renal and systemic vasculitis activity,

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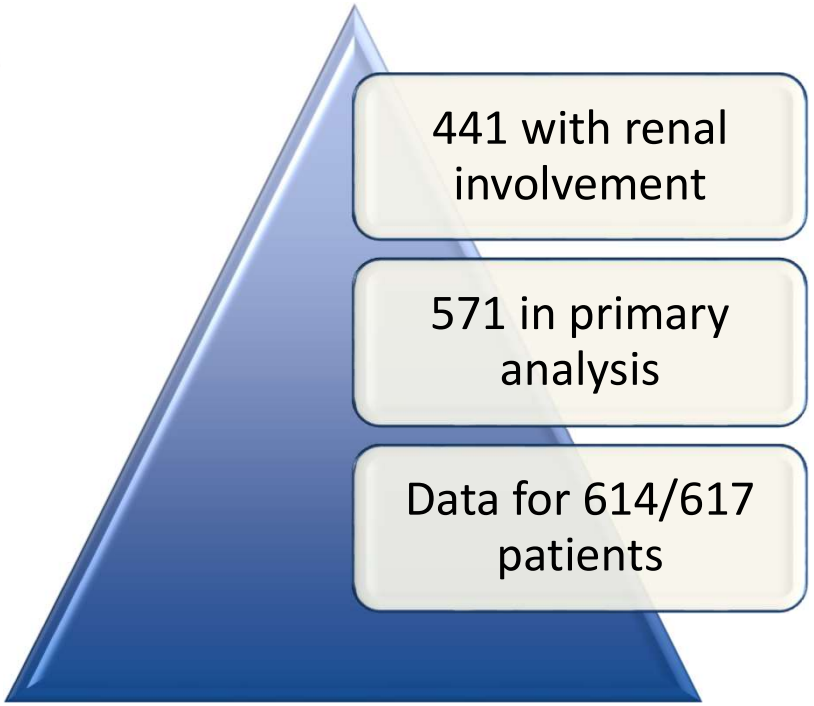
- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.

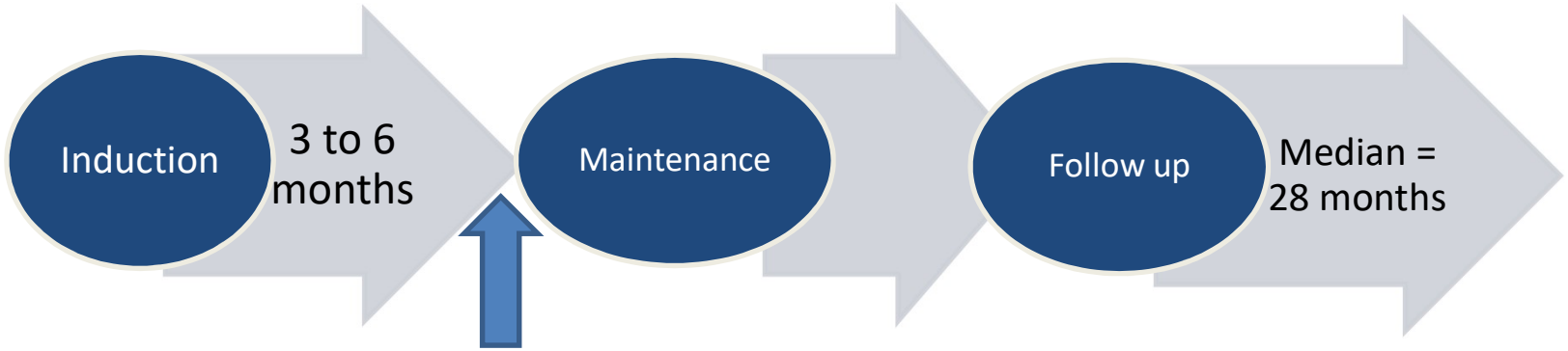
Prognostic value of persistent proteinuria and hematuria after induction therapy in ANCA-associated vasculitis

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

Design – prospective assessment



PROTEINURIA : 24h urine or protein/creatinine ratio on spot

- Death or ESRD
- Relapses and renal relapses

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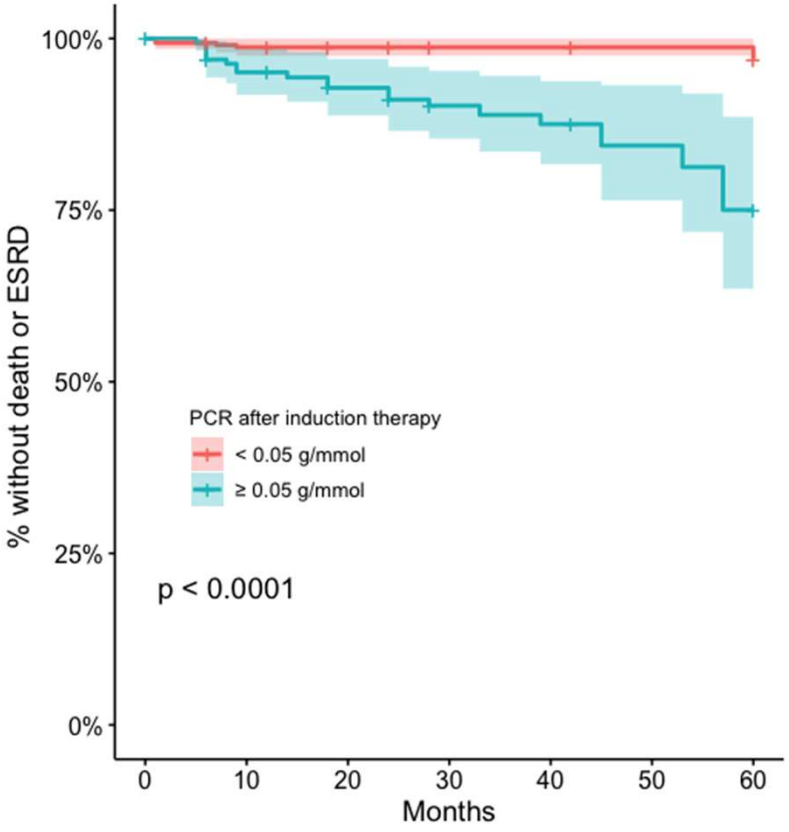
Outcome : Death or ESRD

5% of patients



Multivariate Cox analysis	Adjusted Hazard Ratio	95% Confidence Interval	p value
Male sex	0.99	0.43 - 2.28	0.974
Age	1.03	1.00 - 1.07	0.056
ANCA type (ref: PR3)			
Negative	0.69	0.09 - 5.46	0.723
MPO	2.06	0.86 - 4.96	0.107
eGFR at flare diagnosis	**0.97**	**0.95 - 0.99**	**0.016**
Hematuria after induction therapy	1.88	0.83 - 4.29	0.132
PCR after induction therapy ≥ 0.05 g/mmol	**4.08**	**1.48 - 11.25**	**0.006**

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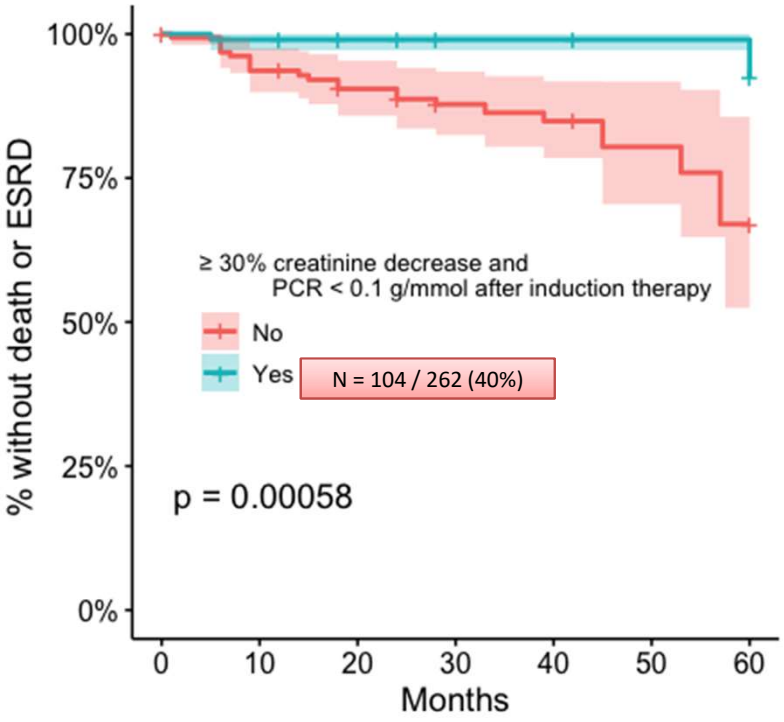
Outcome : Death or ESRD

Patients with sCreat > 130 umol/L at diagnosis



Multivariate Cox Analysis	Adjusted HR	95% CI	p value
Male sex	1.03	0.42 - 2.50	0.955
Age	1.01	0.98 - 1.05	0.391
ANCA type (ref: PR3)			
Negative	1.19	0.25 – 5.75	0.830
MPO	2.09	0.82 - 5.38	0.124
eGFR at flare diagnosis	**0.96**	**0.92 - 0.99**	**0.015**
Hematuria after induction therapy	2.01	0.88 – 4.58	0.098
Proposed surrogate endpoint (≥ 30% creatinine decrease and PCR < 0.1 g/mmol after induction)	**0.11**	**0.02 - 0.46**	**0.003**

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- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.

- Secondary endpoints :
  - sCreat, Delta sCreat, eGFR, renal survival (off-dialysis) and proteinuria (UPCR) at W4, W12, W26, W52
  - BVAS and ANCA positivity at W4, W12, W26, W52, Relapse rate
  - Renal vasculitis activity (urinary MCP-1, KIM-1, Calprotectin, CD163) at W4, W12, W26, W52.
  - Damage score (VDI) at W26, W52 and Glucocorticoid Toxicity Index (GTI) at W12, 26, 52
  - Blood pressure (ABPM and n of antihypertensive drugs), Diabetes (HbA1c), Lipid profile
  - Safety profile of pioglitazone

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- Inclusion criteria :
  - Newly-diagnosed or relapsing AAV (GPA /MPA), with an active disease defined as a BVAS ≥ 3
  - Presence of proteinuria (UPCR >300 mg/g), haematuria (>10 RBC/hpf) and eGFR ≥15 mL/min/1.73 m2 at inclusion
  - Recent (<4 weeks) renal biopsy that confirms renal involvement of ANCA-associated vasculitis
  - Patients aged of 18 to 80 years

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- Non-inclusion criteria :
- Severe kidney injury with eGFR <15 ml/min/1.73m² or dialysis therapy at inclusion
- Alveolar haemorrhage requiring pulmonary ventilation support at inclusion
- Active cancer (except non-melanoma skin cancer) within the past 24 months
- Past history of bladder or urinary tract cancer
- History of Class 3/4 congestive heart failure symptoms, Class 2 heart failure symptoms within the past 3 months and ejection fraction <40% on recent echocardiography
- Chronic liver disease
- Positive serology for HIV, HBV (Ag HBs positivity), HCV at inclusion
- Pregnant or breast-feeding women, or desire to become pregnant within 12 months
- Severe neurologic or psychiatric disease (e.g., dementia or schizophrenia)
- Kidney transplant recipients
- Cyclophosphamide or rituximab use within 26 weeks prior to screening

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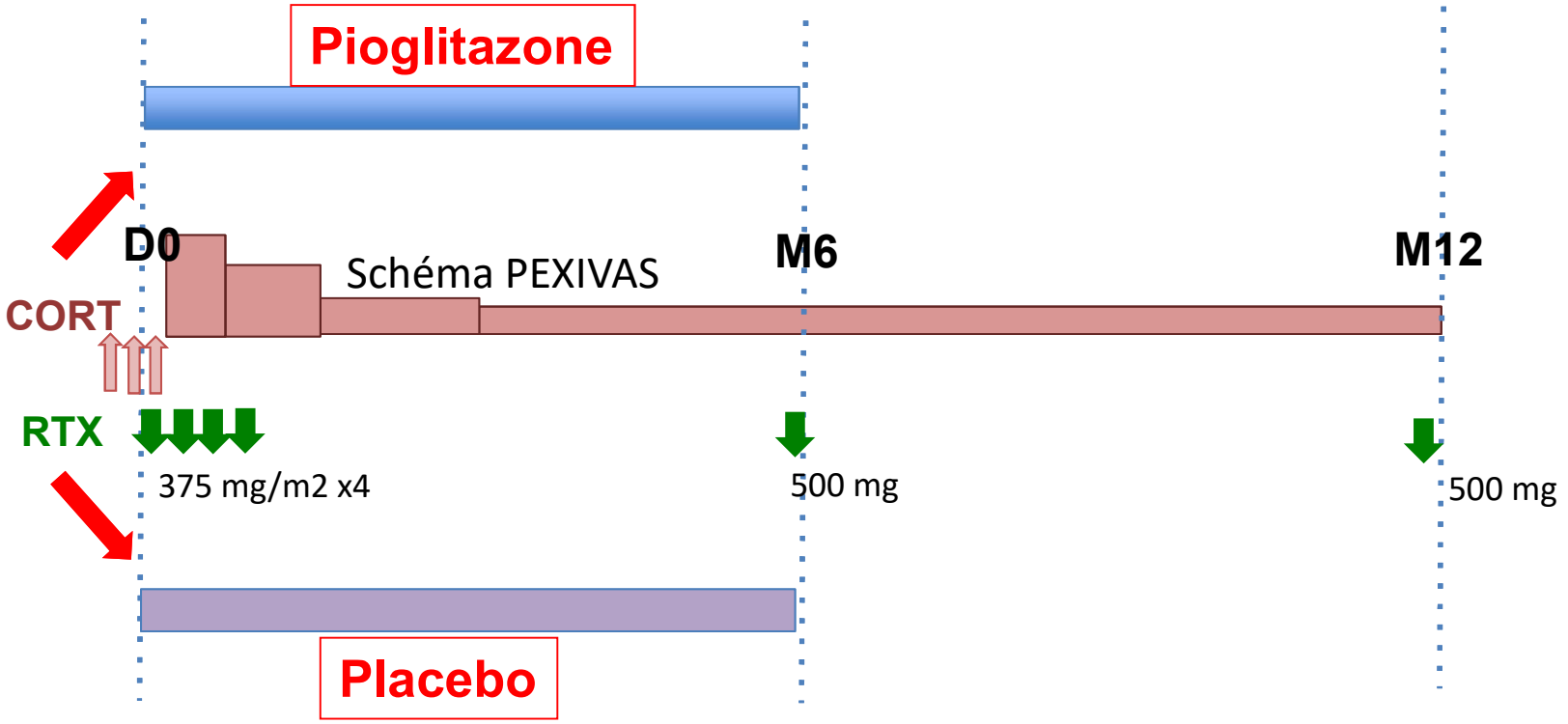
EIG spécifiques

- Carcinomes urothéliaux
  - Pas de sur-risque confirmé sur multiples essais et métanalyses récentes
  - Par précaution : pas de cyclophosphamide, non inclusion si ATCD
- Insuffisance cardiaque :
  - Sur-risque d'OMI et décompensation cardiaque dans qq études chez diabétique
  - Par précaution : non inclusion si ATCD d'insuffisance cardiaque classe III/IV
  - Echo cardiaque à l'inclusion et exclusion si FEVG <40%
  - Surveillance poids et BNP à chaque visite pdt 6 mois et diurétique si besoin
- Hépatite, hypoglycémie, ostéoporose fracturaire
- Œdème maculaire chez patient diabétique
  - Examen ophtalmo si patient diabétique ou ATCD de rétinopathie

RENATO trial



Traitements associés

- Traitements antihypertenseurs (ICa, diurétiques, bétabloquants, alphabloquants) en visant TA <140/90 (135/85 sur MAPA W4 et W12)
- Débuter diurétiques en priorité si prise de poids, OMI ou élévation BNP

  -suspension pioglit/placebo si >3 kg/1 sem, doublement de BNP)

  -arrêt du traitement de l'étude si poussée d'IC congestive
- Pas d'IEC, ARA2 ou iSGLT2 pdt les 6 premiers mois (sauf si HTA >160/95)

  (incitation à les utiliser au delà de M6 si PU >1g/g)
- Utilisation libre des autres antidiabétiques
- Prophylaxies usuelles pneumocystose, ostéoporose cortisonique

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- 128 patients à inclure
- Durée de la période d'inclusion : 3 ans
- Durée du suivi : 1 an
- Nombre de centres prévus: 25
- Date de début des inclusions : avant l'été 2023

MERCI pour votre aide

alexandre.karras@aphp.fr pierre-louis.tharaux@inserm.fr