

Essai RENATO

MULTICENTER **R**ANDOMIZED TRIAL TO **E**EVALUATE THE
EFFICACY OF PIOGLITAZONE TO PROMOTE REN**AL**
TOLERANCE IN ANCA-ASSOCIATED VASCULITIS

Introduction

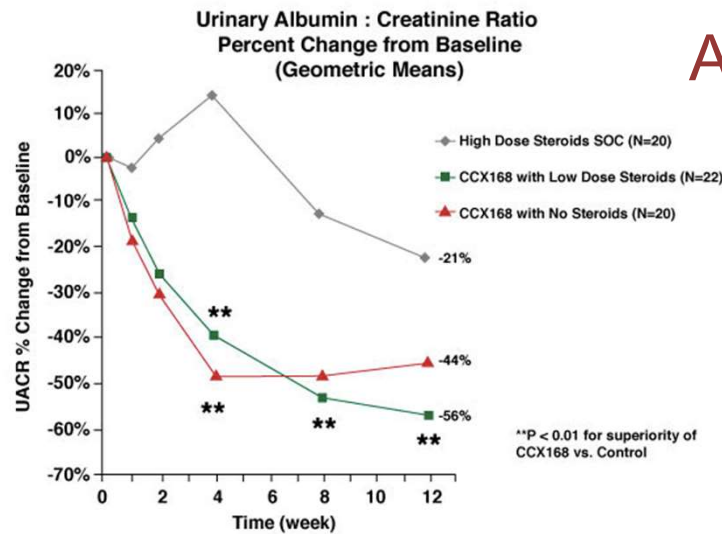
Comment limiter les séquelles rénales d'une poussée rénale de VAA ?

- Dépister et traiter précocément les poussées...

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- Améliorer les schémas d'induction pour une efficacité plus rapide

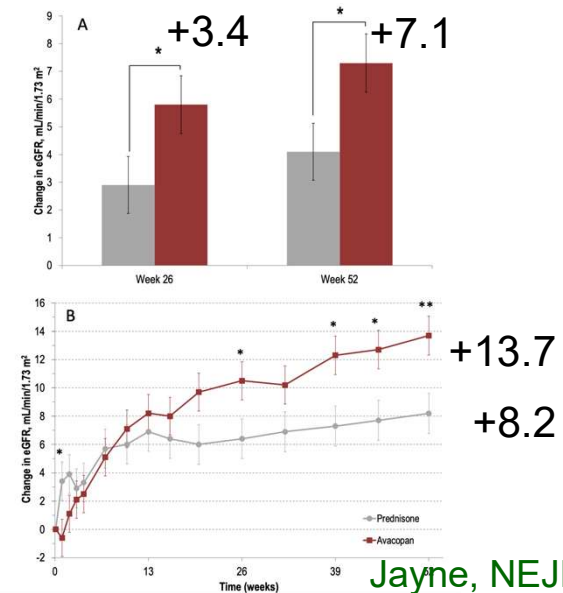


Jayne, JASN 2017

Avacopan ?

All patients

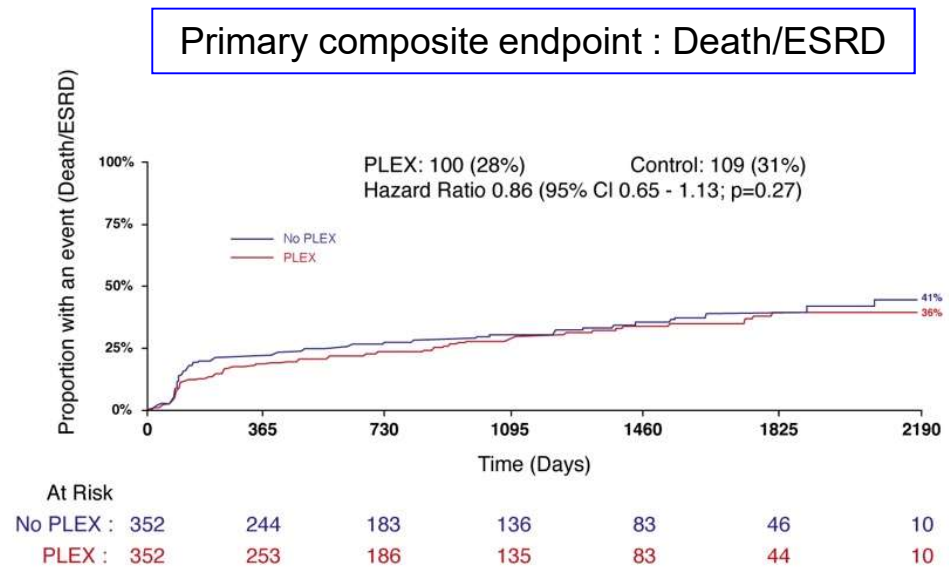
Patients with
initial GFR<30



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- Epurer les ANCA circulants ?



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- Epurer les ANCA circulants ?
- Améliorer la « cicatrisation » rénale ?

Crescentic Rapidly Progressive Glomerulonephritis (RPGN)

Pauci-immunes

ANCA
Activated neutrophils



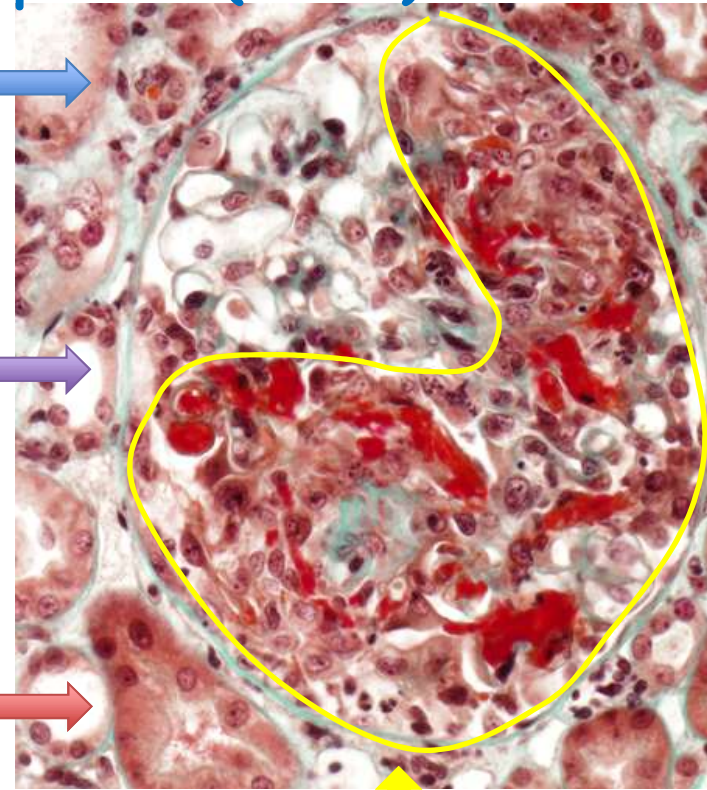
anti-GBM Abs

anti- α 3NC1 / α 5NC1
Autoreactive T Lymphocytes



Immune complexes

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



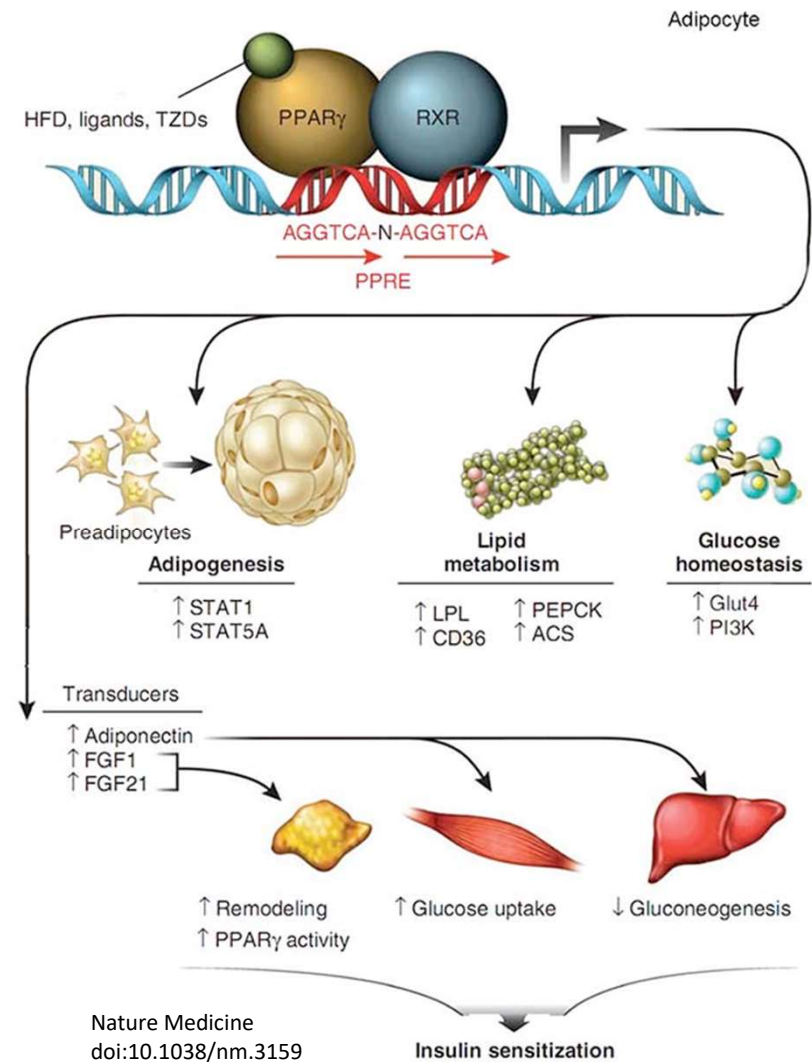
Common mechanisms causing
loss of tolerance of glomerular epithelial cells to vasculitides?

Quel est le métabolisme des podocytes normaux et pathologiques?

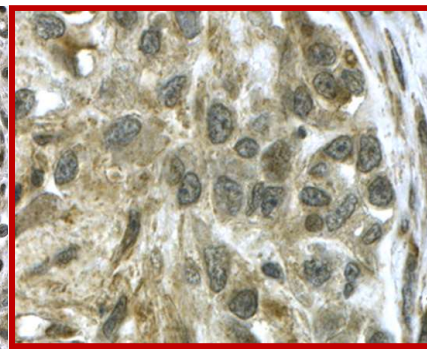
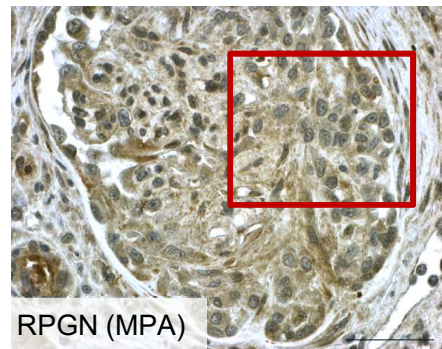
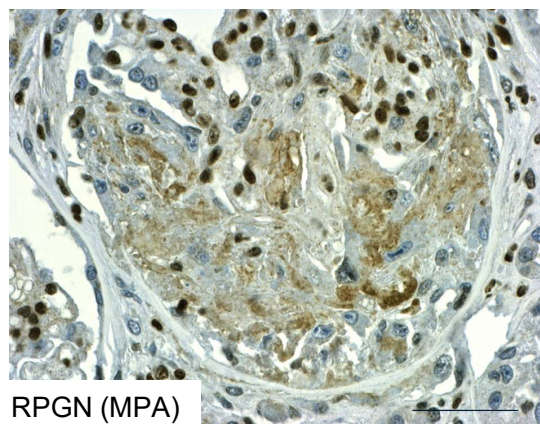
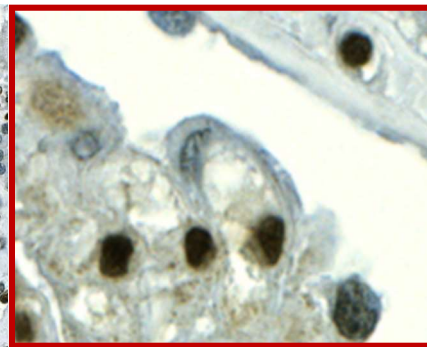
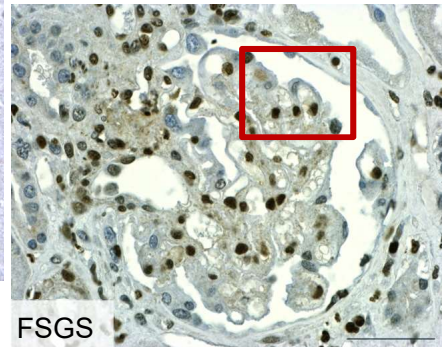
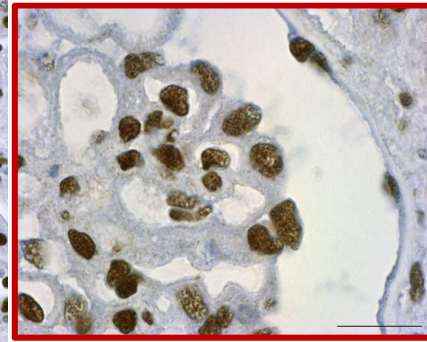
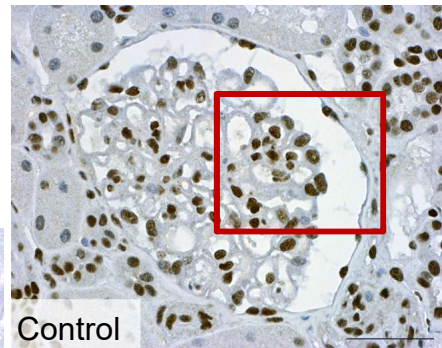
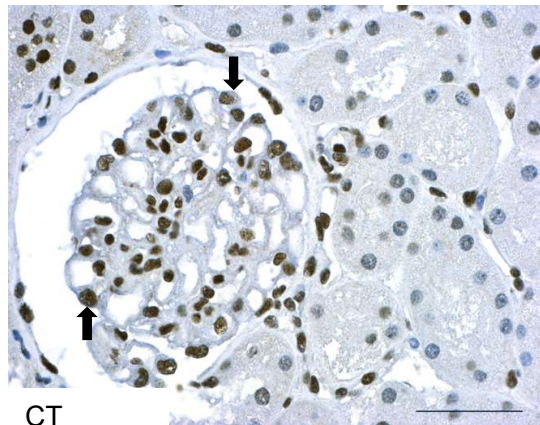
⇒ Les podocytes disposent des systèmes de métabolisation des acides gras libres, filtrés physiologiquement à travers le capillaire glomérulaire.

En particulier le récepteur nucléaire PPARgamma

=> Quel est le rôle de celui-ci?



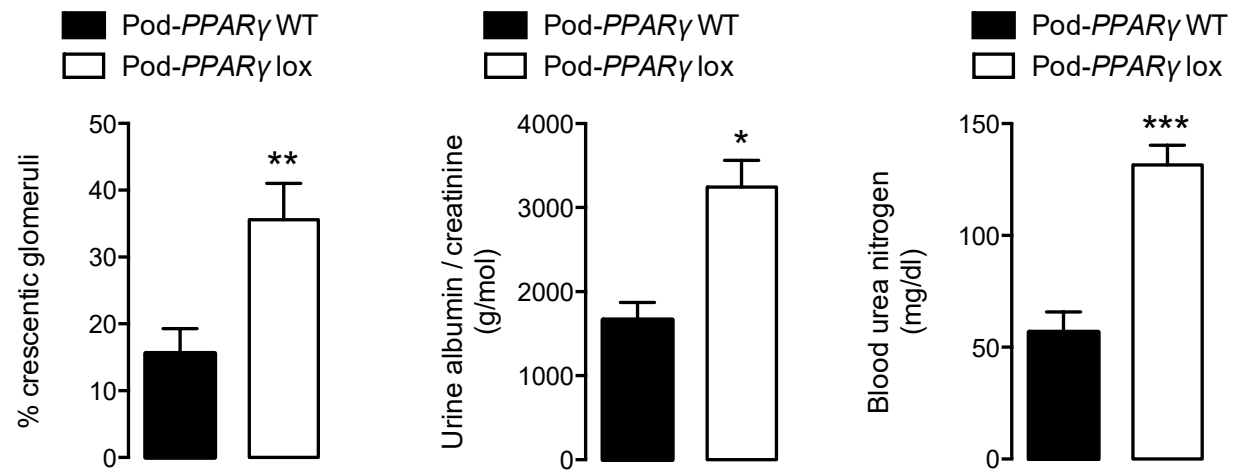
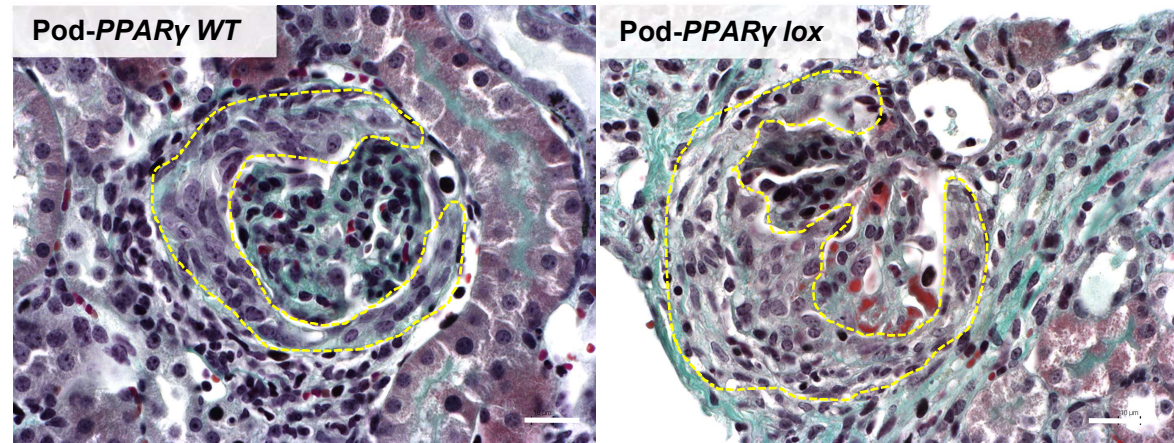
Healthy Glomerular
Epithelial Cells express
PPAR γ constitutively



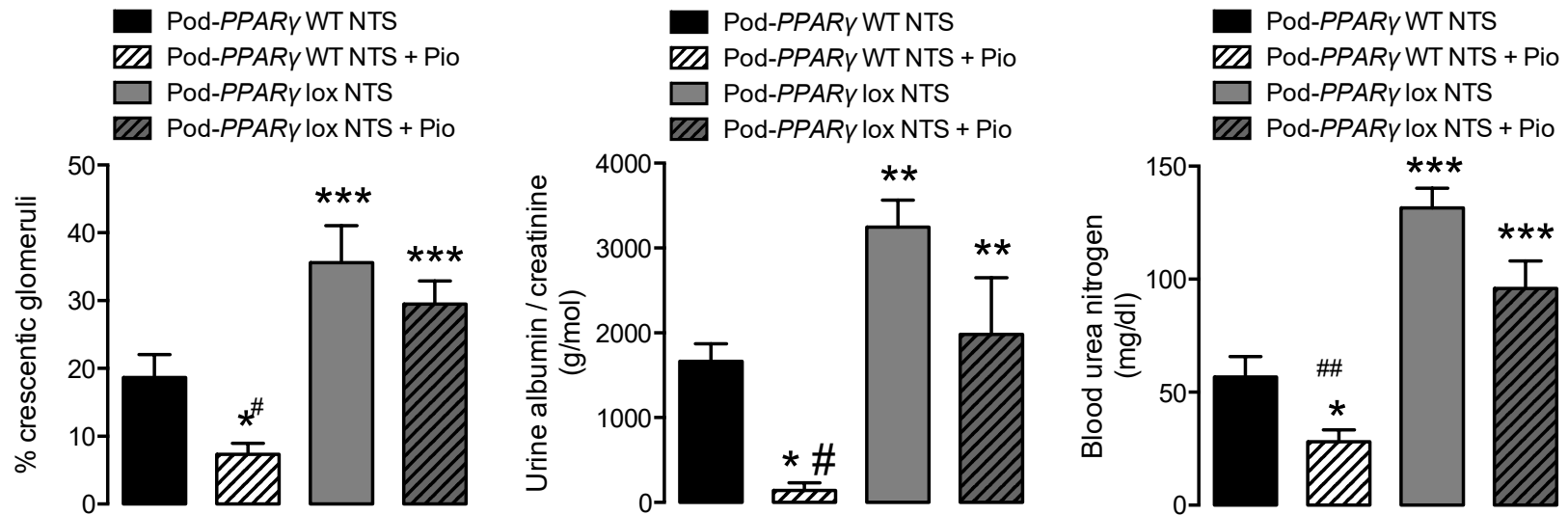
Henique et al.
J Am Soc Nephrol. 2016

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

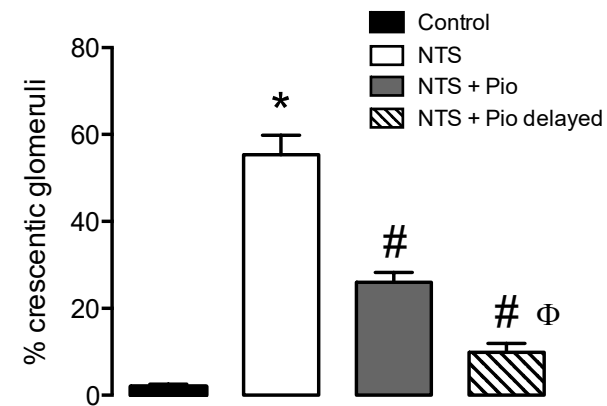
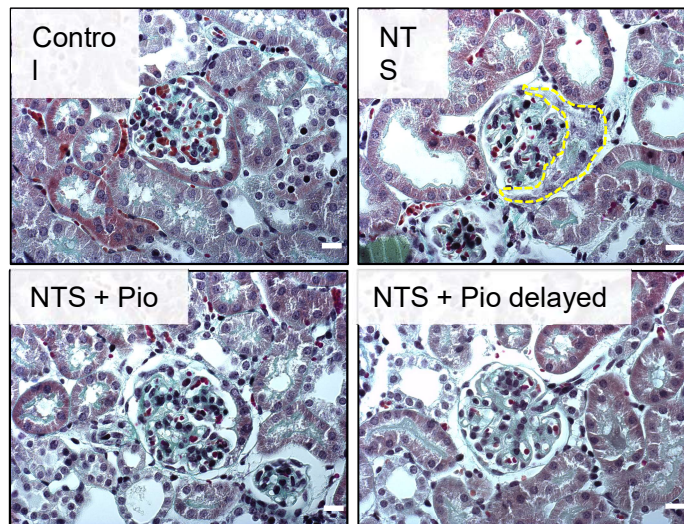
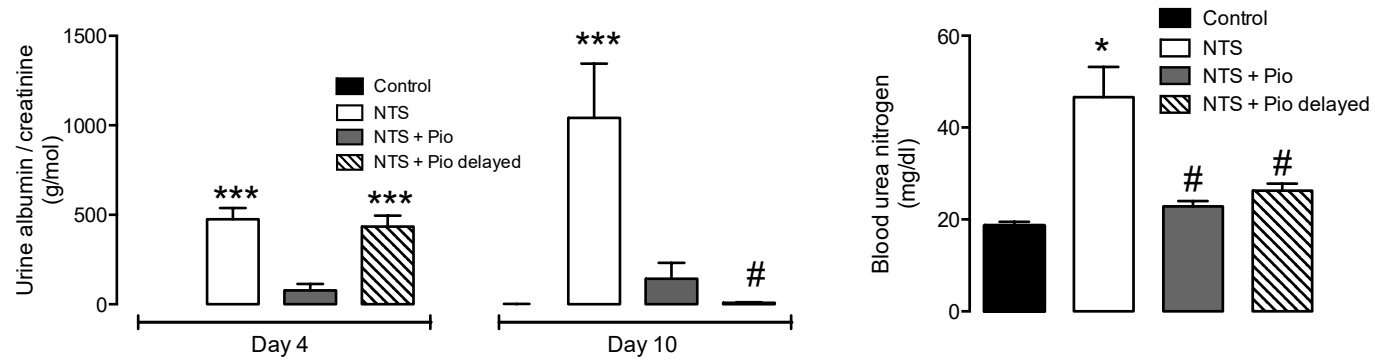
Podocyte Selective PPAR γ Deficiency Aggravates Crescentic RPGN



Pioglitazone Alleviates RPGN in WT mice BUT NOT in Podocyte Selective PPAR γ Deficiency



Delayed PPAR γ Agonism Halts Crescentic RPGN



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

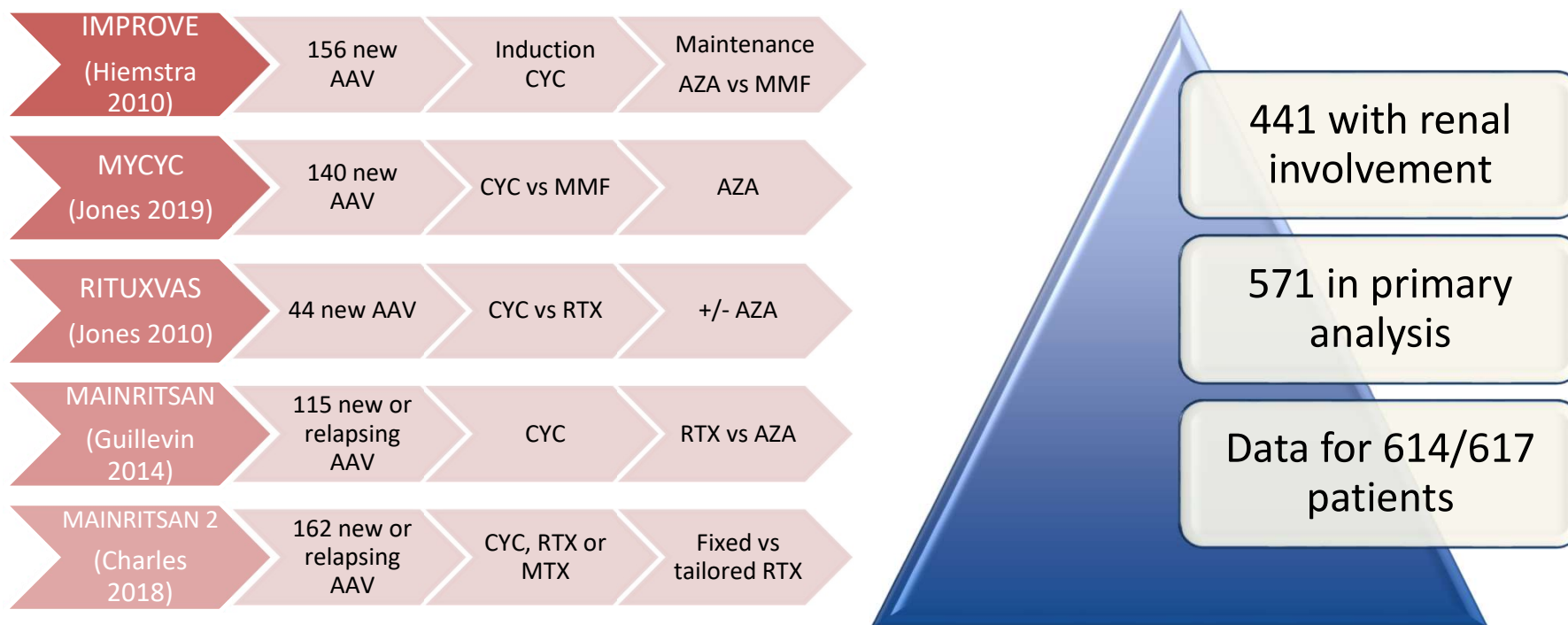
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- Primary objective : to demonstrate a reduction of renal damage in ANCA-associated renal vasculitis, by pioglitazone add-on treatment on top of SOC standardized immunosuppressive regimen with glucocorticoids and rituximab.
- Secondary objectives :
 - 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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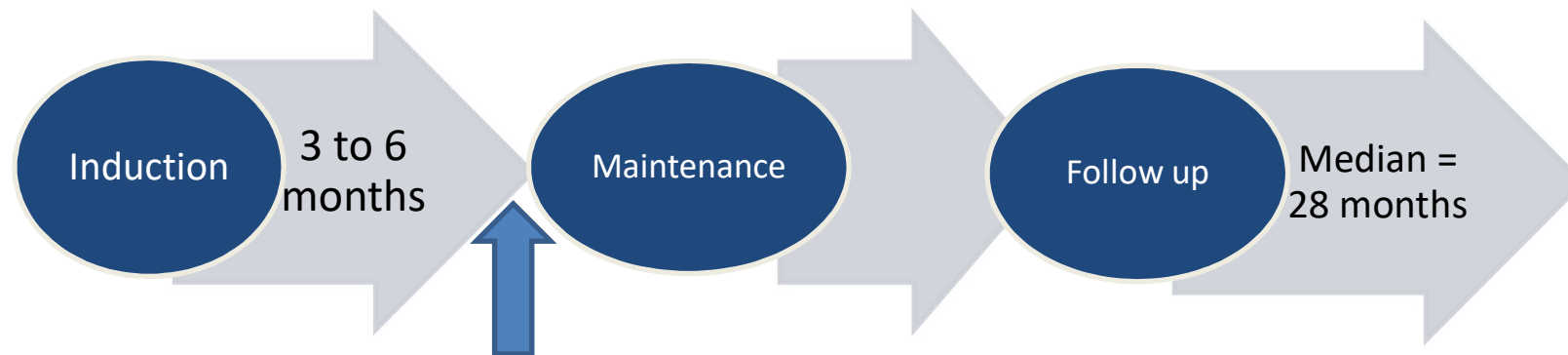
- Primary composite endpoint :
 - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.

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

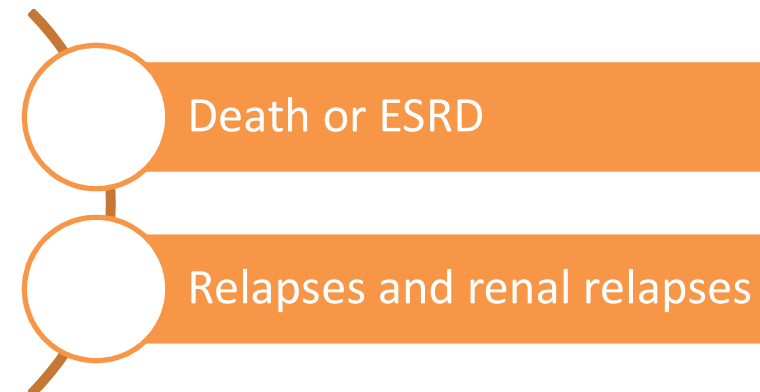


Benichou N, Karras A, ASN 2020

Design – prospective assessment



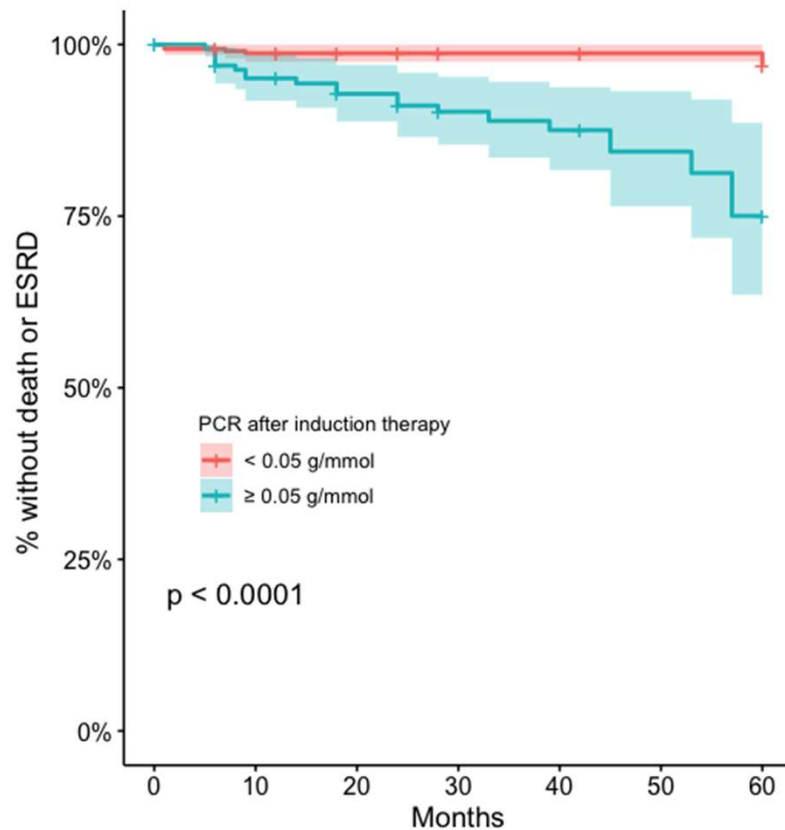
PROTEINURIA : 24h urine or protein/creatinine ratio on spot



Benichou N, Karras A, ASN 2020

Outcome : Death or ESRD

5% of patients

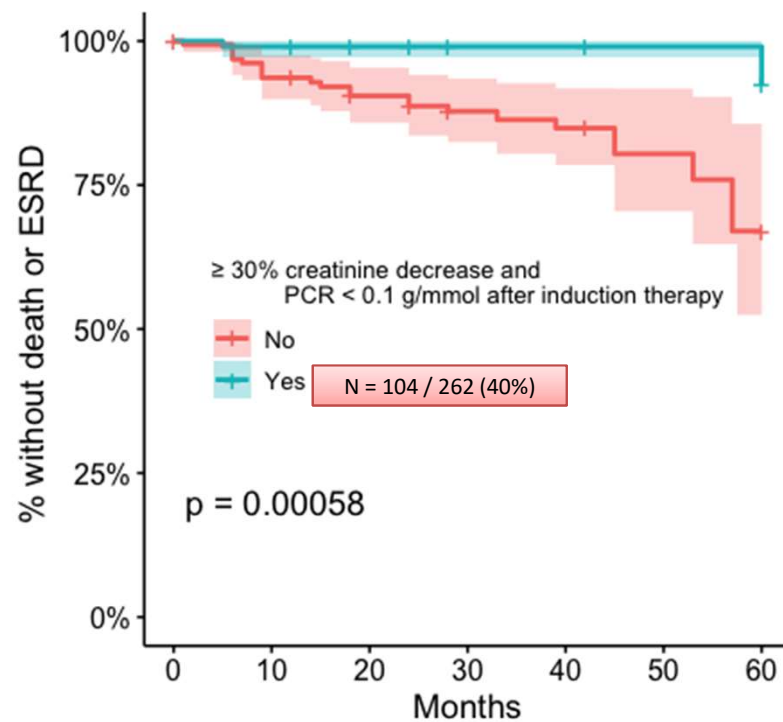


Multivariate Cox analysis	Adjusted Hazard Ratio	95% Confidence Interval	p value
Male sex	0.99	0.43 - 2.28	0.974
Age	1.03	1.00 - 1.07	0.056
ANCA type (ref: PR3)			
Negative	0.69	0.09 - 5.46	0.723
MPO	2.06	0.86 - 4.96	0.107
eGFR at flare diagnosis	0.97	0.95 - 0.99	0.016
Hematuria after induction therapy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

Benichou N, Karras A, ASN 2020

Outcome : Death or ESRD

Patients with sCreat > 130 $\mu\text{mol/L}$ 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 ($\geq 30\%$ creatinine decrease and PCR < 0.1 g/mmol after induction)	0.11	0.02 - 0.46	0.003

Benichou N, Karras A, ASN 2020

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- Primary composite endpoint :
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- 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

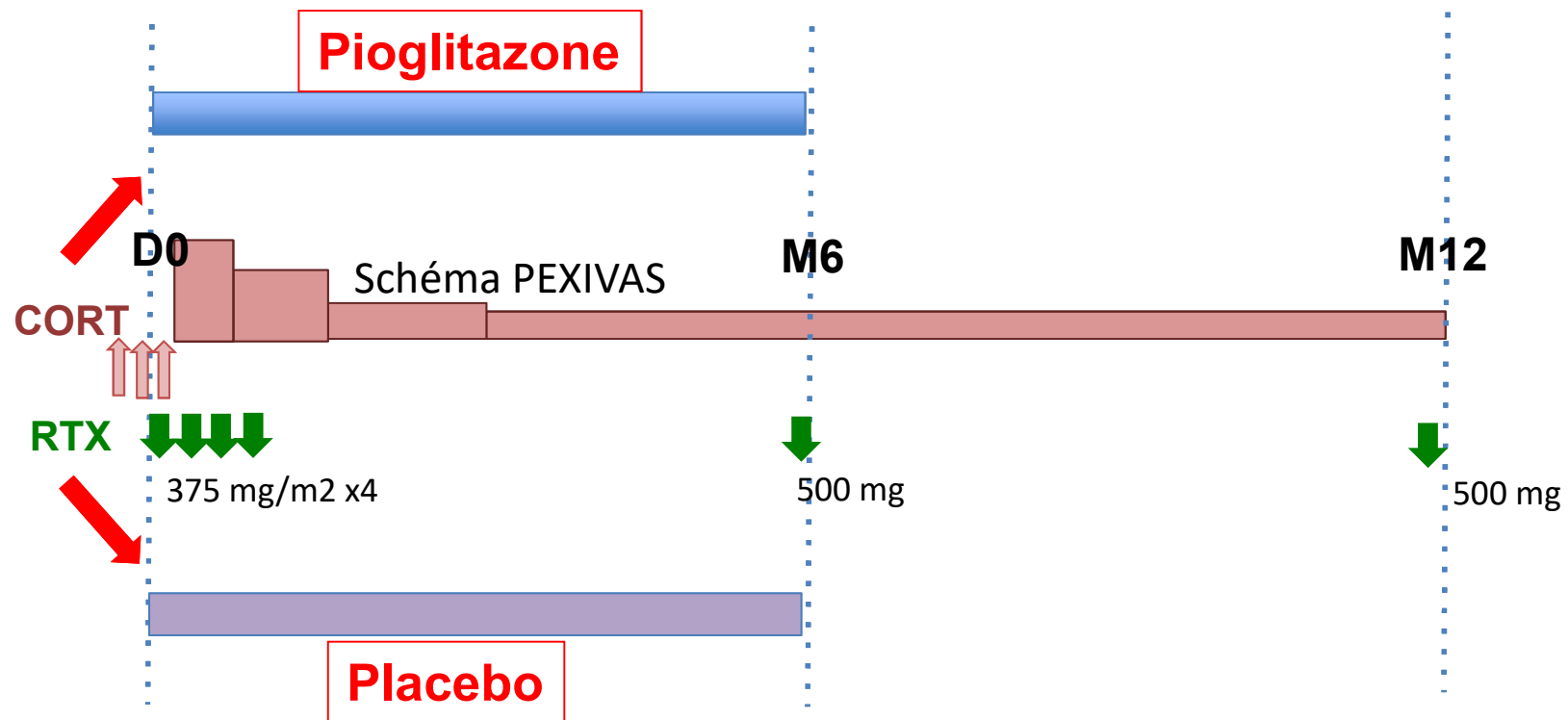
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ElG spécifiques

- Carcinomes urothéliaux
 - Pas de sur-risque confirmé sur multiples essais et métaanalyses 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

RENATO trial



Traitements associés

- Traitements antihypertenseurs (ICa, diurétiques, bêtabloquants, 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)
- 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 « présents » : 25
- Date de début des inclusions : 4^e trimestre 2022

MERCI pour votre aide

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