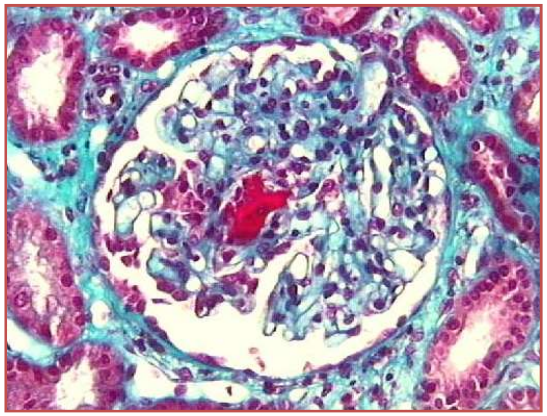
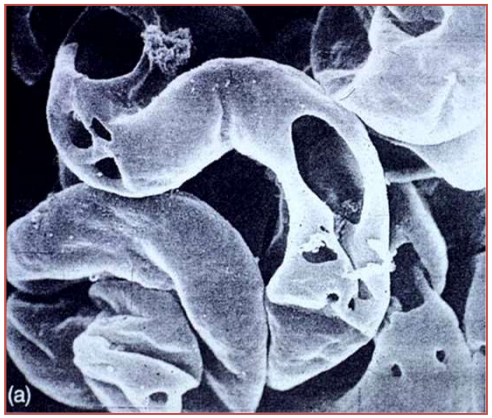
Le Complément dans les vascularites des petits vaisseaux

Alexandre KARRAS

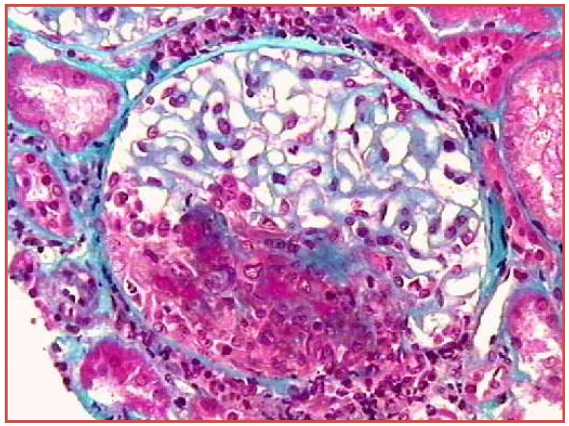
Néphrologie – HEGP, Paris

Vascularite glomérulaire





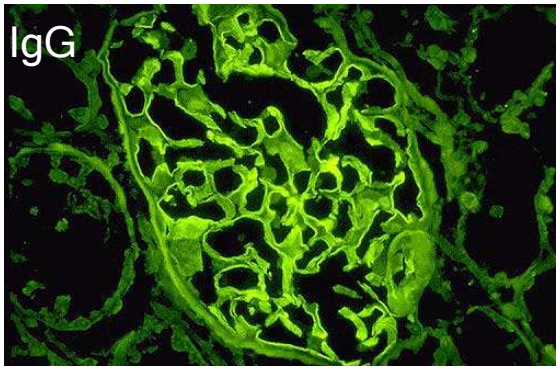
Vascularite du capillaire glomérulaire



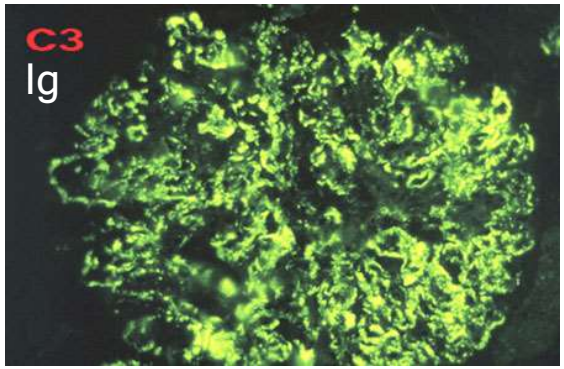
Formation du croissant extracapilaire

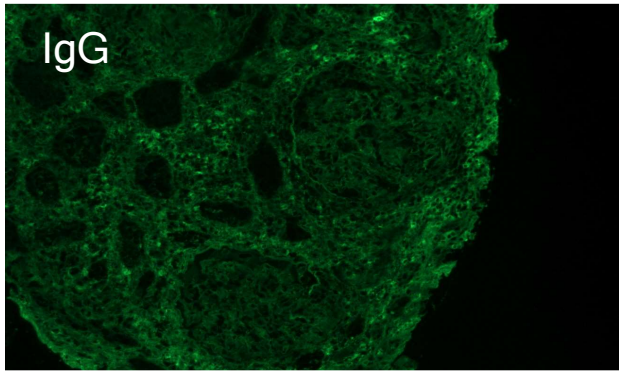
Vascularite glomérulaire

Diagnostic étiologique reposant sur l'analyse en immunofluorescence



Vascularite antiGBM





Vascularite à ANCA

IgA +C3
Vascularite IgA

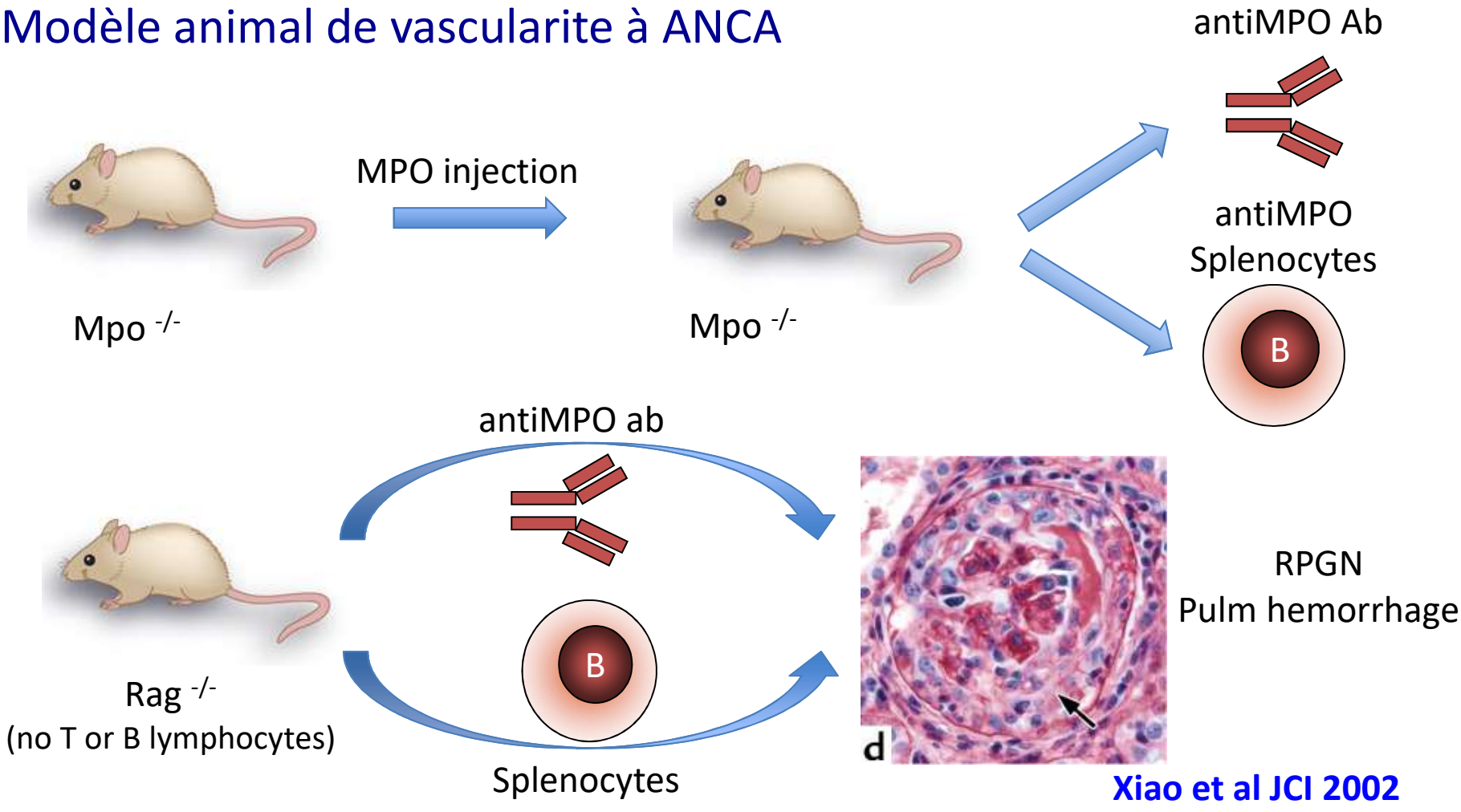
IgG+IgM+C3
Vascularite Cryo

IgG+IgM+IgA+C3+C1q
Vascularite Lupus

Pas de rôle pour le complément dans la vascularite à ANCA ?

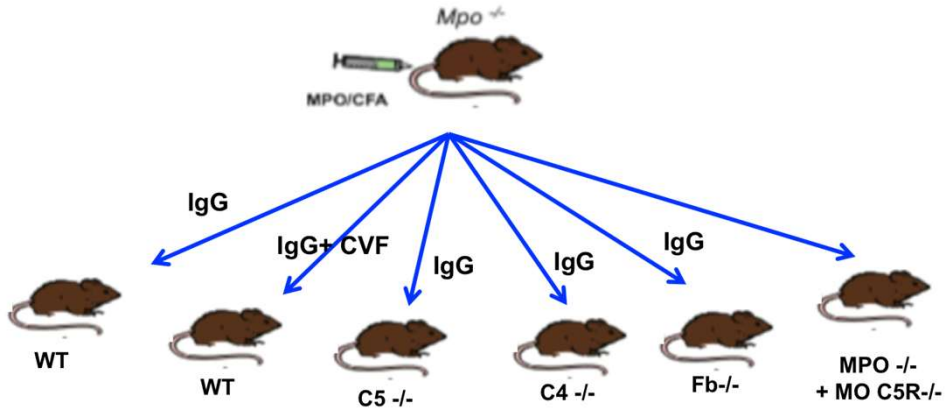
- Système faisant le lien entre immunité innée et immunité adaptative
- Souvent impliqué dans les maladies auto-immunes, notamment si médiées par un auto-anticorps, par le biais d'une activation inappropriée/incontrolée
- L'absence de dépôt n'élimine pas la participation du complément dans la physiopathologie (cf SHUa)

Modèle animal de vascularite à ANCA



Xiao et al JCI 2002

Modèle animal de vascularite à ANCA antiMPO



% croissants	11%	0	0	18%	0	0.5
% nécrose	5%	0	0	9%	0	0

- La déplétion du complément par du CVF (cobra venom factor), une délétion de C5 ou du facteur B, ou une absence de C5R bloque la formation de la GN nécrotique extracapillaire
- C5 et son récepteur C5aR sont nécessaires au développement de la vascularite (mais peut-être aussi la voie alterne du complément ?)

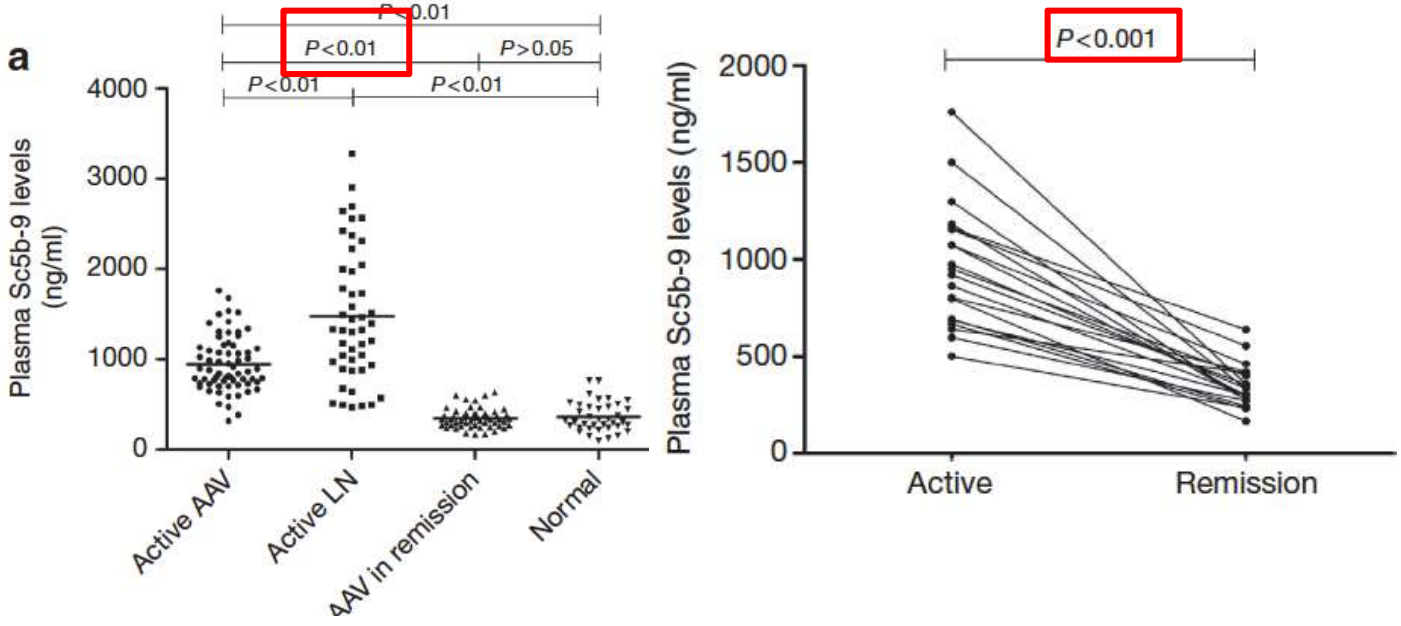
Xiao et al Am J Pathol 2007

Quelles preuves de l'activation du complément dans la vascularite à ANCA chez l'homme ?

Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody–associated vasculitis

Kidney International (2012) **83**, 129–137

Shen-Ju Gou[1,3], Jun Yuan[1,2,3], Min Chen[1], Feng Yu[1] and Ming-Hui Zhao[1]

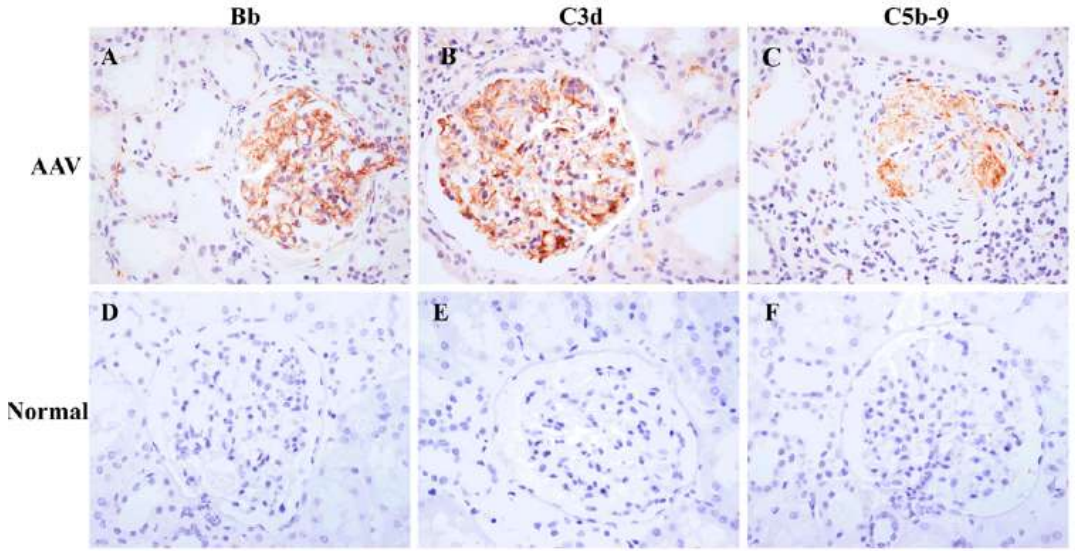


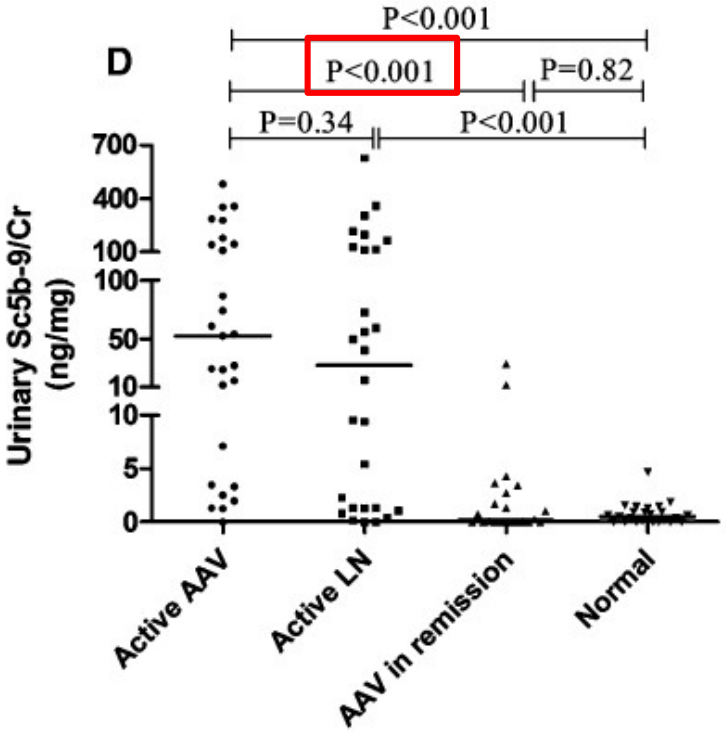
Quelles preuves de l'activation du complément dans la vascularite à ANCA chez l'homme ?

Alternative Complement Pathway Activation Products in Urine and Kidneys of Patients with ANCA-Associated GN

CJASN 2013

Shen-Ju Gou, Jun Yuan, Chen Wang, Ming-Hui Zhao, and Min Chen



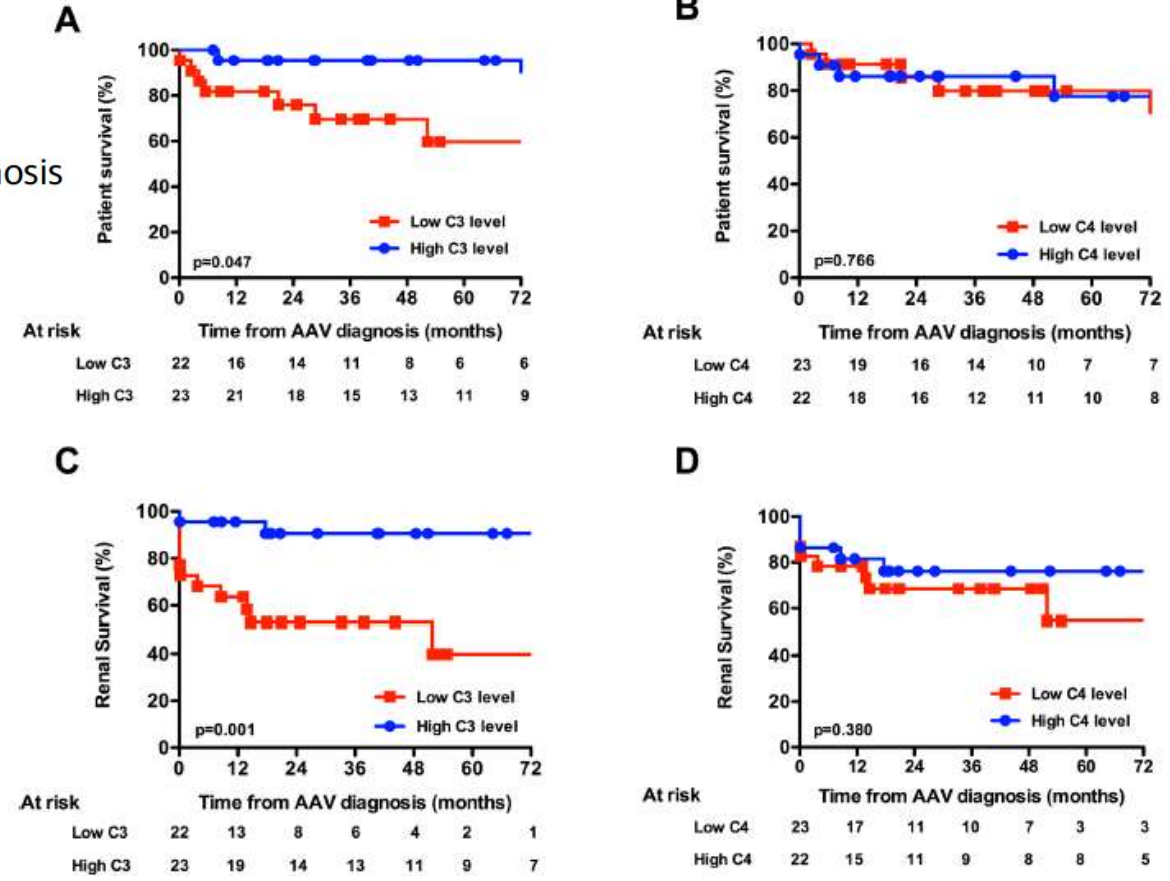


Quelles preuves de l'activation du complément dans la vascularite à ANCA chez l'homme ?

Low Serum Complement C3 Levels at Diagnosis of Renal ANCA-Associated Vasculitis Is Associated with Poor Prognosis

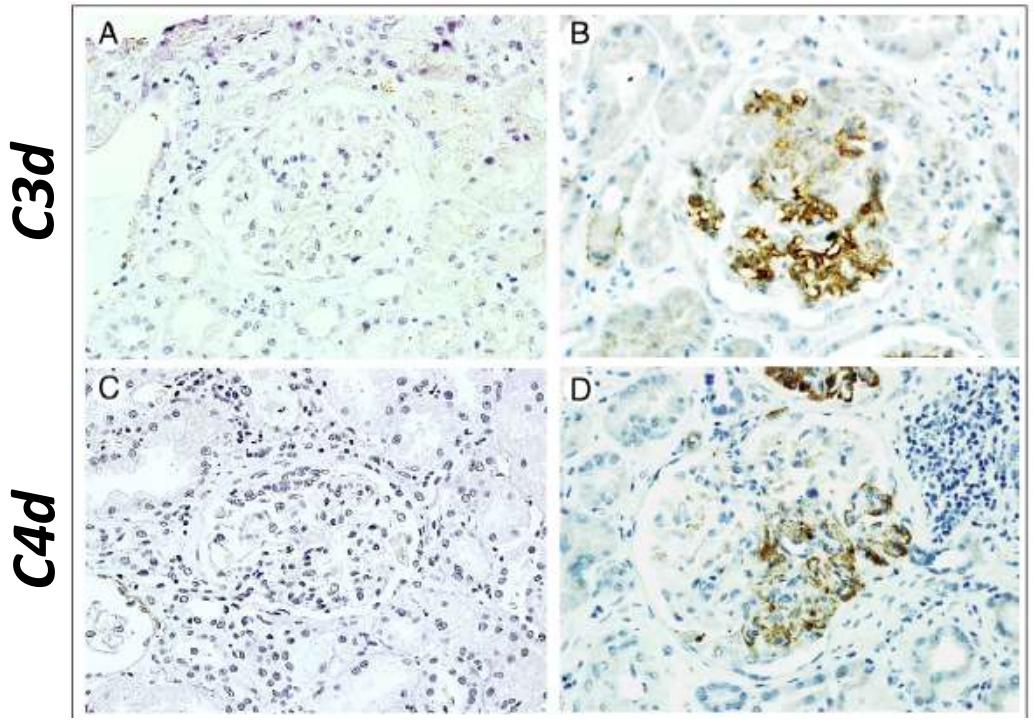
Augusto, PLoS One, 2016

-Tous les patients avaient des taux de C3 >Norme (780 mg/l)
-en séparant patients avec C3 < ou > 1200 mg/l

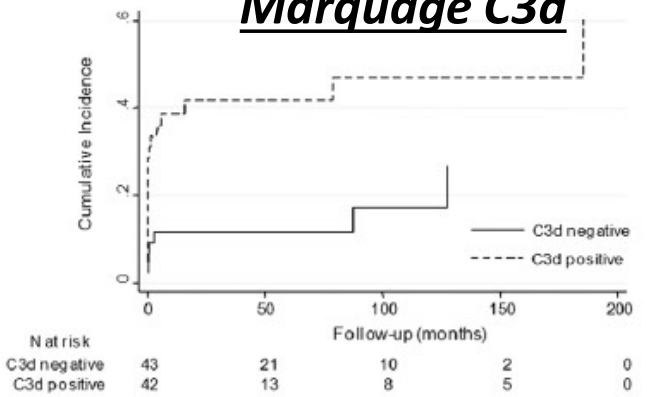


Quelles preuves de l'activation du complément dans la vascularite à ANCA chez l'homme ?

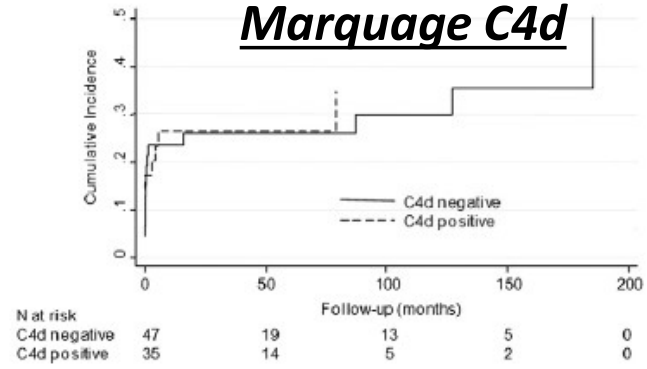
Glomerular C3d as a novel prognostic marker for renal vasculitis *Villacorta, Hum Pathol, 2016*



Marquage C3d



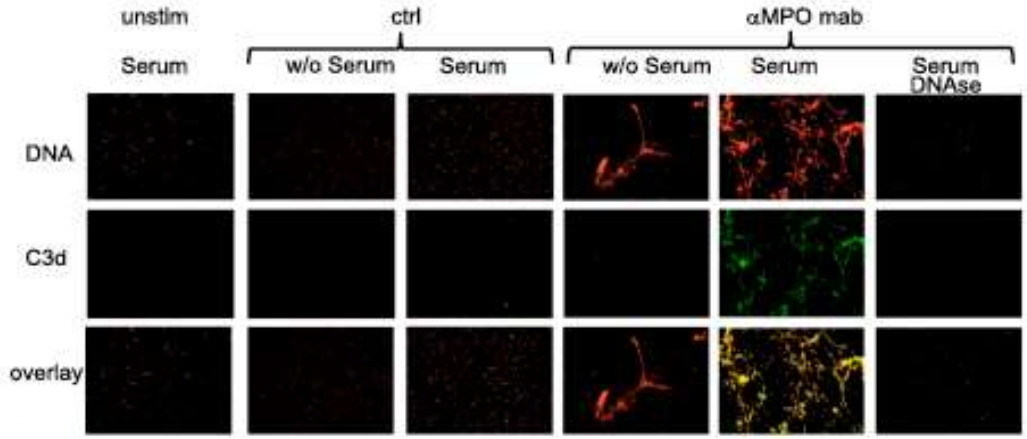
Marquage C4d



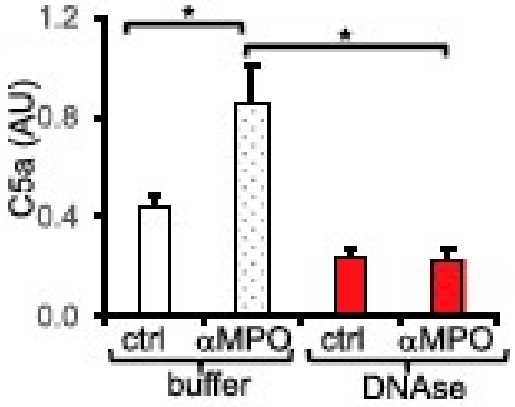
Pourquoi une activation du complement dans la VAA ?

Necroptosis controls NET generation and mediates complement activation, endothelial damage, and autoimmune vasculitis ***Schreiber, PNAS, 2017***

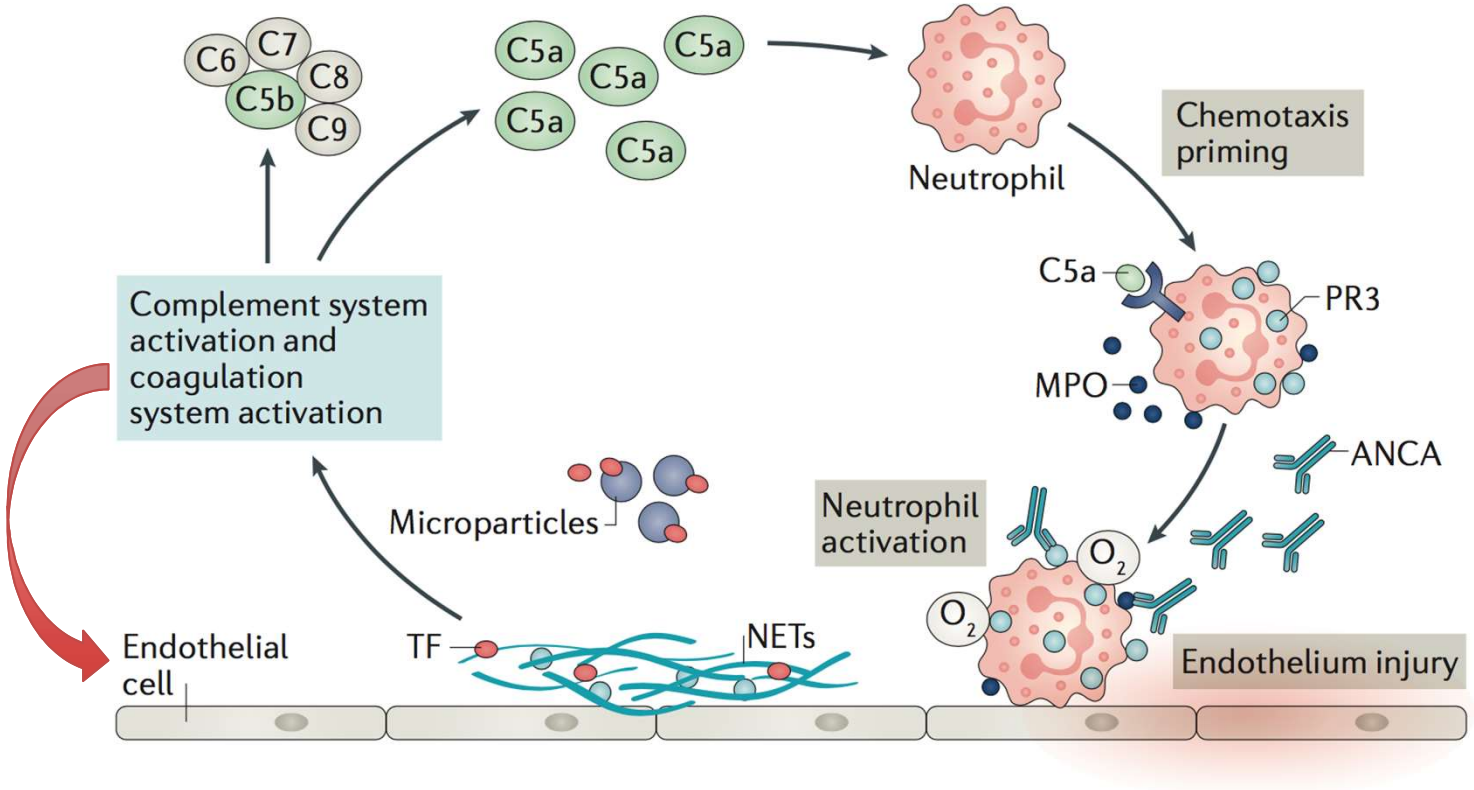
Des PNN primés par le TNF et stimulés avec des ANCA-MPO en présence de sérum engendrent la formation de NET, fixantle C3d



NETs induits par les ANCA-MPO et incubés avec du sérum engendrent l'activation du complément avec production de C5a



Pourquoi une activation du complement dans la VAA ?



Chen, Nat Rev Rheumatol, 2017

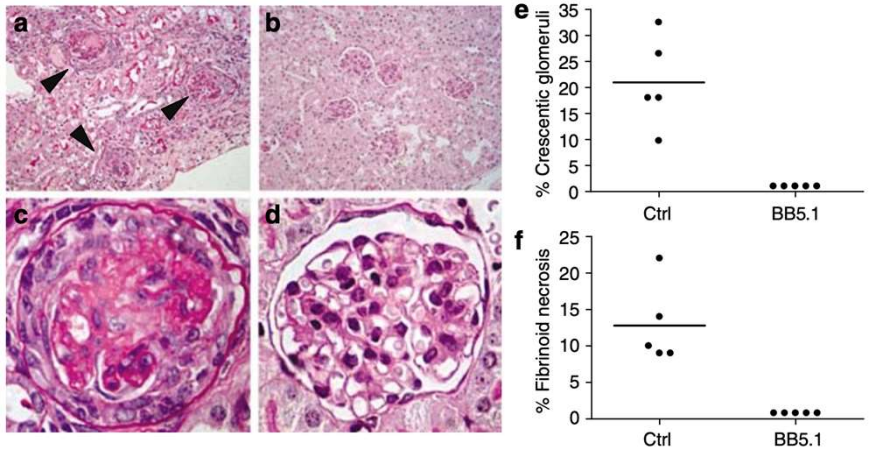
Une nouvelle cible thérapeutique ?

Modèle murin de VAA antiMPO

Inhibition of complement factor C5 protects against anti-myeloperoxidase antibody-mediated glomerulonephritis in mice

D Huugen[1], A van Esch[1], H Xiao[2], CJ Peutz-Kootstra[3], WA Buurman[4], JW Cohen Tervaert[1], JC Jennette[2] and P Heeringa[5]

Kidney International (2007) **71**, 646–654



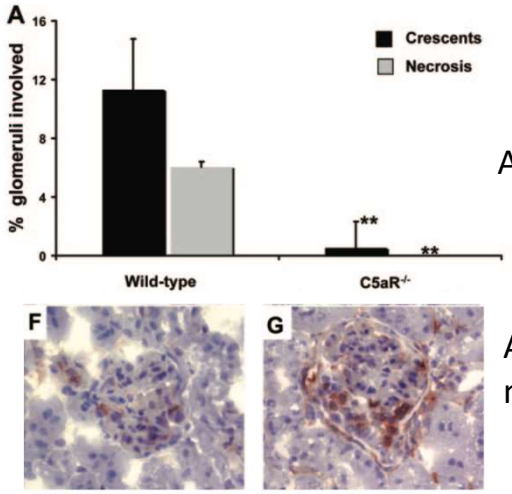
Pretreatment with anti-C5 moAb (BB5.1) prevents development of NCGN
(and Intervention with anti-C5 moAb attenuates NCGN)

C5a Receptor Mediates Neutrophil Activation and ANCA-Induced Glomerulonephritis

Adrian Schreiber,* Hong Xiao,† J. Charles Jennette,† Wolfgang Schneider,* Friedrich C. Luft,* and Ralph Kettritz*

J Am Soc Nephrol 20: 289–298, 2009.

MPO-deficient mice were immunized with MPO and irradiated and received BM cells from WT or C5aR-gene deficient (C5aR-/-) mice



Attenuation of NCGN

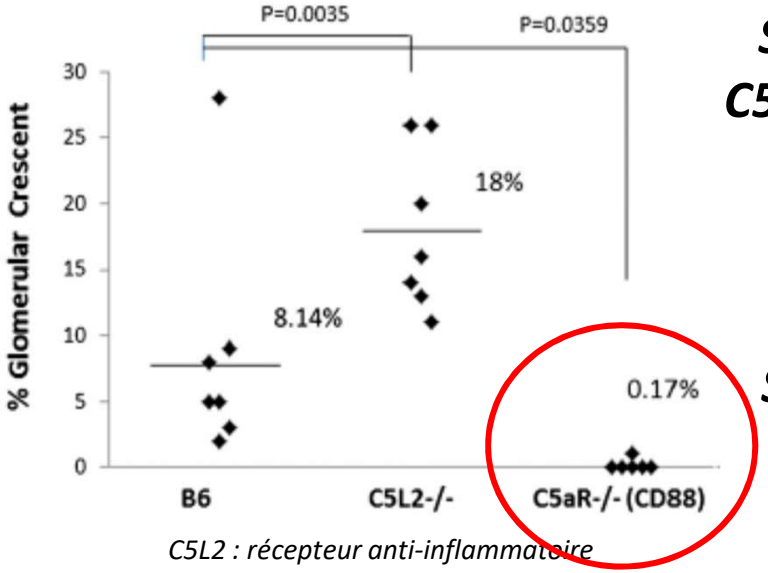
Attenuation of glom. neutrophil influx

Une nouvelle cible thérapeutique ?

C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN ***Xiao, JASN, 2014***

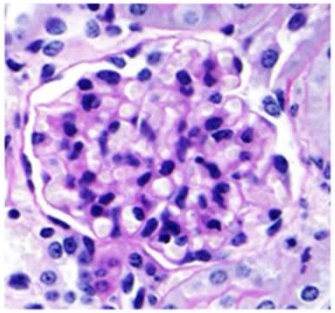
Modèle murin de VAA antiMPO

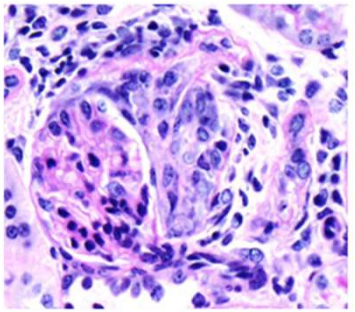
L'inactivation du C5aR inhibe
la formation des croissants



C5L2 : récepteur anti-inflammatoire
C5aR : récepteur pro-inflammatoire

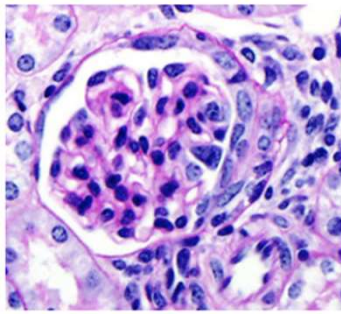
Souris C5aR-/-





Souris C5L2-/-

Souris C6-/-

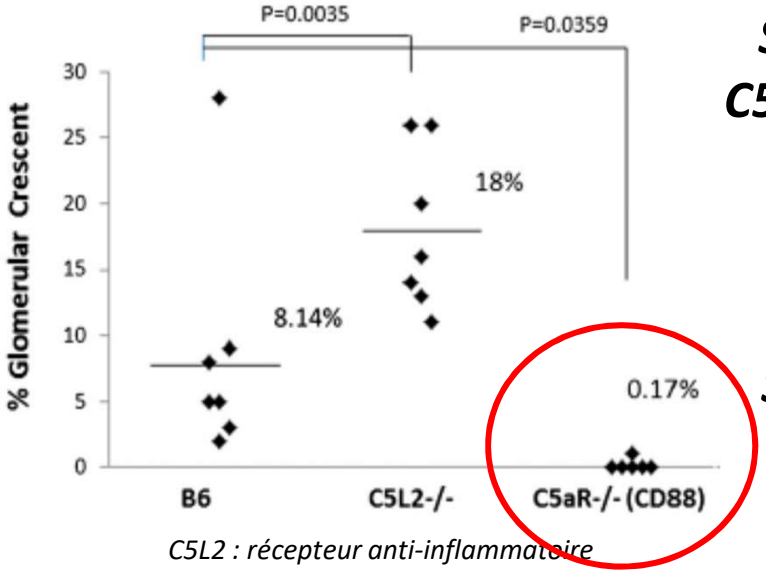


Une nouvelle cible thérapeutique ?

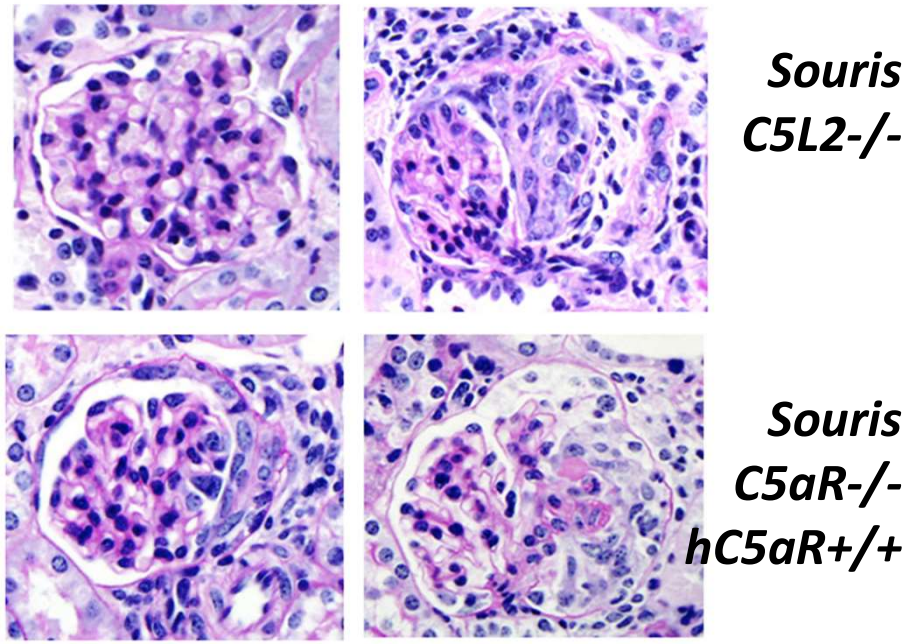
C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN ***Xiao, JASN, 2014***

Modèle murin de VAA antiMPO

L'inactivation du C5aR inhibe
la formation des croissants



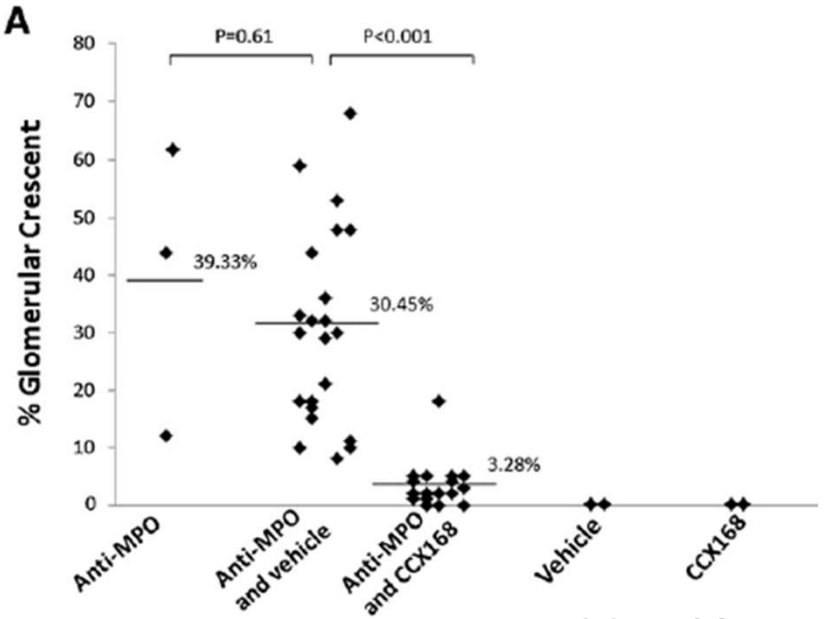
C5L2 : récepteur anti-inflammatoire
C5aR : récepteur pro-inflammatoire

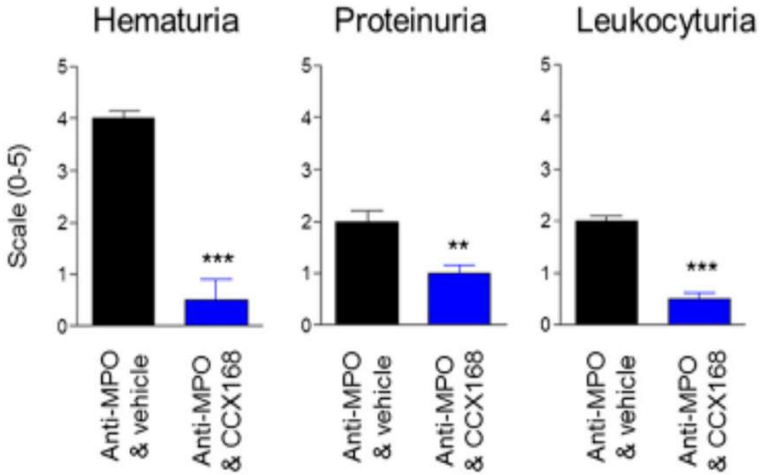


Une nouvelle cible thérapeutique ?

C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN ***Xiao, JASN, 2014***

Modèle murin de VAA antiMPO (avec C5aR humain)





CCX168 : molécule inhibant spécifiquement le hC5aR

= AVACOPAN

Avacopan dans la VAA : essai CLEAR (phase 2)

CLINICAL RESEARCH www.jasn.org

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

N=67 patients

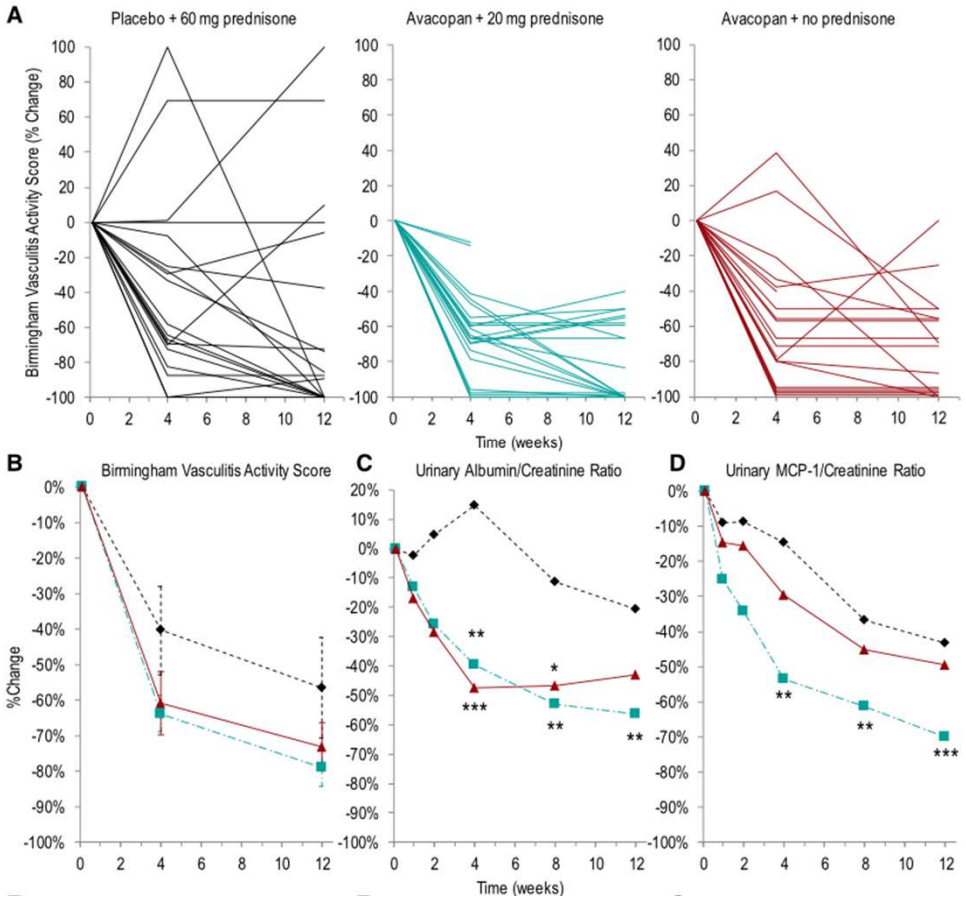
Gp A : placebo + CYC +GC standard dose. (n=23)

Gp B : avacopan + CYC + GC low dose. (n=22)

Gp C : avacopan + CYC + placebo (no GC) (n=22)

Jayne, JASN 2017

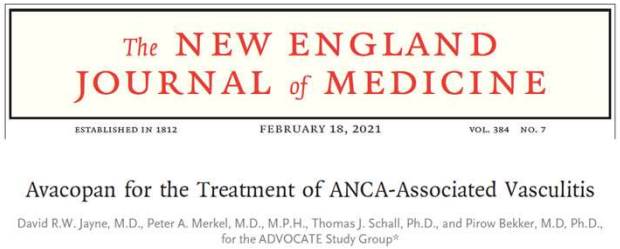
Avacopan dans la VAA : essai CLEAR (phase 2)



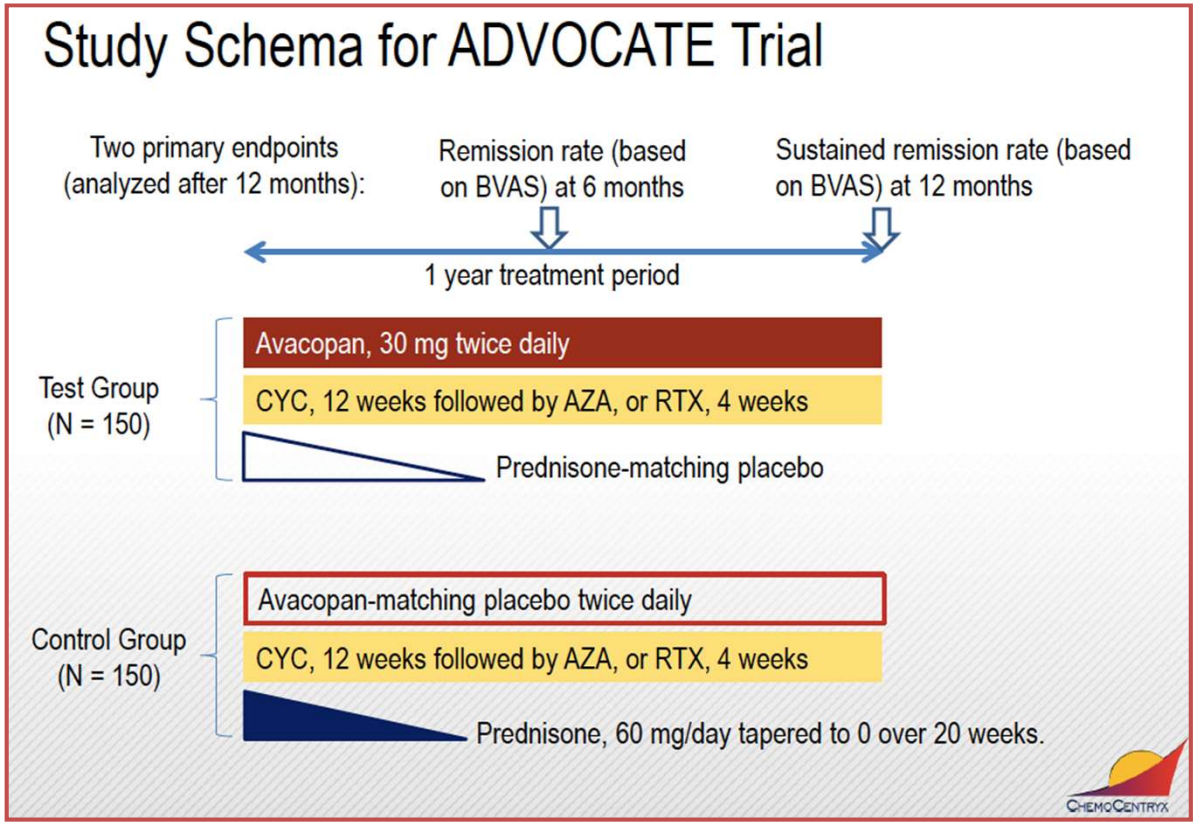
Essai de non-infériorité suggérant que l'avacopan peut permettre de réduire ou remplacer les corticoïdes

Jayne, JASN 2017

Avacopan dans la VAA : essai ADVOCATE (phase 3)



Etude internationale, randomisée/contrôlée de non-infériorité



Jayne, NEJM 2021

Avacopan dans la VAA : essai ADVOCATE (phase 3)

- Remission at 6 months (BVAS of 0 and no receipt of GC for 4 weeks)
  70% in GC group vs. 72% in Avacopan group

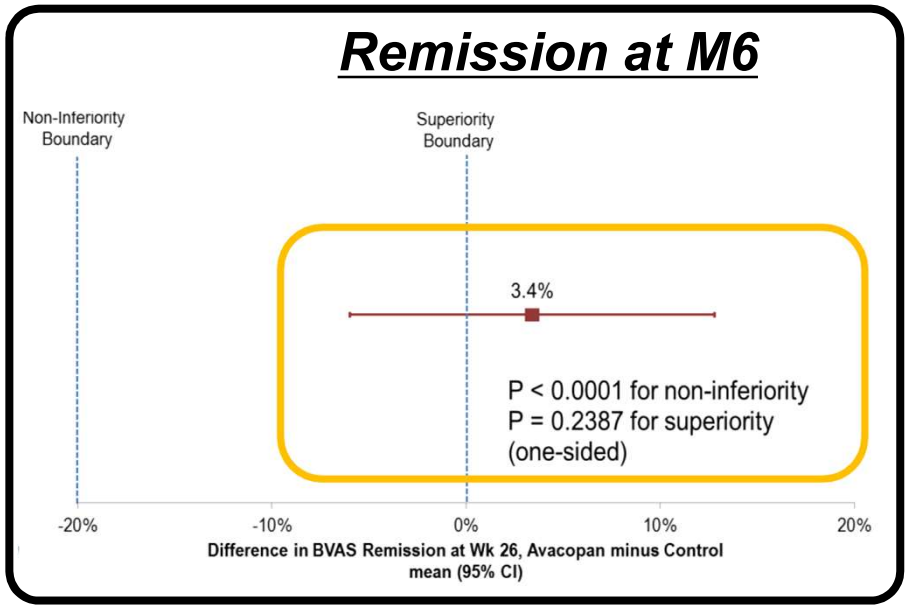


Table S8. Remission at Week 26 for Each Subgroup*

	Prednisone (N=164)	Avacopan (N=166)
All Patients*	115 / 164 (70.1%)	120 / 166 (72.3%)
Disease Status		
Newly diagnosed patients	76 / 114 (66.7%)	76 / 115 (66.1%)
Relapsing disease	39 / 50 (78.0%)	44 / 51 (86.3%)
ANCA Type		
Anti-proteinase 3 positive	50 / 70 (71.4%)	51 / 72 (70.8%)
Anti-myeloperoxidase positive	65 / 94 (69.1%)	69 / 94 (73.4%)
Background Treatment		
Cyclophosphamide	34 / 57 (59.6%)	37 / 59 (62.7%)
Rituximab	81 / 107 (75.7%)	83 / 107 (77.6%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	65 / 90 (72.2%)	65 / 91 (71.4%)
Microscopic polyangiitis	50 / 74 (67.6%)	55 / 75 (73.3%)

Jayne, NEJM 2021

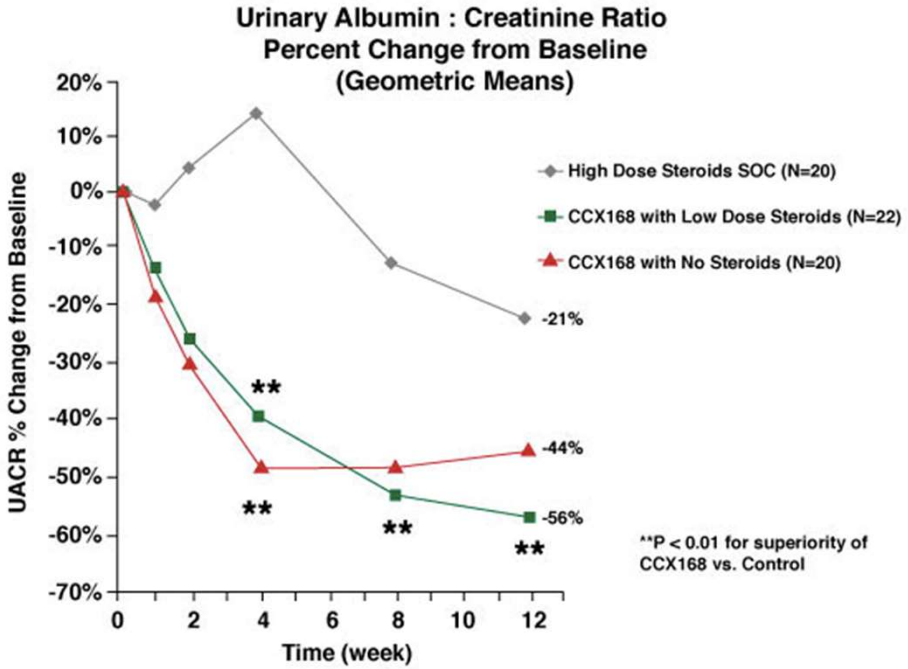
Avacopan dans la VAA : essai ADVOCATE (phase 3)

ADVOCATE Safety Overview

	Prednisone (N=164)	Avacopan (N=166)
Number of any treatment-emergent adverse events	2139	1779
Subject incidence (%) treatment-emergent adverse event	161 (98.2)	164 (98.8)
Subjects with any severe adverse event	41 (25.0)	39 (23.5)
Subjects with any life-threatening adverse event	14 (8.5)	8 (4.8)
Deaths	4 (2.4)	2 (1.2)
Number of serious adverse event	166	116
Subjects incident (%), serious adverse event	74 (45.1)	70 (42.2)
Subjects with any serious infection	25 (15.2)	22 (13.3)
Deaths due to infection	2 (1.2)	1 (0.6)
Subjects with any serious hepatic system adverse event	6 (3.7%)	9 (5.4%)
Subjects with any adverse event potentially related to glucocorticoids (Investigators blinded assessment)	132 (80.5)	110 (66.3)

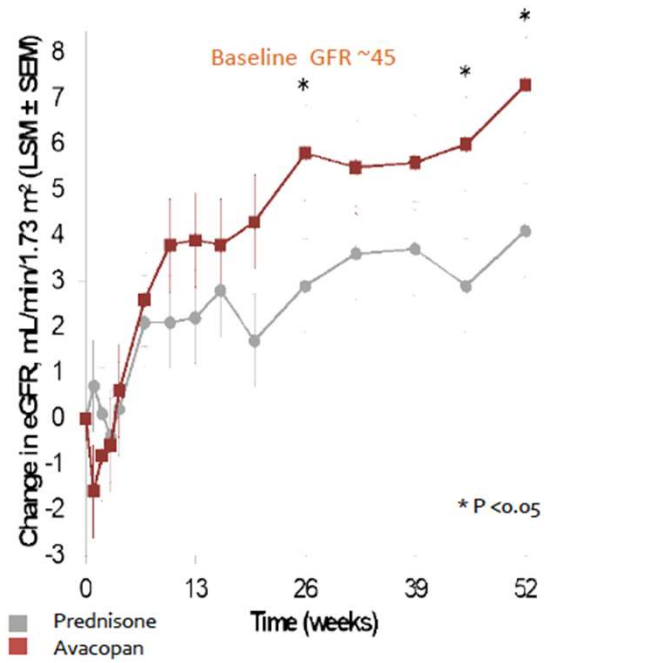
Jayne, NEJM 2021

Avacopan et récupération rénale ?



Etude CLEAR

Improvement in eGFR in all patients with renal disease at baseline



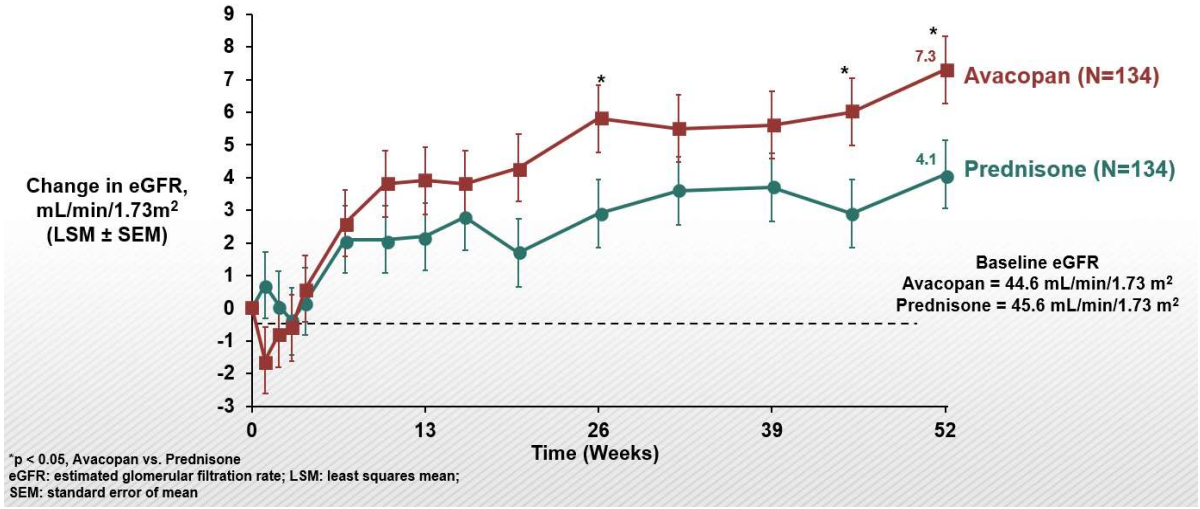
Etude ADVOCATE

Avacopan et récupération rénale ?

Etude ADVOCATE

Patients with Renal Disease at Baseline (268/330 pts)

Jayne, NEJM 2021



+7.3 ml/min/1.73 m2

Delta = 3.2 ml/min

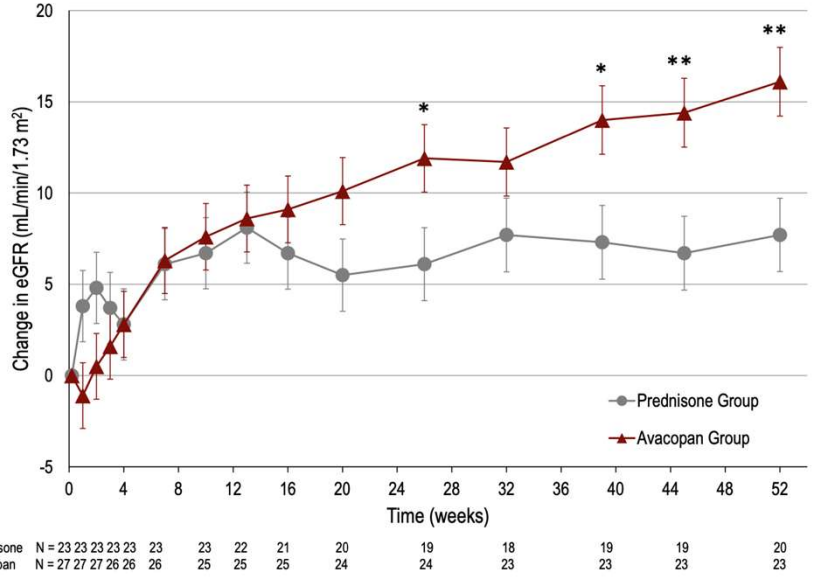
+4.1 ml/min/1.73 m2

Avacopan et récupération rénale ?

Etude ADVOCATE

Subgroup of 50 patients with initial eGFR<20 (median 17.5 ml/min)

Cortazar, Kidney Int Reports 2023



+16.1 ml/min/1.73 m2

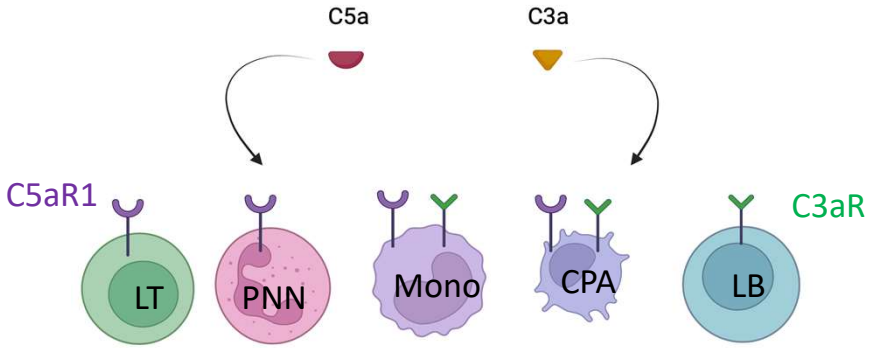
Delta = 8.4 ml/min

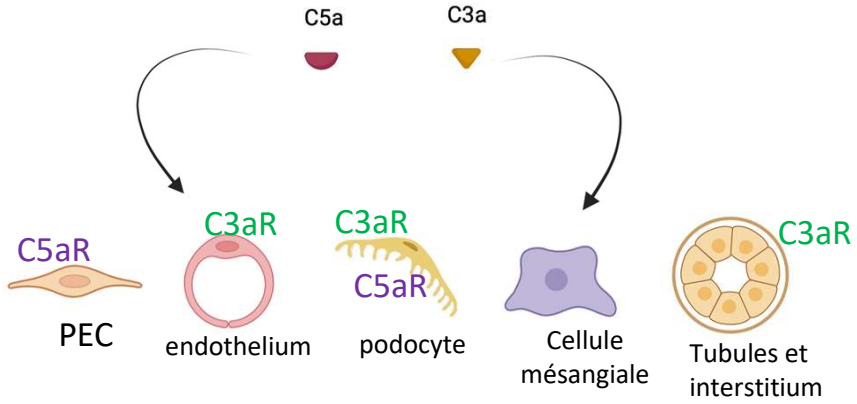
+7.7 ml/min/1.73 m2

Quelle place pour l'avacopan ?

- Epargne cortisonique ?
  - Patients à haut risque d'ES des stéroïdes ?
  - Tout patient ?
- Amélioration de la fonction rénale ?
  - Patients les plus graves ?
  - Utilisation selon facteurs prédictifs biologiques / histologiques ?

Etude de l'axe C5a/C5aR et C3a/C3aR dans la vascularite à ANCA avec atteinte rénale (S. Chauvet –HEGP)

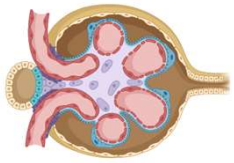




Role pro inflammatoire du C5a/C5aR1 à la phase aigue
Role anti inflammatoire du C3a à la phase aigue
Role pro inflammatoire du C3a en cas d'inflammation persistante

Effet des anaphylatoxines sur les cellules rénales moins bien connu
Modification du cytosquelette (podocyte)
Role profibrosant du C5a et C3a
Activation de la cellules mésangiale

Impact sur l'atteinte rénale?



Identification des patients pouvant bénéficier de l'inhibition du complément ?

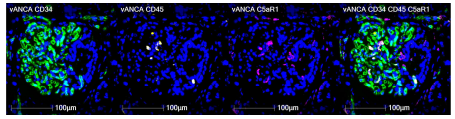
Etude de l'axe C5a/C5aR et C3a/C3aR dans la vascularite à ANCA avec atteinte rénale (S. Chauvet –HEGP)

Vascularite à ANCA
+
atteinte rénale

1ère poussée ou rechute
(avant traitement)

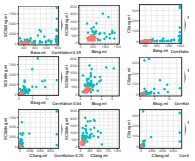
M0

Technique Opale

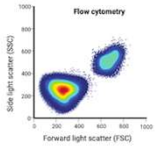


Marquage in situ des populations immunitaires
C3aR et C5aR

M0 puis M3



Dosage du C3a, C5a
et autres fragments d'activation
du complément (Bb, sC5b9..)

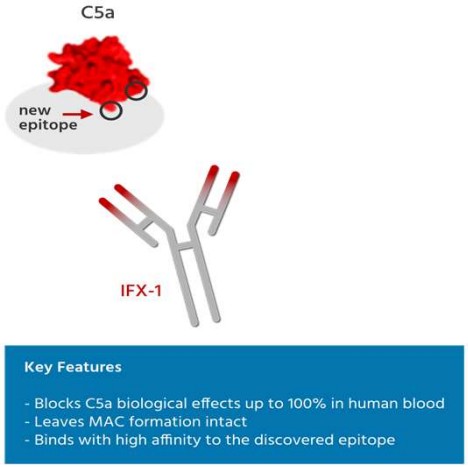


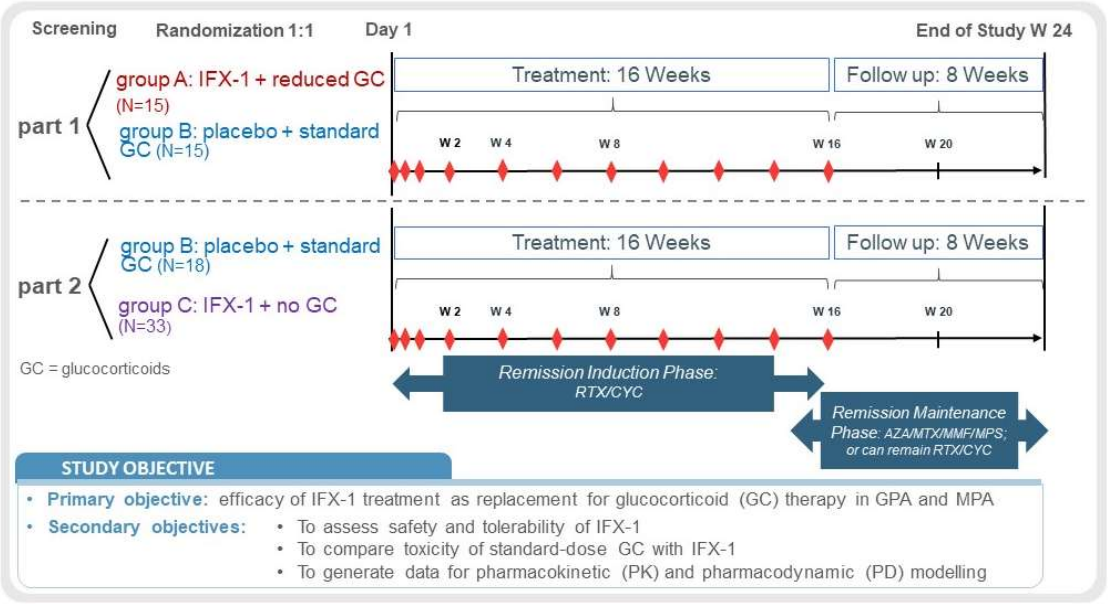
Expression membranaire (granuleux)
C5aR1/C5aR2/C3aR

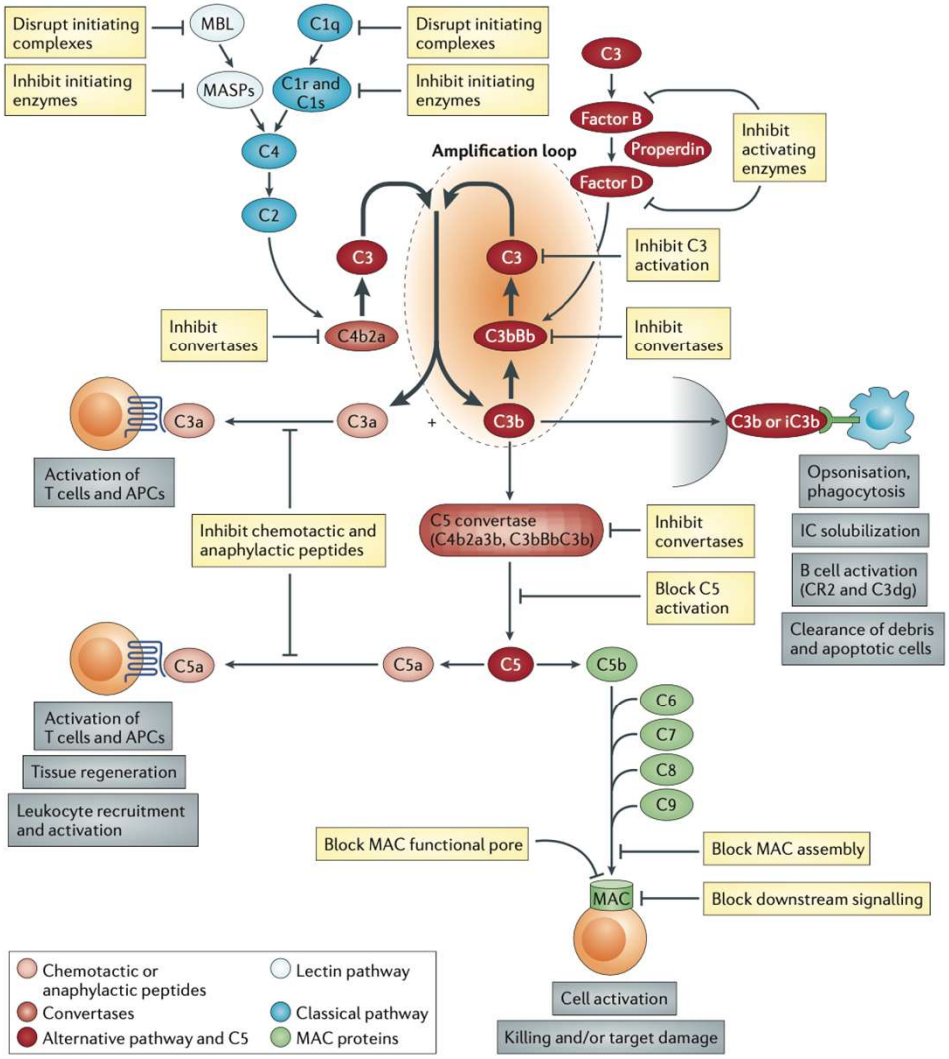
Polymorphisme de C5aR1/R2 et C3aR

Autres anti-compléments ?

- IFX-1 (Ac antiC5a)







Drug	Target	Study description
Ravulizumab	C5 inhibitor	Phase II study of ravulizumab in proliferative LN or IgAN[48]
Avacopan (CCX168)	C5a receptor blocker	Phase II, open-label study to evaluate safety and efficacy of CCX168 in subjects with IgAN[49]
Cemdisiran	Small interfering mRNA inhibitor of synthesis of C5	Phase II study of cemdisiran in adults with IgAN[50]
Pegetacoplan (APL-2)	C3 inhibitor	Phase II study assessing safety and efficacy of APL-2 in glomerulopathies[51]
Iptacopan (LNP023)	Complement fB inhibitor	Phase II study assessing efficacy and safety of LNP023 in patients with primary IgAN (APPLAUSE IgAN [NCT04578834])[52]
IONIS FB-LRx	Complement fB inhibitor	Study assessing efficacy and safety of IONIS-FB-LRx, an antisense inhibitor of complement fB, in adult participants with primary IgAN[53]
Narsoplimab	MASP-2 inhibitor	Study assessing the safety and efficacy of OMS721 in patients with IgAN[54]

Nouvelles pistes thérapeutiques dans les maladies auto-immunes !