Stratégies thérapeutiques et actualités dans la Vascularite à IgA

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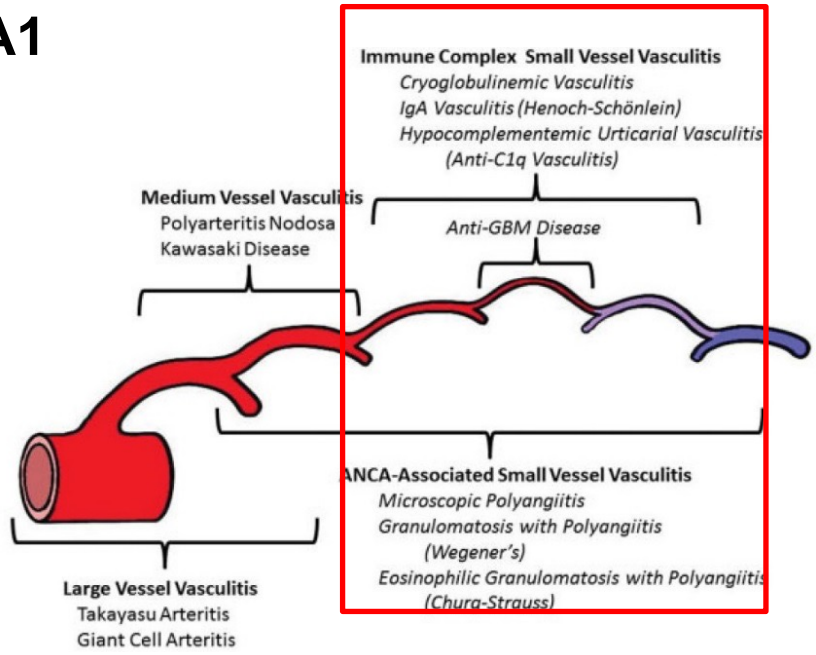
Généralités

- **Vascularite des petits vaisseaux à complexes immuns contenant des IgA1**

- **Post-infectieuse**

- **Sexe ratio H/F :1.5[1]**

- **Age moyen 50 ans[1]**



2012 Revised International Chapel Hill Consensus Conference Nomenclature ofVasculitides

- **Pronostic à court terme conditionné par l'atteinte digestive[2]**

- **Pronostic à long terme conditionné par l'atteinte rénale[3]**

1 Audemard-Verger et al Arthritis and Rheum. 2017
2 Audemard-Verger et al Rheumatology 2020
3 Pillebout et al JASN 2012

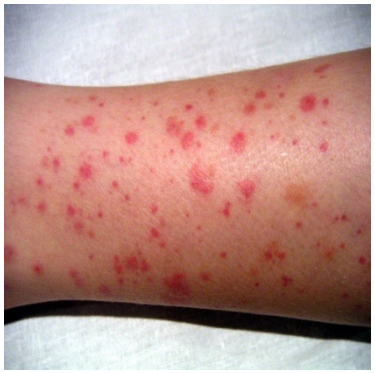
Présentation clinique

VASCULARITE à IgA

Cutanée 100%

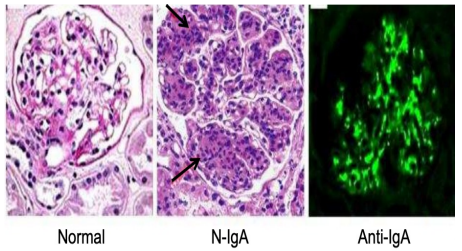
Purpura vasculaire

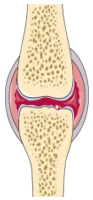
« infiltré, déclive +/- nécrotique »



Rénal 70%

Néphropathie à IgA



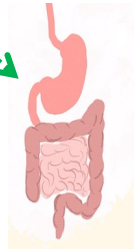


Articulations 60%

Oligoarthalgies

Chevilles++

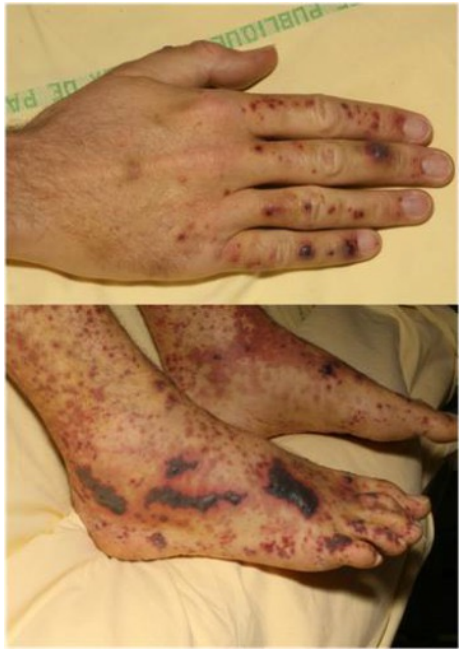
Genou

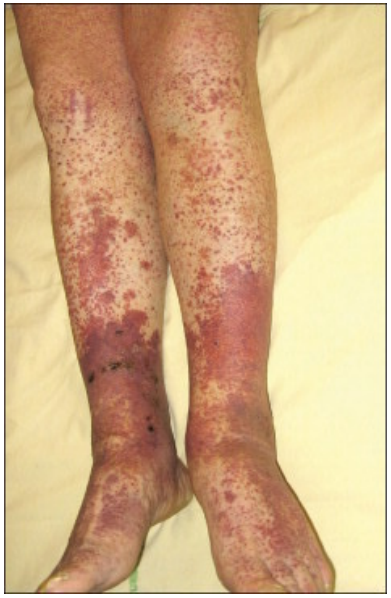


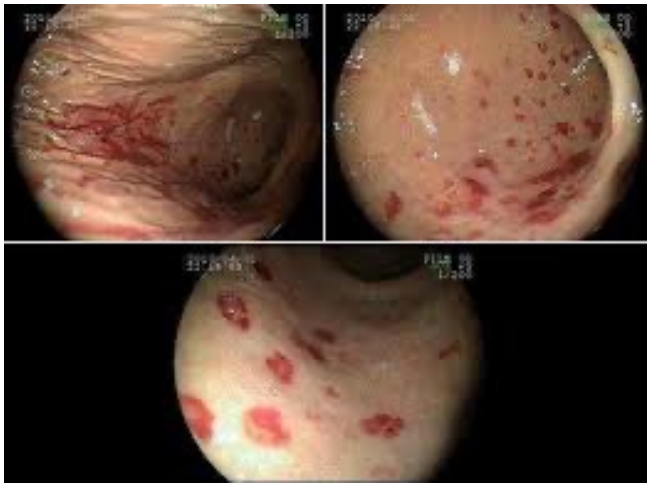
Digestif 50%

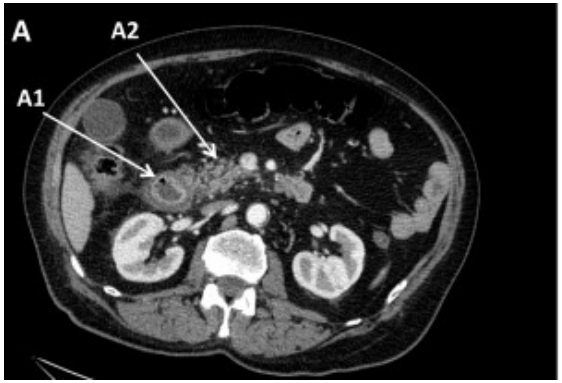
Douleur abdominale, méléna, perforations…

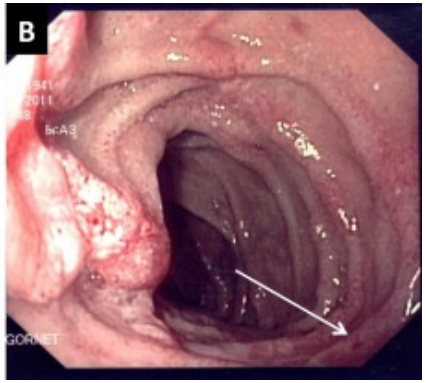
Audemard-Verger et al Arthritis Rheum. 2017

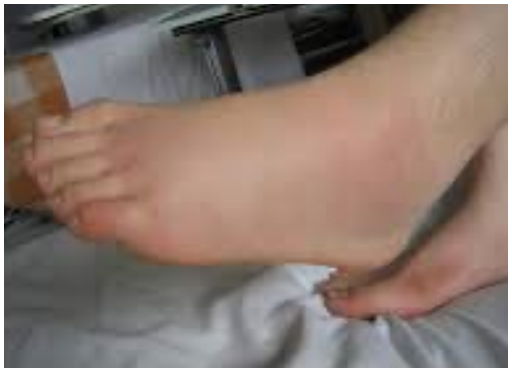


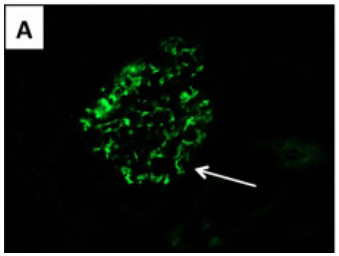


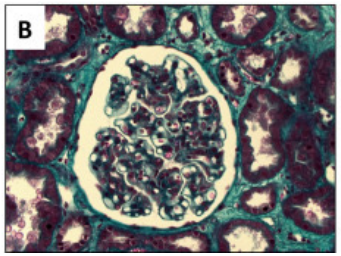


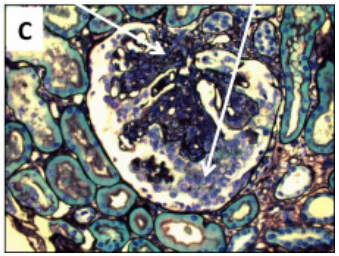








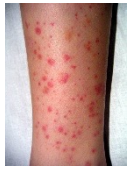




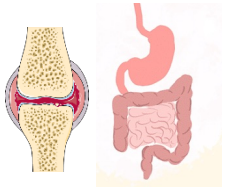
Pillebout et al Revue du Rheum 2017

Diagnostic

Signes Cliniques



+/-



Diagnostics différentiels

Vascularite cryoglobulinémique
Vascularite associée ANCA
Endocardite infectieuse

Signes biologiques

+/- 

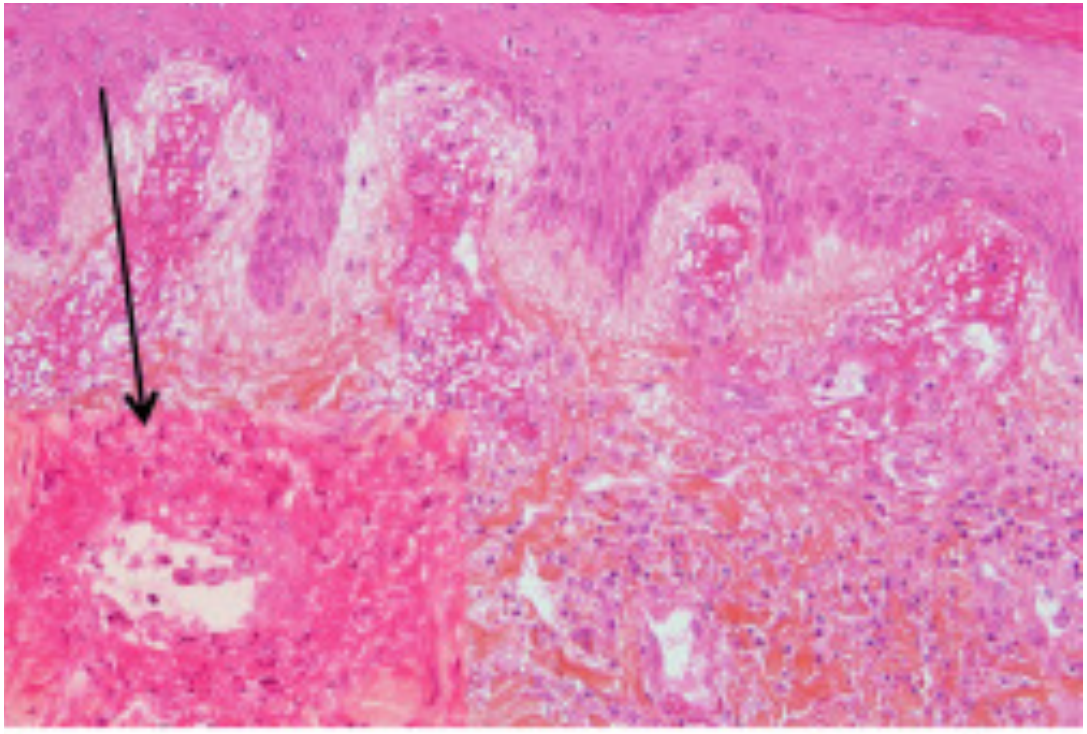
+/- ⇧ Isolée IgA Sériques

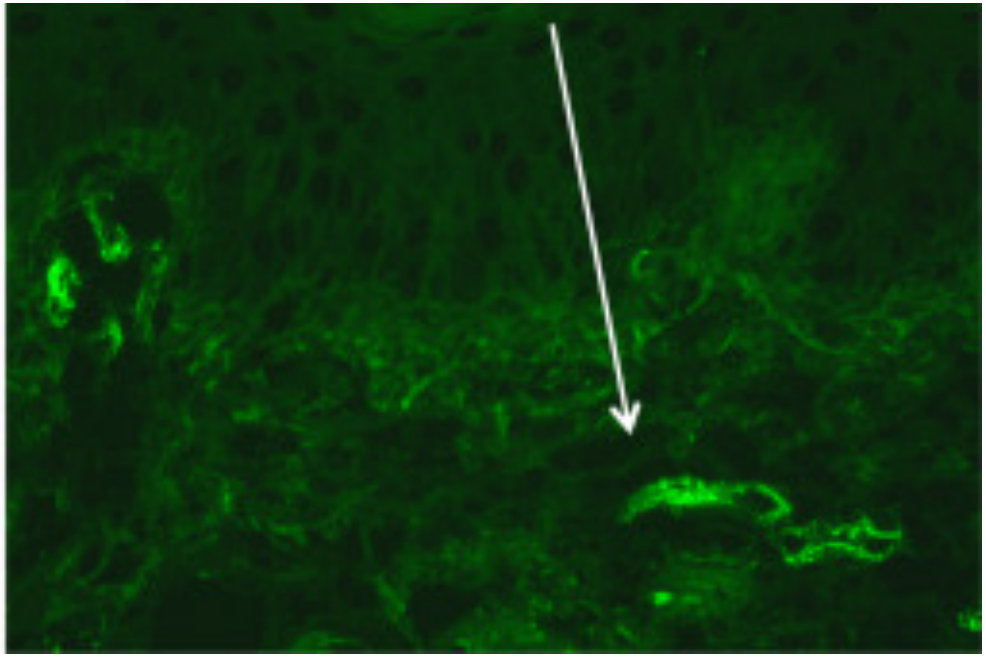
+/- ⇧ CRP

+/-Preuve histologique

Biopsie peau +++
+/- PBR
Pas de biopsie GI

+ Recherche Trigger (vaccin, infection muqueuse, médicament)
Et d'une maladie sous jacente : cirrhose, SPA, cancer muqueux, MGUS IgA

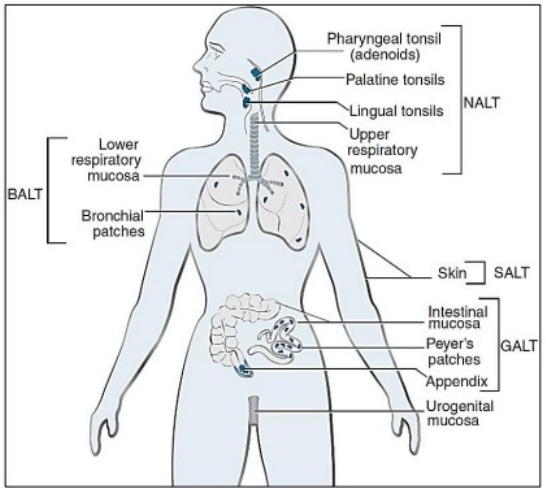




Tips :

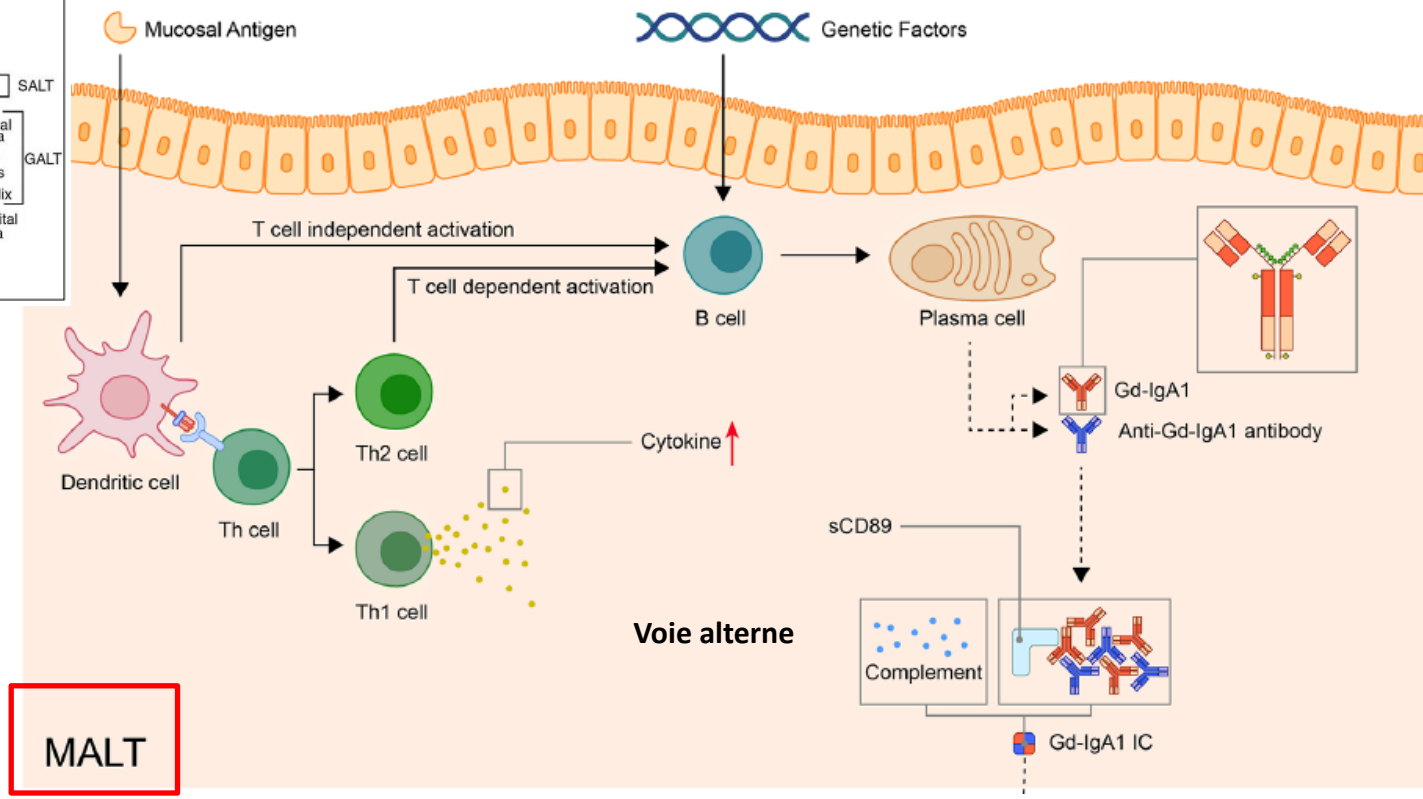
- ✓ **Faire deux biopsies au punch 1 HES 1 IF (état frais)**
- ✓ **Biopsie une lésion purpurique « fraiche »**
- ✓ **Se rappeler que 20% IgA - peau**

Physiopathologie



MALT

Tissu lymphoïde associé muqueuse digestive, respiratoire, urothéliale



Yan Song Front Immunol 2021

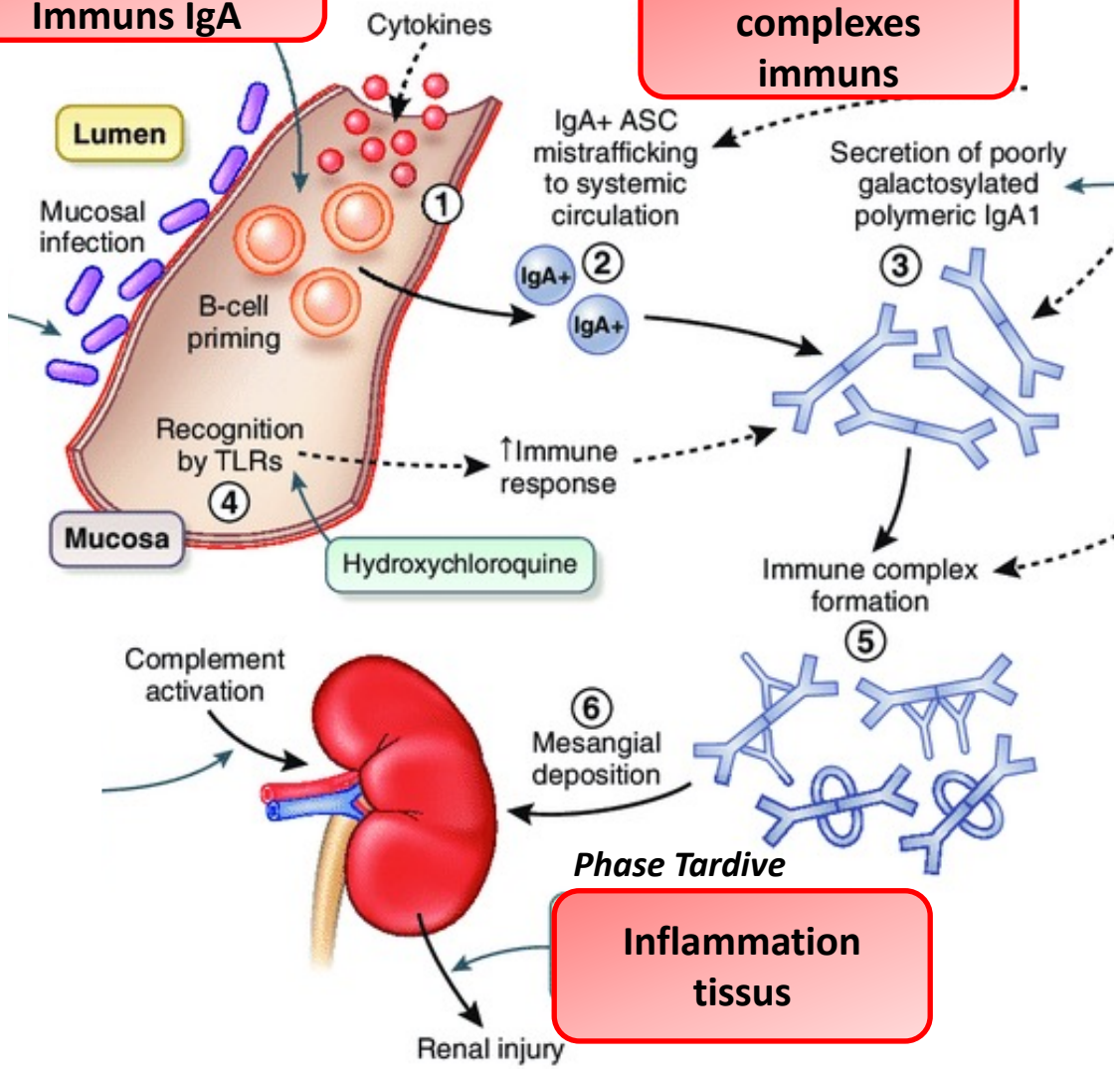
Physiopathologie

Phase précoce

Formation des complexes Immuns IgA

Phase intermédiaire

Circulation des complexes immuns

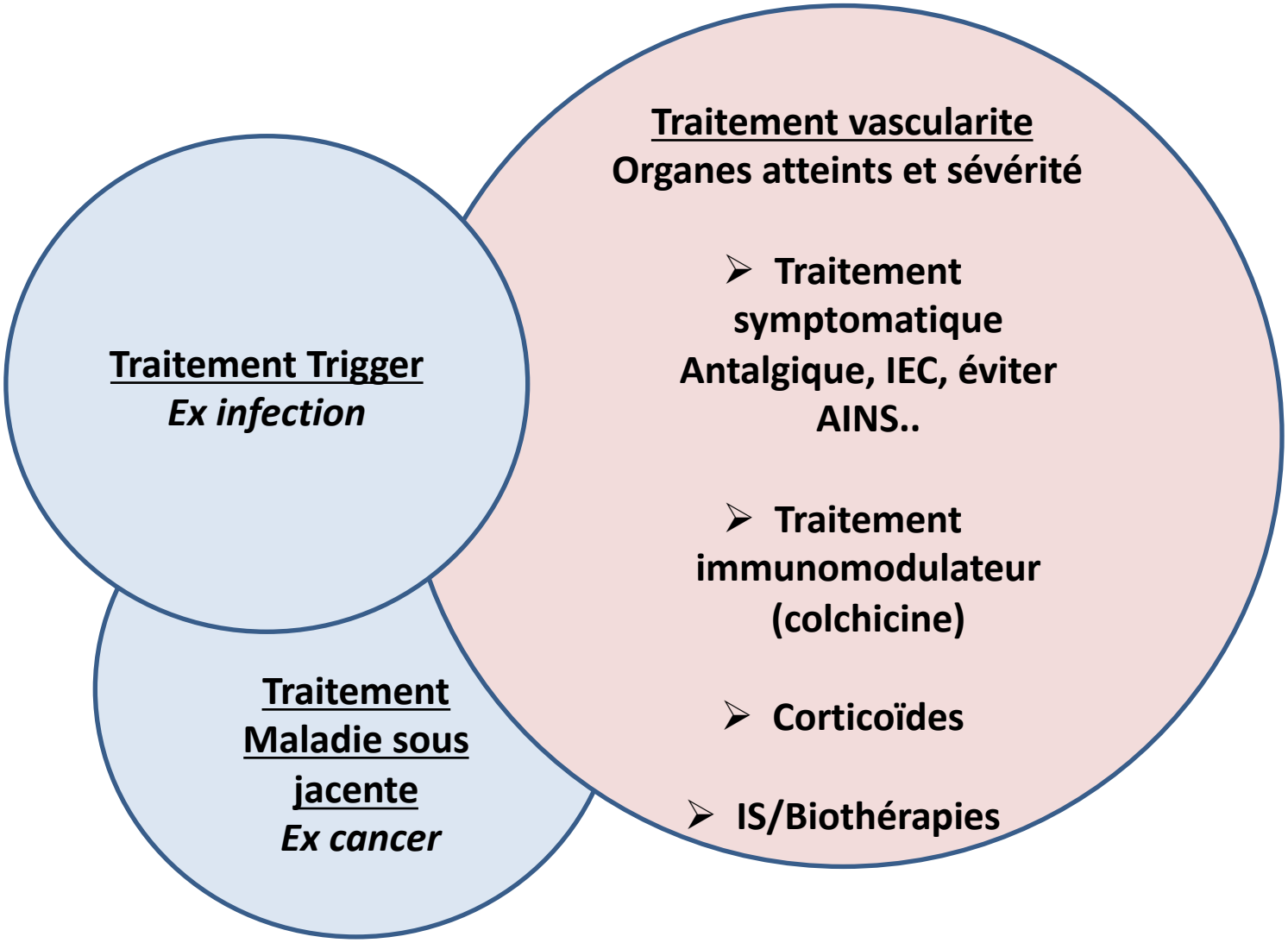


Phase Tardive

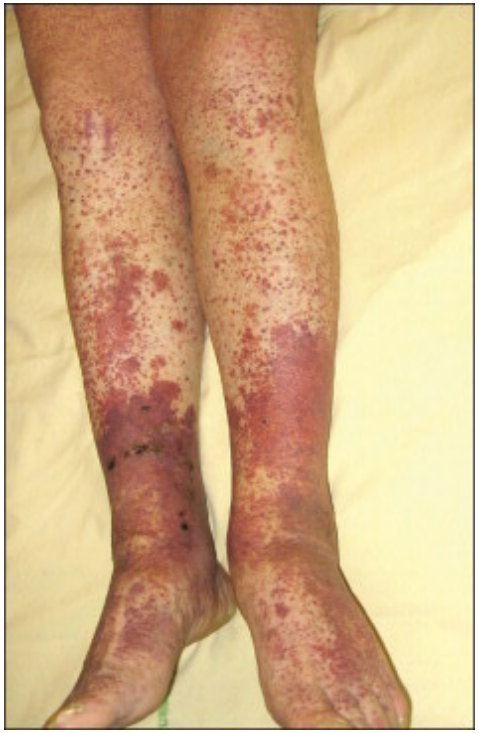
Inflammation tissus

Adapté de Boyd JK, Kidney Int. 2012

Stratégie thérapeutique actuelle



Atteinte Cutanée



✓ **En cas de poussée cutanées isolée aigue:**

- Pas de traitement (repos) sauf si atteinte nécrotique/bulle hémorragique
- *Cortancyl 0,5mg/kg 2 semaines*

✓ **En cas de rechute cutanées :**

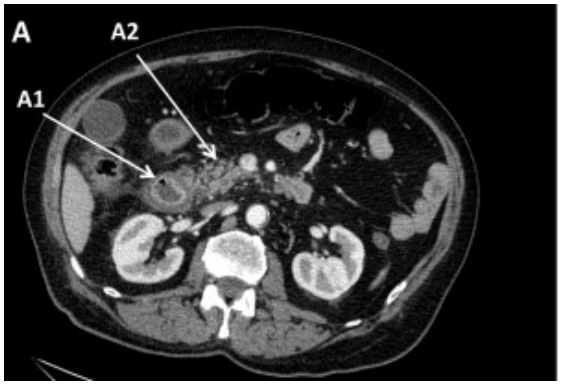
- *Colchicine 1mg/j 6 mois*

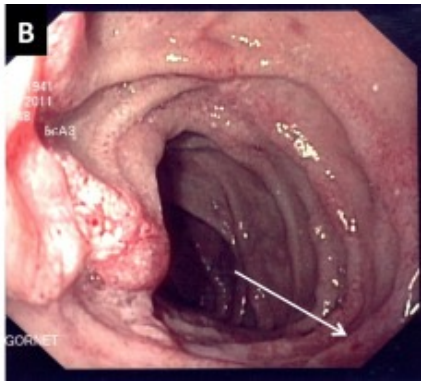
Sais et al 1995; Audemard-Verger et al 2017*; Callen et al.,1985; Callen et al., 1987*

- ***Dapsone 50–150 mg /j*** sans déficit G6PD

Roman et al 2019 *Pediatric case series and review of literature*

Atteinte Digestive





- ✓ **Dans les formes digestives légères** *(douleur abdominale isolée, échographie ou tomodensitométrie normale)*

Traitement symptomatique (régime alimentaire léger et une surveillance étroite)

- ✓ **Dans les cas modérés à sévères**

Traitement par glucocorticoïdes MP + CT per os 4 semaines

- ✓ **Patients réfractaires**

Traitement de sauvetage par échange plasmatique ou cyclophosphamide peut être envisagé

Atteinte Rénale IgA-N

Atteinte rénale et facteurs de mauvais pronostic :

- altération de la fonction rénale
- une protéinurie de type néphrotique
- une protéinurie persistante > 0,5 g/g sous IEC
- Histologie > 50% croissants ou une glomérulonéphrite rapidement progressive (RPGN)

→ Corticostéroïdes +/- IS, RXT, EP

→ Néphroprotecteur IEC, iSGLT2..

Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura

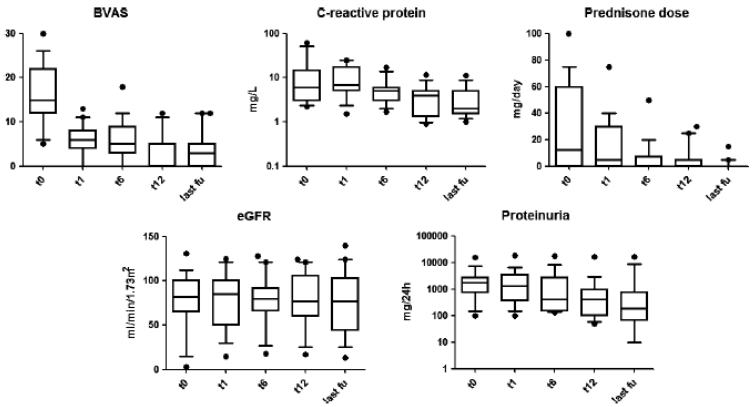
Evangéline Pillebout [1], Corinne Alberti, Loic Guillevin, Amel Ouslimani, Eric Thervet; CESAR study group

Perspectives thérapeutiques

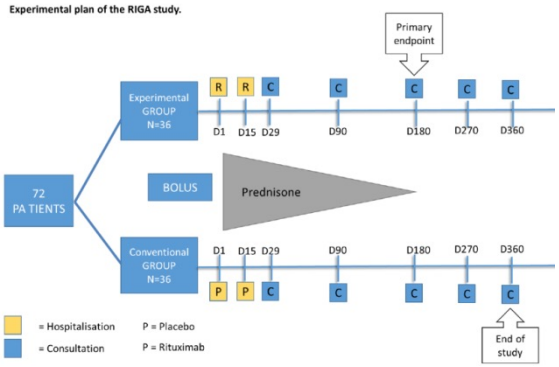
Déplétion des LBs

Rituximab

- **Etude rétrospective IgAV n=22, effet RXT[1]**

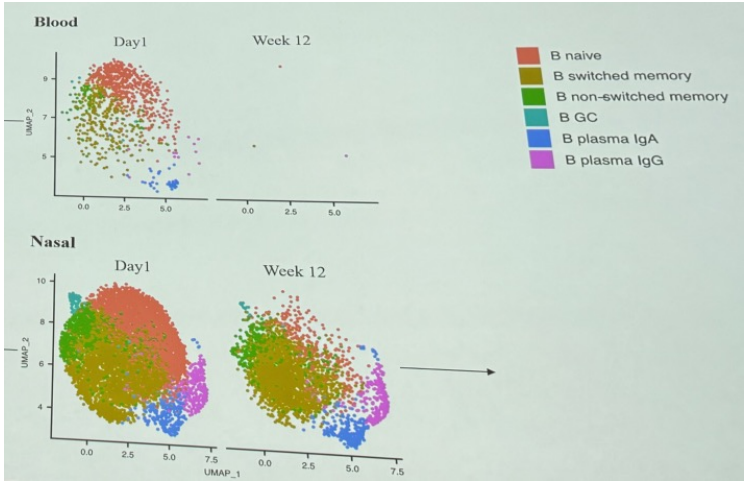


- **PHRC RIGA[2]**



- **RCT négatif IgAN [3]**
  --> Taux IgA1 sérique inchangé[4]

- **Déplétion incomplète LBs ds Tissus[5]**

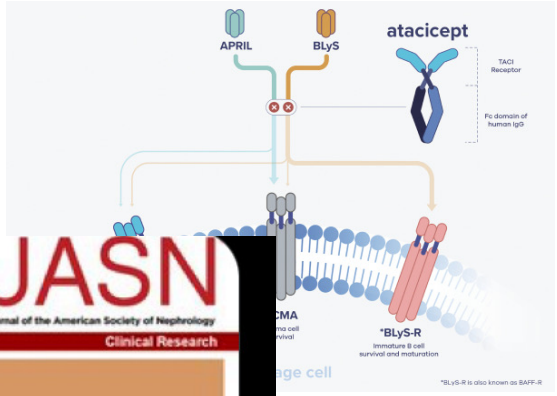


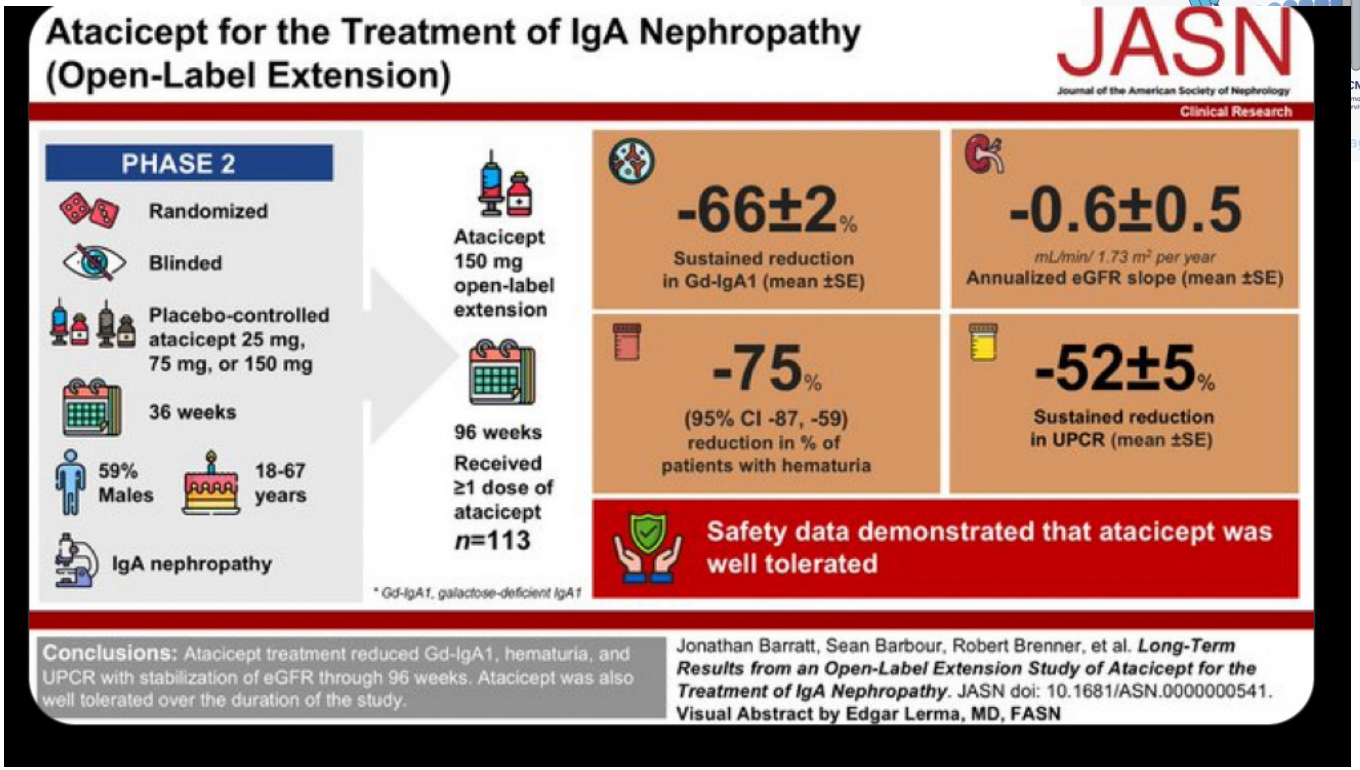
1 Vaglio A Arthritis 2019
2 PHRC RIGA Dr Paule et Pr Terrier
3 Lafayette JASN 2017
3 D Jayne, données non publiées

Déplétion des LBs

- **Antagoniser APRIL ET BAFF**

Atacicept and telitacicept

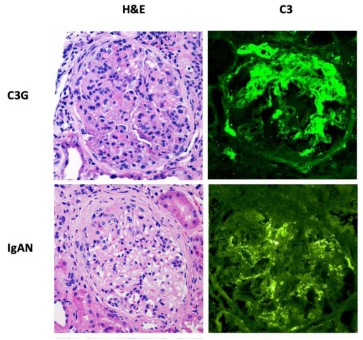




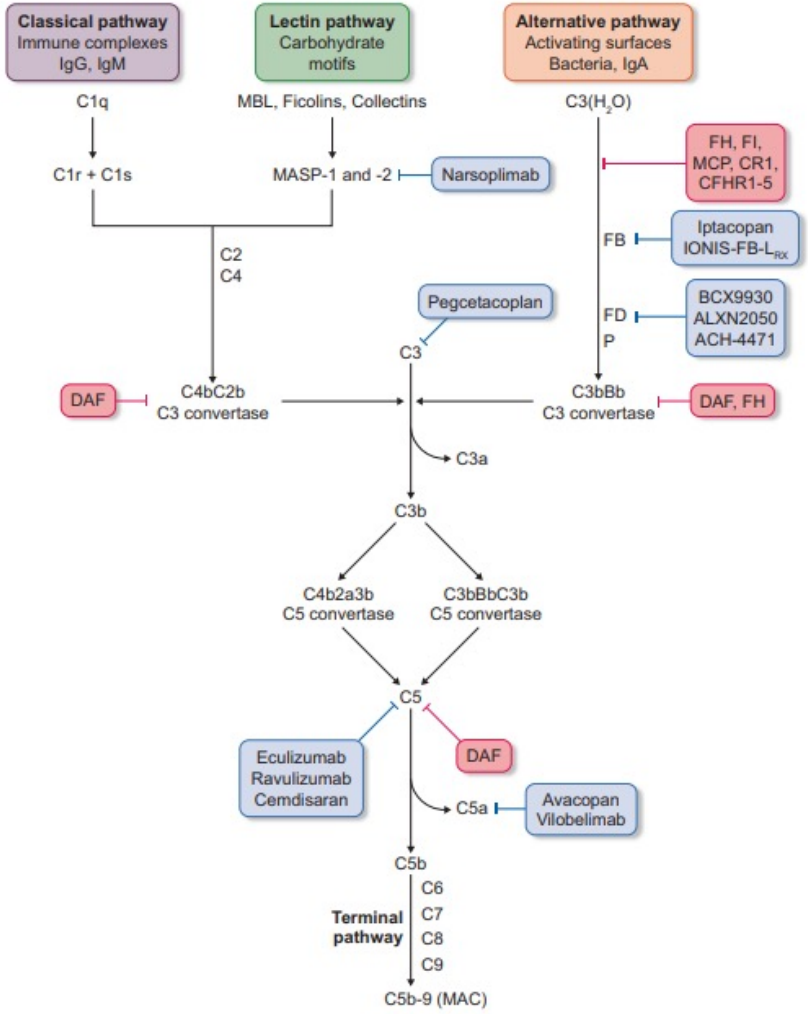
J Barratt Kidney Int 2024

Cibler le complément

- **Les IgA activent la voie alterne du complément**
- **Activation de la voie alterne au cours IgAV[1]**
- **Dépôt de C3, C5-9 au niveau rein, peau[2]**



- **Corrélation entre dépôt complément tissu et gravité de la VIgA[2]**



1Wright RD, Oni L Pediatric Nephrology 2023

2. Yang Y-H, PloS One 2015

Iptacopan Agoniste Facteur B et N IgA

Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy.

kidney INTERNATIONAL ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods

PHASE 2

- Proof of concept, dose-ranging study
- Double-blind
- Randomized
- Biopsy-confirmed primary IgA nephropathy

Intervention

Iptacopan versus placebo (administered orally, twice daily)

Part 1 (3-month treatment)

(N=46)
- Iptacopan 10 mg
- Iptacopan 50 mg
- Iptacopan 200 mg
- Placebo

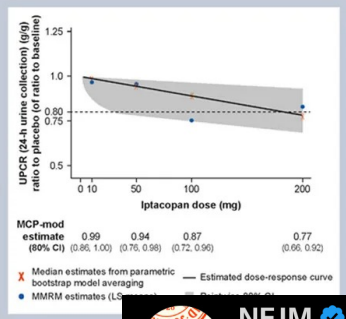
Part 2 (6-month treatment)

(N=66)
- Iptacopan 10 mg
- Iptacopan 50 mg
- Iptacopan 100 mg
- Iptacopan 200 mg
- Placebo

Findings

Primary analysis:

- Statistically significant dose-response effect observed (P=0.038), with a 23% (80% CI: 8–34) reduction in UPCR from baseline achieved with iptacopan 200 mg vs placebo at 3 months



Secondary analysis:

- Strong inhibition of several biomarkers of alter (plasma Bb, Wieslab assay in serum, and urina inhibition observed with iptacopan 200 mg tha month 6

Zhang, 2023

CONCLUSION

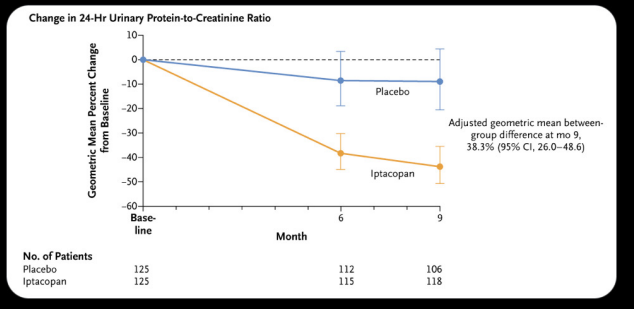
This is the first study to show that selective inhibition of alternative pathw results in a clinically meaningful reduction in proteinuria in patients with I

NEJM @NEJM · 26/10/2024

Original Article: Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy (APPLAUSE-IgAN) nej.md/3UmrOkh

Editorial: Waystations in Progress — Burgeoning Treatment Options for IgA Nephropathy nej.md/4fdz9dV

#KidneyWk | @ASNKidney



Avacopan anti C5aR et N-IgA

Clinical Kidney Journal

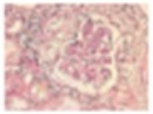
C5a receptor inhibitor avacopan in IgA nephropathy – an open-label pilot study

This study evaluates the safety and efficacy of avacopan in patients with IgAN with persistent proteinuria despite RASi blockage

Methods

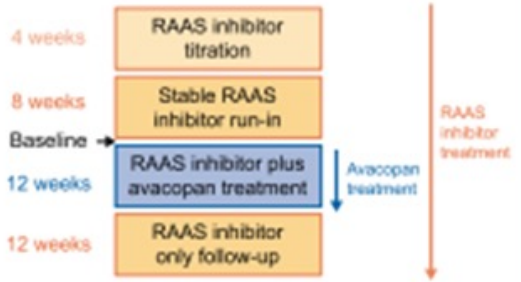
Open-label pilot trial

- ✓ UPCR > 1g/g
- ✓ eGFR > 60 mL/min/1.73 m²



OR

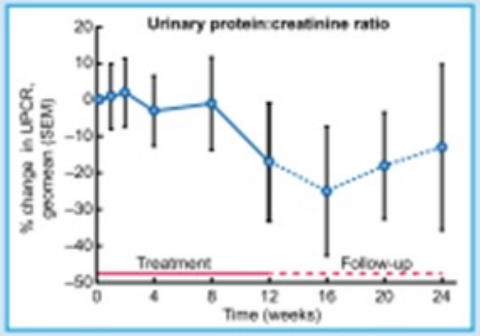
- ✓ eGFR > 45 mL/min/1.73 m² (if eGFR has not declined > 10 mL/min/1.73 m² in 24w)



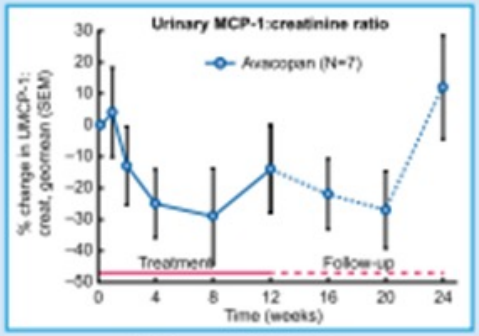
Results

15 patients → Run-in period of 8 w, UPCR > 1g/g → 7 patients

Avacopan 30 mg × 2 day



Improvement in UPCR during treatment



Urinary MCP-1: creatinine decreased 30%

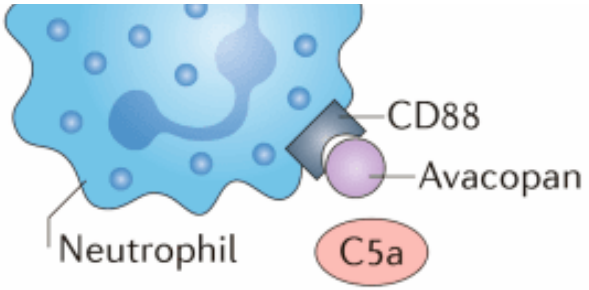
⚠ 1 event: unstable angina – unrelated to avacopan

Conclusion: This short-term trial showed an improvement in the slope of UPCR in 6 out of 7 patients, with ~ 50% improvement in 3 out of 7 patients with IgAN. Longer avacopan treatment duration may be indicated for maximal benefit.

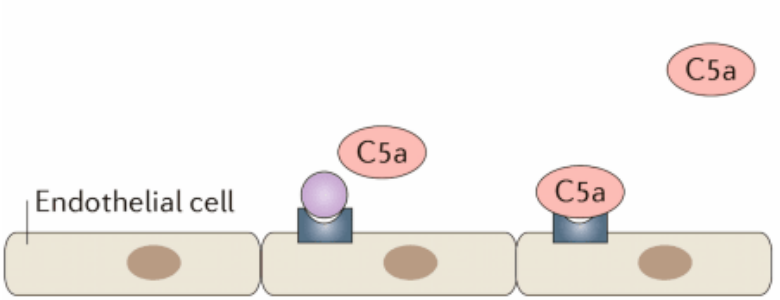
Bruchfeld, A. et al.
Clinical Kidney Journal (2021)
annette.bruchfeld@liu.se
@CKJsocial

Avacopan anti C5aR au cours de la VIgA

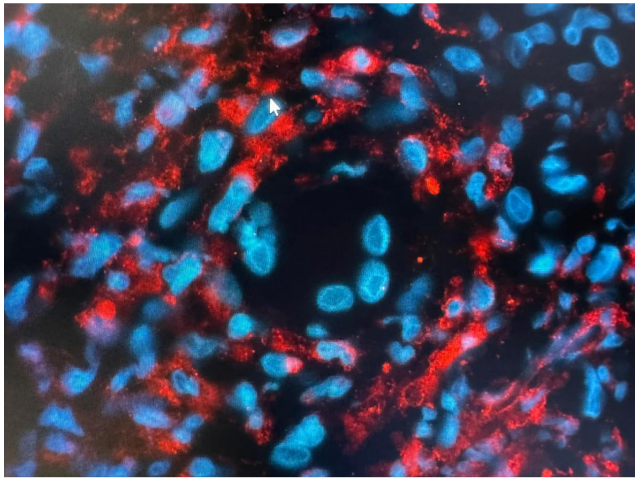
- **Récepteur C5a sur les PNNs mais aussi..**



- **Sur les cellules endothéliales**



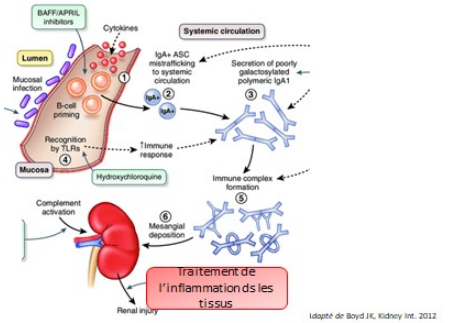
- **Marquage C5aR chez un patient :**



- **LI déposée PHRC the NATIVE study**

Baratt JNDT 2023
Nat Rev Nephrol. 2017

Take Home message



- **Compréhension de la physiopathologie de la vascularite à IgA et l'analogie à la néphropathie à IgA permet d'explorer de nouvelles options thérapeutiques :**

➢ **Complément (Iptacopan, Avacopan, ravulizumab)**
➢ **LB (Atacicept and telitacicept)**

- **Nécessité d'effectuer des essais cliniques au cours des VIgA**

✓ **Un seul RCT publié Etude CESAR.**
✓ **Un seul RCT en cours dans le monde RIGA**

✓ **Lettre d'intention au PHRC-N en cours, un essai international à venir**

✓ **PNDS à venir 2026, recommandations E.U à venir 2025**

European IgAV Study Group