Nephropathy induced by « GBM disorders »

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Nephropathy and GBM disorders

Hereditary

- Nephrin or podocin mutation in MCD
- Collagen mutation in Alport syndrome
- ...

Mediated by Antibodies

- Podocyte antigen in Membranous Nephropathy
- Collagen antigen in Goodpasture syndrome
- …
Alport Syndrome

- Hereditary type IV collagen disease
- Progressive proteinuria, renal fibrosis and kidney failure
- Prevalence: 1-9/100,000
- 3 different patterns of inheritance
  - Autosomal dominant
  - Autosomal recessive
  - X-linked
Treatment

Chaperones  →  Abnormal collagen IV chains

Stem cell-based therapies  →  Abnormal glomerular basement membrane

Hematuria  →  Proteinuria

RG-012  →  miRNA21

RAAS inhibitors  →  RAAS

Paricalcitol  →  Renal fibrosis

Cytokines  →  STAT 3 inhibitors

EGFR inhibitors  →  NF-κB

Bardoxolone  →  CKD
Membranous Nephropathy

- Defined by the presence of subepithelial immune complex with GBM alteration
- Rare auto-immun disease : 1,3 /100 000
- M>F 50 years old
- 1st cause of nephrotic syndrom
- Primary 85%
- Secondary 15%
  - Cancer
  - Lupus
  - Infection
Natural History

100 MN patients never treated by immunosuppressive drug

+35% Nephrotic syndrome owing to the small number of patients and the large standard error of the estimate.

**DISCUSSION**

The results of this study demonstrate that patients with idiopathic membranous nephropathy who receive only symptomatic treatment have a relatively benign course. The probability that end-stage renal disease would not develop was 88 percent after five years of follow-up and 73 percent after eight years. The results of this study and the few other published reports that allow the calculation of survival curves in untreated patients indicate that the probability of maintaining renal function five years after the onset of the disease ranges from 70 to 80 percent.12-14,20-28

+20% ESKD

**RESULTS**

Complete remissions increased as a function of time (Fig. 4). Thirteen (35 percent) of the 37 patients followed for five years continued to have the nephrotic syndrome or sustained proteinuria. Among these patients, six had the nephrotic syndrome throughout the follow-up period, and seven relapsed after a partial remission. Of the 13 patients who had urinary protein excretion >2.0 but <3.5 g per 24 hours at base line, 7 had partial remissions; their protein excretion decreased to 1.5 g per 24 hours, and 6 had complete remissions. In the remaining 6 patients, proteinuria decreased to <1.5 g per 24 hours and decreased to 0.2 g per 24 hours.

**BAD PROGNOSIS:**
- Age > 50 ans
- Male

30-40% MN recurrence after kidney graft

*Schieppati et al., NEJM 1993*
Podocyte Antigens

Proteinuria

THSD7A, 250 kDa, 1657 aa

PLA2R1, 180 kDa, 1463 aa

NEP, 90 kDa, 750 aa

Complement-type repeat
EGF-type repeat
YWTD spacer region
TSP1-like
RGD-like
CysR
FNII
CTLD

Active site
Antibody titer and Outcome

Anti-PLA2R1 Ab

Cohorte n=82

Kanigicherla et al., KI 2013

Anti-THSD7A Ab

Cohorte n=36

Zaghrini et al., KI 2019
Epitope Spreading et Pronostic

Taux de rémission spontanée Spread- à M6 : 45%
Taux de rémission spontanée Spread+ à M6 : 0.05%*

Seitz-Polski et al., JASN 2018 (IF: 8,96)

Seitz-Polski et al., JASN 2016 (IF: 8,96)
Anti-THSD7A antibodies Pathogenicity

Ac anti-THSD7A humains

Tomas et al., JCI 2016
Anti-PLA2R1 antibodies Pathogenicity

n=48

<table>
<thead>
<tr>
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<th>MN patients PLA2R1+</th>
<th>Healthy donors</th>
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<tbody>
<tr>
<td>HEK cells PLA2R1 +</td>
<td>HEK cells PLA2R1 -</td>
<td>HEK cells PLA2R1 +</td>
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<tr>
<td>Complement</td>
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<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td>No complement</td>
<td><img src="image5.png" alt="Image" /></td>
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For rabbit complement + GVB EDTA, the cytotoxicity is only seen in the IgG4 antibody group with a p-value of 0.007.

For rabbit complement + Mg EGTA, the cytotoxicity is also significant in the IgG4 antibody group with a p-value of 0.015.

Lateb et al, submitted
Complement Activation and Prognosis

Hayashi et al., NDT 2017

Bally et al., JASN 2016
Conclusions

Higher dose rituximab protocol is associated with more complete depletion of B-cells and higher rates of remission of PLA2R1-related membranous nephropathy. Lack of epitope spreading was associated with remission in both cohorts.


Visual Abstract by Michelle Rheault, MD
Merci
Structure et ligands de PLA2R1

Figure 1!

PLA2R1 Membranaire

CysR
FN II
CTLD

PLA2R1 soluble

collagène

sucres (mannose-BSA, glucose-BSA)
sPLA2

milieu extracellulaire

milieu intracellulaire

NPXY

Internalisation et dégradation des ligands

Activation de voies de signalisation

Réponses biologiques
- Migration
- Prolifération
- Invasion
- Sénescence/apoptose
- Lésion des podocytes

Adhésion ?

Inhibition des sPLA2

Fonction lectine ?

Autres rôles biologiques?
Dépôts GEM-PLA2R1+

Hayashi et al., NDT 2017
Figure 7. Possible epitope spreading from anti-PLA2R1 to PLA2R1 subepithelial immune deposits leads to larger subepithelial immune deposits involving podocytes, GBM, and endothelial cells.
Anti-THSD7A Ab and Cancer

Hoxha NEJM 2016

40 MN THSD7A : 8 Cancers 20% Hoxha JASN 2016
IgG sub-classes as marker of secondary MN

14 MN LED – 28 MN primaires

10 MN cancer – 15 MN primaires

Haas et al., AJKD 1994
Ohtani et al., NDT 2004

Cambier and Ronco, 2012