Personalized monitoring and treatment in primary membranous nephropathy in the era of PLA2R antibodies

Jack F. Wetzels
Webinar 27 nov 2018
Membranous nephropathy:

most common cause of nephrotic syndrome

incidence 10/million/yr

primary MN: no underlying cause

secondary MN: cancer, systemic diseases, drugs
pMN: the natural history remains unchanged

~50% progression to ESRD
~40-50% spontaneous remission

Rule of thirds?
→ Rule of halves

vd Brand et al. CJASN 2012
Treatment of membranous Nephropathy (old)

Alkylating agents: the only drugs proven effective in RCT’s to prevent ESRD

Ponticelli et al. Kidney Int 1995

Vivekanand Jha et al. JASN 2007;18:1899-1904
2009: discovery of PLA$_2$R-antibodies

- 80% of patients with MN have PLA2R related disease (PLA2R = phospholipase A2 receptor)

Beck et al. NEJM 2009

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The Standard of Care (KDIGO)

Nephrotic syndrome

**Diagnosis:**
Kidney biopsy

**High risk definition**
Proteinuria > 4 g/day, after 6 months

**Treatment:**
Alkylating agents/CNI

Outcome

Individualized patient care

**Diagnosis: the cause of MN is known (in > 80%)**
Do we need a kidney biopsy?

**Prognosis: the KDIGO criteria are insufficient**
Are there better predictors of progression?

**Outcome: also thrombosis:**
Who needs anticoagulant therapy? What therapy?

**Treatment:**
Guidance for personalized therapy? Rituximab?
Diagnosis: Do we need a kidney biopsy?

PLA2R antibody assay is accurate for diagnosing MN
Du et al PlosOne 2014  Sensitivity 0.78 Specificity 0.99 (at least 0.96)
Serological diagnosis of MN

Nephrotic syndrome

Positive

PLA2R antibodies

High risk

Low risk

eGFR < 60 ml/min/1.73m²
Acute kidney injury
Use of immunosuppressive therapy

No biopsy
Wait and see

Negative

Kidney biopsy
(If low biopsy risk)

4% false positive rate: too high if considering immunosuppressive Rx
Take care: differences between PLA2Rab assays

**Western Blot**

Beck et al. NEJM 2009

**Immunofluorescence (IIFT)**

© Euroimmun AG

**ELISA**

© Euroimmun AG

**ALBIA**

Behnert et al 2014

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Radboudumc
**ELISA: least sensitive!**

<table>
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<td>Agreement</td>
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Hofstra et al 2012  
Hoxha et al 2016  
Hoxha et al 2016

Use of ELISA → less likely to diagnose PLA2R associated MN!
Serum antibodies may be initially absent

Case-description:

- A 47-year-old patient diagnosed with iMN in 2005. PLA2R staining in the initial biopsy appeared positive. Treatment (CP) resulted in a complete remission (2006). In June 2013 he developed a relapse.

<table>
<thead>
<tr>
<th>Date</th>
<th>IIFT</th>
<th>Cr (mg/dl)</th>
<th>Albumin (g/dl)</th>
<th>PCR (g/g)</th>
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<td>25-09-2013</td>
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<td>2.4</td>
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<td>2.3</td>
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<td>19-03-2014</td>
<td>positive 3+</td>
<td>0.94</td>
<td>2.2</td>
<td>7.28</td>
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Debiec et al. NEJM 2011
Prognosis: are there better predictors of progression?

<table>
<thead>
<tr>
<th>Remissions</th>
<th>6 months</th>
<th>17 months</th>
<th>23 months</th>
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<tbody>
<tr>
<td>placebo</td>
<td>21%</td>
<td>34%</td>
<td>45%</td>
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</table>

Accuracy of KDIGO recommendations:  < 60%!

GEMRITUX RCT: Rituximab vs placebo
Dahan et al JASN 2017; Alexandra Rousseau (pc); Seitz-Polski 2017
Prognosis: risk prediction I

Accuracy of “old” predictors ~ 75%

Risk score: UPCR + Ccr + ΔCcr

van den Brand J A et al. CJASN
doi:10.2215/CJN.00670112

Branten et al 2005

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**Prognosis: risk prediction II**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Outcome</th>
<th>Progression</th>
<th>No progression</th>
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<td>Baseline</td>
<td>Repeated</td>
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<td>$\text{u}\beta_2\text{m} \geq 1.0\ \mu\text{g/min}$</td>
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<td>0</td>
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<tr>
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<td>$\text{u}\beta_2\text{m} &lt; 1.0\ \mu\text{g/min}$</td>
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<td>2</td>
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<tr>
<td>$\text{u}\beta_2\text{m} &lt; 1.0\ \mu\text{g/min}$</td>
<td>$\text{u}\beta_2\text{m} &lt; 1.0\ \mu\text{g/min}$</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

Accuracy of “old” predictors with repeated measurement after 6-12 months ~ 90%

**NEEDS VALIDATION!**

van den Brand J A et al. CJASN
doi:10.2215/CJN.00670112
# Prognosis: PLA2Rab in risk prediction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>low (n=26)</th>
<th>medium (n=26)</th>
<th>high (n=27)</th>
<th>p-value</th>
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<td>Part. remission</td>
<td>11</td>
<td>8</td>
<td>11</td>
<td>ns</td>
</tr>
<tr>
<td>Compl. remission</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>ns</td>
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<tr>
<td>Spont. remission</td>
<td>10</td>
<td>8</td>
<td>1</td>
<td>&lt;0.01</td>
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</table>

GEMRITUX data; EUROIMMUN Elisa Alexandra Rousseau 2017
Specificity and sensitivity < 80%

<table>
<thead>
<tr>
<th>Remissions</th>
<th>6 months</th>
<th>17 months</th>
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<tbody>
<tr>
<td>PLA2R &lt; 275</td>
<td>30%</td>
<td>43%</td>
</tr>
<tr>
<td>PLA2R &gt; 275</td>
<td>7%</td>
<td>20%</td>
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</table>

Hofstra, JASN 2012
“in house” ELISA - cut off for EUROIMMUN ELISA unknown

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Management algorithm

Nephrotic syndrome

Low risk
Wait and see
Risk?

PLA2R antibodies
Urine LMW
Duration Uprot
Serum creatinine

High risk
Consider treatment

Arterial and venous trombo-embolic events!
Don’t Forget: anticoagulant therapy

Rationale:

Patients with MN are at great risk of venous and arterial thrombosis

Risk: MN>FSGS>IgA

Risk: related to Serum albumin levels

Julia M. Hofstra, Jack F.M. Wetzels
Anticoagulant therapy in pMN

- May consider LMW (prophylactic dose) + acetylsalicylic acid
- No evidence for efficacy of DOAC → do not use!
- Be aware of lack of standardisation of serum albumin assay
  - Immunonephelometric
  - Brome cresol purple (BCP)
  - Brome cresol green (BCG)

BCP = immunonephelometric albumin
BCG: overestimates by + 5g/L

Cut-off: 20 g/L with BCP = 25 g/L with BCG
Treatment of patients with pMN

- Alkylating agents are effective, proven in RCT’s and with renal end-points
- Side effects!
- Can we restrict treatment to high risk-patients?
- Can we use alternative agents?
Treatment can be restricted to high-risk patients

Cohort (n=254): 49% immunosuppressive therapy, 51% supportive treatment
10-years dialysis free survival 86%; threefold higher risk of malignancies

Van den Brand, JASN 2014; CJASN 2014
Treatment of patients with pMN: alternative agents

- Calcineurin inhibitors: induce remission, high relapse rate! Relapses are associated with risk of ESRD. Need more data!

MENTOR study: comparison Rituximab vs CsA
STARMEN trial: comparison cyclophosphamide vs tacrolimus+Rituximab

- Rituximab? cohort study showed high remission rate
Rituximab GEMRITUX: first RCT → more remissions!

<table>
<thead>
<tr>
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<th>NIAT-RTX n=37</th>
<th>NIAT n=38</th>
<th>P value</th>
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<tbody>
<tr>
<td>Remission (6 mo)</td>
<td>13 (35 %)</td>
<td>8 (21 %)</td>
<td>0.21</td>
</tr>
<tr>
<td>Remission at end of follow-up (17 mo)</td>
<td>24 (65 %)</td>
<td>13 (34 %)</td>
<td>&lt;0.01</td>
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<tr>
<td>Remission at end of follow-up (23 mo)*</td>
<td>19/29 (66%)</td>
<td>13/29 (45%)</td>
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</tr>
</tbody>
</table>

NIAT = non-immunosuppressive antiproteinuric therapy; RTX = Rituximab 2 * 375mg/m²
* PLA2R positive patients only

Dahan et al, JASN 2017; Seitz-Polski 2017
Membranous Nephropathy: lessons from RTX studies

Rituximab: many non-responders (with current dose)

Bergamo cohort: n = 100; non-response 35%

GEMRITUX cohort: n = 38; non-response 34%

MENTOR cohort: n = 64; primary non-response 22% (no-remission 41%)
Cyclophosphamide vs Rituximab: adverse events

- $HR_{adj} = 0.27 \ (0.16 - 0.44)$
- $HR_{adj} = 0.32 \ (0.15 - 0.68)$

Van den Brand, JASN 2017
Cyclophosphamide vs Rituximab: difference in partial remission rate

- \( \text{HR}_{\text{adj}} = 0.63 \ (0.45 - 0.89) \)
- \( \text{HR}_{\text{adj}} = 0.88 \ (0.50 - 1.54) \)

Rituximab: fewer partial remissions

Van den Brand, JASN 2017
Results: disappearance of aPLA2R after 6 months
Rituximab is not effective in patients with high PLA2Rab titers

Piero Ruggenenti et al. JASN 2015;26:2545-2558

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Management algorithm

Nephrotic syndrome

PLA2R antibodies
Urine LMW
Duration Uprot
Serum creatinine

Low risk
Wait and see

High risk

aPLA2R low
1a. Rituximab
1b. CNI
2. CYCLOPHOS

aPLA2R high
1. Cyclophos
2. Rituximab (?)dose?"

NEED MORE EVIDENCE!
Anti-PLA2R: guidance of treatment?

**PLA2R positive** 9  2  0  0
**PLA2R negative** 24  22  18  14

aPLA2R at end of CP therapy (12 months) predicts outcome

Bech et al, CJASN 2014
Conclusions: individualized treatment in MN is emerging

• Measurement of aPLA2Rab: reduced need for biopsy
• Be aware of differences between assays!
• Prediction of prognosis: urine LMW proteins, aPLA2Rab, serum creatinine, severity and duration of proteinuria
• Individualized thrombosis prophylaxis (www.gntools.com)
• Be aware of differences in serum albumin assays
Conclusions: individualized treatment in MN is emerging

- Cyclophosphamide should be restricted to high risk patients
- Rituximab and CNI induce remission
- Patients with high PLA2R antibody levels do not respond to rituximab at standard dose
- PLA2R antibody levels may guide therapy
Conclusions: individualized treatment in the future?

- PLA2R epitope spreading?
- Genetic information?
Questions?