How I Treat Membranous Nephropathy

Patrick H. Nachman, MD, FASN
Marion Stedman Covington Professor
May 20, 2017

Treating Membranous Nephropathy:
“after changes upon changes we are more or less the same”

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Simon & Garfunkel: The Boxer 1982
Outline

- Discuss main immunomodulatory treatments
- 1- What is the role of PLA2r antibody testing?
- 2- Review the principal therapeutic options
- 3- Introduce upcoming trial results and future trials

Phospholipase A2 Receptor (PLA2R) as the Target Antigen

- The majority of anti-PLA2R is IgG4.
- PLA2R is present in podocytes as detected by IF of normal human kidney

MN patients with and without anti-PLA2r not distinguishable based on demographics, clinical or histologic* features

“Specificity” of PLA2R Testing

• Prevalence of anti-PLA2R is high in patients with MN and
  » Sarcoidosis: 61% (Larsen 2013*, Stehle’ 2015**)
  » Hepatitis C: 64% (Larsen 2013)
  » Hepatitis B: 64% (Xie 2015**)
  » Malignancy: 25% (Larsen 2013)

• Prevalence is low in patients with MN and SLE, auto-immune or connective tissue disease

• Anti-PLA2R cannot be used to differentiate “idiotopathic” from “secondary” MN
• Anti-PLA2R does not obviate need for cancer screen.

Larsen CP. Mod Pathol 2013; 26:709-15
Xie Q. Am J Nephrol. 2015;41:345-53
Stehle T. Nephrol Dial Transplant. 2015; 30:1047-50

Decline in anti-PLA2R titer appears to precede clinical response

Predictors of outcome

- Reduced GFR at presentation or overtly declining GFR.
- Severity and duration of proteinuria:
  - $\geq 8$ grams/day for $\geq 6$ months assoc’d with a 66% probability of CRI.
  - $\geq 6$ grams/day for $\geq 9$ months had a 55% probability of CRI.
  - $\geq 4$ grams/day for $\geq 18$ months is assoc’d with increased risk of CRI.
- Amount of proteinuria at presentation:
  - non-nephrotic proteinuria have a better 10-year survival rate.
  - $\geq 10$ grams of proteinuria have a 60% probability of ESRD at 8 years.
- **MAYBE** high titer anti-PLA2R antibodies

### Table 3. Outcome in aPLA2R antibody-positive patients (n=79): outcome in different tertiles of antibody titer (EUSA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>aPLA2R=41–175 U/ml (n=26)</th>
<th>aPLA2R=175–610 U/ml (n=26)</th>
<th>aPLA2R=610 U/ml (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial remission</td>
<td>11 (42%)</td>
<td>8 (31%)</td>
<td>11 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complete remission</td>
<td>7 (27%)</td>
<td>9 (35%)</td>
<td>8 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>5 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>7 (27%)</td>
<td>6 (23%)</td>
<td>3 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spontaneous remission*</td>
<td>10 (38%)</td>
<td>8 (31%)</td>
<td>1 (4%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>


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**Anti-PLA2R associated with renal outcome**

DSC = Doubling S. Cr

![Graph showing the association between A-PLA2R and renal outcome]

<table>
<thead>
<tr>
<th>A-PLA2R</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>26</td>
</tr>
<tr>
<td>Mid</td>
<td>29</td>
</tr>
<tr>
<td>High</td>
<td>27</td>
</tr>
</tbody>
</table>

add dcc reference. add hladunewich reference?
Patrick Nachman, 2/18/2015

Patrick Nachman, 2/18/2015
Kaplan–Meier plot for survival in remission, grouped by PLA2R antibody status at end of therapy.

<table>
<thead>
<tr>
<th>Survival In Remission</th>
<th>PLA2R positive</th>
<th>PLA2R negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

©2014 by American Society of Nephrology

Association of Anti-PLA2R with Outcomes after Treatment

Anneke P. Bech et al. CJASN 2014;9:1386-1392

Kaplan–Meier plot for survival in remission, grouped by PLA2R antibody status at end of therapy.
CLINICAL COURSE AND PREDICTORS OF OUTCOME

Definitions

• Complete Remission (CR):
  » Reduction of proteinuria to (near) normal < 300 mg/day,
  » Stable eGFR (poorly defined, generally < 25% decline, undefined period)

• Partial Remission (PR):
  » Reduction of proteinuria by > 50% of baseline AND to < 3.5 g/d
  » Stable eGFR (poorly defined, generally < 25% decline, undefined period)

• (occasional inclusion of normalization of albumin)
**“Natural” history 2010**

- Retrospective study of 328 patients
  - 71% with eGFR>60 ml/min/1.73m²
  - 67% on ACEi &/or ARB
- Spontaneous remission occurred in 31.7%
- Partial remission (PR) in 14.7± 11.4 mo (1-66 mo). -> 50% progressed to complete remission (CR), and 50% remained in PR.
- Time to CR: 38 ± 25.2 mo (4-120 mo)
- 26% of patients with baseline proteinuria 8-12 g/d and 21% of patients with baseline proteinuria > 12 g/d developed a spontaneous remission.


**Predictor of outcome:**

**Remission of proteinuria.**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At onset</strong></td>
<td></td>
</tr>
<tr>
<td>CrCl ml/min</td>
<td>0.97</td>
</tr>
<tr>
<td>(0.96–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria g/d</td>
<td>1.08</td>
</tr>
<tr>
<td>(1.02–1.15)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>0.08</td>
</tr>
<tr>
<td>(0.03–0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>-</td>
</tr>
</tbody>
</table>

Relapses

<table>
<thead>
<tr>
<th>Study</th>
<th>From CR</th>
<th>From PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troyanov: Toronto cohort study</td>
<td>23% median time to relapse 25 [2 – 164] months</td>
<td>45.6% relapse; median time to relapse 8 [1 – 147] months</td>
</tr>
<tr>
<td>Ponticelli: ACTH vs cyclophos</td>
<td>20% to 30% to sub-nephrotic proteinuria</td>
<td>0% to nephrotic range proteinuria</td>
</tr>
</tbody>
</table>


Time to ESRD or 50% reduction in kidney function with PR or CR sustained to each landmark

Landmark analysis of the association of PR and CR with ESRD or 50% reduction in kidney function

<table>
<thead>
<tr>
<th>Relapse Status</th>
<th>n</th>
<th>Multivariable HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Mo</td>
<td>339</td>
<td>0.34 (0.20 to 0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stayed in remission (PR)</td>
<td>317</td>
<td>0.19 (0.04 to 0.83)</td>
<td>0.03</td>
</tr>
<tr>
<td>12 Mo</td>
<td>302</td>
<td>0.40 (0.22 to 0.73)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stayed in remission (CR)</td>
<td>302</td>
<td>0.19 (0.04 to 0.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>24 Mo</td>
<td>255</td>
<td>0.46 (0.24 to 0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stayed in remission (PR)</td>
<td>255</td>
<td>0.24 (0.07 to 0.83)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Treatment: Corticosteroids

3 large RCT of corticosteroids in adults patients. (total n=333)
Meta-analysis:
   Trend towards achieving complete remission at 24-36 months (not stat. significant).
Pooled analysis of RCTs and prospective studies:
   No benefit in inducing a remission.
   No benefit on renal survival.

Treatment: alkylation agents

- Ponticelli: chlorambucil + steroids vs control.
  - Methylprednisolone at 1 g/day x 3 of months 1,3 and 5, + daily oral methylprednisolone (0.4 mg/kg/day) or prednisone (0.5 mg/kg/day).
  - Alternating month: chlorambucil 0.2 mg/kg/day.
  - N= 81
  - Complete or partial remission: 83% of treated vs. 38% of control pts.
  - At 10 years, the probability of a functioning kidney was 92% in the treated patients and 60% in controls.


Cyclophosphamide + corticosteroids

![Graph showing survival without treatment endpoint](image)

Death, dialysis or doubling Cr

Probability of survival without treatment endpoint (%)

Time (months)

p=0.0008

Jha V et al JASN 2007;18:1899
Cyclophosphamide + corticosteroids

An open-label, RCT of supportive therapy vs. “Ponticelli protocol”. 93 patients completed the study; Median follow up: 11 yr (10.5-12 yr). Study endpoints: doubling of Cr, ESRD, or patient death.

Cyclosporine A vs. Placebo

RCT CyA + prednisone x 26 wks (0.15 mg/kg/d) vs. placebo
CyA 3.5 mg/kg/d (trough 125-225 microg/L.) CyA tapered over 4 weeks.
N=51.
40% relapse in both groups.
Renal function was unchanged and equal in both groups.
**Tacrolimus vs Control**

- Tacrolimus 0.05 mg/kg/day.
- Target trough 3-5 ng/ml.
- If no remission after 2 mos, target increased to 5-8 ng/ml.
- Treatment x 12 mos, then tapered off over 6 m.
- N=48.

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**The UK RCT of immunosuppression for progressive MN**

1. **3 groups:**
   - (a) supportive treatment only
   - (b) cyclosporin 5mg/kg/day for 12m
   - (c) prednisolone & chlorambucil 6m (with reduced dose chlorambucil, max 0.15mg/kg/day)

2. **Inclusion:** primary MN, deterioration of ≥ 20% in cGFR over at least 3 months

108 patients recruited btn 1998-2008:
   - 33 Pred/Chlorambucil, 36 CyA, 37 STO;
   - Minimum 3 year follow-up, longer in many.

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Mathieson P et al. Lancet 2013
The UK RCT of immunosuppression for progressive MN

Comparisons: Hazard Ratio (95% CI) and p-value

Cyclosporin vs Supportive care. HR 1.17 (0.7, 1.95), 2p=0.5
Pred / Chlorambucil vs Supportive care. HR 0.44 (0.24, 0.78), 2p=0.003

Mathieson P et al. ASN 2011

Ponticelli vs Tacrolimus+Steroids: RCT

- Modified Ponticelli vs Tacrolimus 0.1 mg/kg/day x 12 m + oral prednisolone (0.5 mg/kg/day) for 6 months.
- Primary end point was achievement of CR or PR

<table>
<thead>
<tr>
<th></th>
<th>Ponticelli (n=32)</th>
<th>Tacrolimus (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR (%)</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>CR (%)</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>PR (%)</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>AE</td>
<td>Leucopenia, Amenorrhea/azoospermia</td>
<td>Rev. nephrotoxicity, GI SE, Tremor</td>
</tr>
</tbody>
</table>

- No significant differences in anti-PLA2R titers at baseline, 6 and 12 months.

Ramachandran R et al ASN 2014; FR OR066
**Ponticelli vs Tacrolimus+Steroids: RCT**

- Randomized, controlled, not blinded, non-inferiority
- Modified Ponticelli vs Tacrolimus 0.1 mg/kg/day x 12 m + oral prednisolone (0.5 mg/kg/day) x 6 m then tapered.

### At 12 m

<table>
<thead>
<tr>
<th></th>
<th>Ponticelli (n=32)</th>
<th>Tacrolimus (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR (%)</td>
<td>77.1</td>
<td>71.4</td>
</tr>
<tr>
<td>CR (%)</td>
<td>51.4</td>
<td>54.3</td>
</tr>
<tr>
<td>PR (%)</td>
<td>25.7</td>
<td>17.1</td>
</tr>
</tbody>
</table>

**AE**
- Leucopenia, Amenorrhea, azoospermia
- Rev. nephrotoxicity
- GI SE, Tremor

**Ramachandran R et al Nephrology (Carlton). 2016; 21:139-146**

### Rituximab

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rituximab dose</th>
<th>N</th>
<th>F/U (months)</th>
<th>CR</th>
<th>PR</th>
<th>CR or PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remuzzi (2002)</td>
<td>375 mg/m²/wk*4</td>
<td>8</td>
<td>5</td>
<td>2/8</td>
<td>3/8</td>
<td>62</td>
</tr>
<tr>
<td>Ruggenenti (2003)</td>
<td>375 mg/m²/wk*4</td>
<td>8</td>
<td>12</td>
<td>2/8</td>
<td>3/8</td>
<td>62</td>
</tr>
<tr>
<td>Ruggenenti (2006)</td>
<td>375 mg/m²/wk*4</td>
<td>23</td>
<td>12</td>
<td>6/23</td>
<td>6/23</td>
<td>52</td>
</tr>
<tr>
<td>Cravedi (2007)</td>
<td>375 mg/m²<em>1(n=11) 375 mg/m²</em>2(n=1)</td>
<td>12</td>
<td>12</td>
<td>2/12</td>
<td>6/12</td>
<td>67</td>
</tr>
<tr>
<td>Fervenza (2008)</td>
<td>1 g * 2, d1&amp;15; ± rpt at 6mos (n=10)</td>
<td>15</td>
<td>12</td>
<td>2/15</td>
<td>6/15</td>
<td>53</td>
</tr>
<tr>
<td>Ruggenenti (2008)</td>
<td>375 mg/m²/wk*4</td>
<td>7</td>
<td>7-59</td>
<td>7/7²</td>
<td>0/7</td>
<td>100</td>
</tr>
<tr>
<td>Fervenza (2010)</td>
<td>375 mg/m²/wk*4 + rpt at 6mos</td>
<td>20</td>
<td>24</td>
<td>4/20</td>
<td>12/20</td>
<td>80</td>
</tr>
<tr>
<td>Cravedi (2011) rescue vs de novo</td>
<td>375 mg/m²/wk<em>4 375 mg/m²</em>1 titrated</td>
<td>22</td>
<td>24</td>
<td>5/22</td>
<td>10/22</td>
<td>77</td>
</tr>
<tr>
<td>Ruggenenti (2012)</td>
<td>375 mg/m²/wk*4 or single dose</td>
<td>100</td>
<td>29 (6–121)</td>
<td>27/100</td>
<td>38/100</td>
<td>65</td>
</tr>
</tbody>
</table>
Rituximab vs Antiproteinuric Therapy Alone

- Randomized controlled trial
- Nonimmunosuppressive Antiproteinuric Treatment (NIAT) vs NIAT + Rituximab.
- Population: Bx proven MN within 2 yrs.
  - Persistent proteinuria > 3.5 g and S Alb < 3g/dl at 6 months with NIAT
  - Primary Endpoint at 6 m + up to 24 m observational period
- Primary Endpoint: Combined CR + PR at 6 months
- 80 patients enrolled, with 77 randomized
- Median follow up 17 m

Dahan K et al J Am Soc Nephrol 2016

Proteinuria

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIAT+Ritux</th>
<th>NIAT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR, 6m</td>
<td>35.1% (19.7-50.5)</td>
<td>21.1% (8.1-34.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>CR + PR, f/up</td>
<td>64.9%(49.5-80.2)</td>
<td>34.2%(19.1-49.3)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>CR, f/up</td>
<td>18.9%</td>
<td>2.7%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Remission was independently associated with PLA2r-Ab < 257RU/ml at baseline

Dahan K et al J Am Soc Nephrol 2016
Rituximab or Cyclophosphamide-Steroids?

Retrospective, observational cohort study
Compared time to adverse events, PR, CR, and a composite of doubling of Cr, ESRD, or death.
100 RTX-treated patients and 103 patients who received daily Steroids-Cyclophosphamide.

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>Events per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>First adverse event</td>
<td>Crude: 0.26 (0.16 - 0.41) 25 67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted: 0.27 (0.10 - 0.44) 25 67</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>Crude: 0.31 (0.15 - 0.68) 9 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted: 0.32 (0.15 - 0.68) 9 30</td>
<td></td>
</tr>
<tr>
<td>Non-serious adverse event</td>
<td>Crude: 0.23 (0.14 - 0.39) 18 58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted: 0.23 (0.13 - 0.41) 18 58</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.78 (0.36 - 1.67) 11 17

Rituximab vs. Cyclosporine in MN: MENTOR Study

Randomized Controlled Trial
126 patients (18-80 y.o)
- RAS blockade for ≥3m prior to randomization.
- Proteinuria ≥5 g/d despite RAS blockade.
- EGFR ≥40 ml/min/1.73 m² while on RAS blocker.

Primary Endpoint: CR or PR at 24 m after randomization.

Anticipated results by ASN Kidney Week 2017
Immune Tolerance Network Study: Mechanistic Focus

Goal:
• Induce immune tolerance with belimumab and rituximab as a treatment mechanism for primary MN

Hypothesis:
• Combined belimumab and rituximab treatment will increase the rate of CR at 104 weeks and promote immune tolerance by increasing the depletion of memory B cells producing anti-PLA_2R autoantibodies and limiting their return, compared to rituximab alone

Primary objective:
• Determine the efficacy of belimumab + rituximab vs. rituximab alone at inducing complete remission

Secondary objectives:
• Assess the efficacy of belimumab + rituximab vs. rituximab alone for inducing partial remission
• Examine the relationship between anti-PLA_2R titers and treatment response
• Evaluate safety and tolerability of combined belimumab and rituximab therapy

Study Design

Study design:
• Multi-center, double-blind, randomized, placebo-controlled trial
• 90 participants randomized 1:1
  • Experimental: IV belimumab q4 weeks + rituximab weeks 8 and 10
  • Comparator: IV placebo q4 weeks + rituximab weeks 8 and 10

Study duration: Total follow-up of 156 weeks
• 52 weeks of treatment
• Primary endpoint at week 104 with additional follow-up to week 156

Study population:
• Adults (18-85 y/o) with biopsy proven MN and anti-PLA_2R positive
• Proteinuria > 3.5 g/day and eGFR > 30 mL/min/1.73m^2 on maximally tolerated RAS blockade
• No treatment with immunosuppressive agents in a pre-specified timeframe

Primary clinical outcome measure:
• Proportion of individuals that are in complete remission (CR) at week 104
  • CR: urinary protein excretion by 24 hour urine collection of ≤ 0.3 g/day with a stable GFR (<20% from baseline while on RAS blockade)
Flow Diagram

Adults (18-85 years old) with primary membranous nephropathy (MN): (n=90)

Randomize 1:1

Experimental (BEL/RTX) arm: (n=45)
- Belimumab 10 mg/kg IV week 0, 2, 4, and q4 weeks from weeks 4-52
- Rituximab 1000 mg IV weeks 8 and 10

Comparator (RTX) arm: (n=45)
- Belimumab IV placebo week 0, 2, 4, and q4 weeks from weeks 4-52
- Rituximab 1000 mg IV weeks 8 and 10

Followup on no study medication week 52 to week 156
Assessment of complete remission at week 104 (primary endpoint)

What do I do?

http://i.imgur.com/I5DFV.jpg
Treatment of MN

- More attention to albuminemia
- Patients without nephrotic syndrome: non immunosuppressive supportive therapy
- Patients with severe nephrotic syndrome: do NOT postpone immunosuppressive therapy: serious complications occur early!
- Choice of immunosuppressive therapy individualized to patient’s characteristics and preferences:
  - Cyclophosphamide + steroids: still best data for CR, PR and prevention of ESKD. Difficult to use!
  - Cyclosporine/tacrolimus: effective for PR>CR, prevention of ESKD (?), high relapse rate!
  - Rituximab: probably effective for CR or PR, unknown for prevention of ESKD. Still awaiting good controlled data!

Future directions

- Anti-PLA2r use in practice:
  - Not using as diagnostic test to replace a biopsy
  - A positive anti-PLA2r does not obviate need for cancer and infectious work-up
  - Not using as determinant for immunosuppressive treatment (yet?)
  - Following as a probable harbinger of remission

- Await results of MENTOR trial Fall 2017
- Looking forward to Immune Tolerance trial
Treating Membranous Nephropathy: things are A-changin’

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May 20, 2017

Membranous Nephropathy Team

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  - Yichun Hu
  - J. Charles Jennette
  - Taewoo Lee
  - Sophia Lionaki
  - Shannon Mahoney
  - Patrick H. Nachman
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- U of Toronto:
  - Sean Barbour
  - Daniel Catran
  - Michelle Hladunewich
  - Heather Reich