In the Name of God the Compassionate the Merciful
Update on Treatment of Membranous Nephropathy

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Membranous Nephropathy:

- Most common primary glomerular disease in older adults (>60 yr)
- Most common cause of nephrotic syndrome in nondiabetic adults
- More common in whites & asians than blacks
- Incidence: 1.2/100,000/yr worldwide
- Male:Female 2:1 ratio
- 70-80% “Idiopathic”
- 20-30% Secondary
- Causes at least 0.7% of cases of ESRD (USRDS)
MN in adults is most often idiopathic (approximately 75%)

Secondary causes

Drugs
- gold, penicillamine

Infections
- hepatitis B and C virus infection

Underlying diseases
- SLE, malignancy
Secondary Membranous

**Causes**
- **Autoimmunity**: Lupus (Class V)
- **Alloimmunity**: Allograft rejection, GVHD
- **Infections**: Hepatitis B, syphilis (?HCV)
- **Malignancy**: esp. solid tumors
- **Medications**: gold, mercury, penicillamine

**Diagnostic clues**
- Systemic disease
- Demographics
  - Children
  - African ancestry
- Histology
  - Mesangial or subendothelial deposits
  - Tubuloreticular inclusions
  - Non-IgG4 immunoglobulins
  - TBM staining for IgG by IF
  - Absence of PLA2R staining
MN.3 We recommend initial therapy with a 6-month course of alternating monthly cycles of an alkylating agent and steroids (1B).

MN. 4 We suggest cyclophosphamide over chlorambucil (2B)

MN. 2 We suggest that therapy be started ONLY in patients with a nephrotic syndrome and “high risk of disease progression”
Proteinuria over time in Spontaneous Remission

- N = 328 with nephrotic syndrome & MN
- 32% experienced spontaneous remission
  - \( \frac{1}{4} \) Partial remission by mean 15 ± 11 mos (range 1-66 mos)
  - \( \frac{1}{4} \) Complete remission by mean 39 ± 25 mos (range 4-120 mos)

Treatment algorithm for MGN based on the 2012 KDIGO

Traitement algorithm for MGN basé sur le 2012 KDIGO
R: alkylating agents improve renal outcome in RCT

Disadvantage: all patients are treated
Howman et al, UK Randomized Controlled Trial
*Lancet*, 2013

- Pred/Chlorambucil group had lower risk of 20% decline in creat clearance and greater fall in proteinuria compared to other groups
- No difference between supportive care and ciclosporin for primary end point or proteinuria
Cancer Risk after Cyclophosphamide for Idiopathic MN patients

- N=272, mean 51 yo, 70% male, median follow-up 6.0 yrs (IQR 3.6-9.5 yrs)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>4.6</td>
<td>1.5 to 18.8</td>
</tr>
<tr>
<td>Univariate-adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>3.3</td>
<td>1.0 to 10.6</td>
</tr>
<tr>
<td>Men</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Prior therapy</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Family history of malignancy</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>CKD stage</td>
<td>5.0</td>
<td>1.5 to 18.8</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>4.3</td>
<td>1.3 to 14.1</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>3.2</td>
<td>1.0 to 9.5</td>
</tr>
</tbody>
</table>

For the average patient, this translates into an increase in annual risk from ~0.3% to 1.0%.

Van der Brand JA et al., CJASN, Jun 2014
Calcineurin inhibitors for MN as 1st line therapy: two RCTs

**Cyclosporine**
- Pred + Cyclosporine (CsA) vs. Pred + Placebo x 26wks

*Partial/complete remissions:*
- At 26 wks: CsA 75% vs. placebo 22% (P<0.001)
- At 78 wks: CsA 39% vs. placebo 13% (P=0.007)

**Tacrolimus**
- Tacrolimus vs. control x 12 mos with 6 mo. taper
- Remission: 94% vs. 35% at 18 mos

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Catran D et al., Kidney Int 2001  
Tacrolimus in iMN:

- Cohort study: FU 30 months
- High remission rate: 84%
- High relapse rate: 44%

Risk of relapse higher:
- Higher baseline proteinuria
- Rapid tapering of tacrolimus

Relapsing patients:
- 17% doubling Screat
- 8% ESRD

Tacrolimus in iMN:

Randomized controlled trial, n= 70

Tacrolimus /prednisone ( n= 35) versus Ponticelli (n=35)

Remission at month 12: 71 versus 77% (ns )

Sustained remission at month 24: 60% (Tacro) versus 85% (P)

Ramachandran, Nephrology 2015
CNI in Membranous nephropathy

**Advantages**
- Very effective in patients with no massive proteinuria and with normal renal function
- Good tolerability
- Corticosteroids likely not needed

**Drawbacks**
- High rates of relapses
- Less effective in patients with massive proteinuria, renal function impairment or renal function decline
- Risk of long-term nephrotoxicity
• Progress over the past decade has dramatically enhanced our understanding of MN pathobiology.

• Ongoing efforts to improve therapy, with strategies that may include targeting B cells & antibody production (rituximab, belimumab, bortezomib), removing or adsorption of pathogenic antibodies, and manipulating complement activation.
Data from studies in animals suggest that the typical subepithelial immune deposits in glomeruli are caused by B-cell-mediated reactions, which promote injury to the glomerular filtering barrier and result in proteinuria.

Thus, agents that specifically interfere with B cells would ideally represent the first step toward selective therapy of IMN.
RITUXIMAB
Chimeric Ab against CD20 surface antigen of B cells

- Glycosylated protein (1328 aa)
- High affinity binding to CD20

Cheson, Exp Opin Biol Ther, 2002
RITUXIMAB

- Rapid depletion of circulating B cells
  Onrust et al., Drugs, 1999

- Inhibition of B cell differentiation and IgG secretion upon CD20 binding by anti-CD20 Abs
  Tedder et al., J Immunol, 1986

Cell lysis through complement activation and antibody-dependent NK cell cytotoxicity
Progress over the past decade has dramatically enhanced our understanding of MN pathobiology

- Expect discovery of new membranous antigens and deeper understanding of how they drive podocyte injury, complement activation, etc.
- Expect a shift in nomenclature to more immunologically accurate terms than “primary” and “secondary” (e.g. Anti-PLA2R membranous nephropathy, etc.)
Phospholipase A2 Receptor

- 185-kD glycoprotein present on normal podocytes
- Found in immune deposits of patients with idiopathic MN
- PLA2R and IgG4 co-localize on biopsy specimens from pts with idiopathic MN in a typical granular pattern
- ~70-80% of patients with idiopathic, but not secondary, MN have antibodies against PLA\textsubscript{2}R

Beck et al., NEJM, July 2, 2009
Rees & Kain, Nature Reviews Nephrology 5, 617-618 (November 2009)
Anti-PLA$_2$R is sensitive & specific for Idiopathic MN

-OR- Could they have two separate diseases?

Qin et al., JASN 2012: 3/10 patients with +anti-PLA2R and “tumor-associated MN” did not improve after tumor resection

Sensitivity ~70%

Specificity ~88%
Anti-PLA$_2$R by biopsy vs. serum


<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Serum Reactivity</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

19% Double-negatives

PLA$_2$R
Malignancy risk in membranous aPLA$_2$R positive vs. aPLA$_2$R negative

Table 4. Multiple Cox regression analysis for patients malignancy-free survival in iMN.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive aPLA2R*</td>
<td>0.078</td>
<td>0.017 – 0.360</td>
<td>0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>1.058</td>
<td>1.009 – 1.109</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>5.274</td>
<td>1.342 – 20.727</td>
<td>0.02</td>
</tr>
<tr>
<td>Proteinuria†</td>
<td>1.201</td>
<td>1.064 – 1.356</td>
<td>0.003</td>
</tr>
<tr>
<td>Immunosuppression†</td>
<td>0.668</td>
<td>0.121 – 3.681</td>
<td>0.64</td>
</tr>
</tbody>
</table>

CI, confidence interval.
* At the time of renal biopsy.

**Malignancy occurrence:**
aPLA2R negative: 10/27 (37%), sooner
aPLA2R positive: 6/64 (9%), later

Timmermans S. et al., AJKD, 62:6, 2013
Patients with high-titer aPLA$_2$R are unlikely to undergo spontaneous remission

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low 41–175 U/ml (n=26)</th>
<th>Middle 176–610 U/ml (n=26)</th>
<th>High &gt;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>

*No treatment with immunosuppressive agents
Anti-PLA₂R level correlates with disease activity in idiopathic MC

Hofstra J M et al. CJASN 2011;6:1286-1291
Anti-PLA2R antibodies predict relapse rate after IS therapy

PLA2R antibody assay
Accuracy for diagnosing MN

Du et al PlosOne 2014
Sensitivity 0.78
Specificity 0.99

C: no need for high risk biopsy

PLA2R antibody assay
Accuracy for differentiating idiopathic vs secondary MN

He et al Sci Rep 2015
Sensitivity 0.68
Specificity 0.97

C: not accurate enough
Suggestions for practical use of anti-PLA$_2$R titers

• If possible, every membranous nephropathy patient should have anti-PLA2R assessed by biopsy and serum

• In aPLA2R-negative patients, look aggressively for secondary causes (but still idiopathic in 20-30%)

• For patients who are aPLA2R positive on biopsy,
  – Absence of serum aPLA2R may suggest impending remission
  – High-titer serum aPLA2R may suggest low likelihood of remission

• Assessing aPLA2R at the end of immunosuppressive treatment may be useful in assessing likelihood of maintaining remission

• Prospective studies using treatment algorithm based on anti-PLA2R level are necessary for proof of concept
Clinical usefulness of autoantibodies to M-type phospholipase A2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN)

Antonella Radice a,*, Barbieri a, Pietro Napodano c, Davide Misceola c, Francesco Londrino k, Fedor G. Kucherenko a

Antibodies against PLA2R are highly specific serological markers of IMN. Anti-PLA2R levels in IMN are associated with disease activity as measured by proteinuria and other biomarkers; positive PLA2R Ab status is linearly associated with proteinuria over time; the probability of halving proteinuria is significantly increased (6.5 times) after negativization of anti-PLA2R Abs; in IMN patients anti-PLA2R Ab serial measurements could help optimal timing and duration of the immunosuppressive therapy.
Membranous Nephropathy: Pilot Study of a Novel Regimen Combining Cyclosporine and Rituximab

Meryl Waldman§, Laurence H. Beck Jr§, Michelle Braun§, Kenneth Wilkins§, James E. Below§ and Howard A. Austin III§

A protocol based on a novel combination of rituximab and cyclosporine that targets both the B-cell and T-cell limbs of the immune system

Table 6. Summary of remission and relapse rates using various immunosuppressive regimens compared to protocol induction/maintenance regimen for treatment of membranous nephropathy

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>6 mo remissions</th>
<th>12 mo remissions</th>
<th>24 mo remissions</th>
<th>Relapse rates during trial period (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% CR</td>
<td>% PR</td>
<td>% CR</td>
<td>% PR</td>
</tr>
<tr>
<td>Cyclosporine (6-24 mo) + steroids</td>
<td>0-7</td>
<td>50-68</td>
<td>7-10</td>
<td>39-40</td>
</tr>
<tr>
<td>Tocilimus (18 mo)</td>
<td>12-23</td>
<td>37-44</td>
<td>26-34</td>
<td>44-48</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0</td>
<td>29-63</td>
<td>0-18</td>
<td>43-63</td>
</tr>
<tr>
<td>Rituximab</td>
<td>10-15</td>
<td>45-50</td>
<td>15-28</td>
<td>35-65</td>
</tr>
<tr>
<td>Rituximab + steroids for 6 mo</td>
<td>0</td>
<td>29-63</td>
<td>0-18</td>
<td>43-63</td>
</tr>
<tr>
<td>Oral cyclosporin for 12 mo + steroids for 6 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MMF + steroids</td>
<td>5</td>
<td>21</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Adenosine triphosphate hormone (synthetic) for 12 mo</td>
<td>19</td>
<td>44</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>Protocol regimen Cyclosporine + rituximab</td>
<td>23</td>
<td>62</td>
<td>54</td>
<td>31</td>
</tr>
</tbody>
</table>

Percentage of complete remissions (CR) and partial remissions (PR) achieved in patients with membranous nephropathy at various time points using other immunosuppresssion regimens.
Three Main RCT

**GEMRITUX**

- n = 80
- Rituximab vs placebo
- 2015
- Short FU (6 mo)
- Remission: 35% vs 21%

**MENTOR**

- n = 126
- Rituximab vs Ciclosporine (expected 2017)

**STARMEN**

- n = 148
- Tacrolimus + Rituximab vs Cyclophosphamide/Prednisone (expected 2018)
A European multicentre and open-label controlled randomized trial to evaluate the efficacy of Sequential treatment with TAcrolimus–Rituximab versus steroids plus cyclophosphamide in patients with primary MEmbranous Nephropathy: the STARMEN study
**First Arm:** Cyclical corticosteroids/cyclophosphamide for 6 months.

Months 1, 3 and 5: 1 g IV methylprednisolone daily (Days 1–3), then oral methylprednisolone (0.5 mg/kg/day) for 27 days (Days 4–30).

Months 2, 4 and 6: Oral cyclophosphamide (2.0 mg/kg/day) for 30 days.

**Second Arm:** Sequential tacrolimus–rituximab

(i) Tacrolimus: Initial dose of 0.05 mg/kg/day oral, adjusted to achieve blood trough levels of 5–7 ng/mL for 6 months. Starting at the end of Month 6, tacrolimus dosage will be reduced by 25% per month, resulting in a complete withdrawal at the end of Month 9.

(ii) Rituximab: A single dose of 1 g IV will be given at Day 180, before the onset of tacrolimus dose reduction.
comparison between the efficacy of sequential tacrolimus–rituximab therapy with a modified Ponticelli protocol (steroids plus cyclophosphamide)

The result of this study will be done by 2018.
A Multicenter Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR)
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- IMN diagnosed by renal biopsy.</td>
<td>- Patients with presence of active infection or a secondary cause of IMN (e.g. hepatitis B, SLE, medications, malignancies).</td>
</tr>
<tr>
<td>- Age 18–80 years inclusive.</td>
<td>- Type 1 or 2 diabetes mellitus: to exclude proteinuria secondary to diabetic nephropathy. Patients who have recent history of steroid induced diabetes but no evidence on renal biopsy performed within 6 months of entry into the study are potentially eligible for enrollment.</td>
</tr>
<tr>
<td>- If female, must be post-menopausal, surgically sterile or practicing a medically approved method of contraception.</td>
<td>- Pregnancy or breast feeding.</td>
</tr>
<tr>
<td>- Patient must be off prednisone or mycophenolate mofetil for &gt;1 month and alkylating agents for &gt;6 months.</td>
<td>- History of resistance to CSA or other calcineurin inhibitors, RTX or alkylating agents. Patients who previously responded to CSA/CNI, RTX or alkylating agents with either a CR or PR but relapsed off CSA/CNI after 3 months, or relapsed off RTX or alkylating agent after 6 months, are eligible.</td>
</tr>
<tr>
<td>- Treatment with an ACEi and/or ARB, for ≥3 months prior to randomization and adequate blood pressure control or If patient is intolerant to even a very low dose of either ACEi or ARB therapy.</td>
<td></td>
</tr>
<tr>
<td>- Proteinuria ≥5 g/24 h using the average from two 24-hour urine collections collected within 14 days of each other despite Ang II blockade for ≥3 months as described above.</td>
<td></td>
</tr>
<tr>
<td>- Estimated GFR ≥40 ml/min/1.73 m² while taking ACEi/ARB therapy or quantified endogenous creatinine clearance ≥40 ml/min based on a 24 h urine collection.</td>
<td></td>
</tr>
</tbody>
</table>

Estimated study completion date of primary trial is September, 2016.
Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up

Karine Dahan*, Hanna Debiec†‡, Emmanuelle Plaister*†‡, Marine Cachanado§, Alexandra Rousseau§, Laura Wakselman§, Pierre-Antoine Michel*, Fabrice Mihout*, Bertrand Dussol†, Marie Matignon†, Christiane Mousson**†, Tabassome Simon§ and Pierre Ronco*† on behalf of the GEMRITUX Study

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† Anti-PLA2R-Ab
‡ CD19 (depleted or very low during first 6 months)

Month -6
Pre-inclusion period
Optimized NIAT

NIAT+ Rituximab
375 mg/m² IV

D0 D1 D8 Month 3 Month 6 End points Month 24

RCT
Observational study
percentage changes in proteinuria

Serum albumin level

Anti-PLA2R-AB level
- serum albumin and PLA2R-Ab levels are early markers of NIAT-rituximab efficacy

- criteria for definition of remission should include serum albumin and PLA2R-Ab levels
Take home ......

- Anti-PLA2R antibodies can be helpful in diagnosing MN, in the identification of high risk patients, and in guiding therapy duration.

- Cyclophosphamide still therapy of choice in patients with renal insufficiency.

- Patients with preserved renal function can be treated with CNI or Rituximab, although trials on renal end-points remain needed.
Thank You!!!