Treatment of Idiopathic Membranous Nephropathy

Nephrology Grand Rounds
Pathophysiology

**Small circulating immune complexes of low-avidity antibody and oligovalent antigen**

- Epithelial podocyte
- Glomerular basement membrane

**In situ immune complex involving native podocyte antigen**

- In situ immune complex
- Antigen

**In situ immune complex involving “planted” antigen**

- Bowman’s space
- Nonnative antigens
- Circulating antibodies
M-Type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

- PLA2R is a major target antigen in IMN.
- 70% of patients with biopsy proven IMN had IgG antibodies that reacted with a reduction sensitive epitope present on PLA2R.
- IgG is subtype 4.
- PLA2R is located on podocytes.
- It is possible presence of PLA2R corresponds to disease activity.
- Antibody most likely the cause of podocyte injury and proteinuria.

Results of Western Blotting of Glomerular Proteins with Serum from Patients with Idiopathic Membranous Nephropathy.

Expression of the M-Type Phospholipase A2 Receptor (PLA2R) in Normal Kidney Tissue and Glomeruli.
Colocalization of the M-Type Phospholipase A2 Receptor (PLA2R) and IgG4 and Reactivity of Eluted IgG4.

Figure 6. Antibody against the M-Type Phospholipase A₂ Receptor (PLA₂R) and Disease Activity in a Patient with Membranous Nephropathy.
# Causes of MN

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (70% to 85%)</td>
<td></td>
</tr>
<tr>
<td>Secondary to an underlying</td>
<td></td>
</tr>
<tr>
<td>disease (15% to 30%)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Hepatitis B,* hepatitis C, syphilis, leprosy</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Systemic lupus erythematosus,* Sjögren’s syndrome, rheumatoid arthritis, thyroaiditis</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>Carcinoma* (lung, gastrointestinal tract, breast), lymphoma</td>
</tr>
<tr>
<td>Drugs</td>
<td>Organic gold,* mercury,* D-penicillamine,* probenecid, captopril</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>De novo in renal allografts,* Kimura’s disease</td>
</tr>
</tbody>
</table>

Natural history

- Spontaneous Complete remission in 5-30% of patients at 5yrs
- Spontaneous Partial remission in 25-40% of patients at 5 yrs
- ESRD in 14 % at 5yrs, 35% at 10 yrs, and 41% at 15 yrs

- Prospective study following 100 patients over 5 yrs

- CR<0.2g, PR: 0.2-2.0, ESRD=CrCl<10

- Results: 24/37 (65%) with CR or PR at 5 yrs, 6/37 (16%) with ESRD at 5 yrs.
Schieppati et al., N Engl J Med 1993; 329:85
Table 3. Probability of Five-Year Kidney Survival According to the Degree of Proteinuria at Base Line.

<table>
<thead>
<tr>
<th>Base-Line Urinary Protein Excretion g/24 hr</th>
<th>No. of Patients</th>
<th>Probability* %</th>
<th>Duration of Follow-up mo</th>
<th>Final Serum Creatinine† mg/dl</th>
<th>Final Urinary Protein Excretion‡ g/24 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.2 to &lt;2.0</td>
<td>24</td>
<td>86±10</td>
<td>51±50</td>
<td>1.0±0.6</td>
<td>1.5±1.4</td>
</tr>
<tr>
<td>≥2.0 to &lt;3.5</td>
<td>13</td>
<td>87±12</td>
<td>52±35</td>
<td>2.0±2.4</td>
<td>3.6±3.4</td>
</tr>
<tr>
<td>≥3.5 to &lt;5.0</td>
<td>19</td>
<td>92±7</td>
<td>53±41</td>
<td>1.3±1.1</td>
<td>2.5±1.1</td>
</tr>
<tr>
<td>≥5.0 to &lt;10.0</td>
<td>34</td>
<td>87±8</td>
<td>58±57</td>
<td>1.3±0.6</td>
<td>1.0±1.0</td>
</tr>
<tr>
<td>≥10.0</td>
<td>10</td>
<td>50±35</td>
<td>28±32</td>
<td>1.7±1.1</td>
<td>3.8±1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Absent</th>
<th>Present</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>probability (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>84±10</td>
<td>68±9</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76±10</td>
<td>78±9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥300 mg/dl (7.7 mmol per liter)</td>
<td>74±11</td>
<td>75±9</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥50 yr</td>
<td>85±8</td>
<td>61±11</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Male sex</td>
<td>86±9</td>
<td>64±10</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Shiiki et al, Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan.

- Retrospective study of 949 patients in Japan

- Results: Renal survival rates were 95.8%, 90.3% 81.1% and 60.5% at 5, 10, 15, and 20 yrs respectively.

- Risk factors affecting renal survival were Cr>1.5, Male >60yrs, Tubulointerstitial lesions>20%.

Renal survival rate, %

Time, years

$N = 949$
<table>
<thead>
<tr>
<th>Parameters</th>
<th>$P$ value</th>
<th>Relative ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.0032</td>
<td>2.36</td>
<td>1.33–4.16</td>
</tr>
<tr>
<td>Age ($\geq$60 years)</td>
<td>0.0023</td>
<td>2.25</td>
<td>1.33–3.78</td>
</tr>
<tr>
<td>Urinary protein ($\geq$10 g/day)</td>
<td>0.49</td>
<td>1.20</td>
<td>0.71–2.02</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>0.49</td>
<td>1.18</td>
<td>0.74–1.88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.078</td>
<td>1.55</td>
<td>0.95–2.52</td>
</tr>
<tr>
<td>Serum creatinine ($\geq$1.5 mg/dL)</td>
<td>0.0001</td>
<td>2.78</td>
<td>1.66–4.67</td>
</tr>
<tr>
<td>Serum total cholesterol</td>
<td>0.31</td>
<td>1.45</td>
<td>0.71–2.94</td>
</tr>
<tr>
<td>Light microscopic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global sclerosis ($\geq$20%)</td>
<td>0.90</td>
<td>0.95</td>
<td>0.42–2.17</td>
</tr>
<tr>
<td>Segmental sclerosis ($\geq$20%)</td>
<td>0.11</td>
<td>2.09</td>
<td>0.84–5.20</td>
</tr>
<tr>
<td>Tubulointerstitial changes ($\geq$20%)</td>
<td>&lt;0.0001</td>
<td>4.08</td>
<td>2.01–8.28</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td>0.24</td>
<td>1.46</td>
<td>0.78–2.73</td>
</tr>
</tbody>
</table>
Prospective study of 108 patients with subnephrotic proteinuria at presentation

Results: 40% remained subnephrotic within 12 months, patients who subsequently developed proteinuria had 4x rate of decline in CrCl as compared to patient who remained subnephrotic

Majority of patients who developed nephrotic range proteinuria did so in the first year.

Group 1: never nephrotic

Group 2: nephrotic post presentation

Group 3: nephrotic at presentation

Non immunosuppressive therapy

- Angiotensin inhibitors
- BP control
- Lipid lowering
- Anticoagulation
ACE/ARB

- Recommended in all patients with proteinuria

- Goal: 60% reduction of proteinuria from baseline value and optimally less than 500 to 1000mg/day

- May significantly reduce the rate of disease progression
ACE/ARB

- Remission more frequent with lower baseline proteinuria

- Rate of remission are higher among patients treated with ACE/ARB, results only significant if proteinuria <8g

- Independent predictors for remission: baseline Cr, baseline protein excretion, and >50 percent reduction in protein excretion at one year.
Immunosuppressive therapy

- Risk stratification to low, moderate and high risk for progression to ESRD

- Measure 24 hr collection for protein, GFR as estimated from creatinine clearance

- Random Uptn/Ucr should not be used for initial decision for treatment but can be used for follow up

- Goal to obtain complete remission
Risk stratification:

- Low risk: Proteinuria remains less than 4g/day and CrCl remains nl for 6 months follow up period. Less than 8% risk of developing CRI in 5 yrs.

- Moderate risk: Proteinuria is between 4-8g/day and persists for more than 6 months. CrCl is normal or near nl and remains stable for more than 6 months. Those patients have 50% risk of progression to CRI in 5 yrs.

- High risk: proteinuria is > 8g/day and persists for 3 months and/or renal function that is either below normal or decreases during observation period. Those patients have 75% risk of progression to CRI in 5 yrs.

Prospective controlled study of 81 patients followed for 10 yrs

Study group received methylprednisolone and chlorambucil for 6 months and control group received symptomatic therapy.

The probability of surviving without developing end-stage renal disease at 10 years was 92% in patients given methylprednisolone and chlorambucil versus 60% in controls (P = 0.0038).
--- treatment group
___ control group

Ponticelli et al., Kidney International 1995;48:1600-1604
Fig. 2. Slope of the mean reciprocal of plasma creatinine in 31 treated patients (—at) and in 25 untreated controls (—■—) followed for 10 years. °P < 0.05 compared to the basal value. *P < 0.01 compared to the basal value. The difference between the two slopes is also statistically significant (P = 0.035).
Randomized controlled trial, 87 patients followed for at least 1 yr

Compared two regimens based on a 6-mo treatment, alternating every other month methylprednisolone with chlorambucil or methylprednisolone with cyclophosphamide.

Results: 36 of 44 (82%) assigned to methylprednisolone and chlorambucil entered complete or partial remission of the nephrotic syndrome, versus 40 of 43 (93%) assigned to methylprednisolone and cyclophosphamide (P = 0.116).
Figure 1. Cumulative probability of obtaining partial or complete remission of the nephrotic syndrome or complete remission alone as a first event in patients given methylprednisolone plus chlorambucil (---) and in patients given methylprednisolone plus cyclophosphamide (——). Data were calculated every 6 mo.
Figure 2. Cumulative probability of relapse of the nephrotic syndrome after complete or partial remission in patients given methylprednisolone plus chlorambucil (—) and in patients given methylprednisolone plus cyclophosphamide (——).
Randomized controlled trial, 93 patients followed for 10 yrs

Compared the effect of a 6-mo course of alternating prednisolone and cyclophosphamide with supportive treatment in adults with IMN.

End points: doubling of serum creatinine, development of ESRD, and quality of life

In tx group 34/43 achieved remission (15 CR, 19 PR),

In control group 16/42 achieved remission (5 CR, 11 PR) (P<0.0001).

10-yr dialysis-free survival was 89 and 65% (P = 0.016)

the likelihood of survival without death, dialysis, and doubling of serum creatinine were 79 and 44% (P = 0.0006) in the two groups.

Figure 2. The course of proteinuria (A) and the Modification of Diet in Renal Disease (MDRD) estimated GFR (eGFR; B) during the follow-up period. ■, group 1, ▲, group 2. *P < 0.05; #P < 0.01; **P < 0.0001.
Randomized trial in 51 patients with idiopathic MGN with nephrotic-range proteinuria

Comparing 26 weeks of cyclosporine treatment plus low-dose prednisone to placebo plus prednisone.

Patients were followed for an average of 78 weeks

Results: 75% percent of the treatment group vs 22% of the control group (P<0.001) had a partial or complete remission of their proteinuria by 26 weeks.

Relapse occurred in 43% (N = 9) of the cyclosporine remission group and 40% (N = 2) of the placebo group by week 52.
Fig. 1. Remissions in proteinuria in the cyclosporine patients [(□) partial, (■) complete] compared with the placebo-treated [(□□) complete, (□) partial] at different time points of the study. At week 26, $P=0.001$; at week 52, $P=0.004$; and week 78, $P=0.007$. Early stops (*) were assessed at the last follow-up.
Prospective randomized trial following 48 patients

To evaluate monotherapy with tacrolimus (12 months then 6 months taper) vs placebo

The probability of remission in the treatment group was 58, 82, and 94% after 6, 12, and 18 months but only 10, 24, and 35%, respectively in the control group.

Nephrotic syndrome reappeared in almost half of the patients who were in remission by the 18th month after tacrolimus withdrawal.
Figure 3 | Percentage of complete (grey) and partial (white) remissions in the tacrolimus (T) and in the control (C) group. Numbers within columns indicate the total number of patients in CR or PR in both groups.
Clinical trial with historic controls, median f/u 23 months, 32 cases and 32 controls

**MMF**, 1 g twice daily, for 12 months versus **cyclophosphamide**, 1.5 mg/kg/d, for 12 months. Both groups also received intermittent methylprednisolone and alternate-day prednisone.

Cumulative incidences of remission of proteinuria at 12 months were 66% in the MMF group versus 72% in the cyclophosphamide group (P = 0.3).

5 patients (16%) in the MMF group vs none in the cyclophosphamide group had disease that did not respond to therapy (P = 0.05).

12 pts (38%) experienced a relapse and 9 pts (31%) were re-treated in the MMF group compared with 4 (13%) and 2 pts (6%) in the cyclophosphamide group (P<0.01 and P = 0.024, respectively).
Thank you