Membranous Nephropathy: New Insights Regarding Treatment

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Rochester, MN
Survival from Renal Failure in Patients with Complete, Partial, and No Remission*

*Troyanov et al: Kidney Int., 2004

*5 pt out of 348 had a creatinine clearance <15 mL/min at initial assessment and were excluded from this analysis
Goal of therapy is to reduce proteinuria and prevent progression to renal failure
A 10-Year Follow-Up
Renal Survival

Treated patients:
- Months: 42, 42, 41, 40, 40, 39, 37, 37, 36, 35, 34, 34, 33, 32, 30, 30, 30, 30, 30, 30

Untreated Patients:

Tacrolimus Monotherapy Randomized Controlled Trial

- Complete remission
- Partial remission

<table>
<thead>
<tr>
<th>Months</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
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<tr>
<td>18</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

- T = tacrolimus; C = control; numbers within columns indicate the total number of pt in CR or PR in both groups
# Traditional Therapies for Idiopathic Membranous Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Safety</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil + corticosteroids</td>
<td>Efficacy in RCT vs placebo</td>
<td>Bone marrow suppression, seizures, malignancy, infertility</td>
<td>Typically limited to severe pts</td>
</tr>
<tr>
<td>Cyclophosphamide + corticosteroids</td>
<td>Small studies suggest efficacy</td>
<td>Leukopenia, infertility, hemorrhagic cystitis, malignancy</td>
<td>Typically limited to severe pts</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Efficacy in RCT vs placebo; frequent relapses once stopped</td>
<td>Hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity (blood levels need to be measured)</td>
<td>Most commonly used in less severe pts; anti-proteinuric effect does not appear to impact underlying disease</td>
</tr>
</tbody>
</table>

The graph shows the percentage of patients in two treatment groups over the course of 60 months. The blue line represents methylprednisolone + chlorambucil, while the orange line represents methylprednisolone + cyclophosphamide.
Unmet need is an effective therapy with a favorable safety profile where risk benefit profile favors earlier initiation of therapy.
Cumulative Incidence of Relapses in Patients Treated with Mycophenolate Mofetil or Cyclophosphamide

P=0.007

Relapse (%)

Pt at risk (no.)

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>MMF</th>
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<tr>
<td>0</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>26</td>
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<td>13</td>
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<tr>
<td>30</td>
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<td>5</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
<td>3</td>
</tr>
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</table>

The Case for Targeting B Cells

• MN is mediated by deposition of IgG antibodies

• Animal studies – immune deposition resulting from B cell activation promote injury to the GBM and proteinuria

• Inhibition of B cells and of pathogenic antibodies is directly related with the beneficial effects of immunosuppressive drugs in experimental MN


Effect of cyclophosphamide:

• Striking direct effects on B cell function

• Suppresses secretion of immunoglobulins

Rituximab in Membranous Nephropathy

Proteinuria (g/24 hr)

Serum creatinine (mg/dL)

Months

*P<0.01 vs months -6 and 0
Urine protein (g/24 hr)

-4  Baseline  28 Days  3  6  9  12  18  24 Months

NR n=2
LR n=1
PR n=12
CR n=5

Fervenza et al: CJASN, 2010
red = anti-PLA$_2$R  blue = proteinuria

Beck, Fervenza, Beck et al., JASN 22:1543, 2011
Patients with event (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Complete or partial remission</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>84</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>18</td>
<td>56</td>
<td>47</td>
<td>23</td>
</tr>
<tr>
<td>24</td>
<td>41</td>
<td>37</td>
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<td>30</td>
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<td>36</td>
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<td>42</td>
<td>17</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>13</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>54</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Ruggenenti et al: JASN, 2012
Membranous Nephropathy

Rituximab

At 6 mo

NR (<25% in proteinuria)

PR

CR

Failure

Retreat at 6 mo

Observation

Exit

Rx stops at 12 mo

Observation for 15 months

CsA

At 6 mo

NR (<25%)

PR

CR

Failure

Continue Rx

Exit

Rx stops at 12 mo

Observation for 15 months
ACTH 1-39

Gong, R. Nat. Rev. Nephrol. 6 Dec 2011
Clinical Outcome of 16 Patients Treated with ACTH 1-24 (Group B)


- Complete remission
- Partial remission
- No response

Treated with ACE inhibitors and/or ARBs
- Administered statins
- Discontinued therapy because of side effects
- Withdrew therapy after 3 mo because of inefficacy

(Group A = 75% vs B = 83%)
Changes in Proteinuria with ACTH Gel Therapy in II Patients with Nephrotic Syndrome Due to Membranous Nephropathy

*Resistant to 2.4 immunosuppressive treatments
Original Article

A pilot study to determine the dose and effectiveness of adrenocorticotropic hormone in nephrotic syndrome due to idiopathic membranous nephropathy

Michelle A. Hladunewich¹, Daniel Cattran¹, Laurence H. Beck², Ayodele Odutayo¹, Sanjeev Sethi³, Rivka Ayalon², Nelson Leung⁴, Heather Reich¹ and Fernando C. Fervenza⁴

¹Division of Nephrology, University of Toronto for the Toronto Glomerulonephritis Registry, Toronto, ON, Canada, ²Division of Nephrology, Boston University School of Medicine, Boston, MA, USA, ³Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA and ⁴Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
## Baseline and Follow-Up Variables in the Overall Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>ACTH Completion</th>
<th>12 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>121±16</td>
<td>124±18</td>
<td>119±16</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>72±8</td>
<td>75±7</td>
<td>74±11</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>9,068±3,384</td>
<td>6,155±4,754*</td>
<td>3,866±4,243*,**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>77±30</td>
<td>78±25</td>
<td>76±30</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>2.72±0.83</td>
<td>3.25±0.60*</td>
<td>3.56±0.76*,**</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>306±133</td>
<td>230±95*</td>
<td>187±49*,**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>182±85</td>
<td>116±52*</td>
<td>93±37*,**</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL (mm/dL)</td>
<td>67±29</td>
<td>66±27</td>
<td>59±23</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>225±190</td>
<td>247±260</td>
<td>176±103</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP, blood pressure; NS is not significant  
*P<0.05 vs. Baseline  
**P<0.05 vs. ACTH completion

# Outcomes at 12 Months of Follow-up by Cumulative Dose

<table>
<thead>
<tr>
<th></th>
<th>880 IU</th>
<th>1,760 IU</th>
<th>2,800 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128±7</td>
<td>115±18</td>
<td>119±18</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78±11</td>
<td>70±7</td>
<td>77±17</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>8,090±5,571</td>
<td>3,120±3,501</td>
<td>1,505±1,072*</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>64±16</td>
<td>78±35</td>
<td>83±28</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>2.75±1.05</td>
<td>3.74±0.40</td>
<td>3.95±0.60**</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>238±17</td>
<td>163±37**</td>
<td>194±60</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>125±31</td>
<td>80±31</td>
<td>91±43</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>75±14</td>
<td>53±24</td>
<td>56±25</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>190±92</td>
<td>147±79</td>
<td>234±159</td>
</tr>
</tbody>
</table>

*P<0.05 for trend across groups  
**P<0.05 vs. 880 IU

[Chart showing Proteinuria (mg/day) vs. Dose of ACTH (IU)]


- Orange dots = anti-PLA$_2$R antibody
- Blue squares = proteinuria
Conclusions

• Both Rituximab and ACTH are potential treatments for idiopathic membranous nephropathy
  o Decrease in proteinuria
  o Improvement in Measures of the Nephrotic Syndrome

• Dose
  o Rituximab: 1g x 2; 375 mg/m2 x 4; 1 g once
  o ACTH: 80 units of the ACTH twice-weekly for at least 3 months is required for this effect
Conclusions

• Side effects with both newer treatments appear to be mild
• Old treatments still very effective
• Anti-PLA$_2$R antibody levels mirror response
First biopsy
Second biopsy
Clinical disease

Immunologic disease

Treatment

100%

Anti-PLA_2R

Proteinuria

Partial remission

Complete remission

Time
Questions & Discussion
Methods

Primary Endpoints

• Change in proteinuria
• Change in serum albumin
• Change in cholesterol profile (Total & LDL cholesterol and triglycerides)
• Side effects/Toxicity

Secondary Endpoints

• Rates of Remission
• Complete remission (CR) = UP ≤0.3 g
• Partial remission (PR) = Reduction in UP >50% plus final UP ≤3.5 g, but >0.3g
• Non-response (NR) = Reduction in UP of <50%
• Progression (P) = Proteinuria increases by >50%
Methods

• Study Intervention: Randomization to 40 or 80 IU of ACTH gel injected subcutaneously twice weekly for 120 days with one year follow-up

• Mayo Clinic dose was increased to 80 IU in patients that did not respond by day 56
Cumulative Probability of Obtaining (P) or (C) Remission

Partial + complete remission

Complete remission

Methylprednisolone + chlorambucil

Methylprednisolone + cyclophosphamide

Months

Cyclosporine in MGN

Cyclosporine

Weekly:

- 2 CR
- 19 PR
- 7 NR

Placebo

Weekly:

- 1 CR
- 4 PR
- 18 NR

31 kDa pro-opiomelanocortin (POMC)

- γ-MSH
- ACTH 1-39
  - α-MSH
  - CLIP
- β-LPH
  - γ-LPH
  - Endorphin
- β-MSH

Gong, R. Nat. Rev. Nephrol. 6 Dec 2011
Malignancies in Wegener’s Granulomatosis: Incidence and Relation to Cyclophosphamide Therapy in a Cohort of 293 Patients

MIKKEL FAURSCHOU, INGE JUUL SORENSEN, LENE MELLEMKJAER, ANNE GITTE RASMUSSEN LOFT, BJARNE SVALGAARD THOMSEN, NIELS TVEDE, and BO BASLUND

**ABSTRACT.**  
Objectives. To describe the incidence of malignancies in a cohort of Danish patients with Wegener’s granulomatosis (WG) and to investigate the cancer risk associated with cyclophosphamide (CYC) therapy in WG.

Methods. In total, 293 patients diagnosed with WG between 1973 and 1999 were studied. Cancer incidence in the cohort was assessed through 2003 by linkage to the Danish Cancer Registry and compared to that of the general population by calculation of standardized incidence ratios (SIR). Analyses were stratified according to treatment with low cumulative CYC doses (≤ 36 g) and high doses (> 36 g, corresponding to treatment with 100 mg CYC/day for > 1 year).

Results. Fifty cancers occurred during 2121 person-years of followup (SIR of cancer of 2.1, 95% CI 1.5–2.7). Significantly increased SIR were observed for acute myeloid leukemia (AML; SIR 19.6, 95% CI 4.0–57), bladder cancer (SIR 3.6, 95% CI 1.2–8.3), and non-melanoma skin cancers (SIR 4.7, 95% CI 2.8–7.3). Leukemias and bladder cancers were diagnosed 6.9–18.5 years after initiation of CYC therapy. The risk of these malignancies was not increased for patients who never received CYC or for patients treated with cumulative CYC doses ≤ 36 g. In contrast, high risks of AML (SIR 59.0, 95% CI 12–172) and bladder cancer (SIR 9.5, 95% CI 2.6–24) were observed for patients treated with cumulative CYC doses > 36 g.

Conclusion. Treatment with high cumulative CYC doses implies a substantial risk of late-occurring, serious malignancies in WG. Patients with WG should be monitored for development of cancer for several decades after cessation of CYC therapy. These findings emphasize the need for development of new treatment regimens in WG. (First Release Oct 15 2007; J Rheumatol 2008;35:100–5)
Rituximab Therapy in Idiopathic Membranous Nephropathy: A 2-Year Study

Fernando C. Ferrenza,* Roshini S. Abraham,† Stephen B. Erickson,* Maria Valentina Irazabal,* Alfonso Eirin,* Ulrich Specks,‡ Patrick H. Nachman,§ Eric J. Bergstrahl,‖ Nelson Leung,* Fernando G. Cosio,* Marie C. Hogan,* John J. Dillon,* LaTonya J. Hickson,* Xujian Li,‖ and Daniel C. Cattran,‖ for the Mayo Nephrology Collaborative Group

*Division of Nephrology and Hypertension, †Division of Clinical Biochemistry and Immunology, Department of Laboratory Medicine and Pathology, ‡Division of Pulmonary and Critical Care, and ‖Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; §Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ‧Department of Nephrology, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada