Evidence-based treatment of Membranous Nephropathy

Vivekanand Jha
Postgraduate Medical Institute
Chandigarh, INDIA

Indian Society of Nephrology

Idiopathic Membranous Nephropathy

Kidney Disease: Improving Global Outcomes

www.kdigo.org
Selecting patients for therapy

- **We recommend** that therapy be started **ONLY** in patients with nephrotic syndrome (1C) and at least one of the following:
  - UPE persistently exceeds 4 g/d, remains > 50% of baseline, AND does not show progressive decline despite antiproteinuric therapy for **at least** 6 mo (1B)
  - the presence of severe, disabling or life-threatening symptoms related to the nephrotic syndrome (1C)
  - SCr rises by ≥ 30% over 6-12 mo, but eGFR is not < 25-30 mL/min/1.73m² AND this change is not explained by superimposed complications. (2C)

Selecting patients for therapy

- **We suggest** patients showing a chronic and persistent serum creatinine >3.5 mg/dl (eGFR < 30 ml/min) and those with marked reduction of kidney size be not exposed to immunosuppressive therapy. *(Not Graded)*
Rationale

- Patients with time averaged proteinuria < 4g/d and those who achieve complete or partial remission have excellent long-term prognosis.
- Risk adversely affected by: male gender, persistent heavy proteinuria and ↑Scr at diagnosis.
- About one-third undergo spontaneous remission, but a prolonged period of observation may be necessary.

Spontaneous remission in IMN

Independent predictors: Baseline serum creatinine and proteinuria, treatment with ACEI/ARB, 50% ↓ in proteinuria during first year of follow-up.
The impact of gender

Predicting progression risk
Initial therapy for IMN

- **We recommend** that initial therapy consist of a 6 month course of alternating monthly cycles of oral and intravenous corticosteroids and oral alkylating agents (1B).
- **We suggest** using cyclophosphamide (CYC) over chlorambucil (CH) (2B)
- **We recommend** patients be managed conservatively for at least 6 months following the completion of the initial regimen before being evaluated for remission unless kidney function is deteriorating. (1C)

Rationale

- Two RCTs with 10 y follow-up have shown prednisolone+alkylating agents to be superior to supportive therapy in inducing remission, preserving long-term decline in renal function including need for dialysis and preserving QOL
- Partial remission is acceptable, but might be achieved after 12-18 mo
- Cyclophosphamide has a superior safety profile compared to Chlorambucil
Chlorambucil + Steroids for MN

Survival without dialysis: Improving Global Outcomes
Ponticelli et al, KI 1995

www.kdigo.org

Cyclophosphamide + Steroids for MN

Kidney Disease: Improving Global Outcomes
Jha et al, JASN 2007

www.kdigo.org
Cyclophosphamide + Steroids for MN

| Parameter       | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
|-----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| At baseline     | 7       | 5       | 44      | 43      | 46      | 46      | 44      | 42      | 0       | 0       | 4.41 ± 1.19 | 4.76 ± 1.07 |
| 1 yr            | 13      | 6       | 30      | 19*     | 33      | 30*     | 36      | 24*     | 0       | 0       | 5.04 ± 1.32 | 6.01 ± 1.56 |
| 2 yr            | 19      | 8*      | 28      | 18*     | 26      | 18*     | 31      | 19*     | 17      | 6*      | 6.18 ± 1.09 | 7.12 ± 1.10* |
| 5 yr            | 26      | 11*     | 24      | 7*      | 24      | 8*      | 34      | 17*     | 28      | 6*      | 6.45 ± 1.12 | 7.36 ± 1.02* |
| 10 yr           | 35      | 16*     | 22      | 6*      | 100     | 7*      | 33      | 36*     | 32      | 13*     | 6.61 ± 1.08 | 7.31 ± 1.03* |

*ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**P < 0.01.

In our patients, oral cyclophosphamide was better tolerated than oral chlorambucil. The suggested

---

**ESRD (p < 0.05). Remissions of proteinuria occurred more frequently after cyclophosphamide treatment (15/17 vs. 5/15; p < 0.01). Side-effects necessitated interruption of treatment in six patients on cyclophosphamide and in 11 on chlorambucil (p < 0.05).**

Kidney Disease: Improving Global Outcomes
Non-remission as a surrogate

![Graph showing survival free from renal failure](image)

*Survival free from renal failure by multivariate analysis.*

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>12</td>
<td>67</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>74</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>106</td>
<td>74</td>
<td>33</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>102</td>
<td>74</td>
<td>33</td>
</tr>
</tbody>
</table>

*P < 0.001 NR<PR<CR*

**Implications of a partial remission in MN**

- A PR was independently predictive of slope and survival from renal failure by multivariate analysis.
- Benefit from immunosuppression could only be shown in high-risk patients.
- Treatment-related PR had the same long-term implication as spontaneous ones.
- Relapses from PR in 47% but usually reversible.
Alternative initial therapies

- **We recommend** that CsA or Tac be used for least 6 months in patients who choose not to receive the aforementioned regimen or have contraindications (1C).
- We **suggest** that CNI be discontinued in patients who do not achieve remission at 6 months (2C).
- We **suggest** that the CNI dosage be reduced 4-8 week intervals to about 50% of the starting dosage for at least 12 months if a CR/PR occurs. (2C)
- We **suggest** that CNI levels be monitored during the initial treatment period and when there is an unexplained rise in sCr (>20%) (not graded).

Rationale

- Two RCTs have shown that CNIs are effective in inducing remission but have a high relapse rate
- Relapse may be brought down by prolonging treatment to 1 year
CsA is effective in inducing remission in high-risk MN

Placebo, n=8
CsA, n=9

Kidney Disease: Improving Global Outcomes

CsA is effective for inducing remission in steroid-resistant MN

Kidney Disease: Improving Global Outcomes

www.kidigo.org
Catran et al. KI 1995

www.kidigo.org
Catran et al, KI 2001
Regimens not recommended or suggested for initial therapy

- **We recommend** that corticosteroid monotherapy should not be used for initial therapy of IMN (1B)
- **We suggest** that monotherapy with mycophenolate mofetil (MMF) should not be used for initial therapy of IMN (2C)
- **We suggest** that rituximab not be used for initial therapy of IMN (2D)
- **We suggest** that ACTH not be used for initial therapy of IMN (2C)

Rationale

- Three RCTs have shown steroid monotherapy to be ineffective
- Other regimes: small numbers, methodological issues, no consistency across studies.
Treatment of IMN resistant to initial therapy

• **We suggest** that patients with IMN resistant to alkylating agent-based initial therapy be treated with a CNI (2C)

• **We suggest** that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent (2C)

Treatment for relapses of nephrotic syndrome in IMN

• **We suggest** that relapses of nephrotic-range proteinuria in IMN be treated by re-institution of the same therapy that resulted in the initial remission (2D).

• **We suggest** that if the 6-month cyclical corticosteroid-alkylating agent regimen was used for initial remission it be repeated *only once* for treatment of a relapse (2B).
Some Research recommendations

- Validation of the utility of antibody against M-type PLA2R in terms of its accuracy of separating primary from secondary MN
- Studies of the value of renal pathology and urinary biomarkers in predicting prognosis and/or treatment responsiveness
- RCTs comparing alkylation agents with CNI and/or MMF as initial therapy.
- RCTs in IMN that assess the efficacy and safety risk of long-term CNI therapy
- RCT comparing corticosteroid-alkylating therapy or CNI against Rituximab
- RCTs to examine the efficacy and safety of MMF, rituximab or ACTH in relapsing patients
Thank you