Recent advances in membranous nephropathy

Turkish Society of Nephrology
Antalya, 16th November 2012

Peter Mathieson
University of Bristol, UK

p.mathieson@bristol.ac.uk
www.theisn.org/
MN: the phenotype
IMN: three recent advances

1. Pathogenesis
2. Genetics
3. Treatment
MN I: aetiology/pathogenesis

1. Autoimmune hypothesis (IgG and C3 deposition, analogies with Heymann nephritis, MHC association)

2. Beck et al reported anti-PLA2R auto-antibodies in 60-70% of 1º cases (NEJM 2009)

3. anti-PLA2R rare in 2º cases, lupus MN
Phospholipase A2 receptor

1. Type I transmembrane glycoprotein, akin to mannose receptor

2. Expressed by podocytes in man (but not in rodents)

3. In other cell types, role in proliferation, senescence, production of prostanoids & pro-inflammatory cytokines

4. Role of PLA2R in podocytes, and effects of anti-PLA2R thereon, not yet known
MN I: anti-PLA2R, current questions

1. Standardisation of assays needed
2. Role in diagnosis: is renal biopsy still essential? Differentiation of 1° and 2°.
3. Role in monitoring, correlation with disease activity
4. Value in treatment decisions: High titre allows selection of poor prognosis pts
1. Known MHC association, less certainty about other loci
2. Recent description of anti-PLA2R auto-antibodies in 60-70% of 1º cases
3. MRC/KRUK DNA collection in five glomerular diseases
4. Prevailing view that very large sample sizes necessary for polygenic diseases
GWAS on 335 samples
France
Pierre Ronco
Netherlands
Jack Wetzels
<table>
<thead>
<tr>
<th></th>
<th>French cohort</th>
<th>Dutch cohort</th>
<th>British cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>75</td>
<td>146</td>
<td>335</td>
</tr>
<tr>
<td>Male (m)</td>
<td>58</td>
<td>109</td>
<td>231</td>
</tr>
<tr>
<td>Female (f)</td>
<td>17</td>
<td>37</td>
<td>104</td>
</tr>
<tr>
<td>Sex ratio (m:f)</td>
<td>3.4:1</td>
<td>2.9:1</td>
<td>2.2:1</td>
</tr>
<tr>
<td>Age at diagnosis (years (+/- SD))</td>
<td>49.8 (15.3)</td>
<td>51.8 (14.2)</td>
<td>52.5 (13.3)</td>
</tr>
<tr>
<td>Chromosome</td>
<td>Gene</td>
<td>SNP</td>
<td>p-Value</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Chrom 2</td>
<td>PLA2R1</td>
<td>rs4664308</td>
<td>$8.6 \times 10^{-29}$</td>
</tr>
<tr>
<td>Chrom 6</td>
<td>HLA-DQA1</td>
<td>rs2187668</td>
<td>$8.0 \times 10^{-93}$</td>
</tr>
</tbody>
</table>
Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism and Genotype Combinations.*

<table>
<thead>
<tr>
<th>SNP rs2187668 (HLA-DQA1)</th>
<th>SNP rs4664308 (PLA₂R1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
</tr>
<tr>
<td><strong>GG</strong></td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td>14/354</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>GA</strong></td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td>23/115</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>6.07 (3.01–12.27)</td>
</tr>
<tr>
<td><strong>AA</strong></td>
<td></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
<td><strong>5/11</strong></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td><strong>20.24 (5.51–74.38)</strong></td>
</tr>
</tbody>
</table>

* Persons who were homozygous for the low-risk allele (GG) constituted the reference category. Numbers of cases and total numbers of subjects are from the joint analysis. OR denotes odds ratio, and SNP single-nucleotide polymorphism.
IMN genetics: next questions

Is chromosome 2 association explained by rare genetic variants/mutations?

Is chromosome 2 association confined to patients positive for anti-PLA2R?

Why is familial MN not more common & why is there male predominance?

What are therapeutic implications of the genetic predisposition to IMN?
MN III: treatment

1. Poor track record of clinical trials in nephrology
2. No agreement on best treatment of IMN
3. Evidence of efficacy for cyclosporin and for prednisolone with chlorambucil
4. Existing trials excluded subset with poor or deteriorating excretory renal function
UK trial (unpublished, in press in *The Lancet*):

1. **Inclusion:** biopsy-proven MN with at least 20% decline in excretory renal function based on at least 3 measurements over ≥ 6/12.

2. **Exclusion:** 2° MN, creat >300μmol/l (3.4mg/dl)

2. Randomised to 1 of 3 groups:
   (a) supportive treatment only
   (b) cyclosporin 5mg/kg/day (aim for trough level 100-200 μg/l), 12months
   (c) prednisolone & chlorambucil 6 months (with reduced dose chlorambucil, max 0.15mg/kg/d)
Baseline characteristics:
[mean (SD) for each, no sig differences]

Age: Cy 58 (11), P/C 58 (12), STO 56 (16) yrs

Calculated creatinine clearance in ml/min:
Cy 49 (18), P/C 50 (16), STO 50 (20)

Proteinuria in g/24h:
Cy 6.8 (4.7), P/C 10.1 (5.3), STO 9.1 (5.3)

Systolic BP in mmHg:
Cy 143 (21), P/C 141 (16), STO 138 (19)
Supportive treatment:

1. Good evidence for angiotensin blockade in patients with heavy proteinuria
2. Anticoagulants for thrombosis, (prophylactically if plasma albumin ≤20g/l)
3. Statins
4. Symptomatic: diuretics, salt restriction etc

Encouraged in all 3 groups [but we didn’t collect data on diet, cholesterol etc]

92% of all patients received ACE inhibitors (92% in STO, 100% in cyclosp, 82% in P/C)
Trial results:

108 patients recruited (2 ineligible, 33 P/C, 36 CyA, 37 STO; original power calc 40 in each group, 120 total) 10 years 1998-2008

3 year follow-up in all cases, longer in many

Deaths 2 P/C, 2 CyA, 1 STO
ESRD 1 P/C, 6 CyA, 4 STO

“Intention to treat” analysis, time to primary end-point (further 20% decline); secondary end-points proteinuria, adverse effects
Comparisons: Hazard Ratio (95% CI) and p-value

Cyclosporin vs Supportive care.  HR 1.17 (0.7, 1.95), 2p=0.5
Prednisolone / Chlorambucil vs Supportive care.  HR 0.44 (0.24, 0.78), 2p=0.0042
Change in 24h protein from baseline

p = 0.048
Mean treatment effect for pred/chlor vs supp is -2.2
2p=0.005 (cycl vs supp)
2p=0.006 (pred vs supp)
Serious adverse events:

Of 50 in prednisolone + chlorambucil group, 28 (56%) haematological, 7 (14%) metabolic

Of 26 in cyclosporin group: 7 (26%) infection, 5 (19%) haematological

Of 17 in supportive therapy group: 5 (29%) metabolic, 3 (17%) haematological

Treatment cessation (incl. temporary): 11, 6, 1

<table>
<thead>
<tr>
<th></th>
<th>Pred/Chlor</th>
<th>Cyclosporin</th>
<th>Supportive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SAE</td>
<td>14 (42%)</td>
<td>22 (59%)</td>
<td>25 (66%)</td>
</tr>
<tr>
<td>At least 1 SAE</td>
<td>19 (58%)</td>
<td>15 (41%)</td>
<td>13 (34%)</td>
</tr>
</tbody>
</table>

$2p = 0.09$
Interpretation:
Prednisolone + chlorambucil is significantly superior to cyclosporin or supportive treatment only in patients with progressive membranous nephropathy.
Treatment effect is maintained to 3 years.
Adverse events frequent in all 3 groups.
Even in best group, only 40% had not had further 20% decline by 3 years.
Better (and earlier) treatments still needed...
Chapter 7: idiopathic membranous nephropathy

Recommend therapy if there is persistent heavy proteinuria, disabling nephrotic syndrome and/or deteriorating eGFR.

Do not use immunosuppression if creat. >3.5mg/dl (309μmol/l).

Recommend initial therapy with “Ponticelli” regimen.

Recommend cyclophosphamide instead of chlorambucil.

Follow-up for at least 6/12 before declaring treatment failure.

Reserve CNIs for Ponticelli refusal, failure or contra-indication.

Do not use MMF; RCTs needed for MMF and/or rituximab.
Suggestions for future trials:

- Cyclophosphamide instead of chlorambucil in subset with deteriorating renal function
- Compare rituximab in randomised fashion. Can it protect renal function/arrest decline?
- Use anti-PLA2R positivity/titre to select bad prognosis patients
- Don’t discard MMF without further study
Take home messages

1. “Idiopathic” membranous nephropathy is associated with anti-PLA2R autoantibodies in about 70% of cases. Rare in 2° MN.

2. Two genes predispose to IMN in western European populations.

3. In subset of patients with IMN that have deteriorating renal function, combination of prednisolone + chlorambucil favoured.
MN genetic study

UK
Robert Kleta, Horia C Stanescu, Alan Medlar, Detlef Bockenhauer, Naina Patel, Kerra Pearce, Mike Hubank, Henry AF Stephens, Valerie Laundy, Sandosh Padmanabhan, Anna Zawadzka, Stephen H Powis, Paul Brenchley, John Feehally, Andrew J Rees, Peter W Mathieson

USA
Mauricio Arcos-Burgos

Germany
Anna Kottgen

Romania
Liviu Dragomirescu, Catalin Voinescu

France
Delphine Bacq-Daian, Benedicte Stengel, Hanna Debiec, Pierre Ronco

Netherlands
Julia M Hofstra, Marieke JH Coenen, Martin den Heijer, Lambertus ALM Kiemeney, Jack FM Wetzels
MN trial

Michael Boulton-Jones
Gill Gaskin
Jo Adu
David Jayne
Donal O’Donoghue
John Feehally
Maria Langdon
Caroline Ferguson
Tracey Chapman
Keith Wheatley
Andrew Howman
Peter Mathieson

Funding:
Medical Research Council
Kidney Research UK
Renal Association
Novartis

All participating nephrologists (esp Chris Isles), nurses and patients