ACTHAR gel for Idiopathic Membranous Nephropathy

By Hladen
Methods:
Study Population 1

- Adults > 18 years
- Biopsy proven idiopathic membranous nephropathy, less than 36 months prior
- < 30% glomerulosclerosis or IFTA
- At least 3 months of RAS blockade, BP < 130/75
- UProt:UCr ratio of ≥ 4; GFR ≥ 40
Methods
study population 2

Exclusions

• Active infections,
• Secondary membranous (hepatitis, SLE, malignancy)
• Type 1 or 2 diabetes
• H/0 acute thrombosis
• Pregnancy or nursing
Methods
study population 3

• Treatment Naive OR

• Documented resistance to immunosuppression routines used in iMN (calcineurin inhibitors + steroids or cytotoxic agent + steroid)

• But eligible if
  • H/o partial response to above regimens OR
  • Significant side effects to above regimens
Design

- Phase 1b/2 dose finding
- Non blinded
- Randomized to two different doses of ACTHAR gel, 40 units or 80 units (i.e. No placebo - both groups with active drug)
- Drug given at day 0, 14 then every week till day 28 then twice a week till day 91 (week 12)
Co-interventions

- For BP control: at discretion of treating nephrologist;
  - Patients already on single or dual RAS Blockade
  - CCB: only nonDHP agents allowed
- 10 mg atorvastatin if severe hyperlipidemia and dose titration up per KDIGO GL
- Salt restriction (2-3 g/day) and dietary protein target of 0.8 g/kg/day - counselling
Results: baseline

- n of 20
- Age 51 +/- 15 years; 63% men (?13 of 20)
- 19 were on RAAS blockade prior, one did not tolerate (hypotension)
- Median disease latency 14 months
- 13 patients treatment naive
Table 1: baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
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<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121 ± 16</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>9068 ± 3384</td>
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<tr>
<td>eGFR (mL/min)</td>
<td>77 ± 30</td>
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<tr>
<td>Albumin (mg/dL)</td>
<td>2.72 ± 0.83</td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>306 ± 133</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>182 ± 85</td>
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<tr>
<td>HDL (mg/dL)</td>
<td>67 ± 29</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>225 ± 190</td>
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</tbody>
</table>

BP = blood pressure; NS is not significant.
Results: overall proteinuric
Actual therapy

- 11 received 80 units per dose (total 1760 units)
- 9 were started on 40 units
  - None responded by 12 weeks
  - 5/9 were given *additional* 12 weeks of 80 units twice a week (2800 units total)
Results: final proteinuria by dose received

- 880 units: 0
- 1760 units: 2.25
- 2800 IU: 4.5
Adverse effects of ACTHAR

- None required discontinuation for side effects
- 3 had Cushingoid appearance
- Acne, bloating, bronzing in 2-3 patients each
- Psychological effects in six patients
- Transient insomnia in six patients
- Blood sugar increase (to > than 130) in six, transient in 5, one required dietary intervention for sustained hyperglycemia
Anti-PLA2R assay

• Western blot using human glomerular extract and recombinant PLa2R

• Baseline assay standardized to compare subsequent intra-patient comparisons
PLA2R results

- 15/20 had detectable levels
- 3 patients cleared completely
- 4 patients had reduction in levels.
- Strong correlation between levels of antiPLa2 and proteinuria