Update on IgA Nephropathy in 2008

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IgA Nephropathy

- Most common idiopathic GN world
- Defined by IgA deposition in mesangium
- Presents- Young – gross hematuria
- Adults – Proteinuria + hematuria
- Not benign hematuria (Berger’s Dis)
- ESRD in 15-20% by 10 yrs from onset and 30-40% by 20 yrs.
- Risk Factors for Progression.
- Rx – Not one therapy fits all.
Pathogenesis

Overproduction of IgA

Antigen in the kidney

Defective structure of IgA

Abnormal IgA interaction with receptor in peripheral blood cells or in mesangium

Primary immunologic abnormality

Evidence for genetic contribution
IgAN in Eastern Kentucky
Cumulative Renal Survival in 220 Patients with IgA Nephropathy

83.3% at 10 years

Johnston PA. Q J Med; 1992; 84:621
Renal Survival Curve for Patients Creatinine < and ≥ 120μmol/L

Johnston PA. Q J Med; 1992; 84:621
Renal Survival Curves in Hypertensive (diastolic ≥ 95 mm Hg or antihypertensive treatment) and Normotensive Patients

Johnston PA. Q J Med; 1992; 84:621
Renal Survival Curves for Pts with Urinary Protein Excretion < 1 g/24 hr and ≥ 1 g/24 hr

Johnston PA. Q J Med; 1992; 84:621
Prediction of Progression in IgAN in 298 Pts

IgAN: $\Delta$ GFR Prediction
(-ml/min/year)

Proteinuria patterns - association with subsequent ESRD in IgAN

A. IgAN 1 – 24-Hr Urine Protein at 1-Year Visit

B. IgAN 2 – 24-Hr Urine Protein at 1-Year Visit

Proteinuria patterns - association with subsequent ESRD in IgAN

A. IgAN 1 – Serum Creatinine at 1-yr Visit

B. IgAN 2 – Serum Creatinine at 1-yr Visit

Difficulties in Treatment Studies in IgAN

- Slow progression in many – requires use of surrogate markers of progression
- Variable rate of progression
- Heterogeneous population- phenotype
- Only a few RTC to define outcome of RX - Recent meta analysis many “of low quality and poorly reported”
- Everyone knows how to treat some of the pts – Nobody is certain how to treat others
Therapy of IgA Nephropathy

- ACE inhibitors, ARB’s, Combinations
- Tonsillectomy
- Glucocorticoids (QD, QOD, Cyclic pulse)
- Fish Oils (n-3 PUFA)
- Immunosuppressives
  - Azathioprine + steroids
  - Cyclophosphamide + steroids
  - Mycophenolate mofetil
IgA ACEinhib Trial Profile

Assessed for eligibility took part in 3-month run-in (n=129)

Not eligible at the end of run-in (n=23)
Proteinuria < 1 g/day/1.73m² (n=13)
Proteinuria >3.5 g/day/1.73m² (n=4)
Lost in run-in phase (n=3)
Severe hypertension (n=3)

Consent withdrawal (n=40)

Randomized (n=66)

Assigned to Benazepril (n=32)
Consent withdrawal after <3 months (n=7)
Lost to follow-up after <3 months (n=2)
Available for intention-to-treat analysis (n=32)
Follow-up analysis (n=23)

Assigned to Placebo (n=34)
Discontinuation (n=2): 1 death
1 pregnancy
Available for intention-to-treat analysis (n=34)
Follow-up analysis (n=34)
BP data during the IgACE trial in ACE-I treated patients and in the placebo group

Survival without end point of 30% reduction of baseline CrCl

Survival without the combined end point of 30% reduction of baseline CrCl and/or increase in proteinuria up to >3.5 g/d/ 1.73 m2
Effect of Converting Enzyme Inhibitor and Losartan in Normotensive Patients with IgA Nephropathy

Urinary Protein Excretion

* = p< 0.05 v basal
# = p<0.05 v other study periods

COOPERATE STUDY

• Combination of ARB + ACEI in 263 pts w. non-DM Renal Disease

• Losartan 100 vs. Trandolapril 3 vs. Combo

• Primary Endpoint Doubling Screat or ESRD

• Side Effects No Different

Effect of ACEI, ARB, or Combination on Blood Pressure


![Graph showing the effect of different medications on blood pressure over time. The graph compares systolic and diastolic blood pressure for Trandolapril, Losartan, Trandolapril + Losartan, and indicates that there is no significant difference (P=NS) between the groups.](image-url Here)
Effect of ACEI, ARB, or Combination on Proteinuria

- Losartan
- Trandolapril
- Trandolapril + Losartan

Median Proteinuria (g/day)

Months

Effect of ACEI, ARB, or Combination on Combined Endpoint of 2xSCr or ESRD


P=0.02
Therapy of IgA Nephropathy

- ACE inhibitors, ARB’s, Combinations
- Tonsillectomy
- Glucocorticoids (QD, QOD, Cyclic pulse)
- Fish Oils (n-3 PUFA)
- Azathioprine + steroids
- Cyclophosphamide + steroids
- Mycophenolate mofetil


Table 1. Effects of Tonsillectomy in IgA Nephropathy

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Follow Up (months, mean)</th>
<th>Remission (%)</th>
<th>Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masuda⁵⁵</td>
<td>NCT</td>
<td>(36)</td>
<td>56.3%*</td>
<td>NM</td>
</tr>
<tr>
<td>Sugiyama⁷²</td>
<td>NCT</td>
<td>(61)</td>
<td>32.1%</td>
<td>NM</td>
</tr>
<tr>
<td>Iino⁷³</td>
<td>NRCT</td>
<td>(36)</td>
<td>25.8%</td>
<td>No benefit</td>
</tr>
<tr>
<td>Tamura⁷⁴</td>
<td>NCT</td>
<td>24</td>
<td>7.6%</td>
<td>NM</td>
</tr>
<tr>
<td>Bene⁵⁶</td>
<td>NCT</td>
<td>48</td>
<td></td>
<td>NM</td>
</tr>
<tr>
<td>Akagi⁷⁵</td>
<td>NCT</td>
<td>24</td>
<td>50%*</td>
<td>NM</td>
</tr>
<tr>
<td>Rasche⁷⁶</td>
<td>NRCT</td>
<td>(41)</td>
<td></td>
<td>No benefit</td>
</tr>
<tr>
<td>Xie⁵⁴</td>
<td>NRCT</td>
<td>(193)</td>
<td></td>
<td>Benefit</td>
</tr>
</tbody>
</table>

Abbreviations: NCT, noncontrolled trial; NRCT, nonrandomized, controlled trial; NM, not mentioned.

* Remission of proteinuria (hematuria is not mentioned).
The efficacy of tonsillectomy on long-term survival in pts with IgAN

- 118 IgAN Bxed 1973-1980
- 48 s/p Tonsilx and 70 w/o Tonsilx follow 192 mo.
- No dif in age, gender, Uprot, Screat, SIgA, BP, histology, Rx.
- Renal survival 90% w Tonsx vs. 64% w/o Tonsx at 240 mo. By MVA tonsilx significant effect on outcome.
- Tonsillectomy has a favorable effect on long-term outcome IF performed early in the course.

Rate of renal survival,%

Time, months since biopsy

Tonsillectomy (+)
N = 48

Tonsillectomy (-)
N = 70

P < 0.05
(Log-rank test)
Fish oil

EPA  DHA

Arachidonic acid

Cyclooxygenase  Lipoxygenase

\( \text{TxA}_3 \)
\( \text{PGI}_3 \)
\( \text{TxA}_2 \)
\( \text{PGI}_2 \)
\( \text{LTB}_4 \)
\( \text{LTB}_5 \)
### Table 2. The Proximate Fatty Acid Composition of Fish Tissue and Fish Oils

<table>
<thead>
<tr>
<th>Finfish Species*</th>
<th>EPA + DHA (g/3-oz serving)</th>
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</thead>
<tbody>
<tr>
<td>Herring</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>1.81</td>
</tr>
<tr>
<td>Atlantic</td>
<td>1.71</td>
</tr>
<tr>
<td>Salmon</td>
<td></td>
</tr>
<tr>
<td>Chinook</td>
<td>1.48</td>
</tr>
<tr>
<td>Pink</td>
<td>1.09</td>
</tr>
<tr>
<td>Sockeye</td>
<td>0.68</td>
</tr>
<tr>
<td>Atlantic, farmed</td>
<td>1.09–1.83</td>
</tr>
<tr>
<td>Atlantic, wild</td>
<td>0.9–1.56</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.34–1.57</td>
</tr>
<tr>
<td>Sardines</td>
<td>0.98–1.70</td>
</tr>
<tr>
<td>Trout, rainbow</td>
<td></td>
</tr>
<tr>
<td>Farmed</td>
<td>0.98</td>
</tr>
<tr>
<td>Wild</td>
<td>0.84</td>
</tr>
<tr>
<td>Tuna</td>
<td></td>
</tr>
<tr>
<td>Light, canned in water</td>
<td>0.26</td>
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<tr>
<td>White, canned in water</td>
<td>0.73</td>
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<tr>
<td>Fresh</td>
<td>0.24–1.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fish Oils</th>
<th>EPA + DHA g/g oil</th>
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</thead>
<tbody>
<tr>
<td>Capsules</td>
<td></td>
</tr>
<tr>
<td>Menhaden oil</td>
<td>0.29</td>
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<tr>
<td>Omega-3 fatty acid concentrates†</td>
<td>0.30</td>
</tr>
<tr>
<td>Omacor™‡</td>
<td>0.85</td>
</tr>
<tr>
<td>Emulsified pouches</td>
<td></td>
</tr>
<tr>
<td>Coromega™§</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Controlled Trial of Fish Oils in IgAN

106 Pts  78M/28F  age 36yo
Uprot > 1 g/D  HBP 60%
Rx Max EPA 12g/D (58) vs Olive oil (51)
Rx 2yr  follow 5 yr
Endpoint 50% increase Pcreat.

Endpoint  6% Rx EPA  vs  33% PBO
Change Pcreat  .03 mg/dl  vs  .14 mg/dl
DDT  10%  vs  40%

% who did not have ≥50% increase in serum creatinine

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Study period

Fish oil (n = 55)

Placebo (n = 51)

P = 0.002

Years
Treatment of IgA Nephropathy with Omega - 3 PUFA

Randomized, placebo controlled 6 month study

<table>
<thead>
<tr>
<th></th>
<th>Fish Oil (N = 15)</th>
<th></th>
<th>Corn Oil (N = 17)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDTA</td>
<td>Ccr</td>
<td>Scr</td>
<td>EDTA</td>
</tr>
<tr>
<td>Pre</td>
<td>63</td>
<td>91</td>
<td>131</td>
<td>69</td>
</tr>
<tr>
<td>6mo</td>
<td>59*</td>
<td>79*</td>
<td>139*</td>
<td>68</td>
</tr>
</tbody>
</table>

UV proteinuria and hematuria unchanged.

Increased LDL cholest with Fish Oil v. Increased HDL with Corn Oil

"We conclude that pts with IgA N with proteinuria and mod. decreased GFR do not benefit from treatment with high dose w-3-PUFA"

Multicenter Controlled Trial of QOD Pred vs QD Omega 3 FA vs PBO in IgAN

IgAN <40yo GFR > 50ml/min Up/Ucr >0.5
33 Pts Randomized to Pred 60mg/m2 QOD x3m with taper x 2yr
32 Pts OM-3 FA 4g/d (1.88g EPA, 1.48 g DHA) x 2 yrs
31 Pts PBO x 2 yrs
Primary end-point GFR < 60% baseline; l HBP Rx ACEi

Despite randomization OM3FA > UVprot than PBO
Neither Rx group showed a benefit over PBO
14 Rx failures 2 Pred, 8 FO, 4 PBO
Major factor associated w RF was higher baseline Up/Ucr

Corticosteroids in IgAN: a controlled trial

86 Pts  Uprot 1-3.5g/D  Pcreat < 1.5 mg/dl
Rx cyclic Pulse SM + QOD stds vs PBO x 6 mo.
Endpoint 50% rise in Pcreat.  Follow 6 yrs

Endpoint  9/43 Rx vs. 14/43 PBO ( p<.05 )
High risk Pts : vascular sclerosis, males,
no Steroid Rx
No major side effects

IgAN: Controlled Trial of Steroids

Pozzi et al. JASN 15:157-163, 2004
IgAN: Controlled Trial of Steroids

Pozzi et al. JASN 15:157-163, 2004
Steroids plus ACEi versus ACEi alone in IgA Nephropathy
A Prospective Randomized Controlled Trial

N = 63
18 to 65 years old
Biopsy-proven IgAN within a one year period
Urine protein excretion of 1-5g/d
Estimated (eGFR) >30ml/min/1.73m² according to a Modified MDRD equation for a Chinese population.

Treated with Cilazapril or Combination of cilazapril + prednisone: 0.8-1.0 mg/Kg/day X 8 weeks tapered by 5-10mg every two weeks

Jicheng L, … Haiyan Wang. ASN2007
Renal survival

(Clinical and histologic features equal except U pro 2g/d vs 2.5g/d in a combination group) BP well-controlled.

Jicheng L, … Haiyan Wang. ASN2007
Patients with advanced renal pathologic lesions get more beneficial effect of preserved renal function with combination therapy

Jicheng L, … Haiyan Wang.  ASN2007
Reduction of urine protein excretion during follow-up

Patients in the combination group had a more rapid and stable reduction of urine protein excretion.
Steroids and Cytotoxic Agents in Progressive IgA Nephropathy

Oral Pred.+ oral Cyclophosphamide (1.5mg/kg/d) for 3 mo then 2 years or more of AZA(1.5mg/kg/d) improved renal survival in “progressive” IgAN in RCT.

Treated = 72% 5 year renal survival
Untreated = 5% 5 year renal survival

Immunosuppressive Rx for IgAN
Change in Proteinuria

Steroids and Cytotoxic Agents in Progressive IgA Nephropathy

Therapy of IgA Nephropathy

- ACE inhibitors, ARB’s, Combinations
- Tonsillectomy
- Glucocorticoids ( QD, QOD, Cyclic pulse )
- Fish Oils ( n-3 PUFA )
- Azathioprine + steroids
- Cyclophosphamide + steroids
- Mycophenolate mofetil
Controlled Trial of MMF in IGA Nephropathy

- 33 pts - Pcreat 1.4 mg/dl UV prot 1.6 g/d
- Low Na+, ACEi
- MMF 2g/d vs. placebo x 2 yrs

<table>
<thead>
<tr>
<th>MMF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pcreat</td>
<td>1.48 - 1.71</td>
</tr>
<tr>
<td>UVprot</td>
<td>1.79 – 1.80</td>
</tr>
</tbody>
</table>

In IgA Nephrop. At mod risk no advantage to MMF

Maes BD et al. KI 65:1842-1849, 2004
MMF in IgA GN: A Controlled Trial
Prospective Randomized Trial MMF in IgAN

24 pts IgAN > 1g UVprot/d randomized to MMF 1.5-2g/d or Conventional RX

Age 43vs47, UVprot 2.0 vs 2.1 g/d, Scr 127 vs 186 uMol BP all similar

At 24 wks proteinuria (1.0 vs 2.4 g/d) Scr (128 vs 205) were lower in Rx group. 8 Rx pts and 2 control had > 40% reduction proteinuria. After D/C MMF proteinuria increased at 48 wks (1.5 v 2.2 NS).

1 Rx pt and 3 control had > 30% increase in Scr.

MMF well tolerated causes decreased UV prot during Rx.

Mycophenolate Mofetil in IgA N:

A Controlled Trial

(Tang et al, KI 68:802, 2005)
Mycophenolate Mofetil in IgA N: A Controlled Trial

(Frisch G…Appel GB et al NDT 2005)
### RCT of MMF in IgAN after ACEi and Fish Oils

**Changes in Urine P/C Ratio from Baseline**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>MMF (N=25)</th>
<th>Placebo (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline</td>
<td>25</td>
<td>1.88</td>
</tr>
<tr>
<td>Randomization</td>
<td>25</td>
<td>1.59</td>
</tr>
<tr>
<td>6 mos MMF/Placebo</td>
<td>22</td>
<td>1.40</td>
</tr>
<tr>
<td>12 mos MMF/Placebo</td>
<td>13</td>
<td>1.52</td>
</tr>
</tbody>
</table>

No evidence of benefit of six months of treatment with MMF  
ASN 2007
Appel’s Therapy for IgAN in 2008

- All pts ACEi or ARB or ACEi/ARB.
- All pts strongly consider Rx w statin.
- All pts consider low protein diet.
- All pts BP <130/80.

- Tonsillectomy for pts with frequent bad URI and tonsillitis.
- Fish Oils for those who want them – Should not replace other therapies.
Appel’s Therapy for IgAN in 2008

Mild Disease- (nl GFR, < 1g Uprot/d, good Bx)

No other Rx. Must have follow to check for increase in Uprot. And Pcreat.

Moderate or Severe Dis. (Abnl GFR, or > 1g Uprot/d, or Bx w signif activity or risk of progression, Crescentic GN)

- Steroids x 6mo
- Cyt + Stds or Consider MMF if other alt. unacceptable.

-High Pcreat. w Bx chronic damage GS-TIF – no immunosuppressives