New Data and New Questions on IgA Nephropathy

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IgA Nephropathy

• Defined by IgA deposition in glomerular 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.

DEMOGRAPHICS OF IgA NEPHROPATHY

IgA N is considered the most common glomerulonephritis in the world.
In native kidney biopsies, IgA N accounts for:

<table>
<thead>
<tr>
<th>Region</th>
<th>of all biopsies</th>
<th>of GN biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A.</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Asia</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>Europe</td>
<td>15%</td>
<td>20%</td>
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</tbody>
</table>

Rare in African-Americans and common in Native-Americans.
In IgA N and HSP, serum IgA1 has reduced terminal glycosylation in the hinge region

Pathogenesis: Gal-deficient IgA1

- IgAN patients have ↑↑ circulating Gal-IgA1
- Predisposed to immune complex formation
- Makes up minority of circulating IgA, but virtually all of the mesangial IgA
- Recognized by naturally occurring Ig's
- Insufficient alone to cause disease
Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch-Schönlein purpura nephritis.


Genetics of IgAN

- >90% cases sporadic, but rare familial cases exist
- GWAS identified >5 genetic loci, explain at least 4-7% disease variance
- Implicated genes: MHC, CFHR1, CFHR3, TNFSF13, DEFA
- Elevated Gd-IgA1 also heritable

The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression

Na Zhao, Ping Hou, Jicheng Lu, Zina Moldoveanu, Yifu Li, Krzysztof Kiryluk, Ali G Gharavi, Jan Novak and Hong Zhang
Glycan-specific IgG antibodies recognize the aberrantly glycosylated IgA1 in IgAN


Pathogenesis: multi-step model

Step 1: Generation of aberrantly galactosylated IgA1 (Gd-IgA1)
- Mucosal antigens as trigger
- Plasma cells in tonsils, marrow produce Gd-IgA1 (genetic risk)

Step 2: Autoantibodies form against Gal-deficient hinge region

Step 3: Circulating immune complexes of polymeric Gd-IgA1 + autoantibodies, get trapped in mesangium

Step 4: Glomerular Damage

Boyd & Barratt, Kidney Int, 2010

Box plots of serum levels of normalized IgG autoantibody (OD/0.5 µg IgG) according to the AR1 evaluated at diagnosis, in both IgAN patients and in diseased (DC) and healthy (HC) controls.

Berthoux F et al. JASN 2012;23:1579-1587
Kaplan–Meier survival curves without dialysis/death event, with time zero set at diagnosis and elevated serum levels of autoantibodies (IgG >1.33 OD and/or IgA >1.79 U/ml) at diagnosis in IgAN patients.

Berthoux F et al. JASN 2012;23:1579-1587

Oxidative Stress and Galactose-Deficient IgA1 as Markers of Progression in IgA Nephropathy

- Sera from IgAN pts showed higher levels of Gd-IgA1, % HAA, and AOPPS but lower levels of SH-Alb.
- AOPPS correlated with serum Gd-IgA1 and %HAA.
- Assessed in 62 pts long term – AOPPs and % HAA correlated with proteinuria at sampling and subsequent proteinuria.
- AOPPS correlated with rate of decline in renal function after sampling.
- Combination of high level of AOPPs and a high level of % HAA was associated with decline in GFR.
- Oxidative stress pathways are activated in IgA N and this may modulate the nephrotoxicity of aberrantly glycosylated IgA1.


Serum levels of galactose-deficient IgA1 and markers of oxidative stress.

**Predictive value of the combination of AOPPs and galactose-deficient IgA1 on eGFR loss**

Camilla R, Suzuki H, Dapra V, Gharavi A, Appel GB, Coppo R.

**Long-term Renal Survival and risk Factors in IgAN 1126 Patients**


**Prediction of Progression in IgAN in 298 Pts**

**IgA Nephropathy:**

Relative Risk of 2xScr after 5.6y

![IgA Nephropathy Graph](image)

**Clinical or Pathologic Features**
- Male Sex
- Age >60y
- Scr
- Upro
- HTN

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**Reduction of Proteinuria Improves Prognosis in IgAN**

- 542 pts with IgAN from Toronto registry
- Followed for 78.1 ± 59 mos
- GFR declined at −4.56 ml/min/1.73 m2/yr
- 30% reached ESRD

Regardles of peak proteinuria, attaining partial remission <1 g/d leads to similarly good outcomes.

- Group 1: 1-2 g/d peak proteinuria
- Group 2: 2-3 g/d peak proteinuria
- Group 3: >3 g/d peak proteinuria

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**Remission of Proteinuria Improves Prognosis in IgA Nephropathy**

![Remission of Proteinuria Graph](image)

Reich H N et al. JASN 2007;18:3177-3183
IgA Nephropathy

IgA nephropathy is morphologically heterogeneous (Roberts, et al. ASN CNE 2008)

MEST-Oxford Classification System

- **Mesangial Hypercellularity**
  0 = <50%; 1 = >50% glomeruli involved

- **Endocapillary proliferation**
  0 = Absent; 1 = Present

- **Segmental glomerulosclerosis**
  0 = Absent; 1 = Present

- **Tubulo-Interstitial Fibrosis**
  0 = <25%; 1 = 25-50%; 2 = >50%

Preliminary Studies Show Good Correlation with Outcome
Combinations of Glomerular Features Impact on Deterioration in Renal Function

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Pt (no.)</th>
<th>Slope (mL/min/1.73)</th>
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<tbody>
<tr>
<td>Minimal mesangial hypercellularity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without segmental sclerosis</td>
<td>M0, S0, E0</td>
<td>12</td>
</tr>
<tr>
<td>With segmental sclerosis</td>
<td>M0, S1, E0</td>
<td>22</td>
</tr>
<tr>
<td>Mesangial hypercellularity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without segmental sclerosis</td>
<td>M1, S0, E0</td>
<td>31</td>
</tr>
<tr>
<td>With segmental sclerosis</td>
<td>M1, S1, E0</td>
<td>88</td>
</tr>
<tr>
<td>Endocapillary proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without segmental sclerosis</td>
<td>M0, S0, E1</td>
<td>21</td>
</tr>
<tr>
<td>With segmental sclerosis</td>
<td>M0/1, S1, E1</td>
<td>90</td>
</tr>
</tbody>
</table>

Clinical and Histopathologic Prognostic Factors in IgA N
Huerta A, Bomback AS, Canetta P...Appel GB  WCN-ISN 2011

154 IgA N pts followed at Columbia U Med Ctr from 2005-2010 (with clinical data available from 1980 to 2010)
M/F - 64%/36%  Age at Ds 32 yo  NHW: 93 HW :17 AA:7 A:37
HBP 46% ; Pcreatine 1.62 mg/dl  eGFR 66 cc/min UV prot 3.7 g/d
Salb 3.7g/dl  Scholesterol 322
Mean time 5.8 years
Most received RAAS blockade and Immunosuppresives

Predictors of CKD V-ESRD and halving of eGFR.
Baseline creatinine and eGFR
Proteinuria
African-American race
Male gender
Tubular atrophy/interstitial fibrosis and cumulative MEST score

Therapy of IgA Nephropathy
- ACE inhibitors, ARB’s, Combinations
- Tonsillectomy
- Glucocorticoids (QD,QOD,Cyclic pulse)
- Fish Oils (n-3 PUFA)
- Immunosuppressives
  - Corticosteroids
  - Azathioprine + steroids
  - Cyclophosphamide + steroids
  - Mycophenolate mofetil
  - Other (Rituxan, ACTH)
ACE Inhibitors in IgA Nephropathy: A Controlled Trial

- A RCT comparing ACEi or ARB to non-ACEi therapy in IgA Nephropathy
- SCr<1.2mg/dl    24 hr urine Protein > 500mg / day
- Follow-up=75 months


Survival without the combined end point of 30% reduction of baseline CrCl and/or increase in proteinuria up to >3.5 g/dl/ 1.73 m2

Subjects at risk

<table>
<thead>
<tr>
<th>Subjects at risk</th>
<th>ACEI</th>
<th>PBO</th>
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</thead>
<tbody>
<tr>
<td>0 months</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>10 months</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>20 months</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>30 months</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>40 months</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>50 months</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>60 months</td>
<td>8</td>
<td>6</td>
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</table>

log-rank test, P= 0.034


Therapy of IgA Nephropathy

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

Tonsillectomy

- Retrospective review of 200 Japanese IgAN, 70 with tonsillectomy
- Tonsillectomy group had more endocapillary hypercellularity, but also received more treatment with steroids and RAS inhibitors
- Clinical remission defined as normal dipstick examination of hematuria and proteinuria on two consecutive visits at least 3 months apart.
- GFR decline defined as >30% loss of eGFR from baseline

![Graphs showing Tonsillectomy impacts on kidney function](image)

![Diagram showing fish oil conversion](image)

**Table 2. The Proximate Fatty Acid Composition of Fish Tissue and Fish Oils**

<table>
<thead>
<tr>
<th>Fish Oil Species</th>
<th>EPA + DHA (g/kg of oil)</th>
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</thead>
<tbody>
<tr>
<td>Herring</td>
<td>1.81</td>
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<tr>
<td>Atlantic salmon</td>
<td>1.71</td>
</tr>
<tr>
<td>Chinook</td>
<td>1.48</td>
</tr>
<tr>
<td>Pink</td>
<td>1.29</td>
</tr>
<tr>
<td>Sockeye</td>
<td>0.69</td>
</tr>
<tr>
<td>Atlantic, farmed</td>
<td>1.20–1.83</td>
</tr>
<tr>
<td>Atlantic, wild</td>
<td>0.78–1.67</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.34–1.97</td>
</tr>
<tr>
<td>Sardines</td>
<td>0.49–1.70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fish Oils</th>
<th>EPA + DHA (g/kg of oil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>0.23–1.29</td>
</tr>
<tr>
<td>Light, canned in water</td>
<td>0.08</td>
</tr>
<tr>
<td>White, canned in water</td>
<td>0.73</td>
</tr>
<tr>
<td>Fish</td>
<td>0.23–1.29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capsules</th>
<th>EPA + DHA (g/kg of oil)</th>
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</thead>
<tbody>
<tr>
<td>Microalgin oil</td>
<td>0.29</td>
</tr>
<tr>
<td>Microalgin oil fatty acid concentrate</td>
<td>0.30</td>
</tr>
<tr>
<td>Omegazyme™</td>
<td>0.85</td>
</tr>
<tr>
<td>Emulsified pouches</td>
<td>0.68</td>
</tr>
<tr>
<td>Coromega™</td>
<td>0.58</td>
</tr>
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</table>
IgA Nephropathy: Fish Oils (Omacor)

Survival Free of ESRD at 8 yrs
Survival Free of 2XScr at 8 yrs

Fish Oil vs Placebo

Multicenter Controlled Trial of QOD Pred. vs QD Omega 3 FA vs PBO in IgAN
99 IgAN < 40 yo, GFR > 50 ml/min, Up/Ucr > 0.5

33 Pts Pred QOD x3mo
32 Pts OM-3 FA 4g/d
31 Pts PBO
End-Point at 2 yrs
GFR < 60% baseline
All HBP Rx ACEi

Neither Rx group showed a benefit over PBO
Therapy of IgA Nephropathy

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

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/1.73m^2 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

Kidney survival estimated based on an increase up to 50% greater than baseline serum creatinine level and a decrease of 25% in estimated glomerular filtration rate (eGFR).

PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF STEROIDS PLUS RAMIPRIL IN PROTEINURIC IgA NEPHROPATHY

n = 97
Proteinuria > 1g/24h - GFR > 50 ml/min

ALL PATIENTS
Ramipril
dose titrated to achieve
BP < 120/80 Proteinuria < 1g/24h

RANDOMISATION
Prednisolone 1 mg/kg/d for 2 months tapered by 0.2 mg/kg per month

Manno C et al. NDT 2009
Benefits of corticosteroids for IgAN limited for patients with reduced GFR

- 25 IgAN pts CUMC. Scrat 1.75 mg/dl eGFR 52 ml/min., proteinuria 3.1g/day on RAAS blockade.
- Alternate day prednisone, start 2 mg/kg for 1 month- tapering off over 5-6 mo.
- Primary outcome a sustained 25% increase in Scratnine
- At > 32 months follow-up, 40% of pts (10/25) experienced a sustained 25% increase in Scratnine.
- By multivariate analysis only predictor of outcome was eGFR <45 ml/min/1.73m2 (p<0.0001, HR 17.6).
- Of 11 pts with eGFR <45 ml/min/1.73m2, 9 reached the outcome in an average of just 12.7 months, vs. only 1/14 pts with higher eGFR.


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


Steroids and Immunosuppressive Agents in Progressive IgA N

Ballarde, F. Roberts, I. JASN 13:142, 2002
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 IgAN
Maes BD et al. KI 65:1842-1849, 2004

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

In IgAN at moderate risk
- no advantage to MMF

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

- A randomized, controlled trial of MMF 2.0gm/d X one year or placebo in 40 patients* with “severe, high-risk” IgA N.
- Average Scr at entry = 2.4mg/dl, UpV > 1.0gm/d;
- All received A-II inhibition
- Follow-up 2 years

<table>
<thead>
<tr>
<th>Mycophenolate Mofetil in IgA N: Controlled Trials</th>
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<tbody>
<tr>
<td>Maes (n=34)</td>
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<tr>
<td>MMF-</td>
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<tr>
<td>eGFR-</td>
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<tr>
<td>Scr-</td>
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<tr>
<td>UpV-</td>
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<tr>
<td>SBP-</td>
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<tr>
<td>ACEi/ARB-</td>
</tr>
<tr>
<td>Histology-</td>
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<tr>
<td>Ethnicity-</td>
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*Courtesy of Dr. Richard Glassock
### Future developments in therapy

- **Rituximab in IgAN Trial** – open-label multicenter RCT (still enrolling)
- **STOP-IgAN Study (Germany):**
  - Randomized, multicenter, open-label study of immunosuppression for IgAN
  - 148 patients, all get ACEi and statin x 6 mos, if proteinuria remains >0.7g/d, randomized to immunosuppression or supportive care
  - If eGFR >60, prednisone QOD x 6mos + IV methylpred at mo 1,3,5
  - If eGFR 30-60, oral CYC/Pred x 3 mos – AZA/Pred for 3yrs
  - Fully-recruited, estimated study completion date: December 2013
- **TESTING study (China):**
  - RCT of oral methylprednisolone or placebo, goal enrollment N=1300! (2017)
- **MMF vs. Glucocorticoids** (Guangzhou, n=150), est. completion June-2013
- **Prednisone/CYC vs. Prednisone** (Guangdong, n=200), est. completion 2015
- New therapeutic targets being revealed by evolving genetic and mechanistic research

### Jerry Appel’s Therapy for IgAN in 2013

- All pts ACEi or ARB or ACEi/ARB.
- All pts strongly consider Rx w statin.
- All pts consider low (Le NOT HIGH) 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.

### J Appel’s Therapy for IgAN in 2013

**Mild Disease-** (nl GFR, < 0.5g Uprot/d, good Bx)
- No other Rx. Close Follow.

**Moderate or SevereDis.** (Abnl GFR, or > 1g Uprot/d, or Bx w risk of progression or Crescentic GN)
- Steroids (We use alternate day) x 6months
- Consider Cyt +Stds or MMF if other therapy not acceptable
- Consider ACTH, rituximab (limited data)

**High Pcreat. w Bx chronic damage GS-TIF – no immunosuppressives**
IgA N 2014 Refs G. Appel

- Wyatt RJ, Julian BA. IgA Nephropathy. NEJM 368:24022414, 2013
- Gharavi, Kryluk et al. Genetics of IgAN Nature Genetics, March 2011
- Kiryluk K, et al Aberrant glycosylation of IgA1 in both pediatric IgA nephropathy and HSP nephritis, Kidney Int. 2011;80:79-87
- Camilla R, ...Appel GB, Coppo R. Oxidative Stress and Galactose-Deficient IgA1 as Markers of Progression in IgAN CJASN 6:1903-1911, 2011
- Reich H N et al. Course and Prognosis of IgAN JASN 2007;18:3177-3183
- Manno C et al. Prospective Randomized Controlled Trial of steroids plus ramipril in proteinuric IgAN. NDT 2009 Epub 23 July