New Data on the Pathogenesis, Dx, and Treatment of IgA Nephropathy

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Division of Nephrology
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Potential Conflicts of Interest

Dr. Appel has research grants with Regulus, Achillion, BM Squibb, EMD Serono, and NIH.

He Lectures for Genentech (ANCA + RPGN), Sanofi-Genzyme (renal side effects of Lemtrada used for M.Sclerosis).

He has consultanthips with: Alexion, Achillion, Ionis, Genentech, Mallinkrodt, Pfizer, Merck, Roche, Bristol-Myers Squibb, Up-to-Date, Genzyme-Sanofi, EMD Serono, Omeros, Regulus.
IgA Nephropathy Case

• A 19 yo WM university student, with no past medical history, develops dark urine while playing soccer with his friends. The urine clears but the dark urine recurs after running to a class two days later.
• His MD finds him to have a BP of 140/90 and no edema, Urinalysis has 3+ protein and 3+ hematuria and red cell casts. Lab shows a BUN of 18 mg/dl and a creatinine of 1.0 mg/dl (88 umol/L) Uprotein is 2g/day.
• Kidney biopsy shows IgAN – Oxford M0E1S0T0C0
Which statement is true regarding the epidemiology and pathogenesis of IgA N?

1) The diagnosis of IgAN requires a kidney biopsy.
2) IgAN comprises 1% of all Bxs in the US but 50% of all Biopsies in Asia.
3) The pathogenesis of IgA N involves hyper-galactosylation of IgA1 molecule at the hinge region.
4) Healthy individuals and blood relatives of IgAN patients have normal levels of galactosylated IgA in their blood.
IgA Nephropathy

- Defined by IgA deposition in glomerular mesangium
- Presents- Young – gross hematuria
  - Adults – Proteinuria + hematuria
- Not benign hematuria (Berger’s Disease)
- ESRD in 15-20% by 10 yrs from onset and 30-40 % by 20 yrs.
- Risk Factors for Progression.
- Rx – Changing Views but clearly NO SINGAL Therapy for Everyone – Must customize therapy in 2018.
DEMnOGRApHICS OF IgA NEPHROPATHY

IgA N is considered the most common “idiopathic” 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>
</tr>
</tbody>
</table>

Rare in African-Americans and common in Native-Americans.
Low O-glycosylation of IgA1


GalNac = N-acetylglactosamine
Gal = Galactose
NeuAc = Sialic Acid
Serum Levels of Gal-deficient IgA1

A. Gharavi 2011

Multi-hit Pathogenesis Model

Hit 1
Galactose-deficient IgA1

Hit 2
Antiglycan Antibodies

Hit 3
Immune Complex Formation and Deposition

Hit 4
ECM and Cytokine Production
Mesangial Proliferation
Complement Activation
Mesangial Immunodeposits
Glomerular Injury

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

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

Na Zhao, Ping Hou, Jicheng Lv, Zina Moldoveanu, Yifu Li, Krzysztof Kiryluk, Ali G Gharavi, Jan Novak and Hong Zhang
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.

Logrank test: $P = 0.004$

Berthoux F et al. JASN 2012;23:1579-1587
GWAS for IgA Nephropathy
20,612 individuals

Multiple signals
HLA-DQ/DR
HLA-DP
TAP1/PSMB8

CFHR3,1-del
VAV3
DEFA5,6
DEFA2,3
ITGAM ITGAX
CARD9
HORMAD2

15 independent risk alleles
(10 distinct genomic regions)
Disease variance explained:
8% in Asians, 6% in Europeans

Kiryluk et al. Nat Gen (2014)
GWAS and Pathogenesis Model

Mucosal innate immunity

Dysregulated response to mucosal antigens
TNFSF13, LIF/OSM, CARD9, VAV3, DEFA

Adaptive Immunity

Defect in allore cognition
MHC alleles

Tissue inflammation and injury, immune complex clearance
Deletion of CFHR1 and CFHR3
ITGAM/ITGAX (CR3 and CR4)

Prevalence and Genetic Risk

6,319 individuals representative of 85 native populations

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

Renal survival curve of 1126 IgAN Pts 83%, 74%, 64% at 10, 15, 20 ys.

Question 2  In our 19 yo college student with IgA N which features are independent prognostic predictor of a poor Outcome?

1) Episodes of gross hematuria at the age 19 yo.
2) Proteinuria with Uprot/Ucreat 2.2.
3) On biopsy mesangial proliferation in 30% of glomeruli and endocapillary proliferation in 40%
4) On biopsy an Oxford score with M0E10S0T0.
Reduction of Proteinuria Improves Prognosis in IgAN

- 542 pts with IgAN from Toronto registry
- Followed for 78 mos
- GFR declined at −4.5 ml/min/1.73 m²/yr
- 30% reached ESRD

Regardless 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

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

IgA
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%

*Developed as prognostic tool, not necessarily guide to treatment*
Pathology: Oxford Classification

**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%

Original MEST score based on data from 265 cases (11 centers)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>1.7</td>
<td>1.2-2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E1</td>
<td>1.4</td>
<td>0.9-2.0</td>
<td>0.1(NS)</td>
</tr>
<tr>
<td>S1</td>
<td>1.8</td>
<td>1.4-2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>2.7</td>
<td>1.6-4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T2</td>
<td>7.2</td>
<td>4.9-10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C1</td>
<td>2.3</td>
<td>1.6-3.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Systematic MEST Meta-analysis:
- 16 studies, 3893 patients, 570 kidney failure events
- “T” category most strongly predictive of ESRD
- “E” category **not** predictive of ESRD
- “C” category (presence of any crescent) was not originally assessed in the Oxford Classification

Cattran et al. Kid Int (2009)
Roberts et al. Kid Int (2009)  
Lv et al. AJKD (2013)
## Updated Oxford Classification and prognosis

<table>
<thead>
<tr>
<th><strong>Mesangial hypercellularity</strong></th>
<th>M1 predictive of worse outcomes (vs. M0)</th>
</tr>
</thead>
</table>
| **Endocapillary proliferation** | E1 independently associated with worse renal survival in 2 studies in which no patients received immunosuppression  
  • E1 NOT predictive of outcomes in studies where patients receive immunosuppression  
  • E1 patients more likely to receive immunosuppression  
  • E1 associated with improved outcome in those treated with corticosteroids |
| **Segmental glomerulosclerosis** | S1 predictive of worse outcomes (vs. S0)  
  • Podocytopathic features associated with ↑proteinuria, faster ↓GFR, but better survival with immunosuppression |
| **Tubulo-Interstitial fibrosis** | Strongest independent predictor of adverse renal outcomes |
| **Crescents, cellular/fibrocellular** | C1 predictive of worse outcomes if no immunosuppression  
  • C1 NOT predictive if immunosuppression used  
  • C2 predictive of worse outcomes regardless of immunosuppression |

• 1147 Pts at 13 European Centers – All IgAN
• Mean follow 4.7 yrs - ESRD events in 135
• 86% RAS blockade  42% steroids/immuno meds
• MST independent predictor of lower GFR and renal survival.
• If GFR < 30 cc/min - M and T still predictive

• Proteinururia predicts progression - < 0.5 g/d vs 0.5-0.9g/d vs 0.9-1.4g/d vs 1.4-1.9 g/dy
Question 3 - Which is/are true about the treatment of IgAN in our 19 yo patient?

1) Since he is only 19 yo he will benefit from tonsillectomy.
2) He should take 3 g of omega 3 fish oils daily for the rest of his life.
3) He should take an ACE inhibitor or ARB to reduce both BP and proteinuria.
4) Given a Uprotein of 2 g/day he should given a 6 month course of tapering corticosteroids.
**Effective:**
- ACEI/ARB (1B)
- Corticosteroids (2C)

**Uncertain:**
- Fish Oils (2D)
- Cyclophosphamide (2D)

**Ineffective:**
- AZA and MMF (2C)
- Tonsillectomy (2C)
- Antiplatelet Agents (2C)

**KDIGO 2012!!!**
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/d/ 1.73 m2

The efficacy of tonsillectomy on long-term survival in pts with IgAN

KDIGO: We suggest that tonsillectomy not be performed for IgAN. (2C)
Tonsillectomy + Steroids vs. Steroids alone

Results at 1 year:
* Proteinuria decreased more in combination group

* No difference in GFR

* No difference in clinical remission (disappearance of proteinuria and/or hematuria)

* Proteinuria disappearance (<0.3g/d) in 24% more patients in combination group, but marginal statistical significance

  T+S = 63%
  S alone = 39%

  \( P = 0.052 \)

Fish oil

EPA       DHA

Arachidonic acid

Cyclooxygenase  Lipoxygenase

TxA3       TxA2
PGL3       PGL2

LTB4       LTB5
<table>
<thead>
<tr>
<th>Finfish Species*</th>
<th>EPA + DHA (g/3-oz serving)</th>
</tr>
</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>
</tr>
<tr>
<td>White, canned in water</td>
<td>0.73</td>
</tr>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Capsules</td>
<td></td>
</tr>
<tr>
<td>Menhaden oil</td>
<td>0.29</td>
</tr>
<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>
IgA Nephropathy: Fish Oils (Omacor)

Donadio J, et al. Semin Nephrol, 2004

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

Fish Oil
Placebo
Multicenter Controlled Trial of QOD Pred. vs QD Omega 3 FA vs PBO in IgAN

99 IgAN <40yo    GFR > 50ml/min    Up/Ucr >0.5

33 Pts  Pred QOD x3mo
32 Pts OM-3 FA 4g/d
31 Pts  PBO

End-Point at 2yrs
GFR < 60% baseline
All HBP Rx ACEi

Neither Rx group showed a benefit over PBO
Glucocorticoids in IgAN

Survival without endpoint (creatinine doubling from baseline)

Log rank P = 0.0003

- 10-years following steroids: renal survival 97% in steroid group vs. 53% in controls
  Relative Risk 0.06; P = 0.006
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

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

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

RAMIPRIL – mean dose 4.5 mg/day

STEROIDS
1/48
98%

CONTROL
ESRD
8/49
8 year renal survival
70%
P = 0.006

Manno C et al. NDT 2009 Epub 23 July
Corticosteroids in the VALIGA study (European IgAN)

- Nested propensity-matched case-control, 184 pairs: CS + RASB vs. RASB alone
- CS associated with superior outcomes, even stratified for baseline GFR and proteinuria
- **GFR loss**: -1.0±7.3 ml/m/1.73m²/y in CS-treated group vs. -3.2±8.3 ml/m/1.73m²/y in CS untreated group (P=.004).
- **Proteinuria <1 g/d**: 84% of CS-exposed vs. 54% with no exposure to CS (P<0.001)

Vladimir Tesar et al. JASN 2015;26:2248-2258
Steroids and Immunosuppressive Agents in Progressive IgAN


STOP-IgAN Trial

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

STOP-IgAN: Design

Run-in phase:
• IgAN, eGFR ≥30, proteinuria >0.75 g/d
• Optimal supportive therapy x 6mo
• ACEi, ARB, statin, BP <125/75

(If Uprot >0.75 g/d -> randomization)

Randomized: Immunosupp vs Supportive care:
• eGFR ≥60: prednisone QOD x 6 mos + IV methylpred at mo 1,3,5 (Pozzi)
• eGFR 30<60: oral CYC/Pred x 3 mos + AZA/Pred for 3yrs (Ballardie)

(36 months followup)

Primary outcome(s):
1. “Remission:” UPC <0.2, ΔeGFR ≤ 5 ml/min
2. “Progression:” ↓eGFR ≥15 from baseline

• N=337 enrolled
• 8.3% dropped out/removed
• 3.6% refused randomization
• 28% sustained Uprot <0.75 g/d

• N=162 randomized
• 80 supportive care alone
• 82 added immunosuppression
  ➢ 55 steroids alone
  ➢ 27 steroids/CYC/AZA
STOP-IgAN Primary End Points

**“Remission”**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Supportive Care</th>
<th>Supportive Care plus Immunosuppression</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-analysis set</td>
<td>4/80</td>
<td>14/82</td>
<td>4.82 (1.43–16.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>Available-case analysis</td>
<td>4/72</td>
<td>14/71</td>
<td>5.38 (1.55–18.66)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**“Progression”**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Supportive Care</th>
<th>Supportive Care plus Immunosuppression</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-analysis set</td>
<td>22/80</td>
<td>21/82</td>
<td>0.89 (0.44–1.81)</td>
<td>0.75</td>
</tr>
<tr>
<td>Available-case analysis</td>
<td>18/76</td>
<td>17/78</td>
<td>0.89 (0.41–1.90)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
STOP-IgAN Final disposition

Supportive care (N=80)
- Remission: 5%
- Neither: 68%
- Progression: 28%

Immunosuppression (N=82)
- Remission: 17%
- Neither: 57%
- Progression: 26%
Adverse Events in STOP-IgAN

- Excluding “not related” and “unlikely related”

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=80)</th>
<th>Corticosteroids (N=55)</th>
<th>Cyc/Steroids/AZA (N=27)</th>
<th>Relative Risk (for combo group vs. CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious adverse event</td>
<td>2 (2.5%)</td>
<td>5 (9%)</td>
<td>8 (30%)</td>
<td>3.26</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (36%)</td>
<td>20 (89%)</td>
<td>24 (89%)</td>
<td>2.44</td>
</tr>
</tbody>
</table>
STOP-IgAN: Conclusions

Authors’ conclusions:
• Immunosuppression did not achieve the coprimary outcome
• More adverse effects* with immunosuppression
• eGFR loss was much lower than expected (-1.6 ml/min/yr)
• Supportive care reduced rate of eGFR loss to such a low level that any additional benefit was abolished

Other considerations:
• Many high-risk patients (28%) “respond” to supportive care
• More patients receiving immunosuppression achieve complete remission
• Many patients (~27% in each group) are treatment-resistant: have progressive loss of eGFR with or without immunosuppression!
Testing study

- Therapeutic Evaluation of Steroids in IgA Neph. Global study (China & Australia)
- RCT of oral methylprednisolone (up to 48 mg/d) vs. placebo x 6-8mo
- 262 IgAN patients randomized, proteinuria >1 g/d, eGFR 20-120
- Primary endpoint: ESKD, death from kidney disease, or 40% loss of eGFR
- Stopped early after median 25 months followup due to excess SAEs
- Interim analysis: significant benefit of steroids on GFR decline and proteinuria

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Methylpred.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with SAEs</td>
<td>4 (3.2%)</td>
<td>20 (14.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>0</td>
<td>11 (8.1%), 2 fatal</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-Averaged proteinuria</td>
<td>2.19 g/d</td>
<td>1.31 g/d</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite renal endpoint</td>
<td>20 (15.9%)</td>
<td>8 (5.9%)</td>
<td>0.02</td>
</tr>
<tr>
<td>ESKD</td>
<td>10 (7.9%)</td>
<td>4 (2.9%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Lv J et al., JAMA, 2017 Aug 1;318(5):432-442
**TESTING study**

**Primary Renal Endpoint**

HR = 0.37 (95% CI 0.17-0.85)

Liu J et al., JAMA, 2017 Aug 1;318(5):432-442
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
# Mycophenolate in IgAN

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>52</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Mixed/NYC</td>
<td>US/Canada</td>
<td>Belgian</td>
<td>Chinese</td>
</tr>
<tr>
<td>MMF dose</td>
<td>2 g/d x 1 yr</td>
<td>25-36 mg/kg/d x 1yr</td>
<td>2 g/d x 3 yrs</td>
<td>1.5-2.0 g/d x 6 mo</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>39 (MDRD)</td>
<td>100.6 ± 42.8 (CrCl, Schwartz or C-G)</td>
<td>71 (Inulin)</td>
<td>72 (CrCl)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.7 g/d</td>
<td>1.48 ± 0.74 g/g</td>
<td>1.6 g/d</td>
<td>1.8 g/d</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134</td>
<td>129</td>
<td>128</td>
<td>121</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>all</td>
<td>all</td>
<td>all</td>
<td>all</td>
</tr>
<tr>
<td>Followup</td>
<td>59-75 wks</td>
<td>54% completed 12mo MMF; only 33% completed 1yr post-Rx followup</td>
<td>3 yrs</td>
<td>6 yrs</td>
</tr>
<tr>
<td>Outcome</td>
<td>50% rise Cr at 2 y:</td>
<td>No differences in:</td>
<td>No differences in:</td>
<td>ESRD rate at 6 yrs:</td>
</tr>
<tr>
<td></td>
<td>- MMF 5/17 (29%)</td>
<td>- Mean proteinuria change at 12/24 mo</td>
<td>- 25% loss inulin clr.</td>
<td>- MMF 2/20 (10%)</td>
</tr>
<tr>
<td></td>
<td>- Placebo 2/15 (13%)</td>
<td>- CrCl at 12/24 mo</td>
<td>- 50% rise sCr</td>
<td>- Control 9/20 (45%)</td>
</tr>
<tr>
<td></td>
<td>- P = 0.4</td>
<td></td>
<td>- Rate of delta-GFR</td>
<td>- P = 0.015</td>
</tr>
<tr>
<td>Conclusion</td>
<td>NEGATIVE</td>
<td>NEGATIVE</td>
<td>NEGATIVE</td>
<td>POSITIVE</td>
</tr>
</tbody>
</table>
Mycophenolate Mofetil With Prednisone Versus Full-Dose Prednisone in IgAN With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD, Wei-Bo Le, PhD, Nan Chen, MD, ..., Zhi-Hong Liu, MD  Am J of Kdy Dis 69:788-795, 2017
Mycophenolate With Prednisone Versus Full-Dose Prednisone in IgAN With Active Proliferative Lesions: A Randomized Controlled Trial
Jin-Hua Hou, Wei-Bo Le, Nan Chen,..., Zhi-Hong Liu, Am J of Kidney Dis 69:788-795, 2017

But fewer side effects with combination therapy
NEFIGAN Trial

TRF-Budesonide ("Nefecon", Pharmalink AB)
• modified oral formulation of Budesonide
• targets ileocecal Peyers patches
• 90% first pass metabolism

NEFIGAN Trial
• Phase 2b
• 150 pts, 62 sites, 10 European countries
• Randomized, double-blind
• NEFECON 16 mg vs 8 mg vs Placebo
  x 9 months treatment
  + 3 months f/u

Bengt C Fellström et al., Lancet, 3/28/2017
NEFIGAN Trial

Subjects:
• 75-85% on ACE and/or ARB
• Mean 39yo, 70% Male
• BP 127-128/78-80 mmHg
• UPCR 0.76–0.83 g/g
• eGFR 72-85 mL/min/1.73m²

Results at 9 months:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>NEF 8 mg/d</th>
<th>NEF 16 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ΔUPCR</td>
<td>+3%</td>
<td></td>
<td>-24%</td>
</tr>
<tr>
<td>Mean ΔeGFR (ml/min/1.73m²)</td>
<td>-4.7</td>
<td>+0.32</td>
<td>+1.95</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>8%</td>
<td>22%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Fellström et al., Lancet, 3/28/2017
A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction


- Randomized, open-label, multicenter
- Rituximab x 1 yr (4g total) vs. usual-care
- 34 patients (17:17)
- Creatinine 1.5 ± 0.5 mg/dl
- Proteinuria 2.1 (range 0.6-5.5) g/d

- No significant effect on GFR
- No significant effect on proteinuria
- No significant effect on Gd-IgA1 levels
- No effect on IgG autoantibodies

Future developments in therapy

Budesonide – Phase 3
APRIL/BAFF inhibitors (Atacicept, Blisibimod)
ACTH Trial (pilot) – fully enrolled
Blockade of the Lectin pathway of complement (Omeros)
Jerry Appel’s Therapy for IgAN

• All pts ACEi or ARB or ACEi/ARB.
• All pts strongly consider Rx w statin.
• All pts consider low (i.e. 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

**Mild Disease**- (nl GFR, < 0.5g Uprot/d, good Bx)

No other Rx. Close Follow.

**Moderate or Severe Dis.** (Abnl GFR, or > 0.5-1g proteinuria/day, or Bx w high risk of progression)

- Steroids (We use alternate day) x 6months.
  
  Watch for infections and side effects!
  
- ? MMF with low dose steroids if other therapy not acceptable.
  - ? ACTH, ? budesonide (limited data)

- Crescentic GN – steroids + Ritux or cyclophosphamide

- High Pcreat. w Bx chronic damage GS-TIF – no immunosuppressives
IgA N 2018 References Bruges Mar 2018  G. Appel, M.D.

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