Nephrology Grand Rounds

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9th October, 2012
CASE

22 y.o Asian female with no significant PMHx presents with LE swelling and abdominal distension.

- Swelling started gradually 3 weeks ago and got rapidly worse in last 4 days
- Periorbital edema in the morning
- Dry cough for 2 weeks
- Abdominal pain-epigastric, intermittent for few days 1 week prior to admission
- Diarrhea for 1 week- no blood in stool
- No fever, chills, sore throat, shortness of breath, arthralgias, rash, hematuria, urinary frequency, dysuria, urgency or frothy urine

Took some medication from chinese pharmacy for 3 days 2 days prior to admission. Medication meant to treat pain and infection
• PMHx and PSHx: Nothing significant

• FHx: No history of kidney disease

• Allergies: NKDA

• SH: Moved from China 4 months ago. No tobacco, EtOH or drug abuse.
PHYSICAL EXAM

- VS: T 99.3  BP 89/45  HR 89  RR 18  SO2 96% on RA
- HEENT: Conjunctiva normal, sclera anicteric, oral mucosa moist
- Resp: clear to auscultation
- CVS: RRR, normal S₁S₂, no m/r/g
- Abd: Soft, mildly distended, nt, bs +
- LE: bilateral pitting
- Skin: no rashes, petechiae or purpura
LABS

- CBC: WBC 3.9  Hgb 13.0  Plt 294
- BMP: Na 140  K 3.8  Cl 108  bicarb 28  BUN 9  Cr 0.3  Ca 7.1
- LFT: T. bili 0.3  AST 21  ALT 19  Alk phos 51  TP 3.7  albumin 1.6
- Lipid panel: HDL 54  LDL 387  Chol 490  TG 246
- UA: moderate blood 2+, protein >300, RBC 10-15, epithelial cell 1-10
- Up/cr 5.6 gm
LABS

- Hepatitis Panel
  - Hep BsAg  negative
  - Hep Bs Ab  negative
  - Hep B c Ab  negative
  - Hep C Ab  non reactive

Complements
- $C_3$ 122
- $C_4$ 24
- ANA negative
IMAGING

- Chest X-ray: Small bilateral pleural effusions
  No focal consolidation

- Renal Ultrasound:
  Right kidney 11.3 cm, left kidney 11.9 cm
  Renal parenchyma is increased in echotecture
  No hydro, renal calculi
  Small amount of pelvic ascites
Diagnosis: IgA nephropathy, mildly mesangioproliferative without active lesions
Light Microscopy
22 glomeruli, none of which are globally sclerotic. One glomerulus shows a possible adhesion between the glomerular tuft and bowmans capsule. Remaining glomeruli are roughly normal in size with normal cellularity. The mesangial areas are mildly thickened. There is no evidence of endocapillary proliferation, crescent formation, glomerulitis, or double contour formation. There is very mild tubular atrophy and interstitial fibrosis occupying less than 5-10% of the cortical area.
Minimal focal chronic interstitial inflammation composed primarily of mature lymphocytes. No evidence of vasculitis in the biopsy
RENAL BIOPSY

Immunofluorescence
Glomeruli have finely granular mesangial reactivity for IgA, C₃ and lambda (2-3+), fibrin (1+), and kappa(trace) with no significant reactivity for IgG, IgM, C₁q or albumin.
Many protein resorption droplets in tubular epithelial cells which are reactive for IgA, kappa, lambda and albumin.
Electron Microscopy
Thin glomerular basement
No subepithelial, intramembranous or subendothelial deposits
Foot processes show fairly extensive effacement (80% of capillary surfaces) with mild reactive changes of the overlying visceral epithelial cells including swelling and microvillus transformation
Mesangial areas are expanded and display immune complex type deposits, particularly in paramesangial areas. Deposits are finely granular
IgA nephropathy was described histologically for the first time in 1968 by Berger and Hinglais as intercapillary deposits of IgA-IgG.

IgA nephropathy is considered to be the most common form of glomerulonephritis in the world.

IgAN is prevalent in all the ethnic groups but Japan and Korea have the highest recorded incidences.

IgAN accounts for 10% of cases of glomerulonephritis in the United States.

CLINICAL PRESENTATION

- 40 to 50% of cases present with episodic macroscopic hematuria, most frequently in the second and third decades of life. Hematuria usually follows intercurrent mucosal infection, commonly in the upper respiratory tract (Synpharyngitic hematuria) or occasionally in the GI tract.
- 30% to 40% of patients present with microscopic hematuria with or without proteinuria (usually <2g/24h)
- 5% of cases present with nephrotic syndrome.
- <5% of cases present with AKI
- CKD, some patients already have renal impairment and hypertension when they are first diagnosed
Thirty percent IgAN cases resolve spontaneously, 30-40% smolder and 30% progress to ESRD within 20-30 years.
Light Microscopy

- Variable
- Typically characterized by an increase in the mesangial cells and mesangial matrix with normal-appearing capillary loops.
- There can be almost normal glomerular architecture, diffuse mesangial proliferative GN, focal segmental GN or in rare cases focal segmental necrotizing GN with extracapillary proliferation
- On occasion, IgAN and minimal change disease coincide, in which case light microscopy is normal but there are mesangial IgA deposits
**PATHOLOGY**

Electron Microscopy

- Typically electron dense deposits are confined to mesangial and paramesangial areas, but in addition, subepithelial and subendothelial deposits can also be seen
- Up to one third of patients will have some focal thinning of the glomerular basement membrane
PATHOLOGY

Immunofluorescence

- Diffuse mesangial IgA deposit
- C3 is codeposited in up to 90% of the cases
- IgG in 40% and IgM in 40% of cases may also be found in the same distribution
- IgA also deposits sometimes along capillary loops (a pattern more common in HS nephritis)
PATHOGENESIS

• IgAN is an autoimmune disease arising from the consequences of increased circulating levels of IgA1 with galactose deficient hinge-region O-glycans

• However, this glycosylation aberrancy alone is not sufficient to induce nephritis

• Current data indicate that at least 4 hits contribute to the development of IgA nephropathy
Fig: Proposed pathways involved in the pathogenesis of IgAN

HIT 1: Hereditary increase in galactose deficient circulating IgA1

Synthesis of O-glycans

- Hinge region of IgA1 extends by 13 AA longer than the hinge region of IgA2

- It can carry up to six relatively short and simple sugar chains, called O-linked glycans each attached by glycosidic linkage to an oxygen atom of a serine or threonine.

- These glycans are synthesized in the stepwise fashion- beginning with the addition of N-acetyl galactosamine (GalNac) by the enzyme N-acetyl galactosyl amino transferase and continuing with the addition of the galactose by the enzyme core1, β1, 3 galactosyltransferase 1 (C1GALT1) and is completed by adding sialic acid to galactose or GalNAc or both.
HIT 1

Rectangle-GalNac, circle-galactose, diamond- sialic acid
40-50% of first degree relatives of IgAN patients have elevated levels of galactose deficient IgA comparable to that of patient’s

GWAS data have identified a major locus on chromosome 22q12.2 influencing susceptibility to IgAN (Nat Genet. ; 43(4): 321–327)
  - This locus is associated with variation in serum IgA levels and has been previously associated with risk of IBD
There are three hypotheses to explain the blocking of the galactosylation:

- Alpha 2,6 sialtransferase is excessively activated and sialic acid is attached to N-acetylgalactosamine, skipping galactose.
- C1β3GALT1 is attenuated, resulting in decreased galactose at O-glycan.
- Stability of C1B3GALTR is decreased by the reduction in its chaperone (Cosmc).
Abnormal miR-148b expression promotes aberrant glycosylation of IgA1 in IgA Nephropathy

- Serino et al reported a comprehensive microarray screening of miRNA in IgAN and revealed a pathophysiological mechanism whereby the miRNA 418b regulates the levels of mRNA encoding C1B3GALT1 in IgAN patients.
- Patients with IgA nephropathy exhibited lower C1GALT1 expression, which negatively correlated with miR-148b expression.
- miR-148b binds to the 3’-untranslated region of C1B3GALT mRNA and breaks it down.
- Level of miRNA-148b expression is significantly higher in IgAN patients.

Abnormal miR-148b...
Abnormal miR-148b ...

Fig: miR-148b regulates C1GALT1 expression at protein level
(A) Transfection of PBMCs of healthy participant with 25 nM miR-148b mimic
(B) IgAN PBMCs transfection with 250 nM miR-148b inhibitor

Variants of C1GALT1 gene are associated with genetic susceptibility to IgA nephropathy

- The C1B3GALT1 single nucleotide polymorphism (SNP) variant is associated with genetic susceptibility to IgAN

- miR-148b binding to the C1b3GALT1 mRNA can be modulated by SNP 1365G/A

- The 1365G enhances binding of miR-148b and 1365A weakens it

J Nephrology 200922:152-159, 2009
HIT2: CIRCULATING ANTIBODIES DIRECTED AGAINST GALACTOSE-DEFICIENT IGA1

- IgG or IgA₁ autoantibodies are formed against Gd-IgA₁

- IgG autoantibodies exhibit unique features in the CDR₃ of the variable region of their heavy chain

- Specifically, the third position in the CDR₃ is typically serine in patients with IgAN, a feature that is necessary for efficient binding of the IgG to galactose-deficient IgA₁

- It is not known that CDR₃ serine substitution originates from somatic mutations that arise during maturation of the antibody producing cells or from inherited germ line mutations

Strongest signal were localized within the MHC complex in the recent GWAS

3 susceptibility loci within MHC complex were identified

- MHC II locus containing HLA-DQB₁, DQA₁ and DRB₁. This effect appeared to be conveyed by a highly protective haplotype DRB*1501-DQA₁*0102-DQB₁*0602 (present in 10-20% of Europeans and 2-10% of Asians)

- Region encompassing 2 genes encoding transporters associated with antigen processing (TAP 1 and TAP2) and 2 genes encoding components of immunoproteosomes (PSMB8 and PSMB9)

- chromosome 6p21 encodes MHC-II molecules DPA₁, DPB₁, DPB2
HIT 3: Formation of Pathogenic IgA1 containing immune complexes

- Mesangial cells represent the primary target of pathogenic deposits formed by circulating immune complexes or by lanthanic deposits of Gd-IgA1, followed by binding of anti-glycan antibodies to form immune complexes in situ.

- IgA1-IgG immune complexes are >800 Kd.
Hit 4: Mesangial deposition of IgA1- Containing immune complexes, Cell activation and initiation of glomerular injury

- Immune complexes from patients with IgAN bind to the cells more efficiently than do uncomplexed IgA1 or immune complexes from healthy controls.
- Complexes with Gd-IgA1 induce cultured human mesangial cells to proliferate, secrete extracellular matrix components and release humoral factors such as TNF, IL-6 and TGF-ß
- Uncomplexed Gd-IgA1 or relatively small immune complexes (<800 kD) have no stimulatory effect on cellular proliferation
Cellular receptors on mesangial cells involved in binding of IgA1 are not well characterized.

None of the IgA receptors (CD89, polymeric Ig receptor, ASGP-R) and complement receptors have been confirmed on human mesangial cells.

CD71 transferrin receptor expressed on the surface of proliferating mesangial cells can bind polymeric IgA1.

CD71 can effectively bind immune complexes containing Gd-IgA1, leading to enhanced expression of CD71.
Immune complexes can activate complement via alternative pathway

GWAS identified a major IgAN susceptibility locus within the CFH (Complement factor H) cluster on chromosome 1q32

Carriers of a common deletion encompassing the neighboring CFHR1 and CFHR3 genes had an approximately 30% decreased risk of developing IgAN. 60% lower who carry 2 copies of deletion
POTENTIAL NEW DIAGNOSTIC AND PROGNOSTIC MARKERS

Serum
- Serum levels of auto antigen, Gd-IgA₁
- IgA and IgG autoantibodies specific for Gd-IgA₁

Urine
Aberrantly glycosylated IgA₁ within immune complexes has been found in the urine of patients with IgAN but not in patients with non-IgAN proteinuric glomerular diseases
POTENTIAL APPROACHES FOR DISEASE SPECIFIC THERAPY

- **Hit 1:**
  - Suppression of synthesis of Gd-IgA1
  - Enzymatic boost of galactose transfer to IgA1 hinge region O-glycans
  - Suppression of sialylation of Galactose deficient O-glycans

- **Hit 2:**
  - Alteration of processing and presentation of Gd-IgA1 O-glycopeptides
  - Specific B-cell depletion therapy

- **Hit 3:**
  - Competitive blockade of immune complex formation by non-cross linking anti-glycan antibodies or specific glycopeptides
  - Suppression of the alternative complement pathway

- **Hit 4:**
  - Targeted CFHR1/3 depletion
  - Blocking mesangial cell signaling induced by nephritogenic IgA1-containing immune complexes (can be theoretically accomplished by Protein-kinase inhibitors)
Clinical features and and outcome of IgA nephropathy with Nephrotic syndrome

- A multicenter observational study was conducted between January 2000 and September 2010 in 1076 patients with biopsy-proven IgAN from four medical centers in Korea.

- The primary outcome was a doubling of the baseline serum creatinine concentration.

- Secondary outcomes included ESRD and death.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of patients with IgA nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>All Patients (N=985)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen positivity, n (%)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
</tr>
<tr>
<td>Mean arterial BP (mmHg)</td>
</tr>
<tr>
<td>Laboratory measurements</td>
</tr>
<tr>
<td>24-h protein excretion (g/dl)</td>
</tr>
<tr>
<td>random UPCR (g/g)</td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
</tr>
<tr>
<td>serum albumin (g/dl)</td>
</tr>
<tr>
<td>total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
</tr>
<tr>
<td>Treatments, n (%)</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>ACEi or ARB</td>
</tr>
<tr>
<td>dual blockades</td>
</tr>
<tr>
<td>corticosteroids</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD and median (range). UPCR, urinary protein-to-creatinine ratio; SCr, serum creatinine; eGFR, estimated GFR; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Figure 2. | Effect of clinical response on renal survival.
TREATMENT

• Proteinuria, Hypertension and GFR are the key determinants of the type of treatment

• The degree of proteinuria is the strongest predictors for outcome in renal failure

• Optimized supportive care is the cornerstone for all patients at risk for progression
Table 1. Supportive therapy of IgAN

**Level 1 recommendations**
- Control blood pressure (sitting systolic BP in the 120s)
- ACE inhibitor or ARB therapy with up titration of dosage or combination ACE inhibitor and ARB therapy
- Avoid dihydropyridine calcium-channel blockers unless needed for BP control
- Control protein intake

**Level 2 recommendations**
- Restrict NaCl intake/institute diuretic therapy
- Control fluid intake
- Non-dihydropyridine calcium-channel blocker therapy
- Control each component of the metabolic syndrome
- Aldosterone antagonist therapy
- Beta-blocker therapy
- Smoking cessation
- Allopurinol therapy
- Empiric NaHCO$_3$ therapy, independent of whether metabolic acidosis is present or not

**Other measures to retard IgAN progression**
- Avoid NSAIDs altogether, or no more than once or twice weekly at most
- Avoid prolonged severe hypokalemia
- Avoid phosphate cathartics
- Ergocalciferol therapy to correct vitamin D deficiency
- Control hyperphosphatemia and hyperparathyroidism; in animal models and in human studies, controlling hyperphosphatemia slows CKD progression
NONESTABLISHED AND CONTROVERSIAL NONIMMUNO-SUPPRESSIVE TREATMENT APPROACHES

- Fish oil therapy
  - Metanalysis of fish oil therapy in patients with IgAN (Dillon JJ: JASN 8:1739-1744, 1997) no significant benefit was noted, although 75% probability of at least a minor effect
- Antiplatelet and Anticoagulant drugs (mostly used on Asia)
- Tonsillectomy, combined with immunosuppression (mostly recommended in Japan)
- Light to moderate alcohol consumption
<table>
<thead>
<tr>
<th>Trial</th>
<th>Pozzi et al., Italy(^{97,96})</th>
<th>Katafuchi et al., Japan(^{99})</th>
<th>Hogg et al., United States(^{26})</th>
<th>Manno et al., Italy(^{95})</th>
<th>Lv et al., China(^{24})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid regimen</td>
<td>Intravenous methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg every other day for 6 months</td>
<td>Oral prednisolone 20 mg/d tapered to 5 mg/d at 18 months</td>
<td>Oral prednisone every other day 60 mg/m(^2) for 3 months, then 40 mg/m(^2) for 9 months, and then 30 mg/m(^2) for 12 months</td>
<td>Oral prednisone for 6 months (1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day per month)</td>
<td>Oral prednisone for 6–8 months (0.8–1 mg/kg/day for 2 months, then reduced by 5–10 mg every 2 wks)</td>
</tr>
<tr>
<td>Control regimen</td>
<td>Supportive only</td>
<td>Dipyridamole</td>
<td>Placebo</td>
<td>Supportive only</td>
<td>Supportive only</td>
</tr>
<tr>
<td>RAS blockade</td>
<td>14% at baseline, allowed during follow-up</td>
<td>2% at baseline; allowed during follow-up</td>
<td>Enalapril if hypertensive</td>
<td>Ramipril in all patients</td>
<td>Cilazapril in all patients</td>
</tr>
<tr>
<td>Key outcome in steroid group versus control</td>
<td>Ten-year renal survival (=absent doubling of serum creatinine), 53% in controls versus 97% in the steroid group</td>
<td>Significant reduction in proteinuria but not ESRD frequency</td>
<td>No benefit in the steroid group versus placebo at 2 years</td>
<td>Mean annual loss of GFR 6.2 ml/min in controls versus 0.6 ml/min in the steroid group</td>
<td>Significantly fewer patients with a 50% increase in serum creatinine in the steroid group</td>
</tr>
</tbody>
</table>
Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or halving of GFR) in patients with IgA nephropathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Steroids group event/total</th>
<th>Control group event/total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Julian 1993</td>
<td>1/17</td>
<td>2/18</td>
<td>0.53 (0.05, 5.32)</td>
</tr>
<tr>
<td>Katafuchi 2003</td>
<td>3/43</td>
<td>3/47</td>
<td>1.09 (0.23, 5.13)</td>
</tr>
<tr>
<td>Lai 1986</td>
<td>0/17</td>
<td>0/17</td>
<td>1.00 (0.00, 90105.34)</td>
</tr>
<tr>
<td>Lv 2009</td>
<td>0/33</td>
<td>2/30</td>
<td>0.18 (0.01, 3.64)</td>
</tr>
<tr>
<td>Manno 2009</td>
<td>2/48</td>
<td>13/49</td>
<td>0.16 (0.04, 0.66)</td>
</tr>
<tr>
<td>Pozzi 2004</td>
<td>1/43</td>
<td>13/43</td>
<td>0.08 (0.01, 0.56)</td>
</tr>
<tr>
<td>Shoji 2000</td>
<td>0/11</td>
<td>0/8</td>
<td>0.73 (0.00, 6856.08)</td>
</tr>
<tr>
<td>Hogg 2006</td>
<td>2/33</td>
<td>4/31</td>
<td>0.47 (0.09, 2.39)</td>
</tr>
<tr>
<td>Overall</td>
<td>9/245</td>
<td>37/243</td>
<td>0.32 (0.15, 0.67) p=0.002</td>
</tr>
</tbody>
</table>

Weights are from random effects analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Study</th>
<th>Relative Risk</th>
<th>P value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>Sample size</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt;64</td>
<td>4</td>
<td>0.30 (0.10, 0.91)</td>
<td>P=0.841</td>
</tr>
<tr>
<td>≥64</td>
<td>4</td>
<td>0.37 (0.06, 2.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;33y</td>
<td>4</td>
<td>0.39 (0.10, 1.55)</td>
<td>P=0.740</td>
</tr>
<tr>
<td>≥33y</td>
<td>4</td>
<td>0.29 (0.09, 0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
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<tr>
<td>&lt;38 mo</td>
<td>4</td>
<td>0.42 (0.13, 1.40)</td>
<td>P=0.578</td>
</tr>
<tr>
<td>≥38 mo</td>
<td>4</td>
<td>0.26 (0.07, 1.03)</td>
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</tr>
<tr>
<td><strong>Steroid dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>3</td>
<td>0.69 (0.25, 1.88)</td>
<td>P=0.030</td>
</tr>
<tr>
<td>Full dose</td>
<td>5</td>
<td>0.14 (0.05, 0.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Steroid duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12mo</td>
<td>5</td>
<td>0.14 (0.05, 0.39)</td>
<td>P=0.030</td>
</tr>
<tr>
<td>&gt;12mo</td>
<td>3</td>
<td>0.69 (0.25, 1.88)</td>
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</tr>
<tr>
<td><strong>Using ACEi in control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>2</td>
<td>0.16 (0.04, 0.59)</td>
<td>P=0.206</td>
</tr>
<tr>
<td>no</td>
<td>6</td>
<td>0.44 (0.18, 1.08)</td>
<td></td>
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<tr>
<td><strong>Baseline proteinuria</strong></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;2.0g/d</td>
<td>4</td>
<td>0.41 (0.16, 1.06)</td>
<td>P=0.315</td>
</tr>
<tr>
<td>≥2.0g/d</td>
<td>4</td>
<td>0.18 (0.05, 0.69)</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;125mmHg</td>
<td>3</td>
<td>0.17 (0.05, 0.60)</td>
<td>P=0.212</td>
</tr>
<tr>
<td>≥125mmHg</td>
<td>3</td>
<td>0.38 (0.09, 1.61)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.1mg/dl</td>
<td>3</td>
<td>0.41 (0.09, 1.92)</td>
<td>P=0.126</td>
</tr>
<tr>
<td>≥1.1mg/dl</td>
<td>3</td>
<td>0.37 (0.06, 2.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Event (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8%</td>
<td>4</td>
<td>0.75 (0.20, 2.90)</td>
<td>P=0.140</td>
</tr>
<tr>
<td>≥8%</td>
<td>4</td>
<td>0.22 (0.09, 0.54)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td>0.32 (0.15, 0.67)</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analysis for the effect of corticosteroid on composite renal endpoint

Effects of steroids on proteinuria in patients with IgA nephropathy

Table 3. Mycophenolate mofetil monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Maes et al., Belgium^4^</th>
<th>Tang et al., China^4^</th>
<th>Frisch et al., United States^4^</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF regimen</td>
<td>2 g/d for 3 years</td>
<td>1.5 to 2.0 g/d depending on body weight for 6 months</td>
<td>Titrated up to 2 g/d for 1 year</td>
</tr>
<tr>
<td>Control regimen</td>
<td>Placebo</td>
<td>Supportive only</td>
<td>Placebo</td>
</tr>
<tr>
<td>RAS blockade</td>
<td>All patients</td>
<td>All patients</td>
<td>All patients</td>
</tr>
<tr>
<td>Key outcome in MMF group</td>
<td>No effect on GFR or proteinuria</td>
<td>Reduction in proteinuria, stabilization of GFR</td>
<td>No effect on GFR or proteinuria</td>
</tr>
</tbody>
</table>
Immunosuppressive Combination therapy is not recommended

- A number of retrospective studies or case series mostly from Asia, have reported beneficial outcomes in high-risk IgAN patients treated with combination of corticosteroids plus cyclophosphamide or azathioprine

- At present, immunosuppressive combination therapy is not warranted in IgAN unless there are features of rapidly progressive glomerulonephritis and/or vasculitic course
| Trial | Bellarde et al., United Kingdom
text goes here | Yoshikawa et al., Japan
text goes here | Yoshikawa et al., Japan
text goes here | Pozzi et al., Italy
text goes here |
|------|-----------------|-----------------|-----------------|-----------------|
| **Combination regimen** | Oral prednisolone 40 mg/d reduced to 10 mg (end of year 2) + oral cyclophosphamide 1.5 mg/kg per day for 3 months, and then oral azathioprine 1.5 mg/kg per day for minimum 2 years and up to 6 years | Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + anticoagulants (heparin followed by warfarin and dipyridamole) | Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + warfarin + dipyridamole | Same as shown in Table 2
text goes here + oral azathioprine 1.5 mg/kg per day for 6 months |
| **Control regimen** | Supportive therapy only | Supportive therapy + anticoagulants (see above) | Above regimen without azathioprine | Same as shown in Table 2
text goes here |
| **RAS blockade** | Inconsistent | Not reported | Prohibited | 45% at baseline |
| **Key outcome in combination group versus control group** | Marked improvement of renal survival at 5 years | Higher reduction in proteinuria and percentage of sclerosed glomeruli | More complete remissions of proteinuria | No difference between groups |
| **Comment** | Study included pediatric patients only | Study included pediatric patients only | | |
Recurrent IgA nephropathy in the transplant patient

- None of the currently available immunosuppressive drugs used after renal transplantation can prevent the histologic recurrence of IgAN.

- There is also no clear evidence that choice of immunosuppression after renal transplantation affects the clinical manifestation or course of recurrent IgA nephropathy.

- Mainly optimized supportive care recommended.
Thank You!