Current treatment recommendations in children with IgA nephropathy

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IgA Nephropathy

• The most common cause of primary (idiopathic) glomerulonephritis in the developed world
• First described in 1968 by Berger and Hinglais
• It was initially considered a benign condition ??
• Long term follow-up of patients indicated that 20–50 % of adults would ultimately progress to end-stage renal failure
Epidemiology

Geographic Variations in the Prevalence of IgA Nephropathy

Data from:
Ozturk, Int Urol Nephrol 2014
Rodicio, Kidney Int 1984
Epidemiology

The explanation for this apparent variability in incidence is uncertain

- racial difference
- differences in biopsy selection practices
- genetic factors and environmental influences
Epidemiology

• In Turkey
  • 17 - 18 % in adults
  • 2 - 7 % in children

Differences in biopsy selection practices?

• In Japan
  • All children between the ages of 6 and 18 years are screened annually
  • Those found to have urinary abnormalities are referred for further investigation
  • Thus, IgAN is the most common primary GN in children
  • Approximately 30 % of biopsy specimens

Özkaya, Pediatr Int, 2004
Ozturk, Int Urol Nephrol 2014
Fidan, Renal Failure 2016
Nakanishi and Yoshikawa, Pediatric Nephrology 2016
Challenges in the management of the pediatric patients

- At present, there is no curative therapy for IgAN

- The variable rate of progression to renal failure

- Differences in clinical and laboratory at presentation
  - Clinical sign (age, hypertension, macroscopic recurrent hematuria)
  - Proteinuria (absence, slight, moderate, heavy)
  - Glomerular filtration rate (normal-abnormal-acute/chronic renal failure)

- Differences in biopsy findings
  - Crescentic GN
Clinical Presentations of IgA Nephropathy and Henoch-Schönlein Purpura in Relation to Age

Data from patients presenting in Liecester, UK, 1980 to 1995
Clinical Presentations of IgA Nephropathy and Henoch-Schönlein Purpura in Relation to Age

Recurrent macroscopic hematuria Coincides with mucosal infection

Number of cases vs. Age (years)
Asymptomatic urine Abnormality (hematuria/proteinuria)
Clinical Presentations of IgA Nephropathy and Henoch-Schönlein Purpura in Relation to Age

Nephrotic syndrome
Chronic kidney disease

Proteinuria

Hypertension

Renal impairment

Clinical Presentations of IgA Nephropathy and Henoch-Schönlein Purpura in Relation to Age
Challenges in the management of the pediatric patients

Randomized controlled trials

- Endpoint of IgAN is development of chronic renal insufficiency
- Most pediatric patients do not develop it during the study period
- Thus, studies of pediatric patients with IgAN may differ markedly from studies of adults with regard to the apparent risk of progressive disease

Wyatt, Pediatr Nephrol 2001
Nakanishi and Yoshikawa, Pediatric Nephrology 2016
Challenges in the management of the pediatric patients

Randomized controlled trials

- Surrogate markers of outcome must be used to evaluate efficacy of therapy for IgAN in clinical trials

- Validation of these surrogate markers may be lacking, resulting in the potential for inappropriate conclusion with regard to therapeutic efficacy

Wyatt, Pediatr Nephrol 2001
Nakanishi and Yoshikawa, Pediatric Nephrology 2016
Challenges in the management of the pediatric patients

Randomized controlled trials

• Most of the randomized controlled trials were performed in adults

• Available evidences for treatment are different between children and adults

• Generally, the evidence for treatments of IgAN in adults supports relatively passive treatments, whereas that in children supports relatively active treatments

Nakanishi and Yoshikawa, Pediatric Nephrology 2016
Challenges in the management of the pediatric patients

Guidelines

• There are several current guidelines for treatment of adults
  – KDIGO, NKF-KDOQI, CANADIAN, JAPANESE

• A guideline for treatment of children
  – JAPANESE

Nakanishi and Yoshikawa, Pediatric Nephrology 2016
UpToDate 2016
Tomino, Pathogenesis and Treatment IgA Nephropathy, 2016
Approach to therapy

- The optimal approach to the treatment of IgA nephropathy is uncertain

- The slow rate of loss of GFR seen in many patients (1 to 3 mL/min per year) hinders the ability to perform adequate studies
Approach to therapy

There are two approaches to the therapy of IgAN

– General interventions to slow progression (not specific to IgAN)
  - to control blood pressure
  - to reduce proteinuria
  - ACE inhibitors, ARBs

– To treat the underlying inflammatory disease
  - Glucocorticoids with or without other immuno-suppressive agents

Nakanishi and Yoshikawa, *Pediatric Nephrology* 2016
UpToDate 2016
Tomino, *Pathogenesis and Treatment IgA Nephropathy*, 2016
KDIGO, *Kidney Int Suppl* 2012
Approach to therapy

– Non-Immunosuppressive Therapies
  • ACE inhibitors, ARBs
  • Coagulation modifying agents
  • Fish-oil

– Immunosuppressive Therapies
  • Glucocorticoids with or without other immuno-suppressive agents

– The Others
  • Tonsillectomy
  • Herbal medicine
Approach to therapy

Patient selection

- Patient selection for therapy is based in part upon the perceived risk of progressive kidney disease.

- Patients with:
  - isolated hematuria,
  - no or minimal proteinuria (less than 500 mg/1.73 m²/day)
  - normal GFR

  Typically not treated and often not biopsied, therefore not identified as having IgAN.

500 mg/1.73 m²/day \(\approx 12\) mg/m²/hour?
Recurrent macroscopic hematuria Coincides with mucosal infection

They should be periodically monitored at 6- to 12-month intervals
Long-term outcome of childhood IgA nephropathy with minimal proteinuria (<0.5 g/day/1.73 m²)

- Retrospectively analyzed 385 children from Japan
- Newly diagnosed with biopsy-proven IgAN
- Between June 1976 and July 2009
- Renal biopsy specimens were evaluated by the Oxford classification criteria
- 106 with minimal proteinuria-IgAN (<0.5 g/day/1.73 m²)

- Clinical and pathological findings between the 106 patients with minimal proteinuria-IgAN and the remaining 279 patients with non-minimal proteinuria were compared
Long-term outcome of childhood IgA nephropathy with minimal proteinuria (<0.5 g/day/1.73 m²)

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>MP-IgAN (n = 106)</th>
<th>Non-MP-IgAN (n = 279)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>11.5 (9.0 - 13.7)</td>
<td>10.3 (8.1 - 12.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Duration from onset to renal biopsy (months)</td>
<td>9.9 (4.0 - 17.9)</td>
<td>5.2 (2.8 - 15.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>45.3 %</td>
<td>45.9 %</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>77.5 ± 16.9</td>
<td>77.8 ± 17.2</td>
<td>0.93</td>
</tr>
<tr>
<td>Gross hematuria episode</td>
<td>58 (54.7 %)</td>
<td>146 (52.3 %)</td>
<td>0.73</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>111.6 ± 23.6</td>
<td>107.9 ± 23.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Proteinuria at biopsy (g/day/1.73 m²)</td>
<td>0.2 (0.2 - 0.3)</td>
<td>1.4 (0.9 - 2.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Long-term outcome of childhood IgA nephropathy with minimal proteinuria (<0.5 g/day/1.73 m²)

<table>
<thead>
<tr>
<th>Pathological findings (Oxford criteria) (%)</th>
<th>MP-IgAN (n = 106)</th>
<th>Non-MP-IgAN (n = 279)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial score (M0/M1)</td>
<td>76/24</td>
<td>46/54</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Endocapillary hypercellularity (E0/E1)</td>
<td>68/32</td>
<td>36/64</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Segmental sclerosis and adhesion (S0/S1)</td>
<td>73/27</td>
<td>57/43</td>
<td>0.0002</td>
</tr>
<tr>
<td>Tubular atrophy and interstitial fibrosis (T0/T1/T2)</td>
<td>99/1/0</td>
<td>100/0/0</td>
<td>0.48</td>
</tr>
<tr>
<td>Crescents (absent/present)</td>
<td>61/39</td>
<td>39/61</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Global sclerosis (absent/present)</td>
<td>95/5</td>
<td>77/23</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
### Long-term outcome of childhood IgA nephropathy with minimal proteinuria (<0.5 g/day/1.73 m²)

<table>
<thead>
<tr>
<th>Principal treatments</th>
<th>MP-IgAN (n = 106)</th>
<th>Non-MP-IgAN (n = 279)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>39 (36.8 %)</td>
<td>40 (14.3 %)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antiplatelet and/or anticoagulant</td>
<td>14 (13.2 %)</td>
<td>23 (8.2 %)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prednisolone (± antiplatelet and/or anticoagulant)</td>
<td>2 (1.9 %)</td>
<td>34 (12.2 %)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prednisolone + immunosuppressant (± antiplatelet and/or anticoagulant)</td>
<td>2 (1.9 %)</td>
<td>85 (30.5 %)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chinese herb (Sairei-to)</td>
<td>9 (8.5 %)</td>
<td>24 (8.6 %)</td>
<td>0.99</td>
</tr>
<tr>
<td>ACEI and/or ARB</td>
<td>32 (30.2 %)</td>
<td>31 (11.1 %)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (7.5 %)</td>
<td>42 (15.1 %)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MP, minimal proteinuria; IgAN, immunoglobulin A nephropathy
Long-term outcome of childhood IgA nephropathy with minimal proteinuria (<0.5 g/day/1.73 m²)

The outcome of patients with a diagnosis of childhood MP-IgAN is good, but that careful long-term observation is required.

End-point of renal outcome: ≥ stage III chronic kidney disease (eGFR<60 ml/min/1.73 m²)

Higa, Pediatr Nephrol. 2015
Approach to therapy

- Non-Immunsuppressive Therapies
  - ACE inhibitors, ARBs
  - Fish-oil
  - Coagulation modifying agents
  - Tonsillectomy

- Immunsuppressive Therapies
  - Glucocorticoids with or without other immuno-suppressive agents

Nakanishi and Yoshikawa, *Pediatric Nephrology* 2016
UpToDate 2016
Tomino, *Pathogenesis and Treatment IgA Nephropathy*, 2016
KDIGO, *Kidney Int Suppl* 2012
Renin-Angiotensin system inhibitors

- Angiotensin inhibition with an ACE inhibitor or ARB slows the rate of progression of most proteinuric chronic kidney diseases.

- This effect is mediated at least in part by lowering both the systemic blood pressure and the intra-glomerular pressure.

- Thereby, they can minimize both proteinuria and secondary glomerular injury (not due to the primary glomerular disease itself).

Nakanishi and Yoshikawa, Pediatric Nephrology 2016
UpToDate 2016
Tomino, Pathogenesis and Treatment IgA Nephropathy, 2016
Renin-Angiotensin system inhibitors

- 44 adults with IgA nephropathy
- Proteinuria (≥0.5 g/day, mean 1.9 g/day)
  S.creatinine ≤1.5 mg/dL
- Either enalapril or other antihypertensive agents (other than ACE inhibitors or ARBs)
- Blood pressure control throughout the study was similar in the two groups
- At follow-up of about 6 years
- Renal survival significantly more likely in the enalapril group (92% vs 55%)
- Significant decrease in proteinuria was only observed in the enalapril group (2 g/day to 0.9 g/day at the last visit)
Renin-Angiotensin system inhibitors

IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

- 65 young patients (range 9 to 35 years)
- Moderate proteinuria (1 - 3.5 g/day/1.73 m²)
- Relatively preserved renal function (creatinine clearance >50 mL/min/1.73 m²)
- Randomly, **benazepril** (0.2 mg/kg/day) or placebo
- Median follow-up: 38 months
Proportion of IgAN patients receiving ACE-I or placebo who reached end point of (A) partial (proteinuria <0.50 g/d per 1.73 m², P = 0.0002) or (B) complete (proteinuria <0.160 g/d per 1.73 m², P = 0.0150) remission of proteinuria (Kaplan-Meier estimates, lo...

Rosanna Coppo et al. JASN 2007;18:1880-1888

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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 in IgAN patients receiving ACE-I or placebo (Kaplan-Meier estimates. log rank. P = 0.034).

Rosanna Coppo et al. JASN 2007;18:1880-1888
Efficacy and safety of lisinopril for mild childhood IgA nephropathy: a pilot study

- Prospective single-arm pilot trial with lisinopril (0.4 mg/kg per day)
- Newly diagnosed, age ≤18 years, 40 children
- IgA-N with minimal or focal mesangial proliferation
- No previous treatment
- Early morning (uP/Cr) of ≥ 0.2 g/g
- 2-year treatment period
- The cumulative disappearance rate of proteinuria determined by the Kaplan–Meier method was 80.9%
- Mean uP excretion was reduced from 0.40 to 0.18 g/m²/day ($p < 0.0001$)
- The efficacy and safety of lisinopril, acceptable
The presence of crescents in glomeruli reduces the anti-proteinuric effects of RAS blockade. In this study, most of reduction in proteinuria occurred within 3 months after RAS blockade, but further reduction of proteinuria was observed until 1 year after RAS blockade.
Renin-Angiotensin system inhibitors

Angiotensin II receptor blockers

• There is no randomized controlled trial for angiotensin II receptor blockers in children with IgAN

• Two studies have demonstrated anti-proteinuric effect of ARBs in combination therapies with ACE inhibitor and ARB (Ilosartan)

• These studies with small number patients were no randomized and controlled

Nakanishi and Yoshikawa, Pediatric Nephrology 2016
Bhattacharje, Pediatr Nephrol 2002
Yang, Clin Nephrol 2005
Combination therapies with ACE inhibitor and ARB

• ARB + ACEi in patients with IgA nephropathy produces a further antiproteinuric effect in short-term studies

• ACEi + ARB compared with monotherapy, 18 to 25 % greater reduction in proteinuria (meta-analyses)

• Despite these observations, the clinical role of combined therapy in the treatment of IgA nephropathy is uncertain
  - Combined therapy was compared with the usual dose rather than a higher dose of a single agent
  - there are no randomized trials that have shown that this regimen improves renal outcomes in patients with proteinuric chronic kidney disease
  - The one trial (COOPERATE) that showed benefit from combination therapy has been retracted by the publisher due to concerns about the reliability of the data

Reid, Cochrane Database Syst Rev 2011
Russo, Am J Kidney Dis 2001
Catapano, Am J Kidney Dis 2008
Retraction-- (COOPERATE), Lancet 2009
UpToDate 2016
Renin-Angiotensin system inhibitors

Treatment of early IgAN by ACEi

- Angiotensin inhibition does not appear to be beneficial in non-proteinuric patients or those with low levels of protein excretion
- 60 Chinese adults with IgAN
- Proteinuria <500 mg/day
- Normal kidney function
- Normal blood pressure <140/90 mmHg
- Randomly ramipril (2.5 mg/day) or placebo
- After five years, there were no differences
  - the incidence of proteinuria or hypertension
  - the rate of kidney function decline
The authors of this topic do not agree on the level of proteinuria which patients require angiotensin inhibition

- 1 g/day or more? [KDIGO]
- 500 mg/day or more?
- 300 mg/day or more?

(this target might provide additional renal protection especially in young)?
Approach to therapy

– Non-Immunosuppressive Therapies
  • ACE inhibitors, ARBs
  • Fish-oil
  • Coagulation modifying agents
  • Tonsillectomy

– Immunosuppressive Therapies
  • Glucocorticoids with or without other immuno-suppressive agents
Fish oil

The Mayo Clinic multicenter study

- Fish oil vs placebo (olive oil)
- 106 patients with IgAN (> 18 years), similar biopsy finding
- 50% or greater rise in serum creatinine
  - 6% of the fish oil group vs 33% of the placebo group after 2-year (p<0.01)
- ESRD or died
  - 10% of the fish oil group vs 40% of the placebo group after 4-year (p<0.01)
- Not significantly reduce proteinuria

Fish oil

Southwest Pediatric Nephrology Study Group

- 96 patients, age between 10-34 years
- GFR of >100 mL/min per 1.73 m²
- Protein excretion 1.4 to 2.2 g/day
  - Omega-3 fatty acids (4g/day) for 2 years, Group I
  - Prednisone alternate-day [60 mg/m² 3 months, 40 mg/m² 9 months, and 30 mg/m² 12 months], Group II
  - Placebo, Group III
- Reduction in GFR to below 60 percent of the baseline
  - 19 %, 9 % and 9 %, respectively
- There was no statistically significant

Fish oil

- Fish oil contains the compound omega-3 polyunsaturated fatty acid
- It reduces renal inflammation by diminishing inflammatory cytokines and eicosanoids in IgAN

- A benefit from fish oil has not been clearly established

- However, fish oil (3.3 g/day or more) can be tried in patients with risk factors for progression
Coagulation modifying agents

Warfarin, urokinase, and antiplatelet agents (dipyridamole)

- Antiplatelet drugs and anticoagulants are used mainly in Asian countries for the treatment of IgAN
- At present there is no sufficient evidence to support the use of coagulation modifying agents
- However, coagulation modifying agents may have a role in combination therapy [Cochrane Database Syst Rev]

Yoshikawa, J Am Soc Nephrol 1999
Barratt, Kidney Int 2006
Reid, Cochrane Database Syst Rev 2011
Approach to therapy

– Non-Immunsuppressive Therapies
  • ACE inhibitors, ARBs
  • Fish-oil
  • Coagulation modifying agents
  • Tonsillectomy

– Immunsuppressive Therapies
  • Glucocorticoids with or without other immuno-suppressive agents
• The tonsils are a source of abnormal IgA that forms immune complexes and deposits in the glomeruli

• Tonsillectomy, usually in combination with some immunosuppressive therapy, is associated with improved renal outcomes in relatively mild renal injury

• However, it could not be recommended for widespread use for treatment, especially for children with IgAN
Tonsillectomy + steroid pulse therapy (TSP) in children with IgAN

- TSP therapy was first reported by Hotta et al.
- Many of the benefits of TSP therapy have been reported, especially in Japan adults.
- Tonsillectomy with steroid pulse therapy is spread widely in Japan as one of the first-line treatment in adult patients.
- However, there have been only few reports concerning the effect of tonsillectomy in Japanese pediatric patients with IgAN.

Tomino, *Pathogenesis and Treatment IgA Nephropathy*, 2016
Tonsillectomy + steroid pulse therapy (TSP) in children with IgAN

- A RCT study 32 children with diffuse IgAN
- 16 children TSP for 2 years
- 16 children prednisolone, warfarin, and dipyridamole including mizoribine (PWDM)
- Decrease protein excretion, no difference
- Activity index on second biopsy, no difference
- An acute exacerbation of IgA nephropathy as a result of tonsillitis, 0 patient in TSP vs 6 patients
Tonsillectomy + steroid pulse therapy (TSP) in children with IgAN

- 11 children with steroid resistant IgAN
- As rescue treatment, TSP, after 24 months
- Protein excretion was significantly decreased
- Second biopsy 6 patients
  - Significantly decrease in activity index
  - No change chronic index
- At 24 months, seven patients had normal urine and four had minor urinary abnormalities.
- None had active renal disease or renal insufficiency
Tonsillectomy + steroid pulse therapy (TSP) in children with IgAN

- 30 children, age > 7 years, relatively poor prognosis (biopsy)
  - 5 patients refused tonsillectomy
  - Group I, 13 children
    Early tonsillectomy, within 3 years after diagnosis
  - Group II
    Later, 12 children
- 2 years follow-up
- Complete remission in 10 (most often in early group)
- The patients refusing surgery failed to attain complete remission of urinary findings
Approach to therapy

- Non-Immunosuppressive Therapies
  - ACE inhibitors, ARBs
  - Fish-oil
  - Coagulation modifying agents
  - Tonsillectomy

- Immunosuppressive Therapies
  - Glucocorticoids with or without other immuno-suppressive agents
• The optimal role of anti-inflammatory therapy in IgA nephropathy is uncertain

• Most nephrologists do not treat mild, stable, or very slowly progressive IgA nephropathy with glucocorticoids or other immunosuppressive therapies

• Glucocorticoids alone or with other immunosuppressive drugs have been widely used to treat moderate to severe IgAN, particularly in pediatric patients
Immunosuppressive therapy should be used in patients with clinical features supporting active disease and progression.

Hematuria + one or more of the following:

- A progressively declining GFR
- Persistent proteinuria >1 g/day after maximal antiproteinuric therapy with ACEIs or ARBs for 3 to 6 months
- Morphologic evidence of active disease based upon kidney biopsy
Immunosuppressive Therapy

• Combined immunosuppressive therapy can be considered in patients with more severe disease
  – More rapidly progressive clinical course and/or histologic evidence of severe active inflammation (e.g., crescent formation)

• Many authors suggest not treating with glucocorticoids in patients with
  – Chronically elevated serum creatinine or
  – Histologic evidence of prominent glomerulosclerosis and tubulointerstitial atrophy or fibrosis

UpToDate, 2016
Nakanishi, Pediatric Nephrology, 2016
Glucocorticoids as sole immunosuppressive therapy

- Glucocorticoid therapy significantly
  - reduced the incidence of ESRD (2.4 % vs 15 %)

- In two trials, glucocorticoids + ACEIs vs ACEIs alone
  - renal event 2.5% vs 19%

- Adverse events
  - majority of these were weight gain and cushingoid features glucocorticoid therapy (24% vs 13%)

Lv, J Am Soc Nephrol 2012
Immunosuppressive Therapy

Glucocorticoids as sole immunosuppressive therapy

- A randomized trial, Italy, 86 adults
- Moderate proteinuria (1 to 3.5 g/d)
- Mild reduction in GFR (serum creat ≈ 1 mg/dL)

- Supportive therapy alone
  (diuretics, antihypertensive, and antiplatelet agents)

  or

- Glucocorticoids
  (1 g of IV MP for 3 consecutive days at the beginning of months 1, 3, and 5, combined with 0.5 mg/kg of oral prednisolone given on alternate days for six months)

- ACE inhibitors were not used routinely in this trial

- The glucocorticoid group had a significantly lower incidence of the doubling in the serum creatinine concentration

  2 vs 21% at 5 years
  2 vs 30% at 10 years

Pozzi, J Am Soc Nephrol 2004
Glucocorticoids as sole immunosuppressive therapy

- A randomized trial, multicenter, Italy, 97 adults
- Protein excretion mean 1.6 g/d
- GFR > 50 mL/min/1.73 m²
- ramipril alone or
- Combined therapy with ramipril + prednisone, six-month course (0.8 to 1 mg/kg/day for two months followed by monthly dose reductions of 0.2 mg/kg/day during the next four months)

- Doubling of the serum creatinine (27% vs 4%) at eight years
- Prednisone also reduced the incidence of end-stage renal disease (14% vs 2%)
Immunosuppressive Therapy

Glucocorticoids as sole immunosuppressive therapy

Patients with apparent MCD (minimal change disease)

• There is a subset of patients with IgA nephropathy with acute onset of the nephrotic syndrome
• Little or no hematuria, preserved kidney function
• Minimal glomerular changes
• Diffuse fusion of the foot processes
• Glucocorticoid therapy alone is clearly beneficial
• Possible minimal change disease and that the presence of IgA deposits is unrelated, particularly in Asian patients
Combined immunosuppressive therapy can be considered in patients with more severe IgAN as defined by a more rapidly progressive clinical course and/or histologic evidence of severe active inflammation (e.g., crescent formation).

There are valuable contributions of the Japanese Pediatric IgAN Study group on this topic.

Nakanishi, *Pediatric Nephrology* 2016
Katafuchi, *Pathogenesis and Treatment in IgA Nephropathy*, 2016
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

• Yoshikawa et al. A prospective controlled randomized clinical trial involving 20 Japanese pediatric renal centers
• Mean age 12 years, 78 children
• Newly diagnosed severe disease defined in all patients

  – Diffuse mesangial proliferation with crescents in ~22% and sclerosis in ~5% of glomeruli
  – Mean creatinine clearance was normal (~150 mL/min/1.73 m²)
  – Mean urinary protein excretion was ~ 1.2 g/day
  – Mean blood pressure was 115/65 mmHg.

Yoshikawa, J Am Soc Nephrol 1999
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

• **Group 1:**
  - 40 patients
  - Follow-up 2 years
  - **Immunosuppressive + Supportive**
    - Prednisolone
      - 2mg/kg/d; 4 weeks
      - 2mg/kg/2d; 4 weeks
      - 1.5mg/kg/2d; 4 weeks
      - 1mg/kg/2d; 21 months
    - Azathioprine 2mg/kg/d
    - Heparin/Warf
    - Dipyridamol 5mg/kg/d

• **Group 2:**
  - 38 patients
  - Follow-up 2 years
  - **Supportive alone**
    - Heparin/Warf
    - Dipyridamol 5mg/kg/d

  Heparin; IV infusion keep the PTT at 60 s for 28 d
  Warfarin single morning dose to maintain the thrombotest at 30 to 50% for 23 months

Yoshikawa, J Am Soc Nephrol 1999
## Immunosuppressive Therapy

### Children with Severe IgA Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean urinary protein excretion</td>
<td>significantly decreased</td>
<td>unchanged</td>
</tr>
<tr>
<td>Mean serum IgA concentration</td>
<td>significantly decreased</td>
<td>unchanged</td>
</tr>
<tr>
<td>Intensity of mesangial IgA deposition</td>
<td>significantly decreased</td>
<td>unchanged</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>normal</td>
<td>1 patient, hypertensive</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>normal</td>
<td>1 patient, CKD</td>
</tr>
<tr>
<td>Glomeruli sclerosis %</td>
<td>unchanged</td>
<td>significantly increased</td>
</tr>
</tbody>
</table>

Treatment of children with severe IgA nephropathy with Pred+AZA+Hep-Warf+Dipyrid for 2 years early in the course of disease reduces immunologic renal injury and prevents increase of sclerosed glomeruli.

Yoshikawa, J Am Soc Nephrol 1999
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

• In 2011, Kamei et al. reported long-term results of a previous RCT (Yoshikawa et al.)

• In a 10-year follow-up study that included 74 of the 78 children

• End-stage renal disease had developed in fewer patients who received prednisolone and azathioprine compared with control therapy (5% vs ~15 %, respectively)
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

2-year combination therapy not only ameliorated the activity of the acute phase of nephritis but also improved the long-term outcome of severe childhood IgA nephropathy.

Kamei, J Am Soc Nephrol 2011
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

- In 2006, Yoshikawa et al. reported the results of another RCT for severe childhood IgA nephropathy
- Prospective, unblinded, randomized, controlled clinical trial
- 20 Japanese pediatric renal centers (The Japanese Pediatric IgA Nephropathy Treatment Study Group)
- A total of 80 children with newly diagnosed IgA nephropathy prednisolone+azathioprine+warfarin+dipyridamole (combination) or prednisolone alone for 2 years.
Immunosuppressive Therapy

Children with Severe IgA Nephropathy

- Age ≤15 yr
- No previous treatment with corticosteroids or immunosuppressive drugs
- Primary end point
  - the disappearance of proteinuria urinary protein excretion <0.1 g/m2/day
- Secondary end points
  - urinary protein excretion at the end of treatment
  - the change in the % of sclerosed glomeruli
  - adverse effects
# Immunosuppressive Therapy

## Children with Severe IgA Nephropathy

### Group 1:
- 39 patients
- Follow-up 2 years
  - **Immunosuppressive + Supportive**
    - Prednisolone
      - 2mg/kg/d; 4 weeks
      - 2mg/kg/2d; 4 weeks
      - 1.5mg/kg/2d; 4 weeks
      - 1mg/kg/2d; 21 months
    - Azathioprine 2mg/kg/d
    - Heparin/Warf
    - Dipyridamol 5mg/kg/d

### Group 2:
- 39 patients
- Follow-up 2 years
  - **Prednisolone alone**
    - Prednisolone
      - 2mg/kg/d; 4 weeks
      - 2mg/kg/2d; 4 weeks
      - 1.5mg/kg/2d; 4 weeks
      - 1mg/kg/2d; 21 months

The use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was prohibited.

Immunosuppressive Therapy

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The rate of reaching the primary end point
Combination group 92.3 % vs Prednisolone alone group 74.4 %

Sclerosed glomeruli %
Combination group; unchange Pred group; increase (significantly)

Adverse effects %; similar

Combination treatment may be better for children with severe IgAN than treatment with prednisolone alone.

Since AZA regimen had often to be stopped due to toxicity
In 2008, Yoshikawa et al. further reported the results of a pilot study of mizoribine instead of azathioprine as part of the combination therapy for treating
Mizoribine, like AZA, is an antimetabolite that exerts its immunosuppressant effect by inhibiting lymphocyte proliferation
Mizoribine was given orally at a dose of 5 mg/kg body weight per day in two divided doses for a total dose of not more than 150 mg/day for 24 months
Primary end point; (urine protein/creatinine ratio <0.2) during the 2-year treatment
Age, between 7-12 yrs, 23 children

The cumulative disappearance rate of proteinuria determined by Kaplan-Meier was 80.4%.

After treatment, the median percentage of glomeruli showing sclerosis was unchanged in comparison with that before treatment.

The efficacy and safety of the mizoribine combination seem to be acceptable for treating children with severe IgAN.

Yoshikawa, Ped Nephrol 2008
There is no trial in children with IgAN

- The efficacy of MMF therapy was evaluated by three small, prospective placebo-controlled randomized trials that were associated with conflicting results.
- MMF should be only considered in selected patients.
- Cyclosporine appears to be effective treatment of nephrotic-range proteinuria in Henoch-Schönlein purpura.
- Although proteinuria may be reduced, calcineurin inhibitors has been limited by the associated nephrotoxicity in IgAN.
- Some studies showed that rising in creatinine was greater than the untreated patients.

Mycophenolate mofetil (MMF) and calcineurin inhibitors
Crescentic glomerulonephritis

• The treatment of crescentic, rapidly progressive glomerulonephritis in patients with IgA nephropathy has not been evaluated in randomized trials

• Observational data suggest possible benefit from regimens similar to those used in idiopathic crescentic glomerulonephritis

• Intravenous pulse methylprednisolone followed by oral prednisone, intravenous or oral cyclophosphamide, and/or plasmapheresis

Tumlin, Nephrol Dial Transplant 2003
UpToDate, 2016
• Should inform but not dictate, guide but not enforce, and support but not restrict

• The 2012 Kidney Disease: Improving Global Outcomes (KDIGO)
• The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)
• Canadian Society of Nephrology commentary
• Japanese Clinical Practice Guidelines for IgA Nephropathy
• Japanese Guidelines for the Treatment of Childhood IgAN
Japanese Guidelines for the Treatment of Childhood IgAN

The treatment of mild childhood IgA nephropathy

The definition of mild childhood IgA nephropathy

The childhood IgA nephropathy filled with all the following criteria

- Clinical findings: mild proteinuria (early morning urinary protein/creatinine ratio less than 1.0 g/g creatinine)

- Pathological findings: moderate or more mesangial proliferation, adhesion, or sclerosis observed in less than 80 % of glomeruli and crescent in less than 30 % of glomeruli
The treatment of mild childhood IgA nephropathy

Guidelines for treatment

Either one of the following treatment is recommended

1. Angiotensin-converting enzyme blocker:
   - Lisinopril 0.4 mg/kg/day once a day (maximum dose: 20 mg/day)
     (Note 1: teratogenicity)

2. Chinese herb:
   - Sairei-to one pack/day, twice a day (body weight 20 kg or less);
     two packs/day, twice a day (body weight 20–40 kg); three packs/day, three times a day (body weight 40 kg or more) (Note 2)
     - Note: One pack of sairei-to is 3 g of TUMURA sairei-to granules and 2.7 g of KANEBOU sairei-to granules
• The treatment of severe childhood IgA nephropathy

• The definition of severe childhood IgA nephropathy

• The childhood IgA nephropathy filled with all the following criteria

• Clinical findings: severe proteinuria (early morning urinary protein/creatinine ratio 1.0 or more g/g creatinine)

• Pathological findings: moderate or more mesangial proliferation, adhesion, or sclerosis observed in 80% or more of glomeruli and crescent in 30% or more of glomeruli

*These guidelines do not cover the patients with rapidly progressive glomerulonephritis syndrome
• The treatment of severe childhood IgA nephropathy

• Guidelines for treatment
  • Combination treatment (cocktail treatment) with adrenocorticosteroid, immunosuppressant, anticoagulant, and antiplatelet drug for 2 years is recommended

I. Adrenocorticosteroid: oral prednisolone
   (A) 2 mg/kg/day (maximum dose: 80 mg/day), three times a day, daily for 4 weeks
   (B) Then, 2 mg/kg/day, once a day, alternative day and gradually taper and discontinue. Standard duration of treatment is 2 years

II. Immunosuppressant:
   oral azathioprine or mizoribine
   Azathioprine; 2 mg/kg/day (maximum dose: 100 mg/day), once a day, for 2 years
   Mizoribine; 4 mg/kg/day (maximum dose: 150 mg/day), twice a day, for 2 years
• The treatment of mild childhood IgA nephropathy
  • Guidelines for treatment
    • Combination treatment (cocktail treatment) with adrenocorticosteroid, immunosuppressant, anticoagulant, and antiplatelet drug for 2 years is recommended

III. Anticoagulant:
  Oral warfarin potassium, once a day in the morning.
  Dosage should be adjusted for 20–50 % of thrombotest
  Start with 0.5–1.0 mg/day for safety

IV. Antiplatelet drug:
  Oral dipyridamole; start with 3 mg/kg/day, three times a day, and 1 week later, if no side effect occurs, 6–7 mg/kg/day (maximum dose: 300 mg/day)