Current Evidence-Based Management of IgA Nephropathy

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IgA nephropathy is heterogenous

- IgAN has a **wide spectrum of clinical presentations**, varying from isolated hematuria to rapidly progressive glomerulonephritis.

- **Different rate of progression** to renal failure.

- Thorough risk assessment is essential to determine management and ensure that the **risks of therapy are balanced by the selection of patients at highest risk of progression**.
Progression of Early IgA Nephropathy

Cumulative Probability of clinical events (%)

- Proteinuria > 1g/d
- Hypertension
- Impaired renal function

Number at risk:
- Proteinuria: 72 49 26 16 10
- Hypertension: 72 60 36 20 12
- Impaired renal function: 72 65 44 28 18

Follow up (years)
0 3 6 9 12

Initial evaluation including assessment of risk of progressive renal disease

- 10.1.3: We suggest the use of pathological features to assess prognosis. *(Not Graded)*

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The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification


IgA nephropathy is the most common glomerular disease worldwide, yet there is no international consensus for its clinicopathological classification. The Oxford Classification of IgA nephropathy was developed to define independent variables predicting renal outcome. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.


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Recommendations for the pathology report

Minimum prognostic data:

- Glomerular “pattern”:
  - Mesangial hypercellularity in > or <50% of glomeruli (M 0/1)
  - Endocapillary hypercellularity – present/absent (E 0/1)
  - Segmental sclerosis/adhesions – present/absent (S 0/1)
  - Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50% (T 0/1/2)

In addition:
- Total number of glomeruli
- Endocapillary proliferation - %
- Cellular/fibrocellular crescents - %
- Necrosis - %
- Global glomerulosclerosis - %

Example summary line: There is an IgA nephropathy showing diffuse mesangial proliferation with focal segmental sclerosis and moderate chronic tubulointerstitial damage (M1,E0,S1,T1)

Pathology

- There is low quality evidence to suggest renal biopsy findings associated with a worse prognosis are the presence and severity of mesangial and endocapillary proliferation, extensive crescents, focal and segmental as well as global glomerulosclerosis, tubular atrophy and interstitial fibrosis
  - (Cattran et al; Roberts et al. KI Sept 2009).

- However no single approach to the objective evaluation of biopsy findings has yet been validated or evaluated prospectively.

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Antiproteinuric & antihypertensive therapy

- **We recommend** long-term ACEi or ARB treatment when proteinuria is >1 g/d. (1B)

- **We suggest** ACEi or ARB treatment if proteinuria is between 0.5 to 1 g/d [in children between 0.5 to 1 g/d per 1.73 m²]. (2D)

- **We suggest** the ACEi or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (2C)

- The goal of blood pressure treatment in IgAN should be < 130/80 mmHg in patients with proteinuria <1 g/d and < 125/75 mmHg when initial proteinuria is >1 g/day. (Not Graded)

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Renal survival by category of time-average -proteinuria

- <0.3 g/day
- 0.3-1 g/day
- 1-2 g/day
- 2-3 g/day
- >3 g/day

Renal survival by category of time-average proteinuria

- Rate of decline of function increased with the amount of proteinuria;
- Those with sustained proteinuria ≥3 g/d lost renal function 25-fold faster than those with <1 g/d.
- Patients who presented with ≥3 g/d who achieved proteinuria <1 g/d had a similar course to patients who had <1 g/d throughout, and fared far better than patients who never achieved this.
- There is as yet no evidence in IgAN that reducing proteinuria below 1g/d in adults gives additional benefit.

ACEI or ARB
Summary of Evidence Profiles

- Quality of Evidence for Outcome
  - ESRD Very Low
  - Proteinuria (Categorical) Moderate
  - Kidney Function (Categorical) Moderate

- Consistency across studies
  - No important inconsistencies
ACEI or ARB Summary of Evidence Profiles

<table>
<thead>
<tr>
<th>Balance of potential benefits and harm</th>
<th>Quality of overall evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Benefits of ACEI or ARB</td>
<td>– Moderate</td>
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Corticosteroids

- We suggest that patients with persistent proteinuria $\geq 1$ g/d despite 3-6 months of optimized supportive care (including ACEi or ARB and blood pressure control) and GFR $>50$ mL/min receive a 6 month course of corticosteroid therapy. (2B)
Corticosteroid regimens in patients with IgA nephropathy

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<tbody>
<tr>
<td>Regimen:</td>
<td>i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3 and 5 followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months</td>
<td>6 month regime of oral prednisone* starting with 0.8-1mg/kg/d for 2 months and then reduced by 0.2mg/kg/d per month for the next 4 months</td>
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</table>

*only about 15% of the patients had received an ACE inhibitor at randomization and BP control was not optimal by contemporary standards

A major limitation of both studies is that all ACEI and ARBs had to be halted for 1 month prior to study inclusion and then an ACEI was started together with corticosteroids in the combination group. Therefore a number of low risk patients may have been included, who would have achieved proteinuria < 1 g/d with ACEI therapy alone.

Steroids in IgA Nephropathy

- A Japanese RCT which used low dose corticosteroids (20 mg/d prednisolone, tapered to 5 mg/d by 2 years) observed no benefit on renal function despite reduced proteinuria with the corticosteroid regimen (Katafuchi R et al AJKD 2003).

- Subjects with IgAN and GFR< 50 ml/min were either excluded from these trials (Pozzi C et al Lancet 1999; Manno C et al NDT 2001) or were few in number (Lv J et al AJKD 2009), so that currently there are no data to assess the value of corticosteroids in this population.

- A recent meta-analysis (Strippoli GF et al AJKD 2009) concluded that corticosteroids reduce doubling of serum creatinine. However, in that analysis, 85% of the weight was contributed by two studies (Pozzi C et al Lancet 1999, Kobayashi Y et al Nephron 1996), both of which lacked optimal antiproteinuric and antihypertensive therapy based on contemporary standards.
Steroid
Summary of Evidence Profiles

• Quality of Evidence for Outcome
  – ESRD Low
  – Proteinuria (Categorical) Low
  – Kidney Function (Categorical) Very Low

• Consistency across studies
  – No important inconsistencies

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Steroid
Summary of Evidence Profiles

Balance of potential benefits and harm
Quality of overall evidence

– Benefits of steroid  – Low to very low

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Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)

- We do not suggest treatment with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating renal function). (2D)

- We suggest not using immunosuppressive therapy in patients with GFR <30 mL/min unless there is crescentic IgAN with rapidly deteriorating renal function. (2C)

- We do not suggest the use of MMF in IgAN. (2C)

An RCT using Corticosteroids combined with cyclophosphamide followed by azathioprine

There are limitations in the applicability of the findings:
- a) there was no steroid monotherapy arm;
- b) use of RAS blockade was not detailed but these agents could not be initiated after the start of the trial;
- c) the follow-up BP was higher than recommended by current guidelines.

Cyclophosphamide

- Two RCTs compared cyclophosphamide, dipyridamole, and warfarin to controls and found no benefit
  - Walker RG et al Clin Nephrol 1990
  - Woo KT & Lee GS Clin Nephrol 1991

- Together with the potential side effects, we do not suggest the use of cyclophosphamide monotherapy.

Azathioprine

- 2 RCTs have used azathioprine plus corticosteroids in adult patients with IgAN:

  - A Turkish RCT tested combined corticosteroid and azathioprine therapy in patients who presented with isolated hematuria and an almost normal GFR; however, such patients have an excellent prognosis and there is consensus that they should not receive immunosuppression.
Azathioprine

• A small British RCT used corticosteroids combined with cyclophosphamide followed by several years of azathioprine in patients with a serum creatinine level of 2 to 3 mg/dl plus a 15% rise within the previous year. The active treatment group achieved a much greater renal survival (72% 5-year survival compared with 6% in control subjects).
  
  – there are limitations of the British study: It studied a highly selected group of patients, there was no steroid monotherapy arm, and supportive therapy did not match today's standards.
  

Azathioprine

• a Japanese RCT of children with IgAN

  – compared a 2-year combination of prednisolone, azathioprine, warfarin, and dipyridamole with prednisolone alone.
  
  – There was complete remission of proteinuria in 92% of the patients who received the combination and in 74% of those who received prednisolone alone.
  
  – GFR remained normal in all children.
  
  – It may be difficult to justify an intense immunosuppression in children on the basis of that relatively soft end point.

Steroid vs Azathioprine + steroid study

- 6-month course of azathioprine to a 6-month corticosteroid regimen would further reduce the loss of GFR in high-risk, adult patients with IgAN.

- At inclusion, all patients exhibited a GFR of 50 ml/min per d and a proteinuria level of 1.5 to 3.5 g/d.
Azathioprine

- Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy

- Treatment-related adverse events were more frequent in the combination group (17%) as compared to the monotherapy group (6%; P=0.01).

MMF

- The findings from RCTs studying MMF in IgAN are variable:
  - A Belgian study (Maes BD et al KI 2004) assessed MMF 2 g/d for 3 years versus placebo in 34 patients with an average initial inulin clearance of 70 ml/min/1.73m² and proteinuria of 1.8 g/d. No difference in proteinuria reduction or preservation of GFR was observed.
  - A North American study (Frisch G et al NDT 2005) found no benefits over 24 months using a 1-year regimen of MMF 2 g/d versus placebo in 32 patients with an initial GFR of 40 mL/min/1.73m² and a proteinuria of 2.7 g/d.
MMF

- A Chinese study in 40 patients with a mean initial GFR of 72 mL/min/1.73m² and mean proteinuria 1.8 g/d found a significant reduction in proteinuria at 18 months with MMF given for 6 months over controls (Tang S et al KI 2005)

- A 6-year follow-up of the same cohort demonstrated a renal survival benefit (Tang S et al KI 2010)

- The antiproteinuric effect of the drug disappeared after nearly 2 years.

MMF

Summary of Evidence Profiles

- Quality of Evidence for Outcome
  - ESRD Low
  - Proteinuria (Categorical) Low
  - Kidney Function (Categorical) Very Low

- Consistency across studies
  - Important inconsistencies for ESRD and Kidney Function (Categorical)
### MMF

**Summary of Evidence Profiles**

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<tr>
<th>Balance of potential benefits and harm</th>
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<tr>
<td>– No difference for MMF</td>
<td>– Low</td>
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**MMF**

- **We do not suggest** the use of MMF in IgAN. (2C)

  - No steroid was given in these trials and all patients received ACE inhibitors.

  - The results of these studies are too heterogeneous to suggest the use of MMF at the present time.

  - The reasons for heterogeneity of outcome require further investigation but different ethnicity or differences in drug levels achieved may be contributory factors.

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Fish Oil

• We suggest using fish oil in the treatment of IgAN. (2D)

Fish Oil

• There is mostly low quality evidence that suggests using fish oil supplements in patients with IgAN but the RCTs evaluating this therapy have reported conflicting results.

• However, given the very low risk profile and the potentially beneficial cardiovascular effects, fish oil can be considered a very safe treatment.
Omega 3 Fatty Acid
Summary of Evidence Profiles

• Quality of Evidence for Outcome
  – ESRD Low
  – Proteinuria (Categorical) Very Low
  – Kidney Function (Categorical) Very Low

• Consistency across studies
  – Important inconsistencies for Kidney Function (Categorical)

Balance of potential benefits and harm Quality of overall evidence

– Benefit for Omega 3 Fatty Acid – Low or very low

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Antiplatelet agents

- We suggest not using antiplatelet agents to treat IgAN. (2C)

Dipyridamole was the most commonly used antiplatelet agent (five studies) followed by trimetazidine and Dilazep (one study each).

Antiplatelet Therapy

- Description of limitations of evidence by authors
  - Suboptimal quality of individual controlled trials
  - Most studies did not assess true outcome of renal death
  - Long-term follow-up studies may yield different set of results
  - The effect of antiplatelet agents alone could not be discerned because patients received other concomitant therapies.
Tonsillectomy

- We suggest that tonsillectomy not be performed for IgAN. (2C)

- Only retrospective analyses (Hotta O et al AJKD 2001; Xie Y et al Kidney Int 2003) as well as one non-randomized trial (Komatsu H et al CJASN 2008) have reported a better outcome for IgAN after tonsillectomy.

- In these studies, tonsillectomy was often combined with other, in particular, immunosuppressive treatment (Hotta O et al AJKD 2001; Xie Y et al Kidney Int 2003; Komatsu H et al CJASN 2008) and thus the specific value of tonsillectomy is not always apparent.

- Furthermore, in other retrospective series, investigators failed to note a benefit from tonsillectomy (Rasche FM et al Clin Nephrol 1999).
Minimal change disease with mesangial IgA deposits

- We suggest treatment as for minimal change disease in nephrotic patients showing pathological findings of minimal change disease with mesangial IgA deposits on kidney biopsy. (2B)

- Patients with nephrotic syndrome and a pathological diagnosis of coincidental minimal change disease and IgAN

- A high percentage (80%) of complete remission in patients using steroid

Crescentic IgAN

- We suggest the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (2D).

- There is no RCT of treatment in crescentic IgAN.

- The three largest observational studies all concluded that immunosuppression is potentially useful.

Crescentic IgAN

- In a study of 25 patients with diffuse crescentic IgAN treated with immunosuppression, 67% of patients maintained sufficient kidney function to avoid renal replacement therapy. 4 had sCr < 124 μmol/l, and only 5 were dialysis-dependent. [Tang Z Clin Nephrol 2002]

- In another study, although an improved outcome was seen in those that receiving immunosuppression their conclusions were cautious as the treated and untreated groups were not comparable. [Pankhurst Nephron Clin Pract 2009]

- The third study also suggests positive effects of immunosuppression [Tumlin JA et al Nephrol Dial Transplant 2003]. They used IV methylprednisolone 15 mg/kg/day for 3 days and monthly IV cyclophosphamide 0.5 g/m² for 6 months. Twelve treated patients were compared with 12 historical controls. After 36 months, the rate of ESRD in the treated group was lower (one out of 12) than in the historical controls (5 out of 12).

Research Recommendations

- An RCT of fish oil in IgAN with preserved renal function with persistent significant proteinuria despite optimal antihypertensive and antiproteinuric therapy.

- An RCT is required comparing MMF with corticosteroids versus corticosteroids alone in patients receiving optimal antihypertensive and antiproteinuric therapy.

- An RCT to investigate the different efficacy of MMF in Asians vs. Caucasians including evaluation of drug and metabolite levels.
Thank you