Current Evidence-Based Management of IgA Nephropathy

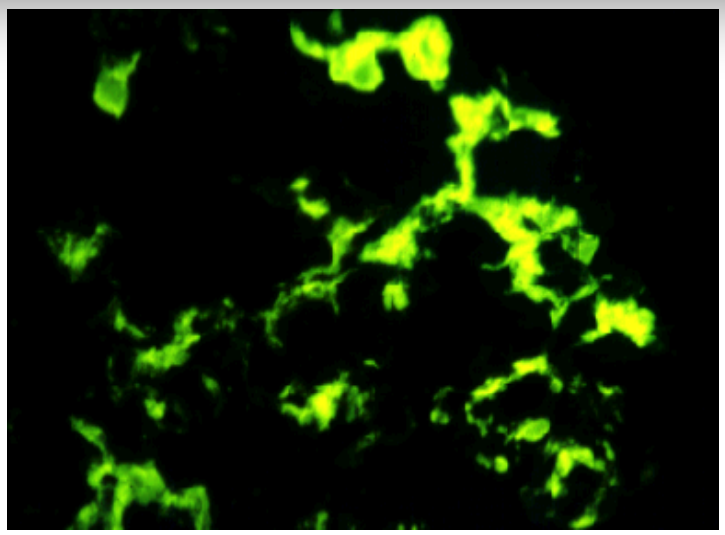
www.kdigo.org

Philip K.T. Li
MD, FRCP, FACP

Honorary Professor of Medicine
Chief of Nephrology & Consultant

Department of Medicine and Therapeutics
Prince of Wales Hospital
Chinese University of Hong Kong

IgA Nephropathy



Kidney Disease: Improving Global Outcomes

www.kdigo.org

IgA nephropathy is heterogenous

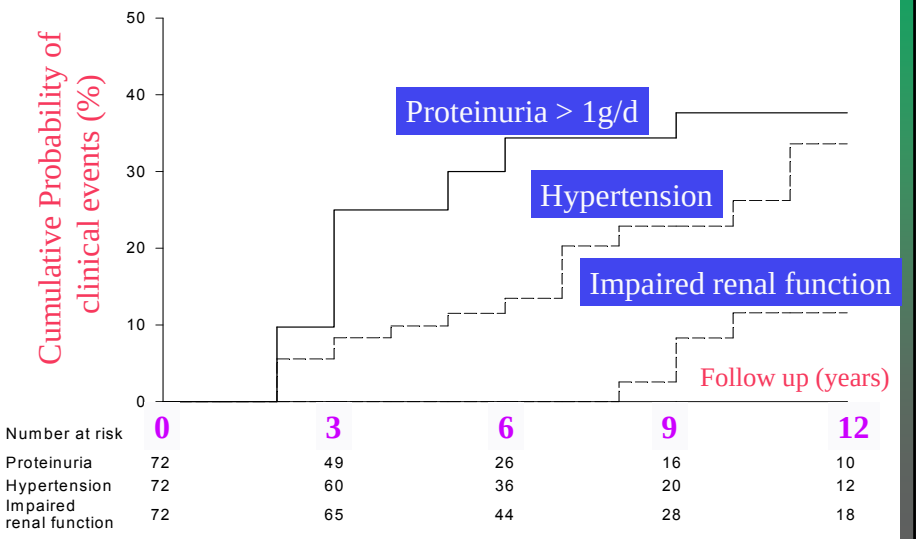
- IgAN has a wide spectrum of clinical presentations, varying from isolated hematuria to rapidly progressive glomerulonephritis.
- Different rate of progression to renal failure.
- Thorough risk assessment is essential to determine management and ensure that the risks of therapy are balanced by the selection of patients at highest risk of progression.

Kidney Disease: Improving Global Outcomes

www.kdigo.org

Progression of Early IgA Nephropathy

Figure 1



Number at risk	0	3	6	9	12
Proteinuria	72	49	26	16	10
Hypertension	72	60	36	20	12
Impaired renal function	72	65	44	28	18

Szeto CC,…Li PKT. Am J Med 2001; 110: 434-7

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*)

original article http://www.kidney-international.org

see commentary on page 477

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

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Daniel C. Cattran[1,†], Rosanna Coppo[2,†], H. Terence Cook[3,†], John Feehally[4,†], Ian S.D. Roberts[5,†], Stéphan Troyanov[6,†], Charles E. Alpers[7], Alessandro Amore[2], Jonathan Barratt[4], Francois Berthoux[8], Stephen Bonsib[9], Jan A. Bruijn[10], Vivette D'Agati[11], Giuseppe D'Amico[12], Steven Emancipator[13], Francesco Emma[14], Franco Ferrario[15], Fernando C. Fervenza[16], Sandrine Florquin[17], Agnes Fogo[18], Colin C. Geddes[19], Hermann-Josef Groene[20], Mark Haas[21], Andrew M. Herzenberg[22], Prue A. Hill[23], Ronald J. Hogg[24], Stephen I. Hsu[25], J. Charles Jennette[26], Kensuke Joh[27], Bruce A. Julian[28], Tetsuya Kawamura[29], Fernand M. Lai[30], Chi Bon Leung[31], Lei-Shi Li[32], Philip K.T. Li[31], Zhi-Hong Liu[32], Bruce Mackinnon[19], Sergio Mezzano[33], F. Paolo Schena[34], Yasuhiko Tomino[35], Patrick D. Walker[36], Haiyan Wang[37], Jan J. Weening[38], Nori Yoshikawa[39] and Hong Zhang[37,*]

IgA nephropathy is the most common glomerular disease worldwide, yet there is no international consensus for its

follow-up. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.

Oxford Classification of IgA nephropathy

Independent pathological variables predicting renal outcome

- mesangial hypercellularity,
- segmental glomerulosclerosis
- endocapillary hypercellularity
- tubular atrophy/ interstitial fibrosis.

Cattran DC, et al. Kidney Int 2009

Kidney Disease: Improving Global Outcomes

www.kdigo.org

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)

Roberts IS, et al. Kidney Int 2009 Sep;76(5):546-56.

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.

Kidney Disease: Improving Global Outcomes

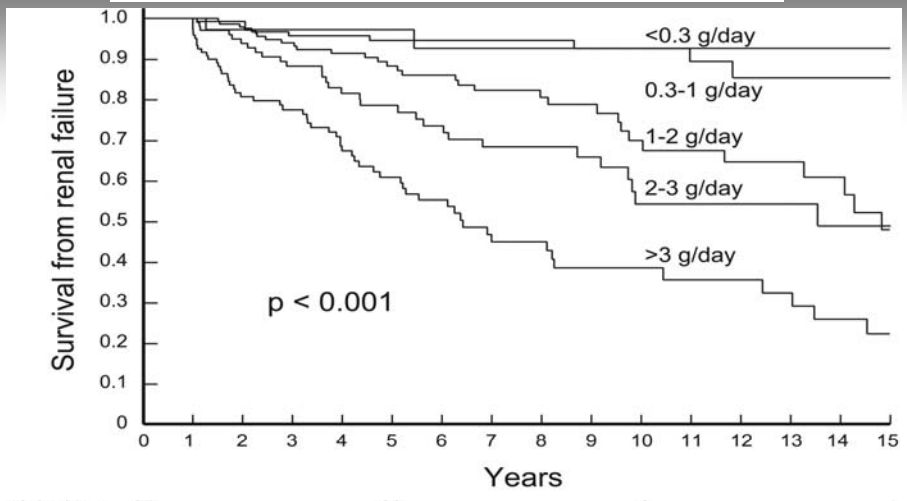
Antiproteinuric & antihypertensive therapy

- **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)

Kidney Disease: Improving Global Outcomes

www.kdigo.org

Renal survival by category of time-average -proteinuria



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Reich HN, et al. J Am Soc Nephrol 18: 3177-3183, 2007

www.kdigo.org

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.

Kidney Disease: Improving Global Outcomes

Reich HN, et al. J Am Soc Nephrol 18: 3177-3183, 2007

www.kdigo.org

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

Kidney Disease: Improving Global Outcomes

www.kdigo.org

ACEI or ARB
Summary of Evidence Profiles

Balance of potential benefits and harm	Quality of overall evidence
– Benefits of ACEI or ARB	– Moderate

Kidney Disease: Improving Global Outcomes

www.kdigo.org

Corticosteroids

- We suggest that patients with persistent proteinuria ≥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)

Kidney Disease: Improving Global Outcomes

www.kdigo.org

Corticosteroid regimens in patients with IgA nephropathy

References:	Pozzi C et al Lancet 1999	Manno C et al NDT 2009; Lv J et al AJKD 2009
Regimen:	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	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

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

Steroid
Summary of Evidence Profiles

Balance of potential benefits and harm	Quality of overall evidence
– Benefits of steroid	– Low to very low

Kidney Disease: Improving Global Outcomes
www.kdigo.org

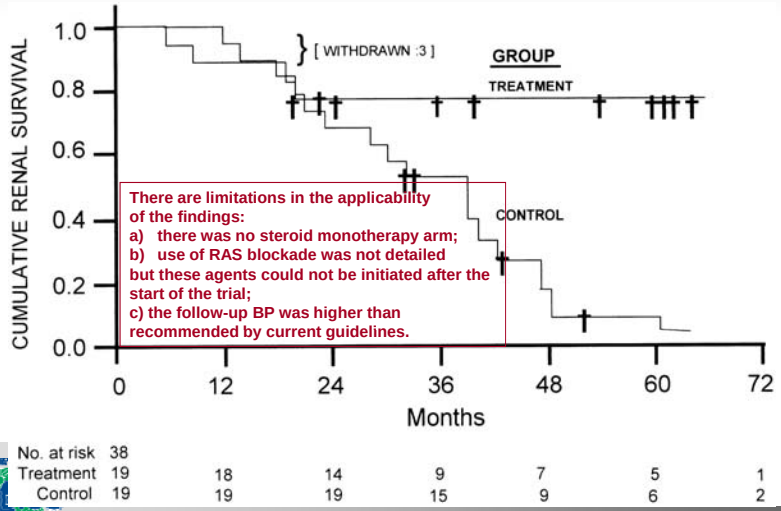
Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)

- 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*)

Kidney Disease: Improving Global Outcomes

www.kdigo.org

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.

Ballardie FW,et al, J Am Soc Nephrol 2002; 13:142-148

www.kdigo.org

Cyclophosphaimide

- 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.
  - (Harmankaya O, et al *Int Urol Nephrol* 2002; 33: 167–171)

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.
    - (Ballardie FW,et al, J Am Soc Nephrol 2002; 13:142-148)

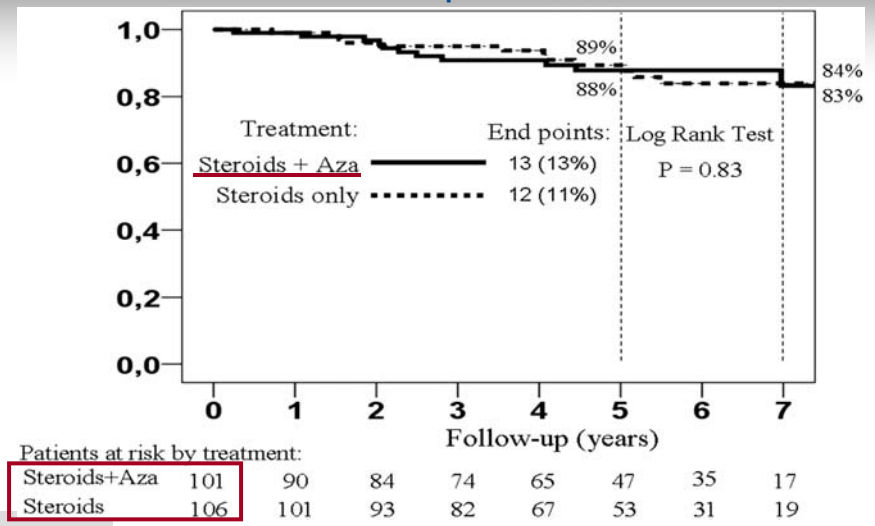
Azathioprine

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.

Yoshikawa N, et al. *Clin J Am Soc Nephrol* 2006; 1: 511–517

Kaplan-Meier renal survival curves : time to a 50% increase in plasma creatinine levels



Kidney Disease: Improving Global Outcomes

Pozzi C, et al. J Am Soc Nephrol. 2010 Oct;21(10):1783-90 www.kdigo.org

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.

Kidney Disease: Improving Global Outcomes

Pozzi C, et al. J Am Soc Nephrol. 2010 Oct;21(10):1783-90 www.kdigo.org

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).

Pozzi C, et al. J Am Soc Nephrol. 2010 Oct;21(10):1783-90

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)

Kidney Disease: Improving Global Outcomes

www.kdigo.org

MMF
Summary of Evidence Profiles

Balance of potential benefits and harm	Quality of overall evidence
– No difference for MMF	– Low

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.

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)

Omega 3 Fatty Acid
Summary of Evidence Profiles

Balance of potential benefits and harm	Quality of overall evidence
– Benefit for Omega 3 Fatty Acid	– Low or very low

Kidney Disease: Improving Global Outcomes
www.kdigo.org

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*)

Tonsillectomy

- 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*)

Minimal change disease with mesangial IgA deposits

- 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

Lai KN, et al. Clin Nephrol 1986; 26: 174-180

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*)

Crescentic IgAN

- There is no RCT of treatment in crescentic IgAN.
- The three largest observational studies all concluded that immunosuppression is potentially useful.

[Tang Z Clin Nephrol 2002, Tumlin JA et al Nephrol Dial Transplant 2003, Pankhurst Nephron Clin Pract 2009]

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 immunosupression [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

www.kdigo.org