Chapter 10: Immunoglobulin A nephropathy

Kidney International Supplements (2012) **2,** 209–217; doi:10.1038/kisup.2012.23

INTRODUCTION

This chapter makes treatment recommendations for primary IgAN. Secondary IgAN will not be discussed. The cost implications for global application of this guideline are addressed in Chapter 2.

10.1: Initial evaluation including assessment of risk of progressive kidney disease

10.1.1: Assess all patients with biopsy-proven IgAN for secondary causes of IgAN. (*Not Graded*)

10.1.2: Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (*Not Graded*)

10.1.3: Pathological features may be used to assess prognosis. (*Not Graded*)

BACKGROUND

IgAN is diagnosed by kidney biopsy and is defined as dominant or codominant staining with IgA in glomeruli by immunohistology.[470] LN should be excluded. The intensity of IgA staining should be more than trace. The distribution of IgA staining should include presence in the mesangium, with or without capillary loop staining. IgG and IgM may be present, but not in greater intensity than IgA, except that IgM may be prominent in sclerotic areas. C3 may be present. The presence of C1q staining in more than trace intensity should prompt consideration of LN.

IgAN is the most common primary GN in the world. The prevalence rate varies across different geographical regions. Typically, it is 30–35% of all primary glomerular diseases in Asia, but can be up to 45%.[471] In Europe, this is about 30–40%. Recently in the USA, IgAN was also reported to be the most common primary glomerulopathy in young adult Caucasians.[472]

Secondary IgAN is uncommon. Cirrhosis, celiac disease, and HIV infection are all associated with a high frequency of glomerular IgA deposition. IgAN has been infrequently associated with a variety of other diseases, including dermatitis herpetiformis, seronegative arthritis (particularly ankylosing spondylitis), small-cell carcinoma, lymphoma (Hodgkin lymphoma and T-cell lymphomas, including mycosis fungoides), disseminated tuberculosis, bronchiolitis obliterans, and inflammatory bowel disease (Crohn's disease and ulcerative colitis). These are usually clinically evident at the time of biopsy. Investigations can include viral serologies (HIV, HBV, and HCV), liver function tests, and electrophoreses of serum immunoglobulins.

IgAN has a wide spectrum of clinical presentations, varying from isolated hematuria to rapidly progressive GN. 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. Definitive outcomes in IgAN are kidney survival and the rate of kidney function decline. Determinants of mortality in IgAN have not been addressed in previous studies, although it is reasonable to assume that CKD increases cardiovascular morbidity and mortality in these patients, as in others with CKD.[473]

RATIONALE

- There is moderate-quality evidence to suggest that accelerated decline in kidney function is associated with proteinuria ≥ 1 g/d in a dose-dependent fashion and independently of other risk factors.[474–477]
- There is moderate-quality evidence to suggest a favourable outcome when time-averaged proteinuria is reduced to <1 g/d.[477] Whether long-term outcome differs in adult patients with a proteinuria between 0.5 and 1.0 g/d compared to <0.5 g/d remains uncertain. In children, expert opinion suggests a goal of proteinuria <0.5 g/d per 1.73 m^2.[478]
- There is moderate-quality evidence to recommend strict blood pressure control, as it is associated with better kidney survival in chronic proteinuric nephropathies, including IgAN.
- There is low-quality evidence to suggest GFR at presentation is associated with the risk of ESRD. However, studies that have assessed the rate of change of kidney function have questioned its association with initial GFR. Proteinuria, blood pressure, and kidney biopsy findings at presentation have been associated with both risk of ESRD and doubling of SCr.
- There is low-quality evidence to suggest kidney 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.[470,479] However, no single approach to the objective evaluation of biopsy findings has yet been validated or evaluated prospectively.
- There is moderate-quality evidence to suggest that IgAN that presents with hematuria and minimal proteinuria is a progressive disease, and that life-long follow-up with regular monitoring of blood pressure and proteinuria is recommended.[480]

Proteinuria is the strongest prognostic factor in IgAN and has a "dose-dependent" effect that is independent of other risk factors in multiple large observational studies, as well as prospective trials. The threshold above which the risk develops in adults is uncertain; some studies indicate 0.5 g/d[481] while others could only demonstrate a higher risk of ESRD and a more rapid rate of decline in kidney function when time-averaged proteinuria was above 1 g/d.[474,477] A large observational study demonstrated that a reduction of proteinuria to <1 g/d carried the same favorable impact on long-term outcome, whether the initial value was 1–2 g/d, 2–3 g/d, or >3 g/d.[477] Other surrogates of long-term outcome, such as a 50% decline in proteinuria, have been used.[482] In children, observational studies have also consistently shown a relationship between the level of proteinuria and outcome, but did not assess a threshold value. Expert opinions in children advocate a cut-off of 0.5 g/d per 1.73 m^2 for partial remission, and 0.16 g/d per 1.73 m^2 for complete remission; these thresholds have been used in RCTs.[478,483]

Uncontrolled hypertension during follow-up is associated with greater proteinuria and predicts a faster GFR decline.[484,485] As in other proteinuric chronic glomerulopathies, a blood pressure goal $<130/80$ mm Hg in patients with proteinuria >0.3 g/d, and $<125/75$ mm Hg when proteinuria is >1 g/d, is recommended.[486,487]

The GFR at presentation has consistently been related to the risk of ESRD. Whether a lower GFR is also accompanied by a faster rate of kidney function decline is questionable; two observational studies have failed to show this relationship.[475,488] Proteinuria, blood pressure, and pathological features should take precedence over initial GFR in the estimation of the future rate of kidney function decline.

Numerous studies have addressed the predictive value of pathology findings. Mesangial[489,490] and endocapillary proliferation,[479,491] extensive crescents,[492–495] FSGS,[496,497] global glomerulosclerosis, tubular atrophy, and interstitial fibrosis[479,491,493,496] are associated with a more rapid rate of deterioration and lower kidney survival using univariate and, at times, multivariate analysis adjusting for clinical assessment. The recent Oxford Classification of IgAN has demonstrated the importance of (i) mesangial hypercellularity; (ii) segmental glomerulosclerosis; (iii) endocapillary hypercellularity; and (iv) tubular atrophy/interstitial fibrosis, as independent pathological variables predicting kidney outcome.[479] This may become the standard, but requires validation before it can be recommended in routine clinical practice. Whether classification of the disease in this manner should impact treatment choice has also not been determined.

Obesity has been identified as an independent risk factor for the appearance of ESRD,[498] and weight loss induces a significant decrease in proteinuria.[499] Some observational studies[500,501] have reported an increased risk of greater proteinuria, more severe pathological lesions, and ESRD among IgAN patients who are overweight (BMI >25 kg/m^2).

Other risk factors have also been studied. Outcomes do not differ between sexes.[217] Children are less likely to reach ESRD compared to adults, but this may be because GFR is higher at presentation in children, even though there is a similar rate of kidney function decline. Different biopsy and treatment practices in the pediatric population limit comparisons to adults. Since the risk factors presented above have been validated in both children and adults, clinicians should consider these before the age of the patient. Similarly, it is uncertain whether geographical or ethnic variations in outcomes are secondary to different biopsy and treatment practices or variations in disease severity.[475] Macroscopic hematuria is more frequent in children, and some studies have associated its presence with a favorable outcome, while others have shown this benefit to be confounded by a higher initial GFR and earlier detection with no independent value.[502,503]

10.2: Antiproteinuric and antihypertensive therapy

10.2.1: We recommend long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (*1B*)

10.2.2: We suggest ACE-I 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 m^2). (*2D*)

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

10.2.4: In IgAN, use blood pressure treatment goals of $<130/80$ mm Hg in patients with proteinuria <1 g/d, and $<125/75$ mm Hg when initial proteinuria is >1 g/d (see Chapter 2). (*Not Graded*)

RATIONALE

Many of the trials using ACE-I/ARBs in IgAN recruited patients with proteinuria ≥ 1 g/d[478,504] while some recruited patients with proteinuria ≥ 0.5 g/d.[505]

In registry data,[477] the rate of decline of function increased with the amount of proteinuria; those with sustained proteinuria ≥ 3 g/d lost kidney function 25-fold faster than those with proteinuria <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 level. There is, as yet, no evidence in IgAN that reducing proteinuria below 1 g/d in adults gives additional benefit.

Several RCTs[478,504–506] have shown that ACE-I and ARBs can reduce proteinuria and improve kidney function (assessed by reduction of the slope of GFR deterioration; Online Suppl Table 44). However, there is, as yet, no definitive study of sufficient duration to show the benefit of either ACE-I or ARBs in reducing the incidence of ESRD.

There are no data to suggest preference of ACE-I over ARBs, or vice versa, except in terms of a lesser side-effect profile with ARBs compared to ACE-I.

One study[507] suggested the combination of ACE-I and ARBs induced a 73% greater reduction of proteinuria than monotherapy (ACE-I 38% and ARB 30%, respectively). A small study of seven pediatric IgAN patients also showed some benefits[508] with a combination of ACE-I and ARB. However, more studies are needed to determine whether the definite benefit of combination therapy is effective, leading to a better kidney outcome.

RESEARCH RECOMMENDATION

- RCTs are needed to compare the efficacy in proteinuric IgAN of combination therapy using ACE-I and ARBs to monotherapy using either alone.

10.3: Corticosteroids

10.3.1: We suggest that patients with persistent proteinuria ≥ 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR > 50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

RATIONALE

- There is low-quality evidence that corticosteroids provide an additional benefit to optimized supportive care (Online Suppl Table 47).
- A 6-month corticosteroid regimen can follow either of two regimens, which have been used in published trials (see Table 26).
- There is no evidence to suggest the use of corticosteroids in patients with GFR < 50 ml/min.
- The available studies do not allow recommendations for preferred dosage regimens. The studies did not report serious side-effects. However, there are other studies with similar regimens in non-IgAN patients that suggest more side-effects with high-dose pulse corticosteroids, including hypothalamic-pituitary-adrenal axis suppression and acute myopathies.

Few RCTs so far have tested the efficacy of a corticosteroid regimen vs. no immunosuppressive therapy. In an Italian trial,[509] a 6-month course of corticosteroids led to better clinical disease remission and long-term outcome[512] than no steroids. However, only about 15% of the patients had received an ACE-I at randomization,[509] and blood pressure control was not optimal by contemporary standards.[513]

Two more recent RCTs[510,511,514] used oral prednisone added to an ACE-I and compared this to an ACE-I alone. In the Italian study,[510] the mean annual GFR loss was reduced from about -6 ml/min to -0.6 ml/min, and in the Chinese study[511] the proportion of patients with a 50% increase in SCr decreased from 24% to 3% with corticosteroid therapy. A major limitation of both studies is that all ACE-I and ARBs had to be halted for 1 month prior to study inclusion, and then an ACE-I 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 ACE-I therapy alone. A further potential confounder is that both studies included patients who had received prior immunosuppression. An American trial in adults and children, all of whom received an ACE-I, also noted reduced proteinuria with corticosteroids (60 mg/m^2 prednisone every other day tapered to 30 mg/m^2 at 12 months) but no difference in kidney function was observed at 2 years.[515]

A Japanese RCT that used low-dose corticosteroids (20 mg/d prednisolone, tapered to 5 mg/d by 2 years) observed no benefit on kidney function, despite reduced proteinuria with the corticosteroid regimen.[516]

Subjects with IgAN and GFR < 50 ml/min were either excluded from these trials[509,514] or were few in number,[511] so that currently, there are no data to assess the value of corticosteroids in this population.

A recent meta-analysis[517] concluded that corticosteroids reduce doubling of SCr. However, in that analysis, 85% of the weight was contributed by two studies,[509,518] both of which lacked optimal antiproteinuric and antihypertensive therapy based on contemporary standards. Of note, an American RCT in children and adults with IgAN[515] noted no difference in reaching the endpoint (> 40% decrease in GFR) between a group receiving ACE-I only vs. ACE-I plus prednisone (60 mg/m^2 per 48 hours for 3 months, reduced to 30 mg/m^2 per 48 hours at month 12). However, few end-points were reached in this trial; thus, it was underpowered to detect small differences.

RESEARCH RECOMMENDATION

- Studies using immunosuppressive agents should always include rigorous blood pressure control and antiproteinuric therapy. This is currently being tested in the STOP-IgAN trial.[519] Newer immunosuppressives (alone or in combination) should be compared in RCTs to a "control" group receiving corticosteroids alone.

Table 26 | Corticosteroid regimens in patients with IgAN

References	Pozzi C *et al.*[509]	Manno C *et al.*[510]; Lv J *et al.*[511]
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[a] starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

IgAN, immunoglobulin A nephropathy.
[a]Prednisone and prednisolone are equivalent and can be used interchangeably with the same dosing regimen.

10.4: Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)

10.4.1: We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (*2D*)

10.4.2: We suggest not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (*2C*)

10.4.3: We suggest not using MMF in IgAN. (*2C*)

RATIONALE

Please consult Online Suppl Tables 51–60

- There is very low–quality evidence from a single RCT in high-risk adults to use a combination of prednisolone (40 mg/d reduced to 10 mg/d by 2 years) and cyclophosphamide (1.5 mg/kg/d) for 3 months, followed by azathioprine (1.5 mg/kg/d) for a minimum of 2 years. This study showed a better kidney survival over controls in a highly selected group of patients.
- There is insufficient evidence that immunosuppressive agents other than steroids used as first-line therapy offer an advantage or equivalence compared to steroids.
- The risk-benefit assessment is strongly impacted by the potential for severe adverse effects of these drugs.

Despite retrospective studies in IgAN supporting the use of immunosuppressive therapy other than corticosteroids, few RCTs have demonstrated a benefit. An RCT using corticosteroids combined with cyclophosphamide, followed by azathioprine, included a highly selected group of patients with SCr >1.47–2.83 mg/dl (>130–250 μmol/l) with a 15% increase within the last year, and initial proteinuria 3.9 ± 0.8 and 4.6 ± 0.4 g/d in the treatment and control groups, respectively. The active treatment group achieved lower proteinuria, a 4-fold lower rate of kidney function decline, and a much greater kidney survival (72% 5-year survival compared to 6% in controls, $P = 0.006$). There are limitations in the applicability of the findings: (i) there was no steroid monotherapy arm; (ii) the use of RAS blockade was not detailed but these agents could not be initiated after the start of the trial; (iii) the follow-up blood pressure was higher than recommended by current guidelines.

Two RCTs compared cyclophosphamide, dipyridamole, and warfarin to controls and found no benefit.[520,521] Given these results and the potential side-effects, we do not suggest the use of cyclophosphamide monotherapy.

Azathioprine

Two RCTs, one in children and another in children and adults, tested azathioprine and corticosteroids in patients with preserved kidney function. They demonstrated a reduction in chronic lesions compared to controls on repeat biopsy.[483,522] Monotherapy with steroids has been shown to preserve kidney function (a plausible surrogate for reduced chronic lesions). In a recent trial in patients with IgAN,[523] adding low-dose azathioprine for 6 months did not increase the benefit of corticosteroids alone, but did increase the occurrence of adverse events.

A study in 80 children with newly diagnosed IgAN[524] compared the effects of the combination of prednisolone, azathioprine, warfarin, and dipyridamole with those of prednisolone alone. There was complete remission of proteinuria (<0.1 g/m^2/d) in 36 (92.3%) of the 39 patients who received the combination and 29 (74.4%) of the 39 who received prednisolone alone ($P = 0.007$). Some side-effects were observed including leucopenia, glaucoma, and aseptic necrosis. The percentage of sclerosed glomeruli was unchanged in the patients who received the combination, but increased in the prednisolone group. In summary of these studies, we do not suggest the addition of azathioprine to corticosteroids for the treatment of IgAN.

An RCT compared 6 months of treatment with corticosteroids plus azathioprine or corticosteroids alone in 207 IgAN patients with plasma creatinine ≤ 2.0 mg/dl (≤ 177 μmol/l) and proteinuria ≥ 1 g/d. After a median follow-up of 4.9 years, a 50% increase in plasma creatinine from baseline occurred in 13% of the combination group and 11% of the monotherapy group ($P = 0.83$); effects on proteinuria and 5-year cumulative kidney survival were also similar in both groups (88% vs. 89%; $P = 0.83$). Treatment-related adverse events were more frequent in the combination group (17%) as compared to the monotherapy group (6%; $P = 0.01$). Thus, in this study, 6 months of treatment with azathioprine did not increase the benefit obtained from steroids alone, but increased the occurrence of adverse events.[523]

MMF

The findings from RCTs studying MMF in IgAN are variable. A Belgian study[525] assessed MMF 2 g/d for 3 years vs. placebo in 34 patients with an average initial inulin clearance of 70 ml/min per 1.73 m^2 and proteinuria of 1.8 g/d. No difference in proteinuria reduction or preservation of GFR was observed. Similarly, a North American study[482] found no benefits over 24 months using a 1-year regimen of MMF 2 g/d vs. placebo in 32 patients with an initial GFR of 40 ml/min per 1.73 m^2 and a proteinuria of 2.7 g/d. In contrast, a Chinese study in 40 patients with a mean initial GFR of 72 ml/min per 1.73 m^2 and mean proteinuria 1.8 g/d found a significant reduction in proteinuria at 18 months with MMF given for 6 months over controls.[526] A 6-year follow-up of the same cohort demonstrated a kidney survival benefit.[527] No steroid was given in these trials, and all patients received ACE-I. 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. Of note is a retrospective cohort

study that suggested delayed severe pneumonia could occur in MMF-treated patients with IgAN.[528] The potential side-effects of using MMF and the heterogeneity of outcomes from these data require better-performed studies before this drug can be recommended as first-line therapy.

Steroid Resistance

The approach to patients, who have no benefit in response to corticosteroids added to optimal antihypertensive and antiproteinuric therapy is unknown; no relevant RCTs have been conducted.

RESEARCH RECOMMENDATIONS

- An RCT is needed comparing MMF and corticosteroids vs. corticosteroids alone in patients receiving optimal antihypertensive and antiproteinuric therapy.
- An RCT is needed to investigate the different efficacy of MMF in Asians vs. Caucasians, including evaluation of drug and metabolite levels.

10.5: Other treatments

10.5.1: Fish oil treatment

10.5.1.1: We suggest using fish oil in the treatment of IgAN with persistent proteinuria $\geq$1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (*2D*)

BACKGROUND

Fish oil supplements have shown a number of beneficial cardiovascular effects, including systolic blood pressure and triglyceride lowering, reduced resting heart rate, improvement in several markers of endothelial damage, and reduction in the risk of sudden cardiac death in patients with established coronary heart disease. Several RCTs have evaluated the effect of fish oil in IgAN.

RATIONALE

Please consult Online Suppl Tables 61–64.

- 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.

In a trial that included 106 patients, fish oil treatment (12 g/d) improved kidney survival and retarded the rate of kidney function loss, without significant reduction of proteinuria.[529] Of note, the outcome of the control group, treated with 12 g/d of olive oil was poor (cumulative incidence of death or ESRD after 4 years was 10% in fish oil–treated patients, 40% in the control group). Longer follow-up confirmed the beneficial influence of fish oil treatment in this study.[530] Another RCT including 34 patients reported a beneficial influence of fish oil (3 g/d) on two end-points: the risk of ESRD, and $\geq$50% increase in SCr.[531] In this study, fish oil reduced proteinuria significantly. In a short-term (6-month) RCT, a significant proteinuria reduction was observed in patients treated with a combination of ACE-I and ARB plus fish oil (3 g/d) in comparison to a control group that received only ACE-I and ARB (percentage of patients with $\geq$50% proteinuria reduction, 80% and 20%, respectively).[532]

In contradiction to these studies, other RCTs failed to detect a significant benefit of fish oil treatment.[533,534] A meta-analysis[535] concluded that fish oils are not beneficial in IgAN, although another meta-analysis that combined clinical trials focused on IgAN, diabetes, lupus nephritis, and other glomerular diseases showed a greater proteinuria decrease in patients treated with fish oil, without changes in renal function.[536] A more recent RCT compared steroids (33 patients), fish oil (4 g/d, 32 patients), and placebo (31 patients) for 2 years.[515] Neither treatment group showed benefit over the placebo group. However, patients in the placebo group had a statistically significant lower degree of proteinuria at baseline.

In trying to explain these discordant results, some authors have proposed that the effects of fish oil in IgAN patients could be dosage-dependent.[537] However, another prospective trial reported that high (6.7 g/d) and low (3.3 g/d) doses of fish oil were similar in slowing the rate of kidney function loss in high-risk IgAN patients.[538] At present, there is no evidence to support the use of high-dose fish oil in IgAN.

We suggest fish oil (3.3 g/d) can be considered in the treatment of IgAN with persistent proteinuria $\geq$1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control).

RESEARCH RECOMMENDATION

- An RCT is needed of fish oil in IgAN to examine preserved kidney function with persistent significant proteinuria, despite optimal antihypertensive and antiproteinuric therapy.

10.5.2: Antiplatelet agents

10.5.2.1: We suggest not using antiplatelet agents to treat IgAN. (*2C*)

RATIONALE

Please consult Online Suppl Table 65.

- There is low-quality evidence to recommend not using antiplatelet therapy in IgAN.

A meta-analysis[539] based on seven studies, most of them performed in Japan, concluded that antiplatelet therapy resulted in reduced proteinuria and protected kidney function in patients with moderate to severe IgAN. However, there were significant limitations of the evidence in this meta-analysis, due to suboptimal quality of individual controlled trials. Importantly, the effect of antiplatelet agents alone

could not be discerned because patients received other concomitant therapies. Thus, in three studies, both treatment and control groups received other agents, including cytotoxics, steroids, antihypertensive agents, and anticoagulants. In three other studies, the intervention group received warfarin (two studies) and aspirin (one study) in addition to the antiplatelet agent (dipyridamole). Dipyridamole was the most commonly used antiplatelet agent (five studies) followed by trimetazidine and Dilazep (one study each).

RESEARCH RECOMMENDATION

- A multicenter RCT is needed to address the role of antiplatelet therapy in IgAN.

10.5.3: Tonsillectomy

10.5.3.1: We suggest that tonsillectomy not be performed for IgAN. (*2C*)

RATIONALE

- There is low-quality evidence to suggest not using tonsillectomy as treatment for IgAN. No RCT has been performed of tonsillectomy for IgAN.

Tonsillectomy may be indicated in those with IgAN for conventional reasons, e.g., recurrent bacterial tonsillitis. Clinical judgment needs to be exercised to decide whether to perform tonsillectomy in a very selected group of patients with a close relationship between paroxysm of gross hematuria and tonsillitis. However, only retrospective analyses[540,541] as well as one nonrandomized trial[542] have reported a better outcome for IgAN after tonsillectomy. In these studies, tonsillectomy was often combined with other—in particular, immunosuppressive—treatment;[540–542] thus, the specific value of tonsillectomy is not always apparent. Furthermore, in other retrospective series, investigators failed to note a benefit from tonsillectomy.[543]

RESEARCH RECOMMENDATION

- A multicenter RCT is needed to address the role of tonsillectomy in IgAN.

10.6: Atypical forms of IgAN

10.6.1: MCD with mesangial IgA deposits

10.6.1.1: We recommend treatment as for MCD (see Chapter 5) in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (*2B*)

BACKGROUND

Patients with IgAN can present with proteinuria within the nephrotic range (>3.5 g/d), and it portends a poor prognosis if this high-grade proteinuria persists during follow-up. However, the typical accompanying findings of complete nephrotic syndrome (edema, hypoalbuminemia, hyperlipidemia) are uncommon. Rarely, some patients with nephrotic syndrome have been identified in whom kidney biopsy shows minimal glomerular changes by light microscopy, diffuse podocyte foot process effacement on electron microscopy, and predominant mesangial deposits of IgA on immunofluorescence. A coincidence of two different glomerular diseases (minimal-change nephrotic syndrome and IgAN) has been proposed as the most likely explanation for such cases.

RATIONALE

- There is low-quality evidence to recommend that patients with nephrotic syndrome and coincidental histological findings of MCD and IgAN should be treated like patients with MCD.

Several series[544,545] have described prompt, complete remissions after corticosteroid therapy in a majority of patients with nephrotic syndrome and a pathological diagnosis of coincidental MCD and IgAN. This initial treatment response and the following clinical course, with a frequent appearance of nephrotic syndrome relapses, are very reminiscent of that of patients with pure MCD. An RCT in IgAN patients with nephrotic proteinuria[546] also showed a high percentage of complete remission in patients with such characteristics.

10.6.2: AKI associated with macroscopic hematuria

10.6.2.1: Perform a repeat kidney biopsy in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (*Not Graded*)

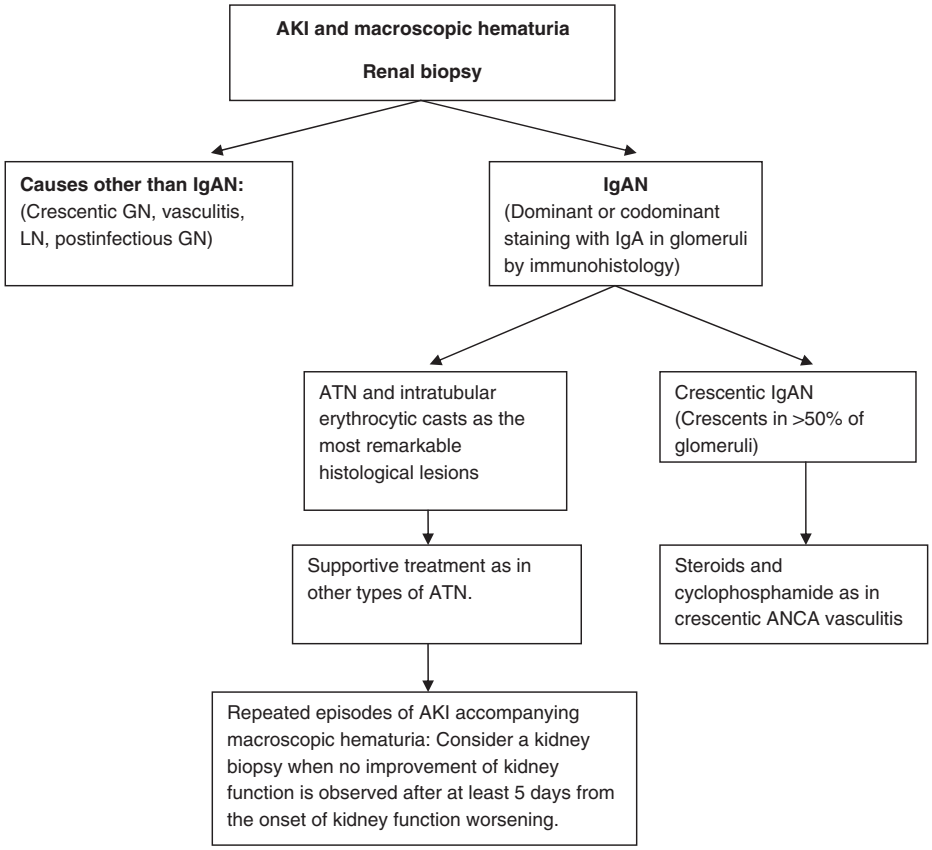
10.6.2.2: We suggest general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only ATN and intratubular erythrocyte casts. (*2C*)

BACKGROUND

Episodic macroscopic hematuria coinciding with mucosal (usually upper respiratory) infections are typical of IgAN. The macroscopic hematuria usually resolves spontaneously in a few days, but in some cases it can persist for several weeks.[547] The development of AKI during macroscopic hematuria episodes is uncommon[547,548] but represents the first manifestation of IgAN in some patients.

RATIONALE

- ATN and intratubular erythrocyte casts are the most common pathological findings in kidney biopsies during AKI accompanying macroscopic hematuria episodes in IgAN.
- Kidney function usually, but not always, recovers completely after the disappearance of macroscopic hematuria.



Algorithm 1 | Management algorithm of patients with AKI associated with macroscopic hematuria.

- Kidney biopsy allows differentiation of tubular damage and tubular occlusion by erythrocyte casts from crescentic IgAN or other coincidental causes of AKI.

Kidney biopsies performed during an episode of macroscopic hematuria typically show mesangial proliferation and occasional segmental crescents.[549] In those cases with AKI coincidental with gross hematuria, the glomerular changes are usually insufficient to account for the AKI. Hematuria by itself may be responsible for the AKI, through tubular injury that is induced by intratubular erythrocytic casts and a possible nephrotoxic effect of the hemoglobin that is released from these casts. Features of ATN and tubules filled by red blood cells are the most relevant histological findings. In a majority of patients, kidney function returns to baseline after the disappearance of macroscopic hematuria,[547–549] but incomplete recovery of kidney function has been described in up to 25% of affected patients.[547] Duration of macroscopic hematuria longer than 10 days is the most significant risk factor for persistent kidney impairment.[547] Continuous supportive care, as in other types of ATN, is the recommended therapeutic approach to these patients. There is no information about the usefulness of corticosteroids in patients with more severe forms of AKI or longer duration of macroscopic hematuria.

However, some patients with AKI and macroscopic hematuria exhibit a crescentic form of IgAN (crescents affecting >50% of glomeruli), whose prognosis is considerably worse.[492–495] A repeat kidney biopsy is suggested in patients with known IgAN who present a protracted AKI accompanying a new episode of gross hematuria, in order to differentiate ATN from crescentic IgAN or other types of AKI (Algorithm 1).

10.6.3: Crescentic IgAN

10.6.3.1: Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. (*Not Graded*)

10.6.3.2: We suggest the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see Chapter 13). (*2D*)

BACKGROUND

Crescentic IgAN has a poor prognosis. In a historical group of 12 untreated crescentic IgAN patients, about 42% reached ESRD in 36 months.[495] Another Japanese study showed that patients with >50% crescents developed ESRD in 75% of

patients by 10 years follow-up.[550] In this study, the patients were divided into four groups: group 1, absence of crescents and fibrous adhesion of glomerular tufts to Bowman's capsule; group 2, less than 25%; group 3, 25-50%; group 4, more than 50%. Ten-year renal survival rates were 100% in group 1, 94.3% in group 2, 81.8% in group 3, and 25.5% in group 4, respectively, indicating that patients with $>50\%$ crescents in glomeruli had a much worse survival than those with $\leq 50\%$ glomerular crescents.

The outcome of IgAN with diffuse crescent formation has also been studied in 25 Chinese IgAN patients.[551] Most of them showed rapidly progressive GN associated with more severe pathological changes, including glomerular, tubular interstitial, and vascular lesions, than in patients with general IgAN. The infiltrates in glomeruli may contribute to the crescentic formation. Diffuse crescent formation was defined by 50% or more of the glomeruli affected.[551] The pathological diagnosis of crescentic IgAN has not been unified among these studies. While some use crescents involving over 50% of glomeruli as the definition,[551] others use the presence of incipient to fulminant cellular crescents, with or without segmental endocapillary proliferation in $>10\%$ of glomeruli.[495] Although there is insufficient evidence for a unifying definition, we suggest a definition of crescentic IgAN as both a pathological finding of over 50% glomeruli having crescents and the clinical feature of rapidly progressive deterioration of renal function.

A recent study of 67 patients[552] with vasculitic IgAN (33 HSP, 34 IgAN) showed that three factors significantly affected kidney outcome: kidney function, blood pressure at presentation, and the amount of chronic damage in the biopsy.

RATIONALE

- There is no RCT of treatment in crescentic IgAN.

The three largest observational studies[495,551,552] all concluded that immunosuppression is potentially useful. 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, four had SCr <1.4 mg/dl (<124 μmol/l), and only five were dialysis-dependent. In another study, although an improved outcome was seen in those receiving immunosuppression, the conclusions were cautious, as the treated and untreated groups were not comparable. The third study also suggested positive effects of immunosupression.[495] This study used i.v. methylprednisolone 15 mg/kg/d for 3 days and monthly i.v. cyclophosphamide 0.5 g/m^2 for 6 months. Twelve treated patients were compared to 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 (five out of 12).

Recommended therapeutic regimens in these reports are varied, but initial therapy has usually included high-dose oral or i.v. corticosteroids plus oral or i.v. cyclophosphamide. In one study, some patients were changed from cyclophosphamide to azathioprine at 3 months. Durations of treatment in these three series varied from 3 to 24 months.

There is only poor-quality evidence to support the use of plasma exchange. One anecdotal report indicated benefit in five patients using plasma exchange in a combination of immunosuppressive therapies.[553]

RESEARCH RECOMMENDATION

- RCTs are needed to investigate the benefits of cyclophosphamide, MMF, and azathioprine in crescentic IgAN.

DISCLAIMER

SUPPLEMENTARY MATERIAL

Supplementary Table 44: Evidence profile of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy.
Supplementary Table 45: Summary table of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 46: Summary table of RCTs examining ACE-I or ARB in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 47: Evidence profile of RCTs examining steroid regimens in biopsy-proven IgA nephropathy.
Supplementary Table 48: Meta-analyses and systematic reviews on immunosuppression for IgA nephropathy.
Supplementary Table 49: Summary table of RCTs examining steroid regimens in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 50: Summary table of RCTs examining steroid regimens in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 51: Meta-analyses and systematic reviews on immunosuppression for IgA nephropathy.
Supplementary Table 52: Summary table of RCTs examining steroid and immunosuppressive regimens in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 53: Summary table of RCTs examining steroid and immunosuppressive regimens in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 54: Evidence profile of RCTs examining AZA in combination vs: AZA alone in biopsy-proven IgA nephropathy.
Supplementary Table 55: Summary table of RCT examining AZA in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 56: Summary table of RCT examining AZA in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 57: Evidence profile of RCTs examining MMF in biopsy-proven IgA nephropathy.
Supplementary Table 58: Meta-analyses and systematic reviews on MMF therapy for IgA nephropathy.

Supplementary Table 59: Summary Table of RCTs examining MMF in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 60: Summary Table of RCTs examining MMF in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 61: Evidence profile of studies examining omega-3 fatty acid treatment in IgA nephropathy.
Supplementary Table 62: Meta-analyses and systematic reviews on fish oil treatment in IgA nephropathy.
Supplementary Table 63: Summary table of RCTs examining omega-3 fatty acids in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 64: Summary table of RCTs examining omega-3 fatty acids in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 65: Meta-analyses and systematic reviews on antiplatelet therapy for IgA nephropathy.
Supplementary Table 66: Summary table of RCT examining immunosuppression and anti-platelets in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 67: Summary table of RCT examining immunosuppression and anti-platelets in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary Table 68: Summary table of RCT examining antiplatelet treatments in biopsy-proven IgA nephropathy (continuous outcomes)*.
Supplementary Table 69: Summary table of RCTs examining miscellaneous treatments in biopsy-proven IgA nephropathy (categorical outcomes).
Supplementary Table 70: Summary table of RCTs examining miscellaneous treatments in biopsy-proven IgA nephropathy (continuous outcomes).
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php