

# Current Therapy for IgA Nephropathy

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## ABSTRACT

IgA nephropathy (IgAN) is a very common glomerulonephritis worldwide. In this review, we discuss therapeutic options in four clinical scenarios encountered in patients with IgAN: first is the patient with minor urinary abnormalities where the mainstay of treatment is long-term, regular follow-up to detect renal progression and hypertension. Second is the typical patient presenting with microhematuria, significant but non-nephrotic proteinuria, hypertension, and variable degrees of renal failure. Here the mainstay of treatment is optimized supportive care. If this does not lower proteinuria below 1 g/d, corticosteroid monotherapy may be effective, as long as the GFR is above 50 ml/min. There is insufficient data to advocate the use of other immunosuppressive drugs or even combination therapy in such patients. Third is the atypical patient with overt nephrotic syndrome, or acute or rapidly progressive kidney injury where a possible vasculitic form of IgAN should be sought and, if present, treated with immunosuppression. In other atypical patients with secondary IgAN, treatment should target the underlying primary disease. And fourth is the transplanted patient with recurrent IgAN where the mainstay of treatment is optimized supportive care.

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Although IgA nephropathy (IgAN) is the most common noninfectious glomerulonephritis worldwide, there are remarkably few randomized controlled trials and very rarely do patient numbers exceed 200. Consequently, most guidelines relating to IgAN in the *KDIGO Clinical Practice Guideline for Glomerulonephritis* (to be published in late 2011) will be based on a low to very low level of evidence and, in many cases, suggestions cannot even be offered. Thus, the majority of patients will continue to be treated based largely on opinion. This review will attempt to incorporate evidence-based recommendations, but it will also cover areas founded exclusively on opinion. We have based the review on four classical clinical scenarios encountered in IgAN patients: that is, the coincidental discovery of minor urinary abnormalities (the majority); the typical patient

who requires close follow-up and treatment; atypical manifestations including overt nephrotic syndrome, acute or rapidly progressive kidney injury, or secondary forms of IgAN; and finally recurrent IgAN after renal transplantation. A synopsis of our suggested approach is given in Figure 1. Supportive care throughout the manuscript refers to measures listed in Table 1, which are not specific for IgAN and which have been shown to retard progression of chronic glomerular diseases.

## THE SILENT MAJORITY

### Most IgAN Likely Goes Unnoticed, Is Very Benign, and Does Not Need Treatment

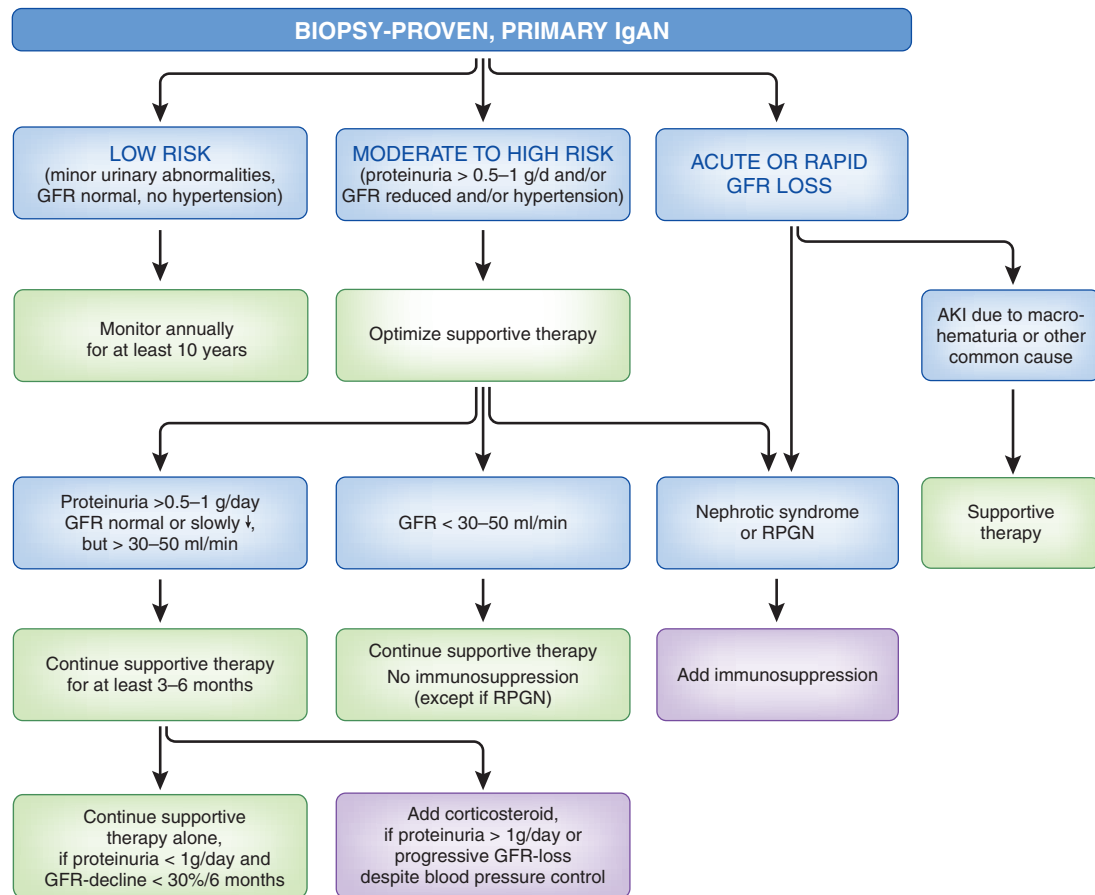
In autopsy series<sup>1</sup> and zero-hour allograft biopsies,<sup>2</sup> glomerular IgA deposits

are detected in 5 to 20% of all cases. Full-blown IgAN with glomerular IgA plus C3 deposits as well as mesangioproliferative changes were noted in 1.6% of Japanese graft kidneys before implantation.<sup>2</sup> Thus, the majority of patients with IgAN must run a clinically inconspicuous course and spontaneous remissions of the disease must exist. Indeed, in Chinese IgAN patients with isolated microhematuria followed for up to 12 years, microhematuria disappeared in 14%, and in less than one third, proteinuria increased above 1 g/d or GFR fell.<sup>3</sup> Repeat biopsy studies confirm that glomerular changes, including IgA deposits, can completely disappear spontaneously or after treatment in both native<sup>4–6</sup> and transplanted kidneys.<sup>7,8</sup> These studies have two important clinical implications: IgAN—at least in early stages—can be spontaneously reversible and patients with isolated urinary abnormalities, particular those in whom IgAN has been confirmed, need to be followed long-term, as there may be progressive disease in approximately 30%. Although such long-term follow-up is often recommended, especially in young patients, at least in our experience it is rarely maintained throughout the necessary 10 or more years. Auto-

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**Figure 1.** Synopsis of suggested therapeutic approaches to patients with IgAN depending on the clinical setting.

mated reminder systems might provide some help here.

## THE TYPICAL PATIENT WITH IgAN

### Proteinuria, Hypertension, and GFR Are Key Determinants of the Type of Treatment

The degree of proteinuria is one of the strongest predictors of outcome in IgAN.<sup>9–11</sup> The risk for renal failure increases with higher proteinuria. *Vice versa*, lowering proteinuria markedly decreases risk regardless of whether the initial proteinuria is mild or in the nephrotic range.<sup>9,11</sup> Whereas most studies use a proteinuria cutoff of 1 g/d, above which increased risk for renal failure develops,<sup>9–11</sup> others contend that an increased risk starts above 0.5 g/d.<sup>12</sup> Furthermore, it is unresolved, which is the best predictor, proteinuria at initial presentation or the level maintained over the first

year or at year 1.<sup>12</sup> Uncontrolled hypertension has an additive effect with proteinuria in driving progression of disease.<sup>9,11</sup> The third consistent indicator of risk is a decrease in GFR at presentation.<sup>10</sup> This is expected since loss of renal function likely identifies the subgroup of IgAN patients who are already progressive. Finally, renal prognosis is worse in obese IgAN patients,<sup>13,14</sup> possibly related to superimposed obesity-related renal changes.<sup>15</sup> Nonsurgical weight loss can indeed lead to a reduction of proteinuria.<sup>16</sup>

In terms of histologic parameters (Figure 2), the IgAN Oxford classification<sup>17,18</sup> may offer important advances by providing evidence that not only chronic fibrotic changes, particularly glomerulosclerosis and tubulointerstitial fibrosis, but also mesangial and endocapillary hypercellularity predict prognosis. Various validation studies, such as the VALIGA study of the European Renal Association (ERA-EDTA),

are ongoing. Whether it is beneficial to base clinical decisions on this classification system, in particular, the novel parameters of mesangial and endocapillary hypercellularity, has not yet been tested. Finally, how the presence of cellular crescents in a patient who does not exhibit a rapidly progressive (vasculitic) course of IgAN should ultimately affect treatment modality is unresolved. There is relative consensus, however, that crescents in <50% of the glomeruli in an otherwise stable patient should not automatically prompt immunosuppression since institution of adequate supportive therapy may indeed lead to resolution of crescents.

### One Size Fits All: Optimized Supportive Therapy Is the Cornerstone for All Patients at Risk of Progression

There is no doubt that an optimized supportive regimen constitutes the corner-

**Table 1. Supportive therapy of IgAN**

|  |
|--|
| Level 1 recommendations  |
| <ul style="list-style-type: none"> <li>• Control blood pressure (sitting systolic BP in the 120s)</li> <li>• ACE inhibitor or ARB therapy with uptitration of dosage or combination ACE inhibitor and ARB therapy</li> <li>• Avoid dihydropyridine calcium-channel blockers unless needed for BP control</li> <li>• Control protein intake</li> </ul>  |
| Level 2 recommendations  |
| <ul style="list-style-type: none"> <li>• Restrict NaCl intake/institute diuretic therapy</li> <li>• Control fluid intake</li> <li>• Non-dihydropyridine calcium-channel blocker therapy</li> <li>• Control each component of the metabolic syndrome</li> <li>• Aldosterone antagonist therapy</li> <li>• Beta-blocker therapy</li> <li>• Smoking cessation</li> <li>• Allopurinol therapy</li> <li>• Empiric NaHCO<sub>3</sub> therapy, independent of whether metabolic acidosis is present or not</li> </ul> |
| Other measures to retard IgAN progression  |
| <ul style="list-style-type: none"> <li>• Avoid NSAIDs altogether, or no more than once or twice weekly at most</li> <li>• Avoid prolonged severe hypokalemia</li> <li>• Avoid phosphate cathartics</li> <li>• Ergocalciferol therapy to correct vitamin D deficiency</li> <li>• Control hyperphosphatemia and hyperparathyroidism; in animal models and in human studies, controlling hyperphosphatemia slows CKD progression</li> </ul>   |

Recommended supportive therapy options in patients with, or at risk of, progressive IgAN (modified after reference 20). The goal is to implement all level 1 recommendations and as many level 2 recommendations as feasible. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug.

stone of any therapeutic approach to IgAN patients at risk for progression. In fact, this will be the only area where there will be KDIGO *recommendations* (as opposed to *suggestions* with lower degree evidence). These measures are summarized in Table 1. In view of space limitations, we will not discuss this issue in detail. The reader is referred to excellent reviews on this topic.<sup>19–21</sup> Of note, most randomized trials in IgAN suffer from lack of optimized and comprehensive supportive care. We therefore initiated the STOP-IgAN trial,<sup>22</sup> which will test in high-risk IgAN patients whether immunosuppression exerts an added benefit after the supportive therapy has been optimized over 6 months. We recently finished recruitment and data are expected by 2014.

### Nonestablished and Controversial Nonimmunosuppressive Treatment Approaches

In a meta-analysis of fish oil therapy in patients with IgAN, no statistically significant benefit was noted, although

there was a 75% probability of at least a minor effect.<sup>23</sup> Long-term follow-up of the largest randomized trial so far<sup>24</sup> noted a better preservation of renal function in the fish oil group. In a smaller Italian randomized trial in proteinuric IgAN patients with preserved renal function, proteinuria decreased by 75% in the fish oil group but remained stable in controls;<sup>25</sup> however, a tendency of the control group toward worse prognostic features at baseline (numerically lower mean GFR, higher proteinuria, and more men) was notable. Essentially no side effects were noted. In contrast, another more recent randomized trial failed to detect a benefit from fish oil;<sup>26</sup> whether this was related to a slightly higher baseline proteinuria in the fish oil group remains unresolved. At present, fish oil in IgAN is literally a matter of taste.

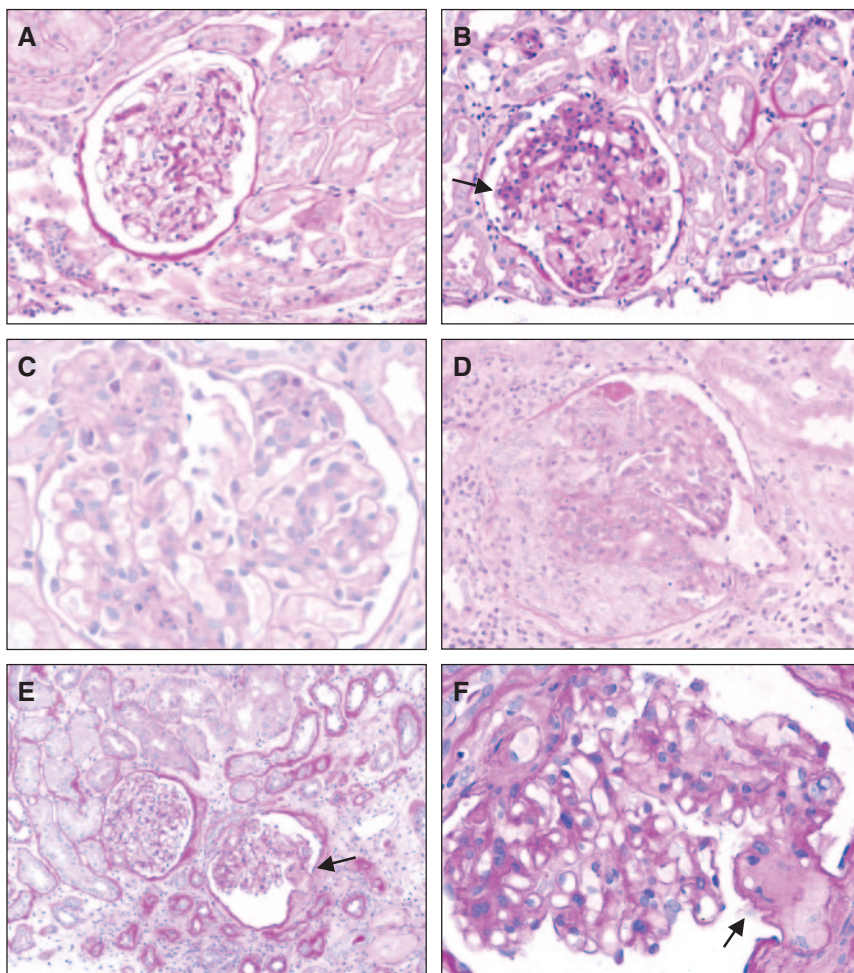
Antiplatelet and anticoagulant drugs are mostly used in Asia for the treatment of IgAN. A small randomized trial suggested benefit from dipyridamole (75 mg three times daily and

warfarin [INR 1.3 to 1.5]) compared with no treatment, but angiotensin-converting enzyme (ACE) inhibitors were avoided in these patients.<sup>27</sup> Most other studies on this topic suffer from the fact that antiplatelet therapy was not standardized (aspirin, warfarin, or dipyridamole were used), often combined with immunosuppression, and were retrospective and nonrandomized. At present, no recommendation on the use of such drugs is possible in IgAN patients.

Tonsillectomy, combined with immunosuppression, in patients at risk for progressive IgAN, is mostly recommended in Japan, based largely on retrospective data.<sup>28,29</sup> A recent small Japanese study in transplanted patients with recurrent IgAN<sup>30</sup> reports that tonsillectomy reduces proteinuria from 880 to 280 mg/d, whereas little change was noted in a non-operated control group. Another recent Japanese study in primary IgAN also reports that tonsillectomy combined with immunosuppression is more effective in inducing remission of proteinuria and/or hematuria than immunosuppression alone.<sup>31</sup> Limitations of both studies include their small size, nonrandomized nature, and nonsystematic renin-angiotensin blockade. Given that other studies have been unable to document a benefit in IgAN patients who are Caucasian,<sup>32,32a</sup> we feel that an adequately powered randomized controlled trial will be required before tonsillectomy can be routinely recommended in the care of IgAN patients. An exception may be when there is a clear temporal relationship between tonsillitis episodes and bouts of macrohematuria.

A recent Finnish study investigated the relationship between alcohol consumption and progression of IgAN.<sup>33</sup> Better kidney function was associated with light-to-moderate alcohol consumption after correction for hypertension and 24-hour protein excretion. Light consumption (one drink per day) in women and moderate consumption (1 to 3 drinks per day) in men appears optimal. Although this certainly does





**Figure 2.** The range of histologic findings in IgA nephropathy with an evaluation based on the Oxford classification.<sup>17,18</sup> All sections are PAS stains. (A) Glomerulus without mesangial proliferation and matrix increase (M0 with the majority of glomeruli showing this phenotype). (B) Glomerulus with segmental mesangial hypercellularity (arrow) (M1 with the majority of glomeruli showing such a phenotype). (C) Endocapillary hypercellularity (E1). (D) Glomerulus with segmental necrosis and extracapillary proliferation. (E) Overview of a case with sclerotic and atrophic changes. Right-sided glomerulus with segmental glomerulosclerosis and a focal adhesion (arrow) surrounded by increased interstitial matrix and tubules with segmental dedifferentiation (tubular atrophy) (S1 for glomerular sclerosis and T1 for tubular atrophy and interstitial fibrosis). (F) Higher magnification of the glomerulus illustrated in Figure 2E with segmental glomerulosclerosis and an adhesion (arrow) (S1).

not establish a causal or even therapeutic relationship, patients should be made aware of these findings.

#### Proteinuric Patients, Despite Optimized Supportive Care, Should Be Given a 6-Month Course of Corticosteroids If GFR Is Above 50 ml/min

Three randomized controlled trials have shown that a 6-month course of corticosteroids in IgAN patients with relatively

preserved renal function, and a GFR above 50 ml/min, can reduce proteinuria and decrease the risk of subsequent renal failure.<sup>34–37</sup> Whereas corticosteroid therapy in the first trial consisted of combined pulse and oral steroids, a purely oral regimen was used in the subsequent trials and appeared effective as well (Table 2). In contrast, in a smaller United States trial,<sup>26</sup> using a much longer but strictly alternating steroid regimen, no benefit was noted at 2 years (Table 2).

Similarly, a low-dose corticosteroid regimen (20 mg/d, tapered over 2 years) from Japan was ineffective in a randomized trial.<sup>38</sup>

Corticosteroid-related side effects, even with the more aggressive Pozzi regimen, were reported to be minor. This is in contrast to the orthopedic literature in which 9 g of methylprednisolone markedly exceeded the threshold of 2 g of methylprednisolone administered within 3 months, above which the incidence of aseptic osteonecrosis starts to rise.<sup>39,40</sup>

Supportive therapy in the IgAN patients was not optimal by current standards in the study of Pozzi *et al.*<sup>36</sup>; a similar benefit was noted after instituting an ACE inhibitor alone.<sup>41,42</sup> This is consistent with a retrospective analysis in 702 IgAN patients where corticosteroid pulse therapy as well as ACE-inhibitor therapy independently reduced progression of disease.<sup>43</sup> Both the trial of Manno *et al.* and Lv *et al.*<sup>35,34</sup> (Table 2) suffer from their study design, as patients were required to discontinue prior ACE inhibitor or angiotensin receptor blocker (ARB) therapy. Then, in the combination groups, they started receiving simultaneously an ACE inhibitor and corticosteroids. Consequently, a high number of patients who would have ended up in a low-risk category with ACE inhibitor treatment alone were assigned additional immunosuppression.<sup>44</sup> In our own ongoing STOP-IgAN study,<sup>22</sup> we noted that, during the 6-month run-in phase, which is meant to uptitrate renin-angiotensin blockers to their maximum anti-proteinuric effect, proteinuria decreased to <0.75 g/d in most patients with IgAN (unpublished data).

A pragmatic approach suggests first optimizing supportive therapy in IgAN patients at risk for progression (see above). If this is not sufficient to lower proteinuria below about 1 g/d, patients should be offered a 6-month trial of corticosteroids as long as their GFR is higher than 50 ml/min (Figure 1). Table 2 suggests that strictly alternating or low-dose corticosteroid therapy is ineffective. It is unresolved which of the three high-dose daily regimens is more beneficial. The longest follow-up data are available for

Table 2. Corticosteroid monotherapy

| Trial  | Pozzi et al., Italy <sup>37,36</sup>  | Katafuchi et al., Japan <sup>38</sup>                       | Hogg et al., United States <sup>26</sup>  | Manno et al., Italy <sup>35</sup>  | Lv et al., China <sup>34</sup>  |
|--|---|---|---|--|---|
| <b>Corticosteroid regimen</b>                      | Intravenous methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg every other day for 6 months | Oral prednisolone 20 mg/d tapered to 5 mg/d at 18 months    | Oral prednisone, every other day 60 mg/m <sup>2</sup> for 3 months, then 40 mg/m <sup>2</sup> for 9 months, and then 30 mg/m <sup>2</sup> for 12 months | Oral prednisone for 6 months (1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day per month) | Oral prednisone for 6–8 months (0.8–1 mg/kg/day for 2 months, then reduced by 5–10 mg every 2 wk) |
| <b>Control regimen</b>                             | Supportive only   | Dipyridamole  | Placebo   | Supportive only  | Supportive only   |
| <b>RAS blockade</b>                                | 14% at baseline, allowed during follow-up   | 2% at baseline; allowed during follow-up                    | Enalapril if hypertensive   | Ramipril in all patients   | Cilazapril in all patients  |
| <b>Key outcome in steroid group versus control</b> | Ten-year renal survival (= absent doubling of serum creatinine), 53% in controls versus 97% in the steroid group  | Significant reduction in proteinuria but not ESRD frequency | No benefit in the steroid group versus placebo at 2 years   | Mean annual loss of GFR 6.2 ml/min in the steroid group  | Significantly fewer patients with a 50% increase in serum creatinine in the steroid group         |

Therapeutic regimens and outcomes in randomized controlled trials in IgAN patients. RAS, renin-angiotensin system; ESRD, end-stage renal disease.

Table 3. Mycophenolate mofetil monotherapy

| Trial  | Maes et al., Belgium <sup>48</sup> | Tang et al., China <sup>46,47</sup>                  | Frisch et al., United States <sup>49</sup> |
|--|------------------------------------|--|--|
| <b>MMF regimen</b>                             | 2 g/d for 3 years                  | 1.5 to 2.0 g/d depending on body weight for 6 months | Titrated up to 2 g/d for 1 year            |
| <b>Control regimen</b>                         | Placebo                            | Supportive only                                      | Placebo                                    |
| <b>RAS blockade</b>                            | All patients                       | All patients   | All patients                               |
| <b>Key outcome in MMF group versus control</b> | No effect on GFR or proteinuria    | Reduction in proteinuria, stabilization of GFR       | No effect on GFR or proteinuria            |

Therapeutic regimens and outcomes in controlled trials in IgAN patients. MMF, mycophenolate mofetil; RAS, renin-angiotensin system.

Table 4. Immunosuppressive combination therapy

| Trial  | Ballardie et al., United Kingdom <sup>66</sup>  | Yoshikawa et al., Japan <sup>64</sup>  | Yoshikawa et al., Japan <sup>65</sup>   | Pozzi et al., Italy <sup>45</sup>  |
|--|---|--|---|--|
| <b>Combination regimen</b>                             | Oral prednisolone 40 mg/d reduced to 10 mg (end of year 2) + oral cyclophosphamide 1.5 mg/kg per day for 3 months, and then oral azathioprine 1.5 mg/kg per day for minimum 2 years and up to 6 years | Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + anticoagulants (heparin followed by warfarin and dipyridamole) | Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + warfarin + dipyridamole | Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine 1.5 mg/kg per day for 6 months |
| <b>Control regimen</b>                                 | Supportive therapy only   | Supportive therapy + anticoagulants (see above)  | Above regimen without azathioprine  | Same as shown in Table 2 <sup>36</sup>   |
| <b>RAS blockade</b>                                    | Inconsistent  | Not reported   | Prohibited  | 45% at baseline  |
| <b>Key outcome in combination group versus control</b> | Marked improvement of renal survival at 5 years   | Higher reduction in proteinuria and percentage of sclerosed glomeruli  | More complete remissions of proteinuria   | No difference between groups   |
| <b>Comment</b>   |   | Study included pediatric patients only   | Study included pediatric patients only  |  |

Therapeutic regimens and outcomes in controlled trials in IgAN patients. RAS, renin-angiotensin system.

the Pozzi regimen.<sup>37</sup> Patient preferences, anticipated risk of side effects in a given patient, and also local conditions should currently dictate the choice of regimen. Successful re-treatments in patients who experienced a relapse of proteinuria after steroid therapy have been reported.<sup>45</sup>

### Data on Mycophenolate Mofetil (MMF) Monotherapy in IgAN Are Inconclusive

Three randomized controlled trials, one each from China,<sup>46,47</sup> Belgium, and the United States<sup>48,49</sup> have assessed the value of MMF in high-risk patients with IgAN (Table 3); a fourth trial<sup>50</sup> is ongoing. One additional study, published in Chinese, reports better proteinuria reduction with 1 to 1.5 g/d MMF, reduced to 0.5 to 0.75 g/d within 12 months, as compared with high-dose oral prednisone.<sup>51</sup> Supportive care and BP control were unclear, rendering an interpretation of this study difficult. In the other Chinese trial, 2 g/d of MMF, on top of an ACE inhibitor, led to better reduction of proteinuria and stabilization of renal function in 20 IgAN patients than ACE inhibitor alone.<sup>46,47</sup> In contrast, the Belgian and United States trials in mostly Caucasian patients found no effect on proteinuria<sup>48,49</sup> despite a design similar to that in the latter Chinese trial.<sup>46,47</sup> Whether ethnic factors, the higher dose of MMF per body weight in the Chinese trials, or other unidentified factors account for these striking differences is unresolved.<sup>52</sup>

At present, it appears prudent to largely restrict the use of MMF to patients of Asian origin who fail to respond to supportive therapy and/or corticosteroids or in whom the use of steroids is problematic because of comorbidities or side effects. If MMF is used in IgAN patients with a reduced GFR, pneumocystis carinii prophylaxis is important, given several deaths in Chinese IgAN patients on MMF.<sup>53</sup>

### Other Immunosuppressive Monotherapy Approaches Are Not Established

Some data have been published on alternative immunosuppressants in IgAN patients, including mizoribine<sup>54</sup> and cyclosporine A.<sup>55,56</sup> None of the evidence is

sufficient at present to suggest their use in IgAN patients. Of note, as discussed below, neither cyclosporine A, tacrolimus, or sirolimus prevent recurrence of IgAN in a renal graft.

### Immunosuppressive Combination Therapy Is Not Recommended

A number of retrospective studies or case series, mostly from Asia, have reported beneficial outcomes in high-risk IgAN patients treated with combinations of corticosteroids plus cyclophosphamide or azathioprine *versus* controls.<sup>57–61</sup> Selection and observation bias as well as nonoptimized supportive measures render an interpretation of these studies difficult. In contrast, one trial from Singapore<sup>62</sup> and one from Australia<sup>63</sup> found no evidence for a benefit of cyclophosphamide, dipyridamole, plus warfarin on renal function as compared with controls.

More recent prospective randomized controlled trials on immunosuppressive combinations in IgAN have also yielded inconsistent outcomes (Table 4). In two Japanese trials, both from the same group,<sup>64,65</sup> children with IgAN and severe histologic changes and/or significant proteinuria, yet normal GFR, received azathioprine plus corticosteroids plus anticoagulants *versus* anticoagulants alone.<sup>64</sup> In the other trial, azathioprine plus corticosteroids plus anticoagulants were tested against steroids alone.<sup>65</sup> In both cases, the combination therapy led to higher rates of complete remission of proteinuria.

In 2002, Ballardie *et al.*<sup>66</sup> published a small randomized trial comparing cyclophosphamide plus corticosteroids followed by azathioprine plus corticosteroids *versus* controls. Renal survival at 5 years was 72% in the immunosuppressed group *versus* 6% in controls.<sup>66</sup> RAS blockade was infrequent and BP control not ideal by today's standards. In addition, the patient group was highly select in that patients exhibited impaired renal function at baseline with reciprocal serum creatinine plots suggesting end-stage renal failure within 5 years, pronounced proteinuria, and no advanced tissue scarring. Finally in 2010, Pozzi *et al.*<sup>45</sup> published a randomized controlled trial in which 207 IgAN patients with a

serum creatinine below 2 mg/dl and a proteinuria above 1 g/d, despite RAS blockade, were assigned to receive corticosteroids or additional oral azathioprine. Outcome after a median of 4.9 years was not different between the two groups.<sup>45</sup>

In general, side effects in the combination therapy groups are more frequent and severe than those in monotherapy groups and include, among others, glaucoma, cataracts, and aseptic necrosis of the femoral head in children,<sup>65,64</sup> myelodysplasia,<sup>66</sup> secondary diabetes,<sup>66</sup> pulmonary tuberculosis,<sup>66</sup> and pneumocystis pneumonia.<sup>45</sup> In our ongoing STOP-IgAN trial, one patient receiving immunosuppressive combination therapy based on the Ballardie protocol<sup>66</sup> died from pneumogenic sepsis (unpublished observation). Clearly, this is a major concern in a slowly progressive disease such as IgAN, which needs to be weighed against the risk of losing renal function.

At present, we feel that immunosuppressive combination therapy is not warranted in IgAN patients unless there are features of rapidly progressive glomerulonephritis and/or a vasculitic course (see below).

### The Patient with GFR below 30 to 50 ml/min: Comprehensive Supportive Therapy Only

Almost all randomized controlled trials exclude IgAN patients with a GFR below 30 ml/min and contain very few patients with a GFR between 30 and 50 ml/min. A case series in patients with a median GFR of 22 ml/min reported benefits from sequential cyclophosphamide or steroid-bolus therapy followed by MMF,<sup>67</sup> but a randomized controlled trial using MMF alone in advanced IgAN failed to induce any benefit.<sup>49</sup> At present there is not enough evidence to advocate immunosuppressive therapy in advanced IgAN once the patient has a serum creatinine above 2.5 to 3 mg/dl, that is, the threshold that sometimes is referred to as the "point of no return."<sup>68,69</sup> Comprehensive supportive therapy, however, must be continued in such patients as it can stabilize renal function for years at even very low levels.<sup>70–72</sup>



## THE ATYPICAL PATIENT

### The Patient with Acute Kidney Injury (AKI) or Rapidly Progressive Loss of Renal Function

AKI resulting primarily from non-disease-specific causes is a common presentation in the rare elderly patient with IgAN.<sup>73</sup> The cause is usually apparent from the history and such patients should receive supportive therapy. In AKI associated with macroscopic hematuria, a repeat renal biopsy is indicated if renal function does not improve within a few days to differentiate acute tubular necrosis with intratubular erythrocyte casts from crescentic and/or necrotizing IgAN. The former again requires supportive care only; macrohematuria longer than 10 days, older age, and decreased baseline GFR are clinical predictors of incomplete recovery from AKI.<sup>74</sup>

In case series of crescentic and/or necrotizing IgAN and either AKI or a rapidly progressive course, there was a seeming benefit from treatment analogous to ANCA-associated vasculitis (steroids and cyclophosphamide).<sup>75–78</sup> Limitations of all these studies include the lack of controls and their usually retrospective nature. Such rare patients can also have anti-GBM antibodies or ANCAs and probably should be treated analogously to Goodpasture's syndrome or ANCA vasculitis, respectively.

### The Patient with Overt Nephrotic Syndrome

Although nephrotic-range proteinuria is not uncommon in IgAN patients, particularly those with poorly controlled hypertension, a complete nephrotic syndrome is distinctly uncommon. In such cases, coincidental IgAN with minimal-change nephropathy should be excluded by electron microscopy and, if present, treatment should be analogous to minimal-change disease. A small randomized controlled trial from 1986 suggests that IgAN patients with nephrotic syndrome, particularly those with mild histologic changes, benefit from a 4-month course of oral prednis(ol)one (40 to 60 mg/d starting dose) in terms of remission of

proteinuria; however, there was no effect on GFR after about 3 years.<sup>79</sup>

### The Patient with Secondary IgAN

Secondary IgAN is most commonly seen in patients with chronic liver and inflammatory bowel diseases; however, associations have been reported for numerous other immunologic and infectious diseases.<sup>80</sup> The treatment of secondary IgAN is primarily directed against the underlying primary disease. In particular, in patients with alcoholic liver disease, 80% of the patients exhibit glomerular IgA deposits,<sup>81</sup> but progressive IgAN is very rare. A discussion of current therapeutic concepts in Henoch-Schönlein purpura is beyond the scope of our review. The reader is referred to recent reviews.<sup>82–84</sup>

### RECURRENT IgAN IN THE TRANSPLANT PATIENT

None of the currently available immunosuppressive drugs used after renal transplantation can prevent the histologic recurrence of IgAN.<sup>8,85</sup> There is also no clear evidence that the choice of immunosuppression after renal transplantation affects the clinical manifestation or course of recurrent IgAN.<sup>8</sup>

Relative consensus exists that patients with recurrent IgAN should mainly receive optimized supportive care. A small case series<sup>86</sup> reported that without renin-angiotensin blockade 4 out of 4 patients with recurrent IgAN progressed to end-stage renal disease compared with 3 out of 9 in the group treated with an ARB. Whether patients with recurrent IgAN should also receive a tonsillectomy, as suggested by a recent small Japanese trial, is currently unresolved.<sup>30</sup>

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images illustrating the Oxford classification of IgAN.

### DISCLOSURES

None.

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