Immunoglobulin A Nephropathy: A Clinical Perspective

JAMES V. DONADIO, JR.* and JOSEPH P. GRANDE†
*Division of Nephrology and Internal Medicine and the †Department of Laboratory Medicine and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

First described in 1968 by Berger and Hinglais (1), idiopathic immunoglobulin A nephropathy (IgAN) is now recognized as the most common primary glomerulonephritis in the world (2,3). Also, we now appreciate as did Berger that renal failure can develop in a substantial number of patients with IgAN (initially thought to be a totally benign process) over variable periods of time (4–9). IgAN is an immune complex-mediated glomerulonephritis defined morphologically by the constant presence of predominant or codominant mesangial deposits of IgA accompanied by a variety of histopathologic lesions (9–11). The etiology is unknown in that no consistent environmental or infectious agent has been shown to be antigenic with an IgA antibody response. Since the original description of the glomerulopathy, idiopathic IgAN has received the bulk of attention in the medical literature, but many diseases have been reported that are sporadically associated with mesangial IgA deposition (Table 1). Schönlein-Henoch purpura, a multisystemic disease, is the most common and arguably considered a part of the spectrum of idiopathic IgAN. The association of many of the secondary disorders may be coincidental because of the high prevalence of IgAN that is usually a long-term and chronic disease. This review offers a perspective on the epidemiology, clinical features, and diagnosis, pathology, outcome, and management of patients with idiopathic IgAN.

Epidemiology

Population epidemiologic studies concerning the incidence of IgAN are meager; most reports relate prevalence rates expressed as a percentage of primary glomerulonephritis or of a total biopsy series originating in referral-based cohort studies (2,7,11). For example, IgAN accounts for 7 to 52% of patients with glomerulonephritis, which ranges from 4 to 44% of total biopsy series, as reported in a recent comprehensive review by Ibels and Györö (7). The high-end prevalence rates are found in Singapore, Japan, Australia, Hong Kong, Finland, and southern Europe, and the lower prevalence rates are reported from the United Kingdom, Canada, and the United States, with the exception of Native Americans living in New Mexico (2,7).

The low prevalence rate reported from the United States is influenced not only by the fact that all published series from the United States are from referral centers in which there is a patient selection bias, but also by a conservative approach taken by nephrologists in our country in recommending renal biopsy in patients who have only an asymptomatic, abnormal urine sediment. It is common practice for patients presenting with isolated hematuria or mild proteinuria not to receive a renal tissue diagnosis, the renal biopsy being reserved for those people who develop increasing amounts of urine protein or a rising serum creatinine concentration, or both. This practice has bearing on comparative outcome studies and recommendations for treatment to be discussed later.

Clinical Features

IgAN occurs at all ages, with the usual age of clinical onset in the second and third decade of life (2,7,8,11). There is a usual male sex predilection ranging from less than 2:1 in Japanese patients to as high as 6:1 in Caucasian patients in northern Europe and the United States. IgAN has a predilection for whites and Asians and is less common in blacks.

IgAN must be highly suspected in any patient in whom there may be one of two common presentations: (1) episodic, macroscopic hematuria, often coincident with an upper respiratory tract infection, less often a gastroenteritis; or (2) asymptomatic with findings on urinalysis of an abnormal urine sediment containing erythrocytes (RBC) and RBC casts and proteinuria in patients in whom the urinalysis was performed as part of an examination for other purposes. Loin pain will accompany macroscopic hematuria in approximately one-third of the cases. The presenting illness of episodic, grossly visible hematuria is more common in younger people, whereas that of an abnormal urine sediment is more frequent in older individuals. For example, in a recently completed, randomized clinical trial of fish oil involving 106 proteinuric patients, a history of macroscopic hematuria was obtained only in patients under 34 yr old, the median age of the study cohort (12).

Unfortunately, abnormalities found on urinalysis may be overlooked or purposely not acted on by further testing until renal function impairment becomes evident. It is imperative to pursue urine sediment changes when first detected so as not to delay making an accurate diagnosis. By definition, a diagnosis of IgAN requires renal biopsy, including immunofluorescence microscopy.

This again raises the controversial issue among nephrologists of performing a renal biopsy under the circumstances of the above-cited presentations without renal function impairment or nephrotic-range proteinuria because of the perception that specific treatment is not available. The approach of prospectively evaluating an asymptomatic patient was an accept-
Idiopathic IgA nephropathy (Berger disease)

Secondary
Schönlein-Henoch purpura—most common; a distinct entity or a multisystemic extension of IgA nephropathy

Diseases of the liver: alcoholic, cryptogenic and primary biliary cirrhosis; hepatitis B (endemic areas); chronic schistosomiasis

Intestine: celiac disease; chronic ulcerative colitis;

Crohn’s disease

Skin: dermatitis herpetiformis; psoriasis

Bronchus/lung: idiopathic pulmonary hemosiderosis;

Cystic fibrosis, sarcoidosis

Neoplasia: carcinoma of lung, larynx, and pancreas;

Nephritis: IgA mononucleosis; IgA mononucleal granulomatosis

Infection: human immunodeficiency virus; leprosy;

Toxoplasmosis

Other systemic/immunologic disorders: systemic lupus erythematosus; cryoglobulinemia; rheumatoid arthritis; psoriatic arthritis; anklyosing spondylitis; Sjögren’s syndrome; antineutrophil cytoplasmic antibody-associated vasculitis; familial immune thrombocytopenia

Table 1. Classification of diseases associated with predominant mesangial IgA deposition

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic IgA nephropathy (Berger disease)</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>Schönlein-Henoch purpura—most common; a distinct entity or a multisystemic extension of IgA nephropathy</td>
</tr>
<tr>
<td>Diseases of the liver: alcoholic, cryptogenic and primary biliary cirrhosis; hepatitis B (endemic areas); chronic schistosomiasis</td>
</tr>
<tr>
<td>Intestine: celiac disease; chronic ulcerative colitis; Crohn’s disease</td>
</tr>
<tr>
<td>Skin: dermatitis herpetiformis; psoriasis</td>
</tr>
<tr>
<td>Bronchus/lung: idiopathic pulmonary hemosiderosis; cystic fibrosis, sarcoidosis</td>
</tr>
<tr>
<td>Neoplasia: carcinoma of lung, larynx, and pancreas; nephritis: IgA mononucleosis; IgA mononucleal granulomatosis</td>
</tr>
<tr>
<td>Infection: human immunodeficiency virus; leprosy; toxoplasmosis</td>
</tr>
<tr>
<td>Other systemic/immunologic disorders: systemic lupus erythematosus; cryoglobulinemia; rheumatoid arthritis; psoriatic arthritis; anklyosing spondylitis; Sjögren’s syndrome; antineutrophil cytoplasmic antibody-associated vasculitis; familial immune thrombocytopenia</td>
</tr>
</tbody>
</table>

able practice until recently, in that rational therapeutic interventions can now be offered to patients who are at risk for developing progressive renal disease based on recently reported treatment studies (12–15).

It is the rule for microscopic hematuria and proteinuria to persist in variable amounts throughout the course of the disease, even in those patients whose presenting illness is microscopic hematuria. Complete and prolonged remission of all clinical signs is uncommon (approximately 4%). To illustrate the importance of direct urine sediment examination, Ibels and Györö (7) showed a positive correlation between the quantity of RBC per milliliter of urine and the number of hyaline casts and progressive renal disease in a cohort of 121 Australian patients with IgAN.

Diagnosis

Having determined that a patient has a clinical renal presentation fitting the above descriptions, a definitive diagnosis of IgAN can be made only by renal biopsy. The first clue in making a proper diagnosis is by careful urinalysis performed on a first morning, freshly voided urine sample. In addition to physicochemical testing for proteinuria, direct examination of the urine sediment, using unstained, bright-field microscopy, is required to identify RBC, leukocytes, and casts, and, in particular, RBC casts, all indicative of glomerular injury. Glomerular injury can also be suspected by finding dysmorphic or glomerular RBC, using an automatic microscopic technique along the lines of a Coulter counter that distributes cells to be examined according to size. The findings of renal (urinary) casts and dysmorphic RBC accompanying either macroscopic or microscopic hematuria clearly indicate to the clinician that bleeding in the urinary tract is glomerular in origin, and this should spare the patient from having to undergo urologic procedures such as cystoscopy and retrograde pyelography.

Qualitative proteinuria can be assessed further by measuring 24-h total urine protein or by semiquantitative protein/osmolar or protein/creatinine ratios on first morning, voided urine samples (16). Also, adults over 50 yr old who are first discovered to have proteinuria in the nephrotic range (protein excretion of 3.5 g or more per 24 h) should be screened for Bence Jones proteinuria by the sulfosalicylic precipitation method and examination by immunofixation electrophoresis to detect monoclonal light chains and immunoglobulins even in very low concentrations.

The presence of an abnormal urine sediment and proteinuria require measurement of renal function, preferably by a clearance technique, to estimate GFR. Serial measurement of renal function is essential in the long-term follow-up of patients with IgAN.

A small group of patients with IgAN will present with severe azotemia, some even requiring dialysis, obviously representing the most aggressive form of the disease. The late referral of a previously undiagnosed patient is also not unusual.

Likewise, on immunofluorescence there may be the rarely reported, coexistent nephrotic syndrome and IgAN marked by IgA mesangial deposits associated with focal and segmental mesangial expansion and minimal or no cellular proliferation. There is no consensus about whether this clinicopathologic combination represents a variant of one or other of the two conditions, or of two different coexisting disorders. Prompt remission of the nephrotic syndrome after steroid treatment, or spontaneously, suggests the phenotypic expression of minimal change disease (17).

There are other laboratory variables, including elevated serum IgA levels, C3 fragments, IgA-fibronectin aggregates, and the presence of circulating IgA-containing immune complexes, which are found in patients with IgAN, but none can replace the renal biopsy for the firm establishment of a diagnosis (11).

Pathology

The typical light microscopic, immunofluorescence, and electron microscopic alterations observed in IgAN are illustrated in Figure 1. The most common light microscopic lesion associated with IgAN is focal or diffuse mesangial hypercellularity, with expansion of the extracellular matrix. This nonspecific finding can be observed in a number of other glomerular disorders, including focal-segmental glomerulosclerosis, diabetic nephropathy, and other glomerular lesion-associated systemic diseases. In addition, patients with IgAN may present with a wide variety of light microscopic glomerular lesions, including segmental necrotizing lesions with crescent formation, segmental or global sclerosing lesions with hyalinosis, membranoproliferative lesions, or diffuse proliferative lesions.

Because the light microscopic features of IgAN are variable and nonspecific, immunofluorescence or immunoperoxidase studies demonstrating a predominant or codominant deposition
Figure 1. Characteristic morphologic alterations in immunoglobulin A nephropathy (IgAN). (A) Light microscopy demonstrating mild expansion of mesangial regions, both with cells and matrix (periodic acid-Schiff stain). Original magnification, ×200. (B) Immunofluorescence microscopy demonstrating brightly staining deposits of IgA, predominantly within mesangial regions. Original magnification, ×200. (C) Electron micrograph demonstrating electron-dense deposits within the mesangial region. The peripheral capillary loop basement membranes (right) are normal. Original magnification, ×7125.
of IgA are essential in establishing a diagnosis of IgAN. The deposits are predominantly within mesangial regions with focal paramesangial/subendothelial extension. Other immune reactants frequently codistribute with IgA, including IgG, IgM, C3, lambda light chain, and kappa light chain (1,18). The findings by electron microscopy parallel those observed by light microscopy and immunofluorescence studies and include mesangial hypercellularity and an increase in mesangial matrix, with deposition of electron-dense deposits within mesangial areas.

A number of tubulointerstitial and vascular changes may be seen in patients with IgAN, including interstitial fibrosis, tubular atrophy, interstitial cellular infiltrates, RBC or protein casts, or vascular sclerosis. Identification of these alterations may provide important prognostic information in patients with IgAN.

**Outcome**

IgAN is characterized by a highly variable clinical course, ranging from a totally benign condition and well-maintained renal function for decades to rapidly progressive renal failure. Many patients have a chronic, slowly progressive decline in renal function over 10 to 20 yr (2–9). The wide variability in clinical course has been addressed in a number of reviews from around the world on the clinical, laboratory, and histologic characteristics that predict development of renal failure in IgAN (2,4–9,19–24). Clinical and laboratory features found to be independently associated with progressive renal disease include the presence of hypertension, the degree of proteinuria, decreased renal function, and persistent microscopic hematuria. Histologic features identified as independent predictors of renal failure were glomerulosclerosis, interstitial fibrosis, and mesangial hypercellularity.

We recently reported the largest study of the clinical course of patients with IgAN in North America and the first in 13 yr (9). We identified a number of the previously reported clinical and histopathologic features associated with progressive disease. Although a large number of histopathologic features were univariately associated with adverse outcome, including interstitial fibrosis, tubular atrophy, interstitial inflammation, and both glomerular and interstitial proliferative activity as assessed by Mib-1 immunostaining, the total glomerular score was the only pathologic marker that provided independent information regarding outcome in a multivariate analysis (9). Although generally accepted that tubulointerstitial changes are major determinants in the progression of renal damage, the primacy of this relationship in patients with IgAN has been questioned. In a series of 39 patients with serial renal biopsies reported by Bennett et al. (25), the change in creatinine clearance rates between the initial and final biopsies did not correlate with the change in interstitial volume (an index of interstitial fibrosis). This finding raises the possibility that, at least in IgAN, interstitial changes may be secondary to the glomerular alterations. In addition, although we found that total glomerular score was the best independent histopathologic predictor of adverse outcome, mesangial hypercellularity did not correlate with renal failure in either the univariate or the multivariate models.

In our recent analysis, overall patient survival was 97 ± 1% (estimate ± SEM) at 5 yr and 89 ± 4% at 10 yr (9). Ultimately, 39 of 148 patients developed end-stage renal failure, the primary end-point of our study. With survival free of renal failure estimated to be 79 ± 4% at 5 yr and 67 ± 5% at 10 yr. The overall 10-yr renal survival of 67% in our study group was below the percentage survivals reported in five recent large cohort studies from Europe, Australia, and Japan (Table 2). In comparing the three most consistent risks for progression (i.e., hypertension, elevated serum creatinine concentration, and increased protein excretion, as reported in these large cohort studies), the percentage of all three risks in our study group (Upper Midwestern United States) was much greater than that seen in the other populations. Many of our patients carried all of these risks, emphasizing that, in general, more advanced cases are seen in referral renal centers in the United States and patients are coming to renal biopsy late in their disease course.

Recent studies have shown that the angiotensin-converting enzyme (ACE/DD genotype was associated with an increased

### Table 2. Renal survival in large cohorts of patients with IgAN relates to prevalence of renal progression risk factors at the time of renal biopsy

<table>
<thead>
<tr>
<th>Geographic Area</th>
<th>n</th>
<th>Renal Survival (%)</th>
<th>Increased Serum Creatinine Concentration</th>
<th>Hypertension</th>
<th>Proteinuria (&gt;3 g/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tübingen, Germany (21)</td>
<td>239</td>
<td>81</td>
<td>34</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>Saint-Etienne, France (22)</td>
<td>282</td>
<td>94&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>United Kingdom (23)</td>
<td>220</td>
<td>83</td>
<td>28</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Fukuoka, Japan (24)</td>
<td>225</td>
<td>74</td>
<td>36</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>New South Wales, Australia (7)</td>
<td>121</td>
<td>86</td>
<td>36</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Upper Midwestern U.S. (9)</td>
<td>148</td>
<td>67</td>
<td>59</td>
<td>47</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> IgAN, immunoglobulin A nephropathy; NA, not available; U.S., United States.

<sup>b</sup> 10 yr after renal biopsy.

<sup>c</sup> After clinical onset of disease.
rate of progressive renal disease in Caucasian (26,27) and Japanese (28) cohorts of patients with IgAN. Furthermore, in the Japanese patients 1 yr after ACE inhibitor therapy, urinary protein excretion significantly decreased in those with the DD genotype but not in other patients with ACE/ID or ACE/II genotypes (28). These findings suggest that the ACE/DD genotype may be a marker for an upregulated renin-angiotensin system, resulting in hemodynamic- and growth factor-related microvascular injury that is thought to play an important role in progressive IgAN. In addition, interference with the renin-angiotensin system may improve renal function in patients who possess the ACE/DD polymorphism (26–28).

In summary, from these outcome studies it has been shown that a composite of clinicopathologic determinants at the time of diagnosis can be used to profile a patient with IgAN who is placed at an increased risk for developing progressive renal disease. Therapeutic strategies can now be offered to patients who carry this high-risk profile.

**Treatment**

Until recently, no therapeutic agent has been shown to favorably influence renal function in spite of multiple interventions reported over the past 17 yr (29). However, in four recently published studies, treatment with corticosteroids (13,14), fish oil (12), and ACE inhibitors (ACEi) (15) slowed renal progression in patients who had the more common chronic, persistently proteinuric form of the disease. In another uncontrolled study, treatment with high-dose immunoglobulins was shown to stabilize renal function in 11 adults with severe IgAN (30).

The use of alternate-day prednisone in children (13) and daily prednisolone in adults (14) has been shown to stabilize renal function more than in nonsteroid-treated patients in whom initial renal function was normal or only mildly impaired (Table 3). The duration of steroid treatment was long term (1 yr and longer), and there were few serious adverse side effects reported either in the child or adult study groups (13,14). However, results from three recently published control trials of steroids have shown no benefit (31–33). Each of these trials included small numbers of patients who were followed for 12 mo or less.

The efficacy of dietary fish oil has been tested in patients with IgAN in four randomized studies with varying results (12,34–36). The rationale for using fish oil in IgAN is based on the premise that n-3 polyunsaturated fatty acids alter the production or action of cytokines and eicosanoids evoked by the initial or by repeated immunological renal injury, thereby influencing mediators involved in ongoing renal damage (37). In the four published randomized clinical trials, two studies showed that fish oil stabilized renal function and two trials reported a decline in renal function (Table 4). The largest study of 106 patients in a double-blind, placebo-controlled trial conducted by our collaborative group provided strong evidence of protection from 2 yr of treatment with a daily dose of fish oil (12 g/d of a 30% concentrate of eicosapentanoic acid and docosahexanoic acid) given to patients with persistent proteinuria greater than 1 g/24 h and deteriorating renal function (serum creatinine <3 mg/dl at study entry) (12). In the study from Japan, renal function did not deteriorate in 9 patients who were treated with fish oil for 1 yr but did decline in 11 who were untreated (34). The study from Sweden might have failed to show a benefit because of the short, 6-mo follow-up period; the changes in renal function were small but statistically significant, yet of little clinical significance (35). In the Australian

**Table 3. Nonrandomized controlled long-term studies of corticosteroid treatment of proteinuric patients with IgAN**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Effect of treatment on Renal Function</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid-Treated Subjects</td>
<td>Control Subjects</td>
<td></td>
</tr>
<tr>
<td>Children and adolescents (13)</td>
<td>13</td>
<td>15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Stabilized</td>
</tr>
<tr>
<td>Adults (14)</td>
<td>20</td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Stabilized</td>
</tr>
</tbody>
</table>

<sup>a</sup> Historically derived from other centers.

<sup>b</sup> Allocated to treatment according to the order of the renal biopsy, and all were given dipyridamole 300 mg/d.

**Table 4. Controlled clinical trials of fish oil treatment of IgAN**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>EPA/DHA* (g/d)</th>
<th>Treatment Duration (yr)</th>
<th>Effect of Treatment on Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese (34)</td>
<td>20</td>
<td>1.6/1.0</td>
<td>1</td>
<td>Stabilized</td>
</tr>
<tr>
<td>Australian (36)</td>
<td>37</td>
<td>1.8/1.2</td>
<td>2</td>
<td>Declined</td>
</tr>
<tr>
<td>Swedish (35)</td>
<td>32</td>
<td>3.3/1.8</td>
<td>0.5</td>
<td>Declined</td>
</tr>
<tr>
<td>U.S. American (12)</td>
<td>106</td>
<td>1.8/1.2</td>
<td>2</td>
<td>Stabilized</td>
</tr>
</tbody>
</table>

<sup>*</sup> EPA, eicosapentanoic acid; DHA, docosahexanoic acid.
the failure to show any benefit from fish oil in a study design similar to ours included only 37 patients and did not mention the number of hypertensive subjects or how they were managed (36). Hypertension is an important risk associated with progressive renal failure.

In a retrospective study from the Toronto Glomerulonephritis Registry, Cattran and associates reported that treatment with ACEi attenuated the decline in GFR based on a comparison of treatment of one group of hypertensive patients with ACEi drugs, another group treated with antihypertensive agents other than ACEi, and a third group of untreated normotensive patients (15). There were similar but lower rates of decline in creatinine clearance between ACEi-treated hypertensive and normotensive individuals compared with the hypertensive patients treated with other agents, suggesting a renal protective effect from the ACEi in hypertensive patients with IgAN. Yet the observed annual decline in estimated GFR in the ACEi-treated patients was similar not only to the normotensive Canadian group, but also to the high-risk patients reported from Sweden (38) and the placebo-treated group in our fish oil trial (12) in whom serial estimates of GFR were determined (Table 5). Moreover, decreases in GFR found in the ACEi-treated hypertensive and normotensive Canadian patients, the high-risk Swedish patients, and the placebo-treated patients were significantly greater than the fish oil-treated group, providing further evidence for the efficacy of fish oil in slowing progressive renal disease and suggesting a more effective therapy than that provided by ACEi inhibitors.

However, with the discrepancy of results in the four clinical trials testing fish oil and in an effort to resolve the issue of which is the better treatment for patients at risk of developing progressive renal disease—corticosteroids or n-3 fatty acids—two randomized clinical trials are currently under way in the United States (39; and Donadio JV Jr., Bergstralh EJ, Offord KP, Spencer DC, Grande JP, for the Mayo Nephrology Collaborative Group: A prospective comparative study of two doses of OmacorTM in the treatment of patients with IgA nephropathy, in progress). The first trial tests the hypothesis that alternate-day prednisone or daily fish oil will retard the decline in renal function in children and young adults with moderate IgAN (39). The study design is a randomized, placebo-controlled multicenter trial conducted by the North American IgA Nephropathy Study Group comprised of both pediatric and internal medicine nephrologists. The second trial tests the hypothesis that an increased amount of n-3 fatty acids will influence clearly progressive IgAN (Donadio et al., study in progress). The design is an open-label, comparative dose study using a highly concentrated form of n-3 polyunsaturated fatty acids (OmacorTM) and is being conducted by our collaborative group. In both of these trials, the ACEi enalapril is being used to treat hypertensive patients. Both of these prospective studies involve 2 yr of treatment, and because patients were entered in the study in late 1995, results are not yet available.

It is evident, of course, that not every patient who was treated with any of these regimens—corticosteroids, fish oil, or ACEi—had a stabilization of renal function. There was relentless progressive loss of renal function in a subset of patients in these study cohorts for which there seems to be no effective treatment. Hence, our rudimentary understanding of progressive renal disease is the reason for a lack of effective therapies to curtail this disease in all patients.

### Renal Transplantation

Because IgAN is more common in young adults, those who develop renal failure are generally in good health, except for renal failure, and at an ideal age for renal transplantation. In a review of renal transplantation at the Mayo Clinic from 1963 to 1988, Frohner and Steriolf reported that IgAN accounted for 10% of renal transplants done in patients with primary glomerulonephritis (41).

After renal transplantation, IgAN has been shown to recur in 20 to 60% of grafts (42–48). This large variability probably relates to the circumstances under which recurrence is diagnosed. Transplant programs that perform serial allograft biopsies in every recipient (42,45) tend to uncover recurrent mesangial IgA deposition more often and earlier than those that reserve graft biopsies for clinical indication only (44,46,48). Initially considered a benign condition (47), allograft losses from recurrent IgAN have been reported in the last 2 yr, casting doubt on the initial premise (45,48,49). An Australian study with 51 grafts in 46 patients revealed that recurrent IgAN was responsible for significant functional deterioration in 29% of 17 biopsy-proven cases and in 36% of those who also had signs

---

**Table 5. Annualized changes in estimated GFR in different patient groups with IgAN**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>GFR Changea (ml/min per yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockholm, Sweden (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all patients</td>
<td>153</td>
<td>-1.4</td>
</tr>
<tr>
<td>males</td>
<td>106</td>
<td>-2.5</td>
</tr>
<tr>
<td>advanced histology</td>
<td>48</td>
<td>-3.4</td>
</tr>
<tr>
<td>proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 g/24 h</td>
<td>72</td>
<td>-3.6</td>
</tr>
<tr>
<td>&gt;3.5 g/24 h</td>
<td>11</td>
<td>-8.8</td>
</tr>
<tr>
<td>hypertension</td>
<td>68</td>
<td>-4.0</td>
</tr>
<tr>
<td>Toronto Glomerulonephritis Registry (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normotensive</td>
<td>33</td>
<td>-6.0</td>
</tr>
<tr>
<td>hypertensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi-treatedab</td>
<td>27</td>
<td>-8.4</td>
</tr>
<tr>
<td>other antihypertensives</td>
<td>55</td>
<td>-12.0P&lt;0.05</td>
</tr>
<tr>
<td>Mayo Collaborative Study Group (U.S.) (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo-treated</td>
<td>51</td>
<td>-7.1</td>
</tr>
<tr>
<td>fish oil-treated</td>
<td>55</td>
<td>-0.3P&lt;0.01</td>
</tr>
</tbody>
</table>

---

a Average annual slopes of 51Cr-ethylenediamine tetra-acetic acid clearance for at least 1 yr in Swedish patients, median annual slopes of creatinine clearance for at least 3 mo in Toronto patients, and mean annual slopes of creatinine clearance for at least 2 yr in U.S. American patients.

b ACEi, angiotensin-converting enzyme inhibitor.
Figure 2. Actuarial renal allograft survival according to donor kidney source. There was 5-yr graft survival of 100% in HLA-2 haplotype-matched living related donor (LRD)-2, 88% in HLA-1 haplotype-matched LRD-1, and 74% in cadaveric donor (CAD) kidneys. All three HLA-mismatched (LRD-0) kidneys were functioning for up to 1.6 yr (longest follow-up) \( (n = \text{number of recipients at risk at a given time}) \). Reprinted with permission from Frohnert PP, Donadio IV, In, Vebosa IA, Holley KE, Sterioff S: The fate of renal transplants in patients with IgAN. Clin Transplant 1997, in press.

Table 6. Recurrence of IgAN in renal allografts according to graft source in several patient groups

<table>
<thead>
<tr>
<th>Study Group and Year</th>
<th>No. of Transplants</th>
<th>CAD</th>
<th>LRD-1</th>
<th>LRD-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France, 1975 (42)</td>
<td>12</td>
<td>1/4</td>
<td>1/1</td>
<td>5/7</td>
</tr>
<tr>
<td>San Francisco, CA, 1986 (50)</td>
<td>13</td>
<td>1/7</td>
<td>4/4</td>
<td>1/2</td>
</tr>
<tr>
<td>Rochester, MN, 1994 (48, 49)</td>
<td>50(^b)</td>
<td>4/12</td>
<td>9/29</td>
<td>1/9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>75</td>
<td>6/23</td>
<td>14/34</td>
<td>7/18</td>
</tr>
</tbody>
</table>

Based on statistically nonsignificant data (50, 51) and then reappeared in a nephrology text as an unreferenced opinion (52). If the number of shared HLA antigens between donor and recipient should increase the risk of IgAN recurrence, then HLA-identical kidneys should suffer the highest rate. All studies with sufficient data to determine rates of recurrence in LRD-1 and in LRD-2 grafts (2.5) are listed with our own results in Table 6. A total of 75 transplants were available for analysis, representing 23 CAD grafts, 34 LRD-1 kidneys, and 18 LRD-2 kidneys. There was no statistical difference in the incidence of IgAN between these patient categories. Thus, LRD transplantation should not be discouraged for fear of disease recurrence. In addition to a recurrence rate of 26% in our patients, there was a 71% incidence of declining glomerular filtration in 14 grafts with recurrent IgAN, which far exceeds that seen in patients without recurrence (14%) (49).

The interval of 2 yr between transplantation and development of recurrence of IgAN and 3 yr to significant loss of allograft function coincides with the Australian study (45). Finally, in our series, there was no relationship between the aggressiveness of the primary disease and the rate of IgAN recurrence, which supports a previous observation by Berger et al. (42).

It appears that D'Amico's observation concerning primary IgAN that the most frequent clinical course is an indolent, slowly progressing chronic disease (2) also applies to recurrent IgAN in the renal allograft.

References


35. Petesset EE, Rekola S, Berglund L, Sundqvist KG, Angelin B, Diczfalusy U, Bjorkholm I, Bergstrom J: Treatment of IgA nephropathy with omega-3 polyunsaturated fatty acids: A pro-


40. Deleted in proof.


