Natural History of Idiopathic IgA Nephropathy and Factors Predictive of Disease Outcome

By Giuseppe D'Amico

Among the numerous studies published in the last 20 years that have calculated the actuarial renal survival and tried to individuate the prognostic role of the clinical and histologic features present at the onset of the disease or the time of biopsy, we chose to critically analyze the results of the most valid (23 studies). Actuarial renal survival at 10 years in adults was between 80% and 85% in most of the European, Asian, and Australian studies, but was lower than this in studies from the United States and exceeded 90% in the few studies on children. Concordance existed in this selected literature on the fact that impairment of renal function, severe proteinuria, and arterial hypertension are the strongest and more reliable clinical predictors of an unfavorable outcome. Extent of proteinuria during follow up was an even stronger predictor. In adult patients, a high score of the glomerular and tubulointerstitial lesions predicted a more rapid progression. When the single lesions were analyzed separately, glomerular sclerosis and interstitial fibrosis appeared to be the strongest, most reliable predictors of unfavorable prognosis. More controversial was the role of crescents and capsular adhesions.

IN ALMOST 50% OF PATIENTS, the clinical presentation of idiopathic IgA nephropathy is episodic, macroscopic hematuria often coincident with an upper respiratory tract infection (or, less commonly, gastroenteritis), which is frequently recurrent. The presenting clinical sign in the remaining patients is the finding of urinary abnormalities, characterized by persistent microscopic hematuria, associated with proteinuria which is usually mild (or even absent, in more than 10% of our patients) and is frequently discovered by a chance urinalysis. Obviously, the asymptomatic urinary abnormalities of this large subgroup are frequently overlooked in geographic areas or institutions with restrictive biopsy policies, with consequent "selection" of the population whose clinical course is monitored. This phenomenon of selection could probably explain why in some surveys severe proteinuria with nephrotic syndrome is reported in a consistent percentage of cases, whereas in less selected populations it is a rare occurrence.

The most common clinical course is an indolent one, a slow progression to renal insufficiency manifesting in some, but not all, patients. However, in a small percentage of cases (approximately 4%), rather prolonged remission of all clinical signs has been reported, even without any treatment, although concomitant disappearance of IgA deposits has been an exceptional phenomenon. A clinical course characterized by more rapid progression is also reported in a few cases, usually associated with the presence of marked extracapillary proliferation and/or segmental necrotizing lesions of the capillary loops.

OUTCOME: ACTUARIAL RENAL SURVIVAL

Despite the relative paucity of relevant symptoms during the clinical course, the outcome is extremely variable and difficult to predict, as we[1] and other[2] have already emphasized many years ago. Some patients who presented with an episode of macroscopic hematuria, after 40 years and dozens of recurrences of the macroscopic hematuria still have a normal renal function and in repeat biopsies, after the four decades, show only mesangial proliferation with scarce segmental glomerular sclerosis or interstitial fibrosis. Some other patients, without previous apparent signs of illness, arrive at the outpatient clinic because of headache of recent onset and elevated serum creatinine, and show at biopsy diffuse glomerular sclerosis and interstitial fibrosis, together with IgA deposition. Within these two extremes of a rather atypical clinical course, every nephrologist has seen patients with a wide range of intermediate clinical behaviors that together outline a chronic disease with low-grade nonspecific clinical manifestations (microscopic hematuria and usually mild proteinuria, sometimes with one or more bouts of gross hematuria associated with acute mucosal infections) and an indolent, slowly progressive course morphologically characterized through time by gradual conversion of an initial mesangial expansion and proliferation to mesangial sclerosis (up to

From the Department of Nephrology and Immunology, San Carlo Borromeo Hospital, Milan, Italy.

Supported in part by EU Grant OLG1-CT-2002-01215 and by the Associazione per la Ricerca in Nefrologia.

Address reprint requests to Giuseppe D'Amico, MD, FRCP, Department of Nephrology and Immunology, San Carlo Borromeo Hospital, Via Pio II, 3, 20153, Milan, Italy. Email: giuseppe.damico@oscb.sined.net

0270-9295/04/2403-0002$30.00/0
doi:10.1016/j.semnephrol.2004.01.001

total sclerosis of a progressively increasing number of glomeruli) and by the gradual conversion of an initial interstitial infiltration of leukocytes to increasingly severe interstitial fibrosis.

This extreme variability of the clinical course, even when (as it frequently happens in IgA nephropathy [IgAN]) no treatment is carried out, explains the controversial results of the hundreds of studies published in the last 20 years that have tried to estimate the rate of progression to end-stage renal failure and to individuate the prognostic role of the clinical and histologic features already present at the onset of the observation period.

A critical analysis of these studies, usually retrospective, is difficult for many reasons: (1) they dealt with largely different selected populations of patients, enrolled in different stages of their course (this bias is particularly evident for this glomerular disease, in which diagnosis depends on the different local policies as to the indications for biopsy, the patients with less severe clinical signs being biopsied in some places but not in others); (2) the patients enrolled were followed for extremely variable periods of time; (3) the enrolled cohorts sometimes included both treated and untreated patients, and the effect of treatment on the natural history was not taken into account, because therapy in this disease has been until now extremely variable and aspecific, and it is still difficult to say if, and to what extent, it has favorably influenced such natural history; (4) the statistical analysis was carried out with different, sometimes incorrect, modalities; and (5) the clinical features, and even more the histologic features, singled out as potential prognostic indicators in these statistical analyses varied from one study to another, making comparisons of results either very difficult or virtually impossible.

For all of these reasons, in the present review, which updates a previous study,[3] we selected those studies that were ranked the best from a methodologic perspective (according to the quality criteria proposed by Roodnat et al.[4]), comprising one-tenth of the hundreds of published studies.

Since new good studies became available, in these last 3 years, we have been even more selective in the criteria of inclusion of the less recent studies. They should meet the following qualifying requirements: (1) large cohorts of patients as nonselected as possible, including those observed in an early stage of disease; (2) definite histologic and clinical criteria for the diagnosis and the outcome of the idiopathic type of the disease; (3) reasonably complete (small percentage of patients lost to observation) and prolonged (at least 5 years on average) follow ups; and (4) accurate statistical evaluation, using lifetime analysis and possibly also multivariate survivorship analysis according to the Cox regression model.

Actuarial Renal Survival in Adults

We selected (Table 1) 21 studies, carried out in different geographic areas on large relatively nonselected cohorts of adult patients, in which actuarial renal survival rate at 10 years using lifetime survivorship analysis was calculated. In Table 1 we also summarized, together with the results of this analysis, some relevant demographic data and clinical features at the time of presentation such as prevalence of renal insufficiency, arterial hypertension, severe proteinuria, and macroscopic hematuria, which better characterize the cohorts studied by the various investigators. It is immediately evident that, even in these selected studies, there is wide variability in the prevalence of the clinical signs typical of more severe stages of the disease, thus indicating that the cohorts included in the various studies have been more or less selected; in fact, at presentation, abnormally high levels of serum creatinine ranged between 2% and 59%, arterial hypertension between 6% and 49%, proteinuria >3 g/24 hours between 1% and 33%, and macroscopic hematuria between 20% and 78%. However, the actuarial renal survival at 10 years reported by the majority of studies in Europe, Asia, and Australia was included in a restricted range (between 81% and 87%), the only exceptions being the data reported by Alamartine et al.[13] in France, Woo et al. in Hong Kong,[18] and Ibels et al.[17] in Australia, indicating a particularly good prognosis (94%, 91%, and 93%, respectively), and those of Payton et al. in the United Kingdom[15] and Katafuchi et al.[20] in Japan, indicating a poorer survival (77% and 74%). A decisively poorer renal survival rate (67% and 57%, respectively) was also reported in two of the three studies from the United States,[25,26] and in the only study from Canada,[27] probably referring to cohorts of more severely ill symptomatic patients, as suggested by the high incidence of renal insufficiency, proteinuria in the nephrotic range, and arterial hypertension at the time of biopsy in the two studies from the United States.

Table 1. Actuarial Renal Survival at 10 Years, and Clinical Features at Presentation, In Large Populations of Adult Patients With IgAN, According to the Most Accurate Studies of the Literature

Authors and Country	Clinical Features at Presentation							
	No. of Patients	Mean Age at Presentation (yr)	High Serum Creatinine (%)	High Blood Pressure (%)	Proteinuria >3 g/24 Hours	History of Macroscopic Hematuria (%)	Mean Duration of Follow-up (months)	Actuarial Renal Survival at 10 Years
Europe								
D'Amico et al (1986), Italy[5]	365	29	24	36	7%	55	79	85%*
Beukhof et al (1986), The Netherlands[6]	75	24	—	37	—	46	92	84%*
Droz et al (1984)[7]; Noël et al (1987), France[8]	280	—	—	6	10%	37	>60	85%*
Velo et al (1987), Spain[9]	153	22	—	—	1%	78	>60	81%*
Bogenschutz et al. (1990), Germany[10]	239	—	34	19	—	26	59	81%†
Rekola et al. (1989, 1990), Sweden[11,12]	209	25	16	11	1%	64	76	83%‡
Alamartine et al. (1991), France[13]	282	28	2	9	3%	27	96	94%*
Johnston et al. (1992), UK[14]	220	30	28	26	32%	—	65	83%‡
Payton et al. (1988), UK[15]	67	32	—	40	—	—	—	77%*
Australia								
Nicholls et al. (1984)[16]	244	32	36	43	6%	39	60	87%‡
Ibels et al. (1994)[17]	121	39	36	31	16%	40	107	93%*
Asia								
Woo et al. (1986), Singapore[18]	151	27	6	33	4%	24	65	91%‡
Kusumoto et al. (1987), Japan[19]	87	27	—	31	15%	—	114	80%*
Katafuchi et al. (1994), Japan[20]	225	32	36	22	16%	20	48	74%‡
Yagame et al. (1996), Japan[21]	206	30	—	—	—	—	110	87%‡
Koyama et al. (1997), Japan[22]	448	>10 in 95%	19	29	3%	24	142	85%*
Li et al. (2002), Hong Kong[23]	168	33	—	28	5%	20	88	82%‡
North America								
Wyatt et al. (1984), USA[24]	58	27					>60	78%*
Radford et al. (1997), USA[25]	148	39	59	47	30%	—	45	67%‡
Haas (1997), USA[26]	109	~40	mean = 2.2 ± 1.9 mg/dL	49	33%	35	>18	57%‡
Bartosik et al. (2001), Canada[27]	298	36	—	—	—	—	70	65%*

* From the time of diagnosis.
† Not specified.
‡ From the time of biopsy.
IgAN, IgA nephropathy.

The influence of treatment on the calculated survival rate was not analyzed in any of the 21 cohorts of patients. Considering that this survival appears to be similar in the studies carried out before 1990, when a restrictive policy of treatment was adopted by the majority of investigators, and in those published in the last several years (when angiotensin-converting enzyme (ACE) inhibitors became an almost universally used therapy, and other therapies, including fish oil and steroids, have been more extensively prescribed), it is reasonable to assume that untreated adult patients with idiopathic IgAN have an actuarial 10-year survival rate ranging between 80% and 85% from apparent onset.

A comparative analysis of the renal survival and of the slope of creatinine clearance on a large cohort of 711 patients from 4 centres (Helsinki, Sidney, Glasgow, and Toronto) in three continents has been carried out very recently.[28] In the four studied cohorts, the actuarial renal survival was extremely variable (95.7%, 87.0%, 63.9%, and 61.6% in Helsinki, Sidney, Glasgow, and Toronto, respectively), as was the median slope of creatinine clearance (−1.24 mL/min/year in Helsinki, −2.95 mL/min/year in Sydney, −3.46 mL/min/year in Glasgow and −3.99 mL/min/year in Toronto). According to the investigators, this geographic variability was explainable only partly by an earlier referral and detection of the disease in the centers with a flatter slope (lead-time bias).

Actuarial Renal Survival in Children

Definitely less numerous are the studies on outcome in sufficiently large cohorts of pediatric patients, and their results do not yet clearly establish whether the renal survival rate of children is better than that of adults.

Only three studies, to our knowledge, have compared the outcome of cohorts of adult and pediatric patients biopsied by the same investigators.[19,24,29] Kusumoto et al.[19] in Japan reported that 10-year actuarial renal survival rate was approximately 80% (see Table 1) in a cohort of 86 adult patients biopsied after the age of 15 years, whereas it was significantly better (approximately 95%) in a cohort of 98 patients biopsied in the same units at the age of ≤15 years. The incidence of arterial hypertension was lower in children than adults (24% vs 31%), whereas that of severe proteinuria in the nephrotic range was comparable (18% vs 15%). Wyatt et al.[24] in the United States compared two cohorts, one of 58 adult patients and the other of 24 patients biopsied at an age ≤17 years, studied in Kentucky. The 10-year actuarial renal survival rate of the adult population was 78% (see Table 1). It was not possible to calculate the 10-year renal survival rate for the pediatric population as a result of the small number of patients; however, after an average follow up from biopsy of 4.9 ± 1.0 years, none of the pediatric patients had reached end-stage renal failure (ESRF). The same group of investigators reported more recently on the long-term prognosis of a larger cohort of 103 pediatric patients diagnosed in Kentucky and Tennessee and biopsied before age 18 years.[30] Predicted 10-year renal survival from the time of apparent onset was 87%, not much better than that of the adult population of the previous study, and predicted 20-year renal survival was 70%. The investigators concluded that "the outcome of pediatric patients with IgAN appears to be as serious as that reported in adult patients. Follow-up of a pediatric patient with persistent clinical findings should be maintained after the patient's care is transferred to a physician caring for adults."

In a third study by Yaguchi et al.,[29] 130 Japanese patients were divided into 3 subgroups: one of patients whose disease became manifest after age 35 years, one of pediatric patients who underwent renal biopsy at under 19 years of age, and a third intermediate group of patients biopsied between 20 and 34 years of age. No lifetime analysis was carried out; however, at the end of the follow up, 9.5% of patients with adult onset had progressed to ESRF vs 2.1% of pediatric patients.

The conclusion that pediatric patients could have a progressive course has been confirmed also by investigators who did not study control cohorts of adult patients, but followed children for sufficiently long periods of time.[31-37] However, the majority of these studies showed a long-term prognosis better than that usually found in adult patients (10-year renal survival rate was 93% in the cohort of 91 children studied by Levy et al.) and less severe clinical signs (hypertension, proteinuria, impaired renal function) and histologic lesions (extent of sclerosis and tubulointerstitial damage) at the time of biopsy. A clinical remission has been described in percentages ranging between 35% and 53%,[31,32,38] and an improvement of the

histologic lesions has been reported at a repeat renal biopsy in some patients.[38]

CLINICAL, HISTOLOGIC, AND GENETIC PROGNOSTIC FACTORS IN ADULTS AND CHILDREN

Among the numerous studies on the clinical and histologic predictors of an unfavorable outcome in adult patients with IgAN, we selected, according to the criteria previously mentioned, 23 studies in which an univariate analysis of the various risk factors, each independently considered, has been performed, usually comparing renal survival rates calculated according to the method of Kaplan and Meyer. A multivariate survivorship analysis of the prognostic factors that had appeared more significant at the univariate analysis, according to the Cox regression model, was associated in 20 of these 23 studies to single out the most powerful independent indicators of bad prognosis.

There are very few long-term follow-up studies of patients with a clinical onset of IgAN during childhood in which the prognostic role of the various clinical histologic factors has been evaluated using the renal survival analysis.[19,30,37] This is probably the result of the previously mentioned slower progression of the disease in these patients and the consequent infrequency of the occurrence of ESRF as an end point for the statistical analysis during the pediatric age.

Clinical Prognostic Factors in Adults (Studies in Unselected Cohorts of Patients)

Table 2 shows that three clinical features at the time of presentation, analyzed in all studies, were found to be strong indicators of unfavorable prognosis according to the univariate survivorship analysis: abnormally high levels of serum creatinine, severe proteinuria (expressed differently in the various studies), and arterial hypertension. Even the extent of erythrocyturia (number of cells/volume unit at sediment microscopic examination) at presentation resulted in a significant predictor in four of the five studies in which it was taken into consideration.

The value of the absence of episodes of gross hematuria in the history or at presentation as a clinical indicator of poor prognosis was also evaluated with the univariate analysis in 19 of the 23 studies and was found significant in 11 of them.

Less significant risk factors appeared to be older age at onset and male sex. Actually, in the study from the Mayo Clinic,[25,41] younger instead of older age and female sex instead of male sex were found to be significant risk factors. A separate metaanalysis of the effect of gender on the progression of IgAN has been recently carried out, selecting 16 studies (partly including those of our Table 2) that contained 1464 patients; there was a positive significant association in the direction of an unfavorable renal outcome in males.[49]

The multivariate survivorship analysis, according to the Cox's model, confirmed that three clinical parameters measured at the beginning of the follow-up period, an elevated serum creatinine, severe proteinuria, and an elevated blood pressure were powerful independent predictors of bad outcome in adult patients. Impaired renal function was a significant risk factor in 14 of the 18 studies in which it was included in the analysis, severe proteinuria appeared to be significant in 17 of 21 studies, and arterial hypertension in 13 of 18 studies (Table 2).

The other clinical parameters predicting outcome at the univariate analysis, ie, the absence of history of macroscopic hematuria, the extent of erythrocyturia, an older age at onset, and male sex, lost their prognostic value at the multivariate analysis in the majority of studies (Table 2).

In a few studies, the predictive roles of proteinuria[27,41,42] and of arterial hypertension[25,27,48] were evaluated considering the values obtained during follow up. As expected, values during follow up were more powerful predictors than the values at the beginning of the observation period. In the study of Kobayashi et al.,[42] only follow-up proteinuria (percent duration of massive proteinuria), but not the initial proteinuria, maintained its predictive value at the multivariate analysis, whereas in the study by Donadio et al.,[41] proteinuria at 1 year was the only independent predictor of ESRF at the stepwise regression analysis. Very recently, a group of Japanese investigators,[50] correlating proteinuria with histologic changes, elaborated a proteinuria index (the product of quantity of proteinuria at the time of observation and duration of proteinuria in years) as the most relable predictor of the progression of the histologic damage.

Not only quantity, but also composition, of proteinuria has been correlated with outcome. In particular, an elevated elevated excretion of proteins

Table 2. Statistical Analysis of the Predictive Value, as Risk-Factors for ESRF, of Some Clinical Features in 23 Studies Selected From the Literature

Authors	Country	No. of Patients	Age	Sex	Reduced GFR	Hematuria: Absence of Macroscopic Hematuria	Hematuria: Marked Erythrocyturia (cell count)	Severe Proteinuria: At Presentation	Severe Proteinuria: During Follow-Up	Arterial Hypertension: At Presentation	Arterial Hypertension: During Follow-Up
Droz et al., 1984[7]	France	244	●■	●■	—	●□	—	●■	—	●■	—
Nicholls et al., 1984,[16] Packham et al., 1996[39]	Australia	845	●	●	●	○	●	●	—	●	—
D'Amico et al., 1986[5] and 1987[40]	Italy	292	●■	○	●■	●□	—	●■	—	●■	—
Beukhof et al., 1986[6]	The Netherlands	75	○	—	●■	●■	●□	●■	—	●■	—
Rekola et al., 1989[11]	Sweden	155	●□	○■	●□	○	—	●■	—	●■	—
Bogenschutz et al., 1990[10]	Germany	239	●□	○	●■	●□	—	●□	—	●□	—
Alamartine et al., 1991[13]	France	282	○	○	○	○	—	●■	—	●■	—
Ibels et al., 1994[17]	Australia	121	●□	—	●■	●□	—	●■	—	●□	—
Johnston et al., 1992[14]	UK	253	●□	○	●■	○	—	●■	—	●□	—
Katafuchi et al., 1994[20]	Japan	225	●□	○	●■	○	○	●■	—	○	—
Yagame et al., 1996[21]	Japan	206	○	○	●■	○	—	●■	—	●□	—
Radford et al., 1997,[25] Donadio et al., 2002[41]	USA	148	● ○■†	● ○■‡	●■	—	—	●□	●■	●□	○□
Haas, 1997[26]	USA	109	—	○	●	●	—	●	—	●	—
Kobayashi et al., 1997[42]	Japan	366	○	○	●■	○	—	●□	●■	●■	—
Koyama et al., 1997[22]	Japan	335	—	—	●■	—	—	●■	—	○	—
Frimat et al., 1997[43]	France	210	○	○■	●■	●■	—	●■	—	●■	—
Vleming et al., 1998[44]	The Netherlands	83	○	○	●■	●□	●□	●■	—	●■	—
Rychlik et al., 1999[45]	Germany and Czech Republic	177	—	—	●■	●■	—	●■	—	●■	—
Daniel et al., 2000[46]	France	194	—	—	●□	●■	●■	●■	—	●■	—
Syrjanen et al., 2000[47]	Finland	223	●□	○	○□	○	—	●■	—	●■	—
Li et al., 2002[23]	Hong Kong	168	—	—	●■	—	—	●■	—	●■	—
Rauta et al., 2002[48] (▲)	Finland	259	—	●□	●□	●□	—	●□	—	●■	●■
Bartosik et al., 2001[27]*	Canada	298	○	○	○	—	—	●■	●■	○	●■

At the univariate analysis ● = significant; ○ = not significant
At the multivariate analysis ■ = significant; □ = not significant
▲ Multivariate analysis refers to the subgroup of patients with normal renal function at diagnosis
* Slope of CrCl over time, instead of renal survival, was used as end point for the statistical analysis.
† Youngest at higher risk;
‡ Female at higher risk.
ESRF, end-stage renal failure; GFR, glomerular filtration rate.

of low molecular weight by SDS–polyacrylamide gel electrophoresis has been found to be a negative prognostic indicator by Nagy et al.[51] and Woo et al.[52] The elevated excretion of these proteins is the consequence of a reduced capacity of tubular cells to reabsorb them, pointing to more severe tubular damage.[53] We confirmed that elevated excretion of one such protein, α1-microglobulin, is also a predictor of bad prognosis (unpublished data). Concerning the prognostic role of follow-up arterial hypertension, a separate survival analysis by Payton et al.,[15] comparing progression of hypertensive patients at presentation who remained hypertensive versus those whose hypertension was controlled by treatment, demonstrated that successfully treated patients had a significantly better renal survival. According to one of the studies reported in Table 2[23] even a family history of hypertension was a significant predictor of worse prognosis by univariate analysis and maintained its significance even by multivariate analysis.

Some of the studies summarized inTable 2 focused also on other potential clinical risk factors. In the study by Syrijanen et al.,[47] two additional laboratory parameters were independent risk factors for progression, even in the subgroup of patients with normal renal function at the beginning of followup and without antihypertensive medication: hypertriglyceridemia and hyperuricemia at presentation. Hypertriglyceridemia and hyperuricemia were also found to be predictors of more rapid progression by Rauta et al.[48] The possible role of hyperuricemia in accelerating the progression of the renal damage in IgAN, even in patients without reduced renal function at the time of diagnosis, has been stressed also by Ohno et al.,[54] and the recent work of the group of Johnson in Houston is contributing to disclose the potential mechanisms underlying this detrimental effect.[55]

Finally, we want to mention another category of potential markers of severity and progression of IgAN that is being investigated in these last years: the urinary concentration of some mediators of the ongoing immunologic process, especially in the tubulointerstitial compartment. The group of Schena studied two of these: epidermal growth factor (EGF) and monocyte chemiotactic peptide-1 (MCP-1); they found that the EGF/MCP-1 urinary ratio measured at the beginning of the follow-up period in 131 patients discriminated between progressors and nonprogressors.[56]

Table 3. Clinical Prognostic Factors According to the Most Accurate Studies in the Literature

Strong predictors*
Severe proteinuria at presentation and during followup
Arterial hypertension at presentation and during followup
Elevated serum creatinine at presentation
Weak predictors†
Absence of any history of recurrent macroscopic hematuria
Male sex
Older age at presentation
Marked erythrocyturia‡

* Significant by multivariate analysis in almost all studies.

† Significant by univariate analysis in the majority of studies and by multivariate analysis in part of them.

‡ Significant, especially in the early stage of the disease.

Clinical Prognostic Factors in Children

The few data on cohorts of patients with a clinical onset during childhood[19,30,37] suggest a comparable predictive value of the clinical factors already analyzed for the adult patients. Severe proteinuria, impairment of renal function, and arterial hypertension were powerful risk factors, whereas less concordant were the results on the predictive value of age (below or above 10 years) at onset, and gender.

All data on the predictive value of the clinical features for the progression of IgAN in adults and children are summarized in Table 3.

Histologic and Immunohistologic Prognostic Factors in Adults and Children (Studies in Unselected Cohorts of Patients)

The critical evaluation and comparison of the results of the statistical analysis performed by the various investigators to define the role of the different histologic lesions as prognostic indicators in adults has been decisively more difficult. This was the result of the marked differences in the criteria for selection and definition of such lesions, even in the 22 studies on adult patients chosen by us as the most valid.

As summarized by Waldo in a Special Report from the American Databank in 1997,[57] the pathologic systems used to classify patients with IgA can be divided into two groups: lumped and split. The lumped systems assess in essence the overall

Table 4. Comparison of Selected Features Between Three Histologic Grading Systems

Haas' Classification System[26]	Grading System of Lee et al[58]	Semiquantitative Methods
Reports a single score (subclass I–V)	Reports a single score (grades I–V)	Reports multiple scores (eg, global index, glomerular score, interstitial score, vascular score, and so on)
Recognizes interstitial fibrosis as an independent risk factor for survival	Observes that glomerular and interstitial activities are related	Glomerular, vascular, and interstitial scores are independently assessed
Descriptive glomerular features in each subclass are defined	Intensity of glomerular damage in each grade is defined	No descriptive histologic features defined in the scoring
Crescent formation is included in subclasses III and IV	Severity of crescent formation is defined in grades II to V	Severity of crescent formation is independently scored from other component scores

severity of the lesions based on the concomitant evaluation of the lesions found in the various compartments. The two most accepted lumped systems of classification are those of Lee[58] and Haas,[26] both proposing five classes of increasing severity, but many other similar systems have been elaborated in other institutions.[11,16,21-23,44] Alternatively, the split systems, that adopted and modified the semiquantitative severity grading of the various lesions initially described by Pirani and Salinas-Madrigal,[59] allow a detailed analysis of each individual lesion in each of the four major compartments of the kidney (glomeruli, tubules, interstitium, and vessels) and permit the elaboration of a global or aggregate score for each compartment. Obviously, the split systems are more complex and elaborated. They eliminate some risks of the lumped systems (lack of flexibility in interpretation and the chance that important isolated pathologic changes will be missed), and allow the identification of the single elementary lesion or compartment score lesion that plays the greatest role in causing progressive renal damage, and the identification of the correlations existing among the various lesions (for instance, how glomerular damage correlates with tubulointerstitial damage). Table 4 summarizes the comparison of the characterizing features of the three major grading systems, as discussed by Lee in his editorial review of 1997.[60]

As summarized in Table 5, different types of lumped or split pathologic systems have been used in the studies chosen by us (the same studies in Table 2, with the exception of that of Syrijanen et al.[47] and in the three additional studies available in children.[30,36,37] The demonstration of their limited comparability is given by the results reported in one of these studies, that of Bartosik et al.[27] The histologic material of 132 patients was classified by these investigators using concomitantly the five classes of the Lee and of the Haas pathologic system; the distribution of patients among the grades was highly uneven and skewed to the left and right, because 14 and 12 patients were included in class I of Lee and Haas, respectively, 45 and 7 in class II, 37 and 45 in class III, 23 and 41 in class IV, and 13 and 27 in class V.

Taking into consideration this variability, we can summarize the results of the most relevant data of the literature (Table 5) as follows:

1. Among the single features semiquantitatively evaluated, the severity of the glomerular sclerosis and of the interstitial fibrosis appear to be strong independent predictors of a progressive course, even at the multivariate analysis. Although their severity is usually correlated, this is not always the case, as stressed by Bogenschütz et al.[10]
2. The presence of extracapillary proliferation, usually characterized by noncircumferential crescents, appears to be a risk factor in almost all studies in which they have been analyzed separately at the univariate analysis, but only in three of the six studies does it remain a significant predictor of progression at the multivariate analysis. In some studies, its prognostic role has been analyzed together with that of tuft adhesions or as "focal segmental glomer-

Table 5. Statistical Analysis of the Predictive Value, as Risk-Factors for ESRF, of Some Histologic Features in 22 Studies Selected From the Literature

Authors	Country	No. of Patients	Classes of Severity According to Lee (LE), Haas (HA) or Other Classification (OT)	Semiquantitative Evaluation of Elementary Lesions						Peripheral Capillary Deposits by IF or EM
				Glomerular (GL), Tubulointerstitial (TI), Vascular (VA), or Total (TO) Score	Global Glomerular Sclerosis	Segmental Glomerular Sclerosis	Crescents	Tubulointerstitial Damage	Vascular Damage	
Droz et al., 1984[7]	France	244	—	●^{TO}	●	●	●	●	—	—
Nicholls et al., 1984,[16] Packham et al., 1996[39]	Australia	640	●^{OT}	—	●	●	●	●	●	—
D'Amico et al., 1986[15] and 1987[40]	Italy	292	—	—	●■	●■	●□	●■	●□	●■
Beukhof et al., 1986[6]	The Netherlands	75	—		●□	○□	○□	●□	○□	—
Rekola et al., 1989[11]	Sweden	155	●^{OT} ■	●^{TO}	●	—	—	●	—	●
Bogenschutz et al., 1990[10]	Germany	239	—	●$^{GL + TI}$	●□	●□	—	●■	○	—
Alamartine et al., 1991[13]	France	282	—	●^{TO}	●	—	○	●	●	—
Ibels et al., 1994[17]	Australia	121	—	—	●■	●■	●□	●■	—	●□
Johnston et al., 1992[14]	UK	253	—	—	—	●□	—	—	—	○
Katafuchi et al., 1994[20]	Japan	225	—	—	●□	●□	●■	●■	●□	○
Yagame et al., 1996[21]	Japan	206	●^{OT} ■†		—	●□	—	—	—	○
Radford et al., 1997[25] Donadio et al., 2002[41]	USA	148		●^{TO} ■^{GL}	●□	—	—	●□	●□	—
Haas, 1997[26]	USA	109	●^{HA}				●	●		○
Kobayashi et al., 1997[42]	Japan	366		●^{TO} ■^{TO}	●□	●□	○	●■	●□	
Koyama et al., 1997[22] (▲)	Japan	335	●^{OT} □	—	—	—	—	—	—	—
Frimat et al., 1997[43]	France	210	●^{LE}	—	—	—	—	—	—	—
Vleming et al., 1998[44]	The Netherlands	83	●^{OT} ■	—	—	—	—	—	—	—
Rychlik et al., 1999[45]	Germany and Czech Republic	177			●■	—	●■	—	—	●□
Daniel et al., 2000[46]	France	194	●^{HA} □	●$^{TI + VS}$ ■^{TI}	—	—	●■	●■	●■	—
Li et al, 2002[23]	Hong Kong	168	●^{OT} ■	●^{GL} ■^{GL}	—	—	—	—	—	—
Rauta et al., 2002[48] (▲)	Finland	259		●^{TO} ■^{GL}	—	—	○	●□	●■	—
Bartosik et al., 2001[27](*)	Canada	132	●^{LE} □							

Abbreviations: ESRF, end-stage renal failure; GFR, glomerular filtration rate.
At the univariate analysis ● = significant; ○ = not significant
At the multivariate analysis ■ = significant; □ = not significant
▲ Multivariate analysis refers to the subgroup of patients with normal renal function at diagnosis
* Slope of CrCl over time, instead of renal survival was used as end point for the statistical analysis,
† Significant only at the analysis based on slope of GFR.

ular lesions"[16,17,20,42] and found to be a strong risk factor even at the multivariate analysis. Unfortunately, none of the studies has analyzed the role of the possible concomitant presence of segmental necrotizing lesions of the capillary loops on which we have recently focused our attention, considering it a particular histologic feature that points to the existence of a vasculitic component (similar to that frequently found in Henoch-Schönlein purpura) and that can be associated with a clinical course characterized by subsequent bouts of exacerbation.[61]

3. The presence of intense and diffuse mesangial hypercellularity and expansion, when considered as a separate prognostic factor (nine studies), was found to be significant in six cases at the univariate analysis,[5,14,20,42,44,48] but never at the multivariate analysis (not shown in Table 5). Even in the studies restricted to patients with disease in the early stage, the extent of mesangial nonsclerotic involvement did not predict outcome. The same behavior applies also to the arteriolar lesions, appearing as significant predictors in eight of 10 studies, but only twice at the multivariate analysis.[45,48]
4. When a global score for the lesions of the various compartments was considered for the statistical analysis, the overall score was the most significant at the multivariate analysis in one study,[42] the glomerular score in three studies,[23,41,48] and the tubulointerstitial score in one study.[46]
5. When a grading system in classes of overall severity was used (10 studies), the classes characterized by more severe morphologic renal involvement were always associated with an unfavorable prognosis at the univariate analysis, and at the multivariate analysis in four of the seven studies.
6. The only immunohistologic feature that appeared to be a significant risk factor at the univariate analysis (four of the eight studies in which it was included among the analyzed factors) was the extension of the IgA deposition from the mesangial area to the subendothelial site of the peripheral capillary wall: however, only in our study[5] was it a significant risk factor at the multivariate analysis. Only in two studies[11,42] was the codeposition of IgG a risk factor at the univariate analysis (not shown in Table 5).

Table 6. Histologic Prognostic Factors According to the Most Accurate Studies in the Literature

Strong predictors*
Widespread global and/or segmental glomerulosclerosis‡
Marked tubulointerstitial lesions‡
Elevated glomerular and/or tubulointerstitial score of lesions§
Classes of highest severity of overall damage‖
Weak predictors†
Marked extracapillary proliferation‡
Marked arteriolar hyalinosis‡
Extension of IgA deposits into the walls of peripheral capillary loops by IF

* Significant by multivariate analysis in the majority of studies.

† Significant by univariate analysis in the majority of studies and by multivariate analysis in some of these.

‡ Semiquantitative evaluation of single lesions.

§ Scoring system of all lesions in each compartment.

‖ Grading systems of overall severity, according to Lee,[58] to Haas,[26] to other investigators.

All data on the predictive value of the histologic features for the progression of IgAN are summarized in Table 6.

Clinical and Histologic Prognostic Factors in Selected Cohorts of Patients Studied in the Early Stage

We want to emphazise again that all the studies summarized in Tables 2 and 5 tried to identify clinical and histologic risk factors on cohorts of patients grouped together, regardless of the stage of their disease progression, as indicated by the fact that, not unexpectedly, the deterioration of renal function at presentation was one of the most powerful independent predictors of bad prognosis in almost all of them. Because such mixtures of patients, first observed at different stages of the disease, could obscure early clinical and pathologic markers for progression, some investigators have restricted their analysis only to patients without deficit of renal function at the time of first presentation. This is the case of the study of Rauta et al from Helsinki,[48] who found that the count of urinary erythrocytes was an independent predictor of progression at the multivariate analysis only in the subgroup of patients with a normal renal function at the beginning of the follow-up period (Table 2).

Even Koyama et al.[22] studied separately the subgroup of patients with normal renal function at presentation and found by multivariate analysis that the class of severity of the histologic lesions, according to their classification, was not a significant independent risk factor in this subgroup with less severe disease. A separate analysis of the 204 patients with normal renal function at the beginning of follow-up was also carried out by the investigators from Melbourne[39]; they found that severe proteinuria, global sclerosis >40%, and presence of lesions typical of focal segmental glomerular sclerosis were the only predictive factors at the univariate analysis (no multivariate analysis was carried out).

Finally, a separate analysis of the 413 patients presenting with a CrCl ≥75 mL/min was carried out, considering only the clinical parameters, in the previously mentioned tricontinental survey on 711 patients of four different units by Geddes et al.[28]; severe proteinuria was the only independent predictor of subsequent slope of CrCl at multivariate analysis, and patients of Helsinki, in comparison with those of Sydney, Glasgow, and Toronto, had a significant less negative slope, independent of clinical parameters.

A slighty different approach to the identification of the significant predictive factors in the initial stage of the disease was used by Szeto et al.[62] of the same group from Hong Kong[23] whose analysis of the entire cohort of patients is summarized in Table 2 and by Nieuwhof et al.[63] Szeto et al.[62] selected a population of 72 consecutive patients who presented with hematuria (either microscopic or macroscopic), minimal proteinuria (≤0.4 g/day), normal renal function, and normal blood pressure. Adverse events such as proteinuria ≥1 g/day, development of hypertension, or occurrence of impairment of renal function (Cr Cl <70 mL/min) were recorded during a postbiopsy median follow up of 84 months. At the end of the follow up, 33% of patients developed proteinuria, 26% hypertension, and 7% renal impairment; age at presentation and overall severity of the histologic lesions were independent predictors for the development of such adverse effects.

Nieuwhof et al.[63] studied the natural history and the risk factors in a small cohort of 27 adult patients without arterial hypertension or impairment of renal function. In the multivariate analysis, a high initial chronicity index according to their histologic classification, marked erythrocyturia, and mesangial deposition of IgG by IF were the most significant independent risk factors.

A different analytical approach to the study of risk factors, which should be more effective than the analysis of renal survival in selecting individualized prognostic indices, has been used by Bartosik et al.[27] in 298 Canadian patients (last study of Tables 2 and 5) and by Geddes et al.[28] in the tricontinental survey on 711 patients of four different units, including the same Canadian unit in Toronto of the previous study, and three other units in Europe and in Australia. In both studies, the annual rate of disease progression has been evaluated by measuring the slope of glomerular filtration rate (GFR) reduction, determined in each patient by fitting a straight line through at least three calculated (Cockcroft–Gault method) creatinine clearance values, using the principle of least squares. In contrast to standard survival plots, that create only two categories, renal failure or renal survival, the measurement of the slope of GFR allowed these investigators to create a scale of progression that included every patient. In the study by Geddes et al.,[28] in which only clinical parameters were evaluated, severe proteinuria, reduced creatinine clearance, and younger age were associated by multivariate analysis with more negative CrCl slope; in addition, patients from Helsinki, but not Sydney or Glasgow, had a significantly slower rate of deterioration, independent of the clinical parameters at presentation, when Toronto was the reference center.

As Tables 2 and 5 indicate, in the study by Bartosik et al.[27] only proteinuria and hypertension, especially at 1 or 2 years from the beginning of follow up, were clinical independent risk factors, together with the class (V) of more severe histologic lesions according to the classification of Lee (the classification of Haas, also used by the investigators, did not discriminate to a comparable extent). Even the statistical significance of the class V of Lee lost its significance when tested in the multiple linear regression model. Therefore, only two clinical parameters, among all the parameters defined in the other studies in Tables 2 and 5 contributed significantly to the accuracy of their model of prediction: mean proteinuria and mean arterial pressure during follow up. By extending the analysis over progressively longer periods of observation, Bartosik et al.[27] tried to establish the

time frame over which their predictive model assumed an accuracy compatible with clinical use. Although there was a continuous gain in accuracy of prediction with these two parameters over 10 years of follow up, the model rapidly gained in accuracy over the first 2 to 3 years of observation, and therefore appeared to have genuine clinical use early in follow up. Bartosik et al. calculated that for every increase of 10 mm Hg per year in mean arterial pressure (MAP), the rate of renal function loss would increase by 2 mL/min/per year, and for every increase in protinuria of 2 g per day, the rate of loss of renal function would increase by 3 mL/min/per year. Their model predicted zero risk of progression for patients with proteinuria <0.2 g/24 hours who were normotensive, in contrast with the results of Szeto et al.[62] that we have described previously.

On the basis of these selected studies, we can agree that, in the early stages, the usual clinical factors (proteinuria and arterial hypertension), plus the amount of counted urinary erythrocytes, are the most powerful predictors of progression, even more than the histologic lesions, probably because these lesions, especially glomerular sclerosis and interstitial fibrosis, are still absent or mild. These studies suggest that the risk for progression can be almost nil in patients whose disease presents with mild microscopic hematuria, only traces of proteinuria, and absence of arterial hypertension.

Genetic Markers of Progression

Blood pressure and protein excretion together only explained one-third of all variability shown in the GFR slope based on the adjusted R^2 of the model of Bartosik et al.[27] As stressed by these investigators, and by Feehally[64] in the editorial that accompanied their paper, other factors such as the influence of gene and race, together with environmental factors, are probably related to progression and might partly explain the variability in the GFR slope of the different patients. An important genetic contribution, at least in the induction of the disease, is suggested by many known facts, such as: 1) familiar clustering of cases of IgAN (reviewed in[65]); 2) geographic and racial differences in disease prevalence (only partly explained by different renal biopsy policies); and 3) various abnormalities of IgA production in the unaffected relatives of patients with the disease (reviewed in[66]).

Over the past 15 years, a large number of studies have been devoted to the search for disease susceptibility and progression genes involved in IgAN using the two main methods that can depict potential genetic markers, ie, case-control studies, searching for a disease–allele association in a given population, or linkage analysis, focusing on concordant inheritance in familial IgAN.[67,68] Although at the beginning this search, largely centered on the genes encoding the human leukocyte antigens (reviewed in[65,66,69,70]), in more recent years a significant number of data have emerged pointing to an association between IgAN and genes outside the major histocompatibility complex (MHC) loci. In particular, a great number of studies have investigated the role of the polymorphisms of the various genes of the renin–angiotensin system (RAS), especially ACE and angiotensinogen (AGT), on the development and progression of the disease (reviewed in[65,69-74]).

An association with progression of IgAN has also been reported by some, but not all, investigators for the gene polymorphisms of T-cell receptor (TCR) α and β chains,[75,76] endothelial nitric oxide synthase,[77] IL-1 receptor antagonist,[78,79] interferon- γ and IL-4,[80] uteroglobulin,[81] and α1 immunoglobulin gene 3′ enhancer.[82] Other possible candidate genes for progression, which have been investigated in Milan in a large population of 350 patients followed for more than 10 years (Cusi et al, unpublished data), are alpha and beta-adducin. More than 15% of the variance in the progression rate could be explained by the genotypes of the two adducins, especially in patients with moderate proteinuria (<1.5 g/24 hrs).

The results of all these studies have been conflicting and equivocal in demonstrating an association with the progression of the disease, with various methodologic problems that have been analyzed in some recent reviews.[65,68-71]

The great majority of the studies have used a combination of the case-control design (to identify an association between gene polymorphisms and the development of the disease) and the retrospective cohort design (to identify an association with the progression of the disease). In particular, the retrospective analyses, on the results of which the association with progression has been evaluated, have been performed with variable and often insufficient length of follow up, and very few of them attempted to account for the effects of the

other independent poor prognostic indicators for disease progression that we have described previously. Racial differences, which are relevant, could also have contributed to the methodologic weakness inherent in these studies. New large prospective studies of well-defined ethnic/racial cohorts are needed to confirm the evidence that some genes could affect the severity of IgAN and its progression to ESRF. An area of recent interest, which can give more valid results, is the study of the possible interaction between specific allelic variants in two different components of the same system, as demonstrated by Pei et al.[83] in Canada for ACE DD genotype and angiotensinogen (AGT) MM genotype (the former genotype adversely affected disease progression only in patients with the latter genotype) or by Yoon et al.[84] in Korea for ACE and platelet-activating factor acetylhydrolase (PAF-AH) gene polymorphisms (only the concomitant presence of the D allele of the ACE gene and of the T allele of the PAF-AH gene was a significant prognostic factor for progression).

With regard to linkage analysis, it can only be applied to pedigrees with familial IgAN. Although it is likely that these kinds of studies detect the locus (loci) responsible for the occurrence in families of IgAN rather than those responsible for IgAN itself, they could be particularly relevant because Schena demonstrated that familial IgAN has poorer outcome than sporadic IgAN.[85] A collaborative whole genome scan of 30 IgAN families from the United States (six kindreds) and Italy (24 kindreds) has recently shown a strong association with a locus on the long arm of chromosome 6 (6q22-23). The chromosomal region with significant linkage is relatively large (6.5 cM), lies 80 cM distal to the major histocompatibility locus, and no obvious candidate has been detected until now.[86] The most likely genetic transmission is a dominant model with incomplete penetrance and locus heterogeneity. The reduced penetrance suggests that the locus imposes an inherited susceptibility to IgAN, whose expression is dependent on other undetected environmental or genetic modifiers. Finally, it is interesting to note that, despite locus heterogeneity (linkage is present only in 60% of the families), both Italian and U.S. kindreds contribute to linkage, whereas no apparent clinical or demographic features distinguish families with or without linkage to 6q22-23.

CAN WE PREDICT THE ULTIMATE OUTCOME FOR THE SINGLE PATIENTS?

All nephrologists with extensive experience will agree that some patients with rather marked proteinuria and/or severe histologic lesions at the time of biopsy could have rather favorable courses, and some patients with moderate proteinuria and/or mild histologic lesions could have progressive courses in the following years.

Even when some impairment of renal function has already developed and glomerular sclerosis is severe, the speed of progression to ESRF is quite variable. Before the time of the generalized treatment with ACE inhibitors in our patients with IgAN, at the beginning of the 1990s, we looked at the records of the outpatient clinic of our Unit, in which all patients have been followed every 6 months for many years.[1] We found 17 untreated patients who started to have a moderate impairment of renal function (moderately high serum creatinine [SCr] levels between 1.5 and 2.3 mg/dL) more than 4 years and up to 16 years before the last visit (average duration of follow up was 110 months) and who, in many subsequent visits (at least 10), up to the most recent one, showed steady levels of SCr (14 patients) or only slight elevation (SCr between 2.4 and 3.0 mg/dL). None of them received steroids, immunosuppressive drugs, or ACE inhibitors for the entire duration of this long period of observation. It is worth emphasizing that 12 of these 17 patients had arterial hypertension at the beginning of this period with stable impairment of renal function, and that three more developed high blood pressure at some time during the subsequent follow up. Moreover, in the many regular determinations during the period of observation, average proteinuria was <1 g/24 hours in the majority of patients, but it was >1.5 g/24 hours and up to 6 g/24 hours in six of them.

In 10 of these 17 patients, biopsies were taken at the beginning of this long period of already established but barely progressive impairment of renal function. By light microscopy, all degrees of proliferative and/or sclerotic lesions, from mild to very severe, and variable degrees of interstitial involvement were found. The only feature that was common to all 10 cases was the absence of IgG by IF. (Had there been such immunoglobulin in the glomeruli prior to the stage at which the biopsy was performed? We cannot answer, obviously.)

We have observed this atypical behavior in many other patients in the last decade, but because it is our policy to treat all of them with ACE inhibitors, the confounding effect of such therapy cannot be excluded for the new patients.

Similar data, demonstrating the possibility of a stabilization of IgAN, even when moderate renal functional impairment has already occurred, have been obtained by Goumenos et al.[87] reporting on the results of a retrospective therapeutic trial with steroids and azathioprine: among the 22 control patients with an established decrease in renal function (corresponding to a serum creatinine >110 mmol/L at the beginning of the trial), who did not receive treatment, 36% maintained stable renal function at the end of a median follow up of 46 months (range, 12–180 months).

In our study in 1993,[1] we calculated that the "point of no return" for a relentless progression to ESRF was a serum creatinine of approximately 3 mg/dL. More recently, the investigators of the German Glomerulonephritis Therapy Group,[88] looking at their population of 115 patients with IgAN, have confirmed this discriminating value.

CONCLUSION

Three clinical features, when present at the time of diagnosis, are strong predictors of an unfavorable outcome: marked proteinuria, arterial hypertension, and impairment of renal function. The latter is in most instances more a marker of advanced, already progressing renal disease than a true marker of bad prognosis of IgAN. However, even marked proteinuria and arterial hypertension are rather nonspecific markers of severity, valid for all glomerular diseases, as already stressed by us.[89]

It has been recently shown that the persistence, or the increase, of already severe proteinuria during follow up is a more reliable marker of a progressive disease. The investigators of the Mayo Clinic in the United States[25,41] and those from Toronto[27] have demonstrated with their mathematical models of prediction that the behavior of proteinuria during the first 1 or 2 years of follow up is of paramount importance for the predictive power of their models. Even for arterial hypertension, its appearance or persistence during follow up increases the risk of progression of the disease. I suppose that the median values of proteinuria and blood pressure during follow up maintain their predictive value even now that we are able to reduce them with the use of drugs that block the renin–angiotensin system.

There is some evidence, which needs to be confirmed in larger trials, pointing to the predictive value, especially in the earliest stages of IgAN, of the extent of microscopic hematuria, measured as count of urinary erythrocytes in the subgroup of patients without episodes of gross hematuria. This fact would be rather unexpected, because every nephrologist knows how variable the extent of microscopic hematuria can be throughout time in the same patient.

Among the histologic features evaluated at the time of biopsy, the two major markers of chronic damage, glomerular sclerosis (both global and segmental) and interstitial fibrosis, represent the strongest predictors of an unfavorable outcome. Even this evidence is rather expected and nonspecific, being valid for all glomerular diseases.[89] The most valid and complete studies that we have analyzed do not permit us to establish which of the two chronic lesions is a more powerful risk factor, although there is some evidence that the tubulointerstitial damage better predicts the outcome.

All studies concur in stressing the strict correlation between the severity of proteinuria during the follow up and the extent of the tubulointerstitial damage, characterized in early stages by the interstitial infiltration of leukocytes and in later stages also by the presence of interstitial fibrosis. This correlation, which, as we said, is not specific for IgAN, points to a pathogenetic role of the longlasting increased tubular traffic of proteins in inducing damage to the tubular cells, activation of the cytokines–growth factors network, and subsequently the influx of monocytes and T-cells and the fibroblast activation in the interstitium.[90-92]

Still controversial, despite the many studies that we have reviewed, the predictive role of two other glomerular features (the extent of the mesangial expansion and/or hypercellularity), and the presence of the noncircumferential crescents frequently found in IgAN.

Mesangial expansion, probably the most precocious sign of glomerular damage induced by the deposition of IgA, appears to be a relatively unreliable marker of progression, even in the early stages of the disease, probably because it can be a reversible lesion, as demonstrated by studies on repeat biopsy.[93-95] In fact, the studies in selected patients biopsied at an early stage (normal renal

function and blood pressure) indicate that proteinuria, count of urinary erythrocytes, and early signs of chronic sclerotic lesions, even focal and segmental, are the only independent risk factors at the multivariate analysis, whereas the extent of mesangial expansion does not have prognostic significance. In one such study[63] in a small number of patients, even the presence of IgG by IF appeared to predict the outcome. Despite the absence of a similar predictive power in the large studies in unselected populations, we cannot exclude that the intensity of the codeposition of IgG at the onset of the disease could have a role in its evolution. As noted previously, in our small group of 10 patients who have maintained for years the same level of moderate renal insufficiency present at the time of biopsy, none had IgG by IF.

More difficult is to define the predictive value of the presence of noncircumferential crescents for the progression of IgAN. Such crescents have been analyzed, in the majority of the studies reviewed by us, as single independent lesions and found to have a moderate predictive value at the multivariate analysis. However, our recent study[61] of a group of patients with active or healed necrotizing lesions, pointing to a vasculitic injury to the glomerular capillary walls characterized by crescents, capsular adhesions, and a particular type of segmental glomerulosclerosis after healing of the necrotic lesions, suggests that all these segmental lesions should be looked for carefully in every biopsy. In our experience, this necrotizing variant of IgAN is rather rare (<10% of biopsied cases), but Shouno et al.[91] have shown in 128 patients with IgAN that, by increasing the number of serial sections examined for any single biopsy specimen from the usual 20 to 100, the incidence of the segmental necrotizing lesions increased from 7% to as much as 30% of biopsies. As we wrote in the previously mentioned paper,[61] it is our opinion that three different types of damage could be induced in IgAN by the deposition of abnormal IgA in the glomerulus: 1) prevalently mesangial activation and damage; 2) more severe damage to the mesangium, extending to the subendothelial side of the peripheral capillary loops (indicated by the IF pattern and by the presence of subendothelial deposits by electron microscopy); and 3) a rare acute endothelial necrotizing damage, pointing to a capillaritis, usually associated with extracapillary proliferation and capsular adhesions, that can give an intermittent aggravation of the clinical course and probably also a less favorable prognosis. Not only is the presence of necrotizing lesions a marker of more severe disease, but also, as indicated by the predictive value of the mesangioparietal pattern by IF in some studies (Table 5), the extension of the IgA deposits to the subendothelial side of the peripheral capillary loops could indicate a greater likelihood of progressive disease.

A special comment is indicated regarding the choice of the pathologic system of analysis and classification of lesions that is more valid for the prediction of the outcome of the disease. Undoubtedly, only the systems that, using the definition of Waldo,[57] we called "split systems," allow the identification of single specific markers of damage such as crescents, adhesions, interstitial infiltration, and so on, that point to specific pathogenetic mechanisms of damage and can have an independent predictive value. However, all investigators agree, and our review of the literature confirms, that the severity of the lesions developing concomitantly in the glomerular, tubulointerstitial, and vascular compartments vary in a concordant way; this explains why the studies using a grading of the histologic lesions based on classes of progressive severity, which measure the cumulative extent of the renal damage ("lumped" systems), allow a good understanding of the overall histologic risk of progression at the statistical analysis.

There is concordance among the investigators that a clinical course characterized by recurrent episodes of gross hematuria is, at least at the univariate statistical analysis, an indicator of a more favorable outcome, despite the more evident acute bouts of clinical exacerbation. This fact suggests that the damaging mechanism responsible for the progressive disease acts more discontinously (perhaps triggered by exogenous antigens coming intermittently from the mucosal surfaces) in patients with such episodes, whereas in those without recurrent macroscopic hematuria, some less evident but continously acting immunologic mechanism (endogenous antigens, autoantigens, or simply a more marked abnormality of circulating IgA antibodies) could induce more severe and progressive damage with time.

We want to emphazise again the concept of "point of no return" in the irreversible progression of IgAN, which we have already commented on. Patients with severe morphologic lesions and a

serum creatinine below 3 mg/dL could have, in some instances, a nonprogressive course for long periods of time. This behavior suggests that the various nonspecific mechanisms, both immunologic and nonimmunologic, universally accepted as responsible for the irreversible worsening of the overall renal functional impairment up to ESRF in all glomerular disease, could in IgAN nephropathy start to become effective when the damage resulting from the primary injuring mechanism is already quite severe and sclerotic lesions quite advanced. We[1] and others[88] agree that, in the case of IgAN, such "point of no return" is a level of serum creatinine higher than 3 mg/dL.

As we have discussed, the clinical and histologic risk factors explain less than 30% of the variability in the slope of decrement of the GFR in IgAN.

The residual variability is probably the result of genetic factors, which, as we documented, are still obscure, and environmental factors (diet ? infections ?). However, it is our impression that the clinical variability of this disease is even wider than that of other chronic idiopathic immune-mediated glomerular diseases. We suspect that such heterogeneity is consequence of the fact that, what we now call IgA nephropathy, is a spectrum of diseases sharing a common pathogenetic marker, the mesangial deposition of IgA immune complexes, but having a subsequent course depending on different and still-unknown mechanisms of progressive immunologic and nonimmunologic damage, some of which probably act in a discontinuous way.

REFERENCES

1. D'Amico G, Ragni A, Gandini E, et al: Typical and atypical natural history of IgA nephropathy in adult patients. Contrib Nephrol 104:6-13, 1993

2. Schena FP: A retrospective analysis of the natural history of primary IgA nephropathy worldwide. Am J Med 89:209-215, 1990

3. D'Amico G: Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis 36:227-237, 2000

4. Roodnat JI, Van Stiphout WAHJ, Rosendaal FR, et al: What do we really know about the long-term prognosis of IgA-nephropathy? J Nephrol 3:145-151, 1991

5. D'Amico G, Minetti L, Ponticelli C, et al: Prognostic indicators in idiopathic IgA mesangial nephropathy. Q J Med 59:363-378, 1986

6. Beukhof JR, Kardaun O, Schaafsma W, et al: Toward individual prognosis of IgA nephropathy. Kidney Int 29:549-556, 1986

7. Droz D, Kramar A, Nawar T, et al: Prognostic factors. Contrib Nephrol 40:202-207, 1984

8. Noel LH, Droz D, Gascon M: Primary IgA nephropathy: From the first described cases to the present. Semin Nephrol 7:351-354, 1987

9. Velo M, Lozano L, Egido J: Natural history of IgA nephropathy in patients followed up for more than ten years in Spain. Semin Nephrol 7:346-350, 1987

10. Bogenschütz O, Bohle A, Batz C, et al: IgA nephritis: On the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. Am J Nephrol 10:137-147, 1990

11. Rekola S, Bergstrand A, Bucht H: IgA nephropathy: A retrospective evaluation of prognostic indices in 176 patients. Scand J Urol Nephrol 23:37-50, 1989

12. Rekola S, Bergstrand A, Bucht H: Development of hypertension in IgA nephropathy as a marker of a poor prognosis. Am J Nephrol 10:290-295, 1990

13. Alamartine E, Sabatier JC, Guerin C, et al: Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analysis. Am J Kidney Dis 18:12-19, 1991

14. Johnston PA, Brown JS, Braumholtz DA, et al: Clinicopathological correlations and long-term follow-up of 253 United Kingdom patients with IgA nephropathy. A report from the MRC glomerulonephritis Registry. Q J Med 84:619-627, 1992

15. Payton CD, McLay A, Boulton Jones JM: Progressive IgA nephropathy: The role of hypertension. Nephrol Dial Transplant 2:138-142, 1988

16. Nicholls KM, Fairley KF, Downling JP, et al: The clinical course of mesangial IgA associated nephropathy in adults. Q J Med 53:227-250, 1984

17. Ibels LS, Györy AZ: IgA nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. Medicine 73:79-102, 1994

18. Woo KT, Edmondson RPS, Wu AYT, et al: The natural history of IgA nephritis in Singapore. Clin Nephrol 25:15-21, 1986

19. Kusumoto Y, Takebayashi S, Taguchi T, et al: Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and adult Japanese. Clin Nephrol 28:118-124, 1987

20. Katafuchi R, Oh Y, Hori K, et al: An important role of glomerular segmental lesions on progression of IgA nephropathy: A multivariate analysis. Clin Nephrol 41:191-198, 1994

21. Yagame M, Suzuki D, Jinde K, et al: Value of pathological grading in prediction of renal survival in IgA nephropathy. Nephrology 2:107-117, 1996

22. Koyama A, Igarashi M, Kobayashi M, et al: Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis 29:526-532, 1997

23. Li PKT, Leung Ho KK, Szeto CC, et al: Prognostic indicators of IgA nephropathy in the Chinese–clinical and pathological perspectives. Nephrol Dial Transplant 17:64-69, 2002

24. Wyatt RJ, Julian BA, Bhathena DB, et al: IgA nephropathy: Presentation, clinical course, and prognosis in children and adults. Am J Kidney Dis 4:192-200, 1984

25. Radford MG, Donadio JV, Bergstralh EJ, et al: Predict-

ing renal outcome in IgA nephropathy. J Am Soc Nephrol 8:199-207, 1997

26. Haas M: Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. Am J Kidney Dis 29:829-842, 1997

27. Bartosik LP, Lajoie G, Sugar L, et al: Predicting progression in IgA nephropathy. Am J Kidney Dis 38:728-735, 2001

28. Geddes CC, Rauta V, Gronhagen-Riska C, et al: A tricontinental view of IgA nephropathy. Nephrol Dial Transplant 18:1541-1548, 2003

29. Yaguchi Y, Tomino Y, Funabiki K, et al: Comparative studies of clinicopathologic changes in patients with adult- and juvenile-onset of IgA nephropathy. J Nephrol 7:182-185, 1994

30. Wyatt RJ, Kritchevsky SB, Woodford SY, et al: IgA nephropathy: Long-term prognosis for pediatric patients. J Pediatr 127:913-919, 1995

31. Linné T, Aperia A, Broberger O, et al: Course of renal function in IgA glomerulonephritis in children and adolescents. Acta Pediatr Scand 71:735-743, 1982

32. Lévy M, Gonzalez-Burchard G, Broyer M, et al: Berger's disease in children. Natural history and outcome. Medicine 64:157-180, 1985

33. Hattori S, Karashima S, Furuse A, et al: Clinicopathological correlation of IgA nephropathy in children. Am J Nephrol 5:182-189, 1985

34. Andreoli SP, Yum MN, Bergstein JM: IgA nephropathy in children: Significance of glomerular basement membrane deposition of IgA. Am J Nephrol 6:28-33, 1986

35. Berg UB: Long term follow up of renal function in IgA nephropathy. Arch Dis Child 66:588-592, 1991

36. Yoshikawa N, Ito H, Nakamura H: Prognostic indicators in childhood IgA nephropathy. Nephron 60:60-67, 1992

37. Hogg RJ, Silva FG, Wyatt RJ, et al: Prognostic indicators in children with IgA nephropathy. Report of the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 8:15-20, 1994

38. Yoshikawa N, Iijima K, Matsuyama S, et al: Repeat renal biopsy in children with IgA nephropathy: Sequential study. Clin Nephrol 33:160-167, 1990

39. Packham DK, Yan HD, Hewitson TD, et al: The significance of focal and segmental hyalinosis and sclerosis (FSHS) and nephritic range proteinuria in IgA nephropathy. Clin Nephrol 46:225-229, 1996

40. D'Amico G, Colasanti G, Barbiano di Belgioioso G, et al: Long-term follow-up of IgA mesangial nephropathy: Clinico-histological study in 374 patients. Semin Nephrol 4:355-358, 1987

41. Donadio JV, Bergstralh EJ, Grande JP, et al: Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol Dial Transplant 17:1197-1203, 2002

42. Kobayashi Y, Kokubo T, Horii A, et al: Prognostic prediction of long-term clinical courses in individual IgA nephropathy patients. Nephrology 3:35-40, 1997

43. Frimat L, Briançon S, Hestin D, et al: IgA nephropathy: Prognostic classification of end-stage renal failure. Nephrol Dial Transplant 12:2569-2575, 1997

44. Vleming LJ, De Fijter JW, Westendorp RGJ, et al: Histomorphometric correlates of renal failure in IgA nephropathy. Clin Nephrol 49:337-344, 1998

45. Rychlik I, Andrasxsy K, Waldherr R, et al: Clinical features and natural history of IgA nephropathy. Ann Med Interne 150:117-126, 1999

46. Daniel L, Sainna Y, Giorgi R, et al: Tubular lesions determine prognosis of IgA nephropathy. Am J Kidney Dis 35:13-20, 2000

47. Syrjänen J, Mustonen J, Pasternack A: Hypertryglyceridaemia and hyperuricemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 15:34-42, 2000

48. Rauta V, Finne P, Fagerudd J, et al: Factors associated with progression of IgA nephropathy are related to renal function. A model for estimating risk of progression in mild disease. Clin Nephrol 58:85-94, 2002

49. Neugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: A meta-analysis. J Am Soc Nephrol 11:319-329, 2000

50. Eiro M, Katoh T, Kuriki M, et al: The product of duration and amount of proteinuria (proteinuria index) is a possible marker for glomerular and tubulointerstitial damage in IgA nephropathy. Nephron 90:432-441, 2002

51. Nagy J, Miltényi M, Dobos M, et al: Tubular proteinuria in IgA glomerulonephritis. Clin Nephrol 27:76-78, 1987

52. Woo KT, Lau YK, Lee GSL, et al: Pattern of proteinuria in IgA nephritis by SDS-PAGE: Clinical significance. Clin Nephrol 36:6-11, 1991

53. D'Amico G, Bazzi C: Pathophysiology of proteinuria. Kidney Int 63:809-825, 2003

54. Ohno I, Hosoya T, Gomi H, et al: Serum uric acid and renal prognosis in patients with IgA nephropathy. Nephron 87:333-339, 2001

55. Kang DH, Nakagawa T, Feng L, et al: A role for uric acid in the progression of renal disease. J Am Soc Nephrol 13:288-289, 2002

56. Schena FP: Markers of progression in IgA nephropathy. J Nephrol 14:554-574, 2001

57. Wyatt RJ, Emancipator SN, Kon V, et al: IgA nephropathy databank: Development of a system for management of renal biopsy acquired data. Am J Kidney Dis 29:817-828, 1997

58. Lee KSM, Rao VM, Franklin WA, et al: IgA nephropathy: Morphological predictors of progressive renal disease. Hum Pathol 13:314-322, 1982

59. Pirani CL, Salinas-Madrigal L: Evaluation of percutaneous renal biopsy. Pathol Ann 3:249-296, 1968

60. Lee SMK: Prognostic indicators of progressive renal disease in IgA nephropathy: Emergence of a new histologic grading system. Am J Kidney Dis 29:953-958, 1997

61. D'Amico G, Napodano P, Ferrario F, et al: Idiopathic IgA nephropathy with segmental necrotizing lesions of the capillary wall. Kidney Int 59:682-692, 2001

62. Szeto CC, Lai FMM, To KF, et al: The natural history of immunoglobulin A nephropathy among patients with hematuria and minimal proteinuria. Am J Med 110:434-437, 2001

63. Nieuwhof C, Kruytzer M, Frederiks P, et al: Chronicity Index and mesangial IgG deposition are risk factors for hypertension and renal failure in early IgA nephropathy. Am J Kidney Dis 31:962-970, 1998

64. Feehally J: Predicting prognosis in IgA nephropathy. Am J Kidney Dis 38:881-883, 2001

65. Hsu SIH, Ramirez SB, Winn PM, et al: Evidence for genetic factors in the development and progression of IgA nephropathy. Kidney Int 57:1818-1835, 2000

66. Schena FP: Immunogenetic aspects of primary IgA nephropathy. Kidney Int 48:1998-2013, 1995

67. Lander ES, Schork NJ: Genetic dissection of complex traits. Science 265:2037-2048, 1994

68. Frimat L, Kessler M: Controversies concerning the importance of genetic polymorphism in IgA nephropathy. Nephrol Dial Transplant 17:542-545, 2002

69. Tang S, Lai KN: Gene polymorphism in IgA nephropathy. Nephrology 6:63-70, 2001

70. Galla JH: Molecular genetics in IgA nephropathy. Nephron 88:107-112, 2001

71. Schena FP, D'Altri C, Cerullo G, et al: ACE gene polymorphism and IgA nephropathy: An ethnically homogeneous study and a meta-analysis. Kidney Int 60:732-740, 2001

72. Suzuki S, Suzuki Y, Kobayashi Y: Insertion/deletion polymorphism in ACE gene is not associated with renal progression in Japanese patients with IgA nephropathy. Am J Kidney Dis 35:896-903, 2000

73. Delos Santos NM, Ault BH, Gharavi AG, et al: Angiotensin-converting enzyme genotype and outcome in pediatric IgA nephropathy. Pediatr Nephrol 17:496-502, 2002

74. Goto S, Narita I, Saito N, et al: A(−20)C polymorphism of the angiotensinogen gene and progression of IgA nephropathy. Kidney Int 62:980-985, 2002

75. Nagasawa R, Matsumura O, Marayama N, et al: T-cell receptor beta-chain gene polymorphism and the prognosis of IgA nephropathy in Japanese patients. Nephron 70:502-503, 1995

76. Deenitchina SS, Shinozaki M, Hirano T, et al: Association of a T-cell receptor constant alpha chain gene polymorphism with progression of IgA nephropathy in Japanese patients. Am J Kidney Dis 34:279-288, 1999

77. Morita T, Ito H, Shehiro T, et al: Effect of polymorphism of endothelial nitric oxide synthase gene in Japanese patients with IgA nephropathy. Clin Nephrol 52:203-209, 1999

78. Shu KH, Lee SH, Cheng CH, et al: Impact of interleukin-1 receptor antagonist and tumor necrosis factor-α gene polymorphism on IgA nephropathy. Kidney Int 58:783-789, 2000

79. Watanabe M, Iwano M, Akai Y, et al: Association of interleukin-1 receptor antagonist gene polymorphism with IgA nephropathy. Nephron 91:744-746, 2002

80. Masutani K, Miyake K, Nakashima H, et al: Impact of interferon-γ and interleukin-4 gene polymorphisms on development and progression of IgA nephropathy in Japanese patients. Am J Kidney Dis 41:371-379, 2003

81. Szelestei T, Bähring S, Kovàcs T, et al: Association of a uteroglobin polymorphism with rate of progression in patients with IgA nephropathy. Am J Kidney Dis 36:468-473, 2000

82. Aupetit C, Drouet M, Pinaud E, et al: Alleles of the α1 immunoglobulin gene 3′ enhancer control evolution of IgA nephropathy toward renal failure. Kidney Int 58:966-971, 2000

83. Pei Y, Scholey J, Thai K, et al: Association of angiotensinogen gene T235 variant with progression of immunoglobin a nephropathy in Caucasian patients. J Clin Invest 100:814-820, 1997

84. Yoon HJ, Kim H, Kim HL, et al: Interdependent effect of angiotensin-converting enzyme and platelet-activating factor acetylhydrolase gene polymorphisms on the progression of immunoglobulin A nephropathy. Clin Genet 62:128-134, 2002

85. Schena FP, Cerullo G, Rossini M, et al: Increased risk of end-stage renal disease in familial IgA nephropathy. J Am Soc Nephrol 13:453-460, 2002

86. Gharavi AG, Yan Y, Scolari F, et al: IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22–23. Nat Genet 26:354-357, 2000

87. Goumenos D, Ahuja M, Shortland JR, et al: Can immunosuppressive drugs slow the progression of IgA nephropathy? Nephrol Dial Transplant 10:1173-1181, 1995

88. Schöll U, Wastl U, Risler T, et al: The point of no return and the rate of progression in the natural history of IgA nephritis. Clin Nephrol 52:285-292, 1999

89. D'Amico G: Natural history and prognosis of chronic primary glomerulonephritis, in El Nahas M (ed): Mechanisms and Clinical Management of Chronic Renal Failure. Oxford, Oxford University Press, 2000, pp 241-264

90. D'Amico G: Tubulo-interstitial damage in glomerular diseases: Its role in the progression of the renal damage. Nephrol Dial Transplant 13:80S-85S, 1998

91. Remuzzi G: Abnormal protein traffic through the glomerular barrier induces proximal tubular cell dysfunction and causes renal injury. Curr Opin Nephrol Hypertens 4:339-342, 1995

92. D'Amico G: Tubulointerstitium as predictor of renal progression in glomerular diseases. Nephron 83:289-295, 1999

93. Katafuchi R, Takebayashi S, Taguchi T: Hypertension-related aggravation of IgA nephropathy: A statistical approach. Clin Nephrol 30:261-269, 1988

94. Yoshikawa N, Iijima K, Matsuyama S, et al: Repeat renal biopsy in children with IgA nephropathy. Clin Nephrol 33:160-167, 1990

95. Hotta O, Furuta T, Chiba S, et al: Regression of IgA nephropathy: A repeat biopsy study. Am J Kidney Dis 39:493-502, 2002