Corticosteroid Effectiveness in IgA Nephropathy: Long-Term Results of a Randomized, Controlled Trial

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Abstract. Proteinuria plays a causal role in the progression of IgA nephropathy (IgAN). A previous controlled trial showed that steroids are effective in reducing proteinuria and preserving renal function in patients with IgAN. The objective of this study was to evaluate the long-term effectiveness of steroids in IgAN, examine the trend of proteinuria during follow-up (starting from the hypothesis that the degree of reduction in proteinuria may influence IgAN outcome), and evaluate how histologic scores can influence steroid response. A secondary analysis of a multicenter, randomized, controlled trial of 86 adult IgAN patients who were receiving supportive therapy or intravenous methylprednisolone plus oral prednisone for 6 mo was conducted. Ten-year renal survival was significantly better in the steroid than in the control group (97% *versus* 53%; log rank test $P = 0.0003$). In the 72 patients who did not reach the end point (doubling in baseline serum creatinine), median proteinuria significantly decreased (1.9 g/24 h at baseline, 1.1 g/24 h after 6 mo, and 0.6 g/24 h after a median of 7 yr). In the 14 progressive patients, proteinuria increased from a median of 1.7 g/24 h at baseline to 2.0 g/24 h after 6 mo and 3.3 g/24 h after a median of 5 yr. Steroids were effective in every histologic class. Cox multivariate regression analyses showed that, in addition to steroids, a low baseline histologic score, a reduction in proteinuria after 6 mo, and no increase in proteinuria during follow-up all were independent predictors of a beneficial outcome. Steroids significantly reduce proteinuria and protect against renal function deterioration in IgAN. The histologic picture and proteinuria during early and late follow-up improve the prediction of outcome, but considerable variability remains outside the model.

The outcome of IgA nephropathy (IgAN) is highly variable: ESRD occurs in 5 to 25% of cases within 10 yr (1–3) and in 25 to 50% within 20 yr (2). Identifying the factors that affect disease progression is extremely important, particularly if they can be modified by treatment. Among the clinical and laboratory characteristics of the disease, it has been found that persistent and severe proteinuria is the most important predictor of a poor outcome (1–10) and that its reduction correlates with better renal function.

The use of steroids in the first-line treatment of IgAN has led to variable results (11–18), but these were difficult to interpret because most of the studies involved small populations of patients with different ages (adults and children), different degrees of IgAN severity, and, more important, different degrees of proteinuria. In 1999, we published the results of a multicenter, randomized, and controlled trial designed to compare the effects of a 6-mo steroid course with those of supportive therapy in 86 patients with biopsy-proven IgAN (19). After 5 yr of follow-up, the risk of a doubling in plasma creatinine levels was significantly lower in the treated patients, who also showed a significant decrease in mean urinary protein excretion after 1 yr that persisted throughout the follow-up. Proteinuria levels did not change in the control group. Here we report the 10-yr results in terms of long-term renal survival, the impact of histologic scores on the response to steroids, and the trend of proteinuria levels during follow-up.

Materials and Methods

Patients

The entry and exclusion criteria of this trial have been reported in detail elsewhere (19). Briefly, between July 1987 and September 1995, 86 eligible adult patients with biopsy-proven IgAN, urinary protein excretion levels of 1 to 3.5 g/d, and plasma creatinine levels of ≤1.5 mg/dl were randomized to steroids ($n = 43$) or supportive therapy alone ($n = 43$). The patients who were assigned to steroids received 1 g of methylprednisolone intravenously for three consecutive days at the beginning of the steroid course and again 2 and 4 mo later; they were also given oral prednisone at a dose of 0.5 mg/kg every other day for 6 mo. The patients who were assigned to the control group received only supportive treatment. All of the patients in both groups were administered diuretics, antihypertensive drugs (including angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers) and antiplatelet agents as needed. Renal biopsy was performed at the beginning of the study in 83 patients and during the previous year in three patients.

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The patients were examined at baseline, every 2 mo for the first 6 mo, and at the end of each follow-up year. At each visit, their body weight, BP, plasma creatinine levels, and 24-h urinary protein excretion were measured and recorded. Hypertension was defined as BP values of >140/90 mmHg repeated twice in a standing position or the need for antihypertensive agents.

The severity of the histologic lesions was scored by analyzing global glomerular sclerosis, focal glomerular sclerosis, crescents, tubular atrophy, interstitial infiltrate, interstitial fibrosis, and vascular sclerosis (19). A score of 0 to 3 points was assigned to each lesion. The total score (0 to 21) was arbitrarily defined to be mild (0 to 7), moderate (8 to 14), or severe (15 to 21).

Outcome Definitions

The primary end point was a 100% increase in plasma creatinine from baseline levels. The secondary end point was a decrease in proteinuria: A reduction to <1 g/d was considered a minimal response; a decrease to <0.5 g/d was considered an optimal response.

Statistical Analyses

The median proteinuria values and interquartile ranges (IQR) during the follow-up period were calculated by dividing the whole sample on the basis of the randomly allocated treatment (steroids or supportive therapy) and the observed end point (a doubling in baseline plasma creatinine levels: yes or no).

The relative risk was used to measure the association between the allocated treatment and minimal or optimal proteinuria responses. As a minimal reduction in proteinuria spontaneously occurred in some of the untreated patients, the net effect of steroids was estimated as the difference between the percentage of patients who achieved a proteinuria response in the treatment and control groups.

Renal survival without an end point was analyzed using the Kaplan-Meier method, with the two groups being compared on an intention-to-treat basis by means of the log-rank test. $P < 0.05$ was used to reject the null hypothesis of no statistical between-group difference.

Cox regression analysis was used to explore the independent prognostic value of steroid therapy, the total renal biopsy score, the presence of hypertension, treatment with ACE inhibitors, and proteinuria levels. In detail, we analyzed the contributions of proteinuria levels at baseline, their variation after 6 mo of follow-up, their mean value throughout the follow-up, and an increase in the last proteinuria value of at least 1 g/24 h over the mean proteinuria level observed during the previous follow-up. We also tested the hypothesis of an interaction between steroids and total biopsy scores to investigate whether the effect of steroids depends on histologic characteristics.

Logistic regression was used to evaluate the prognostic performance of the variables selected from the final Cox model as they became available during the follow-up: We first considered steroid treatment and total biopsy scores, and then analyzed the model by adding the reduction in proteinuria after 6 mo, and finally analyzed the full model by including the difference between the last proteinuria level and the mean level during follow-up. Prognostic performance was evaluated by considering sensitivity (the percentage of true positives among the patients who experienced a doubling in baseline plasma creatinine levels), specificity (the percentage of true negatives among the patients who did not experience a doubling in baseline plasma creatinine levels), and accuracy (the percentage of the sum of true positives and true negatives among all patients). All of the analyses were made using SPSS statistical software for Windows, release 11.

Results

Baseline Characteristics

The baseline characteristics of the patients have been reported in detail elsewhere (19). In particular, the two groups were similar in age, gender, duration of IgAN, plasma creatinine levels, creatinine clearance, urinary protein excretion, the prevalence of hypertension, the frequency and severity of histologic lesions at renal biopsy, and the use of ACE inhibitors.

All of the patients were followed up for at least 1 yr. Twenty-one patients (11 in the steroid group, 10 in the control group) withdrew from the study: Three were lost to follow-up, five developed other illnesses, and 13 were protocol violators, because they were given steroids as a result of relapse or persistence of moderate proteinuria ($n = 8$) or because of appearance of nephrotic syndrome ($n = 5$).

Renal Survival

Ten-year renal survival was significantly better in the steroid group than in the controls (97% *versus* 53%; log rank test $P = 0.0003$; crude relative risk [RR], 0.06; 95% confidence interval [CI], 0.01 to 0.44; $P = 0.006$; Figure 1). One (2.3%) patient in the steroid group and 13 (30.2%) in the control group reached the end point of a doubling in baseline plasma creatinine levels after a median follow-up of 7 yr. One steroid-treated patient and five control subjects started dialysis.

Cox multivariate regression analyses showed that, in addition to steroids (RR, 0.09; 95% CI, 0.01 to 0.80; $P = 0.031$), a low total biopsy score at baseline (RR, 1.22 for each point increase; 95% CI, 1.03 to 1.44; $P = 0.022$), a reduction in proteinuria levels after 6 mo (RR, 0.58; 95% CI, 0.30 to 0.91; $P = 0.016$), and no increase in proteinuria during follow-up (RR, 0.09; 95% CI, 0.01 to 0.80; $P = 0.031$) all were independent predictors of a beneficial outcome (Table 1). The interaction between steroids and the total biopsy score was NS ($P = 0.856$).

We tested three models using the increasing information that became available during the course of the follow-up (Table 2). At baseline, the combination of steroid treatment and renal

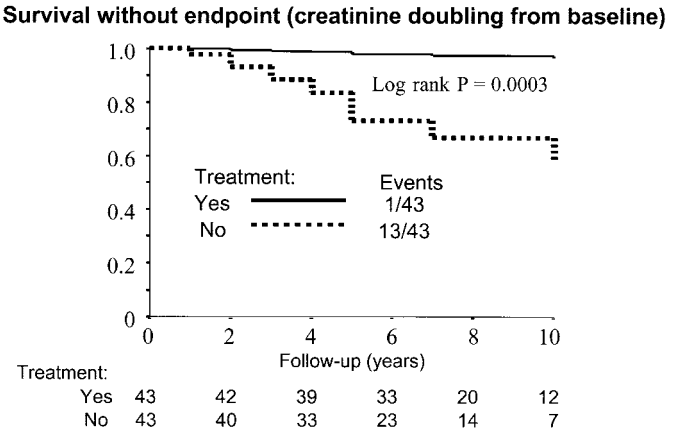

Figure 1. Renal survival estimated on the basis of an increase in plasma creatinine concentrations to >100% above baseline values.

Table 1. Predictive variables related to renal survival at multivariate Cox regression analysis[a]

Variable	B	SE	Wald	*P* Value	RR	95% CI for RR	
						Lower	Upper
Steroid treatment (yes *vs* no)	−2.398	1.110	4.667	0.031	0.09	0.01	0.80
Total histologic score (for each point increase)	0.195	0.085	5.213	0.022	1.22	1.03	1.44
Proteinuria reduction at 6 mo (for each g/d)	−0.538	0.224	5.753	0.016	0.58	0.3	0.91
At least 1 g proteinuria increase at last follow-up *versus* mean follow-up value	2.308	0.683	11.433	0.001	10.06	2.64	38.34
Total histologic score by steroid treatment interaction	−0.039	0.215	0.033	0.856	0.96	0.63	1.47

[a] B, regression coefficient; SE, standard error of B; Wald, Wald statistic; CI, confidence interval; RR, relative risk.

Table 2. Prognostic performance in IgA nephropathy at different follow-up times

Follow-up	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	Accuracy
Baseline							
steroid treatment alone	13	42	30	1	92.9	58.3	64.0
histologic score alone	3	65	7	11	21.4	90.3	79.1
steroid treatment and histologic score	11	46	26	3	78.6	63.9	66.3
Six-month follow-up							
steroid treatment, histologic score, and proteinuria change after 6 mo	10	51	21	4	71.4	70.8	70.9
At least 1-year follow-up							
previous covariates plus increase in last proteinuria value of at least 1 g *versus* previous mean follow-up value	11	61	11	3	78.6	84.7	83.7

bioptic features led to a better prognostic performance than the individual variables alone (sensitivity, 78.6%; specificity, 63.9%; accuracy, 66.3%). In particular, it is worth noting that the sensitivity of renal bioptic findings alone was very poor (21.4%). Adding the information concerning the difference between baseline and 6-mo proteinuria levels improved specificity from 63.9 to 70.8%. When we added the information of last proteinuria value *versus* the previous mean follow-up one, the performance of the model further improved, reaching a sensitivity of 78.6%, a specificity of 84.7%, and an accuracy of 83.7%.

Proteinuria and Steroid Treatment

Figure 2 shows the percentile distribution of proteinuria values in the control and steroid groups. A decrease of proteinuria to <1 g/d (minimal response) after 6 mo was observed in 19 (44%) of the patients who were treated with steroids and in nine (21%) of the control subjects (RR, 2.11; 95% CI, 1.08 to 4.13; number needed to treat [NNT], 4; $P = 0.037$). After 1 yr, 31 (72%) of the treated patients and 13 (30%) of the untreated patients achieved a minimal response (RR, 2.38; 95% CI, 1.46 to 3.90; NNT, 2; $P < 0.001$). The net effect of steroids was 23% after 6 mo and 42% after 1 yr.

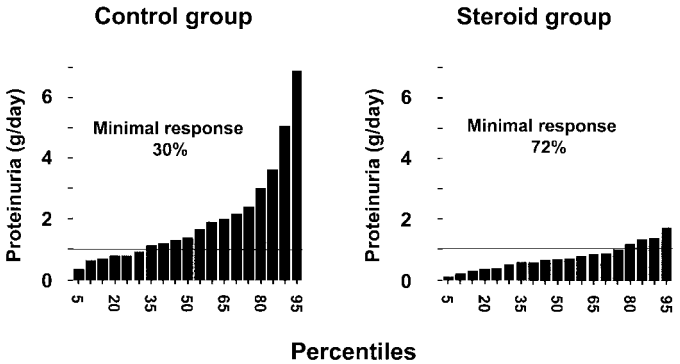

Figure 2. Percentile distribution of proteinuria values after 1 yr in the control and steroid groups.

An optimal proteinuric response (a decrease of proteinuria to <0.5 g/d) after 6 mo was observed in eight (19%) of the treated patients and two (5%) of the untreated patients (RR, 4.00; 95%

CI, 0.90 to 17.76; NNT, 7; $P = 0.089$); after 1 yr, an optimal response was observed in 11 (26%) of the treated patients and two (5%) of the untreated patients (RR, 5.50; 95% CI, 1.30 to 23. 36; NNT, 5; $P = 0.014$). The net efficacy of steroids in achieving an optimal proteinuric response was 14% after 6 mo and 21% after 1 yr.

Of the 13 control patients who achieved a minimal response of proteinuria after 1 yr, seven subsequently experienced a new increase in proteinuria and one reached the end point of a doubling in plasma creatinine levels. Two of the 30 control patients who did not show any remission in proteinuria after 1 yr showed a stable response (proteinuria, 0.1 to 0.3 g/24 h) at the following observations.

When proteinuria is considered as a continuous variable, its levels clearly decreased in the steroid but not in the control group: The median values over the whole follow-up period were, respectively, 0.8 g/d (IQR, 0.6 to 1.3) and 1.7 g/d (IQR, 1.1 to 3.0; Figure 3). It is worth noting that the variability in proteinuria (estimated on the basis of the IQR: *i.e.*, the height of the boxes) increased during the follow-up only in the control group (see the height of the last box of each group).

During the follow-up, five of the control patients presented an increase in proteinuria of >1 g/d over the mean follow-up value, all of whom became cases (*i.e.*, their baseline serum creatinine values doubled after 1 yr). On the contrary, only two patients in the steroid group presented an increase in proteinuria of >1 g/d over the mean follow-up value, but they did not reach the end point (Figure 4).

Of the 13 patients (six in the steroid and seven in the control group) who violated the protocol because they were given steroids with the same schedule of that of the protocol, 12 obtained a decrease of proteinuria (mean decrease, −1.9 g/d; range, 0.2 to 6.5 g/d) after 6 mo; six of them achieved a reduction <1 g/d (minimal response).

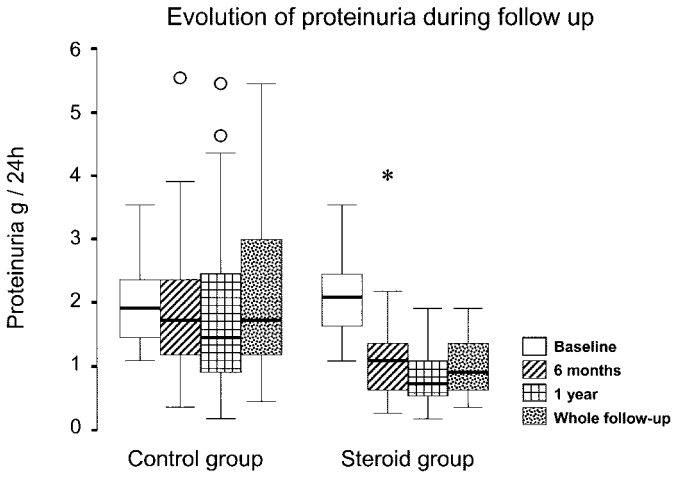

Figure 3. Evolution of proteinuria levels during follow-up in the progressive and nonprogressive groups after a median follow-up of 7 yr. The lines in the middle and those delimiting the boxes indicate the median and 25th and 75th percentile values, respectively. The whiskers at the ends of the boxes are lines that show the distance from the end of the box to the largest and smallest observed values that are <1.5 box lengths from either end. Circles and asterisks, respectively, indicate values that are distant from 1.5 to 3 times and >3 times the length of the box starting from its lower or upper limit.

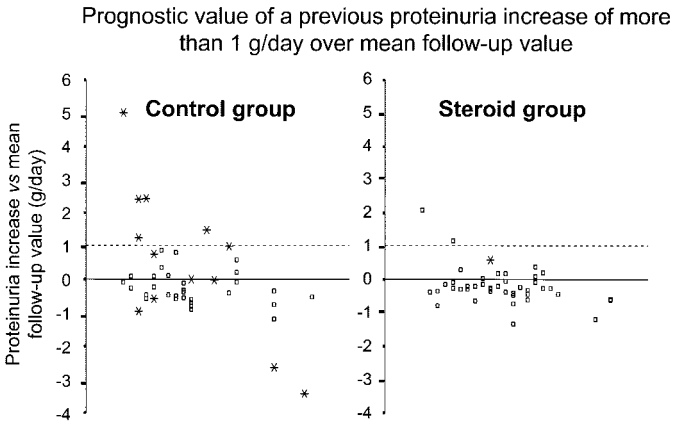

Figure 4. Change in last proteinuria value *versus* mean proteinuria value. *Patients who reached the end point of a doubling in baseline plasma creatinine levels.

Proteinuria and Outcome

The median baseline proteinuria level of the 72 patients who experienced a nonprogressive disease course was not statistically different from that of the 14 patients who reached the end point of a doubling in baseline serum creatinine levels (1.9 g/d *versus* 1.7 g/d; IQR, 1.5 to 2.4 g/d and 1.2 to 2.3 g/d, respectively; $P = 0.263$). However, during the follow-up, proteinuria significantly decreased only in the 72 nonprogressive patients: to 1.1 g/d (IQR, 0.7 to 1.7 g/d) after 6 mo and 0.6 g/d (IQR, 0.3 to 1.2 g/d) at the end of a median follow-up of 7 yr (IQR, 5 to 10 yr). In the 14 progressive patients, proteinuria increased to 2.0 g/d (IQR, 1.3 to 3.1 g/d) after 6 mo and to 3.3 g/d (IQR, 1.9 to 5.2 g/d) after a median follow-up of 5 yr (IQR, 3 to 6 yr). Similarly, the median proteinuria level throughout the follow-up period was lower in the patients who did not reach the end point (1.0 g/d [IQR, 0.7 to 1.5 g/d] *versus* 3.2 g/d [IQR, 2.6 to 4.9 g/d]). Figure 5 shows the evolution of proteinuria in the two groups during the follow-up, expressed as the change in proteinuria values between baseline and after 6 mo of treatment, and the difference between the last proteinuria values and the mean proteinuria levels observed during the previous follow-up. After 6 mo, median proteinuria had decreased by 0.8 g/d (IQR, −1.3/−0.1 g/d) in the nonprogressive patients, whereas it slightly increased by 0.15 g/d (IQR, −0.3/0.8 g/d) in the progressive patients. These absolute variations were significantly different ($P = 0.001$). At the end of follow-up, the last proteinuria value in the nonprogressive patients was 0.3 g/d (IQR, −0.5/−0.1 g/d) lower than the median value during follow-up, whereas it was 0.7 g/d higher in the progressive patients (IQR, −0.7/1.7 g/d; $P = 0.027$).

Histologic Score and Progression of Nephropathy

As previously reported (19), the distribution of the three histologic score classes was similar in the two treatment groups

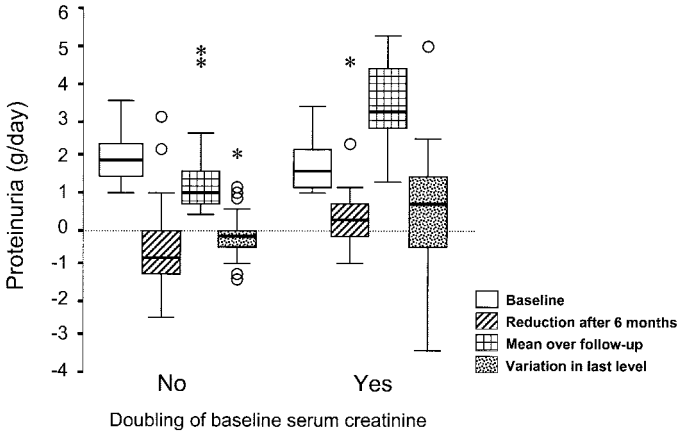

Figure 5. Proteinuria evolution over the follow-up in the groups who did or did not reach the primary end point. The lines in the middle and those delimiting the boxes, respectively, indicate the median and 25th and 75th percentile values. Circles and asterisks, respectively, indicate values that are distant from 1.5 to 3 times and >3 times the length of the box starting from its lower or upper limit.

(Table 3): 23 (53%) treated and 26 (60%) control patients had a mild score, 15 (35%) treated and 15 (35%) control patients had a moderate score, and five (12%) treated and two (5%) control patients had a severe score. However, the distribution of patients who reached a doubling in serum creatinine levels during follow-up was different in the two groups. Only one treated patient (who had a moderate histologic score) progressed toward renal insufficiency, whereas a larger number of the control patients reached the end point: Six (23%) with a mild score, five (33%) with a moderate score, and two (100%) with a severe score.

Hypertension and Treatment with ACE Inhibitors

Twenty-nine (34%) patients were hypertensive at baseline (14 in the steroid group and 15 in the control group). Twenty-four other patients became hypertensive during follow-up (12 in each group); thus, the percentage of hypertensive patients increased to 62%. The proportion of hypertensive patients in the two groups was similar both at baseline and during follow-up. The mean systolic (SBP) and diastolic BP (DBP) were also similar in the two groups at baseline (mean SBP, 137.91 ± 19.64 mmHg and 133.37 ± 20.75 mmHg in the steroid and control groups, respectively, 95% CI, −16.69 to 2.86, $P = 0.15$; mean DBP, 84.77 ± 9.69 mmHg and 83.37 ± 12.33 mmHg in the steroid and control groups, respectively, 95% CI, −11.51 to 1.61, $P = 0.13$) and during follow-up (mean SBP, 133.27 ± 13.16 mmHg and 134.61 ± 16.13 mmHg in the steroid and control groups, respectively, 95% CI, −4.98 to 7.65, $P = 0.67$; mean DBP, 84.41 ± 6.93 mmHg and 84.33 ± 7.61 mmHg in the steroid and control groups, respectively, 95% CI, −3.20 to 3.04, $P = 0.95$).

The antihypertensive treatment included ACE inhibitors, calcium-channel blockers, β-blockers, α-blockers, and α-methyldopa. At baseline, 12 patients were receiving ACE inhibitors (six in each group). During follow-up, 35 other patients were given ACE inhibitors (19 in the steroid group and 16 in the control group). All 47 patients had been taking ACE inhibitors for at least 6 mo (mean, 55.8 mo; range, 6–108; steroid group: mean, 59.3 mo; control group: mean, 51.8 mo).

Of the 72 stable patients, 24 (33%) were hypertensive at baseline and 41 (57%) were hypertensive during follow-up, whereas of the 14 progressive patients, four (29%) were hypertensive at baseline and 11 (79%) were hypertensive during follow-up. Ten (71%) progressive patients and 34 (47%) stable patients were receiving ACE inhibitors in the first 6 yr of follow-up.

Discussion

This prolonged follow-up of patients with IgAN showed a significant difference in renal survival between the two treatment groups: 97% among those assigned to corticosteroids *versus* 53% among those receiving supportive therapy alone. Furthermore, steroid treatment reduced proteinuria to <1 g/d in two thirds of treated patients. The decrease was detectable after 6 mo of follow-up but became even more evident after 1 yr and persisted over time. Approximately 30% of the treated patients did not respond to steroids: Their proteinuria levels remained >1 g/d, but the mean levels were nevertheless lower than those in the untreated patients. The mean proteinuria level in the control subjects remained unchanged with an increase in its variability. Approximately 30% of the control subjects

Table 3. Histologic score and progression of nephropathy in control and treated patients

	Total Histologic Score		
	Mild (0–7) *n* (%)	Moderate (8–14) *n* (%)	Severe (15–21) *n* (%)
All patients ($n = 86$)	49 (57)	30 (35)	7 (8)
Control patients			
all patients ($n = 43$)	26 (60)	15 (35)	2 (5)
progressive patients ($n = 13$)	6/26 (23)	5/15 (33)	2/2 (100)
Treated patients			
all patients ($n = 43$)	23 (53)	15 (35)	5 (12)
progressive patients ($n = 1$)	0	1/15 (7)	0

showed a reduction in proteinuria after 1 yr, but this persisted in <50% of cases.

Unfortunately, it is impossible to identify *a priori* the patients who achieve spontaneous remission in any case and those who fail to respond to steroids. It is interesting to note that the changes in proteinuria during follow-up predicted outcome better than absolute proteinuria values at presentation. This was true both for the degree of the reduction after 6 mo and for an increase of at least 1 g/d over the mean follow-up value: The RR of reaching the end point in these two cases were, respectively, 0.58 and 10.06. These findings are in agreement with those of Bartosik *et al.* (6). In their retrospective study of 298 patients with IgAN, only proteinuria during follow-up together with mean arterial BP during follow-up was significantly and independently related to the rate of renal function deterioration by multivariate regression analysis (6).

Twenty-nine (34%) patients were hypertensive at baseline. This is in agreement with data from the largest series of the literature, in which the prevalence of this risk factor is between 9 and 47% (1,5,20–24); this wide variability is due to the different inclusion criteria of the single series. It is worth noting that the percentage of hypertensive patients at baseline and during follow-up, together with mean values of SBP and DBP, was similar in the two groups. Thus, differences in BP control between the two groups did not significantly contribute to the better renal survival observed in the steroid group.

ACE inhibitors are widely used in the treatment of IgAN, because they improve two major progression factors (hypertension and proteinuria) and can block the negative effects of angiotensin II in the kidney (25). However, large-scale, randomized, prospective studies aimed at testing the effects of ACE inhibitors in this glomerulonephritis are lacking. In 1998, Dillon (26) presented the results of a meta-analysis of ACE inhibitors in patients with IgAN and concluded that, although some benefits were observed in protecting renal function, it was not possible to reach definitive conclusions regarding their effectiveness. In our study, treatment with ACE inhibitors had no effect on the risk of reaching the end point. The histologic scores were specific but not very sensitive in predicting patient outcome, indicating that it is difficult to identify rapidly progressing patients only by means of renal biopsy. Conversely, steroid therapy alone was sensitive but not very specific, and the combination of steroid therapy and histologic scores did not lead to good sensitivity or specificity. The changes in proteinuria levels after 6 mo increased the accuracy of the model from 66.3 to 70.9%, which was further increased to 83.7% by adding the number of patients with an increase in proteinuria of >1 g/d, in which the sensitivity of the model was 78.6% and its specificity was 84.7%. The trend of proteinuria during the first year and particularly an increase of >1 g/d therefore can be considered a good prognostic marker of progression.

The histologic scores of our patients who did not receive steroids represented an important prognostic factor. In this subset of patients, the risk of a doubling in baseline plasma creatinine levels progressively increased from the mild to the severe score class. However, minimal histologic lesions do not exclude progression to ESRD as six (23%) patients with a mild score reached the end point. Steroid administration improved prognosis in every histologic class, and it is worth noting that none of the five treated patients with a severe score reached the end point. The decision as to whether to use steroids course therefore should not be based on histologic scores, at least not in patients with plasma creatinine levels of <1.6 mg/dl.

The course of IgAN is extremely variable, with patients showing very different rates of progression to ESRD and some with renal function deterioration at the time of diagnosis not progressing at all even after decades. This makes it very difficult to assess the effectiveness of any therapeutic approach. However, that our 10-yr results fully confirm those observed after 4 (19) and 7 yr (27) reduces the likelihood of an imbalance between our progressive and nonprogressive patients, which may have occurred in trials with smaller sample sizes (11–18) or shorter follow-up periods (12–18). Therefore, in the past few years, we have begun to propose steroid treatment to all control patients with proteinuria of >1 g/24 h, in searching to ameliorate their renal prognosis.

The exact mechanisms by which steroids alter the course of IgAN are still unclear. One possible hypothesis is that they reduce proliferative lesions during the acute phase of the disease, thus limiting the development of glomerular sclerosis and tubular fibrosis. The results of a small study of 13 children with IgAN seem to confirm our hypothesis insofar as the renal biopsies performed after 2 yr of treatment with prednisone revealed a significant decrease in the activity score, without any significant increase in the chronicity score (17). Similarly, Shoji *et al.* (18) studied 21 patients who had IgAN and were randomized to receive steroids or antiplatelet agents for 1 yr and underwent repeat renal biopsy at the end of treatment, and found a significant improvement in mesangial cell proliferation, mesangial matrix accumulation, and cellular crescents in the corticosteroid but not in the antiplatelet group. Furthermore, the expression of α-smooth muscle actin, a marker of glomerular myofibroblast-like cells, significantly decreased only in the corticosteroid group.

Finally, it is worth pointing out that our steroid schedule seems to be safe even 10 yr after treatment. With the exception of one patient who developed diabetes, the patients who were assigned to the steroid group did not experience any major side effects during follow-up. This confirms the good tolerability previously observed in patients with membranous nephropathy receiving the same schedule (28).

In conclusion, our 6-mo steroid regimen proved to be safe and capable of reducing proteinuria levels and stabilizing renal function over the long-term. The change in proteinuria levels during follow-up seems to be an important prognostic factor. Histologic features at renal biopsy should not be considered a criterion for excluding patients from treatment.

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