IgA nephropathy with severe chronic renal failure: a randomized controlled trial of corticosteroids and azathioprine.

Pozzi C, Andrulli S, Pani A, Scaini P, Roccatello D, Fogazzi G, Pecchini P, Rustichelli R, Finocchiaro P, Del Vecchio L, Locatelli F.
IgA nephropathy with severe chronic renal failure: a randomized controlled trial of corticosteroids and azathioprine.
JN. JOURNAL OF NEPHROLOGY (2013) 26
DOI: 10.5301/jn.5000110

IgA nephropathy with severe chronic renal failure: a randomized controlled trial of corticosteroids and azathioprine.

Claudio Pozzi [1,2], Simeone Andrulli [1], Antonello Pani [3], Patrizia Scaini [4], Dario Roccatello [5], Giambattista Fogazzi [6], Paola Pecchini [7], Roberto Rustichelli [8], Pietro Finocchiaro [9], Lucia Del Vecchio [1], Francesco Locatelli [1]

[1] Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco - Italy

[2] Department of Nephrology and Dialysis, E. Bassini Hospital, Cinisello Balsamo, Milan - Italy

[3] Department of Nephrology and Dialysis, G. Brotzu Hospital, Cagliari - Italy

[4] Department of Nephrology and Dialysis, Spedali Civili, Brescia – Italy

[5] Department of Nephrology and Dialysis, Center of Research on Immunopathology and Documentation on Rare Diseases, Turin – Italy

[6] Department of Nephrology and Dialysis, Ospedale Maggiore IRCCS, Milan – Italy

[7] Department of Nephrology and Dialysis, Istituti Ospitalieri, Cremona – Italy

[8] Department of Nephrology and Dialysis, S. Maria Nuova Hospital, Reggio Emilia - Italy

[9] Department of Nephrology and Dialysis, CNR-IBIM Hospital, Reggio Calabria – Italy

Address for correspondence: Claudio Pozzi Department of Nephrology and Dialysis "Bassini" Hospital Via Massimo Gorki, 50 IT-20092 Cinisello Balsamo, Milan, Italy claudio.pozzi@icp.mi.it

Abstract

Background: Therapeutic nihilism is common in IgA nephropathy (IgAN) and renal insufficiency. Methods: In a randomized controlled trial comparing steroids alone or combined with azathioprine in 253 IgAN patients, we used a separate randomization list for patients with creatinine >2.0 mg/dL. Twenty patients (group 1) were randomized to 3 intravenous pulses of methylprednisolone 1 g at months 1, 3 and 5, and oral prednisone 0.5 mg/kg every other day plus azathioprine 1.5 mg/kg/day for 6 months, followed by oral prednisone 0.2 mg/kg every other day plus azathioprine 50 mg/day for a further 6 months; 26 patients (group 2) received steroids alone. The primary outcome was renal survival (50% increase in plasma creatinine from baseline); secondary outcomes were proteinuria over time and adverse events. Results: Six-year renal survival was not different between the 2 groups (50% vs. 57%; log-rank p=0.34). Median proteinuria decreased during follow-up in the whole population (from 2.45 g/day [interquartile range (IQR) 1.50-3.78] to 1.09 g/day [IQR 0.56- 2.46]; p<0.001), with no between-group difference. Multivariate predictors associated with renal survival were sex of patient, proteinuria during follow-up, number of antihypertensive drugs, angiotensin-converting enzyme inhibitors and treatment including azathioprine. Six patients in group 1 (30%) and 4 in group 2 (15%) did not complete the therapy, because of side effects (p=0.406). Conclusions: Six-year renal survival was similar in the 2 groups. At Cox analysis the addition of azathioprine may be slightly more effective than corticosteroids alone in patients with chronic renal insufficiency, although with an increase of side effects.

Key words: Azathioprine, Chronic kidney disease, Hypertension, IgA nephropathy, Proteinuria, Steroids.

Conflict of interest statement: The authors have no conflict of interest to declare.

Introduction

Up to 15%-20% of patients with IgA nephropathy (IgAN) reach chronic kidney disease (CKD) stage 5 within 10 years, and up to 30%-40% within 20 years (1-3). A "point of no return," which was defined as the level of serum creatinine after which IgAN inevitably progresses toward CKD stage 5, was suggested nearly 2 decades ago (4-6). The awareness of unavoidable progression after reaching a certain stage of renal dysfunction has led to therapeutic nihilism, and so little is known about treatment efficacy and safety in patients with advanced IgAN. Corticosteroids were found to be effective in IgAN patients with plasma creatinine levels of ≤1.5 mg/dL and proteinuria of >1 g/day (7, 8). In 1998, we designed a randomized controlled trial aimed at testing whether the adding of low-dose azathioprine to steroids was more effective than steroids alone (9, 10). In patients with serum creatinine <2 mg/dL, adding low-dose azathioprine to corticosteroids for 6 months did not provide additional benefit for renal survival and proteinuria during follow-up and might increase the risk for adverse events (10).
Given the lack of information about treatment in IgAN patients with CKD stages 3-4, we used a separate randomization list with a longer treatment course (1 year instead of 6 months) in the patients with impaired renal function. This paper describes the findings of this part of the trial (not included in the previous analysis (10)).

Materials and methods

Patients

Eligible patients had to have plasma creatinine >2.0 mg/dL and proteinuria ≥1 g/day; inclusion and exclusion criteria are described in detail elsewhere (9, 10).

Study design

Study protocol details have been published elsewhere (10). The patients were randomly assigned to receive steroids plus azathioprine (group 1: intravenous methylprednisolone 1 g for 3 consecutive days at months 1, 3 and 5, and oral prednisone 0.5 mg/kg every other day plus azathioprine 1.5 mg/kg/day for 6 months followed by oral prednisone 0.2 mg/kg every other day plus azathioprine 50 mg/day for a further 6 months) or steroids alone with the same schedule (group 2) (clinicaltrials.gov identifier: NCT01392833). As per protocol, histological data were only collected from the patients who underwent renal biopsy at enrolment. The histological material was examined using the criteria of the World Health Organization (WHO) as modified by Churg and Sobin (11).

Outcome measures

The primary end point was the progression of CKD, defined as a 50% increase in serum creatinine from baseline (to be confirmed 1 month later). The secondary end points were the evolution of proteinuria over time and adverse events.

Statistical analysis

For descriptive purposes, mean values and standard deviations were used for the normally distributed continuous variables, median values and interquartile ranges (IQRs) for the skewed continuous variables, and absolute numbers for the categorical variables. Cumulative renal survival without reaching the end point of a 50% increase in baseline creatinine was calculated using the Kaplan-Meier method, and the 2 treatment groups were compared on an intention-to-treat basis, using the log-rank test. Multivariate Cox regression analysis was used to estimate the effect of the experimental treatment, adjusted for some possibly prognostic covariates. The explanatory covariates of the final model were selected using a backward stepwise method. The assumption of constant hazard rates over time was checked by means of plots of the logarithm of the survival function against time. All of the analyses were made using SPSS statistical software for Windows, release 17.0. The alpha level of significance was set at 0.05 for all analyses.

Results

Patient characteristics

Trial enrolment began in December 1999 and closed in November 2005. Forty-six out of 253 patients (10) were included in this separate randomization list: 20 patients were assigned to steroids plus azathioprine (group 1) and 26 to steroids alone (group 2) (Fig. 1). At baseline, the 2 groups were similar for age, sex, duration of IgAN, serum creatinine levels and systolic and diastolic blood pressure. Median proteinuria was higher in group 1 than in group 2 (3.2 vs. 2.0 g/day; p=0.020) (Tab. I). Renal biopsy was performed after a median of 0.17 years (IQR 0.02-5.58 years). Histological evaluation of the 23 patients undergoing biopsy at enrolment showed renal lesions consistent with grade III of the Churg and Sobin classification (13); none of the patients showed signs of rapidly progressive glomerulonephritis.

Antihypertensive therapy and renin-angiotensin system blockade

At baseline, nearly all of the patients (43/46; 94%) were hypertensive. Blood pressure values were similar in groups 1 and 2 at baseline (135.5 ± 17.1 / 80.7 ± 10.0 mm Hg vs. 135.0 ± 18.3 / 83.0 ± 11.9 mm Hg) and during the follow-up (135.4 ± 15.8 / 84.0 ± 8.0 mm Hg vs. 135.0 ± 11.8 / 84.0 ± 5.1 mm Hg). The majority of the patients were already being treated with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) (85.0% in group 1 and 84.6% in group 2). Among the 7 patients who were not being treated with renin-angiotensin system (RAS) blockade at baseline, only 1 started an ACEI during followup (group 1).

Renal survival

The patients were followed up for a median of 4.5 years (IQR 2.9-6.1). At intention-to-treat analysis, 10 patients (50%) in group 1 and 11 (42%) in group 2 reached the primary end point of a 50% increase of serum creatinine; 6-year end point–free renal survival was not statistically different between the 2 groups (50% and 57%; log-rank p=0.34) (Fig. 2). Nine patients in group 1 (45%) and 10 in group 2 (39%) started dialysis after a median follow-up of 4.0 years (IQR 2.2-4.8 years) (p=0.81). Similar results were obtained using the per-protocol analysis of the 35 patients who completed the 12-month treatment.

Proteinuria

Median proteinuria decreased significantly during follow-up in the population as a whole from 2.45 g/day (IQR 1.50-3.78) to 1.25 g/day (IQR 0.54-2.43) (p<0.001), with no significant difference between the 2 groups (p=0.634) (Fig. 3). In group 1, it decreased from 3.20 g/day (IQR 1.74-5.54) to 2.73 g/day (IQR 0.82-4.13) (a reduction of 0.43 g/day), and in group 2 from 2.00 g/day (IQR 1.50-3.23) to 1.05 g/day (IQR 0.53-1.47) (a reduction of 0.95 g/day). Eighteen patients (39%) reached a mean proteinuria <1 g/day during follow-up, with no statistical difference between the 2 groups (p=0.364). Given the initial random imbalance at baseline, proteinuria
was significantly higher in group 1 than in group 2 at the various follow-up time points (p<0.001) (Fig. 3).

Multivariate Cox regression analysis

The risk of reaching the primary end point was 91% lower among women, 4.6 times higher for each gram of proteinuria during follow-up, 55% lower for each antihypertensive drug taken during follow-up, 79% lower in the patients who received an ACEI, and 92% lower in the patients who received the experimental treatment (Tab. II). Serum creatinine, proteinuria and the number of antihypertensive drugs taken at baseline had no independent effect on the risk of reaching the end point. Side effects Ten of the 46 randomized patients (6 in group 1 and 4 in group 2) did not complete the 12 months of therapy, because of side effects (p=0.406) (Tab. III). One patient in group 1 withdrew from the study because he was transferred to another center after 6 months.

Discussion

In IgAN patients with serum creatinine levels of >2 mg/dL, we found no benefit for renal survival with the addition of azathioprine to steroids in comparison with steroids alone at primary analysis. Both treatment schedules obtained a significant reduction of proteinuria during follow-up, without any between-group

difference. As there was no control group of untreated patients, we are unable to demonstrate that the reduction in proteinuria was accompanied by a significant reduction in the risk of reaching end-stage renal disease (ESRD). In contrast with univariate analysis, multivariate Cox regression analysis showed that the addition of azathioprine was an independent factor favorably affecting patient outcome. This discrepancy may be due to the fact that the patients in group 1 had higher proteinuria levels at baseline and during follow-up (Fig. 3), possibly masking a benefit of the addition of azathioprine. However, given the small sample size of this randomization list and the fact that renal survival at log-rank test was not different in the 2 treatment groups, great caution is needed in interpreting these findings. The median baseline serum creatinine levels in our patients were similar to those in the patients described in papers concerning the "point of no return" (4, 5). With all of the limitations of historical comparisons, these untreated patients experienced a much faster progression of their nephropathy compared with those of the present study. This indirectly suggests that both immunosuppressive regimens (steroids alone or combined with azathioprine) may slow progression to ESRD even in patients with more advanced disease. Although its effect was not significant ($p=0.406$; Tab. III), adding azathioprine to steroids numerically increased the risk of drug-related adverse events causing premature treatment discontinuation (30% vs. 15%). The higher withdrawal rate among the patients receiving azathioprine may have decreased the likelihood of observing its possible beneficial effects, but the results of the per-protocol analysis were comparable with those of the intention-to-treat analysis.

Only a few other studies have evaluated immunosuppressive therapy in IgAN patients with CKD stages 3-4. The majority were retrospective and enrolled patients with more preserved renal function than ours. Moreover, their treatment schedules were not comparable in terms of the drugs used, their doses or treatment duration, and none compared 2 different immunosuppressive drug regimens. Goumenos et al (14) retrospectively evaluated 114 patients (61 with baseline renal impairment defined as serum creatinine levels of >1.24 mg/dL) and found that, after a follow-up of 46 months, 79% of the patients receiving steroids plus azathioprine had stable renal function but only 36% of the untreated patients. However, the same authors were not able to confirm their positive findings in another retrospective study of 74 patients observed for a longer follow-up period (15), although the patients with severe proteinuria seemed to benefit more from the combination, which was given at higher doses and for a longer period than in our study. Mitsuiki et al (16) retrospectively investigated 35 patients with histologically advanced IgAN: 27 received prednisolone for more than 2 years and cyclophosphamide for 6 months, and 8 received supportive treatment alone. After 5 years, all of the patients in the control group had developed CKD stage 5, whereas the majority of the treated patients were still free of dialysis. Treatment-related side effects were observed in only 2 patients. Roccatello et al (17) obtained favorable results with a combined schedule of steroids and mycophenolate mofetil in a subset of IgAN patients. However, patient characteristics were not comparable with our population, since all of the patients had at least 10% florid crescents. Ballardie and Roberts (18) performed the only prospective, randomized study, in which 38 patients with progressive IgAN received prednisolone 40 mg/day (reduced to 10 mg/day after 2 years) with cyclophosphamide 1.5 mg/kg per day for the first 3 months, followed by the same dose of azathioprine for a minimum of 2 years, or supportive therapy alone. The treated patients experienced significantly better renal survival and a greater reduction in proteinuria levels than those in the control group. Despite the fact that the azathioprine dose was the same as that used in our trial and it was given for longer, the rate of drug-related side effects was lower. This may be partially due to the fact that we enrolled patients with more advanced CKD. Given that only 23 out of 46 patients underwent kidney biopsy at enrolment, we cannot exclude that some patients presenting fresh lesions were together with cases with sclerotic ones, possibly limiting the favorable effect of azathioprine.

Finally, our multivariate Cox analysis showed that ACEI had an independent beneficial effect on renal survival. This is in line with the results of a clinical trial indicating that steroids plus ACEIs preserve renal function better than ACEIs alone in IgAN patients with normal renal function (19), and the findings of Hou et al (20), which indicate that ACEIs also have a renoprotective effect in patients with advanced renal insufficiency of various etiology. As the use of RAS blockers was equally distributed in our 2 groups, it is unlikely that this influenced the study results. In brief, the 6-year renal survival at log-rank test was similar in the 2 groups. The Cox analysis might suggest that the addition of azathioprine may be slightly more effective than corticosteroids alone in patients with CKD stages 3-4, although associated with an increased risk of side effects. Given the small sample size of this patient population, caution is needed in interpreting these findings.

References

1. Koyama A, Igarashi M, Kobayashi M; Members and Coworkers of the Research Group on Progressive Renal Disease. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis. 1997;29(4):526-532.
2. D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis. 2000;36(2):227-237.
3. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med. 2002;347(10):738-748.
4. D'Amico G, Ragni A, Gandini E, Fellin G. Typical and atypical natural history of IgA nephropathy in adult patients. Contrib Nephrol. 1993;104:6-13.
5. 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. 1999;52(5):285-292.
6. Komatsu H, Fujimoto S, Sato Y, et al. "Point of no return (PNR)" in progressive IgA nephropathy: significance of blood pressure and proteinuria management up to PNR. J Nephrol. 2005;18(6):690-695.
7. Pozzi C, Bolasco PG, Fogazzi GB, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353(9156):883-887.
8. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15(1):157-163.
9. Locatelli F, Pozzi C, Del Vecchio L, et al. Combined treatment with steroids and azathioprine in IgA nephropathy: design of a prospective randomised multicentre trial. J Nephrol. 1999;12(5):308-311.
10. Pozzi C, Andrulli S, Pani A, et al. Corticosteroids and azathioprine vs corticosteroids alone in IgA nephropathy. J Am Soc Nephrol. 2010;21:1783-1790.
11. Churg J, Sobin LH. Renal disease: classification and atlas of glomerular disease. Tokyo: Igaku-Shoin; 1982.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999;130(6):461-470.
14. Goumenos D, Ahuja M, Shortland JR, Brown CB. Can immunosuppressive drugs slow the progression of IgA nephropathy? Nephrol Dial Transplant. 1995;10(7):1173-1181.
15. Goumenos DS, Davlouros P, El Nahas AM, et al. Prednisolone and azathioprine in IgA nephropathy: a ten year follow-up study. Nephron Clin Pract. 2003;93:C47-C48.
16. Mitsuiki K, Harada A, Okura T, Higaki J. Histologically advanced IgA nephropathy treated successfully with prednisolone and cyclophosphamide. Clin Exp Nephrol. 2007;11(4): 297-303.
17. Roccatello D, Rossi D, Marletto F, et al. Long-term effects of methylprednisolone pulses and mycophenolate mofetil in IgA nephropathy patients at risk of progression. J Nephrol. 2011 Jun 28. [Epub ahead of print].
18. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J Am Soc Nephrol. 2002;13(1):142-148.
19. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACEinhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009;24(12):3694-3701.
20. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006;354(2):131-140.

Fig. 1 - Patient enrolment and outcomes. sCr = serum creatinine.

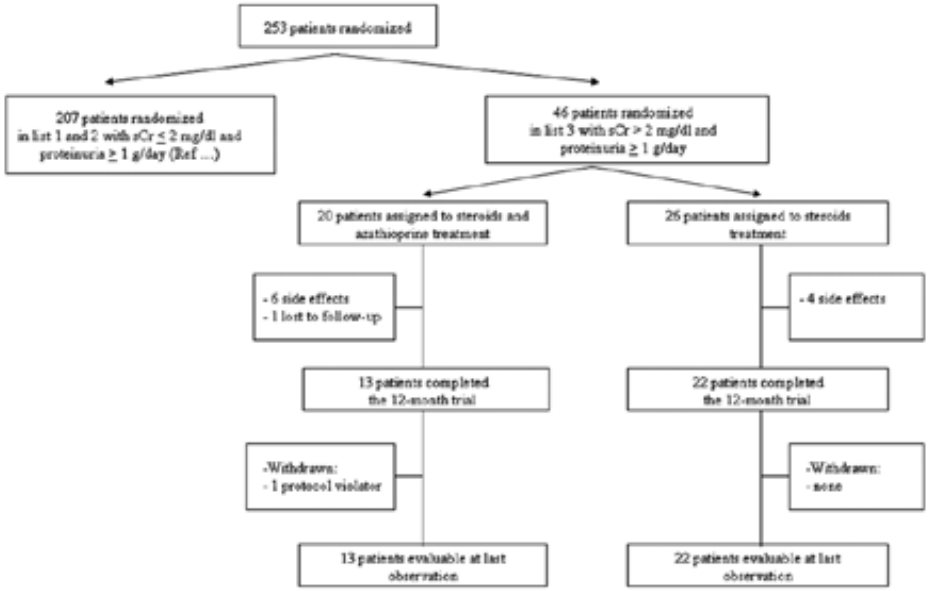

TABLE I. BASELINE CLINICAL AND LABORATORY CHARACTERISTICS BY TREATMENT GROUP

	Treatment			
	Group 1 Steroids + Aza	Group 2 Steroids alone	Total	p Value
No. of patients	20	26	46	
Sex, M/F	17/3 (85% / 15%)	20/6 (77% / 23%)	37/9 (80% / 20%)	0.711
Age, years	43.0 (32.6-52.4)	37.3 (32.7-52.3)	41.6 (32.7-52.2)	0.400
Body weight, kg	73.9 (62.2-89.5)	70.1 (62.6-77.6)	71.4 (62.6-81.4)	0.358
Systolic blood pressure, mm Hg	130 (121-146)	130 (125-146)	130 (125-146)	0.867
Diastolic blood pressure, mm Hg	80 (75-90)	80 (79-90)	80 (79-90)	0.718
No. of pts. treated for hypertension	18 (90%)	25 (96%)	43 (94%)	0.572
No. of pts. treated with ACEI	11 (55%)	11 (42%)	22 (48%)	0.552
No. of pts. treated with ARB	2 (10%)	4 (15%)	6 (13%)	0.684
No. of pts. treated with ACEI and ARB	4 (20%)	7 (27%)	11 (24%)	0.732
No. of pts. treated with statins	3 (15%)	2 (8%)	5 (11%)	0.640
Time from biopsy to enrolment, years	1.1 (0.0-6.5)	0.1 (0.0-4.2)	0.2 (0.0-5.6)	0.161
Serum creatinine, mg/dL	2.60 (2.37-3.04)	2.85 (2.38-3.55)	2.73 (2.39-3.33)	0.381
Estimated creatinine clearance, Cockroft and Gault (12)	36 (29-43)	33 (24-40)	34 (25-41)	0.267
Estimated GFR using MDRD-4 variables (13)	28 (22-32)	25 (20-30)	25 (20-31)	0.296
Proteinuria, g/day	3.2 (1.7-5.5)	2.0 (1.5-3.2)	2.4 (1.5-3.8)	0.020

Values are medians and interquartile ranges, or numbers and percentages. The p values are for differences between groups: Mann-Whitney test (for continuous variables) or Fisher's exact test (for categorical variables).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; Aza = azathioprine; GFR = glomerular filtration rate; MDRD-4 = Modification of Diet in Renal Disease Study 4-variable equation; pts = patients.

Fig. 2 - Kaplan-Meier renal survival curves estimated on the basis of the time to a 50% increase in serum creatinine levels (p value from the log-rank test). Aza = azathioprine.

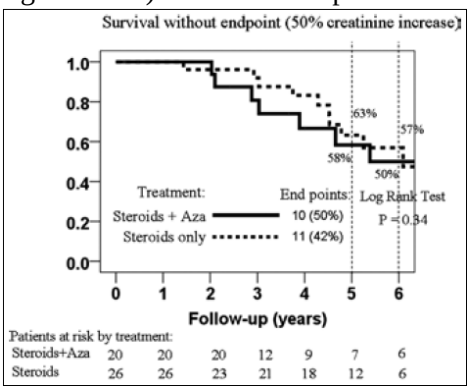

Fig. 3 - Urinary protein excretion at baseline and during follow-up in the 2 treatment groups. The lines crossing the boxes indicate the median value, and the boxes the interquartile range containing 50% of the values; the whiskers show the highest and lowest values that are less than 1.5 box lengths from the 25th or 75th centile. The circles and asterisks indicate more extreme values (outliers). Aza = azathioprine.

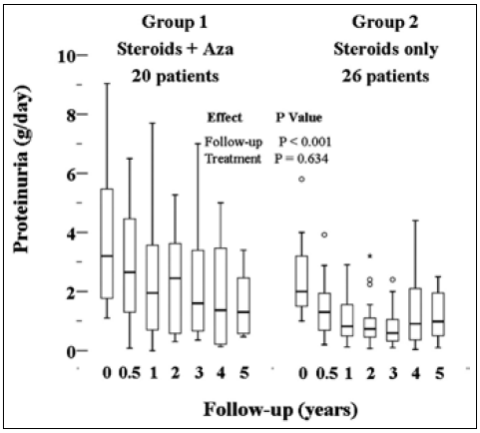

TABLE II

PREDICTIVE VARIABLES RELATED TO RENAL SURVIVAL AT MULTIVARIATE COX REGRESSION ANALYSIS

Variable	B	SE	p Value	RR	RR 95% CI	
Sex (female vs. male)	-2.37	0.89	0.008	0.09	0.02	0.54
Proteinuria during follow-up (for each increase of 1 g/day)	1.54	0.37	<0.001	4.64	2.26	9.54
Number of antihypertensive drugs during follow-up (for each additional drug)	-0.81	0.33	0.014	0.45	0.24	0.85
Treatment with ACEIs during follow-up (yes vs. no)	-1.59	0.73	0.029	0.21	0.05	0.85
Treatment group (steroids +AZA vs. steroids alone)	-2.59	0.91	0.004	0.08	0.01	0.44

Renal survival is estimated on the basis of the time to a 50% increase in plasma creatinine from baseline.
ACEI = angiotensin-converting enzyme inhibitor; Aza = azathioprine; B = regression coefficient; CI = confidence interval; RR = relative risk; SE = standard error of B.

TABLE III SIDE EFFECTS AND OTHER CLINICAL EVENTS BY TREATMENT GROUP

	Treatment group			
	Group 1 Steroids + Aza	Group 2 Steroids alone	Total	p Value*
No. of patients	20	26	46	
No. of patients with at least 1 event	16 (80%)	14 (54%)	30 (65%)	0.065
Total number of events	21	19	40	
Early treatment discontinuation	7 (35%)	4 (15%)	11 (24%)	0.232.
Side effects probably due to treatment:	6 (30%)	4 (15%)	10 (22%)	0.406
Leukopenia	1	0	1	
Liver disease / increased transaminase levels	1	0	1	
Infections	0	2	2	
Arterial hypertension	1	1	2	
Bleeding due to ulcerative esophagitis	1	0	1	
Diabetes	1	0	1	
Depression	1	0	1	
Myalgia	0	1	1	
Other events:				
Insertion of peritoneal catheter	0	1	1	
Dialysis	9 (45%)	10 (39%)	19 (41%)	0.884

Aza = azathioprine.
*P values (chi-squared test) of the between-group differences are only given for the more common events.