

Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy

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ABSTRACT

The optimal treatment for IgA nephropathy (IgAN) remains unknown. Some patients respond to corticosteroids, suggesting that more aggressive treatment may provide additional benefit. We performed a randomized, multicenter, controlled trial to determine whether adding azathioprine to steroids improves renal outcome. We randomly assigned 207 IgAN patients with creatinine ≤ 2.0 mg/dl and proteinuria ≥ 1.0 g/d to either (1) a 3-day pulse of methylprednisolone in months 1, 3, and 5 in addition to both oral prednisone 0.5 mg/kg every other day and azathioprine 1.5 mg/kg per day for 6 months ($n = 101$, group 1) or (2) steroids alone on the same schedule ($n = 106$, group 2). The primary outcome was renal survival (time to 50% increase in plasma creatinine from baseline); secondary outcomes were changes in proteinuria over time and safety. After a median follow-up of 4.9 years, the primary endpoint occurred in 13 patients in group 1 (12.9%, 95% CI 7.5 to 20.9%) and 12 patients in group 2 (11.3%, CI 6.5 to 18.9%) ($P = 0.83$). Five-year cumulative renal survival was similar between groups (88 versus 89%; $P = 0.83$). Multivariate Cox regression analysis revealed that female gender, systolic BP, number of antihypertensive drugs, ACE inhibitor use, and proteinuria during follow-up predicted the risk of reaching the primary endpoint. Treatment significantly decreased proteinuria from 2.00 to 1.07 g/d during follow-up ($P < 0.001$) on average, with no difference between groups. Treatment-related adverse events were more frequent among those receiving azathioprine. In summary, adding low-dose azathioprine to corticosteroids for 6 months does not provide additional benefit to patients with IgAN and may increase the risk for adverse events.

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IgA nephropathy (IgAN) causes ESRD in a significant percentage of patients.¹⁻³ None of the treatment strategies currently used in clinical practice have proved to be more effective than another, although corticosteroids give some results.⁴⁻⁶

In 1999, we found that a 6-month steroid course significantly decreased the risk of a 50% increase in plasma creatinine from baseline at 5 years in comparison with supportive therapy; proteinuria also decreased.⁷ However, 6 months of steroid therapy may not be enough to ensure

stable remission in some patients. Thus, we hypothesized that more aggressive treatment may

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lead to better results, especially in the long term. Previous studies have suggested the possibility that adding immunosuppressants (particularly azathioprine) to corticosteroids may be more effective in preserving renal function^{8,9} and reducing proteinuria.¹⁰ However, azathioprine has mainly been given in combination with other drugs.⁸ Moreover, the sample size⁸ and study design⁹ were inadequate in two of three studies.

The aim of this trial was to assess the efficacy and safety of adding low-dose azathioprine for 6 months to steroids in adult IgAN patients.¹¹ We decided to use azathioprine at low dose and for a relatively short period to decrease the risk of serious side effects of this immunosuppressant in relatively young and healthy subjects.

RESULTS

Enrollment began on May 13, 1998, and was closed on January 10, 2005; the last enrolled patient ended treatment on April 27, 2005. All patients with a histologic diagnosis of IgAN observed in the participating centers during the enrollment period were evaluated; of the 697 consecutive IgAN patients screened, 490 did not fulfill the inclusion criteria or refused to participate. The 207 eligible patients (173 in stratification list 1 and 34 in list 2) were randomly allocated to the experimental treatment (group 1, 101 pa-

tients) or the standard treatment (group 2); all of them were included in the intention-to-treat analyses (Figure 1).

Baseline Characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of the two groups. There was a chance of unbalanced age distribution, with group 1 having younger patients (median 34.8 versus 40.5 years old; $P = 0.02$).

At baseline, 141 patients (68%) were treated for hypertension. The distribution of renin-angiotensin system (RAS) blockade was similar in the two groups (42, 41.6% in group 1; 53, 50% in group 2; $P = 0.27$), except for dual angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) blockade, which was given slightly more frequently in group 2 (5 versus 13%; $P = 0.05$).

According to study protocol, the severity of histologic lesions was evaluated in 90% of the patients in list 1 and was similar in the two groups: grades I, II, and III in 9.0, 45.5, and 45.5% of the patients in group 1 ($n = 88$) and 10.0, 39.0, and 51.0% of the patients in group 2 ($n = 67$).

The patients in the two stratification lists differed in terms of age (median age 36.1 and 41.2 years in lists I and II, respectively; $P = 0.06$), baseline serum creatinine (median 1.20 and 1.36 mg/dl, respectively; $P = 0.009$), frequency of antihypertensive treatment ($n = 113$ [65%] versus 28 [82%], respectively; $P = 0.07$), treatment with ACEI ($n = 49$ [28%] versus 16 [47%], respectively; $P = 0.043$), double RAS blockade ($n = 13$ [8%] versus 6 [18%], respectively; $P = 0.10$), and by study protocol, median time from renal biopsy to study enrollment (median 0.1 and 5.3 years, respectively; $P < 0.001$).

No patient was treated with fish oil before or during the study.

Renal Survival

The patients were followed up for a median of 4.9 years (interquartile range [IQR] 3.0 to 6.4).

The intention-to-treat analysis showed that the primary endpoint occurred in 25 patients (12.1%): 13 (12.9%; confidence interval [CI] 7.5 to 20.9%) in group 1 and 12 (11.3%; CI 6.5 to 18.9%) in group 2 ($P = 0.83$). Renal survival was not different in the two groups (log-rank test $P = 0.83$): 88 and 89% after 5 years and 84 and 83% after 7 years (Figure 2).

Similar results were obtained in the per-protocol analysis of the patients who completed the 6-month treatment and were not protocol violators (data not shown).

Six patients in group 1 (6.0%) and four in group 2 (3.8%) started dialysis.

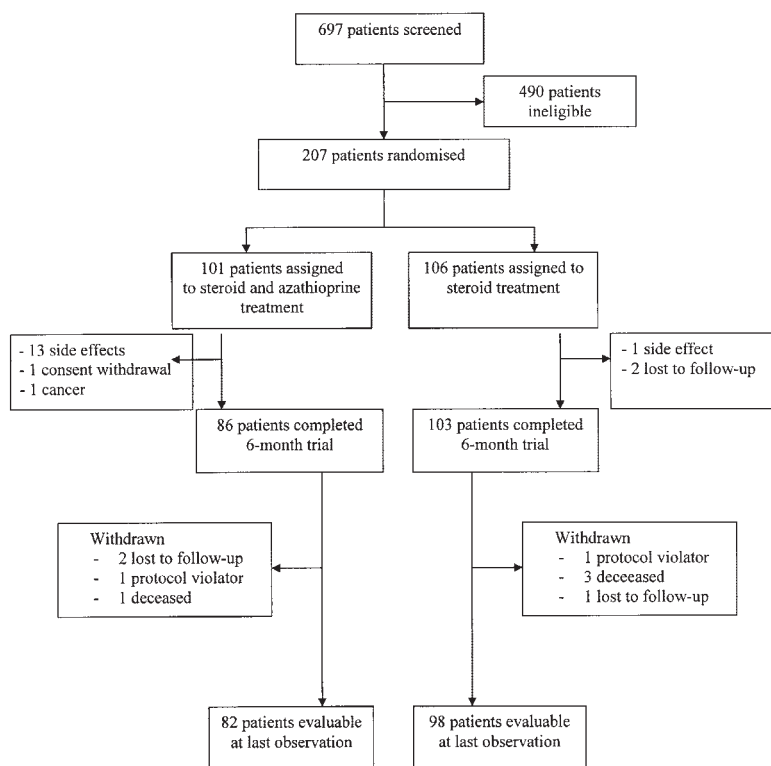


Figure 1. Patient enrollment and outcomes.

Table 1. Baseline clinical and laboratory characteristics by treatment group

	Treatment		Total	P
	Group 1 Steroids + Aza	Group 2 Steroids Alone		
No. patients	101	106	207	
Gender (male/female)	76/25 (75/25%)	75/31 (71/29%)	151/56 (73/27%)	0.59
Age (years)	34.8 (27.7 to 43.9)	40.5 (30.3 to 51.3)	36.4 (28.4 to 48.0)	0.02
Body weight (kg)	72.5 (63.3 to 83.0)	74.5 (64.0 to 81.5)	73 (64 to 83)	0.89
Systolic blood pressure (mmHg)	130 (120 to 140)	130 (120 to 140)	130 (120 to 140)	0.86
Diastolic blood pressure (mmHg)	80 (76 to 90)	80 (75 to 90)	80 (75 to 90)	0.40
No. patients treated for hypertension	67 (66%)	74 (70%)	141 (68%)	0.66
No. patients with RAS blockade before starting the study	42 (42%)	53 (50%)	95 (46%)	0.27
no. patients treated with ACEIs	33 (33%)	32 (30%)	65 (31%)	0.77
no. patients treated with ARBs	4 (4%)	7 (7%)	11 (5%)	0.54
no. patients treated with ACEIs and ARBs	5 (5%)	14 (13%)	19 (9%)	0.05
No. patients treated with statins	13 (13%)	13 (12%)	26 (13%)	1.00
Time from biopsy to enrollment (years)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.3)	0.1 (0.0 to 0.3)	0.84
No. patients with macrohematuria at presentation	25 (24.8%)	21 (19.8%)	46 (22.2%)	0.32
Plasma creatinine (mg/dl)	1.20 (1.00 to 1.50)	1.28 (1.00 to 1.66)	1.20 (1.00 to 1.60)	0.20
Estimated creatinine clearance ³¹	83 (64 to 113)	80 (58 to 95)	81 (60 to 106)	0.07
GFR estimated using MDRD-4 variables ³²	72 (53 to 88)	63 (44 to 85)	66 (48 to 87)	0.06
Proteinuria (g/d)	2.1 (1.5 to 3.5)	2.0 (1.5 to 2.7)	2.0 (1.5 to 3.0)	0.08

Median values and interquartile ranges, or numbers and percentages. *P* values of differences between groups: Mann-Whitney test (for continuous variables) or Fisher's exact test (for categorical variables).

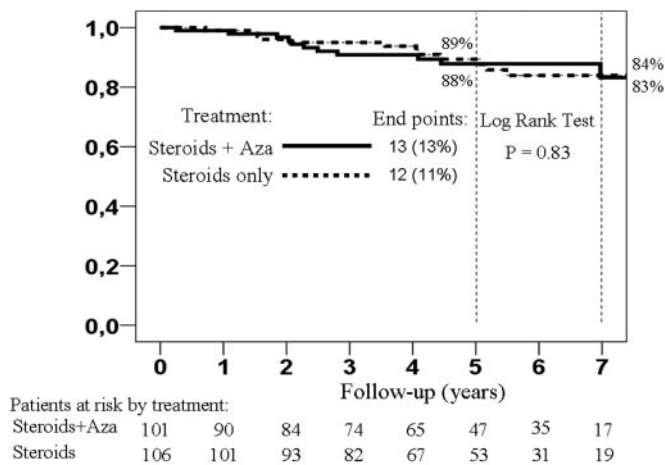


Figure 2. Renal survival is similar in the two treatment groups. Kaplan-Meier renal survival curves were estimated on the basis of the time to a 50% increase in plasma creatinine levels ($P = 0.83$, log-rank test).

Renal survival after 5 years was shorter in list 2 than in list 1 (77 versus 89%; $P = 0.01$), without any between-treatment difference.

Table 2 summarizes the results of the multivariate Cox regression analysis. The risk of reaching the primary end-point was higher in females and in the patients with higher systolic BP, who received more antihypertensive agents or had higher proteinuria levels during follow-up. The use of ACEIs and ARBs (this of borderline significance), and complete proteinuria remission during follow-up, independently correlated with better outcomes. The experimental

treatment (group 1) had no significant independent effect versus the reference category (group 2) (relative risk [RR] of 0.63; CI 0.23 to 1.72; $P = 0.37$). This Cox model was stratified by the randomization list, which proved to be a strong predictor of renal survival (RR 2.50, CI 1.02 to 6.12 for list 2 versus list 1).

Proteinuria

Proteinuria significantly decreased in both groups (Figure 3). Median baseline proteinuria was 2.00 g/d (IQR 1.50 to 3.00) and decreased to 1.30 g/d (IQR 0.92 to 1.88) during the first year of follow-up (-35.0% ; $P < 0.001$) with no between-group difference ($P = 0.58$); throughout the follow-up period, median proteinuria decreased to 1.07 g/d (IQR 0.74 to 1.55, -46.5% ; $P < 0.001$) with no between-group difference: from 2.10 to 1.16 g/d (44.8%) in group 1 and from 1.95 to 0.98 g/d (49.9%) in group 2; $P = 0.57$. There was no rebound of proteinuria after the 6 months of steroid therapy in either group (Figure 3). In most patients (95%), proteinuria decreased by $>50\%$ from baseline regardless of treatment ($P = 0.47$); 54% patients showed complete proteinuria remission (≤ 0.3 g/d) with no between-group difference ($P = 0.55$).

BP and RAS Blockade

During follow-up, systolic and diastolic BP slightly decreased (from 130.7 ± 13.9 to 129.6 ± 9.6 mmHg, $P = 0.10$; and from 82.1 ± 9.7 to 80.8 ± 6.3 mmHg, $P = 0.01$) with no statistical between-group difference. The percentage of patients treated with antihypertensive drugs increased (from 68 to 88%); in

Table 2. Predictive variables related to renal survival at multivariate Cox regression analysis, estimated on the basis of the time to a 50% increase in plasma creatinine from baseline

Variable	B	SEM	P	RR	95% CI for RR	
					Lower Limit	Upper Limit
Gender (female vs male)	1.10	0.52	0.03	3.02	1.09	8.37
Systolic blood pressure during follow-up (for each increase of 1 mmHg)	0.06	0.03	0.01	1.07	1.01	1.12
Proteinuria during follow-up (for each increase of 1 g/d)	0.89	0.18	<0.001	2.43	1.71	3.46
No. antihypertensive drugs during follow-up (for each additional drug)	0.79	0.34	0.02	2.19	1.12	4.28
Treatment with ACEIs during follow-up (yes vs no)	-2.03	0.90	0.02	0.13	0.02	0.77
Treatment with ARBs (yes vs no)	-1.77	1.01	0.08	0.17	0.02	1.22
Complete remission of proteinuria during follow-up: <0.3 g/d (yes vs no)	-1.58	0.71	0.03	0.21	0.05	0.82
Age (for each year)	-0.03	0.02	0.24	0.97	0.93	1.02
Treatment group (steroids + AZA vs steroids alone)	-0.47	0.52	0.37	0.63	0.23	1.72

The model was stratified by list. B, regression coefficient; SEM, standard error of B.

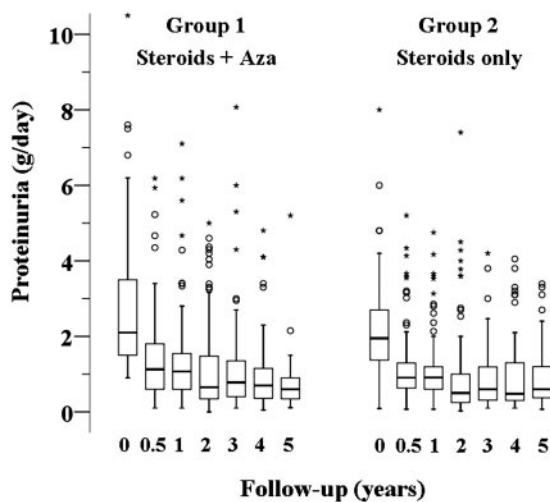


Figure 3. Similar decrease in urinary protein excretion during follow-up in the two treatment groups. The lines crossing the boxes indicate the median and the boxes the IQR 50% of the values; the whiskers show the largest and smallest observed values that are <1.5 box lengths from the 25th or 75th percentile. Circles and asterisks indicate more extreme values (outliers).

particular, 92 patients (44.4%) started RAS blockade during follow-up (48 [47.5%] in group 1 and 44 [41.5%] in group 2). With addition of these patients to those already treated at study entry, 187 patients (90 [89.1%] in group 1 and 97 [91.5%] in group 2; $P = 0.64$) received RAS blockade. These treatments were equally distributed between the two groups during follow-up, and median exposure was also similar: 55 months (IQR 33 to 72) in group 1 and 54 months (IQR 29 to 71) in group 2 ($P = 0.85$).

Repeat Treatments

Thirteen patients (six [5.9%] in group 1 and seven [6.6%] in group 2; $P = 0.84$) received the same protocol regimen a

second time because of relapsed proteinuria (1.2 to 5.1 g/d) intervening after 18 to 60 months of follow-up. Proteinuria again decreased in all cases (data not shown).

Two patients (one in each group) were protocol violators because they received immunosuppressants as rescue treatment.

Clinical Events and Side Effects

Table 3 shows the clinical events and side effects occurring during follow-up.

Eighteen of the 207 treated patients did not complete the 6 months of therapy because they experienced side effects (13 in group 1 and 1 in group 2), were lost to follow-up (2 patients in group 2), withdrew consent (1 patient in group 1), or were diagnosed as having lung cancer (1 patient in group 1). The risk of premature treatment discontinuation was higher in group 1 (14.9 versus 2.8%; $P = 0.002$).

Major side effects were more frequent in the patients receiving azathioprine: 17 (16.8%, CI 10.7 to 25.4%) versus 6 (5.7%, CI 2.4 to 12.1%) ($P = 0.01$).

Eight patients (4%, five in group 1 and three in group 2; $P = 0.43$) developed infections during treatment: five bacterial infections (tonsillitis, pharyngitis, otitis media, trombophlebitis, and dental abscess), two viral infections (herpes zoster), and one case of pneumonia due to *Pneumocistis carinii* requiring drug withdrawal for 2 months. Hepatotoxicity ($n = 5$), anemia and leukopenia ($n = 3$), and gastrointestinal symptoms ($n = 3$), which are all well-known side effects of azathioprine, were observed only in group 1.

Four patients died during the course of the study, one in group 1 and three in group 2 (see legend to Table 3); none of these deaths were considered directly related to the study drugs.

Ten women became pregnant (one woman twice) during the follow-up (from month 13 to month 72). Nine had a normal pregnancy and renal function remained stable during and after it; two patients in group 1 experienced spontaneous miscarriages.

Table 3. Side effects and other clinical events by treatment group

	Treatment Group		Total	P ^a	Percent Risk (95% CI)	
	Group 1 (Steroids + Aza)	Group 2 (Steroids Alone)			Group 1 (Steroids + Aza)	Group 2 (Steroids Alone)
No. patients	101	106	207			
No. patients with at least one event ^b	43	38	81	0.16	42.6 (33.4 to 52.3)	35.9 (27.4 to 45.3)
Total no. events	60	44	104	0.005	59.4 (49.7 to 68.5)	41.5 (32.6 to 51.0)
Early treatment discontinuation	15	3	18	0.002	14.9 (9.1 to 23.2)	2.8 (0.6 to 8.3)
Re-treatments because of proteinuria relapse	6	7	13	0.84	5.9 (2.5 to 12.6)	6.6 (3.0 to 13.2)
Side effects probably due to treatment:	17	6	23	0.01	16.8 (10.7 to 25.4)	5.7 (2.4 to 12.1)
hepatotoxicity	5	0	5			
leukopenia	3	0	3			
gastrointestinal symptoms	3	0	3			
bacterial infections	3	2	5			
viral infections	1	1	2			
<i>Pneumocystis carinii</i> infection	1	0	1			
type 2 diabetes	1	2	3			
hypertension	0	1	1			
Other events:						
death	1 ^c	3 ^d	4			
dialysis	6	4	10			
normal pregnancy	5	4	9			
abortion	2	0	2			
amenorrhea	1	0	1			
lost to follow-up	2	3	5			
systemic lupus erythematosus	1	1	2			
sclerodermia	0	1	1			
extracapillary glomerulonephritism	0	2	2			
pacemaker	1	0	1			
acute myocardial infarction	0	1	1			
acute lower limb ischemia	1	0	1			
transfer to another center	1	1	2			
hepatotoxicity due to anti-inflammatory drugs	0	1	1			
other minor clinical events	1	7	8			

^aP values of between-group differences (χ^2 test) only for more common events.

^bThe numbers below refer to the main event in each patient.

^cDeath after 1 year because of lung cancer.

^dDeaths after 1 year because of liver cancer (one patient), after 3 years because of intestinal infarction (one patient), and after 4 years because of dilated cardiomyopathy (one patient).

DISCUSSION

We have previously shown that steroids are effective in reducing proteinuria and the risk of IgAN progressing to chronic kidney disease (CKD);⁷ this has recently been supported by the results of a clinical trial indicating that steroids plus ACEIs preserve renal function better than ACEIs alone.¹²

Although effective, steroids alone may not be enough to prevent CKD in some patients, which is why we conducted this large, long-term, randomized, controlled study. The addition of azathioprine to 6 months of treatment with steroids was no more effective than steroids alone in reducing the risk of IgAN progression and proteinuria levels, but markedly increased the risk of side effects and premature treatment discontinuation.

Treatment effect did not differ in the two randomization lists.

The worse renal survival in list II is probably explained by the fact that these patients were older, had higher creatinine values, were treated more often with antihypertensive medications, and had a much longer duration of renal disease at baseline than the patients in list I. Indeed, the patients were allocated to one of the two lists according to the timing of renal biopsy.

With the limits of all historic comparisons, overall 5-year renal survival (88%) was similar to that observed in the steroid group of our previous study⁷ (81%), and better than that of the patients receiving supportive therapy alone (64%). This is in line with the results of the meta-analysis by Samuels *et al.*,¹³ who found that steroid treatment significantly reduced the risk of CKD progression and proteinuria in comparison with no treatment. The comparison of the progression rate of CKD we observed with that of other cohorts of IgAN patients coming from clinical trials or ob-

servational studies is difficult because of differences in end-point definition and follow-up length.

Proteinuria decreased less than that in our previous study,⁷ despite a similar schedule of steroid treatment; this may be partially due to the fact that the inclusion criteria of the two studies were slightly different.

Our multivariate Cox analysis showed that mean proteinuria during follow-up is an important predictor of outcome; this supports previously published data indicating that proteinuria during follow-up is more predictive of outcome than proteinuria at presentation.^{14–16}

A number of controlled studies of corticosteroid and cytotoxic drug combinations have involved patients with IgAN,^{8,17–20} but despite the positive results of individual trials,^{8,19,20} a pooled analysis failed to demonstrate any significant reduction in proteinuria or the risk of progression to ESRD with the combined treatment approach.¹³ One randomized, controlled study of children with diffuse mesangial proliferation at renal biopsy has compared azathioprine plus corticosteroids, warfarin, and dypiridamole with steroids alone and found a higher disappearance rate of proteinuria (urinary protein excretion <0.1 g/m² per day) in the group receiving the combined treatment.²⁰ Its relatively short follow-up (2 years) prevents any conclusion being drawn about renal function over time. Steroids and azathioprine were given for 24 months and side effects were more frequent (35%) than in our trial (16.8%), thus justifying *a posteriori* our choice of giving azathioprine for only 6 months to reduce the risk of side effects in a relatively benign disease. However, if this frequency is corrected by treatment duration, azathioprine was probably less tolerated in our study, perhaps because we enrolled adults with more severe disease. Conversely, we cannot exclude the possibility that we have not been able to show higher proteinuria reduction or better preservation of renal function in those receiving azathioprine added to steroids compared with steroids alone because of the lower azathioprine doses and/or shorter treatment duration.

It is possible that immunosuppressants other than azathioprine lead to better results with fewer side effects. Mycophenolate mofetil acts like azathioprine and may be less toxic but it has not yet been clearly proven effective in IgAN.^{21–23} Recently, Tang *et al.*²⁴ reported their long-term experience in 40 Chinese patients randomized to receive either mycophenolate for 6 months or to continue previous RAS blockade. After 6 years, renal survival considering the hard endpoint of the need of renal replacement therapy was much better in the mycophenolate group than in the control group. The antiproteinuric effect of the drug disappeared after nearly 2 years. This behavior is similar to our experience with steroids alone.¹⁴ The relevance of these findings is limited by the small sample size and by a faster than expected progression rate toward ESRD in the control group. To the best of our knowledge, no study has tested the effect of mycophenolate in association with steroids in IgAN.

Mizoribine is another antimetabolite that has been tested in

combination with steroids in children with severe IgAN and led to proteinuria remission in 80% of cases, with less severe but frequent side effects.²⁵

We did not enroll the planned number of patients despite extending the enrollment period, but ours is still the largest clinical trial involving IgAN patients. Its sample size is nearly double that of previous studies of steroids,^{7,26} cytotoxic agents,⁸ or other treatments,^{27–29} although we cannot exclude the possibility that it was underpowered. The fact that the renal survival curves were similar, and the log-rank test *P* value was very high, makes it unlikely that our results would have been different if we had enrolled more patients.

When we designed the study in the 1990s, the renoprotective effect of RAS blockade was not completely established, particularly in IgAN. As a result, one possible weakness of our study is that only some patients received RAS blockade despite the progressive increase in its use over the years and its dose titration was not foreseen. This limitation is reduced by the fact that the number of patients receiving RAS blockade before and after enrollment and the duration of exposure were similar in the two groups. Moreover, only a minority of the patients started this treatment during the first 6 months of the study. Thus, it is unlikely that the clear antiproteinuric effect we observed in the two groups was because of RAS agents and not study treatments. Conversely, it is possible that starting RAS blockade during the course of the follow-up may have influenced proteinuria levels. Anyway, in the study by Manno *et al.*,¹² in which the study design foresaw a well-balanced distribution of ACEI use, steroids plus ACEI were found more effective than ACEI alone.

In conclusion, a 6-month course of corticosteroids plus low-dose azathioprine seems to produce no additional benefit over steroids alone in reducing the risk of progression to ESRD in patients with IgAN, and it may increase the number of adverse events.

CONCISE METHODS

Study Population

Adult patients with IgAN were eligible if they had had plasma creatinine ≤ 2.0 mg/dl and proteinuria ≥ 1.0 g/d for at least 3 months. The main exclusion criteria were steroid or cytotoxic drug treatment during the previous 3 years, contraindications to steroids or azathioprine, or evidence of systemic diseases, diabetes, or severe hypertension, and extra capillary proliferation $>20\%$ at renal biopsy.

Study Design

The study was multicenter (27 centers in Italy and Switzerland), open-label, and randomized (clinicaltrials.gov identifier: NCT00755859). The protocol was approved by the Institutional Review Board of each center, and all of the patients gave their written informed consent. Details of the study protocol have been published elsewhere.¹¹

The patients with IgAN were divided into two strata on the basis of the timing of renal biopsy (no more than 1 year, list 1; or more than 1

year before randomization, list 2), and randomly assigned 1:1 to receive steroids plus azathioprine (group 1, experimental) or steroids alone (group 2, control) using two centralized, computer-generated randomization lists (one for each stratum).

Hypertension was defined as sitting BP levels of >135/85 mmHg recorded twice or the need for antihypertensive drugs. ACEIs, ARB, and statins were given in accordance with the centers' usual policy: target BP was 130/80 mmHg. The histologic material was evaluated by the centers using the criteria of the World Health Organization (WHO) as modified by Churg and Sobin (grade I, minimal glomerular lesions; group II, active glomerular, tubular, and interstitial lesions; group III, active and chronic lesions).³⁰

The planned recruitment and follow-up periods were respectively 4 and 5 years.

Treatments

The patients received 6 months of treatment with 1 g of methylprednisolone given intravenously for 3 consecutive days in months 1, 3, and 5 and 0.5 mg/kg of prednisone given orally every other day plus 1.5 mg/kg per day of azathioprine (group 1) or the same steroid schedule alone (group 2).

Outcome Measures

The primary endpoint was renal survival based on the time to the 50% increase in plasma creatinine from baseline, confirmed the following month. The secondary endpoints were proteinuria over time and adverse events.

Statistical Analysis

Cumulative renal survival without reaching the endpoint was calculated using the Kaplan-Meier method; the two treatment groups were compared on an intention-to-treat basis using the log-rank test, stratified by randomization list.

Patients relapsing during follow-up were retreated with the same schedule; relapse was defined as proteinuria levels equal to or more than baseline after a reduction of at least 50%.

Multivariate Cox regression analysis was used to estimate the RR and 95% CI of the assigned *versus* standard treatment associated with the possibly explanatory prognostic covariates, which were selected using a backward stepwise procedure. The assumption of constant hazard rates over time was checked by plotting the logarithm of the survivor function against time. The two-sided α significance level was set at 0.05 for all of the analyses, which were made using SPSS statistical software for Windows, release 15.

Sample Size

On the basis of our previous study,⁷ a sample size of 173 patients per group was estimated as being large enough to detect an absolute difference in renal survival of 10% between the patients treated with steroids plus azathioprine (group 1, estimated 5-year renal survival 90%) and those receiving steroids alone (group 2, estimated 5-year renal survival 80%), with a power of 80% and a type 1 probability error of 0.05.

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C.P., S.A., A.P., L.D.V., G.B.F., and F.L. contributed to study concept and design and to analysis and interpretation of data. C.P. and S.A. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. P.S., B.V., V.D.C., L.A., L.C., and A.D.P. participated in collection, analysis, and interpretation of the data. C.P., S.A., L.D.V., and F.L. contributed to drafting of the paper. S.A. performed the statistical analysis. C.P. provided administrative support. C.P. and F.L. supervised the study. All authors revised the paper for important intellectual content and have seen and approved the final version.

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DISCLOSURES

None.

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