Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

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Abstract

Background. Immunoglobulin A nephropathy (IgAN) is the most common cause of chronic renal failure among primary glomerulonephritis patients. The best treatment for IgAN remains poorly defined. We planned a long-term, prospective, open-label, multicentre, centrally randomized controlled trial to assess whether the combination of prednisone and ramipril was more effective than ramipril alone in patients with proteinuric IgAN.

Methods. Ninety-seven biopsy-proven IgAN patients with moderate histologic lesions, 24-h proteinuria ≥1.0 g and estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73 m² were randomly allocated to receive a 6-month course of oral prednisone plus ramipril (combination therapy group) or ramipril alone (monotherapy group) for the total duration of follow-up. The primary outcome was the progression of renal disease defined as the combination of doubling of baseline serum creatinine or end-stage kidney disease (ESKD). The secondary outcomes were the rate of renal function decline defined as the eGFR slope over time, and the reduction of 24-h proteinuria.

Results. After a follow-up of up to 96 months, 13/49 (26.5%) patients in the monotherapy group reached the primary outcome compared with 2/48 (4.2%) in the combination therapy group. The Kaplan–Meier analysis showed a significantly higher probability of not reaching the combined outcome in the combination therapy group than in the monotherapy group (85.2% versus 52.1%; log-rank test \( P = 0.003 \)). In the multivariate analysis, baseline serum creatinine and 24-h proteinuria were independent predictors of the risk of primary outcome; treatment with prednisone plus ramipril significantly reduced the risk of renal disease progression (hazard ratio 0.13; 95% confidence interval 0.03–0.61; \( P = 0.01 \)). The mean rate of eGFR decline was higher in the monotherapy group than in the combination therapy group (−6.17 ± 13.3 versus −0.56 ± 7.62 ml/min/1.73 m²/year; \( P = 0.013 \)). Moreover, the combined treatment reduced 24-h proteinuria more than ramipril alone during the first 2 years.

Conclusions. Our results suggest that the combination of corticosteroids and ramipril may provide additional benefits compared with ramipril alone in preventing the progression of renal disease in proteinuric IgAN patients in the long-term follow-up.

Keywords: ACE-inhibitors; corticosteroids; immunoglobulin A nephropathy; proteinuria; randomized controlled trial

Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most common forms of primary glomerular disease [1,2]. Despite initial reports of favourable prognosis, long-term studies showed that end-stage kidney disease (ESKD) may develop in these patients. Clinical and histopathological parameters that identify patients as ‘potential progressors’ have already been described [3–7]. Our retrospective study of 437 IgAN patients showed that ESKD occurred in ~40% of patients within 20 years from the time of renal biopsy [7]. In the multivariate analysis, independent predictors of adverse outcome were absence of recurrent episodes of macrohaematuria at onset, baseline serum creatinine level and urinary protein excretion. Another important factor was the grade of histologic lesions, which increased the risk of ESKD 6-fold [7]. The patients identified as potential progressors may be candidates for several therapeutic approaches that should be evaluated through randomized, controlled trials (RCTs).

The pathogenesis of IgAN is still unknown, and no specific treatment is established, although many approaches have been investigated. Beneficial effects from the long-term use of corticosteroids are reported in retrospective or non-randomized prospective studies [8–10]. The results of RCTs in adult patients are controversial for several reasons, e.g. different outcomes were considered, the sample size was small or the follow-up periods were too short for
a slowly progressing disease [11–15]. Systematic reviews report the beneficial and promising effect of corticosteroids on the progression of renal damage and on urinary protein excretion, although the quality of the studies included in the analysis was suboptimal [16,17]. However, in a long-term RCT [13,18], the beneficial effect of corticosteroids was demonstrated compared with supportive therapy, but this effect was reduced over time.

Furthermore, it is well known that ACE-inhibitors (ACE-I) reduce proteinuria in IgAN patients [19–25] and provide protection against the progression of renal disease in various diabetic and non-diabetic nephropathies [26–28]. A recent RCT evaluated the efficacy of the combination of corticosteroids and ACE-I versus ACE-I alone in IgAN patients, with evidence in favour of the combination therapy with corticosteroids [29]. Conflicting data and a lack of long-term, prospective, randomized studies prevent most treatments from being recommended as standard therapy for IgAN. Corticosteroids seem to be a good treatment for patients with proteinuria, since they ameliorate this symptom and protect against deterioration of renal function.

This body of clinical evidence led us to plan a long-term RCT to assess whether combination therapy with corticosteroids and ramipril improves renal survival compared with ramipril alone in IgAN patients who are potential progressors.

Subjects and methods

Study population

In this prospective, open-label RCT, 97 IgAN patients attending 14 nephrology centres were enrolled between June 2000 and June 2004. A large percentage of patients were recruited in the coordinating centre, and some of them were then followed up in other out-patient hospitals. The Ethics Committee of the coordinating centre was notified of the study protocol as an independent phase IV research study for drugs commonly used in various nephropathies. The study was carried out according to the Declaration of Helsinki (IV Adaptation). All consecutive in-patients or out-patients of both genders with biopsy-proven IgAN who satisfied the eligibility criteria were asked to participate in the study. All patients who gave their informed consent were included in the study.

The inclusion criteria were IgAN diagnosed by a renal biopsy no more than 1 year before randomization and histological grade G2 (moderate) lesions according to our classification [7], age between 16 and 70 years, urinary protein excretion >1.0 g/24 h for at least 2 months and an estimated glomerular filtration rate (eGFR) >50 ml/min/1.73 m², evaluated by abbreviated MDRD formula [30]. In patients with macroscopic haematuria, the renal biopsy was performed at least 30 days after the episode.

The exclusion criteria included treatment with corticosteroids or immunosuppressive drugs in the previous 2 years, acute myocardial infarction or stroke in the previous 6 months, severe uncontrolled hypertension (diastolic blood pressure ≥120 mmHg and/or systolic blood pressure ≥220 mmHg), evidence or suspicion of renovascular disease, insulin-dependent diabetes mellitus, infections, severe liver diseases, malignancies, active peptic-ulcer disease, secondary IgAN or relapse in renal allograft, pregnancy, other contraindications to corticosteroids or ACE-I and alcohol abuse. IgAN patients with fibrinoid necrosis lesions at renal biopsy were also excluded.

The drop out criteria were pregnancy, death, withdrawal of consent and referral to another nephrology centre not participating in the study. Data from drop out patients were collected and analysed for the primary outcome.

Design and study objectives

The primary objective was to assess whether a 6-month course of high-dose corticosteroids added to long-term therapy with ramipril improved renal survival. The secondary objectives were the rate of renal function decline, the effects on the reduction of proteinuria and the side effects of the drugs used.

After a screening assessment, all patients entered a 3-month run-in phase in which eGFR and 24-h proteinuria were evaluated every 2 weeks. At the beginning of this period, in patients already treated with ACE-I and angiotensin II receptor blockers (ARBs), these drugs were withdrawn for at least 4 weeks before performing the laboratory tests. Other antihypertensive agents (besides ACE-I or ARBs) were allowed for blood pressure control in any phase of the study.

At the end of the run-in phase, all eligible patients were randomly assigned to prednisone plus ramipril (combination therapy group) or ramipril alone (monotherapy group). An allocation assignment sequence was generated at the coordinating centre by random number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomization. Central telephone randomization for every eligible patient was performed by the Scientific Secretariat.

In the combination therapy group, the 6-month course of prednisone began with oral prednisone 1.0 mg/kg/day for 2 months and then the dose was tapered by 0.2 mg/kg/day every month. The maximal prednisone dose was fixed at 75 mg/day. In both groups, treatment with ramipril started at a dose of 2.5 mg/day and was then increased by 1.25 mg/day every month to achieve and maintain a systolic and diastolic blood pressure <120–80 mmHg and to reduce 24-h proteinuria to 1.0 g or less; kalaemia was monitored and did not exceed the value of 5.5 mmol/L. Ramipril was administered during the entire follow-up period to both groups. If necessary, some patients received diuretics, antihypertensives, antacids and antilucre medication, and antidiabetic drugs. No antiplatelet, anti-inflammatory and other immunosuppressive drugs were administered. The patients were advised to limit their daily sodium intake and to eat no more than 1.0 g of protein per kilogram body weight per day. Dietary compliance was assessed by measuring 24-h urinary sodium and urea excretion.

The investigators examined each patient at randomization, every month during the first 6 months, and every 3 months thereafter. Blood pressure and heart rate were measured with the patient in a sitting position at each visit in the out-patient unit in the morning, before ingestion of the drugs. Blood and 24-h urinary samples were obtained for assessment of creatinine, urea, sodium, potassium, uric acid, albumin, total proteins, glucose, cholesterol, triglycerides, liver enzymes, bilirubin, complete blood count and protein and urea and sodium urinary excretion. Hypertension was defined as a blood arterial pressure >140–90 mmHg or the need for antihypertensive drugs other than ACE-I.

To assess the severity of renal damage, we distinguished three grades (G) according to our classification, which is published elsewhere [7]. G1 (mild) included IgAN patients with minor or minimal lesions, G2 (moderate) included patients with focal segmental or diffuse proliferative glomerulonephritis and G3 (severe) included patients with sclerotic lesions in advanced chronic glomerulonephritis or ESKD. Mesangial hypertrophy was scored as follows: mild when there were ≤3 mesangial cells and moderate-to-severe when there were >6 mesangial cells on average in at least two glomerular lobules. Sclerosis was defined as the obliteration of capillary loops due to a prevalent increase in matrix or capillary tuft adhesion to Bowman’s capsule or both. Endocapillary proliferation was defined as the obliteration of the capillary tuft by cells (endothelial, mesangial or inflammatory cells). Biopsies were assigned to G2 if one of the following signs was detected: a moderate increase in mesangial cellularity (focal or diffuse), endocapillary proliferation, cellular crescents (up to 50% of the glomeruli involved), segmental sclerosis, tubular atrophy and interstitial fibrosis (up to 1/3 of the cortical area) [7].

Statistical analysis

The primary outcome was the progression of renal disease defined as the combination of doubling of baseline serum creatinine or ESKD, defined as a need for dialysis or renal transplantation. The secondary outcomes were the rate of renal function decline by means of eGFR slope over time and urinary protein excretion. Adverse events and side effects of the drugs were also monitored and recorded in the report form. Results were evaluated on an intention-to-treat analysis in all randomized patients, irrespective of adherence to the assigned treatment. Dichotomous and polychotomous baseline characteristics were compared with the chi-square or Fisher’s exact test. Continuous baseline characteristics were compared with Student’s t-test or the Mann–Whitney U test. In patients with three or more eGFR assessments, the slope over time was estimated by linear regression.
analysis. Renal survival was analysed by Kaplan–Meier curves for censored data; the combination and monotherapy groups were compared with the log-rank test and the Breslow test. Multivariate analysis based on Cox’s regression proportional hazard method was used to assess the relative risk associated with possible baseline prognostic factors such as age, gender, serum creatinine, hypertension and urinary protein excretion. Results were reported as adjusted hazard ratio (HR) with 95% confidence intervals (CI). The sample size was calculated by the difference in the progression of renal disease. No data on the progression of renal disease in selected IgAN patients treated for long time with ACE-I are available. Because the difference in renal survival reported in a previous Italian RCT [13] was 17% between corticosteroids (81%) and a control (64%) group, we assumed a difference of 20% as clinically relevant between our treatment groups. At the beginning of the study, we calculated a sample size of 134 patients on the basis of these assumptions for an α error (type I) of 0.05 (two-tailed test), a β error (type II) of 0.2, a power (1-β) of 0.8, and assumed 2 years of recruitment period and 5 years of follow-up [31]. Subsequently, we prolonged the recruitment period to 5 years, and the sample size was reduced to 120 patients.

Interim analyses were planned at the end of each completed year of treatment for every patient. Statistical guidelines for early stopping of the trial were established a priori according to the Peto–Haybittle methods. The guidelines stated that the trial could be interrupted if renal survival was significantly (P < 0.01) lower or higher in the combination therapy group compared with the monotherapy group. An interim analysis performed after 4 years by an independent monitoring committee found a better outcome in the combination therapy group, and for this reason the study was stopped early after 97 patients were enrolled. Results were analysed by assessors independent from clinical investigators. In all analyses, the SPSS statistical software (release 15.0) was used, and a P-value < 0.05 was considered significant.

Results

Of a total of 220 biopsy-proven IgAN patients assessed for eligibility, 123 were excluded since they did not fulfil the inclusion criteria, as shown in trial profile (Figure 1). The remaining 97 patients were randomized and assigned to treatment with the combination therapy (48 patients) or monotherapy (49 patients). Even though IgAN is a common disease, about 50% of screened IgAN patients met our inclusion criteria. During the run-in phase, ACE-I and/or ARBs were withdrawn in 5/97 (5.1%) patients. All patients were analysed for the primary outcome; six patients (three in each group) withdrew. One woman in the combination therapy group became pregnant after 24 months of follow-up. Four patients (two in each group) were lost to follow-up 12–36 months after randomization. One patient in the monotherapy group had a protocol violation because a 6-month course of corticosteroids was given as rescue treatment. All patients were followed for at least 3 (range, 3–9) years and the median follow-up was 5 years; 50/97 completed 5 years of follow-up.

Baseline characteristics

The clinical and laboratory characteristics are summarized in Table 1. The baseline characteristics in both groups were
similar regarding age, gender, clinical onset, serum creatinine and eGFR, urinary protein excretion, systolic and diastolic blood pressure, as expected from a proper randomization procedure. At renal biopsy, both groups were similar for mesangial and endocapillary proliferation, cellular crescents, global and segmental glomerulosclerosis, interstitial fibrosis and tubular atrophy, with many patients displaying the predominance of active/proliferative lesions on chronic/sclerosing lesions. At baseline, 12 patients were hypertensive (7 in the combination therapy group, 5 in the monotherapy group), and 3 patients developed hypertension during the follow-up (2 in the combination therapy group, 1 in the monotherapy group). The proportion of hypertensive patients was similar in both groups. Hypertension was treated according to the recommendations of the international guidelines (Joint National Committee, National Kidney Foundation and European Society of Hypertension). Four patients in the combination therapy group and three patients in the monotherapy group required the addition of calcium channel blockers or beta-blockers. No statins or diuretics were administered in any patient. Sodium excretion was $138.6 \pm 21.1$ mmol/24 h in the combination therapy group and $134.7 \pm 20.6$ mmol/24 h in the monotherapy group.

**Primary outcome**

After a follow-up of up to 96 months, 2/48 (4.2%) patients in the combination therapy group and 13/49 (26.5%) in the monotherapy group reached the combined outcome of doubling of serum creatinine or ESKD after 8 years (85.2% versus 52.1%; log-rank test $P = 0.003$; Figure 2A). When we considered the probability of not reaching the hard end point of ESKD, survival was also significantly better in combination therapy group than in the monotherapy group (96.7% versus 75.5%; log-rank test $P = 0.024$; Figure 2B). No patient died during the entire follow-up period.

The multivariate analyses by Cox’s proportional hazard method, which considered the combined endpoint of doubling of baseline serum creatinine or ESKD, showed that treatment with prednisone plus ramipril was an independent factor modifying renal survival. The risk was significantly reduced by 87% in the combination therapy group (HR 0.13; 95% CI 0.03 to 0.61; $P = 0.01$); on the other hand, the risk of reaching the combined outcome was significantly increased for each g/24 h increase in baseline urinary protein excretion (HR 2.80; 95% CI 1.31–5.99; $P = 0.008$) and each mg/dl increase in baseline serum creatinine (HR 3.22; 95% CI 1.13–9.19; $P = 0.029$). Even when the multivariate analysis was carried out with ESKD as the unique outcome, the combination of prednisone and ramipril was confirmed as an independent factor that should modify renal survival; in this case, the risk of reaching the outcome was 91% lower in the combination therapy group compared with the monotherapy group (HR 0.09; 95% CI 0.01–0.86; $P = 0.036$) and the risk increased significantly, more than three times for each g/24 h increase in baseline urinary protein excretion (HR 3.41; 95% CI 1.23–9.46; $P = 0.018$).

**Secondary outcomes**

The mean rate of renal function decline was $−0.56 \pm 7.62$ ml/min/1.73 m²/year in the prednisone plus ramipril group and $−6.17 \pm 13.3$ ml/min/1.73 m²/year in the ramipril alone group ($P = 0.013$). No difference in the slope of eGFR was found at different time periods (data not shown).

In the cohort of patients followed for at least 5 years, median urinary protein excretion decreased in both groups
At the end of the follow-up, there was no statistically significant difference in systolic (121.3 ± 9.9 mmHg versus 121.7 ± 10.3 mmHg) and diastolic (76.7 ± 6.8 mmHg versus 76.9 ± 6.1 mmHg) blood pressure between the combination therapy and monotherapy groups, respectively. We also evaluated the maximal ramipril dose reached in the two groups over the entire follow-up period. The median (interquartile range) values were 6.5 (5.0–8.0) mg/day in the combination therapy group and 6.7 (5.2–8.5) mg/day in the monotherapy group, but this difference was not significant.

Safety

The side effects of the drugs were mild in both groups. In the combination therapy group, three patients had striae rubrae and one patient developed glucidic intolerance and was treated with oral antidiabetic drugs. Two patients in the monotherapy group experienced cough that was controlled after the ramipril dose was reduced. Serious adverse events were not observed in both groups.

Discussion

Our study with a long-term follow-up shows that the combination of prednisone and ramipril compared with ramipril alone provides additional benefit by preventing the progression of renal damage in proteinuric IgAN patients with moderate histologic lesions. A 6-month course of prednisone plus ramipril administered during the follow-up ameliorated the 8-year renal survival compared with ramipril alone. We analysed kidney survival using two types of outcomes: the combination of doubling of the baseline serum creatinine or ESKD, and a hard endpoint, i.e. ESKD alone. In the multivariate analyses, the combined therapy significantly reduced the risk of doubling the baseline serum creatinine level or ESKD by 87%, and the risk of ESKD by 91%. The baseline levels of serum creatinine and urinary protein excretion were both independent predictors of the risk of primary outcome. In addition, the use of surrogate endpoints demonstrated that the combined therapy with prednisone plus ramipril reduced 24-h proteinuria more than ramipril alone during the first 2 years, while this effect was less pronounced thereafter. Moreover, the rate of renal function decline, calculated by the slope of eGFR over time, was significantly higher in the monotherapy group. We believe that these results may be due to the anti-inflammatory and immunosuppressive effect on active histologic lesions by early administration of a high dose of corticosteroids and to renoprotection of ACE-I in the long-term period.

The identification of baseline clinical and histologic factors that may influence disease progression in patients with IgAN has stimulated much research. Considering the slow progression of the disease and the relatively aggressive nature of the proposed interventions (corticosteroids and other immunosuppressive regimens), it is important to understand which patients may or may not progress and who might benefit from different therapeutic interventions. A few years ago, our group published a large survival analysis of IgAN patients, focusing on and highlighting the
importance of histologic lesions using an appropriate multivariate approach [7]. After 20 years of follow-up, we demonstrated that patients with mild renal lesions (G1) do not progress to ESKD, while 35.6% of patients with moderate renal lesions (G2) and 92.9% with severe lesions (G3) may progress to ESKD. Thus, the biopsy-proven IgAN patients chosen for our RCT had moderate lesions at renal biopsy, proteinuria and preserved renal function. They were considered potential progressors and good candidates for therapeutic intervention with a high dose of corticosteroids.

The design of RCTs is difficult for several reasons. In many cases, the progression of renal disease is slow and long periods of follow-up with large numbers of patients are required to detect small but significant differences. A few retrospective or non-randomized prospective studies reported some beneficial effects of the long-term use of corticosteroids in adult patients [8–10], but the results of small RCTs were conflicting [11–15]. In a long-term RCT [13,18], carried out several years ago in patients with mild and moderate histologic lesions, moderate proteinuria and preserved renal function, the efficacy of corticosteroids on renal survival, defined as a 50% or 100% increase in baseline serum creatinine, and on urinary protein excretion, was evaluated. However, in this RCT, as in our study, the beneficial effect of corticosteroids on proteinuria decreased over time. Even when the follow-up was extended to 10 years, the primary outcome remained the doubling of baseline serum creatinine and the previous results were confirmed. These findings are in favour of long-term therapy in IgAN patients with renal damage that may progress. We preferred to modify the treatment regimen with corticosteroids because we believe that lower doses of these drugs may be associated with less potential side effects, but equal benefits. At the same time, we prolonged therapy with ACE-I throughout the period of follow-up, trying to achieve the maximal dose tolerated by each patient.

A recent single-centre RCT evaluated the efficacy of combination therapy with corticosteroids and ACE-I versus ACE-I alone in a small number of IgAN patients, with a follow-up period that was too short to evaluate renal survival [29]. In fact, in this trial carried out in patients with both mild and moderate histologic lesions, only a few events were reported, such as a 50% increase in baseline serum creatinine after 3 years of the follow-up period. The authors concluded that further validation was necessary. In contrast, our multicentre study was carried out in a selected population of IgAN patients with moderate lesions at renal biopsy (potential progressors) who were at high risk of progressive renal damage. Furthermore, our study shows the results on kidney survival obtained using a hard and unequivocal endpoint like ESKD, after a long-term follow-up. Thus, our study demonstrates for the first time that combination therapy with a 6-month course of corticosteroids (prednisone) and continuous use of ramipril in proteinuric IgAN patients with moderate histologic lesions is more effective than ramipril alone in slowing the progression of renal disease to ESKD. For all these reasons, we believe that corticosteroids may reduce proliferative and exudative lesions in the acute phase of IgAN, but long-term control of proteinuria is also necessary [32]. ACE-I are fundamental in the long-term management of progressive IgAN because they stabilize systemic and renal blood pressure, reduce the traffic of proteins, and slow the decline in the glomerular filtration rate. In our study, ramipril was administered at similar doses over the duration of the follow-up period in both groups, and its benefit was demonstrated by the permanent reduction of proteinuria.

This study demonstrates the advantages of combination therapy with corticosteroids plus ramipril compared with ramipril alone in IgAN patients after a long-term follow-up. The study has some strengths: the long-term follow-up and the efficacy shown by a hard endpoint like ESKD, which is more informative than the doubling of serum creatinine or other surrogate endpoints. Moreover, the average time after the renal biopsy was very short and no patient had previously received immunosuppressive therapy, avoiding any risk of carry-over effect. Then, the very low number of side effects has led us to believe that a 6-month course of prednisone is a well-tolerated therapy in this kind of patients.

However, there are some limitations. First, the open design of the trial did not include a placebo control in the monotherapy group. Second, the choice of a select group of IgAN patients may limit the applicability of this therapeutic intervention to all IgAN patients. This study was not specifically designed to answer the question whether corticosteroids should be administered to patients exhibiting regression of proteinuria with ACE-I therapy; however, we believe that prednisone should be administered as first line therapy to all IgAN patients with proliferative lesions at renal biopsy, because they are at high risk of progression towards ESKD. On the other hand, patients with mild lesions and those with chronic advanced lesions should be treated only with ACE-I and/or ARBs. Third, most of our patients were non-hypertensive young adults and they received the maximal tolerated dose of ramipril. Fourth, although the multicentre design usually allows us to generalize the results to the whole population, in our RCT a large percentage of patients were recruited in the coordinating centre. Finally, the results obtained in a homogenous Caucasian group may not be applicable to other races, considering the genetic variability of the disease.

Therefore, further RCTs in other IgAN patient populations or observational, prospective studies are necessary to confirm the effectiveness and the benefits of combination therapy in daily clinical practice.

Acknowledgements. We would like to thank Mrs M. Mastrolonardo for the language revision of the text and editorial assistance and Dr G. Loizzo for technical support.

Conflict of interest statement. None declared.

Appendix

Investigators and Institutions—C.M., D.D.T., C. D’Altri, M.R., G. Grandaliano, F.P.S. (Bari); G. Pallotta (Alcamo); F. Cazzato, G. Chiarulli (Acquaviva delle Fonti); A. Tedesco, F. D’Agostino (Andria); S. Iannaccone, A. Milone (Avellino); V. Giancaspro, F. Petraruolo (Bari-Di Venere); A. Mancini (Barletta); S. Pasquali, A. Santoro (Bologna); L.
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Received for publication: 15.1.09; Accepted in revised form: 29.6.09