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NEPHROLOGY - ORIGINAL PAPER

Evaluation of low-dose glucocorticoid regimen in association with cyclophosphamide in patients with glomerulonephritis

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Abstract

Background The treatment of most glomerulonephritides is still based on a combination of an oral corticosteroid and an alkylating agent, with favorable outcomes, but with serious side effects. The objective of this study was to reduce the cumulative corticosteroid dose in patients with high risk of corticosteroid-related adverse events by replacing daily oral corticosteroids with intravenous (iv) methylprednisolone pulses, associated with monthly pulse i.v. cyclophosphamide (according to KDIGO guidelines) in patients with glomerulonephritis.

Methods This was a retrospective cohort study conducted at a single nephrology centre. In the course of a 6-month run-in phase, all the patients received non-immunosuppressive pathogenic treatment. High-risk patients, who still had urinary protein excretion of at least 3.5 g per day at the end of these 6 months, received a combination of corticosteroids and cyclophosphamide. Patients were divided in two groups: group 1 (23 patients)—included patients with high risk of corticosteroid-related adverse events received monthly methylprednisolone 1 g/day, 3 days and i.v. cyclophosphamide for 6 months, and group 2 (84 patients)—received oral corticosteroids (as per KDIGO recommended dose) and i.v. cyclophosphamide. The primary outcome—time to a combined end-point of doubling of serum creatinine, ESRD, need for chronic renal replacement therapy or death; secondary outcomes: complete remission [proteinuria < 0.3 g per 24 h (urinary protein–creatinine rate < 300 mg/g [< 30 mg/mmol]]; partial remission (proteinuria > 0.3 but < 3.5 g per 24 h or a decrease in proteinuria by at least 50% from the initial value) and adverse events.

Results At 6 months, there was no difference in the primary composite end-point: 8.7% patients from the group 1 and 20.2% patients from the group 2 ($P = 0.199$) reached this end-point. Similar data were also recorded at 12 months. Secondary end-points were also similar between treatment groups. More patients receiving oral corticosteroids experienced infections, but without statistical significance.

Conclusion Our data indicate that low i.v. dose corticosteroids and cyclophosphamide administered monthly in patients with high risk of corticosteroid-related adverse events and primary glomerulonephritis are equally effective, with fewer metabolic disorders and infections.

Keywords Low-dose corticosteroids · Primary glomerulonephritis · Remission · Side effects · Infection

Introduction

Glomerular diseases, excluding diabetic nephropathy, account for about 25% of the cases of chronic kidney disease globally [1, 2]. Given the extent of long-term morbidity from glomerular diseases it is important to improve the current management, to minimize disease complications and to avoid progressive renal insufficiency [3].

The treatment of most glomerulonephritides is still based on a combination of an oral corticosteroid and an alkylating agent, particularly in patients with nephrotic syndrome and/

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or with progressive GFR loss [4] with short and long-term benefits, are also related to severe side effects [5]. Expanding evidence encourages the use of intravenous (i.v.) cyclophosphamide therapy replacing oral therapy, with similar efficacy and better safety profile, but with a lower cumulative dose [6, 7]. Extended/repeated steroid therapy is linked to a variety of serious side effects (such as hypertension, adrenal suppression, insulin resistance, diabetes, infection, myopathy, osteoporosis, avascular bone necrosis, cataracts, glaucoma, psychosis, sleep disturbance, behavioural disturbances, and obesity), leading to the development of several low-dose or steroid-free trials [9]. It is true that we can use different protocols with monoclonal antibodies or calcineurin inhibitors and low-dose corticosteroids. However, these options have not yet been proved to be superior to cyclophosphamide, besides being less cost-efficient [8]. Additionally, monoclonal antibodies are not available in all countries. In the last years, some new therapeutic approaches using lower doses of prednisone, associated with standard therapy for primary or secondary glomerulonephritis have been proposed [10]. Results from these studies, although still scarce, are encouraging [11]. At the same time, the response rate to aggressive immunosuppressive treatment is still difficult to predict, even more often in renal patients with several comorbidities. The balance of risk and benefit may be altered by patient-dependent factors.

The objective of this study was to evaluate the efficiency of low-dose corticosteroids and i.v. cyclophosphamide instead of high-dose steroids plus i.v. cyclophosphamide in patients with high risk of corticosteroid-related adverse events and glomerulonephritis. Our working hypothesis was that monthly pulse intravenous combined therapy was safer than continuous oral steroids plus cyclophosphamide, with similar rates of partial or complete remission in patients with glomerulonephritis.

Methods

We realised a retrospective study conducted in one nephrology center, covering the north-east region of Romania—'C.I. Parhon' University Hospital from Iasi, the Nephrology Clinic. The cohort study included all subjects with glomerulopathies with a renal biopsy performed between October 2005 and December 2015; they were assessed for inclusion in the analysis ($N=180$). Patients with organ transplantation, hepatitis B or C, HIV infection, any ongoing infection, pregnancy, lupus, were excluded. Finally, 107 patients were included in the analysis. Primary membranous glomerulonephritis, membranoproliferative glomerulonephritis, and extra capillary glomerulonephritis were the major histological groups included in this analysis. For 6 months, all patients with membranous and membranoproliferative glomerulonephritis received conventional treatment that included renin–angiotensin system inhibitors with the objective to lower blood pressure below 125/75 mmHg. In case of proteinuria persisting above the target of 3.5 g per day of urinary protein excretion blood-pressure control, the dosage of renin–angiotensin system blocker was increased to the maximum approved daily dose or to the highest dose accepted by the patient. Patients received dietary counselling and were advised to avoid nonsteroidal anti-inflammatory medication and other nephrotoxins. At the end of these 6 months, the patients who still had urinary protein excretion of 3.5 g per day or more, received according to the kidney disease: improving global outcomes (KDIGO) guidelines recommendations, an association of corticosteroids and cyclophosphamide [4].

Study treatment and drug dosing

Based on the associated comorbidities, the patients included in this study ($N=107$) were divided in two groups: (1) group 1 ($N=23$ patients)—obese ($N=5$ patients), prediabetes and diabetes ($N=9$ patients), elderly ($N=3$ patients), with severe cardiovascular disease ($N=3$ patients), erosive gastritis ($N=2$ patients), psycho-cognitive disorder ($N=1$ patient), received monthly corticosteroids (methylprednisolone 1 g/day for 3 consecutive days) and intravenous cyclophosphamide (dose adjusted according to the age of the patient and eGFR for 6 months [4]; and (2) group 2 ($N=84$ patients)—received oral corticosteroids (as per KDIGO guidelines recommended dose) and i.v. cyclophosphamide (the dose was adjusted according to the type of glomerulonephritis, age of the patient and eGFR) [4]. The study was conducted in accordance to the ethical principles of the Declaration of Helsinki; we obtained the approval of "Dr. C.I. Parhon" Hospital Ethics Committee.

Follow-up visits

Subjects were followed-up every 4 weeks for 6 months and then at 1 year. Baseline investigations included complete blood counts, renal function tests, glucose level, serum albumin, cholesterol, triglycerides levels, urinalysis, urinary protein–creatinine rate (uPCR). At each follow-up, complete blood counts, renal function tests, and uPCR were performed. The estimated glomerular filtration (eGFR) rate was calculated using CKD-EPI equation at baseline, 6 months, and 12 months. Adverse events were recorded at each visit.

Study end-points

The primary outcome was time to a combined end-point of doubling of serum creatinine, end-stage renal disease (ESRD) and need for chronic renal replacement therapy or

death from any cause; secondary outcomes were: (1) complete remission, defined (according to KDIGO) as proteinuria < 0.3 g per 24 h (uPCR < 300 mg/g [< 30 mg/mmol]); (2) partial remission defined as proteinuria > 0.3 but < 3.5 g per 24 h or a decrease in proteinuria by at least 50% from the initial value and < 3.5 g per 24 h; (3) the effect on eGFR and proteinuria during the 6 months of treatment; (4) adverse events.

Statistical analysis

Statistics were performed using SPSS version 21 (Statistical Packages for the Social Sciences, Chicago, IL) and Stata SE software, version 12 (Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Each variable was noted and analysed further. To evaluate and classify the variable in regard to the normality, we used Shapiro–Wilk test. The parametric variables were presented as mean ± standard deviation (sd), while non-parametric variables are shown as median and interquartile range (25–75%). The nominal variables are expressed through an absolute value and percentage (%). To determine the statistical significance of the observed differences between the two groups, we used *T* Student test and Mann–Whitney test. Cumulative probability of complete or partial remission and mortality was estimated according to Kaplan and Meier. We also tested using time-repeated analysis (using linear mixed models including the study groups, time and the groups by time interaction term) if there was a difference during the follow-up in regard with the eGFR and proteinuria levels between the two study groups. Since these two variables had a non-parametric distribution, we used the logarithmic transformed variables into the models. Group inferences, effect estimates and 95% confidence intervals (CI) were taken from these models. A *P* value of less than or equal to 0.05 was considered statistically significant.

Results

Our cohort was formed by 107 Caucasian patients: 61.5% were men with a mean age at the time of the renal biopsy of 48.2 ± 14.8 years. The mean eGFR among the included patients was 37.3 ml/min per 1.73 m^2 and the mean proteinuria was 3.9 g/day. The baseline characteristics of the study population are described in Table 1. There was no difference between groups regarding their baseline characteristics, with the exception of diabetes mellitus which was present only in the i.v. corticosteroids and cyclophosphamide group (39.1% versus 0%; $P = 0.001$).

The clinical syndromes of the study population are described in Table 2. The nephritic syndrome was significantly more prevalent in the i.v. corticosteroids plus cyclophosphamide group: 52.2% versus 28.5% for the daily oral steroid group; $P = 0.028$. There was a higher number of rapidly progressive glomerulonephritis in group 2, but the

Table 1 Baseline characteristics

	I.v. corticosteroids and cyclophosphamide ($N = 23$)	Oral corticosteroids and cyclophosphamide ($N = 84$)	*P*
Age (years)	50.1 ± 15.6	47.7 ± 14.6	0.492
Male (%)	16 (69.6%)	51 (60.7%)	0.369
Arterial hypertension (%)	14 (60.9%)	41 (48.8%)	0.261
Diabetes mellitus (%)	9 (39.1%)	0 (0%)	0.001
Cardiovascular disease (%)	3 (13.4%)	1 (1.1%)	0.617
Stroke (%)	0 (0)	1(1.1)	1.000
Malignancies (%)	1 (4.3)	3 (3.5)	1.000
Total serum proteins (g/L)	61.7 ± 11.9	58.6 ± 14.4	0.334
Serum glucose (mg/dL)	103 (94; 127)	101 (90; 110)	0.108
Haemoglobin (g/dL)	12 ± 2.2	10.8 ± 2.8	0.072
Leucocytes ($\times 10^3$ μ/L)	7.5 (6.6; 10.1)	8.6 (8.1; 12.8)	0.122
Cholesterol (mg/dL)	232 (170; 324)	230 (162.5; 329.2)	0.884
Triglycerides (mg/dL)	155 (112; 221)	152.5 (108.7; 223)	0.722
Alaninamintransferase (TGP) (U/L)	17 (15; 27)	14 (10; 20)	0.066
Proteinuria/24 h (g/24 h)	2.7 (1.7; 10.5)	2.9 (1.2; 7.5)	0.547
Estimated glomerular filtration rate (eGFR)	37.3 (15.1; 55.9)	30.8 (9.6; 80.1)	0.818
Estimated glomerular filtration rate (eGFR)			
< 60 ml/min/1.73 m^2	19 (82.6)	55 (64)	0.089
> 60 ml/min/1.73 m^2	4 (17.4)	31 (36)	0.089

Table 2 Clinical syndromes and major histological lesions

	I.v. corticosteroids and cyclophosphamide ($N=23$)	Oral corticosteroids and cyclophosphamide ($N=84$)	P
Clinical syndrome			
Nephritic syndrome	12 (52.2%)	24 (28.5%)	0.028
Nephrotic syndrome	9 (39.1%)	34 (40.4%)	0.940
Rapidly progressive glomerulonephritis	1 (4.3%)	16 (19.0%)	0.090
Major histological lesions			
Focal segmental glomerulosclerosis	0 (0)	2 (2.3%)	1.000
Membranous glomerulonephritis	11 (47.8%	34 (40.4%)	0.436
Membranoproliferative glomerulonephritis	8 (34.8%)	11 (13.0%)	0.900
Mesangial glomerulonephritis	0 (0)	2 (2.3%)	1.000
Extracapillary glomerulonephritis	2 (8.7%)	16 (19.0%)	0.248

difference was not statistically significant (4.3% versus 19%; $P=0.090$)—see Table 2. The major histopathological diagnostics identified were also comparable between groups. The number of extra capillary glomerulonephritis was higher in group 2 (19% versus 8.7%; $P=0.248$), but without statistical consequence—see Table 2.

Primary end-points

The primary, as well as the secondary outcome measures were assessed at 6 and 12 months. The rates of treatment response at these time points are summarized in Table 3.

No difference in primary end-points was noted at 6 months: 8.7% patients from the group 1 and 20.2% patients from the group 2 ($P=0.199$)—see Table 3. At 12 months, 13% patients from the first group and 25% patients from the second group reached this primary combined end-point ($P=0.223$)—see Table 3. Moreover, one patient from group 1 (4.3%) and thirteen patients from group 2 (15.5%) required dialysis, $P=0.161$. Two patients from group 2 died (2.4%). The analyses of GFR decline showed no significant difference between the study groups at 6 months and 12 months of follow-up (doubling of serum creatinine, ESRD, need for chronic renal replacement therapy).

Table 3 Major outcomes

	I.v. corticosteroids and cyclophosphamide ($N=23$)	Oral corticosteroids and cyclophosphamide ($N=84$)	P
After 6 months			
Composite outcome *N* (%)	2 (8.7)	17 (20.2)	0.199
GFR decline outcome *N* (%)	2 (8.7)	15 (17.8)	0.168
Complete remission *N* (%)	7 (30.4)	15 (17.9)	0.186
Partial remission *N* (%)	8 (34.8)	20 (23.8)	0.289
Dialysis *N* (%)	1 (4.3)	13 (15.5)	0.161
Death *N* (%)	0 (0)	2 (2.4)	1.000
Adverse events *N* (%)	10 (43.3)	58 (67)	0.075
After 12 months			
Composite outcome *N* (%)	3 (13)	21 (25)	0.223
GFR decline outcome *N* (%)	3 (13)	18 (21.4)	0.329
Complete remission *N* (%)	7 (30.4)	13 (15.5)	0.103
Partial remission	5 (21.7)	20 (23.8)	0.835
Dialysis *N* (%)	2 (8.7)	16 (19.0)	0.240
Death *N* (%)	0 (0)	3 (3.6)	1.000
Adverse events *N* (%)	11 (47.8)	63 (73.2)	0.108

The composite outcome—time to a combined end-point of doubling of serum creatinine, ESRD, need for chronic renal replacement therapy or death; complete remission (proteinuria < 0.3 g/day (uPCR < 300 mg/g [< 30 mg/mmol]); partial remission (proteinuria > 0.3 but < 3.5 g/day or a decrease in proteinuria by at least 50% from the initial value). The GFR decline outcome—combined end-point of serum creatinine, ESRD, need for chronic renal replacement therapy

Secondary end-points

Complete remission

At 6 months, complete remission was founded in 30.4% patients with combined i.v. therapy and in 17.9% patients with oral corticosteroids and i.v. cyclophosphamide ($P=0.186$). Also, at 12 months, there was no statistically significant difference between the two arms (30.4% patients from the first group and 15.5% from the second group—$P=0.103$).

Partial remission

At 6 months, partial remission was noted in 34.8% patients from the first group compared with 23.8% patients from the second group—$P=0.289$. Also, at 12 months, there was no statistically significant difference between the two arms regarding partial remission (21.7% patients from the first group and 23.8% patients from the second group—$P=0.835$).

Proteinuria and eGFR evolution

During the follow-up, we observed significant increases in eGFR and decreases in proteinuria levels. However, there were no significant differences between the two study groups in regard to these changes (Table 4 and Fig. 1).

Adverse events

During the first 6-month period, 43.3% subjects in the i.v. corticosteroids and cyclophosphamide group and 67% subjects from the second group reported at least one adverse event ($P=0.075$). The reported adverse events are summarized in Table 5. More patients receiving oral corticosteroids and i.v. cyclophosphamide experienced infections, but the difference did not reach statistical significance. 9.3% patients from this second group had increases in serum glucose that led to a change/interruption in the steroid regimen. Both groups had an equal number of gastrointestinal disorders.

At 12 months, 47.8% subjects from the first group and 73.2% subjects from the second group reported at least one adverse event ($P=0.108$). Both groups had an equal number of infections or gastrointestinal disorders—see Table 6.

Discussion

In this retrospective cohort study, we compared two immunosuppressive regimens for the treatment of primary glomerulonephritis. Our results suggest that monthly pulse intravenous corticosteroids combined with intravenous cyclophosphamide are not inferior (in terms of doubling of serum creatinine, ESRD, need for chronic renal replacement therapy or death from any cause) to daily oral corticosteroids and monthly intravenous cyclophosphamide after 12 months of follow-up period. Results did not differ between treatment groups for any secondary renal efficacy end-points.

Table 4 Estimated GFR and proteinuria levels evolution during the follow-up across the two study interventional groups

	Baseline	1 month	2 months	3 months	4 months	5 months	6 months	P*	$P^{\dagger}$
Log eGFR, ml/min/1.73 m^2									
Group 1	3.29 (3.08–3.50)	3.65 (3.52–3.77)	3.65 (3.53–3.78)	3.74 (3.61–3.87)	3.74 (3.62–3.87)	3.72 (3.59–3.85)	3.69 (3.56–3.82)	**< 0.001**	0.98
Group 2	3.39 (3.00–3.79)	3.61 (3.38–3.84)	3.72 (3.49–3.95)	3.75 (3.51–3.98)	3.69 (3.46–3.92)	3.70 (3.47–3.93)	3.68 (3.44–3.91)		
$P^{\ddagger}$	–	0.78	0.61	0.96	0.69	0.90	0.93		
Log proteinuria, g/day								**< 0.001**	0.65
Group 1	1.47 (1.31–1.63)	1.16 (1.02–1.29)	1.05 (0.91–1.19)	0.96 (0.81–1.10)	0.91 (0.77–1.06)	0.87 (0.72–1.01)	0.86 (0.71–1.00)		
Group 2	1.56 (1.25–1.86)	1.13 (0.88–1.39)	0.92 (0.67–1.17)	0.99 (0.74–1.24)	0.82 (0.57–1.08)	0.74 (0.49–0.99)	0.67 (0.41–0.92)		
$P^{\ddagger}$	–	0.87	0.39	0.83	0.55	0.41	0.19		

Data are presented as mean (95% CI) at baseline, and least-squares mean (95% CI) at 1 month, 2 months, 3 months, 4 months, 5 months and 6 months. Analysis was conducted using a mixed model for repeated measures, adjusting for baseline values

Group 1 oral corticosteroids and cyclophosphamide, *Group 2* I.v. corticosteroids and cyclophosphamide, *eGFR* estimated glomerular filtration rate

*P value for time effect—trend over time in all arms

†P value for treatment × time interaction—evaluates if changes at one visit are different from the changes at other visits

‡P value for comparison between visits at each moment

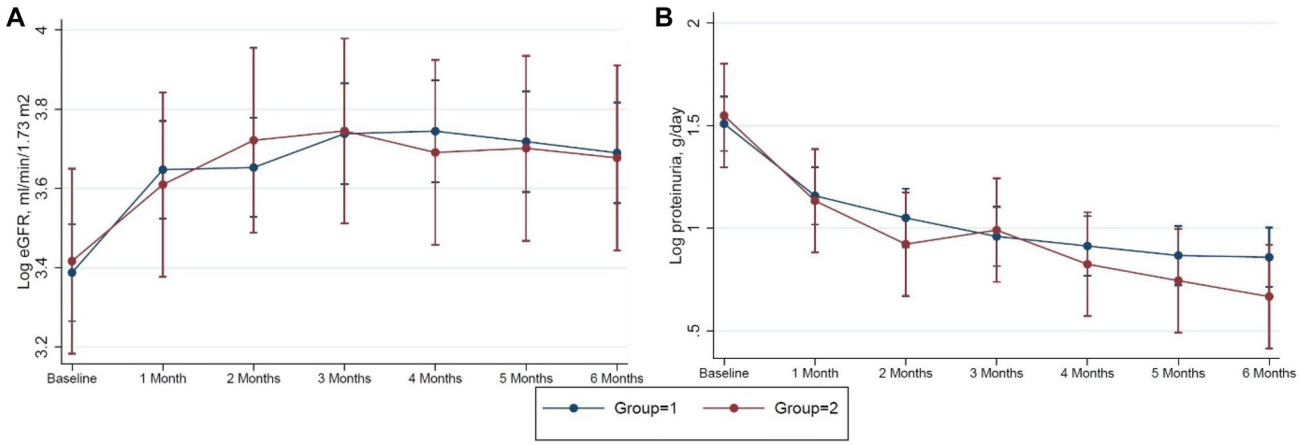

Fig. 1 Estimated GFR (**a**) and proteinuria levels (**b**) evolution during the follow-up across the two study interventional groups. Data are presented as mean (95% CI) at baseline, and least-squares mean (95% CI) at 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months. Analysis was conducted using a mixed model for repeated measures, adjusting for baseline values. Group 1—oral corticosteroids and cyclophosphamide; group 2—I.v. corticosteroids and cyclophosphamide. *eGFR* estimated glomerular filtration rate

Table 5 Adverse events—6 months of treatment

	I.v. corticosteroids and cyclophosphamide ($N=23$) (10.17 patient-years at risk)		Oral corticosteroids and cyclophosphamide ($N=84$) (32.33 patient-years at risk)		Rate ratio (95% CI)
	No. of events	No. of events/100 patient-years	No. of events	No. of events/100 patient-years	
All adverse events	10	98.33	58	179.4	0.55 (0.25–1.08) $P=0.075$
Infections (all of them)	3	29.5	29	86.7	0.33 (0.06–1.06) $P=0.536$
Urinary infections	1	9.83	10	30.93	0.32 (0.01–2.23) $P=0.245$
Pulmonary infections	2	19.67	12	37.12	0.53 (0.06–2.38) $P=0.398$
Cutaneous infections	0	0	3	9.27	0 (0–7.69) $P=0.331$
Digestive infections	0	0	4	12.37	0 (0–4.82) $P=0.262$
Central venous catheters infections	0	0	1	3.10	0 (0–123.98) $P=0.575$
Prediabetes and diabetes mellitus	0	0	8	24.74	0 (0–1.86) $P=0.112$
Mental disorders	1	9.83	2	6.19	1.59 (0.03–30.53) $P=0.703$
Gastrointestinal alterations	1	9.83	3	9.28	1.06 (0.02–13.20) $P=0.960$
Cytolysis	1	9.83	1	3.09	3.18 (0.04–249.53) $P=0.387$
Cushing syndrome	1	9.83	7	21.65	0.45 (0.01–3.53) $P=0.449$
Dermatological alterations	1	9.83	2	6.19	1.58 (0.03–30.53) $P=0.703$
Obesity	1	9.83	2	6.19	1.58 (0.03–30.53) $P=0.703$

Table 6 Adverse events at 12 months

	I.v. corticosteroids and cyclophosphamide ($N=23$) (19.92 patient-years at risk)		Oral corticosteroids and cyclophosphamide ($N=84$) (67.83 patient-years at risk)		Rate ratio (95% CI)
	No. of events	No. of events/100 patient-years	No. of events	No. of events/100 patient-years	
All adverse events	11	55.22	63	92.88	0.59 (0.28–1.14) $P=0.108$
Infections (all of them)	4	20.08	33	48.65	0.41 (0.11–1.16) $P=0.0843$
Urinary infections	1	5.02	10	14.74	0.34 (0.008–2.39) $P=0.281$
Pulmonary infections	3	15.06	15	22.11	0.68(0.13–2.40) $P=0.541$
Cutaneous infections	0	0	3	4.42	0 (0–8.2) $P=0.348$
Digestive infections	0	0	4	5.90	0 (0–5.15) $P=0.278$
Prediabetes and diabetes mellitus	0	0	8	11.8	0 (0–1.99) $P=0.125$
Mental disorders	1	5.02	2	2.95	1.7 (0.03–32.70) $P=0.660$
Gastrointestinal alterations	1	5.02	4	5.9	0.85 (0.01–8.60) $P=0.885$
Cushing syndrome	1	5.02	8	11.79	0.42 (0.009–3.17) $P=0.406$
Dermatological alterations	1	5.02	2	2.95	1.7 (0.03–32.70) $P=0.660$
Obesity	1	5.02	2	2.95	1.7 (0.03–32.70) $P=0.660$

We noticed a higher number of adverse events in the group of patients with oral corticosteroids, but the difference did not reach significance, most probably due to small sample size. The most common type of adverse events was infections—20.1% in the i.v. corticosteroids group versus 48.6% in the oral regimen ($P=0.08$). A total of three patients died during the study, all of them in the oral corticosteroid group; these three deaths were due to severe infections. Treatment discontinuation owing to AE's was responsible for eight study withdrawals, again all in the oral corticosteroids group.

The most effective and safe therapy for patients with glomerulonephritis is not known. Glucocorticoids are still predominant in the treatment of most glomerulonephritides. The most recently published KDIGO guidelines (2012) recommended/suggested corticosteroids ± other immunosuppressive agent, depending on clinical, biochemical, and histological features [4]. These recommendations are based, in general, on high-quality evidence from randomised controlled trials (RCTs). However, these evidences are applicable only in specific individuals with well-defined criteria. These evidences were subsequently extrapolated to other populations and other circumstances, with varying degrees of confidence. However, immunosuppressive regimen should be adapted, based on patient's needs and medical circumstances.

In this context, in the last years, some new therapeutic approaches, using lower prednisolone doses, have been proposed. In a recent study, in patients with IgA nephropathy with active and proliferative lesions, mycophenolate mofetil (MMF) in association with low-dose prednisone had the same efficacy in reducing proteinuria versus full-dose prednisone; additionally, fewer adverse events were noted [10]. At 6 months, complete remission rates were 37% and 38%, ($P=$NS). During the next 6 months period after the discontinuance of the treatment, at 12 months, complete remission proportions were similar in both groups. Additionally, corticosteroid's adverse events as Cushing syndrome and diabetes were significantly less observed in the low-corticosteroid group than in the high-prednisone group [10].

In patients with lupus nephritis recent published works showed that medium doses of corticosteroids regimen (prednisone lower or equal with 30 mg/day) with the rapid tapering to low doses had a similar efficacy with the high-doses therapy [11, 12]. In an observational comparative study including 73 patients with lupus nephritis (III, IV, and V classes), repeated doses of corticosteroids intravenous

administrated associated with reduced oral steroids therapy were correlated with favourable outcomes. The study population was divided into two groups: the first one ($N=29$ patients) received oral prednisone in medium doses (below 30 mg/day), with rapid tapering to low dose (5 mg/day) and every 2 weeks pulses of methyl-prednisolone, to potentiate the effects of i.v. cyclophosphamide. The other group ($N=44$ patients) received the combination of high-dose prednisone and either mycophenolate mofetil or cyclophosphamide. Patients from the first group reached complete remission more frequently [adjusted hazard ratio (HR) 3.8, 95% confidence interval (CI) 2.05–7.09]. The number of pulses of intravenous corticosteroids was correlated with complete remission (adjusted HR 1.09, 95% CI 1.03–1.15). These patients had a lower risk of glucocorticoid-related side effects (adjusted HR 0.19, 95% CI 0.04–0.89) [11, 13]. Favourable results were reported even in patients with active lupus at diagnosis. In a retrospective comparison of patients with SLEDAI score more than 6, corticosteroids in medium doses (prednisone ≤ 30 mg/day) were similarly efficient and with a higher safety than higher doses (>30 mg/day) [11]. Patients from this last group received fivefold higher doses of prednisone, less hydroxychloroquine and less methylprednisolone pulses. SLEDAI score was improved similar in both groups. Glucocorticoid-related adverse effects (osteoporotic fractures, osteonecrosis cataracts and/or diabetes mellitus) were noted only in the last group ($P=0.02$) [11].

There are well known multiple, systemic adverse effects of corticosteroids. These adverse effects can vary from minor (like Cushingoid appearance) to life-threatening (severe infections). There was a significant proportion of infections and diabetes in patients treated with oral corticosteroids in our study, including three deaths. Similar data were also reported in other larger studies. The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study is a multicentre, double-blind, investigator-initiated placebo-controlled, randomized clinical trial that had the aim to establish the safety and efficacy of oral methylprednisolone versus conventional treatment alone in patients with IgA nephropathy [14]. Excess serious adverse effects were observed in 14.7% of patients in the corticosteroid group versus 3.2% of patients in the placebo group ($P=0.001$), mainly because of serious infections (11 [8.1%] vs 0, $P<0.001$), including two infection-related deaths [14].

Our study had some limitations. First of all, the number of participants included was relatively small. Second, the follow-up period was relatively short. Another limitation is its observational nature, with the inherent difficulties to determine cause-and-effect relationships. However, observational studies obtained in the world of clinical practice can be important means to generate and investigate hypothesis, thereby helping investigators to select the interventions that will be more properly assessed by succeeding clinical trials.

Conclusion

Our study suggests that low-dose corticosteroids regimen (monthly pulses + i.v. cyclophosphamide) may be as effective as oral corticosteroids and i.v. cyclophosphamide, with fewer metabolic disorders and infections, in patients with primary glomerulonephritis. Larger multicentre studies are required to extrapolate these results to other adult glomerulonephritis populations in other parts of the world.

Author contributions ARH, LV, DS, MA and AC contributed to the conception of the study, ARH, LV, DS, IN, SH, MA, MO and AC have been involved in drafting of the manuscript; SH, CV, GV, ILM, LF and MO critically revised the manuscript for important intellectual content. All the authors have read and approved the final version of the manuscript, and ensure that this is the case

Availability of data and materials Data and material supporting our findings are present in the hospital records and are available upon request after de-identification of patients' information.

Compliance with ethical standards

Conflict of interest AC is a member of the editorial board of International Urology and Nephrology.

Ethics approval All patients signed informed consent forms approved by the "Dr. C.I. Parhon" Hospital Ethics Committee.

Informed consent Written informed consent covering the publication has been obtained before submission of the manuscript and is available upon request.

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