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Role of corticosteroid therapy in IgA nephropathy; where do we stand?

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ABSTRACT

Background: Current KDIGO guidelines suggest corticosteroids (CS) administration in IgA nephropathy (IgAN) with persistent proteinuria >1 g/d despite 3-6 months of supportive care and estimated glomerular filtration rate (eGFR) >50 mL/min/1.73 m^2. The benefits of CS in patients with eGFR <50 mL/min/1.73 m^2 is unclear.

Objectives: To assess the effect of steroids on disease progression and proteinuria in IgAN patients with eGFR < 50 mL/min/ 1.73m^2 compared with >50 mL/min/1.73 m^2.

Patients and Methods: A cohort of biopsy proven primary IgAN diagnosed between March 2010 - February 2015 who received oral CS with minimum follow-up of 6 months were included. They were categorized into two groups according to their eGFR (group 1 - eGFR <50 mL/min/1.73 m^2, group 2 - eGFR >50 mL/min/1.73 m^2). The eGFR and urine protein creatinine ratio (UPCR) were followed up at entry, 6 months, 12 months and at the end of follow-up. Outcomes studied were change in eGFR, proteinuria and progression to end-stage renal disease (ESRD).

Results: Out of 44 patients, 23 were in group1 and 21 patients in group 2. At the end of follow-up, similar reduction of proteinuria (UPCR) was observed in both groups (P=0.62). However, group 1 had a significant fall in eGFR compared to improvement in group 2 (P=0.004). One in each group has reached CKD stage 5 (P=0.73).

Conclusions: Addition of CS to conservative treatment in IgAN patients with initial eGFR<50 ml/min/1.73 m^2 seems to reduce proteinuria but not beneficial in preventing progression of disease as compared to patients with higher eGFR (>50 mL/min/1.73 m^2).

Original Article

Implication for health policy/practice/research/medical education:
The benefit of using steroids in subgroup of IgA nephropathy patients with eGFR<50 ml/min/1.73 m^2 is unclear. In this retrospective study we compared the effect of steroids on disease progression and proteinuria in IgAN patients with eGFR < 50 mL/min/1.73 m^2 (group 1) to those with >50 mL/min/1.73 m^2 (group 2). Out of 44 patients, 23 were in group1 and 21 patients in group 2. At the end of follow-up, similar reduction of proteinuria (UPCR) was observed in both groups (P=0.62). But there was a significant fall in eGFR in group 1, whereas group 2 showed improvement (P=0.004). Administration of corticosteroids (CS) in addition to conservative treatment seems to reduce proteinuria but not beneficial in preventing progression of disease in IgAN patients with eGFR<50 ml/min/1.73 m^2.

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1. Background

IgA nephropathy, also known as Berger's disease, is the most common form of primary glomerulonephritis worldwide (1). It is characterized by dominant or codominant deposition of the IgA antibody in the mesangial area of glomeruli on immunofluorescence. It has variable clinical presentation and course (1-3). The role of immunosuppressive therapy when added to supportive care in these patients is unclear. The kidney disease improving global outcomes (KDIGO) guidelines regarding IgA nephropathy suggest that the use of systemic glucocorticoids in patients who have >1 g of urinary protein excretion per day and estimated glomerular filtration rate (eGFR) higher than 50 ml/min/1.73 m^2 despite supportive care (2,3). This is based on few randomized controlled trials (4-8). Ballardie et al showed that immunosuppressive combination therapy stabilized eGFR in patients with an aggressive course of IgA nephropathy (9). But the recent STOP- IgAN trial showed that there is no benefit with immunosuppressive therapy compared to full supportive care with angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) (10). Majority of the patients in these studies had eGFR >50 mL/min/1.73 m^2.

The role of steroid usage in addition to supportive care is not well studied in patients with eGFR < 50 mL/min/1.73 m^2. The KDIGO guidelines make no recommendations for use of corticosteroids (CS) in individuals with an initial eGFR ≤50 mL/min/1.73 m^2, who are under-represented in majority of the trials (3-10). The recent analysis from VALIGA study showed that steroids may be of benefit even in this group (11).

2. Objectives

This study was conducted to assess the effect of steroids on disease progression and proteinuria in IgAN patients with eGFR < 50 mL/min/1.73 m^2 compared to those with >50 mL/min/1.73 m^2.

3. Patients and Methods

3.1. Study population

We reviewed the clinical records of all adults (>18 years) admitted to the hospital with a histopathological diagnosis of primary IgA nephropathy between March 2010 and February 2015 after getting ethical committee clearance. Patients who received oral CS for minimum of 3 months in addition to supportive care as treatment and had follow-up for minimum 6 months duration were included. The clinical, serological, biochemical and histopathological data were collected from the case records in detail for all the patients. The clinical and biochemical details included were age, gender, presence of hypertension, micro- or macroscopic hematuria, edema, mean arterial pressure (MAP), urine protein creatinine ratio (UPCR), 24-hour proteinuria, serum creatinine at admission and on follow-up. The histopathological data was collected by using MEST score for all the patients according to OXFORD classification (12,13). The eGFR was calculated by MDRD formula for all the patients adjusted to body surface area (14). The patients were categorized into two groups as per eGFR (group 1 – eGFR <50 mL/min/1.73 m^2, group 2 – eGFR > 50 mL/min/1.73 m^2). The baseline characteristics were compared between the two groups. The eGFR and UPCR were followed-up at study entry, 6 months, 12 months and at the end of follow-up.

The renal outcomes studied were remission (complete/partial) and progression to end stage renal disease on follow-up. The risk factors associated with renal loss and mortality were also studied.

3.2. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained, and 3) the research was approved by the ethical committee of Kasturba Hospital, Kasturba Medical college, Manipal University, Manipal, India.

3.3. Statistical analysis

The descriptive statistics were applied for the analysis of baseline characteristics data and the comparison between the two groups were analyzed by student *t* test for normally distributed data and Mann-Whitney U test for skewed data. The statistical analysis of data was done using SPSS version 15 and *P* value below 0.05 was considered significant.

4. Results

A total of 44 patients with IgA nephropathy were included in the study. Out of 44 patients, 23 (52%) had eGFR< 50 mL/min/1.73 m^2 (group 1) and 21 (48%) had eGFR >50 mL/min/1.73 m^2 (group 2). The mean age of the study population was 31.68 ± 10.16 years. The baseline clinical, histopathological, and treatment characteristics of both the groups are shown in Table 1 and are comparable except eGFR and serum creatinine. Group 1 had a mean serum creatinine of 2.9 mg/dL with an average median eGFR 25.13 mL/min/1.73 m^2. In group 2, the mean serum creatinine was 0.95 ± 0.3 mg/dL which corresponded to a median eGFR 82.7 mL/min/1.73 m^2. 95.7% of group 1 and 85.7% of group 2 had proteinuria > 1g/d and all of them were on ACEi/ARBs as supportive care. All

Table 1. Comparison of baseline characteristics of patients between two groups

Characteristic	Group 1 (n=23) (%) (eGFR < 50 mL/min/1.73 m^2)	Group 2 (n=21) (%) (eGFR > 50 mL/min/1.73 m^2)	P value
Age	31.22 ± 9.4	32.19 ± 11.2	0.75
Male: Female	20: 3	17: 4	0.60
Micro hematuria	22 (95.7)	19 (90.5)	0.49
Macro hematuria	4 (17)	2 (9.5)	0.40
Edema	9 (39.1)	11 (52.4)	0.37
Hypertension	22 (95.7)	19 (90.5)	0.49
MAP (mm Hg)[a]	105.88 ± 11.7	108.47 ± 13.8	0.51
Serum albumin (g/L)[a]	3.53 ± 0.8	3.2 ± 0.8	0.16
UPCR (mg/mg)[b]	2.6 (1.8, 3.3)	2 (1.7, 3.1)	0.25
Proteinuria > 1 g/d	22 (95.7)	18 (85.7)	0.25
24-h urine protein (g/d)[a]	2.9 ± 1.3	2.4 ± 1.1	0.48
Initial eGFR (mL/min/1.73 m^2)[b]	25.13 (19.33, 39.51)	82.7 (76, 115.85)	0.001
Serum creatinine (mg/dL)[a]	2.6 ± 1.1	0.95 ± 0.3	0.001
>3 Antihypertensive medication	8 (34.8)	6 (28.6)	0.22
ACEi/ARBs	22 (95.7)	18 (85.7)	0.25
Fish oil	14 (60.9)	14 (66.7)	0.60
Pulse steroids	7 (30.4)	6 (28.6)	0.89
Cyclophosphamide	3 (13)	1 (4.8)	0.34
M1[c]	8 (34.8)	6 (28.6)	0.50
E1[c]	7 (30.4)	9 (42.9)	0.40
S1[c]	12 (52.2)	8 (38.1)	0.39
T1[c]	6 (26.5)	4 (19.0)	0.58
Crescents	6 (26.5)	5 (23.8)	0.98
Length of follow-up (months)[b]	12 (12, 24)	15 (12, 36)	0.24

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio; ARB, angiotensin II–receptor blocker; ACE, angiotensin-converting–enzyme; MAP, mean arterial pressure.
[a] Mean with standard deviation; [b] Median with interquartile range; [c] MEST score: Mesangial hyper cellularity (M1), Endocapillary hyper cellularity (E1), Segmental glomerulosclerosis (S1), Tubular atrophy and interstitial fibrosis (T1).

patients had received 1 mg/kg/d of oral prednisolone for at least 3 months and later tapered over 6 months. The pulse steroid and cyclophosphamide were used as per standard recommendations in few patients in both the groups based on the discretion of the treating physician and were comparable between the groups as shown in Table 1. The histological features like presence of mesangial proliferation (M1), endocapillary proliferation (E1), segmental sclerosis (S1), interstitial fibrosis and tubular atrophy (T1) according to OXFORD classification and also presence of crescents in the biopsy specimens were equally distributed between the groups. The median follow-up was 12 months in group 1 and 15 months in group 2. At the end of follow-up, it was found that with addition of steroids to supportive care, both the groups had similar reduction in proteinuria (UPCR) (P=0.62; Figure 1, Table 2). In group 1, the median UPCR decreased from 2.6 mg/mg to 1 mg/mg at the end of follow-up. In group 2, the median UPCR

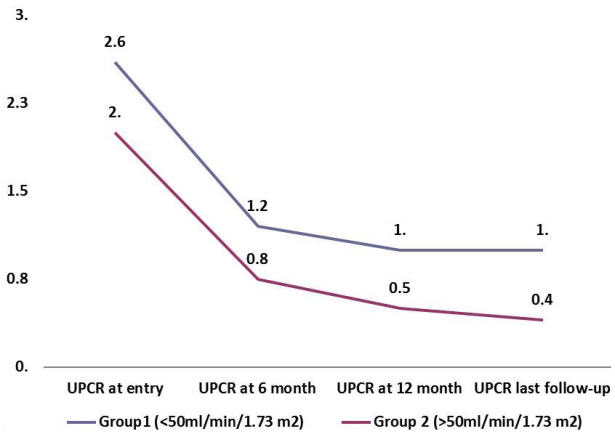

Figure 1. Graph showing comparison of change in UPCR between the groups. (Group 1- GFR < 50 mL/min/1.73 m^2, Group 2- GFR > 50 mL/min/m^2)

decreased from 2.0 mg/mg to 0.4 mg/mg. However, there was a significant difference in change in median eGFR/month between the groups (P=0.004; Table 2,

Table 2. Outcomes at the end of follow-up between groups

Characteristic	Group 1 (n=23) (%) (eGFR < 50 mL/min/1.73 m²)	Group 2 (n=21)(%) (eGFR > 50 mL/min/1.73 m²)	P value
Initial eGFR[a]	25.1 (19.33, 39.51)	82.16 (76, 115.85)	
eGFR at end of follow-up[a]	20.94 (9.36, 37.12)	93.94 (77.48, 129.91)	
Change in eGFR/month[a]	-0.46 (-0.1, -1.08)	+0.38 (+1.06, 0.00)	0.004
Initial UPCR[a]	2.6 (1.8,3.3)	2 (1.7,3.1)	
UPCR at the end of follow-up[a]	1.0 (0.6, 2.0)	0.4 (0.1, 0.95)	
Change in UPCR[a]	1.4 (0.3, 2.0)	1.5 (0.55, 2.75)	0.61
Patients reaching ESRD	1 (4.3)	1 (4.7)	0.73

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.
[a] Median with interquartile range.

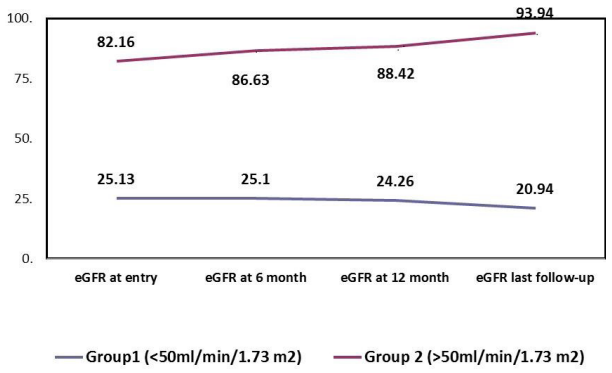

Figure 2. Graph showing comparison of change in eGFR between the groups. (Group 1- GFR <50 mL/min/1.73 m², Group 2- GFR >50 mL/min/m²).

Figure 2). Patients in group 2 had an increase in median eGFR by 0.38 mL/min/1.73 m²/month whereas in group 1 there was a median fall in eGFR by 0.46 mL/min/1.73m² /month, irrespective of the treatment with steroids (Table 2, Figure 2). One subject in each group reached CKD stage 5 ($P = 0.73$) at the end of follow-up. There was no mortality in either group.

5. Discussion

The treatment of IgA nephropathy with CS remains unclear despite various studies. The history of use of steroids dates back to 1986, when an uncontrolled pilot study by Kobayashi et al (15) showed a clear benefit of oral prednisone (40 mg/d tapered over 1–2 years) in patients with early disease (creatinine clearance >70 mL/min) and persisting proteinuria of >1 g/d, at 10 years follow-up (16). In the last decade, randomized controlled trials (RCTs) conducted by Pozzi et al, Manno et al and Lv et al showed a favorable outcome in patients treated with CS for 6-month duration (4-7). These trials were limited by inconsistent about use of ACE inhibitors or ARBs as supportive care (4, 5) or were temporarily halted and then reinitiated at baseline (6, 7). The studies by Coppo et al, Praga et al and Li et al showed clear benefit of supportive care with the use of ACE inhibitors or ARBs in preventing progression of disease and proteinuria compared to placebo or other antihypertensive drugs (17-19).

Contrary to previous studies which favoured use of CS (4-7), the recent IgAN-STOP study (10), which is a well randomized open label study, did not show any benefit in progression of disease in comparison to intensive supportive care with ACE inhibitors and ARBs. The results of all these trials provided conflicting messages and created uncertainty about the benefits of CS treatment in IgA nephropathy. The above studies predominantly involved patients with eGFR >50 mL/min/1.73 m². The 2012 KDIGO guidelines suggest giving CS to patients with eGFR >50 mL/min/1.73 m² and persistent proteinuria >1g/d, despite 6 months of optimized supportive care. It does not recommend use of steroids in subset of patients with eGFR <50 mL/min/1.73 m² (3).

The use of steroids in patients with eGFR <50 mL/min/1.73 m² has been addressed in the VALIGA study which examined the benefit of steroids in this subset of patients in addition to renin angiotensin system blockers (RASBs) compared with RASBs alone, (particularly in patients with proteinuria >1 g/d), suggesting a value in patients with eGFR <50 mL/min/1.73 m2 as well (11).

In our study, group 1 did not benefit in terms of progression of CKD compared to group 2. There was a fall in eGFR by 0.46 (-0.1,-1.08) mL/min/1.73 m²/month in group 1. So there was no benefit found to prevent progression of disease with use of steroids in patients with eGFR<50 mL/min/1.73 m². In group 2 (patients with eGFR >50 mL/min/1.73 m²), there was a significant benefit favoring use of steroids to prevent progression of disease. Since our study is a retrospective study, with patients being on both

supportive care and CS, and there was no separate group which received intensive supportive care alone like in IgAN STOP study, we cannot conclude that steroids may be of benefit in comparison to supportive care alone in patients with eGFR >50mL/min/1.73 m^2.

In our study there was a reduction of proteinuria in both the groups irrespective of their eGFR. (Table 2). Since our patients were on ACE inhibitors /ARBs in addition to steroids, whether the benefit is due to supportive care (ACE inhibitors /ARBs) or addition of steroids, it is difficult to conclude. There were no major complications related to use of steroids in the study population. The infection rates were similar between the groups.

6. Conclusions

In IgAN patients with initial eGFR<50 mL/min/1.73 m^2, use of CS in addition to conservative treatment seems to reduce proteinuria but not beneficial in preventing progression of disease as compared to patients with higher eGFR (>50 mL/min/1.73 m^2). However, there is need for larger prospective randomized controlled trials with long term follow-up to confirm the role of steroids in this subset of IgAN.

Limitations of the study

It is a retrospective study with a small study population and a short follow-up period.

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Authors' contribution

SPN, ASM, DR, and RPA designed and performed the research. SLKN, SP, SK, SS and KS collected the data. SLKN and MV collected the histopathological data. RP, UVM and VG analyzed data and wrote some parts of paper. SPN and SLKL wrote the manuscript. All authors reviewed, edited and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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