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Supportive Management of IgA Nephropathy With Renin-Angiotensin Blockade, the AIIMS Primary IgA Nephropathy Cohort (APPROACH) Study

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Introduction: Renin–angiotensin system (RAS) blockade using angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) is first-line therapy for IgA nephropathy (IgAN). There is a paucity of information on the predictors and magnitude of response to this treatment.

Methods: In a prospective study, treatment-naive patients with IgAN with urinary protein $\geq$ 1 g/d and estimated glomerular filtration rate (eGFR) $\geq$ 30 ml/min per 1.73 m^2 received supportive treatment including ACEi (ramipril) or ARB (losartan) in patients intolerant to ACEi, and optimal blood pressure (BP) control to $\leq$130/80 mm Hg, with a follow-up of 6 months. The primary outcome was remission of proteinuria. Complete remission (CR) was defined as proteinuria $<$ 0.5 g/d and partial remission (PR) as proteinuria $<$ 1g/d with at least a 50% decline from the baseline with stable renal function ($\leq$ 25% reduction in eGFR).

Results: A total of 96 patients were analyzed, with a mean age of 33.3 $\pm$ 10.2 years, baseline eGFR 74.0 $\pm$ 30.9 ml/min per 1.73 m^2, and urinary protein 2.6 $\pm$ 1.2 g/d. In all, 71.9% patients received $\geq$ 75% of the maximum approved dose of ACEi/ARB. Remission was observed in 36.5% (CR, 6.3%) patients at 3 months and in 55.2% (CR, 31.3%) at 6 months. Patients who failed to achieve remission had lower baseline eGFR ($P = 0.002$) and serum albumin levels ($P< 0.001$), asymptomatic hyperuricemia ($P < 0.001$), and higher proteinuria ($P = 0.076$). E1 ($P= 0.053$) and T1/T2 ($P = 0.009$) lesions were more frequent on histology. The ACEi/ARB had to be discontinued in 17 (17.7%) patients. These patients were older ($P= 0.085$) with lower eGFR ($P < 0.002$) and serum albumin levels ($P = 0.001$) and more E1 ($P = 0.012$) and T1/T2 ($P = 0.001$) lesions on histology.

Conclusion: Meticulous supportive therapy with optimal use of ACEi/ARB achieved remission in half of IgAN patients in this study. Increasing the treatment duration to 6 months improved remission rates. Patients with severe clinical and histological disease were less likely to tolerate and respond to treatment with RAS blockade.

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IgA nephropathy (IgAN) is the most common primary glomerular disease in adults, with a 20% to 40% risk of progression to end-stage kidney disease (ESKD) over 10 to 20 years.[1,2] It seems to have ethnic variations, with a more aggressive disease phenotype in Asians.[3] There is a lack of consensus about the optimal treatment strategy for IgAN. Proteinuria is a well-established risk factor for ESKD in these patients, and remission of proteinuria has been accepted as a surrogate end point to assess the efficacy of treatment in preventing or delaying disease progression.[4,5] Studies targeting reduction in proteinuria in IgAN have mainly used renin–angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) with adequate blood pressure (BP) control and immunosuppressive drugs in patients who fail to show response to ACEi/ARB.

Use of ACEi/ARB is known to have reno-protective and anti-proteinuric effects in proteinuric kidney diseases independent of their antihypertensive action.[6,7]

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Randomized controlled trials (RCTs) of ACEi/ARBs have demonstrated their beneficial role in reducing proteinuria in IgAN.[8–10] However more studies are needed to delineate the subgroup of IgAN patients likely to respond, as well as the optimal duration of therapy, the degree of response, and the impact on long-term renal survival.

We prospectively established the AIIMS Primary IgA Nephropathy Cohort (APPROACH) to study multiple aspects of this common primary glomerular disease. Here we present the interim data on the efficacy of non-immunosuppressive supportive treatment, including RAS blockade with ACEi/ARB, using a uniform protocol in these patients.

MATERIALS AND METHODS

The study recruited patients of IgAN followed in our nephrology department prospectively from February 2018 until March 2020 (to allow for a follow-up of 6 months). Informed consent was taken from all the patients prior to enrollment. If the patient was <18 years of age, consent was taken from the legal guardian.

Inclusion criteria were as follows: patients ≥ 14 years of age; biopsy-proven primary IgAN; 24-hour urinary protein ≥ 1 g/d; eGFR ≥ 30 ml/min per 1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]).

Exclusion criteria were as follows: lack of informed consent; eGFR < 30 ml/min per 1.73 m^2; secondary causes of IgA nephropathy, such as chronic liver disease or Henoch–Schonlein purpura; patients with a second coexisting disease on kidney biopsy, such as diabetic nephropathy; patients with systemic disease, such as diabetes or malignancy, that may affect kidney function; patients with C2 lesions as per the Oxford MEST-C[11] score on kidney biopsy; patients with a history of immunosuppressive therapy for >2 weeks in the preceding 6 months; patients using ACEi and/or ARB in the preceding 6 months; patients lost to follow-up before 6 months; and patients who were pregnant or breastfeeding at the time of recruitment.

Baseline data collected were age, sex, body mass index (BMI), presence of hypertension (BP ≥ 140/90 mm Hg or history of taking antihypertensive drugs), systolic and diastolic BP, and laboratory parameters including serum creatinine, albumin, cholesterol, and uric acid, and presence of hematuria (≥ 5 red blood cells per high-power field). Protein and creatinine were checked in a 24-hour urine collection, and the ratio was taken to estimate the 24-hour protein excretion (g/d). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Mean arterial pressure (MAP) was defined as a diastolic pressure plus one-third of the pulse pressure. The MEST-C score of IgA nephropathy was recorded in each patient as per the Oxford classification of IgAN[11] by our renal pathologists.

All patients were initiated on an ACEi (ramipril). The dose was gradually increased to the maximum labeled daily dose or to the maximum tolerated dose. If the ACEi could not be tolerated, it was changed to an ARB (losartan). The first-line antihypertensive agent used was ACEi/ARB, and other antihypertensives were added only after the maximum possible dose of ACEi/ARB was achieved to target BP levels of ≤130/80 (mean arterial pressure [MAP], 96) mm Hg. The average MAP over 6 months was calculated, which was taken as the time-averaged MAP.

Patients were counseled to avoid taking other nephrotoxic agents, including over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, and so forth. A low-potassium diet was explained and reinforced during every visit. The ACEi/ARB therapy was reduced or discontinued if patients had persistent hyperkalemia despite dietary counseling or > 25% decline in eGFR (rechecked twice) that was not explained by any other cause.

Potassium binders or diuretics were not used to treat hyperkalemia and allow continuation of RAS ACEi/ARB. Dyslipidemia if present, was treated as per existing guidelines.[12] Asymptomatic hyperuricemia (defined as serum uric acid level ≥8 mg/dl in male and ≥ 7.5 mg/dl in female patients) was treated with dietary counseling and pharmacologic intervention if required. Other therapies such as fish oil and strict dietary protein restriction were not included in the treatment regimen. Patients were followed up every month with investigations including blood urea, serum creatinine, sodium, potassium, total protein, albumin, and 24-hour urine protein and creatinine for 6 months. During the period of the COVID-19 pandemic, some of the patients who could not come for physical follow-up were monitored telephonically with investigations done locally and home BP records. The primary outcome was evaluated as remission of proteinuria with stable renal function (≤ 25% reduction in eGFR) at 6 months. Complete remission (CR) was defined as proteinuria < 0.5 g/d. Partial remission (PR) was defined as proteinuria < 1 g/d with at least a 50% decline from the baseline. Renal progression was defined as more than 50% sustained decline in eGFR or ESKD irrespective of proteinuria (confirmed twice ≥ 4 weeks apart).

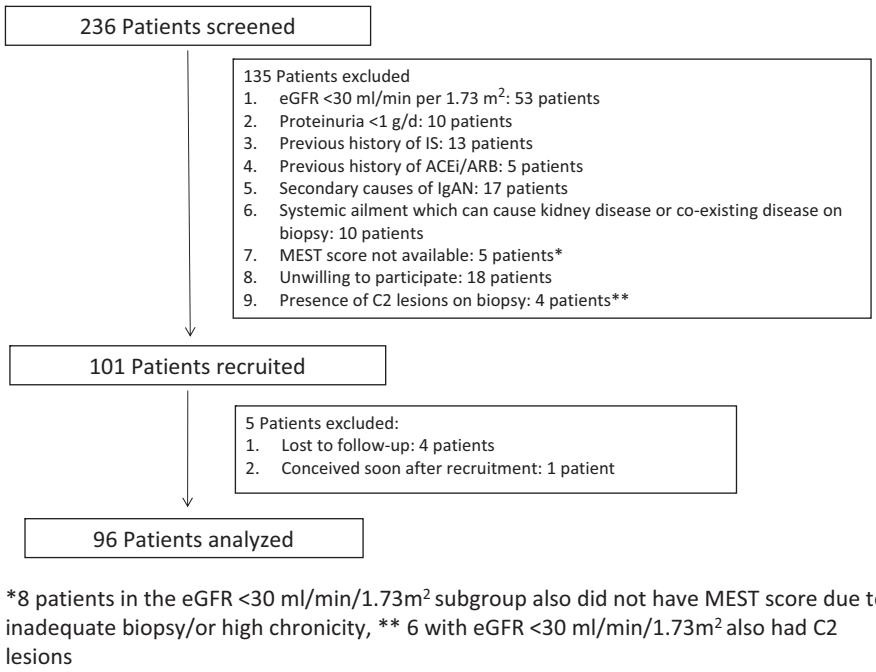

Figure 1. Details of patients screened, recruited, and included in the final analysis. *Eight patients in the eGFR <30 ml/min per 1.73 m^2 subgroup also did not have a MEST score because of inadequate biopsy specimen or high chronicity. **Six patients with eGFR <30 ml/min per 1.73 m^2 also had C2 lesions. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; IS, immunosuppression; MEST, Oxford MEST-C score.

The study was approved by the institute ethics committee (IEC-682/01.12.2017) and registered with the central trial registry (CTRI/2018/01/011414).

Statistical Analysis

Statistical analysis was carried out using Stata 15.1 (StataCorp, College Station, TX). Data were summarized as frequency (%), mean ± SD, or median (range) as appropriate. Categorical and continuous variables were compared between the groups using the χ^2 test/Fisher exact test and independent *t* test/Wilcoxon rank sum test, respectively. Univariate logistic regression analysis was done to calculate the odds ratio (OR) with 95% confidence interval (95% CI) for the clinical and histological characteristics between patients who achieved remission and those who did not achieve remission, and also for patients who did not tolerate RAS blockade compared to those who completed treatment for 6 months. A *P* value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 236 patients with IgAN were screened in the nephrology department of our hospital during the study period (Figure 1), of whom 101 patients with primary IgAN were recruited until March 2020. In all, 96 patients were included in the final analysis (4 patients were lost to follow-up, and 1 patient conceived soon after initiation of ACEi therapy).The baseline profile of the patients is shown in Table 1. The mean age was 33.3 ± 10.2 years, and 77.1% were male. Of the patients, 56 (58.3%) had hypertension. The baseline serum creatinine was 1.3 ± 0.5 mg/dl and the eGFR was 74.0 ± 30.9 ml/min per 1.73 m^2. The 24-hour urinary protein was 2.6 ± 1.2 g/d, and serum albumin was 4.1 ± 0.7 g/dl.

Histologic Characteristics

All patients had undergone kidney biopsy in the preceding 12 months before recruitment. As per the Oxford classification criteria, the distribution of MEST-C lesions was as follows: mesangial hypercellularity, M1: 76 (79.2%), endocapillary hypercellularity, E1: 7 (7.3%), segmental sclerosis, S1: 76 (79.2%,) interstitial fibrosis and tubular atrophy, T1: 27 (28.1%) lesions and T2-2(2.1%). Nine patients (9.4%) had crescentic (C1) lesions.

Details of Supportive Therapy

As shown in Table 2, 81 patients (84.4%) received an ACEi (ramipril), and 15 (15.6%) were given an ARB (losartan). Of the patients, 69 (71.9%) could be given 100% of the maximal approved ACEi/ARB dose, and only 6 patients (6.3%) received < 50% of the maximal dose. Of the 27 patients who received ≤ 50% of maximal ACEi/ARB dose, further dose escalation was not possible because of low BP in 13 patients (48.1%), worsening renal function (> 25% decline in eGFR) in 9 patients (33.3%), and hyperkalemia in 5 patients

Table 1. Baseline characteristics of the patients (N = 96)

Characteristic	Value
Age (yr), mean ± SD	33.3 ± 10.2
Male sex (%)	74 (77.1)
BMI, mean ± SD	23.4 ± 5.2
Hypertension (%)	56 (58.3)
Systolic BP (mm Hg), mean ± SD	134.3 ± 11.3
Diastolic BP (mm Hg), mean ± SD	84.1 ± 7.5
MAP (mm Hg), mean ± SD	100.8 ± 8.2
Urinary protein (g/d), mean ± SD	2.6 ± 1.2
Haematuria (%)	52 (54.2)
Serum creatinine (mg/dl), mean ± SD	1.3 ± 0.5
eGFR (ml/min per 1.73 m^2), mean ± SD	74.0 ± 30.9
eGFR category (%)	
≥ 50 ml/min per 1.73 m^2	71 (74.0)
30–49 ml/min per 1.73 m^2	25 (26.0)
Serum albumin (mg/dl), mean ± SD	4.1 ± 0.7
Serum cholesterol (mg/dl), mean ± SD	188.8 ± 52.0
Serum uric acid (mg/dl), mean ± SD	7.0 ± 1.9
MEST-C lesions (%)	
M1	76 (79.2)
E1	7 (7.3)
S1	76 (79.2)
T1/T2	27 (28.1) / 2. (2.1)
C1	9 (9.4)

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; MEST-C, Oxford MEST-C score.

(18.5%). A total of 54 patients (56.3%) required additional antihypertensive therapy besides ACEi/ARB to control their BP. In all, 26 patients (27.1%) received treatment for dyslipidemia and 44 (45.8%) for hyperuricemia.

Response to Therapy

Figure 2 shows the proportion of patients who achieved the primary outcome of remission, and Figure 3 depicts the trend of proteinuria over 6 months in patients with and without remission. Overall, of the 96 patients included in the study, 35 (36.5%) achieved remission at the end of 3 months, of whom 6 (6.3%) had CR and 29 (30.2%) had PR. At the end of 6 months, 53 (55.2%) patients had responded to supportive therapy, of whom 30 (31.3%) had CR and 23 (24.0%) had PR. A comparison of patients who achieved remission with those who did not is shown in Table 3. Patients who did not achieve remission had a significantly lower baseline eGFR (62.5 ± 26.6 vs. 83.3 ± 31.3 ml/min per 1.73 m^2, $P = 0.002$) and were more likely to have an eGFR <50 ml/min per 1.73 m^2 compared to those who achieved remission (37.2% vs. 17%, $P = 0.035$). They also had significantly lower serum albumin levels (3.7 ± 0.6 vs. 4.3 ± 0.6 g/dl, $P < 0.001$) and higher proteinuria (2.9 ± 1.2 vs. 2.4 ± 1.1 g/d, $P = 0.076$), although it was not statistically significant. They had more E1 (14.0% vs. 1.9%, $P = 0.053$) and T1/T2 (44.2% vs. 18.9%, $P = 0.009$) lesions on kidney biopsy

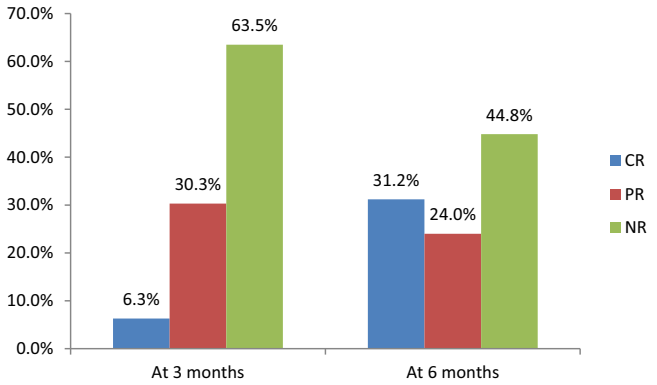

Figure 2. Remission rate at 3 months and 6 months. CR, complete remission; NR, no remission; PR, partial remission.

compared to those who had achieved remission. C1 lesions were more frequent in patients with no remission (14% vs. 5.7%), but this was not significant ($P = 0.179$). The baseline mean serum uric acid level was not similar in the 2 subgroups, but the number of patients with asymptomatic hyperuricemia requiring treatment was significantly higher (69.1% vs. 28.3%, $P < 0.001$) in patients who failed to achieve remission compared to those who did. The need for additional antihypertensive drugs was similar between the 2 groups. The trend of MAP over 6 months is shown in Figure 4. The MAP averaged over 6 months was similar between patients with and without remission (92.5 ± 5.4 vs. 93.0 ± 5.7, $P = 0.629$).

Five patients (5.2%) had renal worsening, with 1 patient progressing to end-stage renal disease by the end of 6 months.

In 17 patients (17.7%), ACEi/ARB had to be discontinued before end of the planned 6 months, mainly due worsening renal function (88.2%). Table 4 shows the characteristics of patients who did not tolerate ACEi/ARB therapy compared to those who completed treatment for 6 months. Patients who did not tolerate treatment were more likely to be older (age 37.2 ± 10.8

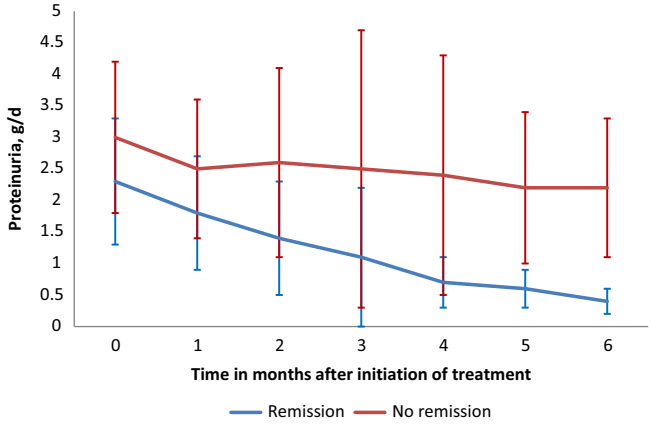

Figure 3. Pattern of reduction in proteinuria over 6 months.

Table 2. Details of supportive therapy

ACEi/ARB (%)	81 (84.4) / 15 (15.6)
Dose of ACEi/ARB achieved (% of maximum labeled dose):	
100%	59 (61.5)
75%	10 (10.4)
50%	21 (21.9)
< 50%	6 (6.3)
Requirement for additional antihypertensives (%)	54 (56.3)
Treatment for dyslipidemia (%)	26 (27.1)
Treatment for hyperuricemia (%)	44 (45.8)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

vs. 32.4 ± 9.9 years, $P = 0.085$) and to have higher baseline proteinuria (3.1 ± 1.5 vs. 2.5 ± 1.1 g/d, $P = 0.088$), although these differences were not statistically significant. These patients had significantly lower baseline eGFR (50.6 ± 25.9 vs. 79.0 ± 29.7 ml/min per 1.73 m^2; $P = 0.002$). In all, 70.6% of the patients who did not tolerate treatment had baseline eGFR < 50 ml/min per 1.73 m^2, compared to 16.5% in those who completed 6 months of treatment ($P < 0.001$). They also had significantly lower serum albumin levels (3.5 ± 0.7 vs. 4.2 ± 0.6 g/dl, $P = 0.001$). On kidney biopsy, E1 (23.5% vs. 2.8%, $P = 0.012$) and T1/T2 (64.7% vs. 22.8%, $P = 0.001$) lesions were also significantly more common in this subgroup. There was no difference in the prevalence of M1, S1, and C1 lesions between the 2 subgroups.

DISCUSSION

IgAN is an important cause of ESKD. Management remains a challenge because of its smoldering disease course and the paucity of well-established treatment recommendations. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest steroid therapy in patients with persistent proteinuria despite 3 to 6 months of supportive treatment including RAS blockers, although the evidence was graded as 2C.[13]

In our cohort, we observed remission of proteinuria in 36.5% patients at 3 months and 55.2% patients at 6 months with RAS blockade and control of BP. Complete remission was achieved in only 6.3% patients at 3 months, which increased to 31.3% at 6 months. So, increasing the duration of therapy not only improves the remission rate but also increases the likelihood of complete remission. Use of ACEi/ARB had to be discontinued before the study completion in 17.7% of our patients chiefly because of worsening renal function (88.2%). Studies from Europe and Asia have consistently reported the benefit of RAS blockers in reducing proteinuria in IgAN, although most of these RCTs had small number of patients.[14–18] In the IgACE trial,[15] partial remission of proteinuria was observed in 40.6% of patients and complete remission in 12.5% of

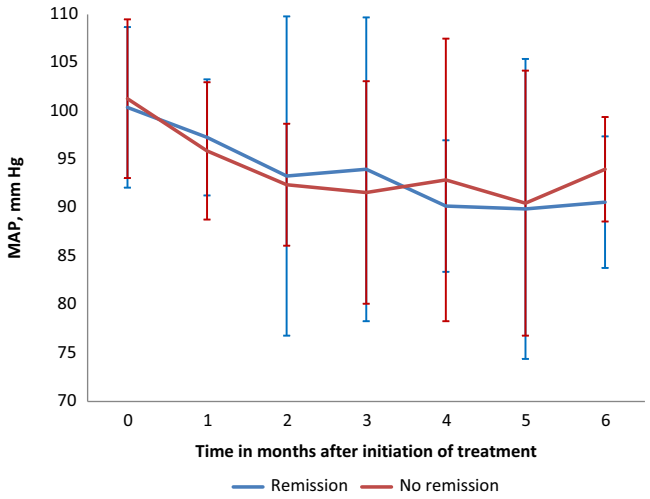

Figure 4. Mean arterial pressure (MAP) over 6 months in patients who achieved remission and in those who showed no response.

patients treated with benazepril versus 8.8% partial remission and no complete remission in the placebo group, thus establishing the superiority of RAS blockers. However the patients in this study had less severe disease compared to our cohort (mean eGFR 116.0 vs. 74.0 ml/min per 1.73 m^2, and mean proteinuria 1.6 vs. 2.6 g/d). Li *et al.*[18] failed to show any benefit with ACEi therapy in patients with early IgAN, probably because they included patients who were already in complete remission (urine protein <0.5 g/d) and used a very low dose of ACEi (ramipril 2.5 mg/d). In the STOP-IgAN trial comparing intensive immunosuppression with supportive therapy,[19] 34.3% patients displayed target reduction in proteinuria to <0.75 g/d by the end of the initial run-in phase of 6 months with only RAS blockade and BP control. In the TESTING trial,[20] which studied the effect of meythlprednisolone on outcomes in IgAN, a decrease in proteinuria was observed in 128 of 523 patients (24.5%) screened at the end of the run-in period of only 4 to 12 weeks with supportive therapy. A further 13.7% patients from the placebo group achieved remission during follow-up after randomization. Although the remission rate is higher in our study, we have to keep in mind that both STOP-IgAN and TESTING trials were not designed to study the efficacy of supportive treatment *per se,* the type and dose of ACEI/ARB used may not have been uniform, and the patients had more renal dysfunction in these studies. The STOP-IgAN trial used a stricter definition of remission (proteinuria < 0.75 g/d), and in the TESTING trial, the run-in period was only 4 to 12 weeks, which may not be adequate for RAS blockade to have an optimal effect.

Our patients who did not respond to supportive treatment (44.8%) had clinically severe disease with

Table 3. Comparison of patients who achieved remission with those who failed to achieve remission

Characteristic	Remission (n = 53)	No remission (n = 43)	OR (95% CI)	P
Age (yr), mean ± SD	31.9 ± 9.3	34.9 ± 11.1	1.03(0.99–1.07)	0.149
Male sex (%)	43 (81.1)	31 (72.1)	1.67 (0.64–4.12)	0.335
Hypertension (%)	28 (52.8)	28 (65.1)	0.6 (0.26–1.35)	0.298
BMI, mean ± SD	23.5 ± 5.0	23.7 ± 4.2	1.02 (0.98–1.05)	0.821
Systolic BP (mm Hg), mean ± SD	133.4 ± 11.9	135.3 ± 10.5	1.02 (0.98–1.05)	0.398
Diastolic BP (mm Hg), mean ± SD	83.9 ± 7.5	84.2 ± 7.6	1.01 (0.95–1.06)	0.840
MAP (mm Hg), mean ± SD	100.4 ± 8.3	101.3 ± 8.1	1.01 (0.96–1.06)	0.609
Serum creatinine (mg/dl), mean ± SD	1.2 ± 0.4	1.5 ± 0.5	3.63 (1.42–9.24)	0.007
eGFR (ml/min per 1.73 m^2), mean ± SD	83.3 ± 31.3	62.5 ± 26.6	0.98 (0.96–0 .99)	0.002
eGFR < 50 ml/min per 1.73 m^2 (%)	9 (17.0)	16 (37.2)	2.90 (1.16–7.10)	0.035
Hematuria (%)	27 (50.9)	25 (58.1)	1.34 (0.59–3.01)	0.482
24-h Urinary protein:creatinine ratio, mean ± SD	2.4 ± 1.1	2.9 ± 1.2	1.40 (0.97–2.02)	0.076
Serum albumin (mg/dl), mean ± SD	4.3 ± 0.6	3.7 ± 0.6	0.16 (0.07–0.38)	<0.001
Serum cholesterol (mg/dl), mean ± SD	185.9 ± 43.9	192.5 ± 60.8	1.00 (0.99–1.01)	0.538
Serum uric acid (mg/dl), mean ± SD	6.9 ± 2.0	7.2 ± 1.9	1.08 (0.88–1.34)	0.459
M1	42 (79.3)	34 (79.1)	0.99 (0.37–2.66)	0.983
E1	1 (1.9)	6 (14.0)	8.43 (0.97–3.01)	0.053
S1	39 (73.6)	37 (86.1)	2.21 (0.77–6.37)	0.141
T1/2	10 (18.9)	19 (44.2)	3.40 (1.36–8.49)	0.009
C1	3 (5.7)	6 (14.0)	2.7 (0.6–11.52)	0.179
Need for additional antihypertensives	27 (50.9)	27 (62.8)	1.63 (0.72–3.69)	0.246
Rx with statin	12 (23.1)	14 (35.9)	1.87 (0.74–4.68)	0.183
Rx for hyperuricemia	15 (28.3)	29 (69.1)	5.65 (2.33–13.71)	<0.001

BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; OR, odds ratio; Rx, prescription.

significantly lower baseline eGFR and serum albumin levels and higher proteinuria (trend toward significance). There was no difference in the incidence of hypertension and baseline MAP between the 2 groups. The subgroup of patients in whom ACEi/ARB had to be discontinued tended to be older and, again, had clinically severe disease with significantly lower baseline eGFR and albumin levels and higher proteinuria (not significant). Patients with eGFR <50 ml/min per 1.73 m^2 were significantly more likely not to respond to treatment and required discontinuation of ACEi/ARBs. The association of low serum albumin with poor tolerance and lack of response to ACEi/ARB may be attributed to the consequent reduction in the intravascular osmotic

Table 4. Profile of patients who completed treatment for 6 months and those who failed to complete treatment

Characteristic	Treatment completed (n = 79)	Treatment discontinued (n = 17)	OR (95% CI)	P
Age (yr), mean ± SD	32.4 ± 9.9	37.2 ± 10.8	1.05(0.99–1.01)	0.085
Male (%)	60 (76.0)	14 (82.4)	0.68 (0.18–2.61)	0.571
Hypertension (%)	55 (55.7)	12 (70.6)	1.91 (0.61–5.93)	0.264
BMI, mean ± SD	23.8 ± 4.8	22.8 ± 3.7	0.95 (0.83–1.08)	0.399
Systolic BP (mm Hg), mean ± SD	133.5 ± 11.3	137.6 ± 10.9	1.03 (0.99–1.08)	0.177
Diastolic BP (mm Hg), mean ± SD	83.7 ± 7.7	85.5 ± 6.5	1.03 (0.96–1.11)	0.372
MAP (mm Hg), mean ± SD	100.3 ± 8.3	102.9 ± 7.7	1.04 (0.97–1.11)	0.245
Hematuria (%)	45 (57.0)	7 (41.2)	0.53 (0.18–1.53)	0.240
24 hour urinary protein creatinine ratio, mean ± SD	2.5 ± 1.1	3.1 ± 1.5	1.44 (0.95–2.18)	0.088
Serum creatinine(mg/dl), mean ± SD	1.3 ± 0.4	1.8 ± 0.4	14.96 (3.54–63.22)	<0.001
eGFR (ml/min/1.73m^2), mean ± SD	79.0 ± 29.7	50.6 ± 25.9	0.95 (0.91–0.98)	0.002
eGFR < 50 ml/min per 1.73 m^2 (%)	13 (16.5)	12 (70.6)	12.18 (3.73–36.3)	<0.001
Serum cholesterol (mg/dl), mean ± SD	189.5 ± 51.7	185.8 ± 54.6	1.00 (0.99–1.01)	0.787
Serum uric acid (mg/dl), mean ± SD	6.9 ± 2.0	7.6 ± 1.6	1.20 (0.91–1.58)	0.203
Serum albumin (mg/dl), mean ± SD	4.2 ± 0.6	3.5 ± 0.7	0.21 (0.08–0.53)	0.001
M1	61 (77.2)	15 (88.2)	2.21 (0.46–10.60)	0.320
E1	3 (3.8)	4 (23.5)	7.79 (1.56–38.93)	0.012
S1	62 (78.5)	14 (82.4)	1.28 (0.33–4.97)	0.722
T1/2	18 (22.8)	11 (64.7)	6.21 (2.02–19.14)	0.001
C1	7 (8.9)	2 (11.8)	1.37 (0.26–7.26)	0.710

BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; OR, odds ratio.

pressure, which increases the risk of acute renal deterioration with ACEi/ARB, especially in patients with impaired baseline renal function. It may also simply reflect the severity of the glomerular disease. Interstitial fibrosis and tubular atrophy (T1/T2 lesions) and endocapillary hypercellularity (E1) were significantly more common in patients who did not achieve remission and also in those who did not tolerate treatment. The presence of crescents (C1) was not associated with lack of remission or discontinuation of RAS blockers. It is probable that proliferative lesions may be less amenable to RAS blockade and require immunosuppression. However, the extent of proliferation may influence the response to treatment. Even the presence of only 1 crescent is labeled a C1 lesion as per the Oxford classification. However, our observations suggest that supportive treatment may be sufficient for some patients with C1 lesions and stable renal function. Initially, all patients with crescents on kidney biopsy were excluded in our study; but subsequently, as we observed that many of the patients with C1 lesions on histology had a stable disease course, the protocol was amended to include them prospectively. Further studies with larger numbers of patients are needed to assess the therapeutic and prognostic significance of C1 lesions on kidney biopsy in IgAN patients. Severe crescentic IgAN with C2 lesions ($\geq$ 25%) on kidney biopsy were excluded and hence could not be evaluated. None of the previous RCTs have examined the significance of renal histology in response to supportive therapy.[14–18]

In all, 71.9% patients received $\geq$ 75% of the maximum approved ACEi/ARB dose, which is better than in the TESTING trial, in which only about 50% of the patients received >80% of the maximum dose.[20] The time-averaged MAP during the study period was similar in patients who achieved remission compared to those with no remission, which suggests that both groups had achieved adequate control of BP. Although the mean serum uric acid level was similar in both groups, asymptomatic hyperuricemia requiring treatment was significantly more common in patients who did not respond to RAS blockers. We cannot say whether hyperuricemia in any way interferes with the antiproteinuric effect of RAS blockers or whether this is simply a reflection of more severe kidney disease.

A limitation of our study is that it is not an RCT. Considering the body of evidence with multiple RCTs that have established the efficacy of RAS blockade in reducing proteinuria, we did not consider it ethical to have a placebo group. Also, our goal was not to examine whether RAS blockers and supportive therapy are effective in achieving remission; rather, we wanted to determine the magnitude of their efficacy and the timing of optimal response, and to define the subgroup of patients who are unlikely to respond to or tolerate this treatment. The patients who have achieved remission may not remain in remission and may experience disease progression in the future; therefore we plan to follow this cohort prospectively for 5 years to delineate the clinical course. Our study comprised solely Indian patients, although ethnic variability has been observed in IgAN. However, it is noteworthy that this response was seen in a cohort of South Asian patients who are known to have a severe disease phenotype with an aggressive course.[21–23]

To conclude, in a well-defined treatment-naive cohort, optimal BP control and an adequate dose of ACEi/ARB was sufficient to achieve remission of proteinuria in half of the patients. Extending supportive treatment to 6 months improved the outcome, significantly increasing the proportion of patients who achieved complete remission. Patients with low eGFR, hypoalbuminemia, and T1/T2 and E1 lesions on histology are less likely to tolerate or respond to supportive treatment and need close monitoring. Further studies are needed to determine whether early initiation of immunosuppressive treatment will benefit this high-risk subgroup. We aim to follow our cohort prospectively to examine the incidence of relapse of proteinuria and the long-term renal survival with supportive therapy in patients with IgAN.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

SB conceptualized and designed the protocol and was responsible for patient follow-up, analysis, and writing the manuscript. MK helped with study conceptualization and performed the statistical analysis. AS and DB assisted with patient follow-up. AB and GS are renal pathologists who reported the kidney biopsy results and gave the MEST-C scores. SKA was involved in study conceptualization and patient follow-up, and also helped in writing the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. STROBE checklist

REFERENCES

1. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol.* 2004;24:179–196.
2. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med.* 2013;368:2402–2414.

3. Yeo SC, Goh SM, Barratt J. Is immunoglobulin A nephropathy different in different ethnic populations? *Nephrology (Carlton)*. 2019;24:885–895.
4. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. 2007;18:3177–3183.
5. Thompson A, Carroll K, Inker L, Floege J. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14:469–481.
6. Lewis EJ, Hunsicker L, Bain RP, Rhode RP, for the CollaborativeStudy Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329:1456–1462.
7. GISEN Group. Randomised placebo-controlled trial of effect of ramipril on declining in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*. 1997;349:1857–1863.
8. Zhao Y, Fan H, Bao BY. Efficacy and safety of renin-angiotensin aldosterone system inhibitor in patients with IgA nephropathy: a meta-analysis of randomized controlled trial. *Iran J Public Health*. 2019;48:1577–1588.
9. Cheng J, Zhang W, Zhang XH, et al. ACEI/ARB therapy for IgA nephropathy: a meta analysis of randomised controlled trials. *Int J Clin Pract*. 2009;63:880–888.
10. Reid S, Cawthon PM, Craig JC, et al. Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev*. 2011;3:CD003962.
11. Working Group of the International IgA Nephropathy Network, the Renal Pathology Society, Cattran DC, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int*. 2009;76:534–545.
12. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
13. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:139–274.
14. Praga M, Gutiérrez E, González E, et al. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol*. 2003;14:1578–1583.
15. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol*. 2007;18:1880–1888.
16. Li PK, Leung CB, Chow KM, et al. HKVIN Study Group. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis*. 2006;47:751–760.
17. Shimizu A, Takei T, Uchida K. Low-dose losartan therapy reduces proteinuria in normotensive patients with immunoglobulin A nephropathy. *Hypertens Res*. 2008;31:1711–1717.
18. Li PK, Kwan BC, Chow KM, et al. Treatment of early immunoglobulin A nephropathy by angiotensin-converting enzyme inhibitor. *Am J Med*. 2013;126:162–168.
19. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373:2225–2236.
20. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. 2017;318:432–442.
21. Chacko B, John GT, Neelakantan N, et al. Presentation, prognosis and outcome of IgA nephropathy in Indian adults. *Nephrology (Carlton)*. 2005;10:496–503.
22. Mittal N, Joshi K, Rane S, et al. Primary IgA nephropathy in north India: is it different? *Postgrad Med J*. 2012;88:15–20.
23. Bagchi S, Singh G, Yadav R, et al. Clinical and histological profile of patients with primary IgA nephropathy seen in a tertiary hospital in India. *Renal Fail*. 2016;38:431–436.