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Tacrolimus decreases proteinuria in patients with refractory IgA nephropathy

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Abstract

In clinical practice, some IgA nephropathy (IgAN) patients show resistance to or are unable to achieve complete remission using steroids and/or immunosuppressants. The current study aimed to assess the efficacy and safety of tacrolimus in the treatment of cases of refractory IgAN.

In this retrospective observational study, 34 primary IgAN patients with refractory proteinuria received tacrolimus for at least 12 months. Complete remission, partial remission, and other clinical data were measured at 1, 3, 6, and 12 months after the initiation of treatment.

After 12 months, complete remission was achieved in 20 (58.8%) patients and partial remission in 5 (14.7%) patients, yielding a total response rate of 73.5%. The mean time for response to tacrolimus for those who achieved complete remission and partial remission was 7.0±4.7 weeks. Serum creatinine (Scr), uric acid, estimated glomerular filtration rate, alanine aminotransferase, aspartate transaminase, white blood cell count, blood pressure, blood glucose, total cholesterol, and total triglyceride were stable over time. Three patients demonstrated a loss of eGFR >15 mL/min·1.73 m^2 from baseline. Three cases of upper respiratory infection and 2 cases of urinary tract infection were observed during the study. Patients who achieved complete remission had better renal function and lower baseline proteinuria than partial remission and nonresponder patients. Crescent formation in biopsy specimens was seen more often in nonresponder patients.

Tacrolimus was safe and effective at lowering proteinuria in refractory IgAN patients. Lower baseline proteinuria and better renal function were associated with a higher probability of complete remission, while crescent formation was associated with a worse prognosis.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate transaminase, CYC = cyclophosphamide, IgAN = IgA nephropathy, LEF = leflunomide, MMF = mycophenolate mofetil, Scr = serum creatinine, TC = total cholesterol, TG = total triglyceride, TwHF = *Tripterygium wiforbii* Hook F, UA = uric acid, UACR = urine albumin to creatinine ratio, WBC = white blood cell count.

Keywords: IgA nephropathy, proteinuria, tacrolimus

1. Introduction

Primary IgA nephropathy (IgAN) is the most common glomerulonephritis among patients who undergo renal biopsy in China.[1] Proteinuria is an important clinical parameter in the evaluation of IgAN prognosis. Usui et al[2] reported that renal insufficiency developed in 17.2% of 203 IgAN patients with proteinuria 0.5 to 0.9 g/day and in 3.5% of 197 patients with proteinuria < 0.5 g/day during a mean follow-up duration of 6.7 years. Therefore, Usui et al[2] suggested that proteinuria > 0.5 g/day increased patient risk of developing end-stage renal disease (ESRD). Studies have shown that steroids and/or immunosuppressive agents can reduce proteinuria in patients with IgAN.[3–5] Despite this, however, some patients show resistance to or are unable to achieve complete remission using steroids and/or immunosuppressants.

Several studies have shown that tacrolimus, a potent calcineurin inhibitor, is effective in patients with refractory IgAN. However, its effective dose has not been defined, and some side effects were previously reported, including nephrotoxicity, severe infection, gastrointestinal symptoms, and metabolic complications.[6,7] The present study aimed to evaluate the safety and efficacy of tacrolimus in IgAN patients with a urine albumin to creatinine ratio (UACR) > 500 mg/g cr following a full dose of steroids and/or immunosuppressive agents.

2. Materials and methods

2.1. Patients

This retrospective study included 34 renal biopsy-proven primary IgAN patients with refractory proteinuria who were treated in Tongji Hospital between March 2016 and June 2017. Refractory proteinuria was defined as a UACR >500 mg/g cr after regular steroids and/or immunosuppressant therapy was performed. The immunosuppressants included cyclophosphamide (CYC), mycophenolate mofetil (MMF), leflunomide (LEF), and *Tripterygium wiforbii* Hook F (TwHF). Exclusion criteria were as follows: currently pregnant or lactating; confirmed active hepatitis B/C virus infection or malignant tumor; estimated glomerular filtration rate (eGFR; estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation[8]) < 30

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mL/min 1.73 m^2 or Scr > 2 mg/dL; and use of other immunosuppressant under study. The study was approved by the Ethical Committee of Tongji Hospital (Wuhan, China) and written informed consent was obtained from all patients.

2.2. Treatment protocol

Tacrolimus was given at 1 mg/day divided into 2 doses at 12-hour intervals after other immunosuppressants (e.g., CYC, MMF, LEF, TwHF) were stopped. The dose was adjusted according to a target trough level of 4 to 6 ng/mL and the largest dose was 2 mg/day. The dose of concomitantly administered steroid was not changed or was gradually tapered throughout the study period depending on each patient's clinical status. Patients on renin-angiotensin system blockade therapy were maintained on the same dose.

2.3. Histological evaluation

The histologic score was derived from primary pathologic diagnostic reports using light microcopy. Mesangial hypercellularity and endocapillary hypercellularity were evaluated according to MEST score. The severities of crescent formation, global glomerular sclerosis, ischemic sclerosis, segmental sclerosis, and tubular atrophy/interstitial fibrosis in each case were graded semiquantitatively from 0 to 4: 0 = absent; 1 = <25%; 2 = ≥25% and <50%; 3 = ≥50% and <75%; 4 = ≥75%.

2.4. Data collection and evaluation

The primary outcomes were complete remission and partial remission. Complete remission was defined as a decrease in UACR to a level ≤200 mg/g cr, while partial remission was defined as a 50% decrease in UACR but a level >200 mg/g cr. Time required to achieve remission was defined as the time from the start of tacrolimus therapy to the day on which complete remission or partial remission was achieved. UACR, Scr, uric acid (UA), eGFR, alanine aminotransferase (ALT), aspartate transaminase (AST), white blood cell count (WBC), and blood pressure were measured and recorded at each visit. These data were collected at 1, 3, 6, and 12 months after the initiation of therapy. Blood glucose, total cholesterol (TC), and triglyceride (TG) levels were collected at 6 and 12 months after the initiation of therapy. In addition, decreases of >15 mL/min 1.73 m^2 in eGFR from baseline were recorded.[9]

2.5. Statistical analysis

For the statistical analysis, we used 1-way analysis of variance or Wilcoxon rank-sum test for continuous variables and Pearson Chi-square test or Fisher exact test for qualitative variables. In all analyses, SPSS 19 (SPSS Inc., Chicago, IL) was used. Values of $P < .05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 34 patients (8 men, 26 women; mean age, 34.7 ± 8.3 years) with refractory IgAN were included in our study. The baseline characteristics of included patients at renal biopsy and onset of tacrolimus therapy are listed in Tables 1 and 2, respectively.

The mean urinary protein excretion and serum albumin at the time of renal biopsy were 1.50 ± 1.39 g/day and 38.3 ± 6.0 g/L, respectively, and only 2 of 34 patients presented as nephrotic syndrome S. The mean Scr was 82.3 ± 34.0 μmol/L, while the mean eGFR was 96.6 ± 33.9 mL/min·1.73 m^2. Seven patients had an eGFR < 60 mL/min·1.73 m^2 at renal biopsy, but it was > 30 mL/min 1.73 m^2 in all cases (Table 1). The median interval

Table 1

Clinical data at the time of renal biopsy.

No.	Gender	Age	Clinical data at the time of renal biopsy				
			Proteinuria g/d	Salb g/L	Scr μmol/L	eGFR mL/min·1.73 m^2	BP mm Hg
1	F	27	0.78	39.7	70	103.3	98/56
2	F	27	2.68	35.2	53	127.1	111/69
3	F	31	1.00	33.7	91	73.7	110/70
4	F	28	0.44	48.2	37	141.1	118/84
5	F	34	0.61	42.3	106	60.4	110/80
6	M	20	0.40	36.8	33.5	186.2	100/60
7	F	33	0.58	41.7	50	125.1	130/95
8	F	33	1.44	39.6	76	90.3	110/80
9	F	35	1.55	33.7	68	101.2	111/78
10	F	30	0.26	41.2	64	114.4	143/90
11	F	33	0.40	46.2	57	119.0	115/78
12	F	45	0.17	42.6	115	50.7	128/76
13	F	37	1.12	38.1	64	111.2	120/80
14	F	44	2.28	37.3	106	56.3	145/106
15	M	33	0.52	46.5	92	96.5	145/89
16	F	33	0.96	32.6	64	111.2	128/80
17	F	42	0.94	36.1	68	98.4	110/86
18	M	27	6.69	23.2	179	44.1	135/87
19	F	31	1.84	36.6	108	84.1	120/90
20	F	42	1.02	39.8	43	122.6	125/89
21	M	50	3.34	35.8	95	113.8	122/79
22	F	28	4.60	23.3	92	75.9	114/78
23	M	23	0.19	42.5	108	84.1	140/96
24	F	24	1.50	39.3	47	134.1	104/78
25	F	38	2.68	30.4	42	138.2	110/80
26	F	48	1.26	42.1	79	77.6	157/92
27	F	42	0.62	45.7	60	119.5	110/80
28	F	25	0.53	43.6	47	132.2	110/70
29	F	48	1.18	34.5	122	45.6	103/65
30	F	48	1.30	42.5	83	73.1	145/94
31	M	29	2.37	31.6	80	117.5	140/90
32	M	38	0.33	46.2	137	56.8	143/100
33	F	46	3.31	38.6	110	46.8	147/94
34	M	27	2.06	35.1	151	53.8	150/100

BP = blood pressure, eGFR = estimated glomerular filtration rate, Salb = serum albumin, Scr = serum creatinine.

Table 2

Clinical data before tacrolimus treatment.

No.	Time since diagnosis, mo	Immunosuppressants before tacrolimus treatment	Clinical data at the onset of tacrolimus therapy			
			UACR mg/g Cr	Scr μmol/L	eGFR mL/min·1.73 m^2	BMI
1	7	LEF+ TwHF	581.4	71	100.9	25.1
2	16	LEF+ TwHF	676.2	58	121.7	22.9
3	10	LEF+ TwHF	941.5	82	80.0	17.1
4	10	LEF	514.5	43	133.3	20.3
5	25	LEF+ TwHF	613.9	97	65.9	23.4
6	114	LEF	596.4	76	124.0	22.9
7	25	LEF+ TwHF	545.6	51	121.7	24.7
8	20	LEF+ TwHF	612.3	75	90.5	18.1
9	10	LEF+ TwHF	816.4	68	100.5	22.4
10	33	LEF+ TwHF	517.6	47	162.7	21.6
11	6	TwHF	931.3	69	100.1	19.6
12	26	TwHF	2141.6	90	66.7	20.8
13	7	LEF+ TwHF	614.7	71	94.0	25.4
14	19	LEF+ TwHF	503.8	119	47.9	24.7
15	51	LEF	612.6	80	111.1	21.9
16	17	LEF+ TwHF	1010.2	74	92.0	20.0
17	44	LEF+ TwHF	1004.9	76	83.6	21.6
18	6	LEF+ TwHF	1821.8	136	61.0	21.5
19	6	TwHF	1696.5	90	73.6	21.5
20	12	TwHF	1042.3	49	115.8	21.6
21	29	TwHF	537.8	110	67.1	21.7
22	56	MMF	1241.7	118	54.2	19.9
23	15	MMF	504.7	103	87.8	19.4
24	9	LEF	521.9	54	127.2	26.3
25	180	LEF+ TwHF	596.4	146	39.1	17.8
26	19	LEF+ TwHF	519.8	78	77.7	23.2
27	162	TwHF	531.8	57	110.1	24.0
28	8	LEF+ TwHF	509.5	48	131.3	18.2
29	16	LEF+ TwHF	3346.0	102	56.2	23.4
30	19	LEF+ TwHF	584.5	76	80.2	22.0
31	46	MMF	1813.3	84	107.7	27.5
32	31	LEF+ TwHF	1082.0	133	58.0	30.4
33	14	CYC	863.7	100	58.3	26.2
34	16	LEF	873.1	137	60.5	26.0

BMI = body mass index, CYC = cyclophosphamide, LEF = leflunomide, MMF = mycophenolate mofetil, TwHF = *Tripterygium wiforbii* Hook F, UACR = urine albumin to creatinine ratio.

between diagnosis (renal biopsy) and start of tacrolimus was 18 months (range, 6–180). All patients had been treated with regular steroids and/or immunosuppressants before tacrolimus therapy: 1 patient received CYC, 3 received MMF, 5 received LEF, 6 received TwHF, and 19 received LEF + TwHF. The UACR levels of all 34 patients were persistently >500 mg/g cr and diagnosed as refractory IgAN. At the onset of tacrolimus therapy, the baseline levels of UACR, Scr, and eGFR were 921.2 ± 608.9 mg/g cr, 84.4 ± 28.2 μmol/L, and 90.1 ± 29.4 mL/min·1.73 m^2, respectively (Table 2).

3.2. Response to tacrolimus therapy

Changes in clinical findings are summarized in Table 3. The UACR level decreased significantly 1 month after the initiation of tacrolimus therapy (921.2 ± 608.9 vs 500.0 ± 478.5, $P < .001$). This significant decrease in UACR continued until 12 months (921.2 ± 608.9 vs 210.1 ± 205.7, $P < .001$), whereas Scr, UA, eGFR, ALT, AST, WBC, and blood pressure did not change over time. The mean tacrolimus trough level was 4.5 ± 2.0 (range, 2–10.2) ng/mL. As shown in Fig. 1, the response rate was 52.9%

Table 3

The change of clinical data during follow-up period.

	Baseline	1 mo	3 mo	6 mo	12 mo	*P*
UACR, mg/g Cr	921.2 ± 608.9	500.0 ± 478.5	354.3 ± 304.4	294.8 ± 286.8	210.1 ± 205.7	<.001
Scr, μmol/L	84.4 ± 28.2	87.9 ± 27.2	87.6 ± 31.3	85.9 ± 30.6	89.4 ± 35.7	.970
eGFR	90.1 ± 29.4	86.0 ± 27.2	87.3 ± 28.8	88.7 ± 27.9	86.6 ± 28.4	.977
UA, μmol/L	331.0 ± 103.7	330.1 ± 86.4	361.4 ± 87.7	321.9 ± 79.4	340.9 ± 109.7	.674
ALT, U/L	14.4 ± 7.3	14.7 ± 5.0	10.2 ± 3.7	15.6 ± 14.0	15.4 ± 10.4	.728
AST, U/L	17.5 ± 3.4	17.6 ± 5.7	18.4 ± 5.4	17.9 ± 5.8	18.6 ± 6.0	.981
WBC, ×10^9/L	8.86 ± 3.48	12.88 ± 1.88	9.22 ± 5.15	9.10 ± 2.24	7.12 ± 1.11	.201
MAP, mm Hg	93.9 ± 9.0	93.3 ± 9.5	95.2 ± 11.7	92.3 ± 8.5	93.7 ± 8.9	.807
TC, mmol/L	4.44 ± 0.82	/	/	4.85 ± 0.70	4.80 ± 0.72	.128
TG, mmol/L	1.38 ± 0.66	/	/	1.62 ± 0.51	1.57 ± 0.59	.291
Blood glucose, mmol/L	5.23 ± 0.93	/	/	5.34 ± 0.37	5.37 ± 0.36	.712

ALT = alanine aminotransferase, AST = aspartate transaminase, MAP = mean arterial pressure, TC = total cholesterol, TG = triglyceride, UA = uric acid, WBC = white blood cell count.

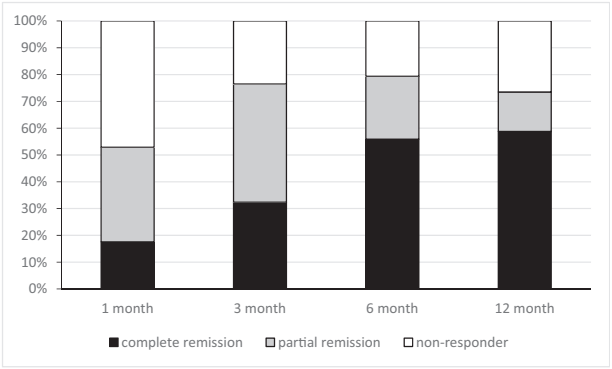

Figure 1. Response rate at different follow-up time points.

(complete remission, 17.6%), 76.5% (complete remission, 32.4%), 79.4% (complete remission, 55.9%), and 73.5% (complete remission, 58.8%) at 1, 3, 6, and 12 months, respectively, after the onset of tacrolimus therapy. Nine (26.5%) patients were resistant to tacrolimus therapy. The time to achieving remission was less than 1 month in 17 patients, including complete remission in 6 and partial remission in 11. The mean time for response to tacrolimus for those who achieved complete or partial remission was 7.0 ± 4.7 weeks.

3.3. Predictive factors of remission

Clinical and histological characteristics of complete remission, partial remission, and non-responder patients are summarized in Table 4. We found that the baseline UACR, Scr, and eGFR at the onset of tacrolimus treatment and crescent formation in biopsy specimens were statistically different among the 3 groups. Patients who achieved complete remission had a lower baseline UACR and better renal function (lower Scr and higher eGFR) than the partial remission and nonresponder patients. Furthermore, crescent formation was seen more often in biopsy specimens of nonresponder patients than remission patients. No significant differences in other values were observed among the 3 groups.

3.4. Adverse events

During tacrolimus treatment, 3 of the 34 patients demonstrated a loss of eGFR $> 15\,mL/min{\cdot}1.73\,m^2$ from baseline. The baseline eGFR of them were 54.2, 61.0, and $107.7\,mL/min{\cdot}1.73\,m^2$, respectively. Three patients developed an upper respiratory infection and 2 had a urinary tract infection that did not require hospitalization. Blood glucose level, TC, TG, UA, and blood pressure remained stable.

4. Discussion

Proteinuria is thought to be an important predictive risk factor for renal dysfunction in IgAN patients. Studies have shown that IgAN patients could obtain benefit from steroids and/or immunosuppressants.[3–5] However, in clinical practice, some patients are unable to achieve complete remission though the use of regular steroids and/or immunosuppressants and are more likely to progress to ESRD.

Tacrolimus has been used as a therapeutic agent in various glomerular diseases, particularly refractory nephrotic syndrome.[10,11] Some authors have also tried to use tacrolimus in the treatment of IgAN. They started with 0.05 to 0.1 mg/kg/day

Table 4

Comparison of clinical and histological characteristics between patients who achieved complete remission and partial remission.

	Complete remission (n = 20)	Partial remission (n = 5)	Nonresponder (n = 9)	*P*
At renal biopsy				
Proteinuria, g/d	1.14 ± 0.84	2.34 ± 2.55	1.79 ± 1.51	.17
Scr, μmol/L	74.5 ± 30.5	115.8 ± 40.0	81.1 ± 30.0	.05
eGFR, mL/min·1.73 m^2	104.9 ± 25.3	66.2 ± 31.0	95.3 ± 44.7	.07
At the onset of tacrolimus therapy				
Age	33.5 ± 7.2	39.4 ± 10.5	34.7 ± 9.2	.37
Gender: M/F	7/13	2/3	2/7	1.00
BMI	22.3 ± 3.2	23.0 ± 2.67	22.4 ± 2.9	.89
UACR, mg/g Cr	677.3 ± 202.2	1941.4 ± 985.5	896.4 ± 383.4	<.001
Scr, μmol/L	73.7 ± 26.8	97.6 ± 23.5	100.7 ± 24.5	.03
eGFR, mL/min 1.73 m^2	101.8 ± 27.4	74.4 ± 20.7	72.8 ± 26.9	.02
MAP, mm Hg	93.5 ± 10.0	95.2 ± 6.3	94.1 ± 14.5	.95
Time since renal biopsy, mo	24.9 ± 34.2	22.2 ± 15.5	24.3 ± 31.1	.21
Concomitant treatment				
ACEI/ARB	10 (50.0%)	2 (40.0%)	7 (77.8%)	1.00
Corticosteroids	17 (85.0%)	3 (60.0%)	7 (77.8%)	.25
Mean tacrolimus trough levels, ng/mL				
Mean tacrolimus dose, mg/d	4.3 ± 1.4	4.7 ± 2.0	4.4 ± 1.9	.46
Histological score	1.3 ± 0.3	1.4 ± 0.3	1.6 ± 0.1	.01
Mesangila hypercellularity (M0/M1)	5/15	1/4	2/7	.96
Endocapillary hypercellularity (E0/E1)	13/7	2/3	7/2	.37
Crescent formation	0.15 ± 0.37	0.40 ± 0.89	0.89 ± 1.05	.04
Globalglomerular sclerosis	0.65 ± 0.93	0.80 ± 0.45	0.67 ± 0.50	.93
Ischemic sclerosis	0.60 ± 0.55	0.65 ± 0.59	0.64 ± 0.57	.83
Segmental sclerosis	0.45 ± 0.61	0.20 ± 0.45	0.33 ± 0.71	.70
Interstitial lesion	1.40 ± 0.75	1.40 ± 0.55	1.67 ± 0.71	.64

E0 = nonendocapillary hypercellularity present, E1 = endocapillary hypercellularity present, M0 = Mesangial hypercellularity score <0.5, M1 = mesangial hypercellularity score >0.5.

of tacrolimus, adjusted the dose according to the trough level of 5 to 10 ng/mL, and demonstrated that tacrolimus could induce proteinuria remission in refractory IgAN patients.[6,7] A double-blind randomized controlled trial conducted by Kim et al[12] also found that tacrolimus could effectively reduce proteinuria in patients with IgAN and a normal blood pressure. However, the effective dose of tacrolimus to reduce proteinuria was not defined in renal diseases. In other reports, a lower dose (0.05 mg/kg/day) and fixed dose (2–3 mg/day) were also used.[13,14] In the present study, we started with a lower dose (1 mg/day) and a lower trough level (4–6 ng/mL), and the largest dose was 2 mg/day. We observed a significant decrease in proteinuria at 1 month and complete remission of proteinuria in 58.8% of patients and partial remission in 14.7% at 12 months. The mean time to a response to tacrolimus for those who achieved complete or partial remission was 7 weeks; 17 patients achieved remission in 1 month. Therefore, tacrolimus could induce rapid proteinuria remission in refractory IgAN patients, consistent with the results by Zhang et al.[6]

The underlying mechanism of the antiproteinuric action of tacrolimus in IgAN is likely multifactorial. It has been proven that tacrolimus can suppress the immune response by downregulating transcription factors that are essential for the transcription of cytokine genes in T cells. In our study, the enrolled patients had already received a full dose of steroids and/or immunosuppressants, so the immunosuppressive mechanism could not explain the quick remission of the proteinuria; thus, nonimmunological mechanisms may be involved. One proposed mechanism is that the intraglomerular hemodynamic changes induced by tacrolimus could reduce protein permeability.[13,15] Zhang et al[6] proposed that tacrolimus could cause the recovery of synaptopodin by inhibiting the expression of calcineurin, resulting in cytoskeletal stabilization in podocytes. This might be another mechanism by which tacrolimus induces proteinuria remission.

The predictive factors for the probability of remission in refractory IgAN are unclear. Caro et al[16] reported that proteinuria degree at baseline was the only factor for remission in idiopathic membranous nephropathy, that is, the lower the baseline proteinuria, the higher the probability of remission. Here, we found that patients with lower proteinuria and better renal function at baseline might be more likely to achieve complete remission, while crescent formation might predict a worse prognosis.

The main side effects of tacrolimus include gastrointestinal effects, nephrotoxicity, and metabolic complications.[6,7,10,11] However, the number of side effects was low in our study. Three patients showed a loss of eGFR $> 15\,mL/min{\cdot}1.73\,m^2$ from baseline, and 2 of them had severe renal function injury before tacrolimus treatment. However, the possible reason for the eGFR loss in our patients is unclear because we lack histological evidence to verify the existence of drug-associated nephrotoxicity. In addition, 3 cases of upper respiratory infection and 2 of urinary tract infection were observed during the study, and all recovered after receiving appropriate treatment. Also, blood glucose level, TC, TG, UA, and blood pressure was stable at the 12-month follow-up.

This study is limited by its retrospective observational design, small sample size, and short duration. The doses of steroids or tacrolimus were not standardized across the patient cohort; rather, they were adjusted according to the patients' clinical status. In addition, we could not fully confirm that the use of concomitant steroids during the tacrolimus treatment period had no effect on the subsequent results, although these patients showed steroid resistance. The confounding factors mentioned above might obscure relationships between therapy and outcome. Moreover, the patients enrolled in this study were primarily female (26 of 34 patients), relatively young (34.7 ± 8.3 years), and most had normal renal function, implying a relatively good prognosis in these refractory IgAN patients. The effect of tacrolimus on patients with a reduced eGFR requires investigation in future studies.

In conclusion, this retrospective study showed that tacrolimus could induce rapid proteinuria remission in refractory IgAN patients. Patients with better renal function and lower baseline proteinuria were more likely to achieve complete remission, while crescent formation was associated with worse prognosis.

Author contributions

Data curation: Tingyang Hu.
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Supervision: Yongman Lv.
Writing – original draft: Tingyang Hu.
Writing – review & editing: Yongman Lv.

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