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ORIGINAL ARTICLE

Long-term outcomes of initial therapy for idiopathic membranous nephropathy

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Abstract

Background The objective of this study is to determine whether initial steroid therapy is actually effective for the treatment of iMN, and we examined a 40% reduction in estimated glomerular filtration rate (eGFR) and remission rates.

Methods This was a retrospective study between 1993 and 2013. First, we divided patients with iMN having a urinary protein level of ≥1 g/gCre into two groups: those who had received steroid therapy (Group S_1; $n = 52$) within 6 months of diagnosis and those who had received supportive therapy (Group H_1; $n = 31$). Second, we compared 20 cases using propensity score matching (Group S_2, Group H_2). Third, we compared patients with a urinary protein level of 1–3.5 g/gCre (Group S_3, $n = 18$; Group H_3, $n = 19$) and those with a urinary protein level ≥3.5 g/gCre (Group S_4, $n = 34$; Group H_4, $n = 12$). The primary endpoint was a 40% reduction in eGFR, and the secondary endpoint was the achievement of complete remission (CR).

Results In Group S_1 and Group H_1, a 40% reduction in the eGFR was observed at the end of 5 years in 18 and 17% of the patients, respectively ($P = 0.93$); at the end of 10 years, these rates had increased to 43% and 50%, respectively ($P = 0.88$). The CR rates at the end of 5 years were 58% and 32%, respectively ($P = 0.02$), while the rates at 10 years were 65 and 39%, respectively ($P = 0.02$). No difference in renal outcomes was observed between Group S_1 and Group H_1. No significant differences were observed between Group S_2 and Group H_2, between Group S_3 and Group H_3, or between Group S_4 and Group H_4.

Conclusion Initial steroid therapy is not superior to supportive care within the first 6 months after diagnosis in terms of a 40% reduction in eGFR.

Keywords Idiopathic membranous nephropathy · Steroid therapy · Supportive therapy · Reduction in eGFR

Introduction

Idiopathic membranous nephropathy (iMN) is the most common cause of primary nephrotic syndrome, especially among the elderly [1]. About 30% of patients develop end-stage renal disease (ESRD) within 20 years [2, 3]. There is no standard treatment for iMN. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that the initial therapy should be supportive and that treatment should only be started once the urinary protein excretion level reaches ≥4 g/gCre. The guidelines also recommend that supportive therapy be performed for at least the first 6 months after diagnosis [4]. The KDIGO guidelines recommend that the first-line immunosuppressive therapy should be cytotoxic drugs, such as cyclophosphamide, plus glucocorticoids, or a calcineurin inhibitor [5, 6]. Recent reports have indicated that rituximab and tacrolimus are effective for achieving a complete remission of proteinuria [7–9]. iMN may spontaneously recur in approximately 30% of patients. In Japan, corticosteroids are administered after diagnosis [10–12], and steroid monotherapy has been reported to induce remission [2, 13]. However, since iMN is common among the elderly, measures to avoid complications arising from

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immunosuppression are needed, since steroid therapy can cause adverse effects, such as infection, osteoporosis, and impaired glucose tolerance.

In the present study, we compared patients with and those without initial steroid therapy during the first 6 months after diagnosis, focusing on a 40% reduction of eGFR and rates of complete remission (CR).

Materials and methods

Patients

Data were extracted from our hospital records for patients over 16 years of age who had undergone a renal biopsy between 1993 and 2013. A total of 1970 renal biopsies were performed during this period, and 151 (7.7%) cases were diagnosed as having membranous nephropathy. Seventeen cases that had undergone a re-biopsy and four cases that were diagnosed as having some other form of glomerulonephritis or secondary membranous nephropathy were excluded. Among the remaining 134 cases, a total of 114 patients were registered as having iMN, and 97 of these patients had a urinary protein level of $\geq$1 g/gCre at the time of their renal biopsy. In addition, cases that received other immunosuppressive drugs (such as cytotoxic drugs or calcineurin inhibitors), within 6 months of biopsy, were excluded. Finally, 83 patients (Group S_1, Group H_1) were included in the analysis.

Study design

The patients were divided into those who received initial steroid therapy within 6 months after diagnosis (Group S_1, $n = 52$) and those who received supportive therapy (Group H_1, $n = 31$), and the renal outcomes and the rates of remission were retrospectively examined using clinical and pathological data.

In addition, propensity score matching was used to compare two groups of 20 patients each (Group S_2, Group H_2). Furthermore, we divided 37 cases with a urinary protein level of 1–3.5 g/gCre (Group S_3, $n = 18$; Group H_3, $n = 19$) and 46 cases with a urinary protein level of more than 3.5 g/gCre (Group S_4, $n = 34$; Group H_4, $n = 12$) into two groups according to their and compared their outcomes.

Treatment

In the steroid therapy group, the initial dose of prednisone was 0.8 mg/kg/day, and the doctors in charge of the patient decided when to begin dose reduction.

For cases with a urinary protein level higher than 3.5 g/gCre, or uncontrollable edema, we suggested therapy. The decision to initiate treatment was made by the doctors in charge of the patient decided whether to continue receiving treatment at some point during the first 6 months of treatment.

For the patients in Group S_1, whose urinary protein level had increased at 6 months after biopsy and who had not experienced any adverse effects from the initial steroid therapy, the steroid dose was increased for some patients; for other patients who had an increased risk of diabetes and infection, the attending doctors prescribed the use of other immunosuppressive drugs. Supportive therapy included the administration of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) and antiplatelet and anticholesterol agents. The treatment used for Group H_1 patients after 6 months was selected based on the patients' background, such as the presence of diabetes and their age. After 6 months, for patients with a urinary protein level over 3.5 g/gCre, we increased the dose of RASS inhibitors, and selected steroid therapy as the first-line treatment; however, two patients were treated with other immunosuppressants because of depression or their refusal to undergo steroid therapy.

Study endpoints

Proteinuria was used to determine the therapeutic outcome. According to the 2011 Guidelines for the Treatment of Nephrotic Syndrome [11], CR is regarded as a proteinuria level of <0.3 g/gCre.

The primary study endpoint was a 40% reduction in the estimated glomerular filtration rate (eGFR), and the secondary endpoint was the achievement of remission. The outcomes of both groups were examined at 5 and 10 years.

Statistical analyses

The statistical analyses were performed using the Chi-square test, the Pearson and Spearman correlation coefficients for analyses of parametric and nonparametric data, and the Kaplan–Meier method. Data were given as proportions, medians, and interquartile ranges. All the statistical analyses were performed using the JMP software package version Pro11.2, and P values of less than 0.05 were considered to indicate a significant linear or nonlinear trend. A Cox regression analysis was used to determine the incidences and hazard ratios (HR) of a 40% reduction in the eGFR and a CR.

To account for differences between patients with and those without steroid therapy, a one-to-one propensity matching analysis was also performed. The initial variables included were proteinuria, serum total protein, albumin,

total cholesterol, and immunoglobulin levels. The propensity score was used as the sole criterion for matching pairs of patients. A matched pair was formed when a patient selected from Group S_1 had a propensity score that was nearest to that of a patient in Group H_1.

Results

The baseline characteristics of the 83 patients with a urinary protein level of ≥1 g/gCre are listed in Table 1. Proteinuria and the serum total protein, albumin, total cholesterol, and IgG levels showed significant differences between the two groups. The incidences of morbidities, such as hypertension and diabetes mellitus, did not differ significantly between the two groups. Histopathologically, the presence of global sclerosis and tubulointerstitial fibrosis and deposition of C3 and IgG4 did not differ significantly between the two groups; however, the incidences of focal segmental sclerosis (FGS) were 29 and 6%, respectively, and these values were significantly different ($P = 0.01$) (Tables 1, 2, 3, 4).

Fourteen patients (27%) in Group S_1 received immunosuppressive drugs (mostly cyclosporine) within 6 months of biopsy. Seven patients (23%) in Group H_1 received steroid therapy at some timepoint at least 6 months after the biopsy, and immunosuppressive drugs were added to the treatments of four patients (13%) in Group H_1. The rates of relapse in the two groups were different ($P = 0.001$). Two patients (3.9%) in Group S_1 developed ESRD, and three patients (5.8%) in Group S_1 died because of myocardial infarction, alcoholic liver dysfunction, or malignant lymphoma. One patient (3.2%) in Group H_1 died because of hepatocellular carcinoma. Six patients (12%) in Group S_1 developed diabetes mellitus, but none of the patients in Group H_1 developed diabetes (Tables 5, 6, 7, 8).

Figure 1 shows the Kaplan–Meier plots for the incidences of a 40% reduction in the eGFR and CR. A 40% reduction in the eGFR at the end of 5 years was observed in 18% of the patients in Group S_1 and 17% of the patients in Group H_1 ($P = 0.93$), while the incidences at 10 years were 43% for Group S_1 and 50% for Group H_1 ($P = 0.88$). A CR was observed at the end of 5 years in 58% of the patients in Group S_1 and 32% of the patients in Group H_1 ($P = 0.02$), and at the end of 10 years in 65% of the patients in Group S_1 and 39% of the patients in Group H_1 ($P = 0.02$) (Fig. 1a, b). Cox regression analyses for the incidence of a 40% reduction in the eGFR showed significant differences according to the presence of segmental sclerosis (HR 6.21; 95% confidence interval 1.36–30.12; $P = 0.02$) and diabetes mellitus (HR 4.61; 95% confidence interval 1.01–19.98; $P = 0.04$) (Table 9). However, the presence of steroid use and patient age (≥65 years), sex, eGFR (<45 mL/min/1.73 m^2), proteinuria (≥3.5 g/gCre), serum albumin level (<2.0 g/dL), hypertension, global sclerosis (<20%), and tubulointerstitial fibrosis were not selected as significant factors.

Using propensity score matching for patients with a urinary protein level of ≥1 g/gCre (Table 2), we compared 20 cases in each treatment group which were performed using significant differences of the background, serum total protein, albumin, total cholesterol, and IgG. For Group S_2 and Group H_2, the median ages differed between the two groups (Table 2). No other differences in outcomes were observed between the two groups (Table 6). When compared using the Kaplan–Meier method, a 40% reduction in the eGFR was observed at the end of 5 years in 13 and 18% of the patients, respectively ($P = 0.74$); at the end of 10 years, these rates had increased to 63 and 56%, respectively ($P = 0.56$). The CR rates at the end of 5 years were 55 and 25%, respectively ($P = 0.05$), while the rates at 10 years were 65 and 30%, respectively ($P = 0.03$) (Fig. 1c, d).

Next, we divided the patients with a urinary protein level of 1.0–3.5 g/gCre into two groups: Group S_3 ($n = 18$) and Group H_3 ($n = 19$). The serum albumin levels and total cholesterol, and immunoglobulin levels differed between the two groups (Table 7). The rate of relapse for the two groups was also different ($P = 0.03$) (Table 7). Using the Kaplan–Meier method, a 40% reduction in the eGFR was observed at the end of 5 years in 15 and 9% of the patients, respectively ($P = 0.64$); at the end of 10 years, these rates had increased to 29 and 43%, respectively ($P = 0.57$). The CR rates at the end of 5 years were 61 and 32%, respectively ($P = 0.07$), while the rates at 10 years were 72 and 37%, respectively ($P = 0.03$) (Fig. 1e, f).

Finally, 46 patients with massive proteinuria (≥3.5 g/gCre) were analyzed (Table 8). Since the numbers of patients in Group S_4 ($n = 34$) and Group H_4 ($n = 12$) were relatively small, we could not perform propensity score matching. The median serum albumin levels were significantly different ($P = 0.04$) (Table 4). No differences in patient outcomes or the incidences of complications were observed between the two groups (Table 8). When compared using the Kaplan–Meier method, a 40% reduction in the eGFR was observed at the end of 5 years in 19 and 29% of the patients, respectively ($P = 0.59$); at the end of 10 years, these rates had increased to 50 and 60%, respectively ($P = 0.72$). The CR rates at the end of 5 years were 67 and 25%, respectively ($P = 0.04$), while the rates at 10 years were 50 and 25%, respectively ($P = 0.13$) (Fig. 1g, h).

Two patients (6%) in Group H_1, 1 patient (5%) in Group H_2, 2 patents (11%) in Group H_3, and no patient in Group H_4 experienced spontaneous remission at 6 months.

Among the cases in Group H_1 who did not receive steroid therapy at 6 months after diagnosis, 9 patients (29%) experienced spontaneous remission after a median

Table 1 Baseline characteristic (proteinuria ≥1 g/gCre)

Characteristics	Group S_1 ($N = 52$)	Group H_1 ($N = 31$)	P value
Age (year)	57.5 (17–81)	60 (36–77)	0.16
Sex (M/F)	28/24	17/14	0.93
Time since diagnosis (months)	7 (1–154)	6.5 (1–144)	0.30
Serum creatinine (mg/dL)	0.78 (0.36–3.87)	0.72 (0.43–3.3)	0.96
eGFR (mL/min/1.73 m^2)	74.4 (16.5–120.9)	75.7 (11.3–104.4)	0.75
Proteinuria (g/day)	4.22 (1.05–25)	2.46 (1.05–11)	0.02*
Hematuria (/HPF)	4 (0–100)	4 (0–80)	0.71
Serum TP (g/dL)	4.9 (4–6.8)	5.6 (3.7–6.8)	<0.009*
Serum Alb (g/dL)	2.5 (1.2–3.8)	2.9 (1.8–4.4)	<0.0002*
TG (mg/dL)	186 (70–762)	186 (57–572)	0.97
TC (mg/dL)	324.5 (167–672)	285 (190–484)	0.03*
IgG (mg/dL)	677.5 (254–1630)	882 (431–1470)	0.02*
SI index	0.2 (0.009–2.94)	0.17 (0.005–1.2)	0.80
SBP (mmHg)	131 (84–192)	132 (102–192)	0.73
MAP (mmHg)	93 (57–133)	102 (51–130)	0.34
HT	15 (28.9%)	13 (41.9%)	0.22
DM	6 (11.5%)	3 (9.7%)	0.79
Treatment with ACEI/ARB (%)	31 (59.6%)	22 (71.0%)	0.30
Antiplatetes	48 (92.3%)	26 (83.9%)	0.23
Anticholesterol	43 (82.7%)	28 (90.3%)	0.34
Global sclerosis (%)			
<20%	46	28	0.79
≥20%	6	3	
Segmental sclerosis	15 (29%)	2 (6%)	0.01*
Tubulointerstitial fibrosis			
0	13	4	0.35
1	29	22	
2	8	5	
3	2	0	
Deposition of C3	45 (92%)	30 (97%)	0.37
Deposition of IgG4	18 (95%)	15 (94%)	0.9
Ultrastructural stage			
I	1	0	0.62
I–II	5	2	
II	4	4	
II–III	5	1	
III	5	2	
III–IV	2	1	
IV	0	1	

eGFR estimated glomerular filtration rate, *TP* total protein, *Alb* albumin, *TG* triglyceride, *TC* total cholesterol, *SI* selectivity index, *SBP* systolic blood pressure, *MAP* mean blood pressure, *HT* hypertension, *DM* diabetes mellitus, *ACEI* Angiotensin-converting enzyme Inhibitor, *ARB* Angiotensin II receptor blocker, *IgG4* IgG4 from IgG subclass staining

* $P < 0.05$

period of 24 months (6–120 months); 4 patients (40%) in Group H_4 experienced spontaneous remission after a median period of 42 months (24–120 months).

Relapses of proteinuria of ≥1 g/gCre occurred in 18 cases (34.6%) in Group S_1 after a median period of 66 months (17–144 months) and in 1 case (3.2%) in Group H_1 after a median period of 108 months ($P = 0.001$) (Table 5). Relapses occurred in 5 cases (25%) in Group S_2 and in 1 case (5%) in Group H_2 ($P = 0.08$) (Table 6).

Table 2 Baseline characteristic, after matching in proteinuria ≥1 g/gCre

Characteristics	Group S_2 ($N = 20$)	Group H_2 ($N = 20$)	P value
Age (year)	58 (35–67)	64 (48–77)	0.014*
Sex (M/F)	10/10	11/9	0.75
Time since diagnosis (months)	12 (1–154)	5 (1–144)	0.83
Serum creatinine (mg/dL)	0.78 (0.48–1.2)	0.7 (0.46–3.3)	0.63
eGFR (mL/min/1.73 m^2)	72.0 (44–130.4)	73.5 (11.3–111.8)	0.92
Proteinuria (g/day)	2.79 (1.05–9.71)	3.25 (1.13–11)	0.48
Serum TP (g/dL)	5.4 (4.1–6.8)	5.5 (3.7–6.8)	0.92
Serum Alb (g/dL)	2.9 (2–3.8)	2.8 (1.8–4.1)	0.78
TC (mg/dL)	304 (216–418)	292 (190–484)	0.74
IgG (mg/dL)	686 (401–1410)	823 (452–1470)	0.75
SBP (mmHg)	130 (101–186)	134 (111–192)	0.23
HT (*n*)	8 (40%)	11 (55%)	0.34
DM (*n*)	3 (15%)	3 (15%)	1.0

eGFR estimated glomerular filtration rate, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *SBP* systolic blood pressure, *HT* hypertension, *DM* diabetes mellitus

* $P < 0.05$

Table 3 Baseline characteristic (proteinuria 1–3.5 g/gCre)

Characteristics	Group S_3 ($N = 18$)	Group H_3 ($N = 19$)	P value
Age (year)	57.5 (17–60)	63 (36–77)	0.13
Sex (M/F)	6/12	10/9	0.23
Time since diagnosis (months)	10 (2–154)	12 (1–144)	0.43
Serum creatinine (mg/dL)	0.65 (0.36–1.01)	0.66 (0.43–0.86)	0.56
eGFR (mL/min/1.73 m^2)	76.8 (49–192.0)	79.2 (65.7–111.5)	0.68
Proteinuria (g/day)	2.2 (1.1–3.3)	1.9 (1.1–3.0)	0.24
Serum TP (g/dL)	5.6 (4.2–6.8)	5.6 (4.6–6.8)	0.17
Serum Alb (g/dL)	3.0 (1.9–2.8)	3.2 (2.6–4.4)	0.04*
TC (mg/dL)	313.5 (216–564)	249 (190–407)	0.008*
IgG (mg/dL)	690 (254–1410)	928 (528–1470)	0.03*
SBP (mmHg)	126 (84–164)	131 (102–154)	0.27
HT (*n*)	4 (22%)	3 (17%)	0.52
DM (*n*)	3 (17%)	2 (11%)	0.59

eGFR estimated glomerular filtration rate, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *SBP* systolic blood pressure, *HT* hypertension, *DM* diabetes mellitus

* $P < 0.05$

After 6 months, five cases (42%) in Group H_4 continued to exhibit nephrotic syndrome. After two patients in Group H_4 began taking steroids (one at 13 months, the other at 108 months), one attained a CR at 21 months, and the other attained a CR at 132 months (Table 8).

We performed a Cox regression analysis to examine relapses in proteinuria of over 1 g/gCre (Table 10). Using a multivariate analysis, differences in steroid therapy (HR 9.40; 95% confidence interval 1.58–185.63; $P = 0.01$) and a proteinuria level of over 3.5 g/gCre (HR 9.11; 95% confidence interval 1.74–65.73; $P = 0.008$) were observed.

Discussion

We examined the long-term outcome of iMN according to the initial therapy in patients over 16 years. We found that corticosteroid monotherapy within 6 months showed a tendency to induce early remission but did not have a significant impact on a 40% reduction in eGFR, compared with supportive therapy.

In Japan, supportive therapy is recommended and there is no standard treatment for iMN patients with a proteinuria level of less than 3.5 g/gCre [11, 12]. However, some moderate-quality evidence recommends that corticosteroid

Table 4 Baseline characteristic (proteinuria ≥3.5 g/gCre)

Characteristics	Group S_4 ($N = 34$)	Group H_4 ($N = 12$)	P value
Age (year)	57.5 (24–81)	54.5 (48–74)	0.73
Sex (M/F)	22/12	7/5	0.69
Time since diagnosis (months)	5 (1–72)	5 (1–22)	0.33
Serum creatinine (mg/dL)	0.83 (0.38–3.87)	0.84 (0.46–3.3)	0.44
eGFR (mL/min/1.73 m^2)	70.5 (16.5–130.4)	59.8 (11.3–111.8)	0.41
Proteinuria (g/day)	6.0 (3.5–25)	5.37 (3.5–11)	0.31
Serum TP (g/dL)	4.8 (4–6.2)	5.1 (3.7–6.5)	0.26
Serum Alb (g/dL)	2.3 (1.2–3.2)	2.6 (1.8–3.4)	0.04*
TC (mg/dL)	338.5 (167–672)	339.5 (190–484)	0.94
IgG (mg/dL)	641 (273–1630)	633.5 (431–1293)	0.90
SBP (mmHg)	134 (92–192)	135 (116–192)	0.62
HT (*n*)	11 (32%)	7 (58%)	0.11
DM (*n*)	3 (8.8%)	1 (8.3%)	0.96

eGFR estimated glomerular filtration rate, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *SBP* systolic blood pressure, *HT* hypertension, *DM* diabetes mellitus

* $P < 0.05$

Table 5 After 6 months from initial therapy (proteinuria ≥1 g/gCre)

	Group S_1 ($N = 52$)	Group H_1 ($N = 31$)	P value
Observation period (months)	88 (0–240)	48 (0–228)	0.04*
Treatment with PSL (*n*)		7 (22.6%)	
Immunosuppression drugs (*n*)	14 (27%)	4 (13%)	
	CyA 7, MZ 4, MMF 3	CyA 3	
	IVCY 2, RTX 1	IVCY 1	
Prognosis			
ESRD, dialysis (*n*)	2 (3.9%)	0	0.27
Death (*n*)	3 (5.8%)	1 (3.2%)	0.60
Relapse (*n*)	18 (34.6%)	1 (3.2%)	0.001*
Relapse (median) (months)	66 (17–144)	108	
Complication			
HT (*n*)	1 (1.9%)	0	0.44
DM (*n*)	6 (11.5%)	0	0.05*
DVT (*n*)	3 (5.8%)	0	0.17
Malignant tumor (*n*)	5 (9.6%)	2 (6.5%)	0.62
Infection (admission) (*n*)	5 (9.6%)	1 (3.2%)	0.28
CVD (*n*)	3 (5.8%)	2 (6.5%)	0.71
Mental disorder (*n*)	1 (1.2%)	0	0.44

PSL prednisolone, *CyA* cyclosporine, *MZ* mizoribine, *MMF* mycophenolate mofetil, *IVCY* intravenous cyclophosphamide, *RTX* rituximab, *ESRD* end-stage renal disease, *HT* hypertension, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *CVD* cardiovascular disease

* $P < 0.05$

monotherapy not be used to induce remission or to delay the onset of progressive renal failure and the kidney disease.

Global Outcomes (KDIGO) guidelines recommend that patients with iMN only receive supportive care for at least the first 6 months after diagnosis [4]. In this study, we used corticosteroid therapy, but studies in other countries have shown that the effect of corticosteroids did not differ from that of a placebo [13–15]. If cases likely to experience spontaneous remission could be identified before therapy, we could decrease the rates of excessive treatments and complications [16]. Cattran et al. [14] reported a randomized control trial comparing 6 months of prednisone treatment with a control group. Eighty-one patients

Table 6 After 6 months from initial therapy, after matching in proteinuria ≥1 g/gCre

Characteristics	Group S_2 ($N = 20$)	Group H_2 ($N = 20$)	P value
Observation period (months)	114 (12–240)	67 (0–228)	0.17
Prognosis			
ESRD, dialysis (*n*)	2 (10%)	0	0.15
Death (*n*)	1 (5%)	1 (5%)	1
Relapse (*n*)	5 (25%)	1 (5%)	0.08
Relapse (median) (months)	96 (17–120)	108	
Complication			
HT (*n*)	0	0	
DM (*n*)	2 (10%)	0	0.15
DVT (*n*)	1 (5%)	0	0.31
malignant tumor (*n*)	1 (5%)	2 (10%)	0.55
Infection (admission) (*n*)	1 (5%)	1 (5%)	1
CVD (*n*)	0	1 (5%)	0.31
mental disorder (*n*)	1 (5%)	0	0.31

ESRD end-stage renal disease, *HT* hypertension, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *CVD* cardiovascular disease

* $P < 0.05$

Table 7 After 6 months from initial therapy (proteinuria 1–3.5 g/gCre)

Characteristics	Group S_3 ($N = 18$)	Group H_3 ($N = 19$)	P value
Observation period (months)	96 (0–240)	48 (0–240)	0.6
Prognosis			
ESRD, dialysis (*n*)	0	0	
Death (*n*)	1 (5.6%)	0	0.30
Relapse (*n*)	4 (22%)	0	0.03*
Relapse (months)	99 (84–144)		
Complication (*n*)			
Hypertension (*n*)	1 (5.6%)	0	0.30
DM (*n*)	1 (5.6%)	0	0.30
DVT (*n*)	0	0	
malignant tumor (*n*)	0	1 (5.3%)	0.32
Infection (admission) (*n*)	0	0	
CVD (*n*)	1 (5.6%)	1 (5.3%)	0.97
mental disorder (*n*)	1 (5.6%)	0	0.30

ESRD end-stage renal disease, *HT* hypertension, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *CVD* cardiovascular disease

* $P < 0.05$

received prednisone (45 mg/m^2) on alternate days for 6 months. No differences were observed between the two groups. This previous study differed from ours in that the median ages were 46 years for the PSL group ($n = 81$) and 45 years for the control group ($n = 77$), which were younger than our cases. The period of therapy was also shorter.

Our study suggested that the presence of segmental sclerosis and the presence of diabetes mellitus were risk factors for renal outcome regardless of steroid therapy. Wakai et al. reported that focal glomerulosclerosis (FGS) in iMN was associated with a poorer outcome than MN without FGS among patients with MN, and patients of MN with FGS had a higher urinary protein level [17].

Concerning relapses, steroid therapy within the first 6 months after diagnosis did not appear to be correlated with relapse, since the total follow-up duration for patients who had initially received steroids was longer than that for those who had received supportive care only. Caro et al. reported that the amount of proteinuria and the withdrawal of drugs were correlated with remission [9].

What we most want to know is how to predict the natural course of remission. Beck et al. [18] reported a correlation between phospholipase A_2 antibodies (PLA_2R-Ab)

Table 8 After 6 months from initial therapy (proteinuria ≥3.5 g/gCre)

Characteristics	Group S_4 ($N = 34$)	Group H_4 ($N = 12$)	P value
Observation period (months)	88 (0–240)	66 (0–228)	0.54
Prognosis			
ESRD, dialysis (*n*)	2 (5.9%)	0	0.39
Death (*n*)	3 (8.8%)	0	0.29
Relapse (*n*)	14 (41.2%)	3 (25%)	0.32
Relapse (months)	48 (24–144)	108 (60–120)	0.09
Complication (*n*)			
Hypertension (*n*)	1 (2.9%)	0	0.55
DM (*n*)	5 (14.7%)	0	0.16
DVT (*n*)	3 (8.8%)	0	0.29
malignant tumor (*n*)	5 (14.7%)	1 (8.3%)	0.57
Infection (admission) (*n*)	5 (14.7%)	1 (8.3%)	0.57
CVD (*n*)	2 (5.9%)	1 (8.3%)	0.77
mental disorder (*n*)	0	0	

ESRD end-stage renal disease, *HT* hypertension, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *CVD* cardiovascular disease

* $P < 0.05$

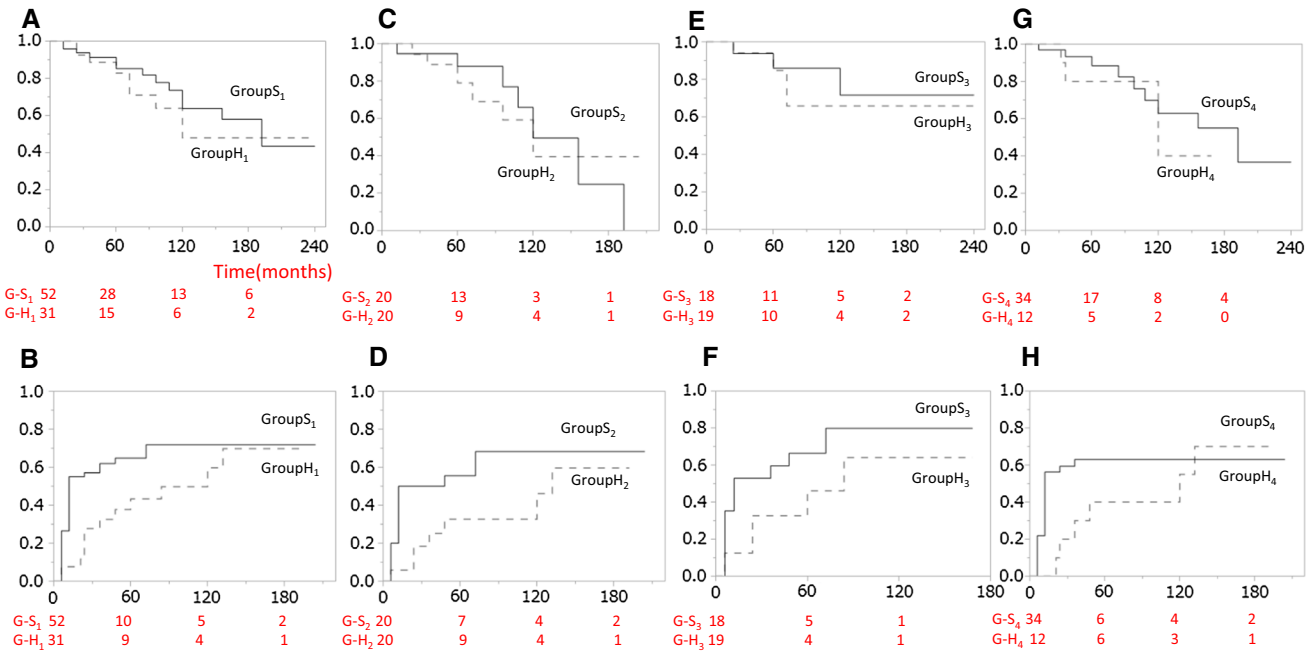

Fig. 1 Incidences of complete remission (CR) and a 40% reduction in the estimated glomerular filtration rate (eGFR) in patients receiving steroid therapy (Group S) and patients receiving supportive care (Group H). The Kaplan–Meier plots show the cumulative incidences of iMN. The *X-axis* represents the follow-up period (months), and the *Y-axis* represents the incidences of a 40% reduction in the eGFR or CR. **a** Comparison of a 40% reduction in the eGFR between Group S_1 and Group H_1 (proteinuria >1 g/gCre; difference not significant, log-rank test); **b** comparison of CR between Group S_1 and Group H_1 (proteinuria >1 g/gCre; $P = 0.02$, log-rank test). **c** Comparison of a 40% reduction in the eGFR between Group S_2 and Group H_2 (using propensity score matching; proteinuria >1 g/gCre; difference not significant, log-rank test). **d** Comparison of CR between Group S_2 and Group H_2 (using propensity score matching; proteinuria >1 g/gCre; $P = 0.03$, log-rank test); **e** comparison of a 40% reduction in the eGFR between Group S_3 and Group H_3 (proteinuria 1–3.5 g/gCre; difference not significant, log-rank test); **f** comparison of CR between Group S_3 and Group H_3 (proteinuria 1–3.5 g/gCre; $P = 0.03$ after 10 years, log-rank test). **g** Comparison of a 40% reduction in the eGFR between Group S_4 and Group H_4 (proteinuria >3.5 g/gCre; difference not significant, log-rank test); **h** comparison of CR between Group S_4 and Group H_4 (proteinuria > 3.5 g/gCre; $P = 0.02$ after 5 years, log-rank test)

Table 9 Cox proportional hazards model for incidences of 40% reduction in the estimated glomerular filtration rate (eGFR)

	Univariate analysis			Multivariate analysis		
	Hazard ratio	HR (95% CI)	*P* value	HR	HR (95% CI)	*P* value
Therapy (PSL)	0.77	0.33–1.87	0.55	0.41	0.13–1.29	0.13
Age (≥65 year)	0.92	0.36–2.18	0.85	1.10	0.35–3.30	0.86
Sex (male)	0.66.	0.27–1.45	0.31	1.45	0.49–4.99	0.51
eGFR (<45 mL/min/1.73 m^2)	1.21	0.40–5.19	0.75	1.12	0.20–5.03	0.89
Proteinuria (≥3.5 g/gCre)	1.89	0.15–4.96	0.15	1.18	0.36–4.27	0.79
Serum Alb (<2.0 g/dL)	1.46	0.23–5.07	0.63	2.45	0.29–13.12	0.37
HT (*n*)	1.78	0.75–4.12	0.19	1.22	0.41–3.58	0.72
DM (*n*)	2.15	0.62–5.80	0.20	4.61	1.01–19.98	0.048*
Sclerosis (>20%)	1.72	0.40–5.14	0.42	0.42	0.05–1.87	0.26
Segmental sclerosis (*n*)	2.39	0.90–5.78	0.08	6.21	1.36–30.12	0.02*
Tubulointerstitial fibrosis (moderate to severe) (*n*)	1.76	0.97–26.30	0.05	3.07	0.89–10.70	0.08

PSL prednisolone, *eGFR* estimated glomerular filtration rate, *Alb* albumin, *HT* hypertension, *DM* diabetes mellitus

* $P < 0.05$

Table 10 Cox proportional hazards model for incidences of relapse

	Univariate analysis			Multivariate analysis		
	Hazard ratio	HR (95% CI)	*P* value	HR	HR (95% CI)	*P* value
Therapy (PSL)	8.65	1.79–155.5	0.004*	9.40	1.58–185.63	0.01*
Age (>65 year)	0.82	0.26–2.15	0.70	0.72	0.35–3.30	0.61
Sex (male)	1.42.	0.56–3.52	0.45	2.59	0.71–9.43	0.15
eGFR (<45 mL/min/1.73 m^2)	1.67	0.47–4.61	0.39	0.77	0.16–3.38	0.74
Proteinuria (≥3.5 g/day)	2.88	1.04–10.14	0.04*	9.11	1.74–65.73	0.008*
Serum Alb (<2.0 g/dL)	1.44	0.33–4.34	0.58	0.51	0.08–2.60	0.43
HT (*n*)	0.77	0.25–2.02	0.61	1.10	0.29–3.86	0.88
DM (*n*)	0.78	0.12–2.73	0.73	2.32	0.31–12.92	0.38
Sclerosis (>20%)	0.53	0.08–1.86	0.35	0.38	0.05–1.67	0.22
FGS (*n*)	1.78	0.62–4.52	0.26	1.07	0.27–4.01	0.93
Tubulointerstitial fibrosis (moderate to severe) (*n*)	0.62	0.14–1.89	0.43	0.43	0.09–1.66	0.23

PSL prednisolone, *eGFR* estimated glomerular filtration rate, *Alb* albumin, *HT* hypertension, *DM* diabetes mellitus

* $P < 0.05$

and iMN for the first time. PLA_2R-Ab are positive in 60–80% of the general population and about 50% of the Japanese population [19, 20]. The PLA_2R-Ab level is associated with clinical activity [21–24]. In Japan, the rate of PLA_2R-Ab positivity is relatively low, so it would be difficult to use PLA_2R-Ab as a marker of iMN. Blood sampling for anti-PLA2R was not performed in the present study.

A major limitation of this study was the choice of treatment during the first 6 months, since we did not choose the primary treatment according to a precise protocol. Second, we chose patients with a proteinuria level of ≥1 g/gCre, because the number of patients with a level of ≥3.5 g/gCre was relatively small. Third, we could not measure the levels of PLA_2R-Ab and similar markers because of the difficulty associated with measuring these markers.

In conclusion, we believe that steroid therapy is not superior to supportive care within the first 6 months after diagnosis in terms of a 40% reduction in eGFR. Thus, we recommended the use of supportive therapy, in agreement with the KDIGO guidelines.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Ethical approval The present study was conducted with the approval of the Research Ethics Committee of the Tokyo Women's Medical University (Approval No.: 3513). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent for biopsy was obtained from all individual participants included in the study.

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