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ORIGINAL ARTICLE

Corticosteroid therapy in IgA nephropathy with minimal change-like lesions: a single-centre cohort study

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Keywords: efficiency, IgA nephropathy, minimal change lesion, prednisone, safety

ABSTRACT

Background. There is a lack of high-quality evidence that advocates the use of corticosteroids for IgA nephropathy (IgAN) with minimal change-like lesions (also called IgAN with minimal change disease, MCD-IgAN).

Methods. Twenty-seven biopsy-proven adult MCD-IgAN patients were enrolled. Daily single dose of 1 mg/kg (maximum 60 mg/day) prednisone was given until complete remission (CR), followed by gradually decreasing dosage. The clinical data were collected from baseline up to 12 weeks of treatment (Certification No. 2011NLY-006, Clinical trials gov ID. NCT01451710).

Results. The patient cohort consisted of 15 males and 12 females. The mean age of the patients was 29.2 ± 10.8 years (range 18–60 years) at the time when they were subject to renal biopsy. All patients had hypoalbuminaemia (23.7 ± 4.13 g/L) and heavy proteinuria (>3.5 g/24 h). Cumulative CR (proteinuria < 0.4 g/24 h) rates were 3.70, 48.1, 92.6 and 100% after 1, 2, 4 and 8 weeks of treatment, respectively. Two cases relapsed after CR, one at 6 weeks of treatment, likely due to

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failure to follow the corticosteroid withdrawal schedule, and the other one at 8 weeks of treatment accompanied with an upper respiratory infection. Infection, alanine aminotransferase elevation (>2-folds), fasting blood glucose (FBG) elevation (>6.2 mmol/L) and hypopotassaemia (<3.5 mmol/L) occurred in 2, 5, 2 and 5 cases, respectively, but were eliminated after treatment.

Conclusion. Corticosteroid therapy is likely effective and safe for MCD-IgAN patients.

INTRODUCTION

IgA nephropathy (IgAN) is the most common form of glomerulonephritis (GN) worldwide, accounting for 45.3% of all primary GN cases. Among patients with IgAN, 20–40% will reach end-stage renal disease in <20 years after renal biopsy [1]. The clinical manifestations of IgAN vary considerably, and include nephrotic syndrome (NS) in some patients. However, NS exists in only 5–9% of IgAN patients [1, 2]. A subgroup of the IgAN patients with NS were characterized by a sudden onset of typical NS (heavy proteinuria, hypoalbuminaemia, hyperlipidaemia and oedema), a lack or mild degree of microscopic haematuria or hypertension and a preservation of renal function. The light microscopic (LM) findings of renal biopsy were essentially normal, but electron microscopy (EM) identified diffuse foot process effacement. These IgAN patients with NS responded well to steroids. It has been suggested that this uncommon condition represents a variant of IgAN, known as IgAN with minimal change-like lesions or IgAN with minimal change disease (MCD-IgAN). Twenty years ago, Lai *et al.* first described this type of IgAN, and found that corticosteroids were effective for up to 80% of the patients [3]. Our retrospective analysis on 61 MCD-IgAN patients showed that corticosteroids resulted in a remission in 91.8% of the patients, but 76.8% of them relapsed [4]. In recent years, MCD-IgAN has received much more attention for its unique clinical and pathological features, including its sensitivity to corticosteroids [5 6]. KDIGO (Kidney Disease: Improving Global Outcomes) recommends corticosteroids for MCD-IgA patients just as for MCD patients, but the grade of the recommendation is 2B [7] because of a lack of high-quality evidence for the efficiency and safety of the therapy. Here, we designed a single-centre cohort study in order to prospectively evaluate the efficiency and safety of corticosteroids in MCD-IgAN patients.

MATERIALS AND METHODS

This study was carried out following the Declaration of Helsinki (IV Adaptation), and was approved by the Ethics Committee of Jingling Hospital (Certification No. 2011NLY-006, Clinical trials gov ID. NCT01451710). All patients had given their informed consent before treatment.

Patients

Inclusion criteria. (i) Subjects included should be 18 to 60 years old, male or female; (ii) biopsy findings should include IgA deposition predominantly or co-dominantly present in the mesangial region as shown by immunofluorescence microscopy (IM), minimal change like lesions as shown by LM, diffuse podocyte foot process effacement (>50% of the capillary surface area involved) and electron-dense material deposits in the mesangium as shown by EM and (iii) patients should be initially treated for typical NS with heavy proteinuria (>3.5 g/24 h) and hypoalbuminaemia (serum albumin < 30 g/L).

Exclusion criteria. Patients are excluded if they have one or more of the following conditions, (i) serum creatinine (Scr) >2.0 mg/dL, or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, (ii) red blood cell (RBC) number of urinary sediments >10^6/mL, (iii) rheumatoid arthritis, ankylosing spondylitis, Henoch–Schölein purpura, systemic lupus erythematosus, liver cirrhosis or other secondary IgAN, (iv) association with type 2 diabetes or obesity (body mass index, BMI > 28 kg/m^2), (v) alanine aminotransferase and/or aspartate aminotransferase more than two times of the normal value, and hepatitis B virus DNA and/or hepatitis C virus RNA > 10^3 copies/mL of serum, (vi) presence of deep vein thrombosis (including renal vein, lower extremity vein, inferior vena, etc.) and/or pulmonary artery thrombosis, and (vii) uncured peptic ulcer, myocardial infarction, heart failure, cerebral haemorrhage or other severe cardiac or cerebral vascular disease episode within 3 months prior to recruitment.

Treatment protocol

All patients were initially treated with prednisone in a daily dose of 1 mg/kg/day (maximum 60 mg/day) immediately after the diagnosis was proven by renal biopsy for 6 weeks or until 2 weeks after complete remission (CR). After that, the dosage was first reduced by 10 mg, followed by tapering 5 mg every 2 weeks down to 30 mg/day, and then 2.5 mg every 2 weeks down to 15 mg/every-other-day, in order to prevent relapse.

Combination therapy

(i) When hypertension occurred during the course of study, a calcium channel antagonist or β-adrenergic receptor blocker was used, and angiotensin-converting enzyme inhibitors or angiotensin receptor blocker was avoided; (ii) statins or other antilipemic agents were used when hyperlipoidaemia existed; (iii) low-molecular weight heparin, warfarin and/or rivaroxaban were used alone or in combination when needed; (iv) oral antidiabetic agents and/or insulin was used when hyperglycaemia occurred and (v) Other immunosuppressive drugs, such as cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, methylprednisolone or Tripterygium wilfordii, were avoided.

Protocol study

Data collection. All eligible patients were given corticosteroid, and were studied for 12 weeks, during which the patients were examined at baseline and the 1st, 2nd, 4th, 8th and 12th

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week. The rates of remission, the time to reach remission and the safety of the therapy were determined.

General information collection. Age and gender of the patients, and the time from the onset of NS to renal biopsy, etc. were recorded.

Renal pathology

All kidney samples were examined by routine LM, IM and EM. Renal pathology data included the information about global or segmental sclerosis, crescentic and tubulointerstitial lesions. IgG, IgM, IgA, C3, C4, C1q and fibrin-related antigens were scored using a semi-quantitative scale from 0 to 4+ by IM. The tubulointerstitial lesions were semi-quantitatively quantified into three grades: mild (<25%), moderate (25–50%) and severe (>50%).

Laboratory data

Blood. Blood samples were tested for levels of albumin, nitrogen, Scr, alanine aminotransferase, aspartate aminotransferase, FBS, postprandial blood glucose, cholesterol, triglycerides and electrolytes.

Urine. Urine samples were tested for RBCs in urinary sediments. The 24-h urinary protein excretion (UPE) was measured twice by the Biuret method (normal value < 0.4 g/24 h) at baseline and the 1st, 2nd, 4th, 8th and 12th week, and the mean UPE was used. The patients were on normal diet and free of diuretics and albumin treatments 3 days before urine collection.

Side effects and complications

Side effects and complications related to drugs or the disease itself were recorded. Elevation of alanine aminotransferase was determined when its level was above twice the normal value (>100 U/L); FBS elevation was defined by an FBS level >6.2 mmol/L, and hypopotassaemia by a serum potassium level of <3.5 mmol/L.

Definitions of efficiency

(i) CR was defined as the absence of proteinuria (24-h UPE < 0.4 g/24 h), serum albumin >35 g/L and Scr < 1.24 mg/dL; (ii) partial remission (PR) was defined as a 24-h UPE ≤ 3.5 g/24 h and a decline of >50% of the baseline value with an Scr elevation of <15% of the baseline value; (iii) no response was defined as a 24-h UPE >3.5 g/24h, or a decline < 50% of baseline value or increase, and/or an Scr level >50% of the baseline value and (iv) Relapse was defined as the recurrence of heavy proteinuria and hypoalbuminaemia after CR.

Safety endpoints

(i) Doubling of Scr, or eGRF declined >25% of the baseline; (ii) new onset of diabetes mellitus; (iii) new onset of peptic ulcer; (iv) new onset of thromboembolism; (v) severe water, electrolyte or acid–base disorders, which must be treated with blood purification and (vi) elevated alanine aminotransferase level that was above twice the normal value (>100 U/L) and was not reduced by treatment for 2 weeks.

Criteria for withdrawal

Patients were withdrawn from the study if they (i) reached the end of the study, (ii) had a new onset of acute renal failure or doubling of Scr, which were not eliminated in 2 weeks after the stimulating factors had been removed, (iii) suffered side effects or complications related to the treatment and were not suitable for further treatment, (iv) died due to any causes and (v) requested withdrawal from the study.

Statistical analyses

Descriptive statistics were used for general clinical and histopathological data analyses. Quantitative variables with normal distributions were expressed as mean ± SD. Qualitative variables were expressed as percentages. The data collected before and after treatment were compared by a self-control *t*-test for difference. The SPSS software (version 13.0; SPSS Inc, Chicago, IL) was used for all statistical analyses. Statistical significance was determined as $P < 0.05$.

RESULTS

Patient enrolment

The first patient was enrolled on 11 March 2011. Until February 2012, 45 MCD-IgAN patients were diagnosed in Jinling Hospital. Among them, there were six cases who failed to receive scheduled corticosteroid doses at the beginning, three cases positive for an HBV marker, and two cases each of ANA positivity, 24-h urine mercury increase, abnormal glucose metabolism or failure of follow up. In addition, there was one case with BMI over 28 kg/m^2. In total, 27 cases were enrolled and completed in this study.

General conditions

Among the 27 patients, 15 were male and 12 were female, and their mean age was 29.2 ± 10.8 years. Most of the patients were younger than 40 years (74.1%), but six were 40–50 years old (22.2%), and one was older than 50 (3.70%) years. The mean time from onset to renal biopsy was 1.15 ± 0.848 (0.25–6) months. All patients presented with typical NS, including oedema, heavy proteinuria, hypoalbuminaemia and hyperlipidaemia. Blood analysis showed that all patients had a hypoalbuminaemia (<30.0 g/L) and hypercholesterolemia (>6 mmol/L), 55.6% of the patients had hypertriglyceridaemia (>2.2 mmol/L) and no patients had an elevated Scr. Urine analysis showed that all patients had heavy proteinuria. The incidence of trace microscopic haematuria (RBCs in the urinary sediment <10^6/mL) was 37.0% (Table 1).

LM revealed global glomerulosclerosis in 25.9% of the patients with a mean percentage of 4.50 ± 1.72% (3.03–6.35%). The IM demonstrated a diffuse, granular deposition of IgA in the mesangium. IgG, IgM, C3 and C1q depositions in the glomeruli were observed in 11.1, 18.5, 51.9 and 7.4% of the patients, respectively. C4 deposition was not found in any of these patients. Twenty-one cases (77.8%) had mild but not moderate or severe tubulointerstitial lesions. EM revealed diffuse podocyte foot process effacement and electron-dense deposits in the mesangium of all patients.

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Table 1. Main laboratory findings at renal biopsy			
Parameter		n	$\bar{x} \pm S$
Blood	Hypoalbuminaemia (<30.0 g/L)	27	23. 7 ± 4.13
	Normal serum creatinine (mg/dL)	27	0. 820 ± 0.241
	Hypercholesterolaemia (>6 mmol/L)	27	9.64 ± 1.87
	Hypertriglyceridaemia (>2.2 mmol/L)	15	2. 94 ± 1.59
Urine	Heavyproteinuria(>3.5 g/24 h)	27	8.05 ± 3.65
	RBCs of urinary sediments (>10^4/mL and <10^6/mL)	10	31.9 ± 35.2

In addition to corticosteroids, 11 patients (40.7%) received low-molecular weight heparin therapy and 5 (18.5%) received statin therapy temporarily.

Efficiency

After the treatment, oedema disappeared in all patients, and they had an increased serum albumin level, alleviated proteinuria and a lowered serum cholesterol level (Figure 1). Serum albumin, cholesterol and proteinuria at each time point after treatment were significantly different from those before treatment. All patients achieved CR within 8 weeks of the therapy. Both the number of RBCs in the urinary sediment and the number of patients with microhaematuria decreased during the treatment, but these were not significantly different from those before treatment (Table 2).

Safety endpoints

During the whole study, no patient reached the safety endpoints.

Relapse and side effect

Two cases relapsed during the study, one at 6 weeks due to failure to follow the corticosteroid-tapering schedule, and the other one at 8 weeks due to upper respiratory infection. Both of them achieved CR again after regaining corticosteroids (1 mg/kg/day). Infection, alanine aminotransferase elevation, FBS elevation and hypopotassaemia occurred in 2, 5, 2 and 5 cases, respectively. Among them, one case with severe pulmonary infection recovered after antibiotics treatment (moxifloxacin, cefoperazone/sulbactam), continuous venovenous haemofiltration and bi-level positive airway pressure ventilation (BioPAP). This patient received prednisone at 10 mg/day during the period of infection and the scheduled doses were restored thereafter. No recurrence of proteinuria occurred. The rest of these patients also recovered after corticosteroid withdrawal and supportive therapies (Table 3).

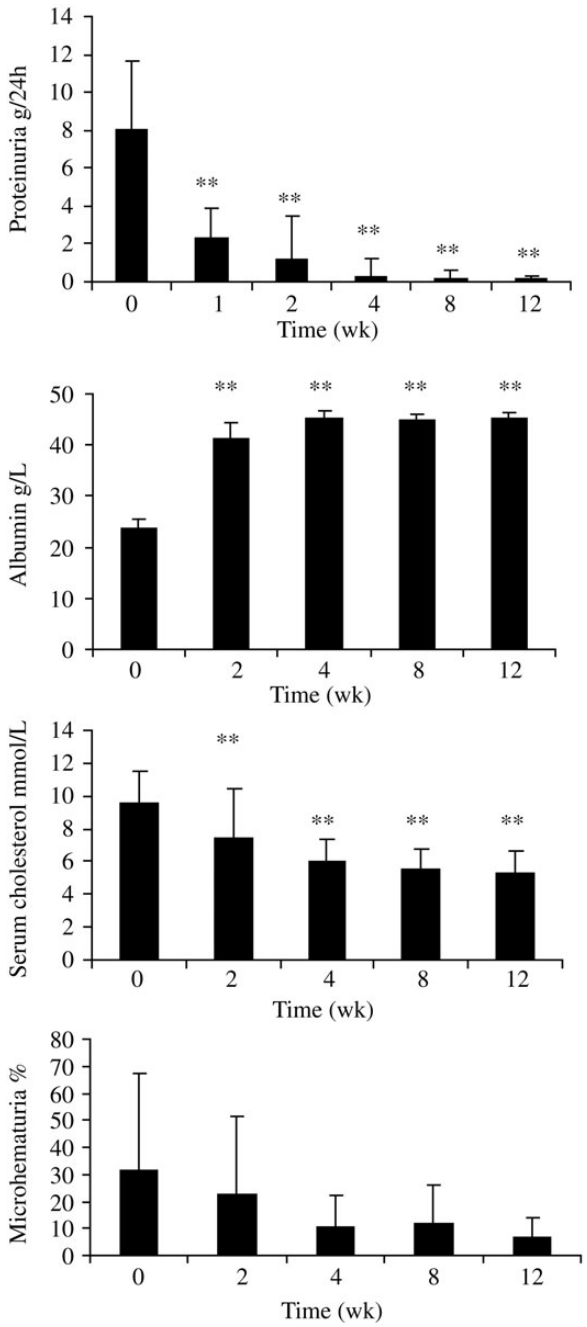

FIGURE 1. The changes of main laboratory data after treatment compared with 0 week, $^{**}P < 0.01$.

DISCUSSION

Many studies have demonstrated that proteinuria is the most important predictor of renal failure in IgAN [8]. NS is uncommon, occurring in only 5–10.2% of the patients with IgAN [2, 9, 10]. The patients of IgAN with NS have heterogeneous

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Table 2. Main laboratory findings after treatment and the time to achieve CR

Time (week)	Proteinuria			Microhaematuria		Serum albumin (g/L)	Serum cholesterol (mmol/L)
	(g/24 h)	Number of CR/ cumulative	CR rates (%)/cumulative	RBC of urinary sediments (10^4/mL)	*n* (%)		
0	8.05 ± 3. 65			31.9 ± 35.2	10 (37.0)	23.7 ± 4.13	9.64 ± 1.87
1	2.30 ± 1.55**	1	3.7	ND	ND	ND	ND
2	1.21 ± 2.26**	12/13	44.4/48.1	22.6 ± 28.7	9 (33.3)	41.5 ± 6.56**	7.49 ± 2.98**
4	0.279 ± 0.960**	12/25	44.4/92.6	10.9 ± 11.1	8 (29.6)	44.9 ± 3.42**	6.09 ± 1.29**
8	0.226 ± 0.389**	2/27	7.41/100	12.0 ± 13.9	3 (11.1)	45.2 ± 1.08**	5.59 ± 1.12**
12	0.208 ± 0.098**	0/100	0/100	7.20 ± 6.82	5 (18.5)	45.4 ± 3.68**	5.42 ± 1.28**

Note: A—albumin, Ch—cholesterol, compared with 0 week, $^{**}P < 0.01$. ND—not detected.

Table 3. Side effects

Type	*N*	%	Notes and responses to management
Infection	2	7.41	One suffered mild upper respiratory infection. The other had a severe lung infection and recovered by antibiotics and non-invasive positive pressure ventilation-BioPAP.
ALT elevated	5	18.5	The mean level was 150 ± 49.1 (105–207) U/L, and decreased to normal after supporting treatment and corticosteroid withdrawal.
FBS elevation	2	7.41	The levels were 6.61 and 8.52 mmol/L, respectively, and decreased to normal after corticosteroid withdrawal.
Hypopotassaemia	5	18.5	The mean level was 3.24 ± 0.168 (2.96–3.39) mmol/L, and increased to normal after taking food rich in potassium.

responses to corticosteroids with some of them responding well. The effectiveness of corticosteroids on IgAN patients with NS is associated with the glomerular histology, and the patients with minimal change like lesions are most sensitive to corticosteroids in terms of remission [3, 11, 12]. Our previous retrospective study also supported this notion [13]. Almost all of the previous studies were retrospective. In the only prospective study, the sample size was small, the patients enrolled were heterogeneous clinically and histologically, and the initial prednisolone/prednisone dosage was 40 mg/day [3]. To gain stronger evidence for the therapy, we performed this prospective study.

In our study, all patients achieved CR within 8 weeks in the corticosteroid treatment, demonstrating that corticosteroids are indeed effective in adult MCD-IgAN patients.

Lai *et al.* reported that all eight cases with MCD-IgAN achieved significant remission after 6–8 weeks of corticosteroid therapy with an initial prednisolone/prednisone dosage of 40 mg/day, but half of them relapsed. Among these eight patients, four had haematuria (macroscopic and/or microscopic), two had hypertension and two had renal insufficiency. Under EM, two patients had small subendothelial deposits and one had conspicuous subendothelial and discrete subepitheial deposits [3]. In 2009, Kim *et al.* reported 12 patients of IgAN with steroid-responsive NS. All of the patients achieved CR with steroid therapy, and the median time to CR (proteinuria < 0.3 g/day) was 2 months. Seven episodes of relapse took place in five patients during follow-up (median duration of which was 30 months). In addition to heavy proteinuria, hypoalbuminaemia and diffusely effaced foot processes, 33% of the patients had hypertension and 91.7% of them had macroscopic and/or microscopic haematuria [9]. In 2012, Kim *et al.* reported 1076 cases with IgAN [10]. Among these cases, 100 patients (10.2%) presented with NS, and 48 (48%) and 32 (32%) of them achieved CR and PR, respectively; in addition, 24 (24%) underwent SR. Histological findings of their renal biopsies by both Haas and Oxford classification correlated with CR and SR, i.e., the milder the histological change, the higher the rate of remission. In the study, typical histological features of MCD were observed in only 45.8% of the patients with NS [10]. In our present study, all 27 cases with MCD-IgAN achieved CR in 8 weeks, which was superior to previous studies. We think that there may be two reasons to explain the difference, (i) the clinical manifestations and pathological changes were relatively homogeneous in our patients. Except for some patients who had mild microhaematuria, no patient had hypertension or high Scr clinically. Moreover, except for the few patients that had a global

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glomerulosclerosis, no case had moderate or severe tubulointerstitial lesions. This observation not only explained why they were all sensitive to corticosteroids, but also suggested that our definition of MCD-IgAN in this study was appropriate and (ii) there may be ethnic/racial differences in clinical manifestations and pathological changes of MCD-IgAN patients. Ethnic/racial differences have been shown in the clinical manifestations and pathological changes of IgAN patients [1]. There are also racial differences between Asian and Caucasian adult MCD patients, as evidenced by the observation that the Asian adult MCD patients were more sensitive to corticosteroids than the Caucasian counterparts [14–16]. In fact, there have been more studies with Asian populations concerning clinical and pathological characteristics and response to steroid treatment of MCD-IgAN [3, 4, 9–11].

What is the essential entity of MCD-IgAN? Lai *et al.* have proposed that this kind of disease should be defined as a special type of IgAN because it not only has the clinical and pathological features of MCD and is sensitive to corticosteroids, but also has the clinical and pathological features of IgAN [3]. In the study by Kim *et al.*, they found that some patients were of typical IgAN based on the first renal biopsy, but developed foot process effacement as evidenced by the second biopsy performed at the nephrotic stage. Meanwhile, some other patients were diagnosed as MCD but not IgAN from the initial biopsies, and they developed IgAN based on the biopsies later. They considered that these cases represent the co-existence of IgAN and MCD [9]. It is important to properly define this type of disease. Is it a special type of IgAN that is followed by MCD lesions, or a special MCD that is followed by IgA deposition in mesangial region? Alternatively, do IgAN and MCD develop independently and thus co-exist in the same patients? Further studies are required to address these issues.

Corticosteroids are safe for adult patients. Tse *et al.* reported that corticosteroids were safe and the side effects of corticosteroids were more common in patients over 50 years old compared with younger patients [17]. Waldman *et al.* [14] also showed in their study with 88 adult MCD patients who received corticosteroids that the complications relating to steroid use were mild and not frequent. In our present study, infection, high alanine aminotransferase activity, high FBS level and hypopotassaemia occurred in 7.41, 18.5, 7.41 and 18.5% of the patients, respectively, during corticosteroid therapy. Our observation has further supported that corticosteroid treatment is safe for adult MCD-IgAN patients. Although our present study has prospectively supported that corticosteroids are as safe and efficient for MCD-IgAN patients as for MCD patients, thus having provided additional clinical evidence to support the KDGIO recommendation of use of corticosteroids for MCD-IgAN patients, there are two limitations in this study. First of all, our study lacked a control group. Since corticosteroid therapy had been known to be safe and efficient for MCD-IgAN patients based on our and others' previous retrospective studies, it would be inappropriate to recruit a group of such patients to whom no corticosteroid would be given simply for control purpose. Second, the period of the entire study was not long enough. High relapse rates have been observed in MCD-IgAN patients receiving corticosteroids in previous studies in contrast with our present study. One obvious reason is the short time of our study, which was only 12 weeks. We are still following up these patients to evaluate the long-term efficiency of the therapy and the relapse.

In conclusion, to the best of our knowledge, this is the first prospective study, in which all 27 cases achieved CR in 8 weeks in the corticosteroid therapy. In the 12-week study, two patients relapsed. The incidence of side effects of this therapy was low, and even if occurred, they were generally mild and acceptable. Thus, our study supports that corticosteroids are as safe and efficient for MCD-IgAN patients as for MCD patients. Nevertheless, investigation of the long-term efficiency and relapse is warranted.

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ORIGINAL ARTICLE

Pre-dialysis chronic kidney disease in children: results of a nationwide survey in Japan

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ABSTRACT

Background. Chronic kidney disease (CKD) in children is a progressive and intractable condition that may severely impair the child's growth, development and quality of life. Epidemiological information on pediatric CKD, particularly in Asians, is scant.

Methods. We conducted a nationwide, population-based survey of Japanese children aged 3 months to 15 years with pre-dialysis CKD to examine the prevalence of pediatric CKD

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