The combination therapy of steroids, tacrolimus and mycophenolate mofetil in idiopathic membranous nephropathy coexisting with type 2 diabetes mellitus: a retrospective study

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Abstract

Background: Idiopathic membranous nephropathy (IMN), one of the most common causes resulting into nephrotic syndrome in adults, is usually clinically treated with steroids and/or other immunosuppressive agents. However, the treatment on the patients with IMN coexisting with type 2 diabetes mellitus (DM) is still challenging. There are few convincing literatures available on the efficacy and safety of therapeutic regimens in this subgroup of patients to guide clinical practice.

Methods: We retrospectively collected and analyzed the data of twenty-three patients who underwent renal biopsies between January 2013 and March 2018 in our institute and were diagnosed with IMN coexisting with type 2 DM. Nine patients received prednisone combining with tacrolimus and mycophenolate mofetil (group 1), while 14 patients received prednisone and intravenous cyclophosphamide (group 2). The primary endpoint was measured by percentage of patients achieved complete remission (CR) or partial remission (PR), the secondary endpoints included changes of urinary protein excretion from baseline and treatment-related adverse events.

Results: The remission rates were compared between the group 1 and the group 2 at both 6 months (44.4% versus 50%, P>0.05 ) and 12 months (77.8% versus 64.3%, P>0.05 ). Significant decrease in urinary protein excretion was observed in both groups during treatment, which was significantly greater in group 1 than that in group 2. No significant renal impairment was observed during the follow-up period. Infections and worsening glycemic control were the most common adverse effects of two therapy. Patients treated with prednisone plus cyclophosphamide were more likely to develop worsening diabetes, while infections tended to be more common in patients treated with prednisone combining with tacrolimus and mycophenolate mofetil.

Conclusions: The combination therapy of prednisone, tacrolimus and mycophenolate mofetil is one of the effective and safe options for patients with IMN and type 2 DM.

Introduction

Idiopathic membranous nephropathy (IMN) is one of the most common causes resulting into nephrotic syndrome in adults [1]. About 30% of patients with IMN can achieve spontaneous remission [2], and approximately 30–40% patients with persistent nephrotic syndrome progress to ESRD over 10 years [3,4]. IMN is also the most common non-diabetic renal disease(NDRD), accounted for 45% of NDRD in a retrospective study in Iran [5], and 19.2% in the study done by Soni S S et al. [6], who concluded that the shorter duration of diabetes and the absence of retinopathy, especially when associated with nephrotic proteinuria, strongly predict NDRD[6]. Compared with diabetic nephropathy(DN), NDRD was associated with better renal outcomes in patients with type 2 DM [7].

Corticosteroids plus cyclophosphamide has become the classic therapy for IMN treatment. Although the “Ponticelli Regimen” is recommended as the initial treatment of IMN in the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis [8], its application is limited in treatment of diabetics patients with IMN due to some treatment-related adverse effects, such as deterioration of glycemic control, increasing the risk of cancers, and reproductive toxicity [9].

However, except one study from Indian examining the response to immunosuppressive medications in IMN patients with diabetes [10], almost all of the current published literature available are derived from studies on isolated IMN. In 2010, a multicenter randomized controlled trial in China showed that the decrease in urinary protein and the remission rate of patients with IMN was significantly greater in the prednisone plus tacrolimus group than that in prednisone plus cyclophosphamide(CTX) group at 6 months [11]. Mycophenolate mofetil had been proved to reduce proteinuria in some patients with IMN that were previously resistant to steroids or cyclosporine treatment [12]. In 2007, Zhihong Liu et al proposed a new therapy as an induction regimen for class V+VI lupus nephritis, including prednisone, tacrolimus and mycophenolate mofetil, with the initial dosage of 0.6–0.8mg/kg/d, 4mg/d, and 1g/d, respectively. The results showed that
the therapy was well tolerated on patients and was better than intravenous cyclophosphamide for inducing complete remission of class V+VI lupus nephritis patients with few adverse effects [13]. This study of Liu et al [13] provides an important basis for the application of combination therapy in IMN as IMN and IV+V lupus nephritis have the similar immune disorder and glomerular damage. Inspired by this, we have tried to treat IMN patients with type 2 DM with combination therapy for many years, in which the relatively lower dosages of prednisone and tacrolimus may mitigate the risks of infections and worsening of diabetes. Therefore, we performed the retrospective study and analyzed the data of this subset of IMN, and compared the efficacy and adverse effects between the combination therapy of steroids, tacrolimus and mycophenolate mofetil and conventional steroids plus cyclophosphamide therapy.

Materials And Methods

In this retrospective study, all patients gave their written informed consent according to the Declaration of Helsinki. Twenty-three newly diagnosed, biopsy-proved IMN (stage I–III) with type 2 DM patients between January 2013 and March 2018 in our department were investigated. None of them were treated with glucocorticoids or any other immunosuppressive agents until the pathological diagnosis was confirmed by light microscopy, immunofluorescence and electron microscopy. Exclusion criteria were as following: (1) positive test for hepatitis B and C virus and HIV; (2) systemic lupus erythematosus or positive antibodies to double-stranded DNA; (3) malignancy; (4) peptic ulcer; (5) serious or potentially life-threatening infections; (6) previous immunosuppressive therapy, interrupting immunosuppressive therapy or switching to traditional Chinese medicine therapy on patient’s own initiative; (7) without complete clinical data due to irregular follow-up or turning to other hospitals for treatment; (8) pregnancy or inadequate contraception.

Medication Regimens

In group 1, the dosage of daily oral prednisone was 10 mg/d. The dosage of tacrolimus started at 0.05 mg/kg/d, given orally in two divided doses 12 hours apart, and was titrated within the first month to maintain a blood trough concentration within 5 to 10 ng/ml. The dosage of MMF was initiated at 1 g/d twice daily (every 12h). The initial dosages of prednisone, tacrolimus and MMF in the group 1 were maintained for six months, and then tapered gradually according to the patient’s remission status.

In group 2, the CTX pulse therapy was given monthly by parenteral route, it was applied for two consecutive days with a dosage of approximately 0.8–1 g/month for 6 months, followed by 0.8–1 g every 3 months (accumulated dosage was 6–8g). The dosage of daily oral prednisone was started at 1 mg/kg/d for 8 weeks, and then tapered gradually until a maintenance dosage of 20 mg/d had been reached.

Oral hypoglycemic agents or subcutaneous insulin and detailed dietary guidance are administered for glucose control. All patients received supportive care including angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blocker (ARB) to help decrease the excretion of urinary protein and control blood pressure, aspirin for prophylactic anticoagulant therapy if serum albumin concentration was less than 20g/L or there were additional risks for thrombosis, statins for hyperlipidemia.

Efficacy and Safety Assessments

The primary efficacy parameter was the percentage of patients reaching complete remission (CR) or partial remission (PR). The definitions of complete and partial remission are as follows, complete remission (CR): urinary protein excretion<300mg/d maintains at least 1 week, accompanied by a serum albumin concentration>35g/L, and a normal serum creatinine; partial remission (PR): urinary protein excretion<3500mg/d and a 50% or greater reduction from baseline values and maintains at least 1 week, with an improvement or normalization of the serum albumin concentration, and
stable serum creatinine. A secondary efficacy parameter was the decrease of urinary protein excretion. Safety assessments included infections, worsening of diabetes, leucopenia, and other such clinical manifestations.

**Statistical Analysis**

The Student t test was used to compare the differences of quantitative parameters between groups if the data were normally distributed, otherwise, the nonparametric test would be used. Changes of clinical parameters from baseline in each group were evaluated with the use of the paired-samples t test or Wilcoxon signed ranks test. The chi-square test and Fisher’s exact tests was used to compare differences of qualitative results and the percentages of remissions. Adverse events were tabulated by descriptive statistics. P value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed with SPSS software package (version 18.0).

**Results**

**Baseline Characteristics of the Patients**

Baseline characteristics of the whole group of patients are given in Table 1. From January 2013 through March 2018, twenty-three patients with IMN coexisting with type 2 DM were included in this study. A majority of the patients were male. The mean ± standard deviation age was 53.83 ± 7.61 years and the mean ± standard deviation proteinuria was 7.79 ± 3.53 g/day. Only two patients had a proteinuria level of <3.5 g/day, (3.28 and 2.75 g/day, respectively). There was no significant difference in fast blood glucose(HBG), haemoglobin A1c(HbA1c), estimated glomerular filtration rate(eGFR), serum creatinine and urine protein excretion between the two groups of patients at baseline.

**End Points**

After 6-month treatment, one patient was in CR (one in group 2) and ten in PR (four in group 1 and six in group 2). After 12-month treatment, three patients were in CR (one in group 1 and 2 in group 2) and thirteen in PR (six in group 1 and seven in group 2). The percentages of remission (CR+PR) in the group 1 vs the group 2 were 44.4 vs 50%, respectively, by 6 months ($P = 1.0$), and 77.8 vs 64.3% by 12 months ($P = 0.657$), which showed similar between the two groups (Table 2).

**Changes of Clinical Parameters During Follow-up Period**

The urine protein excretion significantly decreased in both groups during treatment. It decreased from 9464±3787 mg/24h to 4286±1922 mg/24h ($P<0.01$, by month 2), 3465±2339 mg/24h ($P<0.01$, by month 6) and 2225±2344 mg/24h ($P<0.01$, by month 12) in group 1; in group 2, the excretion of urinary protein decreased from 6709.87±3018.87 mg/24h to 5554±4354 mg/24h ($P>0.05$, by month 2), 3812±3508 mg/24h ($P<0.05$, by month 6) and to 2431±2518 mg/24h ($P<0.01$, by month 12) (Table3). The percentages of patients with nephrotic-range proteinuria also decreased in both groups during follow-up period (Figure 4).

At the same time, serum albumin concentration significantly increased from 24.90±3.55 g/L to 32.96±6.31 g/L ($P<0.01$, by month 2), 35.54±6.88 g/L ($P<0.01$, by month 6), and 39.54±8.19 g/L ($P<0.01$, by month 12) in group 1; in group 2, the serum albumin concentration started significantly increased from 6-month treatment, from 27.88±6.08 g/L to 34.85±8.61 g/L ($P<0.05$, by month 6), 37.89±8.61g/L ($P<0.01$, by month 12) (Table3).

The change of urinary protein excretion from baseline value was significantly greater in group 1 than that in group 2 (−5177±2823 vs −1155.01±4022.23 mg/24h by 2 months, $P = 0.016$; −5998.86±3052.98 vs −2897.52±3714.45 mg/24h by 6 months, $P = 0.049$; −72391±1889 vs −4278±3201 mg/24h by 12 months, $P = 0.021$)(Table4, Figure 2). In addition, the
change of serum albumin concentration from baseline value was also significantly greater in group 1 by 2 months (8.06±3.37 vs 2.62±6.86 g/L, \( P = 0.039 \)) (Table4, Figure 3).

The level of blood urea nitrogen (BUN), serum creatinine (Scr) and estimated glomerular filtration rate (eGFR) remain stable during follow-up period (Table3). There were no differences in the mean values of BUN, Scr or eGFR between each follow-up and baseline value in the two groups (Table3). After 1 year treatment, the change of eGFR from baseline value was increased by 5.9 and 4.31 ml/min/1.73 m\(^2\) in group 1 and group 2 respectively (\( P = 1.0 \)) (Table4).

**Adverse effects of treatment**

As shown in Table5 and Table6, infections and deterioration of diabetes were the most common complications in these treatment regimens, and occurred mostly within the first 6 months after treatment. Nine of 23 patients of IMN coexisting with type 2 DM (four in group 1 and five in group 2) needed hospitalization during follow-up period because of infections (3 patients developed pneumonia, 3 patients developed urinary tract infection, 2 patients developed herpes zoster or varicella, and 1 patient developed pneumonia coexisting with herpes zoster or varicella). Infections tended to be more common in group 1 than in group 2 (44.4 vs 35.7%, \( P = 1.0 \)) although there was no statistical significance. Worsening of diabetes was another major adverse effect in these patients with type 2 DM. Compared with the baseline value, haemoglobin A1c was significantly greater by month 2 (\( P = 0.31 \)) and by month 6 (\( P = 0.005 \)) in group 1; In group 2, the same phenomenon was observed by month 2 (\( P = 0.00 \)), but there was no difference by month 6 (\( P = 0.23 \)). Compared with group 1, haemoglobin A1c in group 2 was higher by month 2 (\( P = 0.043 \)), and it was similar by month 6 in these two treatment groups (\( P = 0.052 \)) (Table6). Comparison of other indicators revealed numerically lower incidences of leucopenia and nausea or vomiting in group 1.

**Discussion**

Up to now, the researches in diabetics with IMN mainly focus on the analysis of pathological and clinical characteristics, only few of them aim at the therapeutic effects and prognosis of immunosuppressive drugs. Therefore, we conducted the retrospective study to evaluate the efficacy and safety of the combination therapy of steroids, tacrolimus and mycophenolate mofetil in this subgroup.

It has been proven that tacrolimus could suppress the immune response by inhibiting T cell activation and suppressing IL–2 transcriptions [14]. Mycophenolate mofetil can inhibit the type 2 isoform of inosine monophosphate dehydrogenase (IMPDH), which is expressed in activated lymphocytes, and induce apoptosis of activated T-lymphocytes [15]. Thus, the combination therapy was supposed to act on the inflammatory and membranous lesions synchronously.

Previous studies have shown that the remission rate of IMN patients treated with ACEI/ARB is less than 10% at the 6th month, which is significantly lower than that treated with tacrolimus [16], and remission, especially complete remission, rarely occurs spontaneously within 6 months in patients with massive proteinuria. Meanwhile, the risk of infections and thromboembolic events in DM patients, which is much higher than those without DM [17], will further increase because renal hypertension, hypoproteinemia and hyperlipidemia are difficult to control in IMN patients who have not achieved remission [18]. Severe complications, such as acute myocardial infarction, cerebral infarction and massive pulmonary embolism, can lead to a significant decline in the quality of life, paralysis or even death of patients. Although it does not result in better preservation of renal function, early treatment shortens the duration of nephropathy [19]. Therefore, we did not follow them for up to 6 months, and started immunosuppressive therapy immediately. At the same time, all patients in our study received ACEI/ARB at the maximum tolerable dose to help decrease the excretion of urinary protein and control blood pressure by suppressing excess activation of the RAAS.
The remission rate is one of the key points of our observation. After 6 months treatment, none of 9 patients in the group 1 and one of 14 patients in the group 2 achieved complete remission, the partial remission rates in the group 1 and the group 2 were similar (44.4 vs 50% respectively). After 12 months treatment, the remission rates (CR+PR) increased to 77.8% in the group 1 and 64.3% in the group 2, and there was no significant difference as well although a trend of better improvement in the group 1 was observed. The remission rate in the group 2 of our study was higher than that of an observational study in India (50% vs 18%) after treatment with the Modified Ponticelli (MP) regimen for 6 months [10]. Different dosages of steroids and cyclophosphamide in regimens may be the critical factor contributing to the difference in remission rates between the two studies, that are much higher in the MP regimen used by the study of India, accompanied by a higher risk of more frequent and severe adverse effects, thereby limited their efficacy. The remission rate in patients using prednisone plus cyclophosphamide therapy of our study was lower than that in a randomized controlled study in China (50% vs 65% by month 6, 64.3% vs 69% by month 12), in which patients with type 2 DM were not included [11]. This difference between the two studies also suggests that type 2 DM itself may also be a factor that makes IMN difficult to achieve complete or partial remission.

Another important finding of our study was that the reduction of urinary protein excretion in the group 1 was significantly higher than that in the group 2, especially in the first two months after treatment, that was consistent with the results of previous studies [11,16]. It suggests that steroids plus tacrolimus therapy or tacrolimus monotherapy maybe have much more advantages in decreasing the values of urinary protein excretion over ACEI, ARB and cyclophosphamide regimens. It has been demonstrated that 24-hour urinary protein levels is significantly positively correlated with progression to end-stage renal disease (ESRD) and it is determined as an independent risk factor for the progression of ESRD [20]; remission, even partial, can significantly improve the long-term prognosis of patients with IMN [21].

Therefore, the combination therapy of steroids, tacrolimus and mycophenolate mofetil maybe an alternative therapeutic regimen for patients with IMN coexisting with type 2 DM because of its superiority in decreasing the excretion of urinary protein, increasing plasma albumin concentration, alleviating edema symptoms and risks for thrombosis reducing, thereby improving patients life quality. In addition, the change of serum albumin concentration from baseline value was also greater in the group 1 than that in group 2, although the difference did not reach statistical significance by month 6 and 12, which might be responsible for the relatively small sample size.

Studies have indicated that patients treated with tacrolimus had a greater risk of nephrotoxicity [22,23]. Early pathological changes of tacrolimus-induced nephrotoxicity in patients with renal allografts include myocyte and tubular vacuolation whereas long term changes include interstitial fibrosis and tubular atrophy, arteriolar hyalinosis, medial arteriolar hyalinosis [24,25]. The increase in serum creatinine and reduction in eGFR were also observed in IMN patients received tacrolimus [22]. Previous studies have shown that the nephrotoxicity of calcineurin inhibitors is time-dependent and dosage-dependent, and the tolerability of tacrolimus appears to improve as the dose is reduced [25–27]. No patient was performed repeat renal biopsy during the follow-up period, which made it hard to identify the pathological changes of the kidney. However, serum creatinine and eGFR remained stable in IMN patients with type 2 DM who received tacrolimus in our study. In our present study, the follow-up period for the patients treated with tacrolimus was 12 months; the initial dosage of tacrolimus was 0.05 mg/kg/d and the patients had the normal renal function prior to treatment with tacrolimus. This relatively short follow-up duration, low dosage of tacrolimus and normal kidney function at baseline may explain the reasons that patients were free from nephrotoxicity. The risk of potential nephrotoxicity of tacrolimus in a long period of treatment need to be investigated in the further study.

Treatment-related adverse effects were another important aspect needed to be concentrated in our current research. Worsening of diabetes caused by steroids and tacrolimus was the most common adverse effect in both groups. In patients with known DM, steroids exacerbate hyperglycemia through decreasing peripheral insulin sensitivity, increasing hepatic glucose production, and inhibiting the production and secretion of pancreatic insulin [28,29]. The diabetogenicity of calcineurin inhibitors has also been confirmed in both animals and humans [30]. In an open-label, randomized,
multicenter study, 33.6% of patients received tacrolimus after renal transplantation developed new onset DM or impaired fasting blood glucose at 6-month treatment [31]. However, there was no significant difference in fasting blood glucose levels between the two groups at any time point. Haemoglobin A1c (HbA1c), as a useful clinical parameter of monitoring long-term glycemia control, was found to be significantly higher in the group 2 at 2 months after treatment in our study, which may be attributed to excessive steroid dosage as 1 mg/kg/d compared to only 10mg/d in the combination therapy. It has been demonstrated by well-designed, randomized clinical trials that control of blood glucose levels can dramatically reduce the risk of vascular disease among individuals with DM [32,33]. In other words, the combination therapy may be more suitable for diabetic patients because of its relatively mild effect of boosting blood glucose levels. Infections are another treatment-related adverse effect in diabetic patients receiving steroids or immunosuppressive therapy. In our study, the most frequently involved organs are lungs and urinary system. Herpes zoster infection also accounts for a large proportion. The infection rate in the combination therapy group is higher than that in the prednisone plus cyclophosphamide therapy group without significant statistical difference. Incidences of other side effects, such as leucopenia and nausea or vomiting, revealed numerically lower in the combination therapy group.

Several limitations should be noted for this study. Firstly, its retrospective nature and the relatively small sample size would inevitably bring some bias in evaluating the efficacy and safety of the two regimens. Secondly, relatively short duration of follow-up makes it hard to determine relapse and risk of long-term complications. Thirdly, our study did not include patients with stage IV of IMN or patients with impaired renal function.

Our results suggested that the combination therapy with steroids, tacrolimus and MMF is a very useful therapeutic option in treatment of patients with IMN coexisting with type 2 DM. However, further investigation is needed to evaluate this regimen’s long-term efficacy and safety.

**Abbreviations**

IMN: idiopathic membranous nephropathy;

DM: diabetes mellitus;

CTX: cyclophosphamide;

NDRD: non-diabetic renal disease;

MMF: mycophenolate mofetil;

ACEI: angiotensin converting enzyme inhibitors;

ARB: angiotensin receptor blocker;

MP: Modified Ponticelli;

ESRD: end-stage renal disease;

FBG: fast blood glucose;

HbA1c: haemoglobin A1c;

BUN: blood urea nitrogen;

Scr: serum creatinine;

eGFR: estimated glomerular filtration rate;
UA: uric acid;
STP: serum total protein;
SAlb: serum albumin;
TC: total cholesterol;
TG: total triglyceride;
CR: complete remission;
PR: partial remission.

**Declarations**

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Not applicable.

**Authors’ contributions**

Lining Jia and Ronguo Fu developed the initial study and analysis plan, Li Wang, Xiaotao Ma and Heng Ge performed the study, Hao Wang, Peiyao Ren and Gaofei Yan completed all data collection, Yinhong Wang completed data analysis and drafted the initial manuscript, Xuefei Tian reviewed and edited the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The study was approved by Xi’an Jiaotong University Health Science Center (Xi’an, China). All participants have written informed consent before the study.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.
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### Table 1. Baseline characteristics of patients

|                          | Group 1     | Group 2     | P    |
|--------------------------|-------------|-------------|------|
| Male, n/n%               | 7 (77.8)    | 6 (46.9)    | 0.19 |
| Biopsy age (yr; mean±SD) | 54.11±10.04 | 53.64±5.99  | 0.88 |
| Of IMN,n                 |             |             |      |
| Stage 1                  | 5           | 6           |      |
| Stage 2                  | 4           | 7           |      |
| Stage 3                  | 0           | 1           | 1.0  |
| FBG (mmol/L)             | 6.91±2.19   | 5.74±1.06   | 0.10 |
| HbA1c (%)                | 6.95±0.71   | 6.71±1.21   | 0.29 |
| WBC (×10⁹/L)             | 6.62±2.34   | 7.15±2.09   | 0.58 |
| RBC (×10¹²/L)            | 4.51±0.49   | 4.55±0.67   | 0.86 |
| Hb (g/L)                 | 137.00±13.51| 137.35±19.02| 0.96 |
| PLT (×10⁹/L)             | 208.77±47.39| 218.14±75.09| 0.74 |
| Urine protein excretion (mg/24h) | 9464±3787 | 6709±3018 | 0.06 |
| Urine protein excretion >3.5g | 91 (100%)   | 128 (85.7%) | 0.50 |
| BUN (mmol/L)             | 4.98±1.45   | 4.91±1.47   | 0.85 |
| Scr (μmol/L)             | 78.29±31.30 | 67.64±21.98 | 0.48 |
| eGFR (mL/min/1.73m²)     | 99.57±28.88 | 105.73±33.47| 0.65 |
| UA (μmol/L)              | 347.87±52.78| 308.56±110.07| 0.49 |
| STP (g/L)                | 46.18±3.97  | 51.37±8.40  | 0.18 |
| SAlb (g/L)               | 24.90±3.55  | 27.88±6.08  | 0.19 |
| TC (mmol/L)              | 6.73±1.71   | 6.98±2.04   | 0.77 |
| TG (mmol/L)              | 2.84±1.15   | 2.85±1.20   | 0.99 |

FBG: fast blood glucose; HbA1c: haemoglobin A1c; BUN: blood urea nitrogen; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; UA: uric acid; STP: serum total protein; SAlb: serum albumin; TC: total cholesterol; TG: total triglyceride.
### Table 2. Complete and partial remissions rates

| Group       | CR(%) | PR(%) | Remission rate(%) | $P$  |
|-------------|-------|-------|-------------------|------|
| **By 6 months** |       |       |                   |      |
| Group 1 n=9 | 0 (0.0) | 4 (44.4) | 44.4             | 1.00 |
| Group 2 n=14 | 1 (7.1)  | 6 (42.9) | 50               |      |
| **By 12 months** |       |       |                   |      |
| Group 1 n=9 | 1 (11.1) | 6 (66.7) | 77.8             | 0.657|
| Group 2 n=14 | 2 (14.3) | 7 (50.0) | 64.3             |      |

CR: complete remission, PR: partial remission.

### Table 3. Clinical parameters during follow-up period

|                      | By 2 months | By 6 months | By 12 months |
|----------------------|-------------|-------------|--------------|
|                      | Group 1     | Group 2     | Group 1      | Group 2     | Group 1      | Group 2     |
| FBG (mmol/L)         | 7.47±2.69   | 5.85±1.82   | 7.79±2.79    | 5.62±0.97   | 2225±2344    | 2431±2518   |
| Urine protein excretion (mg/24h) | 4286±1922   | 5554±4354   | 3465±2339    | 3812±3508   | 2225±2344    | 2431±2518   |
| BUN (mmol/L)         | 6.58±2.01   | 6.39±1.66   | 6.68±2.16    | 4.97±1.14*  | 7.11±2.93    | 5.51±1.50   |
| Scr (μmol/L)         | 85.52±31.57 | 63.50±15.38 | 84.26±43.21  | 63.45±16.23 | 77.91±35.86  | 61.53±12.92 |
| eGFR (mL/min/1.73m²) | 89.96±28.27 | 109.87±27.71 | 100.60±44.4  | 108.95±27.07 | 105.48±39.12 | 110.04±21.25 |
| STP (g/L)            | 55.12±9.58  | 53.31±7.64  | 58.3±8.10    | 56.87±8.60  | 61.63±8.98   | 62.05±8.28  |
| SAlb (g/L)           | 32.96±6.31  | 30.50±6.66  | 35.54±6.88   | 34.85±8.61  | 39.54±8.19   | 37.89±8.61  |
| TC (mmol/L)          | 9.08±3.76   | 6.96±2.48   | 6.43±3.94    | 5.91±2.14   |              |             |
| TG (mmol/L)          | 3.41±1.42   | 3.28±2.66   | 3.17±1.43    | 2.40±0.84   |              |             |

FBG: fast blood glucose; BUN: blood urea nitrogen; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; STP: serum total protein; SAlb: serum albumin; TC: total cholesterol; TG: total triglyceride, *$P<0.05$ versus group 1.
**Table 4.** Changes of clinical parameters from the baseline value during follow-up period

| Parameter                        | Change of | Change of | Change of | Change of | Change of |
|----------------------------------|-----------|-----------|-----------|-----------|-----------|
|                                  | urine protein excretion (mg/24 h) | BUN (mmol/L) | Scr (μmol/L) | eGFR (mL/min/1.73 m²) | STP (g/L) |
| By 2 month                       | Group 1   | 5177±2823 | 1.22±2.11  | 6.27±20.40 | 4.03±17.61 | 8.14±8.7  | 8.06±3.37 |
|                                  | Group 2   | 1155±4022 | 1.31±1.94  | 5.54±22.36 | 5.30±41.61 | 1.94±9.10 | 2.62±6.86 |
|                                  | *P*       | 0.016     | 0.90       | 0.221     | 0.616     | 0.12      | 0.039     |
| By 6 month                       | Group 1   | 5998±3052 | 1.70±2.39  | 5.97±21.32 | 1.03±24.19 | 12.11±6.65 | 10.64±4.71 |
|                                  | Group 2   | 2897±3714 | 0.06±1.79  | 4.18±16.23 | 3.21±28.19 | 5.50±12.39 | 6.96±9.05 |
|                                  | *P*       | 0.049     | 0.074      | 0.209     | 0.851     | 0.166     | 0.196     |
| By 12 month                      | Group 1   | 7239±1889 | 2.13±3.60  | 0.38±21.72 | 5.90±30.02 | 15.44±5.85 | 14.64±6.11 |
|                                  | Group 2   | 4278±3201 | 0.59±2.14  | 6.10±12.21 | 4.31±24.20 | 10.67±13.31 | 10.00±10.45 |
|                                  | *P*       | 0.021     | 0.21       | 0.426     | 1.00      | 0.975     | 0.244     |

BUN: blood urea nitrogen; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; STP: serum total protein; SAlb: serum albumin.

**Table 5.** Adverse events

| Parameter                        | Group 1\(n=9\) | Group 2\(n=14\) | *P* |
|----------------------------------|----------------|-----------------|-----|
| Infection\(\%\)                 | 4\(\text{44.4\%}\) | 5\(\text{35.7\%}\) |     |
| Pneumonia                        | 2               | 2               |     |
| Herpes zoster                    | 1               | 2               |     |
| or varicella                     |                 |                 |     |
| Acute pyelonephritis             | 1               | 2               |     |
| Nausea or vomiting               | 1               | 3               |     |
| WBC\(<4\times10^9/\text{L}\)    | 0               | 1               |     |

**Table 6.** Haemoglobin A1c (HbA1c) during follow-up period

| Parameter | Group 1\(n=9\) | Group 2\(n=14\) | *P* |
|-----------|----------------|-----------------|-----|
| Baseline Value | 6.95±0.71   | 6.71±1.21      | 0.29|
| By 2 months  | 7.41±0.44   | 8.07±0.85      | 0.043|
| By 6 months  | 7.55±0.49   | 7.04±0.89      | 0.052|

**Figures**
Figure 1

Enrollment of patients and treatment assignments

Figure 2

Change of urine protein excretion from baseline (mg/dl)

Group 1

Group 2

months

*
Change of urine protein excretion (mean±SD, mg/d) from baseline value at each follow-up evaluation in two groups, *P<0.05 versus the group 1.

Figure 3

Change of serum albumin (mean±SD, g/L) from baseline value at each follow-up evaluation in two groups, *P<0.05 versus the group 1.
Percentages (%) of patients with nephrotic-range proteinuria decreased at each follow-up evaluation in two groups.

Figure 4