Comparison of Different Therapeutic Regimens for Idiopathic Membranous Nephropathy in Diabetic Patients: Postprint

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Abstract

Purpose: To compare the efficacy and prognosis of different therapeutic regimens in patients with type 2 diabetes mellitus complicated by idiopathic membranous nephropathy (IMN). Methods: This retrospective study consecutively enrolled 89 patients with type 2 diabetes mellitus complicated by IMN, who were stratified into three groups based on initial treatment: calcineurin inhibitors (CNIs), cyclophosphamide (CTX), and other therapies. Using overall response (TR) and complete response (CR), a 30% decline in estimated glomerular filtration rate (eGFR) or progression to end-stage renal disease (ESRD) as outcome measures, survival analysis was utilized to compare differences among treatment regimens regarding these endpoint events. Results: In patients with type 2 diabetes mellitus complicated by IMN, no statistically significant differences were observed between the CNIs and CTX groups in CR (P=0.68) or TR (P=0.20); however, the former demonstrated a higher risk of renal function deterioration (P=0.010), a trend that persisted in multivariate COX regression analysis. Conclusion: In type 2 diabetes mellitus complicated by IMN, CNIs therapy achieves similar proteinuria remission as CTX but is associated with a higher risk of renal function decline.

Full Text

Abstract

Objective: This study was designed to compare the efficacy and safety of calcineurin inhibitors (CNIs) and cyclophosphamide (CTX) in treating idiopathic membranous nephropathy (IMN) in patients with type 2 diabetes.

Methods: We included 89 IMN patients with type 2 diabetes and classified them into three groups according to their initial treatment regimens. We em-

ployed Kaplan-Meier analysis and Cox regression models to assess the association between different therapeutic regimens and IMN remission, and risks of developing a 30% decline in eGFR or ESRD.

Results: In Kaplan-Meier survival analysis, IMN patients initially treated with CNIs had higher risk of developing a 30% eGFR decline or ESRD (P=0.010), as opposed to those treated with CTX. The association remained significant in multivariate Cox regression analysis. The probability of achieving complete remission (P=0.68) and total remission (P=0.20) was similar between the two groups.

Conclusions: In patients with type 2 diabetes and IMN, treatment with CNIs or CTX did not differ in proteinuria remission. However, CNIs were associated with higher risk of renal function deterioration compared with CTX.

Key words: Type 2 diabetes; idiopathic membranous nephropathy; calcineurin inhibitors; cyclophosphamide.

Introduction

Over the past four decades, the prevalence of type 2 diabetes mellitus (DM) in China has soared from 0.67% to 10.4% [1]. Membranous nephropathy is one of the most common non-diabetic kidney diseases [2, 3]. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend cyclophosphamide (CTX) combined with glucocorticoids (GCC) and calcineurin inhibitors (CNIs) or combined with GCC as initial therapy for idiopathic membranous nephropathy (IMN) [4]. For IMN patients with DM, using GCC may worsen glucose metabolism disorders, so clinicians tend to prefer CNIs or combined low-dose GCC regimens. Meta-analyses have shown comparable efficacy between these two treatment approaches in general IMN patients [5], but studies comparing their efficacy and side effects in DM patients are lacking. Therefore, this retrospective study analyzed the efficacy and prognosis of different treatments in type 2 DM patients with IMN treated at Peking Union Medical College Hospital.

Methods

Study Subjects

This retrospective study included adult type 2 diabetes patients with biopsy-proven membranous nephropathy treated at Peking Union Medical College Hospital between January 2004 and April 2015. Type 2 diabetes was diagnosed according to the American Diabetes Association criteria [6], and IMN pathological diagnosis followed the "Guidelines for Renal Biopsy Pathological Diagnosis" [7]. Exclusion criteria were: (1) kidney disease onset before diabetes diagnosis; (2) presence of secondary MN factors such as malignancy, hepatitis B or C virus infection, or autoimmune diseases; (3) concurrent IgA nephropathy, diabetic nephropathy, or other pathological types; and (4) lack of follow-up records at our hospital. A total of 89 patients met these inclusion and exclusion criteria.

Based on their initial and subsequent treatment regimens, patients were divided into three groups: CTX+GCC group (n=22), CNIs with or without GCC group (n=48, including 47 receiving cyclosporine A and 1 receiving tacrolimus), and other treatment group (n=19, including 6 receiving Tripterygium wilfordii, 2 receiving leflunomide, and 11 receiving supportive therapy only).

Data Collection and Definitions

We retrospectively collected pathological data and baseline and follow-up clinical information. Baseline data referred to information within two weeks before initiating each group' s respective treatment, including gender, age, type 2 diabetes duration, blood pressure, height, weight, serum albumin, serum creatinine, 24-hour urinary protein, fasting blood glucose, smoking history, and hypertension history. Follow-up data included follow-up date, serum albumin, serum creatinine, 24-hour urinary protein, fasting blood glucose, and medication use. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Hypertension diagnosis met either of the following criteria: (1) previously diagnosed hypertension with current antihypertensive medication use, or (2) systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg within two weeks of baseline treatment [3]. Nephrotic syndrome (NS) was defined as 24-hour urinary protein 3.5 g and serum albumin <30 g/L [8]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and chronic kidney disease (CKD) staging was determined based on eGFR levels [9, 10]. Proteinuria endpoints included complete remission (CR) or total remission (TR), where TR included CR or partial remission (PR). CR was defined as 24-hour urinary protein <0.3 g, and PR was defined as 24-hour urinary protein 3.5 g with 50% reduction from baseline [4]. The renal function endpoint was defined as eGFR decline 30% from baseline on two consecutive follow-up visits (interval >1 month) or progression to ESRD. Follow-up ended when patients reached an endpoint, changed treatment regimen, were lost to follow-up, or until March 2018.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, otherwise as median (Q1, Q3). Categorical variables were expressed as number (%). Continuous variables were compared using ANOVA or Wilcoxon rank-sum test, and categorical variables were compared using chi-square test or Fisher' s exact test. Kaplan-Meier survival analysis and Cox regression analysis were used to compare the impact of treatment regimens on various endpoints. Statistical analysis was performed using Stata software (version 14.0, Texas 77845 USA). $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of patients in each group are shown in . No significant differences were observed among groups in gender distribution, age, BMI, hypertension, baseline eGFR, fasting blood glucose levels, or proportion receiving renin-angiotensin system inhibitors (RASi). Compared with the CTX and CNIs groups, the other treatment group had lower proportions of nephrotic syndrome and baseline 24-hour urinary protein levels, but higher serum albumin; these parameters did not differ significantly between CTX and CNIs groups. The CTX group had shorter diabetes duration compared with the CNIs and other treatment groups. The proportions of patients receiving GCC, total steroid dose, and initial steroid dose decreased sequentially in the CTX, CNIs, and other treatment groups, though total steroid treatment duration did not differ significantly among groups. In the CTX group, median CTX treatment duration was 5.3 (3.2-7.5) months, and mean cumulative dose was (183.0±116.7) mg/kg. In the CNIs group, mean initial cyclosporine A dose was (2.6±0.7) mg/kg.

Treatment Outcomes

Proteinuria Remission During a median follow-up of 2.9 (1.1-4.7) years, 31 patients achieved CR, including 9 (40.9%) in the CTX group, 19 (39.6%) in the CNIs group, and 3 (15.8%) in the other treatment group. The median time to CR was 1.5 (0.6-3.1) years. An additional 30 patients achieved PR. Log-rank analysis showed no statistically significant differences in CR or TR between the CTX and CNIs groups (CR: CTX vs CNIs, P=0.68; other treatment vs CNIs, P=0.10; TR: CTX vs CNIs, P=0.20; other treatment vs CNIs, P=0.42). These trends persisted after multivariate adjustment in Cox regression analysis ().

Renal Function Decline During follow-up, 20 patients experienced eGFR decline 30% or progression to ESRD, including 1 (4.6%) in the CTX group, 18 (37.5%) in the CNIs group, and 1 (5.3%) in the other treatment group. Log-rank test showed that both the CTX group (P=0.010) and other treatment group (P=0.019) had lower risk of renal function decline compared with the CNIs group ([Figure 2: see original paper]). In Cox regression analysis, after adjusting for gender, age (<60, 60 years), serum albumin (25, >25 g/L), 24-hour urinary protein (<8, 8 g), eGFR (90, >90 mL/min/1.73 m^2), fasting blood glucose (6, >6 mmol/L), RASi treatment (yes/no), glucocorticoid treatment (yes/no), and diabetes duration (2, >2 years), the CTX group showed significantly lower risk of renal function decline compared with the CNIs group (HR=0.074, 95%CI 0.008-0.66, P=0.020), while the other treatment group had comparable risk to the CNIs group (HR=0.14, 95%CI 0.010-2.0, P=0.15).

Fasting Blood Glucose Analysis

During follow-up, mean fasting blood glucose levels were (7.1±2.3), (7.4±2.5), and (7.3±2.4) mmol/L in the CTX, CNIs, and other treatment groups, respectively, with no statistically significant difference (P=0.45). A total of 25 patients had fasting blood glucose 8 mmol/L detected at any point, including 9 (40.9%) in the CTX group, 20 (41.7%) in the CNIs group, and 4 (21.1%) in the other treatment group. Log-rank test showed comparable risk of developing fasting blood glucose 8 mmol/L between the CTX and CNIs groups (CTX vs CNIs: P=0.91) and between the other treatment and CNIs groups (other treatment vs CNIs: P=0.14). After adjusting for gender, age (<60, 60 years), serum albumin (25, >25 g/L), 24-hour urinary protein (<8, 8 g), eGFR (90, >90 mL/min/1.73 m^2), baseline fasting blood glucose (6, >6 mmol/L), RASi treatment (yes/no), glucocorticoid treatment (yes/no), and diabetes duration (2, >2 years), these associations remained non-significant (CTX vs CNIs: HR=0.59, 95%CI 0.23-1.5, P=0.26; other treatment vs CNIs: HR=0.74, 95%CI 0.18-3.1, P=0.68).

Discussion

This retrospective study demonstrates that in diabetic patients, CTX combined with glucocorticoids and CNIs with or without glucocorticoids as initial treatment for idiopathic membranous nephropathy achieve similar proteinuria remission rates, but CTX carries lower risk of renal function decline.

In recent years, studies on the effects of CTX and CNIs on proteinuria remission in IMN patients have yielded inconsistent results [5, 11]. A recent meta-analysis incorporating 21 RCTs with over 1,000 patients found that CNIs were non-inferior to CTX for IMN remission [12]. Our study found similar results in IMN patients with DM, with comparable probabilities of achieving total or complete remission between CTX and CNIs as initial treatment.

The primary concern with using CNIs to treat IMN is their potential to cause renal function decline [13], though study results have been mixed. For progressive IMN, cyclosporine treatment may increase the risk of renal dysfunction compared with alkylating agents [14]. However, a 2014 meta-analysis by Chen Y et al. found no significant difference in renal function decline (death, ESRD/dialysis, serum creatinine increase of 100% or 50% from baseline) between CSA and alkylating agents in IMN patients [5]. Using eGFR decline 30% from baseline as the outcome measure [15], our study found that CNIs treatment was associated with higher risk of renal function decline compared with CTX in diabetic patients with IMN. Therefore, the potential nephrotoxicity of CNIs should be considered when selecting treatment regimens for this population.

Our study found no significant differences in fasting blood glucose among patients receiving different treatment regimens during follow-up. However, fasting blood glucose is not a sensitive indicator of poor glycemic control following glucocorticoid use, and adjustments to hypoglycemic medication doses during

follow-up may affect fasting glucose levels. Therefore, fasting blood glucose may not fully reflect the impact of treatment regimens on glucose control.

As a retrospective study, this research has inherent limitations, including unbalanced confounders. Additionally, all included patients underwent renal biopsy, which is often performed selectively, potentially introducing selection bias. These factors may affect the reliability of our conclusions, and well-designed prospective studies are needed for validation.

In conclusion, in patients with diabetes and idiopathic membranous nephropathy, cyclophosphamide and calcineurin inhibitors achieve similar proteinuria remission rates and comparable risks of fasting blood glucose elevation, but CNIs are associated with higher risk of renal function decline. Therefore, differences in renal effects among treatment regimens should be considered when managing these patients.

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Note: Figure translations are in progress. See original paper for figures.