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ORIGINAL ARTICLE

Comparison of different therapies in high-risk patients with idiopathic membranous nephropathy

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tacrolimus

Background/Purpose: Immunosuppressive therapy plays an important role in patients with high-risk idiopathic membranous nephropathy (IMN), but the therapeutic modality is still controversial.
Methods: Corticosteroid combined with oral tacrolimus (TAC, target trough blood concentration of 4–8 ng/mL), intravenous cyclophosphamide (CYC, 750 mg/m^2/mo, or oral mycophenolate mofetil (MMF, 1.5–2.0 g/d) were randomly administered for 9 months to 90 patients with IMN proved with renal biopsy with severe proteinuria (>8 g/d).
Results: Eighty-six of the 90 patients completed the study. The total remission (TR) rates in the TAC group were significantly higher than those in the CYC group at 1 and 2 months ($p < 0.01$) and the MMF group at 1–4 months ($p < 0.01$). The TR rates were 83.3%, 73.3%, and 70.0% in the TAC, CYC, and MMF groups at 9 months ($p = 0.457$), and there were no significant differences between the three groups from 5 to 9 months. Furthermore, TAC reduced proteinuria and ameliorated hypoalbuminemia more quickly and effectively than CYC and MMF. We observed no severe adverse events in the three groups.
Conclusion: Tacrolimus combined with corticosteroid had tolerable adverse effects and induced the remission of IMN more effectively and more rapidly. This is the first prospective randomized cohort study to compare three different therapies in patients at high risk for IMN. It provides strong evidence for choosing optimal treatment for patients with IMN. The long-term efficacy of this treatment strategy should be investigated further in future studies.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Introduction

Idiopathic membranous nephropathy (IMN) is one of the leading causes of primary nephrotic syndrome regardless of race.[1,2] The interaction of circulating autoantibodies with native antigens and the embedding of these autoantibodies in the podocyte cell membrane—basement membrane interface are generally regarded as the fundamental pathobiological mechanism of the disease. The *in situ* formation of subepithelial immune deposits alters glomerular capillary permeability through complement-mediated injury of the podocyte and its slit pore membrane,[3] and abnormal activation of the immune system is essential for the occurrence and development of IMN. IMN is also regarded as a podocytopathy, and podocytes play a central role in proteinuria and renal function loss during this process.[3]

Treatment of IMN is controversial because of different possible types of IMN disease progression. Generally, approximately one third of patients achieve spontaneous remission, but another one third of patients will suffer from end-stage renal disease (ESRD).[4] The patients with considerable proteinuria are prone to ESRD. Immunosuppressive therapy is important in the treatment of IMN, especially in high-risk patients.[5] The Kidney Disease: Improving Global Outcomes (KDIGO) initiative recommends that the initial therapy for IMN should be started only in patients with nephrotic syndrome whose urinary protein excretion persistently exceeds 4 g/d, remains at >50% of the baseline value, and does not show a progressive decline during antihypertensive and antiproteinuric therapy over an observation period of at least 6 months (1B) or in patients with severe, disabling, or life-threatening symptoms related to their nephrotic syndrome (1C).[6] Early treatment is relatively important, and if successful, it can reduce the risk of complications associated with nephrotic syndrome.[7]

The immunosuppressive treatment of IMN is still a matter of debate. Some authors observed that oral cyclophosphamide (CYC) was effective when used early in the course of IMN,[8–10] whereas other investigators found that the use of intravenous CYC combined with oral corticosteroids was safer and more effective.[11] Although mycophenolate mofetil (MMF) monotherapy did not decrease proteinuria or increase partial and complete remissions in IMN compared with a control group that underwent basic treatment,[12] a regimen of MMF with prednisolone can induce remission in more than 60% of patients with IMN.[13] Tacrolimus (TAC) monotherapy was recently suggested to be a useful therapeutic option for patients with IMN.[14] Furthermore, several IMN trials are being performed to compare a TAC-corticosteroid combination with a CYC-steroid combination.[15–18] Other investigations have shown that the actin cytoskeleton of podocytes is a direct target of the antiproteinuric effect of the calcineurin inhibitor.[19] Our recent study also confirmed that TAC can reduce angiopoietin-like-4 in podocyte to decrease proteinuria in the early phase in experimental membranous nephropathy.[20] TAC could have the added benefits of antiproteinuria activity in IMN independent of its immunological effects. The current prospective randomized cohort study was conducted to compare different immunosuppressive therapies to identify agents that offer a greater remission rate with fewer adverse effects.

Patients and methods

Patients

This prospective randomized cohort study was conducted from January 2009 to May 2013. Ninety adult patients from the Second Affiliated Hospital of Harbin Medical University in China aged 18 to 75 years were recruited for this study. All participating patients signed the informed consent. They all received a diagnosis of membranous nephropathy by renal biopsy and laboratory examination. All of them had persistent proteinuria (> 8 g/d) after observation for at least 1 month and met the diagnostic criteria for nephrotic syndrome. They had not previously received any immunosuppressive treatment. The patients who had serum creatinine levels >133 μmol/L, active infection, diabetes mellitus, autoimmune disease, tumors, liver function test abnormalities, or active peptic ulcer disease were excluded. This study was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University and was conducted according to the principles of the Declaration of Helsinki.

Study design and immunosuppressive regimens

The 90 patients were randomly administered corticosteroid combined with TAC, CYC, or MMF. TAC was administered at 0.05 mg/kg/d divided into two doses at intervals of 12 hours initially. The dose was adjusted to achieve a blood trough concentration of 4—8 ng/mL for 6 months and then reduced to 2—4 ng/mL in the subsequent 3 months. CYC was administered by intravenous injection at a the dose of 750 mg/m^2 once a month for 6 months, which was then reduced to 750 mg/m^2 every 3 months. Patients received MMF at 1.5—2.0 g/d in two doses. Oral corticosteroid was administered at a dose of 0.5 mg/kg/d in the TAC group and 1 mg/kg/d in the other two groups for 2 months, which was reduced by 5 mg/d every 2 weeks to 20 mg/d. At that point, corticosteroid was tapered to zero according to the condition of the patient. This study lasted for 9 months after the immunosuppressants were prescribed.

Symptomatic treatment

Antihypertensive agents were administered to achieve a target blood pressure (systolic < 130 mmHg and diastolic < 80 mmHg). Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers were not initiated during follow up, but were continued in patients who were already on such treatment prior to recruitment. Anticoagulant drugs and simvastatin were also prescribed to all the patients.

Outcome parameters

The end point of this study was complete remission (CR) or partial remission (PR). CR was defined as a daily proteinuria