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ORIGINAL ARTICLE

Early initiation of immunosuppressive treatment in membranous nephropathy patients

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Background: Suggestion for the management of idiopathic membranous nephropathy (IMN) includes 6 months of observation, followed with steroid plus alkylating agent. However, delayed immunosuppression exposes the kidneys to persistent damage. This study aimed to examine the benefit of early immunosuppression in IMN patients.
Method: A retrospective study was performed. From 1993 to 2013, 161 IMN patients were enrolled. Patients receiving immunosuppression within 6 months after diagnosis were classified as initial-treatment group, whereas other patients as initial-no-treatment group. The clinical outcomes and complication were examined.
Result: Patients in the initial-treatment group had lower serum albumin concentration, less diabetes, and were younger. Steroid monotherapy is the main immunosuppression (64.5%) in this group. The initial-treatment group had a higher complete and partial remission rate than the initial-no-treatment group 6 months (52.9% *vs.* 35.0%, $p = 0.05$) and 12 months (71.1% *vs.* 45.0%, $p = 0.003$) after diagnosis. A similar result was seen between initial-steroid monotherapy and initial-no-treatment patients. Early immunosuppression is an independent predictor of

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remission within 1 year [hazard ratio (HR) = 2.09; 95% confidence interval (CI) = 1.25—3.49; $p = 0.005$] and estimated glomerular filtration rate (eGFR) decline over 50% during the follow-up. (HR = 0.33; 95% CI = 0.13—0.86; $p = 0.02$). The initial-treatment group also had a low frequency of eGFR decline over 50% ($p = 0.001$) and low combined end-stage renal disease/mortality ($p = 0.001$) compared with the initial-no-treatment group, but without more immunosuppression-related complication.

Conclusion: In contrast to Western countries, early immunosuppression (even steroid monotherapy) in our patients is associated with better remission in the 1st year and renal preserve. Further randomized controlled trials are needed to clarify the benefit of early immunosuppression in IMN patients, especially with oriental ethnic background.

Introduction

Membranous nephropathy (MN) is a major cause of nephrotic syndrome of non-diabetic origin in adults.[1,2] About 75% of cases are idiopathic and 25% are secondary which relates to a variety of causes, including autoimmune, infection, drugs, and malignancies.[3—7] The characteristic pathological change is capillary walls thickening resulting from immune complex formation on the subepithelium of the glomerular basement membrane.[8] Most idiopathic MN (IMN) is now believed to be an autoimmune disease where the podocyte is the target and the source of autoantigen,[9—12] such as M-type transmembrane phospholipase A2 receptor or thrombospondin type-1 domain-containing 7A.[13,14]

Based on the concept of underlying immune dysfunction in IMN, the main management of MN depends on immunosuppression in addition to supportive care with angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), lipid-lowering agents, adequate control of blood pressure and patient education.[15—17] According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline in 2012,[18] treatment with Ponticelli regimen is recommended. This regimen is a 6-month course of chlorambucil/cyclophosphamide and steroids in alternating monthly cycles.[19] This regimen increases the probability of remission of proteinuria and has long-term benefits for renal function preservation.[20] Observation without immunosuppression for 6 months is also suggested because spontaneous remission rate was over 30%, and a high complication rate of Ponticelli regimen was found.[21] However, delayed treatment of immunosuppression exposes patients with no later remission to persistent damage during observation. The best strategy is to find a predictor to predict whether the patient will get spontaneous remission or she/he needs immunosuppression or not. However, there is no such predictor available at present. The efficacy of corticosteroid monotherapy is also still being debated. Two randomized control trials in Western countries have shown that oral steroid monotherapy is not superior to placebo therapy alone in IMN.[22,23] In a Japanese study, corticosteroid monotherapy was associated with significantly better renal survival than supportive therapy only. However, there is still no randomized controlled trial examining the responsiveness of Asian patients with primary MN to steroid monotherapy.[24] In Western countries, the risk of end-stage renal disease (ESRD) in IMN patients is around 20—40% 10 years after diagnosis,[25,26] while the risk in Asian countries is lower than 10% during follow-up.[24,27,28] These studies indicate that the outcome of IMN is variable among different races and geography.

In this retrospective study, we enrolled IMN patients who were diagnosed during 1993 to 2013. The clinical characteristics, predictors of remission, and risk factors for renal survival in these patients were examined. The issue of timing of immunosuppression and the outcome of steroid monotherapy are also described.

Methods

Patients

From 1993 to 2013, patients aged older than 18 years old with the pathological diagnosis of MN at National Taiwan University Hospital were screened. We excluded patients with secondary MN, inadequate laboratory data record before/after renal biopsy, followed-up less than 1 year, and those who took immunosuppressant before biopsy. All clinical data were collected until March 2016.

Clinical parameters

The demographic characteristics and initial laboratory data of enrolled patients prior to biopsy were recorded. These data included age, sex, body mass index, diabetes (DM), hypertension (HTN), blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR, calculated by Chronic Kidney Disease Epidemiology Collaboration formula),[29] serum albumin, total cholesterol, and the magnitude of urine protein loss [either urine protein/creatinine ratio (UPCR) or daily urine protein loss].

The degree of proteinuria was evaluated using UPCR. The date of achieving the first remission in each patient was recorded. Renal function decline was expressed as the ratio of the latest eGFR to the initial eGFR. The latest eGFR was recorded at the last clinic visit before March 2016 or before the occurrence of ESRD or death.

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