Int J Clin Exp Med 2014;7(1):255-261
www.ijcem.com /ISSN:1940-5901/IJCEM1311017

Original Article

Effect of steroid and cyclosporine in membranous nephropathy that is resistant to steroid and/or cytotoxic treatment

Melahat Coban[1], Remziye Nur Eke[2], Filiz Kizilates[3], Secil Ucar[4], Fatih Dede[5]

[1]Department of Nephrology, Antalya Education and Research Hospital, Antalya, Turkey; [2]Department of Family Practice, Antalya Education and Research Hospital, Antalya, Turkey; [3]Department of Infectious Disease and Clinical Microbiology, Antalya Education and Research Hospital, Antalya, Turkey; [4]Department of Ear, Nose and Throat Diseases, Private Acıbadem Fulya Hospital, Istanbul, Turkey; [5]Department of Nephrology, Ankara Numune Education and Research Hospital, Ankara, Turkey

Received November 19, 2013; Accepted December 16, 2013; Epub January 15, 2014; Published January 30, 2014

Abstract: Membranous Nephropathy (MN) is a glomerular disease characterized by proteinuria. The etiology is unknown in many cases, while in some patients MN may be secondary to infection, to other diseases, or to exposure to drugs and toxic substances. The prognosis of the disease is variable, 1/3 of patients can have spontaneous remission; patients with nephrotic proteinuria, those with advanced tubulointerstitial changes and those with increased serum creatinine at presentation have a poorer prognosis. Although MN is one of the most common causes of adult-onset Nephrotic Syndrome (NS), its management is still controversial. Corticosteroids have been used for many years as the basic treatment, though with controversial results. Controversial results have been obtained with cytotoxic agents. Cyclosporine has been shown to be effective in the treatment of this disease. We have evaluated the results of 23 patients (14 males, 9 females aged between 26-53) diagnosed with Idiopathic MN (IMN) who have received cyclosporine because of the relapse or persistence after steroid and/or cytotoxic treatment. At the end of a 12-month follow-up, 8 patients had (34.8%) complete remission, 8 (34.8%) had partial remission, 2 (8.7%) had persistent proteinuria and 5 patients (21.7%) had no response to the treatment. There was a significant decrease in proteinuria throughout the study. There was no significant difference in total protein, albumin and creatinine levels between before and after the treatment. Our results indicate that patients with MN who do not respond well or have-relapse after steroid and/or cytotoxic therapy, should be offered cyclosporine. We think that in the future; long-term studies which are prospective and randomized with an extensive number of patients will be effective on the treatment of MN.

Keywords: Membranous nephropathy, steroid, cyclosporine

Introduction

Membranous Nephropathy (MN) is characterized by the uniform thickening of the glomerular basal membrane by sub-epithelial immune complex deposition. Immune complexes are seen as granular IgG on the immune florescent and electron-dense deposits on the electron microscope [1].

Until today, Idiopathic MN (IMN) has been presented as the leading cause of primary or idiopathic Nephropathic Syndrome (NS) in adults. However, in recent studies Focal Segmental Glomerulosclerosis (FSGS) has been reported as the most common cause of idiopathic NS in Western countries [2]. Most textbooks argue that idiopathic MN shows peak incidence rates for people aged 40-60 (mean age 55). IMN is 2/1 more common in men than in women [3].

Although there might be secondary causes (drugs, systemic lupus erythematosus, malignities, viral infections etc.), MN with unknown etiology is called idiopathic or primary MN. D-penicillamine, captopril, clopidogrel, lithium, probenecid, sulindac and NSAI drugs are the ones that cause MN most frequently. The most

common types of cancer associated with MN are lung, prostate, colon, kidney, breast and stomach cancers, successively [4].

MN may cause progressive loss of renal function and this is more frequent in patients with proteinuria of more than 8-10 gr/day and with high serum creatinine at presentation [5, 6]. Some patients demonstrate spontaneous remission and their renal function remain stable for years while almost half of the patients have final stage renal failure or lose their life due to developing complications in 10-15 years after the symptoms have started [7].

The symptomatic treatment of MN comprises anti-hypertensive, antiproteinuric, antihyperlipidemic, anticoagulant treatment and edema control. The cases with slight edema must be treated by limiting salt intake in patients' daily diet and administering a low dose of hydrochlorothiazide while severe cases must be treated by high dose of diuretics. In cases being resistant to high dose of loop diuretics, a combination of loop diuretics and hydrochlorothiazide might be useful. For blood pressure control, sodium-limited diet and medication (ACE inhibitor or ARB) is preferred. A protein-limited diet, an ARB or ACE inhibitor and NSAI's are used in an antiproteinuric treatment.

There is no fixed consensus on the specific treatment of MN. The effects of steroids on MN are controversial. Despite the controversial results, steroids have remained the basic treatment of MN for many years. Recent meta-analysis studies comparing steroid-based treatment and symptomatic treatment have demonstrated that the use of steroids is not more effective on remission and 5-year renal survival [8]. Immune suppressive agents (chlorambucil, cyclophosphamide) reduce proteinuria and provide significant recovery for long-term renal survival [9, 10]. Some studies have shown that steroid therapy is significantly helpful when used with cytotoxic therapy.

Materials and methods

Our study included 23 patients who presented with NS to the Nephrology Department at Numune Training and Research Hospital in Ankara between March 2004 and June 2009, and had renal biopsies, after which they were diagnosed with MN and the secondary causes were eliminated. After the diagnosis, patients were given prednisolone and/or cytotoxic therapy (Endoxan or MMF or azathioprine) for at least one year. However, the patients were followed whose proteinuria continued for 3.5 gr/day on 24-hour urine collection and to whom cyclosporine A were additionally administered after stopping the cytotoxic therapy. Levels of serum urea, creatinine, total protein, albumin, lipid profile, hgb, hepatitis panel, GFR and proteinuria on 24-hour urine collection were assessed before the treatment and on the 0-3-6-9-12th months during cyclosporine therapy.

Conservative treatment was planned according to the visits. All patients received ramipril and/or valsartan (the highest tolerable dose), aspirin and famotidine throughout the study. In addition, all patients were also administered lipid lowering drugs.

Data analysis was made using SPSS (Statistical Package for Social Science) version 11.5 for Windows. Descriptive statistics describe the mean ± standard deviation or median mode (minimum-maximum) for continuous variables whereas they describe the number of cases and rates (%) for nominal variables.

Wilcoxon Signed-Rank Test with Bonferroni's Correction was used for analyzing whether there was a statistically significant change among follow-up times with regards to clinical measurements. Further, Spearman's Correlation Test with Bonferroni's Correction was used for analyzing whether there was a statistically significant correlation between the duration of the disease and the amount of drug doses, and the clinical measurements obtained in the post-treatment period compared to the pre-treatment. Mann Whitney's U Test with Bonferroni's Correction was used for analyzing whether the change that occurred in gender-based clinical measurements after the treatment was statistically significant.

In all possible comparisons, Bonferroni's correction was made in order to take a Type I mistake under control. The results for $p<0.0033$ were accepted to be statistically significant.

Definitions

Complete remission, partial remission and persistent proteinuria with normal and stable renal

Table 1. Demographic Features

Variables	n=23
Age	37.3 ± 7.7 (23-53)
Gender	
Male	14 (60.9%)
Female	9 (39.1%)
Body Mass Index	26.1 ± 3.5
Hypertension	6 (26.1%)
Hyperthyroid	1 (4.3%)
Duration of disease (day)	1170 (390-5760)

Table 2. Duration of Drug Use and Cyclosporine Dose for the Disease

Variables	n=23
Endoxan (day)	90
Azathioprine (day)	675 (270-1080)
Mycophenolate mofetil (day)	60 (60-60)
Cyclosporine (day)	450 (379-870)
Prednol (day)	540 (300-4110)
Cyclosporine (dose) - mg/kg/day	4 (3-5)

Table 3. Albumin Levels at the Follow-up Times

Time	Albumin
Pre-treatment	29 (18-98)
Post-treatment 3rd month	33 (25-48)
Post-treatment 6th month	35 (10-49)
Post-treatment 9th month	35 (10-44)
Post-treatment 12th month	37 (18-49)
p[a]	0.296

[a]Friedman test.

function were respectively defined as ≤0.2 g/10 mmol creatinine, 0.2-2.0/10 mmol creatinine and 2.1-3.4 g/10 mmol creatinine, respectively.

Results

Twenty-three patients with MN were included in our study. There were 14 (60.9%) male patients and 9 (39.1%) female patients. The age range was between 26 and 53 years with an average of 37 years. The average body mass index was 26. Before the treatment, 26% of the patients had HT and 1 patient had hyperthyroid symptoms. The average duration of disease estimated from the date of the first biopsy onwards was 1170 days. The demographic features of the cases are shown in **Table 1**.

Table 4. Total Protein Levels at the Follow-up Times

Time	Total Protein
Pre-treatment	54 (47-98)
Post-treatment 3rd month	59 (50-73)
Post-treatment 6th month	60 (33-76)
Post-treatment 9th month	62 (33-75)
Post-treatment 12th month	62 (41-79)
p[a]	0.080

[a]Friedman test.

Table 5. Creatinine Levels at the Follow-up Times

Time	Creatinine
Pre-treatment	1 (0.69-1.0)
Post-treatment 3rd month	1 (0.69-1.0)
Post-treatment 6th month	1 (0.82-3.0)
Post-treatment 9th month	1 (0.60-3.1)
Post-treatment 12th month	1 (0.60-2.4)
p[a]	0.307

[a]Friedman test.

Table 6. Proteinuria Levels at the Follow-up Times

Time	Proteinuria
Pretreatment	6500 (1100-12000)
Post-treatment 3rd month	2100 (58-8792)
Post-treatment 6th month	1800 (90-9654)
Post-treatment 9th month	730 (50-11540)
Post-treatment 12th month	900 (27-18000)
p[a]	<0.001

[a]Friedman test.

Patients were administered cyclosporine for 450 days long on average. Duration of drug use and Cyclosporine döşe are shown in **Table 2**. The cyclosporine dose they received was 4 mg/kg/day on average. No statistically significant difference was observed among albumin and total protein levels throughout the 12 month-study period (p=0.296, p=0.080, respectively). The albumin levels are shown in **Table 3**. No statistically significant difference was observed among creatinine levels throughout the follow-up period compared to the pre-treatment period (p=0.080) (**Table 4**).

No statistically significant decline was observed at proteinuria on the 3rd, 6th and 9th months among follow-up times compared to the pre-

treatment period (p<0.001) (**Table 5**). Proteinurea levels are shown in **Table 6**. No statistically significant difference was observed at triglyceride, total cholesterol, and LDL cholesterol levels during the follow-up compared to the beginning of the treatment (p=0.511, p=0.052, p=0.120, respectively).

At the end of our study, 8 (34.8%) patients had complete remission, 8 (34.8%) patients had partial remission, 2 (8.7%) patients had persistent proteinuria and 5 (21.7%) patients had no response to the treatment. Three patients had relapse despite the drug-induced reduction in proteinuria levels throughout the follow-up. The average duration of remission in patients with complete remission was 9 months whereas it was 6 months in patients with partial remission. At the end of a 12-month follow-up period, 2 patients had DM, 4 patients had HT, 5 patients had nephrotoxicity, 4 patients had hyperpotassemia, 4 patients had high uric acid, 5 patients had hyperlipidemia, 1 patient had gingival hyperplasia and 5 patients had increased hair growth, but no patients developed hepatotoxicity in relation to the known side effects of cyclosporine. However, the treatment was never interrupted as no side-effect was serious enough to cause an interruption. No side effects were observed in 7 patients.

GFR levels of all patients were >100 at the beginning, but 5 patients had a decrease in their GFR levels and increase in creatinine levels at the 12th month follow-up visit.

Discussion

Although there are a lot of controlled studies using steroid and immune-suppressive regimens, the treatment of MN is still controversial. According to some authors, there is no need for a specific treatment as the clinical course of the disease is stable, while others suggest treating patients using aggressive cytotoxic drug protocols.

Two controlled studies demonstrated that administering steroids alone was not effective enough for the treatment of membranous nephropathy [11, 12]. Immune-suppressive drugs have been used for the treatment of membranous nephropathy for adults since 1986. These agents (chlorambucil, cyclophosphamide) reduce proteinuria and leads to significant long-term recovery for renal survival [9, 10].

The combination of oral steroids and cytotoxic drugs is another approach. It is the best and the most widely accepted Ponticelli regimen. This regimen involves a 6-month cyclic change occurred when methylprednisolone (1 gram IV/day for 3 days) is administered, which is followed by oral prednisolone for 1 month and oral chlorambucil for the next month [13]. In Ponticelli's study, it was observed that 10% of the treatment group and 50% of the control group developed renal dysfunction and 4 of 39 patients in the control group and 1 one of 42 patients in the treatment group needed dialysis at the end of a 5-year follow-up. At the end of the 10-year follow-up period, 88% of the treatment group and 47% of the control group developed complete remission or partial remission of nephrotic syndrome. Eight per cent of the treatment group and 40% of the control group had renal insufficiency [14, 15].

There are a few controlled studies carried out on the use of cyclosporine for the MN treatment. Cattran et al reported the development of remission without any serious impairment of the renal function with the use of cyclosporine in the treatment of MN [16]. In spite of this, the relapse rate was 33% at the end of a one-year treatment, which was found similar to that observed for other cytotoxic drugs [17, 18]. Nevertheless, a combination of cyclosporine and steroids was administered in all these studies.

Alexopoulos et al compared patients receiving cyclosporine and steroids to those receiving cyclosporine alone for 6 and 12 months long. At the end of a six-month study, 19% of the combined-therapy patients and 5% of the monotherapy patients had complete remission, and the statistical significance was emphasized [19]. At the end of a 12-month follow-up, 35% of the combined-therapy patients and 20% of the mono-therapy patients had complete remission. Partial remission was observed in the rest of the patients. Throughout this period, no relapse was observed in the patients. The rate of the complete remission was similar to the results of the study conducted by Rostoker et al., in which a high dose of cyclosporine was used for 15 months. The results were better

than those reported by Cattran et al. Rostoker et al. [20] reported that 4 patients had complete remission and 7 patients had incomplete remissions after the cyclosporine treatment carried out on 15 patients with nephrotic syndrome. At the end of a 12-month study conducted by Cattran et al. it was observed that only 7.1% of the patients had complete remission while 39% patients had partial remission. According to Cattran, all these results demonstrated that administering low dose of cyclosporine alone or in combination with steroids in a 12-month long period led to increased complete remission in patients.

Guasch et al. reported that in 10 of 14 patients with MN there was a decrease from nephrotic range proteinuria to the non-nephrotic range in 2-4 weeks after the treatment [21]. In our study, a significant decrease was observed after the 3rd month in the proteinuria levels of patients who were administered cyclosporine, which showed the efficiency of the treatment ($p<0.001$).

Meyrier reported that 20% of the patients had complete remission and 25% of them had partial remission after receiving cyclosporine [22]. In our study, it was observed that 34.8% of the patients receiving cyclosporine had complete remission and 34.8% had partial remission, 8.7% persistent proteinuria, and 21.7% had no response after the end of an 12-month follow-up.

In a study conducted in Germany, only 14 of 41 patients receiving cyclosporine alone or a combination of cyclosporine and steroids had complete remission, and the mean response time was found as 7 months [23]. Thus, adding prednisolone into the treatment in low doses might be influential in remission. However, cyclosporine was added without changing the steroid dose that the patients received in our study. At the end of a 12-month of observation, the mean duration of complete remission was 9 months whereas it was 6 months in patients with partial remission.

Even though the latest studies demonstrated that the rate of spontaneous remission [24] and progression in female patients was slower [25, 26], no significant difference was observed on the levels between male and female patients in our study.

Nowadays cyclosporine is increasingly used in the treatment of MN. It has been shown to reduce proteinuria in patients resistant to steroids. It has been suggested that it can be used in patients who do not respond to cytotoxic treatment, and that cyclosporine can even be preferred instead of cytotoxic treatment. However, the side effects of the treatment are significant. Besides minor side effects such as hypertrichosis, nausea-vomiting, headache, and gingival hyperplasia, major side effects may also appear such as hypertension, hyperkalemia and nephrotoxicity. In this study, 2 patients had DM, 4 patients had HT, 5 patients had nephrotoxicity, 4 patients had hyperpotassemia, 4 patients had high uric acid, 5 patients had hyperlipidemia, 1 patient had gingival hyperplasia and 5 patients had increased hair growth, but no patients developed hepatotoxicity. No side effects were observed in 7 patients. Furthermore, no side effect was serious enough to cause an interruption in the treatment of the patients.

Cyclosporine is a nephrotoxic drug, which may cause hypertension and progressive renal insufficiency. This risk depends on the dose and age of the patients [27]. Risk is higher especially in patients with high plasma creatinine level and whose renal biopsy revealed a tubulointerstitial lesion at the beginning [28]. Therefore, cyclosporine is not recommended for the treatment of patients whose creatinine clearance is under 60 ml/min. and/or have serious hypertension and/or have serious interstitial fibrosis and tubular atrophy detected in the renal biopsy. In our study, no patient had a GFR level under 60 ml/min at the beginning. Despite this, 5 patients had decreased GFR levels and increased creatinine levels at the end of the follow-up. Six patients had hypertension but their blood pressure was regulated by medication and diet.

Patients who do not have any contraindications for receiving cyclosporine must be monitored in case nephrotoxicity might develop due to arteriolar change and irreversible interstitial fibrosis. When there is a 30% increase in plasma creatinine, the nephrotoxicity risk is 10-12%, whereas that risk is estimated as 50% when plasma creatinine level increases 2-fold from the baseline level. If plasma creatinine level increases more than 30% from the baseline level, it is recommended to stop cyclosporine

for at least one month for the sake of safety. If plasma creatinine level falls under 10% of normal or baseline level, the drug could be administered again. In our study, 5 patients developed drug-induced nephrotoxicity. Two of these patients had complete remission while 3 of them had partial remission. The medication was not interrupted when there was 30% of increase in creatinine levels in comparison to the baseline levels.

In conclusion, cyclosporine can be considered as a secondary care treatment for treating serious MN with nephrotic proteinuria. Indeed, remission might last for many years in patients having a response to the 6-month therapy of methylprednisolone and chlorambucil or cyclophosphamide. If relapse occurs in patients with a response to the first course of treatment, the same course of treatment can be administered again. However, administering 6-month steroid and alkylating agents by changing them might result in long-term side effects, and not be safe. Thus, if there is no response from patients, cyclosporine can be administered. However, after the interruption of steroids, it is better to wait for at least 12 months before starting cyclosporine in order to see the late term response. In our study, we did not wait for the time to pass and cyclosporine was started in all patients within 3 months at the latest.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Filiz Kizilates, Antalya Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıklari ve Klinik, Mikrobiyoloji AD, Antalya, Turkey. Tel: 00 90 242 249 18 00; Fax: 00 90 242 249 44 62; E-mail: filizkizilates@gmail.com

References

[1] Davison AM, Cameron JS, Kerr DNS, Ogg CS, Wilkinson RW. The natural history of renal function of in untreated idiopathic membranous glomerulonephritis in adults. Clin Nephrology 1984; 22: 61-67.

[2] Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA Jr, Germain MJ. Changing incidence of glomerular diseases in adults. Am J Kidney Dis 2000; 35: 878-83.

[3] Hogan SL, Muller KE, Jenette JC, Falk RJ. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis 1995; 25: 862-75.

[4] Ponticelli C, Glassock RJ. Treatment of primary glomerulonephritis. 2nd edition. 2010; pp: 267.

[5] Pei Y, Cattran D, Greenwood C. Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. Kidney Int 1992; 42: 960-966.

[6] Bazzi C, Petrini C, Rizza V, Arrigo G. A modern approach to selectivity of proteinuria and tubulointerstitial damage in nephrotic syndrome. Kidney Int 2000; 58: 1732-1741

[7] Ponticelli C, Zucchelli P, Imbasciati E, Cagnoli L, Pozzi C, Passerini P, Grassi C, Limido D, Pasquali S, Volpini T. Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nefropathy. N Eng J Med 1984; 310: 946-50.

[8] Hogan S, Muller KE, Jennette JC, Falk RG. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis 1995; 25: 862-875.

[9] Ponticelli C, Zucchelli P, Passerini P, Cesana B, Locatelli F, Pasquali S, Sasdelli M, Redaelli B, Grassi C, Pozzi C. A 10-years follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int 1995; 48: 1600-1604.

[10] Ponticelli C, Altieri P, Scolari F, Roccatello D, Cesana B, Melis P, Valzorio B, Sasdelli M, Pasquali S, Pozzi C, Piccoli G, Lupo A, Segagni S, Antonucci F, Dugo M, Minari M, Scalia A, Pedrini L, Pisano G, Grassi C, Farina M, Bellazzi R. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclosphosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 1998; 9: 444-450.

[11] Cattran DC, Delmore T, Roscoe J, Cole E, Cardella C, Charron R, Ritchie S. A randomized controlled trial of prednisone in patients with idiopathic membranous neprhopathy. N Engl J Med 1989; 320: 210-215.

[12] Cameron JS, Healy MJ, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolene in idiopathic membranous nephropathy with nephrotic syndrome in adults: the MRC Glomerulonephritis Working Party. QJM 1990; 74: 133-156.

[13] Kincaid-Smith P. Pharmacological management of membranous nephropathy. Curr Opin Nephrol Hypertens 2002; 11: 149-54.

[14] Ponticelli C, Passerini P. Treatment of membranous nephropathy. Nephrol Dial Transplant 2001; 16: 8-10.

[15] Ponticelli C, Zucchelli P, Passerini P. A 10-year follow up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int 1995; 48: 1600-4.

[16] Cattran DC, Appel GB, Hebert LA. Cyclosporine in patients with steroid-resistent membranous nephropathy: a randomized trial. Kidney Int 1995; 59: 1484-1490.
[17] Ehrenreich T and Churg J. Pathology of membranous nephropathy. In: Sommers SC, eds. Pathology Annual. New York: Appleton-Century-Crofts; 1986. pp: 145-146.
[18] Ponticelli C and Villa M. Does cyclosporine have a role in the treatment of membranous nephropathy? Nephrol Dial Transplant 1999; 14: 23-25.
[19] Alexopoulos E, Papagianni A, Tsamelashvielli M, Leontsini M, Memmos D. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. Nephrol Dial Transplant 2006; 21: 3127-32.
[20] Rostoker G, Belghiti D, Maadi AB. Long-term cyclosporine A therapy for severe idiopathic membranous nephropathy. Nephron 1993; 63: 335-341.
[21] Guasch A, Suraniy M, Newton L, Hall BM, Myers BD, Short-term responsiveness of membranous glomerulonephropathy to cyclosporine. Am J Kidney Dis 1992; 20: 472-481.
[22] Meyrier A, Antiproteinuric and immunological effects of cyclosporine A in the treatment of glomerular diseases. Nephrol Dial Transplant 1992; 7: 80-84.
[23] Fritsche L, Budde K, Farber L, Charisse G, Kunz R, Gaedeke J, Neumayer HH. Treatment of membranous glomerulopathy with cyclosporine A: how much patience is reguired? Nephrol Dial Transplant 1999; 14: 1036-8.
[24] Laluck BJ, Cattran DC. Prognosis after a complete remission in adult patients with idiopathic membranous nephropathy. Am J Kidney Dis 1999; 33: 1026-32.
[25] Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P. Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study. Am J Kidney Dis 2000; 35: 157-65.
[26] Neugarten J, Acharya A, Silbiger SR. Effects of gender on the progression of nondiabetic renal disease: a meta-analysis. J Am Soc Nephrol 2000; 11: 319-29.
[27] Feutren G, Mihatsch MJ. Risk factor for cyclosporine-induced nephropathy in patients with autoimmune diseases. N Engl J Med 1992; 326: 1654-1660.
[28] Meyrier A, Noel H, Auriche P, Callard P and the Collaborative Group of the Societe de Nephrologie: Long-term renal tolerance of cyclosporine A treatment in adult idiopathic nephrotic syndrome. Kidney Int 1994; 45: 1446-1456.