Nephrourol Mon. 2017 January; 9(1):e42473. doi: 10.5812/numonthly.42473.

Published online 2016 November 14. **Research Article**

# Comparison of the Efficacy of Tacrolimus Versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy

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**Received** 2016 September 30; **Accepted** 2016 November 06.

## Abstract

**Background:** Immunosuppressive drugs have received the most attention for Idiopathic Membranous Nephropathy (IMN) that include alkylating agents such as tacrolimus and cyclosporine.
**Objectives:** This study was aimed to evaluate the efficacy of tacrolimus versus cyclosporine in the treatment of IMN in the Western region of Iran.
**Methods:** This clinical trial and double-blind study was performed on IMN patients based on the primary biopsy with a range of 15 to 70 years. The patients with secondary membranous nephropathy such as hepatitis B, hepatitis C and systemic lupus erythematosus were censored from the study. Group C was treated with cyclosporine 3 - 6 mg/kg/d and a low dose of prednisolone and Group T was treated with tacrolimus 0.05 mg/kg/d and low dose of prednisolone.
**Results:** 68 patients were entered in our study, 34 patients were randomly selected in Group T and 34 patients in Group C. The 24-hour urine protein reduced significantly in the two groups after the 3rd and the 6th month compared with the baseline. Uric acid increased in Group T after 3 and 6 months compared with the baseline ($P < 0.05$), but there was no significant difference in Group C. Creatinine clearance increased in two groups after 3 and 6 months compared with the baseline, however, it has been just as significant in Group T after 6 months. There was no significant difference in the two groups after 3 or 6 months from the first dialysis.
**Conclusions:** Cyclosporine and tacrolimus reduce proteinuria and serum creatinine after 6 months. Nonetheless, tacrolimus reduces urea and cyclosporine increases it. However, since the prevalence of the side effects of both drugs is similar, tacrolimus has better results in the treatment of IMN patients compared with cyclosporine.

*Keywords:* Nephropathy, Cyclosporine, Tacrolimus, Proteinuria

## 1. Background

Idiopathic membranous nephropathy (IMN) is the most prevalent glomerular disease which causes nephrotic syndrome (NS) in adults. Over 70% of patients are present with severe proteinuria and have a high risk of renal failure (1). IMN is the most prevalent form of NS in adults. The disease shows a benign or indolent period in the majority of patients, with a rate of spontaneous complete or partial relapse of NS as high as 30% or more (2). The efficacy and safety of immunosuppression are still controversial for IMN (3). Immunosuppressive drugs have received the most attention for IMN that includes alkylating agents such as chlorambucil, cyclophosphamide as well as calcineurin inhibitors such as cyclosporine and tacrolimus, mycophenolate mofetil, rituximab and adrenocorticotropic hormone (4). Tacrolimus has been used for treatment of IMN, however most patients who achieved relapse showed a high remission rate when tacrolimus was omitted after 6 - 12 months of therapy (5). Cyclosporine is effective in treating NS with IMN in adults, but its high relapse rate has remained a major concern (6). Furthermore, cyclosporine is an established option for treatment of IMN patients at a moderate or high risk of disease progression (4).

## 2. Objectives

This study evaluated the efficacy of tacrolimus versus cyclosporine in the treatment of IMN in the West of Iran.

## 3. Methods

### 3.1. Patients

This clinical trial and double-blind study was evaluated by the ethics committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (Thesis code: 9838)

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and is registered at http://www.irct.ir (registration number IRCT2014101912685N3). This study was performed on IMN patients based on a primary biopsy with a range of 15 to 70 years of age and who were referred to the special clinic of Kermanshah University of Medical Sciences. The patients with secondary membranous nephropathy such as hepatitis B, hepatitis C and systemic lupus erythematosus were censored from the study. The patients were divided into two groups that in terms of age and sex were matched with each other. One group (Group C) was treated with cyclosporine 3 - 6 mg/kg/d and a low dose of prednisolone and another group (Group T) was treated with tacrolimus 0.05 mg/kg/d and a low dose of prednisolone. All patients in the two groups were treated for 6 months. The laboratory results for each patient was diagnosed before the treatment as well as 3 and 6 months after the first treatment. The primary outcomes were complete or partial remission that defined as 24-hour urinary protein excretion < 0.3 or 3.0 g (with at least 50% reduction compared with baseline), respectively, in at least two consecutive visits (7).

### 3.2. Statistical Analysis

The analysis of the data was done with the SPSS version 16, a t-test was done to compare the difference between the mean values in two groups and a chi-square test was done for the correlation between the sex in two groups. P value < 0.05 was considered statistically significant.

## 4. Results

Sixty-eight patients were entered in the study, 34 patients were randomly selected in the tacrolimus group (Group T) and 34 patients in the cyclosporine group (Group C). The mean age for group T was 39.4 years and for group C was 36.2 years, without a significant difference between the two groups (P = 0.340). Furthermore, 13 patients (38.2%) were male in Group T and 16 patients (47%) in Group C. There was no significant difference between the two groups (P = 0.624). The difference between the other variables in the two groups was analyzed in Table 1. The differences were not significant (P > 0.05).

Table 2 shows the laboratory results in the two groups after the 3rd and the 6th month from the first dialysis versus the baseline as well as each other. Cholesterol reduced after 3 and 6 months versus baseline and 6 months versus 3 months in two groups (P < 0.05). Furthermore, the triglyceride reduced after 3 and 6 months compared with the baseline in Group T (P < 0.05), however in Group C, it reduced just after 6 months and has been significant (P < 0.05). The 24-hour urine protein reduced significantly in the two groups after 3 and 6 months compared with the baseline (P < 0.001). Fasting glucose increased after 3 and 6 months in the two groups versus the baseline (P < 0.05) and increasing after 6 months compared with 3 months was only significant in Group T (P < 0.05). Uric acid increased in Group T after the 3rd and 6th month compared with the baseline (P < 0.05), however in Group C, there was no significant difference (P > 0.05). Creatinine clearance increased in two groups after 3 and 6 months compared with the baseline, however it was just as significant in Group T after 6 months (P = 0.002). Systolic blood pressure decreased in two groups after 3 and 6 months compared with the baseline, however it was just as significant in Group T after 6 months (P = 0.033).

The number of patients with side effects in the two groups has been shown in Table 3. There was no significant difference in the two groups after the 3rd or 6th month from the first dialysis (P > 0.05).

## 5. Discussion

Based on our knowledge, there were few studies that showed the efficacy of tacrolimus versus cyclosporine in the treatment of IMN. Therefore, this study reports the affections of both drugs in IMN patients. The observation time for cyclosporine to effectively induce complete remission (CR) of NS in IMN adults should be at least 6 months. Long-term and low-dose of cyclosporine therapy is safe and effective to maintain CR in those responders (6). Cyclosporin A therapy at a dosage of 3 - 5 mg/kg/d is effective in inducing remission of NS in adult IMN patients within three months, with a response rate of 80% (8). One study (9) reported that starting treatment earlier with tacrolimus or intravenous cyclophosphamide (combined steroid) for 24 weeks was useful for Chinese adults with IMN in inducing relapse of severe proteinuria and quicker remission was seen in tacrolimus therapy. A total of 42 patients with IMN (range, 16 - 69 years) were treated with tacrolimus and prednisone that could delete IMN significantly. Prolonged tacrolimus treatment at a low blood concentration can reduce the illness persistently, with a low recurrence rate and gratifying safety (5). Praga et al. (10) reported approvingly the efficacy of tacrolimus monotherapy in IMN patients with NS and Ballarin et al. (11) used a combination of tacrolimus, prednisone and mycophenolate mofetil in IMN therapy and demonstrated a 73.4% the remission rate. In addition, a clinical trial in China reported an 85% remission rate with tacrolimus versus 65% with cyclophosphamide in IMN patient therapy (12). A total of 259 patients in four studies showed that therapy with tacrolimus plus corticosteroid had a higher complete remission rate compared to therapy with cyclophosplamide plus corticosteroid (P < 0.05),

**Table 1.** The Baseline Variables of the Patients

| Variables | Group T[a] ,n = 34 | Group C[b] ,n = 34 | P Value |
|---|---|---|---|
| **Sex, n (%)** | | | 0.624 |
| Male | 13 (38.2) | 16 (47.0) | |
| Female | 21 (61.8) | 18 (53.0) | |
| **Age** | | | |
| Mean ± SD | 39.4 ± 13.5 | 36.2 ± 14.3 | 0.340 |
| **Urea, mg/dL** | | | |
| Mean ± SD | 44.6 ± 23.8 | 34.8 ± 17.5 | 0.060 |
| **Creatinine, mg/dL** | | | |
| Mean ± SD | 1.3 ± 0.7 | 1.3 ± 0.8 | 0.490 |
| **Cholesterol, mg/dL** | | | |
| Mean ± SD | 251.1 ± 42.0 | 282.5 ± 123.2 | 0.730 |
| **Triglyceride, mg/dL** | | | |
| Mean ± SD | 240.9 ± 88.9 | 251.0 ± 114.9 | 0.680 |
| **24-hour urine protein, mg/24 hrs** | | | |
| Mean ± SD | 3899.3 ± 1102.0 | 3917.8 ± 1499.2 | 0.950 |
| **Fasting glucose, mg/dL** | | | |
| Mean ± SD | 94.9 ± 14.5 | 91.9 ± 13.6 | 0.380 |
| **Uric acid, mg × 100** | | | |
| Mean ± SD | 6.1 ± 1.4 | 6.5 ± 1.6 | 0.420 |
| **Creatinine Clearance, %** | | | |
| Mean ± SD | 77.2 ± 21.8 | 73.2 ± 33.3 | 0.750 |
| **Systolic blood pressure, mmHg** | | | |
| Mean ± SD | 126.2 ± 16.1 | 128.5 ± 18.8 | 0.520 |
| **Diastolic blood pressure, mmHg** | | | |
| Mean ± SD | 81.3 ± 4.8 | 81.3 ± 7.3 | 0.920 |
| **Hemoglobin concentration, g/dL** | | | |
| Mean ± SD | 12.2 ± 1.1 | 12.5 ± 1.4 | 0.360 |

[a] Group T: treated with tacrolimus.
[b] Group C: treated with cyclosporine.

however it was not significant on total remission, partial remission and adverse effects. During the entire follow-up period, serum creatinine level remained stable in both groups. Tacrolimus is more effective than cyclophosphamide by achieving complete remission in patients with IMN (3). A meta-analysis study, including 359 Chinese patients (10), showed that tacrolimus-based therapy was associated with a faster response than cyclophosphamide at the 6th month, however, without significant difference between the two groups at the 12th month in Chinese adults (13). Cyclosporine (7) and tacrolimus (10) reduce proteinurea in MN. A total of 122 MN patients with NS and stable renal function were treated with tacrolimus. The duration of that treatment was 17.6 (± 7.2) months, including a full-dose and a tapering period. Tacrolimus monotherapy was an effective and safe option for the treatment of MN with stable renal function. Remissons were frequent in patients with PR and could partially be prevented by a longer reducing period (14). Xu et al. (15) reported that there were fewer side effects in the tacrolimus group compared with the cyclophosphamide group, indicating a better treatment tolerance in the tacrolimus group. Chen et al. (12) proposed that the remission rate at the end of the 6th month was significantly more in the tacrolimus group compared with

**Table 2.** The Laboratory Results in Two Groups After the First Dialysis

| Mean of Variables | After 3 Months | P Value[a] | After 6 Months | P Value[a] | P Value[b] |
|---|---|---|---|---|---|
| **Urea** | | | | | |
| Group T[c] | 39 | 0.060 | 38.6 | 0.082 | 0.969 |
| Group C[d] | 38.1 | 0.214 | 41.2 | 0.058 | 0.198 |
| **Creatinine** | | | | | |
| Group T | 1.2 | 0.180 | 1.2 | 0.180 | 0.690 |
| Group C | 1.2 | 0.340 | 1.2 | 0.920 | 0.840 |
| **Cholesterol** | | | | | |
| Group T | 225.3 | 0.002 | 208.4 | 0.001 | 0.001 |
| Group C | 227.6 | 0.001 | 196.5 | 0.001 | < 0.001 |
| **Triglyceride** | | | | | |
| Group T | 210.2 | 0.028 | 211.6 | 0.035 | 0.530 |
| Group C | 245.3 | 0.210 | 208.0 | 0.004 | 0.010 |
| **24-hour urine protein** | | | | | |
| Group T | 1968.0 | < 0.001 | 1433.4 | < 0.001 | 0.210 |
| Group C | 2406.3 | < 0.001 | 1783.3 | < 0.001 | 0.110 |
| **Fasting glucose** | | | | | |
| Group T | 104.4 | 0.001 | 111.3 | < 0.001 | 0.020 |
| Group C | 100.5 | 0.002 | 100.6 | 0.001 | 0.930 |
| **Uric acid** | | | | | |
| Group T | 6.6 | 0.009 | 6.9 | 0.005 | 0.040 |
| Group C | 6.7 | 0.310 | 6.4 | 0.900 | 0.250 |
| **Creatinine Clearance** | | | | | |
| Group T | 79.2 | 0.420 | 93.6 | 0.002 | 0.006 |
| Group C | 80.2 | 0.670 | 93 | 0.080 | 0.080 |
| **Systolic blood pressure** | | | | | |
| Group T | 122.3 | 0.068 | 93.6 | 0.033 | 0.570 |
| Group C | 125.5 | 0.127 | 126.0 | 0.319 | 0.630 |
| **Diastolic blood pressure** | | | | | |
| Group T | 80.3 | 0.220 | 78.7 | 0.059 | 0.090 |
| Group C | 79.1 | 0.070 | 79.3 | 0.110 | 0.870 |
| **Hemoglobin concentration** | | | | | |
| Group T | 12.3 | 0.920 | 12.4 | 0.530 | 0.360 |
| Group C | 12.3 | 0.140 | 12.3 | 0.360 | 0.900 |

[a] Compared with the baseline.
[b] After 6 months compared with after 3 months.
[c] Group T: treated with tacrolimus.
[d] Group C: treated with cyclosporine.

the cyclophosphamide group (85% versus 65%, $P < 0.05$). The decrease of proteinuria was significantly greater in the tacrolimus group. At the end of the 12th month, the relapse rates were comparable between these 2 groups. Patients treated with tacrolimus were more likely to develop glucose intolerance or diabetes mellitus, infection and hypertension. Tacrolimus plus corticosteroids is another therapeutic regimen for IMN that its short-term efficacy

**Table 3.** Number of Patients with Side Effect in Two Groups

| Time after the first intervention | Group T[a] ,n = 34 | Group C[b] ,n = 34 | P Value |
|---|---|---|---|
| **After 3 months, n (%)** | 9 (26.5) | 11 (32.3) | 0.590 |
| **After 6 months, n (%)** | 21 (61.7) | 16 (47.3) | 0.220 |

[a] Group T: treated with tacrolimus.
[b] Group C: treated with cyclosporine.

might be better than cyclophosphamide plus prednisone. Praga et al. (10) reached complete remissions in 32% of patients after 18 months of tacrolimus therapy. Naumovic et al. (16) recently concluded that a prolonged course of cyclosporine for 24 months led to a constant increase in cumulative relapse rates from 50% in 6 months to 80% by 18 months as well as complete remissions increased from 0 in 6 months to 40% by 18 months. Maintenance therapy with low-dose cyclosporine (1.4 - 1.5 mg/kg daily; trough levels > 100 ng/mL), possibly in connection with low-dose steroids (0.1 mg/kg daily), may help decrease the likelihood of relapses (17). In two studies that were used by Du Buf-Vereijken et al. (18, 19), the patients with clear evidence of reducing renal function and persistent nephrotic-range proteinuria during the observation period were randomized to take treatment with cyclosporine for 12 months or placebo. Compared with placebo, cyclosporine-treated patients demonstrated significantly decreased proteinuria (halving of proteinuria in 50% of treated patients compared with no improvement in placebo patients) and slower rates of reduction in kidney function as measured by the change in the slope of creatinine clearance. These improvements were sustained at 75% of the patients for up to 2 years post-treatment. Some patients in the treated group progressed to the end stage (11% versus 50%, respectively). Goumenos et al. (20) reported that during a mean follow-up of 48 months, there were no differences in rates of doubling of serum creatinine between the cyclosporine-treated patients than among those taking alkylating agents. This study showed that treatment with cyclosporine 3-6mg/kg/d or tacrolimus 0.05mg/kg/d induces remission in IMN patients over 3 months and 6 months after dialysis. In conclusion, cyclosporine and tacrolimus reduce proteinuria and serum creatinine after 6 months. Nonetheless, tacrolimus reduces urea and cyclosporine increases it and because the prevalence of the side effect of both drugs is similar, tacrolimus has better results in the treatment of IMN patients compared with cyclosporine. A number of studies are needed to assess the long-term efficacy and safety of these treatment regimens.

## Acknowledgments

There is no acknowledgement.

## Footnotes

**Authors' Contribution:** Hamidreza Omrani designed and interpereted the study; Sima Golmohamadi did the drafting of the manuscript and collected the data; Fateme Hichi and Masoud Sadeghi entered, analyzed and interpreted the data; All authors revised the article.

**Conflicts of Interest:** The authors have no financial conflicts of interest.

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