Treatment of idiopathic membranous nephropathy with the combination of steroids, tacrolimus and mycophenolate mofetil: results of a pilot study

José Ballarin, Rafael Poveda, Jordi Ara, Laurea Pérez, Francesca Calero, Josep M. Grinyó and Ramón Romero

Nephrology Departments of Fundació Puigvert, Hospital Universitari de Bellvitge, Hospital Germans Trias i Pujol and Hospital de Vic. Barcelona, Spain

Abstract

Background. Membranous nephropathy is a common cause of nephrotic syndrome (NS) in adults. Its treatment is still under debate.

Methods. We report our experience in a pilot study using initially low doses of steroids and tacrolimus (Tac). After 3 months of treatment, mycophenolate mofetil (MMF) was added if the proteinuria was higher than 1 g/day.

Results. In accordance with this standard, 21 patients entered the study. A proteinuria level lower than 1 g/day was reached at month 3 of therapy with steroids and Tac in 11 patients. These patients continued this treatment for 12 months. MMF was added in nine cases after the third month and triple therapy was maintained for 12 more months. Two patients were withdrawn because of side effects. At the end of the treatment, remission of the NS was present in 15 out of all the patients (71.4%). Remission of the NS was complete in eight (53.3%) patients and partial in seven (46.7%) others. The remaining four patients did not respond. There were no significant changes in renal function. At a mean time of 23.1 months after treatment was discontinued, 11 (73.3%) patients had relapsed.

Conclusions. In this trial, treatment with tacrolimus showed a good efficacy but a high relapse rate when it was discontinued.

Keywords: membranous nephropathy; treatment; steroids; tacrolimus; mycophenolate mofetil; association

Introduction

Idiopathic membranous nephropathy (IMN) is a common cause of nephrotic syndrome (NS) in adults and is characterized by a chronic course and great variability in its evolution. In the long term, up to 30% of untreated patients experience spontaneous remission, another third have slow progression and remain proteinuric and 40% progress to end-stage renal disease (ESRD) [1–7]. Based on these data, some nephrologists recommend immunosuppressive therapy and others tend towards conservative treatment [8–10].

Ponticelli and other authors [11–16] have provided evidence that alkylating agents improve renal survival in patients with IMN and NS. Other therapies such as cyclosporine (CsA) have been found to be effective in reducing proteinuria in some studies [17–21].

Tacrolimus (Tac) shares its anticalcineurin mechanism of action and potential nephrotoxic effect with CsA. However, the immunosuppressor effect of Tac is considered to be more potent than that of CsA and leads to better long-term renal function than CsA in renal transplantation [22,23]. It also has a more favourable cardiovascular risk profile [24,25]. Based on these presumed advantages of Tac over CsA and reports about its effects in experimental and clinical MN [26,27], we decided to include Tac in this study.

Mycophenolate mofetil (MMF) has become one of the standard immunosuppressive agents used for organ transplantation [28–30]. In view of its antiproliferative effect on lymphocytes T and B, the inhibitor effect on antibody synthesis and adhesion molecule action, which result in anti-inflammatory and antifibrotic properties, it has been employed in the treatment of a variety of immunological diseases such as systemic lupus erythematosus, vasculitis, minimal change nephropathy and others [31–39]. The association of steroids, Tac and MMF is one of the most effective therapies in renal transplantation.
Patients and methods

A pilot trial was performed in four nephrology Departments in Barcelona. The study protocol was approved by each centre's Ethics Committee. Patients gave their written informed consent according to the Declaration of Helsinki.

Inclusion criteria were: age at entry between 18 and 75 years; membranous nephropathy diagnosed by renal biopsy; persistent NS after 6 months of treatment with full dose of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptors blockers (ARB) and creatinine clearance more than 60 ml/min/1.73 m². If proteinuria was >10 g/day and serum albumin <20 g/l, immunosuppressive therapy was initiated at the same time as ACEI. Exclusion criteria were systemic diseases, malignancy, diabetes, active infection, active peptic ulcer, pregnancy or inadequate contraception and previous immunosuppressive therapy. Treatment with ACEI or ARB was continued during the entire follow-up period. All patients were receiving 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy; prophylactic low-weight heparin therapy was used if albumin levels were <20 g/l and diuretics were given if necessary.

The initial dose of prednisone was 0.5 mg/kg/day for the first month and was tapered to 7.5 mg/day at month 6. The starting dose of Tac was 0.05 mg/kg/day to achieve target whole-blood trough levels of 5–7 ng/ml. If proteinuria was >1 g/day at the end of month 3 with this therapy, Tac was reduced to maintain blood levels between 5–7 ng/ml and continued for a period of 9 more months (group 1). If proteinuria was >1 g/day, the dose of Tac was reduced as in group 1 and MMF was introduced at a dose of 0.5 g bid (group 2). The dose of MMF was further adjusted to achieve target whole-blood trough levels of 2–4 mg/l and triple therapy was maintained for 9 more months. After this period was completed, immunosuppressive therapy was tapered to zero over 3 months in both groups. Patients were seen every week during the treatment period. Clinical and laboratory data and side effects of the treatment were recorded. Furthermore, ACEI therapy and follow-up were continued after immunosuppressive therapy was stopped to monitor the nephropathy evolution.

NS was defined to exist when the proteinuria level was >3.5 g/day, accompanied by hypoalbuminemia (<30 g/l).

Complete remission (CR) was defined when there was a proteinuria level of <0.3 g/day with normal serum albumin and normal renal function, and partial remission (PR) when there was a proteinuria level between 0.3 and 2.5 g/day, or a decrease in proteinuria of 50% from previous values together with normal serum albumin and normal renal function.

Primary outcome was the number of partial or CRs in proteinuria at months 3 and 12. The secondary outcome was the cumulative percentage of patients whose creatinine increased >30% of the basal value in spite of reduction of the Tac dose. Other outcomes included the relapse rate of NS after the treatment was stopped and the cumulative percentage of patients who discontinued therapy because of adverse events or non-compliance.

Results

Between May 2001 and February 2004, 21 adult patients diagnosed with MN by renal biopsy and showing idiopathic character, were included in this study. One patient received immunosuppressive therapy at initiation because of low serum albumin, 16 were treated with an ACEI, three with an ARB and one with a combination of an ACEI and ARB for at least 6 months before the start of the immunosuppressive therapy. Proteinuria before and after this period of treatment was 7.0 (SD = 3.5) and 10.7 (SD = 5.4) g/day, respectively. There was an increase in proteinuria in 12 patients. The interval between biopsy and treatment is 12.6 (SD = 7.7) months and between diagnostic of proteinuria and treatment 23.7 (SD = 16.3) months.

Baseline characteristics of the whole group of patients are given in Table 1. A majority of the patients were male. Creatinine clearance was >60 ml/min in all of them and they all had severe NS with mean proteinuria of 10.7 (SD = 5.4) g/day, ranging from 4.8 g/day to 26.3 g/day in spite of ACEI or ARB treatment. Only two patients had a proteinuria level of <6 g/day, (4.8 and 4.9 g/day, respectively).

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>21</th>
</tr>
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<tbody>
<tr>
<td>Male-female ratio</td>
<td>16/5</td>
</tr>
<tr>
<td>Age at time of biopsy (years)</td>
<td>46.2 (SD = 12.5) (30–72)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>92.7 (SD = 18.0)</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>24.7 (SD = 6.3)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>10.7 (SD = 5.4)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>94.1 (SD = 27.8) (61–140)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.5 (SD = 11.7)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>80.4 (SD = 9.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.0 (SD = 4.6)</td>
</tr>
<tr>
<td>Total follow-up perioda (months)</td>
<td>23.1 (3-37)</td>
</tr>
</tbody>
</table>

*Follow-up after start of therapy: median was used instead of mean.

Descriptive values are X, mean, (minimum–maximum) or otherwise indicated.
At the end of the third month of therapy, proteinuria was less than 1 g/day in 11 patients and prednisone and Tac treatment was maintained in these patients for the entire treatment period (group 1). MMF was added after the third month in nine patients because proteinuria persisted higher than 1 g/day in spite of prednisone and Tac therapy (group 2).

Mean values of proteinuria, serum albumin, serum cholesterol, serum creatinine, creatinine clearance, blood levels of Tac and mycophenolic acid (MPA) and blood pressure at regular intervals before and after the start of therapy are shown in Table 2. The data correspond to the whole group of patients as well as for groups 1 and 2. Neither the baseline glomerular filtration rate (GFR) nor proteinuria were significantly different between the two groups of patients at baseline. They only differed in gender distribution: the number of males and females was nearly the same in group 1 while there were only males in group 2. The mean dosage of MPA to achieve whole-blood trough levels of 2–4 mg/l (at months 6, 9 and 12) was 1.6 ± 0.91 g/day.

At month 3 proteinuria decreased to a mean value of 0.9 g/day in group 1 and to 4.5 g/day in group 2. Mean albuminemia values were normal (more than 30 g/l) at month 3 in group 1 but only at month 6 in group 2. At month 12, mean proteinuria decreased to 0.8 (SD = 0.7) g/day in group 1 and to 2.7 (SD = 2.2) g/day in Group 2. Mean value of serum cholesterol level was normal at month 12 in group 1 but not in group 2. Renal function remained stable. In the whole group of patients, mean serum creatinine at the onset of treatment was 92.7 (SD = 18.0) µmol/l, 94.9 (SD = 20.6) µmol/l after 3 months of treatment and 94.2 (SD = 24.3) µmol/l at the end of treatment. There was no difference between the groups in Tac blood level at month 3 [7.1 (SD = 2.1) and 7.4 (SD = 1.3) in group 1 and 2, respectively]. Mean levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were normal in both groups during the follow-up.

One patient was withdrawn early in the third month of therapy due to tremor and one at month 2 due to non-compliance. A third patient presented hyperglycaemia, but the plasma glucose level returned to normal value after the Tac dose was reduced. Abdominal pain and diarrhoea were observed in one patient during MMF therapy and were improved after the MMF dose was reduced.

Renal outcome is presented in Figure 1. At the third month, in group 1, all patients but one who maintained hypoalbuminemia, were in partial remission. In group 2, three were in PR but with proteinuria higher than 1 g/day. At month 12, eight patients were in CR (six in group 1 and two in group 2), seven in PR (four in group 1 and three in group 2), and four patients of group 2 did not respond. Time to CR ranged from 4 to 12 months [mean: 8, 2 months (SD = 3.5)] and to PR from 1 to 4 months [mean: 2, 4 months (SD = 1.4)]. We did not find any difference in Tac levels between responders and non-responders, regardless of MMF.

After the treatment was stopped, the mean follow-up period was 13.4 (SD = 7.3) months. At the end of the follow-up, four of the patients who were in CR and all the patients who were in PR had relapsed at a mean follow-up after the end of the therapy of 2.5 (SD = 1.2) and 3.2 (SD = 1.4) months, respectively. All of them showed normal renal function. There was no difference in Tac levels, during all the period of treatment, between the patients who relapsed and those who don’t relapse.

### Table 2. Laboratory parameters and blood pressure values during treatment and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>End of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteinuria (g/day)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WG</td>
<td>10.7 (SD = 5.4)</td>
<td>2.5 (SD = 2.5)</td>
<td>2.4 (SD = 2.4)</td>
<td>1.7 (SD = 1.9)</td>
<td>1.8 (SD = 1.9)</td>
</tr>
<tr>
<td>G1</td>
<td>9.7 (SD = 5.0)</td>
<td>0.9 (SD = 1.62)</td>
<td>1.4 (SD = 1.3)</td>
<td>0.8 (SD = 0.7)</td>
<td>1.0 (SD = 0.7)</td>
</tr>
<tr>
<td>G2</td>
<td>12.1 (SD = 6.1)</td>
<td>4.5 (SD = 2.6)</td>
<td>3.8 (SD = 2.8)</td>
<td>2.7 (SD = 2.2)</td>
<td>2.8 (SD = 2.4)</td>
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<tr>
<td><strong>Serum albumin (g/l)</strong></td>
<td></td>
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<tr>
<td>WG</td>
<td>24.7 (SD = 6.3)</td>
<td>33.8 (SD = 5.9)</td>
<td>38.6 (SD = 4.4)</td>
<td>40.1 (SD = 4.9)</td>
<td>39.1 (SD = 4.7)</td>
</tr>
<tr>
<td>G1</td>
<td>24.6 (SD = 4.3)</td>
<td>35.3 (SD = 4.0)</td>
<td>39.6 (SD = 4.0)</td>
<td>41.4 (SD = 3.2)</td>
<td>40.5 (SD = 3.9)</td>
</tr>
<tr>
<td>G2</td>
<td>24.3 (SD = 8.5)</td>
<td>31.7 (SD = 7.7)</td>
<td>38.6 (SD = 4.4)</td>
<td>38.3 (SD = 6.2)</td>
<td>37.6 (SD = 5.2)</td>
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<tr>
<td><strong>Serum cholesterol (mmol/l)</strong></td>
<td></td>
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<tr>
<td>WG</td>
<td>7.6 (SD = 2.3)</td>
<td>7.3 (SD = 4.0)</td>
<td>5.3 (SD = 0.9)</td>
<td>5.1 (SD = 1.4)</td>
<td>5.0 (SD = 1.5)</td>
</tr>
<tr>
<td>G1</td>
<td>7.9 (SD = 1.8)</td>
<td>6.2 (SD = 0.7)</td>
<td>5.5 (SD = 1.0)</td>
<td>4.7 (SD = 0.7)</td>
<td>4.8 (SD = 1.1)</td>
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<tr>
<td>G2</td>
<td>7.5 (SD = 2.8)</td>
<td>6.7 (SD = 2.7)</td>
<td>5.0 (SD = 0.8)</td>
<td>5.6 (SD = 1.9)</td>
<td>5.4 (SD = 1.9)</td>
</tr>
<tr>
<td><strong>Serum creatinine (µmol/l)</strong></td>
<td></td>
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<tr>
<td>WG</td>
<td>92.7 (SD = 18.0)</td>
<td>94.9 (SD = 20.6)</td>
<td>96.6 (SD = 17.2)</td>
<td>94.2 (SD = 24.3)</td>
<td>88.4 (SD = 21.1)</td>
</tr>
<tr>
<td>G1</td>
<td>85.2 (SD = 16.9)</td>
<td>84.7 (SD = 16.8)</td>
<td>94.8 (SD = 22.1)</td>
<td>81.2 (SD = 21.7)</td>
<td>77.9 (SD = 15.6)</td>
</tr>
<tr>
<td>G2</td>
<td>102.6 (SD = 16.3)</td>
<td>106.8 (SD = 20.0)</td>
<td>98.9 (SD = 20.7)</td>
<td>110.4 (SD = 16.8)</td>
<td>101.6 (SD = 20.2)</td>
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<tr>
<td><strong>Creatinine clearance (ml/min/1.73 m²)</strong></td>
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<tr>
<td>WG</td>
<td>94.1 (SD = 27.8)</td>
<td>91.6 (SD = 24.2)</td>
<td>84.7 (SD = 14.4)</td>
<td>90.9 (SD = 23.6)</td>
<td>93.8 (SD = 20.3)</td>
</tr>
<tr>
<td>G1</td>
<td>99.3 (SD = 31.3)</td>
<td>98.2 (SD = 24.1)</td>
<td>84.0 (SD = 14.0)</td>
<td>99.6 (SD = 21.3)</td>
<td>100.0 (SD = 19.1)</td>
</tr>
<tr>
<td>G2</td>
<td>86.5 (SD = 25.7)</td>
<td>83.4 (SD = 24.6)</td>
<td>85.7 (SD = 16.0)</td>
<td>81.1 (SD = 23.4)</td>
<td>87.6 (SD = 20.7)</td>
</tr>
<tr>
<td><strong>Tacrolimus blood level (µg/l)</strong></td>
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<tr>
<td>WG</td>
<td>7.4 (SD = 1.9)</td>
<td>5.5 (SD = 1.4)</td>
<td>5.9 (SD = 1.8)</td>
<td>7.1 (SD = 1.2)</td>
<td>5.6 (SD = 1.5)</td>
</tr>
<tr>
<td>G1</td>
<td>7.1 (SD = 2.1)</td>
<td>5.6 (SD = 1.5)</td>
<td>6.6 (SD = 2.0)</td>
<td>7.4 (SD = 1.3)</td>
<td>5.5 (SD = 1.4)</td>
</tr>
<tr>
<td>G2</td>
<td>7.4 (SD = 1.3)</td>
<td>5.5 (SD = 1.4)</td>
<td>5.2 (SD = 1.3)</td>
<td>7.4 (SD = 1.3)</td>
<td>5.2 (SD = 1.3)</td>
</tr>
<tr>
<td><strong>MPA blood level (mg/l)</strong></td>
<td></td>
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<tr>
<td>G1</td>
<td>3.4 (SD = 0.9)</td>
<td></td>
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<tr>
<td>G2</td>
<td>3.4 (SD = 0.9)</td>
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</table>

WG, whole group of patients; MPA, mycophenolic acid.
Discussion

We report a pilot study on the treatment of patients diagnosed with IMN with NS, normal renal function and high risk of progression to renal failure. After 6 months of ACEI/ARB II with persistence of the same clinical picture, immunosuppressive therapy was initiated, including the combination of a low dose of steroids and Tac for 3 months and then the addition of MMF in cases with persistence of proteinuria higher than 1 g/day. Double or triple therapy was maintained in every case for 1 year in full doses and in tapering doses for 3 months more.

We decided to use an anticalcineurinic agent because of its reported effectiveness in reducing proteinuria in this nephropathy [20]. Tac was preferred over CsA because it is a more potent inhibitor of antigen-driven T-cell activation, cytokine production and lymphocyte proliferation in vitro [41] and demonstrates greater immunosuppressive power with better adverse effect profile in renal transplantation [22,24,25]. The decision to add MMF in the case of persistence of moderate proteinuria under a low-steroid and Tac regimen is based on previous reports that indicate that MMF can decrease proteinuria in some cases of IMN [32,34,35], which makes it possible to lower the Tac dose and reduce the risk of iatrogenic nephrotoxicity. We have also considered the clinical background offered by the good results of this triple therapy in renal transplantation [40]. Such a combination of low-dose steroids plus Tac and MMF is, to our knowledge, a new approach to IMN therapy. The whole-blood levels of MMF that we have used are probably not really informative: MPA is highly protein bound and only free MPA is pharmacologically active. In a recent study, it was shown that in renal transplant patients with hypoalbuminemia, there is a significant relationship between low albumin concentration and increased percentage of free MPA. The cut-off value of albumin that differentiated normal from elevated percentage free MPA (3%) in this patient population was 31 g/l [42].

There is general agreement in IMN therapy to only treat nephrotic patients at risk for disease progression with immunosuppressive agents. However, identifying them is a contentious point. Some nephrologists are in favour of restricting alkylating agents to patients with renal impairment and reported good results in clinical studies [13–16], some others start them at serum creatinine values as low as possible [43] and some others prefer to avoid anticalcineurinic agents in patients with renal failure [44]. Cattran et al. [45,46] described and validated a method of predicting outcome in IMN, showing that proteinuria >3.5 g/day for more than 6 months has an accurate prediction power of 75% for renal failure. According to this criterion, we only treat patients in the ‘high risk’ category since the mean proteinuria of our patients prior to the start of immunosuppressive therapy was >10 g/day and we wait 6 months under ACEI/ARBII treatment before the start of immunosuppressive therapy except in one case of massive proteinuria. Furthermore, previous ACEI/ARB treatment could increase the accuracy of these selection criteria since poor antiproteinuric response to ACEI in patients with primary glomerulopathies is a disease progression marker [47]. No patient in our group of patients showed decrease in proteinuria during the ACEI/ARBII therapy period. On the contrary, proteinuria increased in most of them.

Nineteen patients completed the treatment period. Among them, 11 cases (52.4%) showed a decrease of proteinuria to values <1 g/day at month 3 of treatment with steroids and Tac. Ten of them achieved remission (six cases total and four partial) at the end of therapy.
In nine cases (42.8%), MMF was added at month 3 of therapy due to persistent proteinuria > 1 g/day. Among them, five patients achieved remission at the end of therapy (two complete and three partial). Thus, of the whole group, 15 (71.4%) of the patients were in remission at the end of treatment period: eight in complete (53.3%) and seven in partial (46.7%) remission.

Cattran et al. [20] conducted a randomized trial lasting 26 weeks in which 51 patients with IMN were treated with low-dose prednisone plus CsA or only steroids and placebo. At the week 26 evaluation, 75% of the CsA group vs 22% of the steroid group had a PR or CR of the NS. With Tac we have obtained a higher percentage of CR (53.3 vs 7%, respectively) and the time to remission is shorter (9 weeks, range: 4–36 weeks).

In comparison with the results of Ponticelli’s group, the remission rate that we obtained at 1 year of treatment is higher than the remission rate obtained with chlorambucil (58% at 1 year of follow-up, 54% at 2 years of follow-up), although the probability of being in remission with chlorambucil at 10 years is 88% [48] and two-thirds of these remissions are complete. With cyclophosphamide and prednisone, the same authors obtained better results than we did (remission rate 93% at 1 year of follow-up).

Secondary effects have been scanty with our schedule. One patient was withdrawn from our study because of tremor (a second one was excluded because of non-compliance). We did not observe any decrease in GFR during all the follow-up period. Similar results are reported by Cattran et al. [19,20] in their two trials with CsA. In the study including cyclophosphamide and prednisone, the rate of withdrawal is 10%, and 25 to 66% of the patients suffered from less severe side effects, essentially bone marrow depression and infections [42].

Long-term toxic effects of these immunosuppressive schedules should also be studied given that prolonged therapies with alkylating agents, at the doses used in the treatment of MN, involve a risk of neoplasia [49]. Relapse after ceasing treatment is a problem in IMN. Eleven of the 15 patients who were in partial or CR relapsed at a mean time of 1.6 (SD = 1.3) months after the cessation of therapy. This high incidence of relapses has already been observed with CsA. After 24 months of CsA treatment, Goumenos et al. [21] observed a relapse in five of 14 patients who had been in partial or CR. In the controlled study by Cattran [20], 48% of the patients treated with CsA relapsed by 78 weeks after they had been treated for 26 weeks.

The effect of MMF addition is difficult to assess in our trial because the decrease in proteinuria observed in some patients after its introduction could be a late effect of Tac. Furthermore, the whole remission or relapse rates after stopping therapy obtained with Tac and MMF are not better than those reported in the literature with CsA alone.

In conclusion, in this pilot study, treatment with Tac, steroids and MMF appears to be associated, in the short term, with > 70% of complete or partial remissions in patients with NS and IMN. The remission rate is similar to that reported with CsA. However, one of the differences seems to be that remissions are achieved more quickly with Tac and the rate of CR is higher. Tac has a very high relapse rate after it is discontinued; the same as occurs with CsA.

Treatment with Tac showed a good clinical tolerance and efficacy, but the frequency of relapse after it is discontinued could make prolonged therapy necessary. In this case, nephrotoxicity could cast a shadow over the global results of the therapy.

It is necessary to study if long-term maintenance with a lower dose may be a therapeutic alternative, focusing attention on the eventual occurrence of nephrotoxicity. Additional controlled trials are required to determine the optimal duration of treatment and which strategies can produce more durable responses and avoid toxicity.

Conflict of interest statement. None declared.

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Treatment of idiopathic membranous nephropathy


Received for publication: 20.11.06
Accepted in revised form: 11.5.07