Mycophenolate Mofetil/Prednisolone Versus Methylprednisolone/Chlorambucil Treatment in Idiopathic Membranous Nephropathy Stage III-IV

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Abstract

Background. In 1984 Ponticelli et al. published the results of a controlled study where patients with idiopathic membranous nephropathy (IMN) and nephrotic syndrome were randomized to receive supportive therapy or to be given a six month therapy with methylprednisolone and chlorambucil alternated every other month, with significantly better outcome in treated patients. Mycophenolate mofetil (MMF) is a new immunosuppressive drug which presented some effects on the nephrotic syndrome in IMN previously resistant to steroids and cytotoxic agents.

Methods. To assess whether methylprednisolone/chlorambucil or methylprednisolone/MMF may have better therapeutical index in patients with advanced IMN we compared two regimens based on a 6-mo treatment. 1) Alternating every month methylprednisolone/chlorambucil or 2) giving simultaneously methylprednisolone/MMF. The study was not randomized. Nephrotic patients with biopsy proven stage III-IV idiopathic membranous nephropathy and normal renal function were divided in two age and sex matched groups by accidental choice. 1st group patients (n=23) were given methylprednisolone 1g/i.v./daily for 3 consecutive days followed by oral steroids 0,4mg/kg/d for 27 days alternated every other month with chlorambucil 0,2mg/kg/d for 30 days. The whole treatment lasted 6 months. 2nd group (n=12) received MMF 2g/d and steroids 0,4mg/kg/d for 6 months, followed by slow tapering over the steroids during the further 6 months to 20mg/d and MMF to 1,5/d. The follow-up period was one year.

Results. Proteinuria in the 1st group of patients significantly decreased after 6 months (5,5+-0,58 to 1,82+-0,6g/d, p<0,05) and one year (0,74+-0,27g/d, p<0,01), with complete remission of the nephrotic syndrome in14/23, partial in 7/23 and persistent in 2/23. Proteinuria in the 2nd group of patients also presented significant decrease (8,87+-2,23 to 4,51+-1,01g/d, p<0,05) after 6 months, and one year (1,23+-0,26, p<0,01). Complete remission was obtained in 2/12 and partial in the other 10 patients. There was no significant difference between the two groups for the decreasing trend of proteinuria.

Conclusions. We can conclude that both regimens were effective in our patients, especially steroids/MMF treatment, taking into consideration the higher degree of proteinuria at start of the treatment.

Key words: membranous nephropathy, mycophenolate mofetil, nephrotic syndrome

Introduction

Idiopathic membranous nephropathy (IMN) is an immune-complex mediated renal disease which is usually associated with the nephrotic syndrome (1,2). The course of the disease is variable (3,4,5). Some patients maintain normal kidney function with or without a spontaneous remission of proteinuria, while others progress to end-stage renal failure or die from complications related to the nephrotic syndrome. In 1984 Ponticelli et al. published the results of a controlled study where patients with IMN and nephrotic syndrome were randomized to receive supportive therapy or to be given a six months therapy with methylprednisolone and chlorambucil alternated every other month (6). After a median follow-up of 5 years treated patients had more remissions of the nephrotic syndrome and showed better survival than untreated controls. Later, the same authors presented better outcome of the patients with grade I and II IMN, compared to grade III-IV (7).

On the other hand, mycophenolate mofetil (MMF), as a new immunosuppressive drug was reported to present some effects on the nephrotic syndrome in IMN previously resistant to steroids, cytotoxic agents, or cyclosporine (8,9,10,11).

The aim of the present study was to assess whether steroids/chlorambucil or steroids/MMF may have better therapeutical index in patients with advanced IMN, stage III-IV. We compared these two regimens based on 6-mo treatment and one year follow-up period.

Patients and methods

Patients: Patients of either sex, between the ages of 15 and 65 with a biopsy proven stage III-IV membranous nephropathy using standard procedure, and a nephrotic syndrome defined as proteinuria exceeding 3,5 g/d and plasma albumin concentration of <25g/l, were considered eligible for the study. All patients were normotensive in the absence of any antihypertensive medication and their serum creatinine levels were within normal range. The criteria for exclusion were previous treatments and positive laboratory tests or investigations which could suggest membranous nephropathy associated with diabetes mellitus, malignancy,
systemic lupus erythematoses, infections or exposure to drugs that could induce the disease.

The patients were divided into two age and sex matched groups by random approach.

T**reatment**: 1**st** group of patients (n=23) were given methylprednisolone 1g/v/d for three consecutive days followed by oral steroids 0.4mg/kg/d for 27 days, alternated every other month with chlorambucil 0.2mg/kg/d for 30 days, a treatment previously described by Ponticelli. The whole treatment lasted 6 months.

2**nd** group of patients (n=12) received MMF 2g/d and steroids 0.4mg/kg/d for 6 months, followed by slow tapering of steroids to 20mg daily and MMF to 1.5g/d for the next 6 months. After the initial induction therapy and the significant decrease in proteinuria, we have maintained both groups of patients on a small dose of maintenance immunosuppression.

**Follow-up:** The entire follow-up period (through an out-patient clinic) was for one year.

RBC and WBC count, proteinuria, plasmaprotein levels, renal function and blood pressure were controlled monthly during the 1-year follow-up. Complete remission was defined as protein loss to 0.2g/d, partial 0.2-2g/d, with normal serum creatinine, <108 micromol/l.

**Results**

1**st** group of patients: The criterion for including the patients with IMN in the study was the presence of nephrotic syndrome, and since there was no randomization process, patients treated with steroids/chlorambucil had lower degree of baseline proteinuria, accidentally. Proteinuria decreased significantly after 6 months, 5.5±0.58 to 1.823±0.6g/d, p<0.05, and one year, 0.74±0.27g/d, p<0.01. Complete remission of the nephrotic syndrome was noted in 14/23 (58.3%), partial in 7/23 (29.1%) and two patients did not respond to the treatment. Mean value of proteinuria was note in the nephrotic range after 6 months, with further decrease after the end of the treatment.

2**nd** group patients: By the same aforementioned absence of the randomization procedure, patients treated with steroids/MMF accidentally had higher degree of baseline proteinuria (8.87±2.23g/d). However, it was significantly decrease after 6 months of treatment (4.51±1.01g/d, p<0.05), be it still within the nephrotic range. Proteinuria decreased to non-nephrotic ranges after one year of treatment, 1.23±0.26, p<0.01. All patients responded to the treatment, but complete remission was rare, in 2/12 (16.7%) and partial in 10/12 (83.3%) of the cases, respectively.

Of note, the significant difference between the groups for the decreasing trend of proteinuria was not reached neither after a year of follow-up.

The safety parameters of the two regimens were comparable with one herpes infection in each of the groups. None of the patients needed discontinuation of treatment in any of the two regimens?

**Discussion**

Although some patients with idiopathic membranous nephropathy can rarely show a rapid evolution towards uremia, the disease generally runs a slowly progressive course, leading to renal failure in unfavorable cases only after 10 or more years. Only few studies reported the natural long-term outcome of the idiopathic membranous nephropathy. In these studies the actuarial 10-year kidney survival ranged between 50% and 70%. The possibility that alternating corticosteroid and alkylating agents might interfere with the natural outcome of idiopathic membranous nephropathy has been tested by a Collaborative Italian Study (6,12,13). These data show that a 6-months therapy with methylprednisolone and chlorambucil can achieve a sustained remission of the nephrotic syndrome and can preserve renal function even in the long-term. The possibility of alternating 2 different agents may attenuate their toxicity. Proteinuria in our patients treated with alternative use of steroids and chlorambucil after 6 months decreased to non-nephrotic ranges, with further decrease during the other 6 months besides discontinuation of the therapy.

Mycophenolate mofetil, as a new immunosuppressive drug, is a specific inhibitor of inosine monophosphate dehydrogenase, which is involved in de novo purine synthesis. MMF is a suppressor of both T and B cell proliferation. The drug can produce selective inhibition of the lymphocyte functions, deoxyguanosine nucleotide depletion and also has effects on non-immune cells preventing fibrosis and vascular smooth muscle cell proliferation. MMF can improve the disease in glomerular diseases with nephrotic syndrome including membranous nephropathy (14,15). It can reduce the proteinuria with a consequent improvement or stabilization of the renal function. We administered MMF in patients with membranous nephropathy and severe nephrotic syndrome. The entire group of patients responded to the treatment, and proteinuria decreased significantly after 6 months, be it still within the nephrotic range. Non-nephrotic proteinuria was achieved after 12 months of follow-up under treatment.

Comparing the results observed in the two groups of patients, we could conclude that both regimens were effective. Although steroids/chlorambucil treatment seems to be more effective after the first 6 months (proteinuria decreased to non-nephrotic range), both groups presented with almost equal difference in decrease of proteinuria after 6 months of treatment (3.68 ± 0.02 vs 4.36 ± 1.22 g/d). This could be explained by the higher baseline proteinuria in the steroids/MMF. However, after 12 months of follow-up, there was no significant difference between the degrees of proteinuria in both groups of patients, i.e. the decreasing trends of proteinuria were similar. In addition, complete remissions were more frequent in steroids/chlorambucil group, but none of the patients treated with steroids/MMF was observed as a non-responder. Thus, we could not say the
steroids/chlorambucil group was more effective, again, because of the higher baseline proteinuria in steroids/MMF group.

Conclusion

In conclusion, steroids/MMF treatment was shown to be as safe and efficient as the treatment with steroids/chlorambucil. Further clinical trials should clarify the long-term effect of the relatively new treatment with steroids/MMF in IMN.

References