A Retrospective Study on the Efficacy of Corticosteroid-Alone Therapy in Membranous Nephropathy Patients

Moritsugu Kimura, Masao Toyoda, Keiko Kobayashi, Makiko Abe, Takako Kobayashi, Mayuko Kato, Masaaki Miyauchi, Naoyuki Yamamoto, Mayumi Maruyama, Tomoya Umezono, Makoto Nishina, Mitsunori Yagame, Masayuki Endo and Daisuke Suzuki

Abstract

**Objective** Membranous nephropathy (MN) is the most common cause of adult-onset nephrotic syndrome and its management is still controversial. The aim of this study was to determine the effectiveness of corticosteroid-alone therapy for controlling proteinuria in MN.

**Methods** Twenty-three patients, which had moderate proteinuria (admission 24-hour urinary protein excretion 1.0 to 3.5 g/day) with primary MN were studied retrospectively.

**Results** Thirteen patients received corticosteroid-alone therapy combined with rest and dietary therapy (steroid group), while the other 10 patients were treated with rest and diet alone (non-steroid group). These two groups did not differ with respect to their laboratory features at the time of admission. After discharge, 5 of 13 patients of the steroid group dropped out. Therefore, only 8 patients could be followed up. As the result, 5 of 8 patients (62.5%) achieved complete remission (CR) and 3 of 8 patients (37.5%) had incomplete remission (ICR), so none of the patients failed to improve. On the other hand, 3 of 10 patients of the non-steroid group dropped out. Then, 7 patients were followed up. None of the 7 patients showed improvement during follow-up and 5 of these 7 patients were started on corticosteroids. Finally, as this result, 4 of 5 patients (80%) could achieve CR by 2 years after hospital discharge. Moreover, in the remaining 2 patients from the non-steroid group, no remission could be achieved even 2 years after discharge.

**Conclusion** These results suggest that long-term corticosteroid-alone therapy is beneficial for controlling proteinuria in patients with MN.

**Key words:** complete remission, incomplete remission, no response, moderate proteinuria, steroid group, non-steroid group

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Introduction

Membranous nephropathy (MN) is extremely rare in infants and children, in whom its incidence is estimated to be less than 1%. In contrast, MN is the most common underlying cause of adult nephrotic syndrome, accounting for 20-40% of total cases. MN can be classified as primary or secondary, with the known causes of secondary MN including the following: 1) infections (hepatitis viruses and other organisms), 2) autoimmune diseases, 3) drug reactions, and 4) malignancies. When a diagnosis of MN is established, the cause is always investigated and priority is given to treatment of the underlying disease in patients with secondary MN. Histological examination of renal biopsy specimens reveals a relatively slight increase of mesangial cells and mesangial matrix, with selective subepithelial deposition of immune complexes and diffuse thickening of the basement membrane on Periodic Acid Schiff (PAS)-stained sections. With regard to the treatment of MN, it has been suggested that specific treatment is unnecessary because spontaneous remission will occur, whereas other authors have recom-
mended corticosteroid therapy. Accordingly, an evidence-based treatment policy has not yet been established. Since spontaneous remission is known to occur, MN was thought to have a relatively favorable prognosis. In fact, from the Caucasian population data, end-stage renal disease (ESRD) develops in 20% to 40% of patients at 10 to 15 years (1). On the other hand, Japanese MN was thought to run a more benign course than in the Caucasian population (1-3). Recently, however, it has been found that approximately 40% of Japanese MN patients show progression to ESRD, therefore the prognosis is worse than that was previously believed (4). Against such a background, it is important to establish a reliable treatment regimen for MN. Therefore, we evaluated the efficacy of corticosteroid-alone therapy in our patients with MN.

Subjects and Methods

The subjects were selected from among 112 patients with a histopathological diagnosis of MN made by renal biopsy at our hospital between 1985 and 2001. Of these 112 patients, 41 continued treatment at our hospital after diagnosis and were enrolled as the subjects, excluding patients with secondary MN. In order to evaluate the effect of corticosteroid therapy retrospectively, the subjects were divided into three groups according to admission 24-hour urinary protein excretion, heavy: (24-hour urinary protein excretion ≥3.5 g/day), moderate: (24-hour urinary protein excretion 1.0 to 3.5 g/day) and mild: (24-hour urinary protein excretion <1.0 g/day). Because of the retrospective study, for the appropriate comparison of corticosteroid therapy effectiveness, to compare the similar levels of proteinuria and similar levels of subject numbers, the 23 patients with moderate proteinuria (admission 24-hour urinary protein excretion 1.0 to 3.5 g/day) were selected (Fig. 1). Then they were divided into a steroid group and a non-steroid group before performing similar evaluations (e.g., the changes of urinary protein excretion). Intergroup comparison was done with respect to demographic and baseline data (gender, age, blood pressure, etc.) and changes in laboratory data (blood urea nitrogen, serum creatinine (Cr), total protein, serum albumin, triglycerides, total cholesterol, 24-hour urinary protein excretion, creatinine clearance, etc.) (Table 1). In these 23 patients, the outcome was also assessed for 2 years after discharge from hospital. Moreover, with respect to proteinuria, we used the following three categories: Complete remission (CR) was defined as absence of proteinuria and normalized serum albumin concentration at least for 1 month. No response (NR) was defined as inability to reduce proteinuria after therapy. Incomplete remission (ICR) was defined as a category between CR and NR (Fig. 2). Steroid pulse therapy was not given and the oral route of administration was always used. In addition, the dosage of corticosteroids was similar for all patients (0.6-0.8 mg/kg/day). Patients receiving immunosuppressive therapy were excluded. In the present study, we could find 3 patients with using angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) in these 23 patients (one steroid group patient and two non-steroid group patients).

For statistical analysis, the significance of differences between two groups was assessed by Student’s t-test or the Mann-Whitney U-test, and p<0.05 was considered to indi-
Table 1. Clinical Characteristics of 23 Patients with Moderate Proteinuria at the Time of Admission

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>Steroid group (n=13)</th>
<th>Non-steroid group (n=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>52.2±5.8</td>
<td>54.7±12.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.8±12.0</td>
<td>141.1±20.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.5±13.8</td>
<td>84.6±15.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>13.6±2.7</td>
<td>14.7±3.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.77±0.26</td>
<td>0.84±0.13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>5.1±0.79</td>
<td>5.2±0.94</td>
<td>n.s.</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.0±0.54</td>
<td>3.0±0.69</td>
<td>n.s.</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>165.6±60.3</td>
<td>184.3±90.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>244.6±137.0</td>
<td>224.0±105.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
<td>964.9±577.1</td>
<td>1002.4±368.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgA (mg/dl)</td>
<td>296.6±177.9</td>
<td>346.0±138.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgM (mg/dl)</td>
<td>156.2±57.8</td>
<td>135.4±49.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Urinary protein (g/day)</td>
<td>3.0±0.60</td>
<td>1.9±0.62</td>
<td>n.s.</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>77.3±25.0</td>
<td>85.3±24.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of admission (days)</td>
<td>42.2±16.6</td>
<td>27.2±15.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are expressed as mean±S.D.  n.s. = not significant

![Figure 2](image)

Moderate proteinuria: 1.0 g/day ≤ UP < 3.5 g/day  
N = 23

- Steroid group  N = 13
- Non-steroid group  N = 10

- Steroid group  N = 8
- Drop out  N = 5
- Decision on treatment  N = 5
  - CR  N = 5
  - ICR  N = 3
  - NR  N = 0

- Non-steroid group  N = 7
  - Steroid therapy started after discharge  N = 5
    - CR  N = 4
    - ICR  N = 1
    - NR  N = 0

Figure 2. Grouping and clinical outcomes in moderate proteinuria patients.

Results

Among the 23 patients, 13 (56.5%) were treated with corticosteroid-alone therapy. The 24-hour urinary protein excretion was 2.35±0.68 g/day on admission in the steroid group and was 1.96±0.62 g/day in the non-steroid group, showing no significant difference. Serum levels of total protein and albumin were respectively 5.15±0.79 and 2.80±0.54 g/dl in the steroid group versus 5.35±0.94 and 3.03±0.69 g/dl in the non-steroid group, again with no significant intergroup differences being found. The duration of hospital stay was 42.2±18.6 days for the steroid group and 27.2±15.3 days for the non-steroid group.
days for the non-steroid group, it tend to long in the steroid group but not statistically significant (Table 1).

When the changes of 24-hour urinary protein excretion during the hospital stay were assessed, there was no significant change in either the steroid group or the non-steroid group (Table 2). Among the 23 patients with moderate proteinuria, 5 patients had dropped out in the steroid group. Therefore, only 8 patients could be followed up in our hospital for 2 years. Among these 8 patients, 5 (62.5%) achieved CR and 3 (37.5%) showed ICR, so none of the patients failed to improve. On the other hand, 3 of 10 patients had dropped out in the non-steroid group, and then 7 patients were followed up. Among for the 7 patients that could be followed up in the non-steroid group who did not receive corticosteroids during their hospital stay, on the other hand, the caring physician detected a lack of improvement during outpatient follow-up and 5 of these 7 patients were eventually started on corticosteroids. Of these 5 patients, 4 (80%) achieved CR by 2 years after hospital discharge and 1 (20%) achieved ICR. In the remaining 2 patients from the non-steroid group, no remission was seen even 2 years after discharge from hospital (Fig. 2). In present study, we could not find patients with a doubling of baseline Cr level in these 23 patients. Moreover, only 3 patients showed worsening by the definition that renal function failure progression was more than a 30% increase of Cr level as compared with at admission. These 3 patients included 2 of the steroid group and 1 of the non-steroid group; (Cr 0.3→0.5 mg/dl; steroid group, Cr 0.9→1.6 mg/dl; steroid group, Cr 0.6→1.1 mg/dl; non-steroid group).

**Discussion**

MN patients with severe proteinuria have a worse prognosis than patients with mild proteinuria and no nephrotic syndrome and, according to Davison et al approximately 50% of untreated MN patients with nephrotic syndrome show impairment of renal function (5). The 24-hour urinary protein excretion is closely related to the outcome of MN (6) and it is important to decrease urinary protein loss.

There have been reports indicating that steroid therapy is useful (7-11), however, others have shown that it is ineffective (12, 13). Tang et al found that steroid therapy alone therapy induced remission in up to 71% of patients (14), and other reports from Japan also revealed that steroid therapy induced an increase in the remission rate (2, 4). However, there are also reports that the low protein diet or ACE-I, ARB therapy is equivalent to steroid therapy with respect to improvement of urinary protein excretion (15, 16). It is therefore an open question as to whether steroid therapy is the most effective treatment for MN. In the present study, only 3 subjects received an ACE-I or ARB therapy during the follow-up period, so the effect of such drugs on MN could not evaluated. However, patients who achieve spontaneous remission without corticosteroid therapy or nonresponders to corticosteroids are not uncommon in the clinical setting. Therefore, it was thought necessary to establish a treatment plan for MN and evaluate the role of corticosteroid-alone therapy.

Zucchelli et al divided 33 MN patients into steroid and non-steroid groups for comparison, as we did in the present study (11). They found complete remission in 39% and 14% of the steroid and non-steroid groups, respectively, while the corresponding rates of renal failure were 24% and 44%. There were significant differences of these outcomes between the two groups, indicating that steroid therapy is effective for the treatment of MN. In the present study, when the changes of 24-hour urinary protein excretion were compared between the steroid and non-steroid groups, no significant decrease of discharge urinary protein excretion was demonstrated in either group. This finding suggests the possibility that corticosteroid-alone therapy is not particularly effective in a relatively short admission period. On the other hand, Funabiki et al have reported that treatment with corticosteroid can be beneficial in long-term follow-up of patients with MN (17). For this reason, we monitored the prognosis for 2 years after discharge in the patients who could be followed for this period. In the steroid group patients who received corticosteroid-alone therapy since hospital admission and could be followed for 2 years, 62.5% patients achieved CR and 37.5% patients had ICR, so none of the patients failed to improve. On the other hand, none of the 7 patients in the non-steroid group (who did not receive corticosteroids during their hospital stay) showed improvement during follow-up on an outpatient basis and 5 of these 7 patients were started on corticosteroids. As a result, 80% patients could achieve CR by 2 years after hospital discharge. Moreover, in the remaining patients from the non-steroid group, no remission could be achieved even 2 years after discharge. The results of the present study indicate that long-term corticosteroid-alone therapy is likely to have a beneficial effect on urinary protein excretion in MN patients. Concerning
the relationship between the efficacy of corticosteroids and the dosage, some studies have shown that aggressive steroid therapy may reduce proteinuria in MN patients (18). In the present study population, steroid pulse therapy was not given and the oral route of administration was always used. In addition, the dosage of corticosteroids was similar for all patients (0.6-0.8 mg/kg/day), so the dose-response relationship was difficult to investigate. Based on these considerations, it is important to conduct a detailed prospective study on the efficacy of corticosteroid-alone therapy in relation to the 24-hour urinary protein excretion and treatment regimen in MN patients.

The present study has suggested that corticosteroid-alone therapy can induce CR or ICR in a large fraction of MN patients. Recent studies suggest that combination therapies with immunosuppressive agents such as methylprednisolone pulse therapy with chlorambucil and steroid with cyclosporine may induce early remission (19, 20). Meanwhile, a recent Japanese report did not clarify whether the effect of combination with cyclophosphamide is superior to that of steroid-alone therapy. Taken together, there is a possibility that Japanese patients are highly sensitive to corticosteroid-alone therapy. Therefore, more precise randomized and controlled prospective studies are needed.

References