**Outcome of idiopathic membranous nephropathy using targeted stepwise immunosuppressive treatment strategy**

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**Abstract**

**Background.** The natural course of idiopathic membranous nephropathy (IMN) is variable and the role of immunosuppressive therapy is controversial. In our centre, the strategy has been conservative: the immunomodulating treatment (glucocorticoids and/or cyclosporine A) has been targeted to patients at high risk of developing progressive renal disease and the cytotoxic drugs have been used cautiously. The aim of this retrospective observational study was to evaluate the efficacy of this strategy.

**Methods.** We evaluated the clinical course and outcome of IMN patients diagnosed between 1993 and 2003. Risk assessment was done during an observation period of ≥6 months after the initial renal biopsy. Patients were followed up until death, the development of end-stage renal disease (ESRD) or the last clinical visit (before December 2006). Treatments and their side effects were recorded.

**Results.** One hundred and forty-two patients with membranous nephropathy were diagnosed of which 81 were idiopathic. The clinical course of 76 IMN patients (38 high risk and 38 low risk) were followed up [mean duration 66 ± 40 (median 59) months]. Thirty-five patients were treated with immunosuppressive drugs, and at last follow-up, 71% of them were in complete or partial remission. The overall response rate of this therapy was 83%. 11% of the high-risk patients had reached ESRD. For the high-risk patients, 10-year survival (alive with glomerular filtration rate >10 mL/min/1.73m²) was 79%. No major side effects were observed.

**Conclusions.** This study suggests that targeted, stepwise, cytotoxic drug-sparing immunosuppressive treatment in IMN was associated with favourable renal, as well as overall survival among patient at risk of developing ESRD.

**Keywords:** Immunosuppressive treatment; membranous nephropathy; survival

**Introduction**

Idiopathic membranous nephropathy (IMN) is one of the most common causes of the nephrotic syndrome (NS) among the adult population. The pathogenesis of this immunological disorder has at least partially been revealed as Beck et al. [1] recently reported on autoantibodies against M-type phospholipase A2 receptor, normally expressed on podocytes. Its natural course varies considerably and an important factor contributing to renal outcome is the amount and duration of proteinuria [2–6]. About one-third of patients present with a benign clinical picture with only low-level proteinuria. Overall, two-third of the patients enter complete (CR) or partial remission (PR) and they have an excellent long-term renal survival [6–8]. One-third of the patients have persistent heavy proteinuria and they are at risk of eventually progressing to end-stage renal disease (ESRD) [2, 3, 9]. Many studies have also suggested that the prognosis of IMN may depend on the geographical region [10–13].

Despite numerous investigations over the past decades, the treatment of IMN has remained controversial [14–16]. It is probable that immunomodulating agents can modify the clinical course of IMN in terms of better renal and overall survival [17, 18], but there is no consensus concerning the appropriate strategy for immunosuppressive medication nor the indications for this treatment. Moreover, some studies have failed to show a clear benefit in terms of overall survival from immunosuppressive treatment [7, 15, 16]. Another challenge is to identify the high-risk patients to focus the potentially harmful therapies on those who would get the...
best benefit from them. Predictive models concerning risk categorization have been developed, and they are mainly based on the level and duration of proteinuria [4, 19].

We have previously reported that the probability of survival of IMN is relatively good in our country [3]. Therefore, our approach to treat these patients has been rather conservative and the immunomodulating therapy has mainly been used in patients evaluated to be at risk of developing progressive kidney disease. The aim of this single-centre study was to retrospectively evaluate the clinical course and survival of patients with IMN. The main focus was to assess the evolution of the disease in patients in whom the decision to apply individualized stepwise immunomodulating therapy was done on the basis of a simplified ESRD risk stratification.

Materials and methods

Patients

We evaluated retrospectively the clinical course of all IMN patients diagnosed by renal biopsy between 1993 and 2003 at the Division of Nephrology, Helsinki University Hospital. For the purpose of the study, the patients were identified from the biopsy registry. Patients with probable secondary MN (associated with systemic lupus erythematosus, malignancies, hepatitis B or C or drugs) and patients with concomitant renal disease detected by renal biopsy (e.g. diabetic nephropathy) were excluded from further analysis. Diagnosis of MN in renal biopsy was made by a renal pathologist and was based on typical findings in light microscopy and immunofluorescence [20]. Electron microscopy was used as additional investigative procedure.

Clinical data was collected starting from the time of renal biopsy until death, the development of ESRD or the end of follow-up (last clinical visit before December 2006). At these time-points, creatinine concentration (\(\text{P-Cr, } \mu\text{mol/L}\)) to convert to mg/dL: divide by 88; measured by Jaffe’s kinetic assay until 2002; thereafter, photometric, enzymatic assay has been used), estimated glomerular filtration rate (eGFR), calculated by the Modification of Diet in Renal Disease Study Equation, \(\text{mL/min/1.73m}^2\) [21], 24-h urinary protein excretion rate (dU-prot, g/24 h; measured using photometric bromocresol purpura reaction assay) were reestimated, as well as the patient’s response to treatment and probable side effects. Clinical data was collected starting from the time of renal biopsy until death, the development of ESRD or the end of follow-up (last clinical visit before December 2006). At these time-points, creatinine concentration (\(\text{P-Cr, } \mu\text{mol/L}\)) to convert to mg/dL: divide by 88; measured by Jaffe’s kinetic assay until 2002; thereafter, photometric, enzymatic assay has been used), estimated glomerular filtration rate (eGFR), calculated by the Modification of Diet in Renal Disease Study Equation, \(\text{mL/min/1.73m}^2\) [21], 24-h urinary protein excretion rate (dU-prot, g/24 h; measured using photometric bromocresol purpura reaction assay) and plasma albumin (g/L, measured using photometric bromocresol purpura reaction assay) were recorded. eGFR values >90 mL/min/1.73m² were approximated to 90 mL/min/1.73m² because of limitations of this formula in high glomerular filtration rate (GFR) values [21]. Patient characteristics were recorded and assessment for risk category for progression to renal insufficiency was defined (high versus low risk; see below) at the beginning of follow-up (initial renal biopsy) and during the observation period. Cardiovascular disease comprised coronary, cerebral or peripheral vascular disease or hypertension. All immunomodulating treatment given to patients was recorded, as well as the patient’s response to treatment and probable side effects.

Definitions

NS was defined as proteinuria in excess of 3 g/24 h, whereas values between 0.3 and 2.9 g/24 h were assigned as persistent proteinuria. A patient was classified as being at high risk of developing renal failure, if (i) he/she had eGFR <60 mL/min at time of renal biopsy or if eGFR declined <60 mL/min during the observation period of ≥6 months after renal biopsy in conjunction with the nephrotic syndrome and (ii) a mean dU-prot >6 g during the observation period or a dU-prot value of >10 g in two consecutive samples. Response to treatment was defined as a change from NS to either PR or CR during follow-up. CR was defined as a reduction in proteinuria >0.3 g/24 h with eGFR >45 mL/min, PR was defined as a reduction of proteinuria of at least 50% and <3 g/24 h. If neither of these was achieved, it was defined as no response (NR) for treatment. Relapse was defined as dU-prot exceeding 3 g in two consecutive measurements in patients having achieved CR or PR. ESRD was defined by (i) the requirement for permanent dialysis support or (ii) eGFR value <10 mL/min.

Treatment protocol

Some patients met the high-risk criteria already at the time of the initial renal biopsy. In order to assess the risk category of the remaining patients, the clinical course was carefully assessed during the observation period. During this time, only conservative treatment (comprising dietary salt restriction, angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin II receptor blockers and possibly other blood pressure lowering medication, diuretics, statins and anticoagulants) for nephrotic syndrome was given. If heavy proteinuria persisted and/or eGFR declined <60 mL/min/1.73m², the patient was classified as having a high risk for progressive kidney disease, and immunomodulating treatment was considered. This treatment was individually tailored according to the following guidelines. The initial therapy comprised corticosteroids starting with 1 g intravenously (i.v.) methylprednisolone pulses over three consecutive days followed by oral alternate-day steroids, starting with 80 mg and tapered to 4 mg >8 months. Three patients were treated only by oral corticosteroids. If corticosteroids were considered contraindicated (patients with type 2 diabetes, body mass index >30 kg/m², metabolic syndrome or severe mental disorders) or they were non-effective, cyclosporin-A (CyA) microemulsion (Sandimmun Neoral®; Novartis, Switzerland) with or without a low-dose corticosteroid was the second-line choice. The initial CyA dose of 3 mg/kg/day was later adjusted aiming at 12-h trough levels between 80 and 120 µg/L (measured by using specific radioimmunoassay, CYASPE). If response was achieved, the treatment was continued for a minimum of 1 year. If CyA failed to induce remission, oral cyclophosphamide (CP; with or without low-dose corticosteroids) was considered. CP was given for 3–6 months at a dose of 1–2 mg/kg. If all these treatments were non-effective, rescue therapy was done with mycophenolate mofetil (MMF; CellCept®, Roche, Switzerland) aiming at a dose of 2 g/day. If CR or PR was achieved, the MMF treatment was continued for at least 1 year.

Statistical analysis

For continuous variables, the results were expressed as mean (± standard deviation) and comparisons were made by independent samples \(t\)-test. Missing values were replaced by serial means. For categorical variables, comparisons were made by chi-square test. P-value <0.05 was considered significant. For estimation of kidney function survival, the end point was defined as patient death or development of Stage IV chronic renal disease (eGFR <30 mL/min). Another analysis for overall patient survival was made with the end point defined as patient death or development of ESRD. The probability of these clinical events were estimated according to Kaplan and Meier and log-rank test was used for comparison. Statistical analysis was performed using SPSS v.17 software.

Results

A total of 142 MN patients were biopsied in our centre between 1993 and 2003. Forty-four patients had a probable underlying condition and were classified as secondary MN. In 17 MN biopsies, there was a concomitant renal disease. All these were excluded from further analysis. Eighty-one patients had IMN. Their baseline characteristics are listed in Table 1. Thirty-eight patients were classified as high-risk patients, and the remaining 42 patients as low-risk patients, respectively. In one patient, there was insufficient data to evaluate risk category. In four low-risk patients, no follow-up data was available, and they were excluded from further analysis, leaving 38 low-risk patients for final analysis. Because it is well known that the long-term outcome of non-nephrotic patients is excellent, only the nephrotic patients were selected for further analysis. They were divided into two groups according to the treatment strategy (treated versus not treated with immunosuppressive medication). Baseline characteristics of these two groups are listed in Table 2. The mean duration of follow-up was 66 ± 40 (median 58, range from 2 to 200 months) months. During this period, a total of 35 patients were treated with immunosuppressive medication (five were later considered low-risk patients). Eight high-risk patients and the rest of low-risk
patients did not receive immunomodulating agents, the high-risk patients mainly due to advanced age. The treated patients had significantly more proteinuria and they also used more often ACEI/angiotensin II receptor blockers (ARBs) as well as statins. The difference in renal function did not reach statistical significance. The mean observation time before initiation of immunosuppressive treatment was 12.6 ± 19.9 (median 8, range from 0 to 120) months. By the time of the initiation of the treatment, the mean P-Cr had increased from 87.6 ± 23 l mol/L (at biopsy) to 104.50 ± 50 l mol/L (P = 0.001) and eGFR decreased from 79 ± 14 to 72 ± 20 mL/min/1.73m² (P = 0.006). The immunomodulating treatment algorithm and its effects are illustrated in Figure 1.

**Effects of corticosteroids**

Twenty-six patients were initially treated with high-dose steroids, three patients received only oral steroids. Twelve patients (46%) responded initially but three patients relapsed after the course. Two patients received an additional course of steroid and entered complete remission. Of the 12 patients responding to steroids, 5 patients had CR, 6 patients PR and 1 NS at last follow-up. Fourteen patients (54%) did not respond to steroids.

**Effects of cyclosporin**

Overall 21 patients were treated using CyA (in 9 patients as initial treatment, in 12 patients who were steroid resistant) and 14/21 (67%) had initial response. Seven of them relapsed after discontinuation of CyA and four responded to new course of CyA. The mean duration of CyA treatment (separate courses added together) was 25.7 ± 17.8 (median 22.5, range from 2 to 65) months.

**Other immunomodulating agents and overall response to treatment**

Six patients with no response to CyA were given oral CP (only one patient responded). Three patients were further treated with MMF (all responded). In summary, of the 35 patients treated with either steroids, CyA or both, 26 (74%) had an initial response. Ten patients relapsed after treatment, but in seven patients, a new response was achieved by repeated or additional courses of immunomodulating
agents. Considering also the effect of CP and MMF, the overall response rate achieved was 83%.

**Side effects of the treatment, cardiovascular complications and causes of death**

Even though there were no deaths or life-threatening infections in the treatment group during the study, some patients had considerable side effects. One patient suffered from a serious toxic hepatitis related to CP, which resolved completely after withdrawal of CP. Two patients had gastrointestinal bleeding which led to interruption of immunosuppressive treatment. One patient had rhabdomyolysis after CyA had been combined to statin therapy. Treatment with both agents was interrupted but was continued successfully with adjusted doses after the patient had recovered. Two patients had cataract related to steroid treatment. Six patients developed impaired glucose tolerance related to steroid use. Two patients gained weight considerably during steroid course. One patient had reversible leucopenia related to CP, and another patient had a relapsing cellulitis, which led to the interruption of CP.

In the untreated group, four deaths occurred (two in the high-risk group, two in the low-risk group). Causes of death were: acute myocardial infarction (one), infection (one), undetermined (two). IMN probably was contributing to the deaths from myocardial infarction and infection. There were no deaths among the treated patients during the follow-up. This may reflect the positive effect of treatment and on the other hand, the cautious approach to immunomodulation.

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In the analysis (ii), the mean survival time in treated nephrotic patients was 175 months and 116 months for the untreated group. Five-year survival was 88 and 85%, and 10-year survival was 83 and 57%, respectively. The differences were not statistically significant. For high-risk patients, the 10-year survival was 79%.

**Discussion**

In this study population, the outcome of IMN patients was quite favourable. Even of patients with medium to high risk for progression, 79% were alive and off dialysis after 10 years. Patients received immunomodulating treatment.
mainly based on individual risk assessment, in order to aim therapy at patients at risk for developing renal insufficiency. The majority of the patients used ACEi or ARB and statins. The estimation of risk category has been based on several factors, of which evolution of renal function and the amount and duration of proteinuria are probably the most important ones [6, 19]. Cattran et al. [4, 19] developed a predictive model for risk assessment, which is based on proteinuria. According to this model, the baseline risk of renal failure was 26%. If proteinuria ≥4 g/day persisted for 12 months, the risk increased to 47%, if proteinuria was >6 g/24 h for >8 months, it was 55% and proteinuria ≥8 g/24 over 6 months increased the risk to 66%. For practical purposes, we slightly modified this model by accepting a mean proteinuria of 6 g/day for 6 months as a risk factor. Thus, evidently some of the patients were ‘medium-risk patients’ according to Cattrans classification. In addition to that patients with severe proteinuria >10 g/day or reduced GFR during the observation period were also classified as high-risk patients.

Several agents have been used and studied in treatment of IMN [22]. Corticosteroids belong to most regimens, but have been used as single agents, too [23–29]. The efficacy of steroids as the only immunosuppressive agent is a matter of controversy. Some studies have shown beneficial effects in terms of higher prevalence of remission of proteinuria and better renal survival [12, 23, 29], while other studies have failed to prove it [24, 25]. Most modern recommendations do not recommend steroids as first line therapy.

Ponticelli et al. published in 1984 a regimen comprising alternate-month courses of high-dose steroid and chlorambucil [17]. The efficacy on this treatment has since then been well documented and has probably been the most widely used immunosuppressive regimen for IMN [30, 31]. Later, the same authors showed that CP yield similar results to chlorambucil but is better tolerated [27]. Cytoxic agents carry, however, considerable risk for serious adverse events, which has been demonstrated in clinical trials, too [32].

Cyclosporine alone or combined with low-dose steroids is effective in inducing remission in IMN [18, 33]. Relapse may, however, occur after the treatment [33]. The use on MMF has spread from organ transplantations to primary glomerular diseases, such as IMN. Several small clinical trials have suggested for its efficacy, but long-term survival data and randomized controlled studies are still lacking [26, 34]. Moreover, promising results have been reported on the use of synthetic adrenocorticotropic hormone, ACTH, tacrolimus and recently with rituximab [35–38].

Thus, it is evident that the clinical course of IMN can be affected by immunomodulating treatment. However, these drugs may cause serious adverse effects and the crucial question is the balance between the benefits and drawbacks. Who should be treated? According to several studies, they are the patients that are presumed to be at risk of developing progressive renal insufficiency [17, 18]. The main difference in our treatment protocol compared with many other centres was the avoidance of cytotoxics as primary treatment. Instead, we have used i.v. pulse methylprednisolone combined with subsequent oral alternate-day steroid with 8-month taper. Almost half of the patients responded initially. Interestingly, this finding is supported by a report from Japan [39], suggesting that this approach may be of value in selected patients and selected populations. Ponticelli et al. also compared this type of therapy with his ‘traditional’ chlorambucil-based regimen. Chlorambucil was more effective in inducing remission, but
during long-term follow-up, the differences diminished [28]. Cyclosporine was given to the majority of patients in our study and only six patients received CP. Serious adverse events were rare and no patient in the treatment group died. Despite the avoidance of cytotoxics, the outcome of patients was quite favourable. The patients were also treated actively by supportive treatment comprising antiproteinuric medication (ACEi, ARBs) and statins, which may have had an impact on the results.

For evaluation of outcome, we had two separate end points, which both included certain level of renal insufficiency and patient death. We compared the outcome of nephrotic patients who were or were not treated by immunosuppressive medication. The outcome of these groups did not differ statistically (Figure 3A and B), although there was a trend towards better survival among the treated generally high-risk patients. This suggests that targeting immunomodulating treatment individually may alter the course of IMN in nephrotic patients. The end points in the evaluation were a composite of renal and patient survival but actually all end points reached in the treated group were renal and in untreated group patient deaths, only one patient had also renal failure. Notably, the 10-year survival in high-risk group was almost 80%.

Our study has evidently some limitations. The study population is rather small and from a single centre. Also the number of patients reaching end points was low. On the other hand, the patients were closely monitored and immunomodulating therapies were given using rather constant regimens.

In conclusion, this observational retrospective study demonstrates the efficacy and safety of cytotoxic-sparing targeted immunosuppressive treatment for IMN. Even though cytotoxic therapy was used cautiously, many patients were exposed to long lasting immunosuppression. To solve this problem of resistant or relapsing IMN, whole new drugs with a different mechanism of action are needed. Will for example rituximab be the answer remains to be confirmed in future studies.

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References


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