Restrictive use of immunosuppressive treatment in patients with idiopathic membranous nephropathy: high renal survival in a large patient cohort

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Summary

Background: Immunosuppressive treatment initiated at an early stage in patients with idiopathic membranous nephropathy (iMN) improves renal survival. Treatment should ideally be restricted to high-risk patients.

Aim: To evaluate the efficacy of a restrictive immunosuppressive treatment strategy for patients with iMN.

Design: Prospective cohort study evaluating a predefined treatment protocol.

Methods: From 1988, we adopted a restrictive treatment strategy: immunosuppressive treatment, mainly consisting of cyclophosphamide and steroids, was advised only in patients with renal insufficiency or severe intolerable nephrotic syndrome. We evaluated this strategy in a large patient cohort. To exclude any bias, we included all adult patients with iMN biopsied in the study period with a serum creatinine (Scr) <135 μmol/l, a proteinuria ≥3.0 g/day and/or a serum albumin (Salb) ≤30 g/l at the time of biopsy. Analysis was according to the intention-to-treat principle.

Results: We studied 69 patients. At the time of biopsy, mean age was 51 years, Scr 90 μmol/l, Salb 23 g/l and proteinuria 6.7 g/day. Average follow-up was 5.5 years. Thus far 33 (48%) patients have received immunosuppressive therapy, mainly because of renal insufficiency (n=24). Status at the end of follow-up was: complete remission n=22 (32%), partial remission n=24 (35%), nephrotic syndrome n=15 (22%), persistent proteinuria n=1 (1.4%), ESRD n=6 (8.7%), death n=1 (1.4%; due to bladder carcinoma after cyclophosphamide therapy). Patient survival was 100% at 5 and 7 years. Renal survival was 94% at 5 years and 88% at 7 years.

Discussion: In patients with iMN, a restrictive treatment policy assures a favourable prognosis, while preventing exposure to immunosuppressive therapy in >50% of the patients.
Introduction
The treatment of patients with idiopathic membranous nephropathy is still a matter of debate. Some authors have argued against the use of immunosuppressive drugs. A meta-analysis of randomized studies found no prove for a beneficial effect of immunosuppressive therapy on renal survival. However, the recent publication of the long-term follow-up data of the randomized, controlled trial conducted by Ponticelli and his collaborators has provided hard evidence that immunosuppressive therapy is effective and improves renal survival. In the latter study, treatment, which consisted of a combination of chlorambucil and steroids, was started at an early stage, i.e. before significant deterioration of renal function had occurred. Since only up to 40–50% of untreated patients will progress to end-stage renal disease (ESRD), such a strategy of early treatment start will expose many patients unnecessarily to immunosuppressive treatment. In view of the potential side-effects of therapy, many investigators have been reluctant to adopt the Ponticelli treatment strategy, although the efficacy of their regimen is not debated. Uncontrolled studies have suggested that immunosuppressive therapy is effective even when started in patients with established renal insufficiency. We and others have shown that immunosuppressive treatment offers a clear renal survival benefit over untreated historic control patients. However, thus far there are no data to suggest that such a restrictive treatment policy is safe and assures an outcome which is comparable to that obtained by Ponticelli et al.

The present report summarizes the efficacy of such a restrictive treatment strategy applied to a large cohort of patients with idiopathic membranous nephropathy, a nephrotic syndrome and normal renal function at the time of renal biopsy.

Methods
Treatment strategy
For more than two decades, we have been actively recruiting patients with idiopathic membranous nephropathy for participation in ongoing studies directed at the identification of prognostic risk factors. Treatment guidelines have been developed for the follow-up of these patients. Until 1988, most patients were treated with alternate-day high-dose prednisone monotherapy. From 1988 onwards, we used a more restrictive treatment strategy. Immunosuppressive therapy was advised only in patients with renal insufficiency (serum creatinine ≥ 135 μmol/l and/or an increase in serum creatinine of >50%) or severe intolerable nephrotic syndrome (prolonged proteinuria ≥ 8 g/day). Details of our immunosuppressive treatment regimens have been described. Initially, immunosuppressive therapy consisted of the combination of chlorambucil and corticosteroids, or a combination of i.v. cyclophosphamide and i.v. methylprednisolone. The latter combination was ineffective. In 1991, we started to use a combination of oral cyclophosphamide and steroids, and this treatment has been the treatment of choice after an analysis of our data suggested that cyclophosphamide was more effective and better tolerated than chlorambucil. Cyclophosphamide treatment consisted of oral cyclophosphamide in a dose of 1.5–2 mg/kg bodyweight/day for 12 months. In most patients, the corticosteroid regimen consisted of three consecutive i.v. pulses of 1 g methylprednisolone at the beginning of the first, third and fifth month of therapy, and oral prednisone in a dose of 0.5 mg/kg bodyweight on alternate days for six months. Repeated courses of immunosuppressive therapy were offered to patients in whom previous therapy showed no effect, or who relapsed to nephrotic range proteinuria, together with a rise in serum creatinine of more than 50% over the lowest value attained during or after the previous course of immunosuppressive treatment.

The study protocol, on the treatment of patients with membranous nephropathy, has been approved by the University Hospital Ethics Committee.

Patient selection
To exclude any bias, we have identified all patients with membranous nephropathy from the pathology registries of our university hospital and five referring hospitals. We have included only patients with a first renal biopsy in the study period, aged ≥18 years, and with a serum creatinine < 135 μmol/l, a proteinuria ≥ 3.0 g/10 mmol creatinine and/or a serum albumin ≤ 30 g/l at the time of biopsy. Follow-up should have lasted at least 6 months. We excluded patients with a secondary membranous nephropathy on clinical and laboratory grounds. Patients were followed prospectively at their local hospitals at regular intervals. For this study, we have evaluated the patient records, retrieved relevant laboratory data and when applicable, we have specified the time of start, the type and the duration of immunosuppressive therapy. The indication for starting immunosuppression was noted. Follow-up started at the time of renal biopsy and continued until December 2002, or ended at the time of death or onset of ESRD.
Calculations and statistics

For descriptive statistics, results are given as means ± SD or medians with range when appropriate. Creatinine clearance was calculated according to Cockcroft and Gault.\(^2\)\(^7\) Proteinuria was expressed per 10 mmol creatinine (protein-creatinine index). Complete remission of proteinuria (CR), partial remission (PR), persistent proteinuria (PP) and nephrotic range proteinuria (NS) were defined as a protein-creatinine indices of ≤ 0.2, 0.21–2.0, 2.1–3.4 and ≥ 3.5 g/10 mmol creatinine, respectively, where in case of remission, renal function should have improved or at least stabilized. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one third of the pulse pressure (systolic minus diastolic blood pressure). For calculations of renal survival, the time of renal death was defined as the start of renal replacement therapy. The cumulative probabilities of death and ESRD were estimated according to Kaplan and Meier.

Results

In the period from 1988 to 2002, idiopathic membranous nephropathy was diagnosed in 87 patients. For this study, we excluded 18 patients because of renal insufficiency (n = 8; median serum creatinine at time of biopsy 218 [149–324] μmol/l) or non-nephrotic proteinuria (n = 5) at the time of renal biopsy, age < 18 years (n = 2) or follow-up < 6 months (n = 3). Thus the study cohort comprised 69 patients.

Patient characteristics at the time of renal biopsy are given in Table 1.

Mean follow-up after renal biopsy was 5.4 (range 0.5–14.1) years, 37 patients had been followed for > 5 years, nine for > 10 years. Four patients were lost to follow-up: two because they moved (one in CR, one with persistent proteinuria), one because of non-compliance (in PR) and one for unknown reason (with persistent nephrotic syndrome).

Follow-up, with emphasis on the use of immunosuppressive therapy, is detailed in Figure 1. Thus far, 33 patients have been treated with immunosuppressive drugs. In 24 patients, immunosuppressive therapy was started because of renal insufficiency. For these patients, the mean time between renal biopsy and start of the immunosuppressive therapy amounted to 11 (range 0.5–103) months and total follow-up time from renal biopsy was 65 (range 16–169) months. If we analyse the data according the intention-to-treat principle, patient survival was 100% at 5 and 7 years, and renal survival 94% at 5 years and 88% at 7 years (Figures 2 and 3). At the end of follow-up, 22 patients were in complete remission (32%), 24 in partial remission (35%), one patient had persistent proteinuria (1.4%) and 15 patients had a nephrotic syndrome (22%). Six patients had progressed to ESRD (8.7%) and one patient had died (1.4%), due to disseminated bladder carcinoma, occurring after a cumulative dose of only 20 g cyclophosphamide.

It is evident from Figure 1 that the advised treatment protocol was not adhered to by 13 patients (white boxes in Figure 1). In three patients with established renal insufficiency, no immunosuppressive therapy was given because of old age (n = 2; 73 and 83 years old, respectively) or patient refusal (n = 1). Two patients with proteinuria < 8 g/day were treated with prednisone. Furthermore, eight patients with severe nephrotic syndrome (n = 5) or renal insufficiency (n = 3) were treated initially with prednisone monotherapy, reflecting the reluctance of patients and/or doctors to use alkylating agents, especially in patients with preserved renal function. As expected, prednisone monotherapy proved ineffective in seven out of eight patients, thus necessitating a second, more aggressive course of immunosuppressive therapy. In four of these patients, serum creatinine exceeded 200 μmol/l at the time that the second course of therapy was started. To determine the potential influence of these protocol violations on patient outcome, we have analysed our data for the subgroup of patients who were treated according to the predefined protocol (n = 56; 82%) thus including untreated patients with preserved renal function (n = 33) and patients treated with a combination of steroids and cyclophosphamide or chlorambucil because of renal insufficiency (n = 21) or a severe nephrotic syndrome (n = 2). These patients are indicated in Figure 1 with gray boxes. In this subgroup analysis, patient survival was 100% at 5 and 7 years and 89%
at 10 years, whereas renal survival was 97% at 5 and 7 years and 86% at 10 years follow-up.

Seven patients were initially treated with prednisone (n = 5) or cyclophosphamide (n = 2) because of severe proteinuria with normal renal function. Five of them progressed to renal insufficiency necessitating a second course of immunosuppression; four had a persistent proteinuria > 5.3 g/10 mmol creatinine after the start of the first course. In these five progressors, serum creatinine at the start of the first and at the start of the second immunosuppressive course was 85 (range 79–115) and 189 (range 162–489) μmol/l (p < 0.01) and proteinuria 9.1 (range 8.1–46.0) and 6.6 (range 5.3–13.0) g/10 mmol creatinine (p = NS), respectively.

**Discussion**

Our data clearly show that a restrictive treatment strategy applied to nephrotic patients with idiopathic membranous nephropathy results in high patient and renal survival. We feel that our study...
thus provides some arguments against the unrestric-
tive use of immunosuppressive therapy in patients
with idiopathic membranous nephropathy.

Admittedly, our study is not a randomized,
controlled trial, but a cohort study. We feel that
the data are representative. Our patient cohort is
large, and included only patients who were
nephrotic at the time of biopsy. To exclude any
referral bias, we have retrieved all patients who
were diagnosed with idiopathic membranous
nephropathy in the study period, using the pathol-
gy registries. Furthermore, in our analysis we have
included the data of all patients, irrespective of
their course and given treatment (intention-to-treat
principle). Our data must be compared with those
reported by Ponticelli et al.\textsuperscript{3,4} The Italian investiga-
tors have conducted a randomized, controlled study
in patients with idiopathic membranous nephropa-
thy and nephrotic syndrome, who were randomized
for either no treatment or treatment with a combina-
tion of chlorambucil and steroids. This study
provided hard evidence that unrestricted immuno-
suppressive treatment improves renal survival. The
baseline characteristics of the patients in Ponticelli’s
and our study were quite similar with respect to
proteinuria and renal function (Table 2). It is evident
from Table 2 that the outcome in our patient cohort
was better than in the untreated group of patients
from Ponticelli’s study, thus supporting the efficacy
of immunosuppressive therapy. Most importantly,
however, our patient cohort fared almost as well
as the treated patients with respect to remission
rate and development of renal failure. Admittedly,
follow-up in our study was less than the 10 year
follow-up reported by Ponticelli et al. The esti-
mated 10-year renal survival in our patients is 78%
(95% CI 58–98%), clearly lower than the 92%
survival rate reported by Ponticelli et al. (95% CI not
provided). These differences in renal survival can be
attributed to the fact that, especially in the initial
study period, some of our patients received the less
effective prednisone monotherapy. If we analysed
our data ‘per protocol’, renal survival was 97% at
7 years and 86% at 10 years. In our treated patients,
serum creatinine at the start of immunosuppressive
therapy averaged 150 ± 54 μmol/l.

The outcome in our patient cohort is clearly
better than that reported by Stirling et al.\textsuperscript{19} These
authors reported the outcome in a group of
patients with idiopathic membranous nephropathy,
in whom immunosuppressive treatment, which
consisted of a combination of chlorambucil and
steroids, was restricted to patients with renal
insufficiency. Although the number of remissions
was higher and the percentage of patients reaching
ESRD lower than in a historical control group of
untreated patients, the differences did not reach
statistical significance. We feel that these seemingly
discordant results can be explained (Table 2).
Stirling et al. initiated immunosuppressive therapy
at a late stage, serum creatinine averaging
267 μmol/l at start of treatment. Furthermore, they
did not use intravenous methylprednisolone in all
their patients, and in earlier publications they
have indicated that the outcome in patients not
receiving i.v. methylprednisolone is not as good.\textsuperscript{28}
Last but not least, the type of immunosuppression
is important. We have previously demonstrated
that in patients with renal insufficiency chlorambucil
is less well tolerated and less effective than
cyclophosphamide.\textsuperscript{12}

Our data thus indicate that it is unnecessary
to use immunosuppressive treatment in all patients
with membranous nephropathy. On the other
hand, it is evident from the data presented in
Table 2, that the treatment should be started

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**Figure 2.** Patient survival. Numbers of patients at risk are
given in parentheses.

**Figure 3.** Renal survival. Numbers of patients at risk are
given in parentheses.
before severe renal insufficiency has developed. We feel that the good renal survival in our patients who were treated per protocol suggests that treatment should be started as soon as deterioration of renal function becomes apparent, as reflected by a rise of serum creatinine > 50% or a value of serum creatinine > 135 μmol/l. It might well be that starting therapy at an earlier time point might even prove slightly more effective. In this respect it could be advantageous to identify patients at high risk for renal insufficiency at an earlier stage, using prognostic markers such as urinary excretion of IgG, β2-microglobulin or α1-microglobulin.23,24,29

When comparing our treatment schedule, consisting of 12 months of cyclophosphamide with the Ponticelli regimen (3 months of chlorambucil or cyclophosphamide), safety issues are a concern. If cyclophosphamide is given for >3 months, there is an increasing risk of persistent amenorrhea and azoospermia. Therefore, in patients who wish to become pregnant, we currently replace cyclophosphamide by azathioprine after 3 months. Bladder cancer is also a serious complication of long-term cyclophosphamide therapy, although bladder cancer is particularly observed if duration of treatment exceeds 2 years and the cumulative dosage exceeds 100 g.30,31 Our current regimen contains approximately 40 g of cyclophosphamide. Although it would be tempting to use the 3 months regimen, we are somewhat concerned about the efficacy. In fact, we have demonstrated that 12 months of cyclophosphamide is more effective (and less toxic) than 3 months of chlorambucil.12 Thus, it is quite possible that the efficacy of a drug regimen is dependent on the duration of treatment. Furthermore, the efficacy of the Ponticelli regimen has only been demonstrated in low-risk patients.3,4,32 The optimal timing and dosage of cyclophosphamide therapy is an important topic for future studies. Until these issues are resolved, we favour a 12-month regimen as initial treatment in patients with membranous nephropathy and renal insufficiency.

### Conclusions

In patients with idiopathic membranous nephropathy and nephrotic syndrome, a restrictive use of immunosuppressive therapy assures a favourable prognosis while preventing exposure to immunosuppression in over half of the patients. The optimal time of start of immunosuppressive therapy needs to be further defined.

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<th>Table 2 Results of different treatment strategies in patients with idiopathic membranous nephropathy and nephrotic syndrome</th>
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CR, complete remission; PR, partial remission; NS, nephrotic syndrome; ESRD, end-stage renal disease. *Approximate values derived from graphs. Values are means ± SD, or medians [range].
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