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Early versus late start of immunosuppressive therapy in idiopathic membranous nephropathy: a randomized controlled trial

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Abstract

Background. Immunosuppressive therapy in idiopathic membranous nephropathy (iMN) is debated. Accurate identification of patients at high risk for end-stage renal disease (ESRD) allows early start of therapy in these patients. It is unknown if early start of therapy is more effective and/or less toxic than late start (i.e. when GFR deteriorates).

Methods. We conducted a randomized open-label study in patients with iMN, a normal renal function and a high risk for ESRD (urinary β2m >0.5 μg/min, UIgG >125 mg/day). Patients started with immunosuppressive therapy (cyclophosphamide for 12 months, and steroids) either immediately after randomization or when renal function deteriorated (ΔsCr ≥+25% and sCr >135 μmol/l or ΔsCr ≥+50%). End points were remission rates, duration of the nephrotic syndrome (NS), renal function and complications.

Results. The study included 26 patients (24 M/2 F), age 48 ± 12 years; sCr 96 μmol/l (range 68–126) and median proteinuria 10.0 g/10 mmol Cr. Early treatment resulted in a more rapid onset of remission ($P = 0.003$) and a shorter duration of the NS ($P = 0.009$). However, at the end of the follow-up (72 ± 22 m), there were no differences in overall remission rate, sCr (93 versus 105 μmol/l), proteinuria, relapse rate and adverse events.

Conclusions. In high-risk patients with iMN, immunosuppressive treatment is effective in inducing a remission. Early treatment shortens the duration of the nephrotic phase, but does not result in better preservation of renal function. Our study indicates that treatment decisions must be based on risk and benefit assessment in the individual patient.

Keywords: cyclophosphamide; immunosuppressive treatment; membranous nephropathy; randomized controlled trial; renal outcome

Introduction

Idiopathic membranous nephropathy (iMN) is one of the most common causes of the nephrotic syndrome in adults. The natural course of the disease is highly variable; 14–56% of patients develop a spontaneous remission, whereas 34–62% of patients develop renal insufficiency [1]. The role of immunosuppressive therapy in iMN is heavily debated, and very recent reviews have doubted the efficacy of immunosuppressive therapy [2–4].

Until recently, only one randomized controlled trial supported the efficacy of immunosuppressive therapy on hard end-points [5]. This study favoured treatment of all patients with iMN and a nephrotic syndrome with chlorambucil and prednisone. Implementation of this treatment strategy in daily clinical practice has the potential to cause harm, since ∼50% of patients will be exposed unnecessarily to immunosuppressive therapy. Therefore, most authors advocate to restrict immunosuppressive therapy to patients with established renal insufficiency, the best predictor of end-stage renal disease (ESRD) [6–8]. When compared with historical controls, patients with renal failure benefited from immunosuppressive therapy [9]. Unfortunately, patients with renal insufficiency are more prone to develop treatment-related complications [1,10].

It is now possible to identify patients with iMN at high risk for ESRD at an early stage. Cattran *et al*. developed an algorithm that comprises clinical parameters like duration and level of proteinuria and creatinine clearance to calculate a predictive score in the individual patient [11]. We and others showed that high-risk patients can be identified with high accuracy by measuring markers of renal tubular injury in the urine [12–15].

The identification of high-risk patients should enable improved treatment. First, treatment could be restricted to high-risk patients, thus avoiding unnecessary exposure to toxic therapy. Secondly, treatment could be started at an early stage, i.e. before the onset of renal failure. However, it is undetermined if such a treatment strategy is feasible. It is questioned, whether immunosuppressive therapy is really effective in high-risk patients. Furthermore, it is unknown if early start of therapy is advantageous by reducing the number of complications of the nephrotic syndrome by better preserving renal function and by limiting treatment-related side effects.

Our study was aimed to answer some of these questions. Our study also was intended to evaluate the potential of a larger study directed at evaluation of the cost–efficacy of two treatment strategies.

Subjects and methods

We conducted a prospective, randomized controlled, open-label study from May 1998 till May 2005. This study was registered at clinicaltrials.gov (NCT 00135954). The study protocol met criteria required by the Declaration of Helsinki and was approved by the ethics committee of our centre. Patients were recruited in our university hospital or one of the referring regional hospitals. All patients gave written informed consent.

The study included adult patients (age 18–75 years) with biopsy-proven iMN. Eligible patients had to have a nephrotic syndrome (proteinuria $\geq$3.5 g/day and serum albumin $\leq$35 g/l) with normal renal function (defined as serum creatinine $<$135 μmol/l) and a high risk for ESRD. The high risk for ESRD was defined as urinary beta2-microglobulin (Uβ2m) $>$ 0.5 μg/min and urinary IgG $>$ 125 mg/24h. The threshold for Uβ2m is based on our previous observations [13]. For UIgG, we adapted the threshold from Bazzi's *et al*. [14], which is lower than we observed (125 versus 250 mg/day), because our data were derived from the pre-ACE-inhibitor era.

We excluded patients in whom a secondary cause of MN was suspected based on clinical or laboratory criteria and patients who had previously been treated with immunosuppressive drugs. Other exclusion criteria were systemic diseases, pregnancy or inadequate contraception, active infection, unstable angina pectoris, diabetes mellitus, clinical evidence of renal vein thrombosis, liver function test abnormalities ($>$2 times the upper limit of normal), use of NSAIDs, active peptic ulcer disease and gastrointestinal diseases that could impair the resorption of oral medication.

The patients were randomized to receive early or late immunosuppressive treatment. Group A started immunosuppressive therapy immediately after randomization. Group B started treatment when renal function deteriorated. Renal function deterioration (RFD) was defined as an increase of serum creatinine with $\geq$25% reaching a level of $\geq$135 μmol/l or an increase of serum creatinine with $\geq$50%.

The immunosuppressive treatment regimen has been previously described [16]. In brief, therapy consisted of oral cyclophosphamide (CP) 1.5 mg/kg BW/day for 12 months, methylprednisolone 1 g intravenously on Days 1, 2, 3, 60, 61, 62, 120, 121 and 122 and oral prednisone 0.5 mg/kg BW/day for 6 months, and subsequently tapered by decreasing the dose by 5 mg/week. For prevention of gastric symptoms, famotidine 1 dd 20 mg was added. From 1999 onwards, we also added trimethoprim–sulfamethoxazole, 480 mg/day in the first 4–6 months, to prevent pneumocystis jiroveci pneumonia. In young fertile patients, the treatment regimen was modified because of the infertility risk associated with the use of CP; in these patients, after 3 months of treatment CP was replaced by azathioprine 1.5 mg/kg BW/day for the remaining 9 months.

All patients were aggressively treated to decrease blood pressure (target value 130/80 mmHg), primarily by using angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors were used to decrease serum cholesterol levels in the case hyperlipidaemia persisted 6 months after randomization. Anticoagulant drugs were not routinely prescribed. All patients were advised to use a moderately salt-restricted diet.

Follow-up time started from the moment of randomization. The patients who started treatment were seen at least every 4–8 weeks during the treatment year. The patients who were randomized to 'late' treatment were seen every 2–3 months. Blood pressure, laboratory data and side effects of therapy were registered. To be included in the final analysis, at least 1 year of follow-up after randomization was required.

The main outcome parameter was the incidence of remissions as a primary event (either complete or partial). An important secondary outcome parameter was the time to the first remission. Other outcome parameters were the period of nephrotic proteinuria, the serum creatinine, estimated GFR (eGFR), proteinuria at the end of the follow-up and major side effects (hospitalizations, infections).

Definitions and calculations

To correct for inappropriate 24-h urine collections, amount of proteinuria was expressed as a protein–creatinine index (grams per 10 mmol of creatinine).

Partial remission (PR) was defined as a protein–creatinine index $<$2.0 g/10 mmol Cr, and complete remission (CR) was defined as a protein–creatinine index $\leq$0.2 g/10 mmol Cr. In the case of remission, renal function should have improved or at least stabilized. Nephrotic range proteinuria was defined as a protein–creatinine index $\geq$3.5 g/10 mmol Cr. Relapse was defined as nephrotic proteinuria ($\geq$3.5 g/10 mmol Cr) after a period of remission (proteinuria $<$2 g/10 mmol Cr). We estimated GFR by applying the four-variable MDRD equation [17].

Sample size

Early treatment seems justified, when there are large differences in the first years after the start of therapy. Sample size calculation was made assuming a rate of partial or complete response to therapy of 80% [9,18], and a rate of spontaneous remissions of 30% in the group with postponed treatment [1]. To detect the estimated differences with a one-sided test with a type I error of 5% and a power of 80%, $\sim$13 patients per group are needed. To anticipate a 10% loss to follow-up, we aimed to include a total of 30 patients.

Statistical analyses

For descriptive statistics, data were presented as means ($\pm$ SD) or medians (range) when appropriate. Analyses were made on an intention-to-treat basis; thus, in the case of a second course of therapy, results of the new treatment were incorporated into the calculations of the last follow-up data. The *t*-test, Mann–Whitney *U*-test and Wilcoxon signed-rank test were used for comparison between and within groups.

Cumulative probabilities of a clinical event (e.g. partial or complete remission) were estimated according to Kaplan and Meier. The generalized Wilcoxon (Breslow) test was used to compare the interval for the appearance of these events. All statistics were performed using SPSS software, version 14.0 (Chicago, IL, USA). Differences were considered significant with a P-value $<$0.05.

Results

From May 1998 till May 2005, we evaluated 162 patients with iMN; 57 patients met criteria for enrolment. Of these, 29 agreed to participate in the study. Fifteen patients were randomized for early treatment (group A) and 14 for postponed treatment (group B). During the first year of the study, three patients were excluded because of the

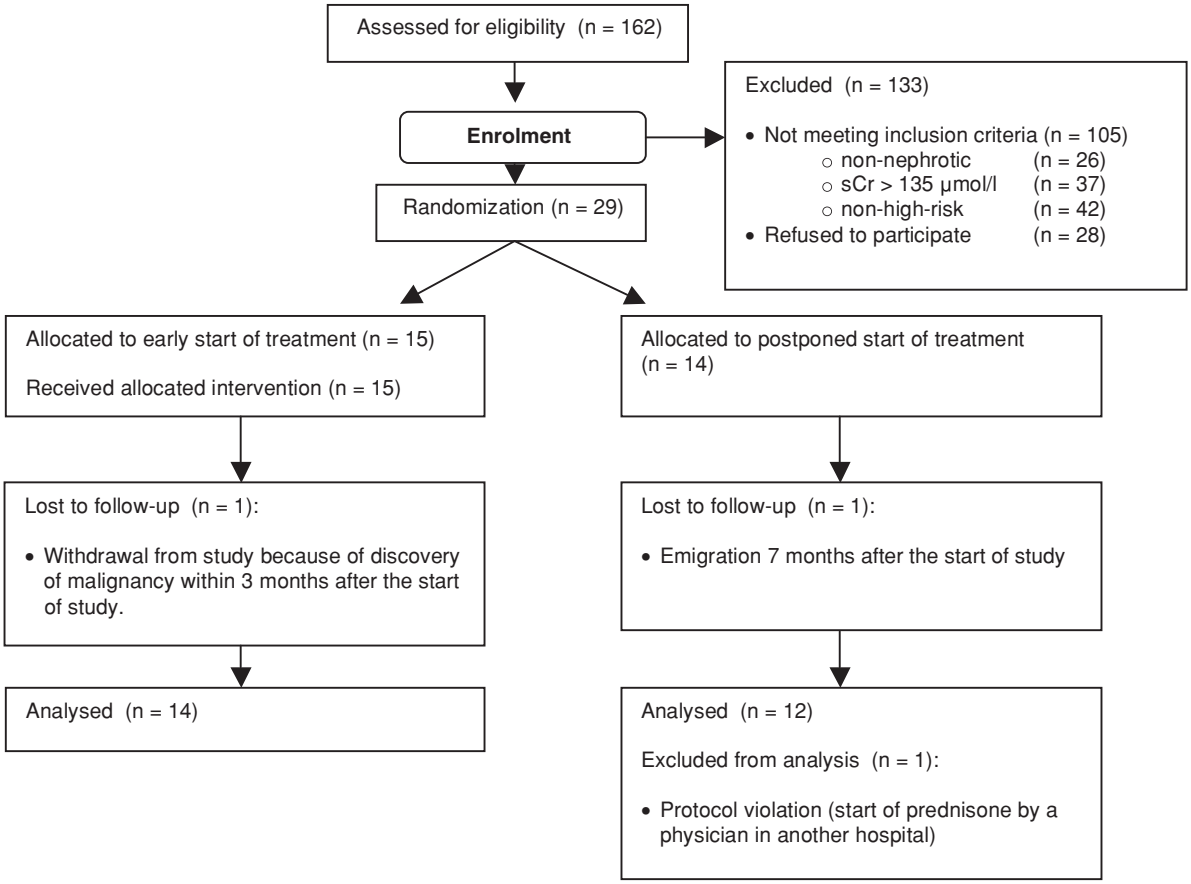

Fig. 1. Flow-chart of enrolment procedure.

Table 1. Baseline characteristics

	Group A Early treatment ($n = 14$)	Group B Postponed treatment ($n = 12$)
Sex (male/female)	13/1	11/1
Age (years)	48 ± 13	49 ± 10
Time from renal biopsy to study start (months)	5 (1–16)	7 (1–19)
Serum creatinine (µmol/l)	94 (68–122)	101 (75–126)
Serum albumin (g/l)	22.6 ± 4.8	22.3 ± 3.8
eGFR (ml/min/1.73m^2)	81 ± 17	76 ± 13
Proteinuria (g/10 mmol Cr)	9.6 (5.9–14.4)	12.0 (5.6–17.2)
Mean arterial pressure (mmHg)	92 ± 18	88 ± 14
ACE inhibitor and/or ARB at study start	14 (100%)	10 (83%)
Lipid-lowering drugs at study start	13 (93%)	8 (67%)

Values are expressed as median (range), mean ± SD, or number (percentage). There were no significant differences in baseline characteristics between groups.
eGFR, estimated glomerular filtration rate (by MDRD-4 equation); ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

following reasons: discovery of a malignancy and withdrawal from the study within 3 months; protocol violation (start of prednisone by a physician in another hospital) and loss to follow-up due to emigration 7 months after randomization (Figure 1). Thus, the final analysis included 26 patients. There were no significant differences in baseline characteristics between groups (Table 1).

Fourteen patients received early treatment (group A). Early treatment was started 2 weeks after randomization (range 0–5 weeks). In group A, three patients were treated according to the modified treatment scheme with azathioprine (see 'Methods').

Group B (postponed treatment) comprised 12 patients. During the follow-up, 8 patients (67%) needed therapy [median 14 months after randomization (range 2–35)] because of deterioration of renal function. The mean creatinine at the start of immunosuppressive treatment was 159 ± 21 µmol/l and the mean GFR was 44 ± 7 ml/min/1.73 m^2. Two patients received modified treatment with azathioprine after 3 months.

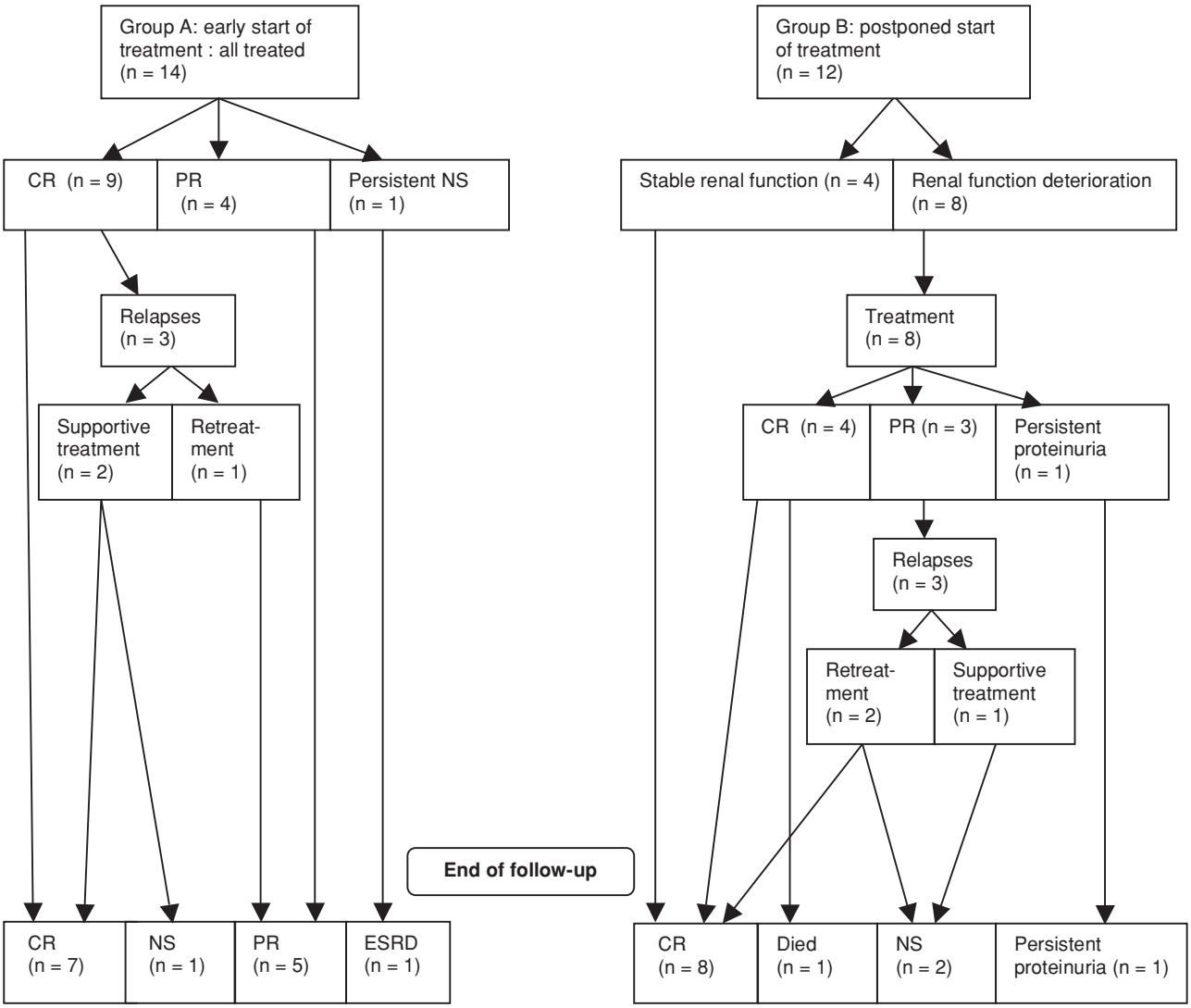

Fig. 2. Flow-chart of treatment and events during the follow-up in the two groups. CR = complete remission, PR = partial remission, NS = nephrotic syndrome, ESRD = end-stage renal disease.

Remissions

In the first year of the study, remission occurred significantly ($P < 0.001$) more often in group A (71%) than in group B (8%).

The course of the disease in both groups is depicted in Figure 2. Overall, early treatment induced a remission in 13 out of 14 patients in group A. Remission was partial in four patients (29%) and complete in nine patients (64%). The cumulative incidence of a partial or complete remission as a primary event was 93%. In group B, four patients reached a spontaneous complete remission of proteinuria (33%). The other eight patients were all treated because of RFD and remission occurred in seven of them (three partial, four complete). The overall cumulative incidence of remission was 92%. Although there was no difference in the overall remission rate, early treatment resulted in a more rapid onset of remission ($P = 0.003$) as depicted in Figure 3.

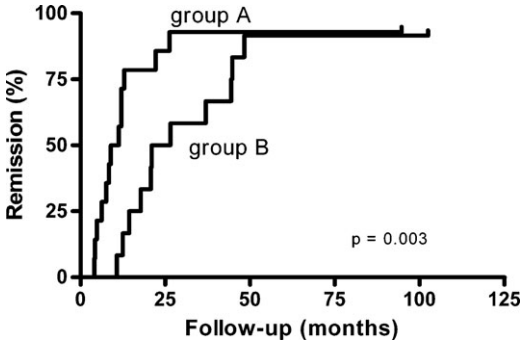

Fig. 3. Cumulative incidence of partial remission of proteinuria in patients with early (group A) or late (group B) start of treatment. Time to remission is significantly different between groups ($P = 0.003$, Breslow test).

The duration of the nephrotic syndrome in the time period between the start of the study and the occurrence of the primary remission was significantly shorter in group A

Table 2. Clinical status and laboratory parameters at the last follow-up

	Group A Early treatment ($n = 14$)	Group B Postponed treatment ($n = 12$)
Follow-up (months)	73 ± 20	71 ± 26
Clinical status		
Remission	12 (86)	8 (67)
Complete	6 (43)	7 (58)
Partial	6 (43)	1 (8)
Persistent proteinuria	0	1 (8)
Relapse[a]	1 (7)	2 (17)
ESRD	1 (7)	0
Death	0	1 (8)
Serum creatinine (μmol/l)	93 (64–487)	105 (79–264)
Serum albumin (g/l)	37.9 ± 5.4	40.5 ± 6.9
Proteinuria (g/10 mmol Cr)	0.77 (0.08–5.41)	0.18 (0–7.12)
eGFR (ml/min/1.73 m^2)	76 ± 25	68 ± 18

Values are expressed as median (range), mean ± SD, or number (percentage). There were no significant differences in outcome parameters between groups.
[a]Relapse: nephrotic proteinuria (≥3.5 g/day) after a period of remission (proteinuria <2 g/day).
eGFR, estimated glomerular filtration rate (by MDRD-4 equation).

(6 months, range 1–25) than in group B (15 months, range 2–46, $P = 0.009$).

Renal function

An (temporary) increase in serum creatinine of 25% at any time point during the follow-up occurred in three patients (21%) in group A and in nine patients (75%) in group B ($P = 0.005$). Within both groups, the mean serum creatinine and GFR at the start and at the last follow-up did not differ significantly, indicating that renal function in group B improved during treatment.

Relapse rate/retreatment

In group A, three patients (23%) relapsed to nephrotic syndrome 36 months after treatment (range 25–106 months). One patient achieved a spontaneous complete remission, and another was retreated with CP and steroids for 6 months, followed by a course of azathioprine. With this regimen, a partial remission was achieved. In the third patient, the relapse was only recently diagnosed. In group B also, three patients (27%) relapsed to nephrotic syndrome 38 months after treatment (range 13–76 months). Two of them were retreated. The first patient received 6 months of CP and steroid therapy, followed by azathioprine for 1 year and achieved a complete remission. The second patient started retreatment with 3 months of CP and steroids, followed by mycophenolate mofetil. At the end of the follow-up, the patient had just started this treatment and nephrotic proteinuria still persisted. The third patient has not been retreated yet, as the relapse was diagnosed shortly before the last follow-up date.

Last follow-up

At the last follow-up (72 ± 22 months), one patient in group A who never reached a remission had progressed to ESRD. Another patient in group A had nephrotic proteinuria due to relapse. All others were in stable remission (Table 2). In group B, one patient had died of unknown cause, while in complete remission 16 months after treatment. One patient had persistent proteinuria despite treatment and another two patients had relapsed at the last follow-up. Eight patients were in stable remission. There were no differences in serum creatinine (93 versus 105 μmol/l), eGFR or proteinuria between groups (Table 2).

Adverse events

An overview of reported adverse events is listed in Table 3. We listed adverse events as most probably due to treatment (e.g. infections, leukocytopaenia) or most probably due to nephrotic syndrome (e.g. thromboembolic events). Overall, nine patients in group A and six patients in group B developed one or more adverse events ($P = 0.48$). Two patients in group A and six patients in group B needed hospitalization. Dose reduction of the immunosuppressive drugs because of side effects was necessary in four patients in group A and in six patients in group B. Infections seemed to be more frequent in patients in group B, and they appeared to be more severe based on data of hospitalization and dose reduction. In group A, one patient did not complete treatment with azathioprine because of suspicion of azathioprine-induced hypersensitivity. In group B, two patients did not complete treatment with CP because of CP-induced hepatitis and severe CMV–alveolitis, respectively.

Although differences between groups were not statistically significant (intention to treat analysis), the patients in group B, when treated, tended to have more frequent and more severe side effects. In a per protocol analysis, 75% of treated patients in group B needed dose reduction (versus 29% of patients in group A) and 75% were admitted to the hospital at least once because of a severe side effect (versus 14% of patients in group A). These data support the notion that immunosuppressive therapy is more toxic in patients with renal insufficiency.

Table 3. Adverse events

	Group A, $n = 14$		Group B, $n = 12$	
	No. of patients (%)	Dose reduction	No. of patients (%)	Dose reduction
Treatment related				
Bone marrow depression				
Leucocytopaenia	2 (14)	2	1 (8)	1
Anaemia	3 (21)	1	0 (0)	–
Infections				
Respiratory	1 (7)	–	1 (8)	1
All others	4 (29)	1	5 (42)	3
Malaise/arthralgia	3 (21)	–	0 (0)	–
Liver test abnormalities/hepatitis	0 (0)	–	2 (17)	2
Steroid-induced diabetes	1 (7)	–	0 (0)	–
Other	1 (7)	1	0 (0)	–
Related to nephrotic syndrome				
Renal vein thrombosis	1 (7)	–	1 (8)	–
Other venous thromboembolism	1 (7)	–	0 (0)	–
Myocardial infarction	0 (0)	–	1 (8)	–
Overall				
No. of patients with one or more AE	9 (64)		6 (50)	
No. of patients needing dose decrease	4 (29)		6 (50)	
No. of hospitalizations	2 (14)		6 (50)	

Numbers do not add up because one patient can have more than one adverse event. There were no significant differences in adverse event rates between groups.
AE, adverse event.

Discussion

Our study provides firm support for the efficacy of a CP-based treatment regimen in patients with iMN at a high risk for ESRD. Immunosuppressive treatment resulted in a higher remission rate, when compared to a supportive approach. Our study thus confirms the conclusions from the randomized controlled trials that proved the superiority of immunosuppressive therapy with alkylating agents over standard care, when used in all patients with iMN and a nephrotic syndrome [5,19]. Our data indicate that treatment efficacy is maintained when restricting treatment to high-risk patients with iMN.

When comparing early versus late start of therapy, there is no difference in the overall remission rate during the follow-up. Still, early start of treatment resulted in a marked reduction in duration of the nephrotic phase. Since the nephrotic syndrome is associated with complications such as thrombosis and infections, early start of treatment may offer benefits.

On the other hand, we did not observe differences in clinical status at the end of the follow-up, nor in complication rate or adverse events between early and late treatment start. Admittedly, our study lacks sufficient power to exclude small differences. Our findings with respect to renal function are in line with our observations in a larger patient cohort that CP-based therapy was able to improve renal function in >90% of treated patients [9].

Our study was partly intended to evaluate the prospect of a larger, multicentre study aimed at performing a rigorous cost-efficacy analysis of early versus late treatment. In such an analysis, various outcome parameters should be accounted for such as complications of the nephrotic syndrome, complications of the treatment, including infertility and malignancies, and proteinuria and renal function during the follow-up.

However, our experience with the current study has provided arguments against such an endeavour. First, many patients refused to participate in this study. The main reason was that patients did not want to be randomized for aggressive versus non-aggressive therapy.

Secondly, and most importantly, we feel that the average outcome of a larger study is not applicable to the individual patient. It is evident that the risk to develop complications of the nephrotic syndrome versus the risks of treatment varies to a large extent between patients. These risks are largely dependent on individual patient characteristics. It seems impossible to take these into account in the setting of a randomized trial. We feel that our data provide sufficient support for an individualized treatment strategy where the timing of the start of immunosuppressive therapy is guided by the patient characteristics.

An assessment of risks and benefits in the individual patient should be performed to make a decision about the start of therapy (Table 4). The risks of prolonged nephrotic syndrome, i.e. thrombo-embolic and infectious complications, will favour early start of treatment in patients with a past history of thrombosis, cardiovascular disease and infections, especially in the case of severe hypoalbuminaemia. On the other hand, the risk of treatment-related complications, i.e. infertility, infections and steroid-associated side effects, favours late start of treatment in patients with planned parenthood, a past history of diabetes mellitus, osteoporosis or respiratory infections. Finally, age must be taken into account. Elderly patients are more prone to develop treatment-related complications, whereas the likelihood to develop ESRD during lifetime is often small.

What else can be learned from our study?

Table 4. Start of immunosuppressive therapy in membranous nephropathy: factors relevant for the decision in the individual patient

	Favours early treatment	Favours late treatment
Age		
Younger	X	
Older		X
Comorbidity		
COPD/respiratory		X
Cardiovascular disease	X	
Diabetes mellitus		X
Osteoporosis		X
Previous thromboembolism	X	
Previous exposure to cytotoxic agents		X
Serum albumin <20 g/l	X	
Planned parenthood		X

Obviously, we were able to identify high-risk patients with iMN since two-third of initially untreated patients developed RFD within 3 years after randomization. The predictive accuracy based on the threshold value of 0.5 μg/min for Uβ2m and 125 mg/day for UIgG, respectively, is reasonable. If we had used 250 mg/day as a threshold value for UIgG, then only 2 out of 10 patients would have developed a spontaneous remission. We advocate the latter threshold value, which when combined with Uβ2m results in a predictive accuracy of 90% [13]. Of note, the mean Uβ2m excretion tend to be higher in the eight patients in group B who progressed to RFD compared to the four patients who developed a spontaneous remission (3.8 versus 0.5 μg/min, $P = 0.06$), indicating that the chance of a spontaneous remission is related to the level of Uβ2m excretion. Other baseline characteristics did not differ between progressors and non-progressors in group B.

Of note, thrombo-embolic complications occurred in two patients randomized for early start of treatment. In these patients, the thromboembolic event occurred shortly after the administration of intravenous methylprednisolone. It has been suggested before that corticosteroids can be thrombogenic in nephrotic syndrome [20]. Therefore, we suggest to use low-molecular-weight heparin in the first months of treatment, especially when serum albumin is <20 g/l.

Finally, although side effects of treatment were not significantly different between the groups, the data support the notion that immunosuppressive therapy is less well tolerated in patients with renal insufficiency.

Our study has several limitations. The number of patients included is relatively small. However, all patients included had a high-risk for progression to renal insufficiency and a low chance of spontaneous remission, which provided enough power to evaluate remission rates. Next, the frequency of follow-up visits was different in the two groups, as patients in group A who immediately started immunosuppressive treatment were seen more often during this treatment. Finally, the treatment schedule of oral CP during 12 months might be questioned, as previous studies reported good effect of a 3-month course [5,19]. Of note, those studies included not only high-risk patients, but also those with a high chance of spontaneous remission, so the results might not be applicable to our current study population. Our current treatment schedule was based on previous experience in high-risk patients [9].

In conclusion, treatment efficacy is maintained when restricting CP-based treatment to high-risk patients with iMN and a nephrotic syndrome. In these patients, treatment can safely be postponed until renal function deteriorates. However, there might be a larger risk of treatment-related side effects. Our study suggests that treatment decisions in the individual patient must be based on an individualized assessment of risks and benefits.

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Conflict of interest statement. Data were previously presented at the 41st annual meeting of the *American Society of Nephrology* (Philadelphia 2008) and published in an abstract format (*J Am Soc Nephrology* 2008; 19: 60A: FC264).

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Functional analyses indicate a pathogenic role of factor H autoantibodies in atypical haemolytic uraemic syndrome

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Abstract

Background. Atypical haemolytic uraemic syndrome (aHUS) is associated with defective complement regulation. Recently, an autoimmune aHUS form has been described that is associated with complement factor H (CFH) autoantibodies. The aim of this study was to address the pathologic relevance of CFH autoantibodies in aHUS.

Methods. CFH autoantibodies were identified and antibody levels were analysed in three aHUS patients during the disease course by the ELISA method. Epitope mapping was performed using recombinant factor H fragments and domain-mapped monoclonal antibodies. The effect of the antibodies on cell-protective activity of CFH was measured by haemolytic assays. CFH:autoantibody complexes were analysed by ELISA.

Results. All three autoantibodies bound to the C-terminal domain of CFH, which is essential for CFH binding to cell surfaces. In patient 1, plasma exchanges and immune adsorption temporarily reduced the autoantibody titre and led to temporary clinical improvement. In patient 2, plasma exchanges and long-term immunosuppression strongly reduced the CFH autoantibody level, and induced a stable remission of aHUS. Patient 3 had lower autoantibody levels that decreased during the follow-up and is in good clinical condition. The patients' plasma samples caused enhanced lysis of sheep erythrocytes, and the degree of lysis correlated with the CFH autoantibody titre and the amount of CFH:autoantibody complexes. An addition of purified CFH to aHUS plasma or removal of IgG inhibited the haemolytic activity.

Conclusion. These results support a direct role of the autoantibodies in aHUS pathology by inhibiting the regulatory function of CFH at cell surfaces and suggest that reduction of the autoantibody titre is beneficial for the patients.

Keywords: autoantibody; complement; factor H; haemolytic uraemic syndrome

Introduction

Haemolytic uraemic syndrome (HUS) is a severe kidney disease characterized by microangiopathic haemolytic anaemia, low platelet count and acute renal failure. The