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ORIGINAL ARTICLE

Treatment pattern in patients with idiopathic membranous nephropathy—practices in Sweden at the start of the millennium

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Abstract

Background: Idiopathic membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome in adults and may result in end-stage renal disease (ESRD). In this retrospective study, we describe the outcomes and treatment patterns of patients with idiopathic MN in six nephrology clinics in the western part of Sweden.

Methods: Seventy-three consecutive patients with biopsy-proven MN in the years 2000–12 were classified as idiopathic, i.e. secondary forms were excluded. The patients were followed retrospectively for a mean period of 83 months and clinical data were collected through the medical files.

Results: A high proportion (88%) of the patients received supportive treatment with angiotensin-converting enzyme inhibition, angiotensin receptor blockade and/or statins. At the end of follow-up, 43 patients were in complete remission, 12 in partial remission, 10 patients had developed ESRD and 8 patients had on-going proteinuria. Fifty-one per cent of the patients received immunosuppressive therapy and the choice of therapy varied between and within the clinics. There was a tendency to initiate specific treatment at an early point instead of awaiting a possible spontaneous remission (21% of the patients), and non-recommended therapy such as corticosteroids only was used in a high proportion of these cases (47%).

Conclusions: Even though the treatment recommendations in idiopathic MN have not changed the last decade, the question of whom and when to treat seems to lead to uncertainty. Recent studies have presented promising results supporting the PLA_2R antibody the predictive marker needed for this patient group. The diverse treatment approach presented in this study might have resulted in a worse outcome than expected. Hopefully, unnecessary exposure to immunosuppressive therapy or delayed treatment can be avoided through better support, education and treatment forums, and thus result in an improved outcome.

Key words: end-stage renal disease, glomerulonephritis, membranous nephropathy, proteinuria

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Introduction

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults [1], and the natural history of the idiopathic form varies. Without treatment, approximately one-third of patients undergo spontaneous remission, one-third progress to end-stage renal disease (ESRD) and one-third have persistent proteinuria and a stable kidney function for several years [2]. Factors indicating poor prognosis are male gender, old age, high levels of proteinuria, abnormal renal function at presentation, tubulointerstitial inflammation and fibrosis, and higher levels of glomerulosclerosis [3, 4]. Factors indicating better long-term prognosis are low-grade proteinuria and low levels of anti-phospholipase A_2 receptor (anti-PLA_2R) antibodies at presentation, female gender and attaining complete or partial remission of proteinuria [3, 5–8]. Supportive treatment with statins is recommended [9], as well as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), the latter due to their potent effect on lowering proteinuria which significantly increases the probability of a spontaneous remission [7].

The highly variable clinical outcome makes it difficult to predict renal prognosis and the need for immunosuppressive treatment. Therefore, the Toronto group developed an algorithm based on clinical parameters of proteinuria and creatinine clearance over a 6-month observation period [2]. Thus, patients with proteinuria <4 g/day are considered low-risk patients and immunosuppressive therapy is not recommended [9, 10]. Patients with a stable renal function and proteinuria between 4–8 g/day are at medium risk of progression and an observation period of 6 months is recommended before initiation of immunosuppressive therapy. Finally, persistent proteinuria >8 g/day or decline in renal function indicates a worse prognosis and treatment is usually started without delay [9]. Moreover, a previous study has shown that immunosuppressive treatment started in the early stage of the disease is not necessarily beneficial to renal outcome [11, 12]. The treatment recommendations in Sweden were published in 1997 [13] and have been influenced by international experience [14]. The basic therapeutic principles have not really changed over the study period, even though the guidelines have evolved in complexity over the years [9]. Thus, in this study, we applied these guidelines [14] on 73 patients with idiopathic MN and investigated the treatment pattern in six nephrology clinics in the western part of Sweden.

Materials and methods

Ethical statement

The study was approved by the Regional Ethical Review Board of Gothenburg, approval number 432-09. Participants in this study gave written informed consent. The youngest patient was 15 years old at time of diagnosis, but all patients were >18 years old at time of inclusion in this study. This study adheres to the Declaration of Helsinki.

Patient population

Patients were identified on the basis of the renal biopsy files of the Department of Pathology at Sahlgrenska University Hospital. All 210 adult patients with biopsy-proven diagnosis of MN between January 2000 and April 2012 were considered for inclusion in this retrospective study. Patients who had moved to other parts of Sweden ($n = 34$), declined to participate in the study ($n = 10$) or who had missing medical records ($n = 11$) were excluded. Among the remaining 155 patients, care was taken to identify idiopathic cases. Thus, 28 patients were considered to have malignancy-associated MN or had a history of malignant disease, 44 patients had lupus and 10 patients had other secondary forms of MN. The remaining 73 patients were diagnosed with idiopathic MN and the follow-up period was at least 12 months after diagnosis.

Clinical parameters

Demographic data included age, sex and smoking at presentation. Laboratory and clinical data collected from the medical files included data at the time of renal biopsy on serum creatinine, urine total albumin, blood pressure and serum cholesterol, and time from symptoms to diagnosis, from diagnosis to specific treatment and from diagnosis to remission. The treatment data included exposure to conservative treatment such as ACEIs, ARBs and use of HMG-CoA reductase inhibitors (statins), and also exposure to immunosuppressive agents.

Definitions

Date of renal biopsy was set as the date of diagnosis of idiopathic MN. The glomerular filtration rate was estimated (eGFR) using the Modification of Diet in Renal Disease formula (MDRD) [15]. Proteinuria at diagnosis was defined as the urinary quantification closest to the date of histologic diagnosis. Total urine albumin (g/day) or urine albumin-to-creatinine ratio (ACR) was measured in all patients, but in the text we use the term proteinuria. Nephrotic-range albuminuria was defined as albumin excretion >3.5 g/day, and since nephrotic-range proteinuria is normally defined as proteinuria >3.5 g/day, our definitions of complete and partial remission (CR and PR) might be slightly too generous, but this had no influence on our conclusions. CR was defined as albuminuria <300 mg/day (or urine ACR <30 mg/mmol). PR was defined as albuminuria falling by ≥50% from baseline albuminuria to a level between 300 mg/day and 3.5 g/day (urine ACR < 350 mg/mmol), accompanied by a normalization of serum albumin and a stable serum creatinine. ESRD was defined as progression of kidney failure to eGFR <15 mL/min/1.73 m^2, measured GFR by Cr-EDTA clearance, initiation of dialysis or kidney transplantation. Smoking was defined as active smoking or a prior history of smoking. Therapy with ACEIs, ARBs and statins was defined as any exposure to these classes of drugs during the follow-up period. Immunosuppressive treatment was reported as intention-to-treat regardless of the duration of the therapy. Cyclophosphamide as well as calcineurin inhibitors and mycophenolate mofetil were used in combination with corticosteroids. Corticosteroids as single treatment are described as corticosteroids only. Synthetic adrenocorticotropic hormone (ACTH) was administered as subcutaneous injections. Monoclonal antibody (rituximab) was administered intravenously.

Histopathological evaluations

All biopsy specimens were examined using light microscopy, immunohistochemistry (IgG, IgA, IgM, C1q, C3, C5b-9, kappa and lambda chains) and electron microscopy. These investigations demonstrated a membranous pattern and excluded other glomerulonephritides including lupus.

Data analysis

SPSS (PASW Statistics 18.0 for Mac) was used for statistical analysis (ANOVA). The data are presented as mean ± SEM or median.

Results

Baseline characteristics

Seventy-three patients with biopsy-proven idiopathic MN were included. The male/female ratio was 1.7/1, and the average age was 53 ± 2 years (range 15–83). Fifty-eight per cent of the patients had proteinuria (measured as albumin excretion in the urine) ≥4 g/day at time of kidney biopsy, and the overall cohort generally showed preserved renal function with a mean serum creatinine of 102 ± 11 μmol/L and eGFR of 80 ± 4 mL/min/1.73 m^2. The median time from symptom to kidney biopsy was 5 months (range 0.5–360) and median length of follow-up was 83 months (range 12–164) (Table 1).

Table 1. Demographic data of the study population

Patients (N)	73
Males/females	46/27
Age, years	52 ± 2 (15–83)
Creatinine, μmol/L	102 ± 11 (45–789), *n* = 73
eGFR, mL/min/1.73 m^2	80 ± 4 (7–188), *n* = 73
Serum albumin, g/L	24 ± 1 (8–43), *n* = 73
Urine albumin, g/day	5.3 ± 0.4 (1–14), *n* = 72
≤4 g/day	42%
4.1–7.9 g/day	38%
≥8 g/day	19%
Serum cholesterol, mmol/L	8.7 ± 0.6 (3.5–16.7), *n* = 24
Systolic blood pressure, mmHg	133 ± 2 (100–155), *n* = 35
Diastolic blood pressure, mmHg	80 ± 2 (60–100), *n* = 35
Time from symptom to biopsy, months	Median 5 (0.5–360)
Time from biopsy to specific treatment, months, 38 patients	Median 4 (0–108)
Length of follow-up, months	82 ± 4 (12–164)

The data are presented as mean ± SEM (range).

Clinical outcomes

At the study end 43 patients were in CR, 12 patients in PR and 10 patients had developed ESRD (Figure 1). Three patients experienced a persistent proteinuria and a slight increase in serum creatinine, but did not reach ESRD during the studied period. Five patients with previous CR had a relapse of the nephrotic syndrome a few months prior to the end of follow-up, and in total 14 patients experienced a relapse of the nephrotic syndrome at some point during the follow-up time (Table 2).

Three male patients died during the studied period. The cause of death of the two patients with ESRD was cardiovascular disease (heart failure in combination with infection in one case and ischaemic heart disease in one case). The third patient had attained PR 4 years after initiation of cyclophosphamide therapy and died due to complications of asbestosis and cardiovascular disease.

Treatment

Sixty-five patients (88%) received supportive treatment with ACEIs (*n* = 25) or ARBs (*n* = 16) or a combination of ACEIs and ARBs (*n* = 24), and 49 patients (66%) received statins. Thirty-six patients (49%) received supportive treatment only and no immunosuppression. In 37 patients (51%) immunosuppressive agents were given at some point during the follow-up period. Median time from diagnosis to treatment was 4 months (range 0–108). In our aim to describe the treatment pattern through a clinical perspective, the patients were categorized into three subgroups according to how well they fulfilled criteria for

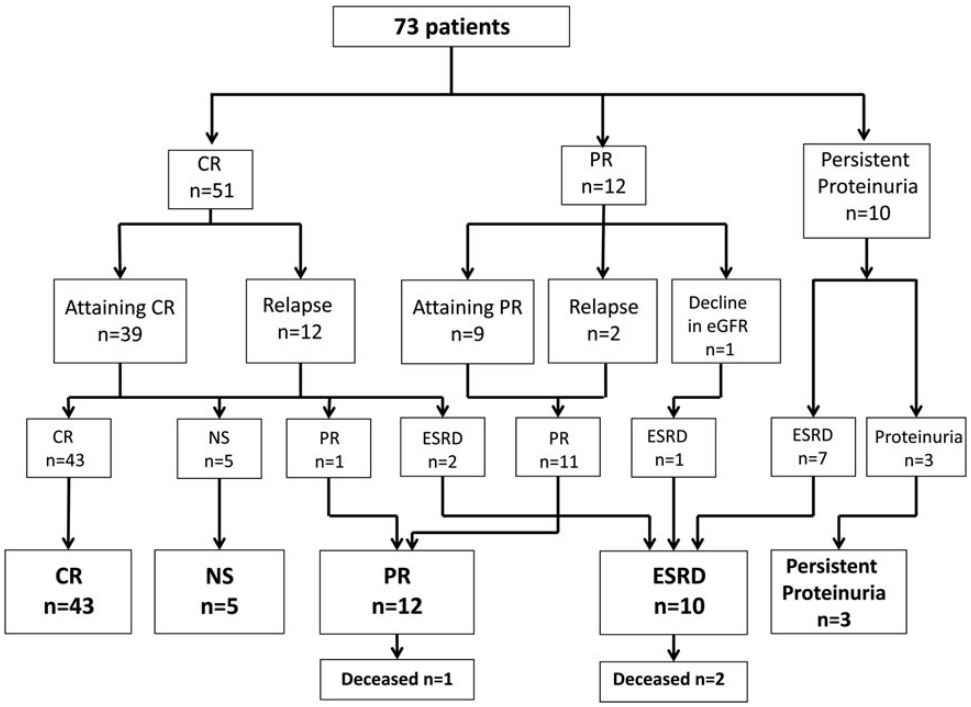

Fig. 1. Flow chart of the patients included in the study and their clinical outcomes. The patients were categorized into three groups according to their clinical outcomes: CR, PR or persistent proteinuria. The worst outcome was seen in the latter group in which seven patients developed ESRD and two patients deceased. Most relapses were found in the largest group, patients with previous CR, and in five patients the relapses occurred shortly prior to study end. NS, nephrotic syndrome.

Table 2. Relapses of the nephrotic syndrome during the follow-up period

Previous treatment	Patient	Group	Previous remission	Relapse (months after remission)	Treatment of relapse	Outcome at study end
No specific treatment	1	C	CR	30	ACEI	NS
	2	C	CR	20	ACEI	NS
	3	A	CR	22	CyA/MMF	PR
	4	C	CR	31	ACEI	NS
ACTH	5	B	CR	55	ARB	CR
	6	A	CR	41	ACEI	NS
	7	A	CR	32	No	NS
	8	B	CR	11	No	CR
Cyclophosphamide	9	A	CR	21	CyA	ESRD
	10	A	CR	39	CyA	ESRD
Glucocorticoids	11	B	CR	1	ACTH	CR
MMF	12	A	CR	2	No	CR
No specific treatment	13	C	PR	120	No	PR
CyA, Ritux	14	A	PR	8	CYP	PR

Groups A-C are as categorized in the text below. Median time from previous remission to relapse was 22 months. Treatment of relapse was influenced by the initial therapy; no patient was given the same therapy twice. Five patients experienced a relapse shortly prior to study end and conservative treatment was initiated in four of these cases. NS, nephrotic syndrome; MMF, mycophenolate mofetil; CyA, cyclosporine; CYP, cyclophosphamide-based treatment; Ritux, rituximab.

immunosuppressive treatment based on the clinical and laboratory data. The criteria we used were those described by the Toronto group, published in 2000 [14].

Group A: Patients with persistent nephrotic-range proteinuria, decline in renal function during follow-up time, severe side effects of the nephrotic syndrome and/or ESRD at presentation

Twenty-eight patients were categorized into this group, and proteinuria (measured as albumin excretion in urine) at the time of kidney biopsy was ≤4 g/day in 7 patients, 4–8 g/day in 15 patients and ≥8 g/day in 5 patients (there was missing data for one patient who presented with ESRD). Twenty-one patients received treatment with ACEIs and/or ARBs and mean follow-up time was 69 ± 7 months (range 12–138).

Twenty-two patients in Group A received specific treatment; first-line treatment with cyclical Ponticelli regimen was not used in any of the cases. Thus, a modified regimen based on the Dutch treatment scheme was used [16], consisting of two consecutive days of 1 g intravenous methylprednisolone followed by oral corticosteroids 0.5 mg/kg body weight every other day combined with orally administered cyclophosphamide 2 mg/kg body weight every day for 6 months. Outcomes of first-line treatment with immunosuppressive therapy are presented in Figure 2A. Second-line treatment was given to 10 of the 22 treated patients due to resistance to the initial treatment (Figure 2B).

The outcomes of Group A patients at the end of follow-up are presented in Figure 2C. Six patients had attained CR, 8 patients were in PR, 4 patients had persistent nephrotic-range proteinuria and 10 patients had developed ESRD. In total, seven patients in Group A relapsed (Table 2).

Six patients in Group A were not given immunosuppressive therapy and they all developed ESRD. One of these patients presented with serum creatinine 789 μmol/L and dialysis was initiated shortly after renal biopsy. A further two patients had serum creatinine 285 and 272 μmol/L, respectively (eGFR 18 and 20 mL/min/1.73 m^2) at the time of renal biopsy, and according to the medical records specific treatment would be of more risk than benefit in these patients. The fourth patient had a rapid decline in renal function with serum creatinine increasing from 104 to 312 μmol/L in 3 years. eGFR was 12 mL/min/1.73 m^2 when the patient died due to cardiovascular disease, and according to the medical records comorbidity was the main reason for not initiating treatment. The fifth patient presented with serum creatinine 124 μmol/L and total urine protein of 5.3 g/day at time of renal biopsy, and protein excretion was reduced to 1 g/day after treatment with ARB. Measured GFR at presentation was 38 mL/min/1.73 m^2, and after 1 year 22 mL/min/1.73 m^2; dialysis was started 7 years after biopsy. Finally, the sixth patient presented with a serum creatinine of 125 μmol/L (eGFR 51 mL/min/m^2) and despite conservative treatment proteinuria persisted and dialysis was started 8 years after renal biopsy.

Group B: Patients not fulfilling criteria for immunosuppressive treatment, still receiving treatment

Based on clinical and laboratory data from the medical records we categorized 15 patients into this group. Fourteen patients received ACEIs and/or ARBs and mean follow-up time was 95 ± 9 months (range 53–164).

In 4 cases, the reason for not fulfilling treatment criteria was subnephrotic proteinuria (measured as albumin excretion in urine) (2.0, 2.2, 2.4 and 2.5 g/day) at the time of initiation of therapy, and in 11 cases, short time from renal biopsy to specific treatment (the time ranged from 0 to 2 months). In none of these cases did the medical record provide information regarding the indication for immunosuppressive therapy at this early point, such as the presence of severe, disabling or life-threatening symptoms related to the nephrotic syndrome, persistent proteinuria or a rapid decline in renal function. In this group, four patients had proteinuria (measured as albumin excretion in urine) ≤4 g/day, five patients 4–8 g/day and six patients ≥8 g/day at the time of renal biopsy. Outcomes after first-line immunosuppressive treatment are presented in Figure 3A. One patient who attained partial remission received a second-line therapy and thereafter went into complete remission. Three patients experienced a relapse of the nephrotic syndrome (Table 2), but at the end of follow-up,

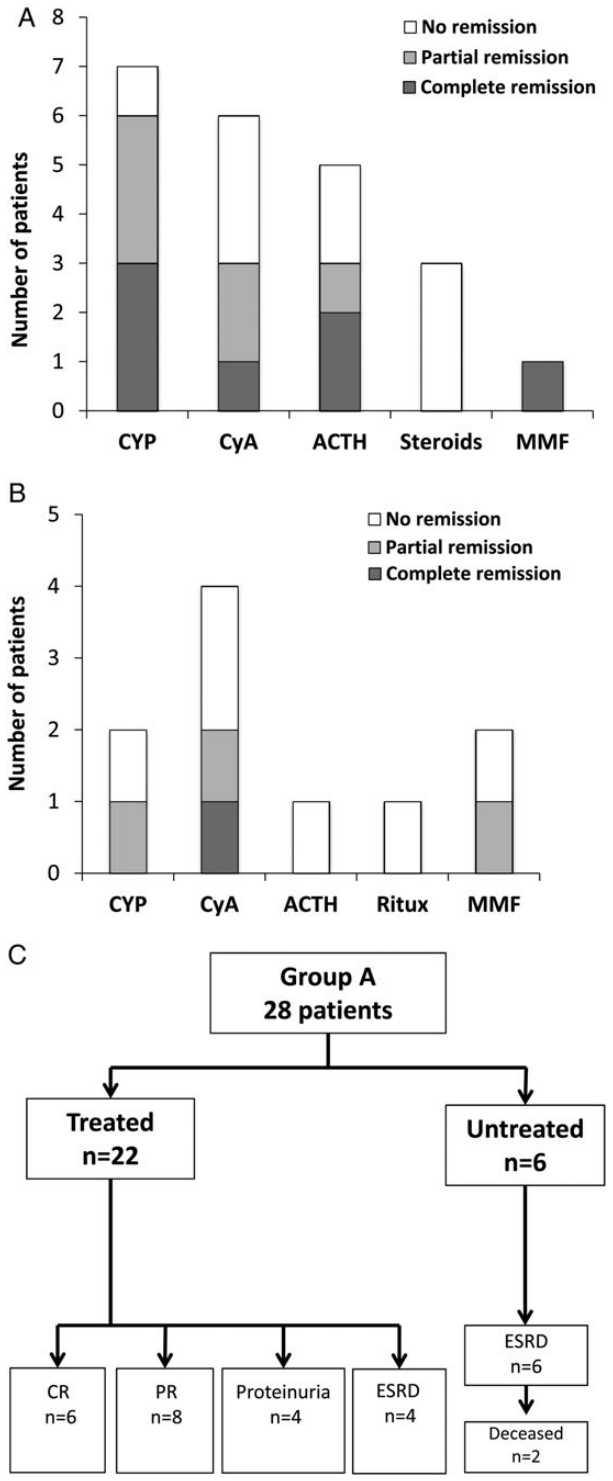

Fig. 2. (**A**) Outcomes after first-line immunosuppressive treatment of Group A patients. Bars representing numbers of patients in CR, PR or no remission. Twenty-two of 28 patients in Group A received specific treatment, and treatment strategy varied. (**B**) Outcomes after second-line treatment given to 10 patients. (**C**) Total outcome of Group A patients at study end. CYP, cyclophosphamide-based treatment; CyA, cyclosporine; Steroids, corticosteroids only; MMF, mycophenolate mofetil; CR, complete remission, PR, partial remission; ESRD, end-stage renal disease.

14 patients had achieved CR and one patient had attained PR (Figure 3B).

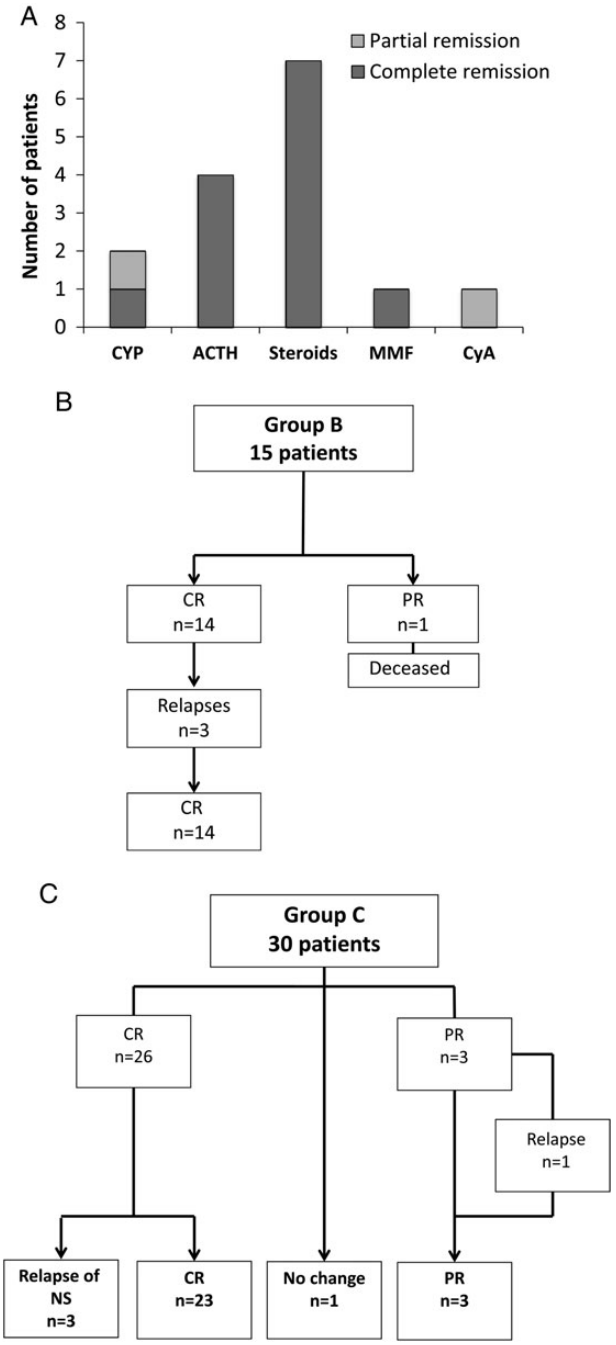

Fig. 3. (**A**) Outcomes after first-line immunosuppressive treatment in Group B patients. Bars represent numbers of patients in CR or PR. Five different therapies were used and half of the patients received corticosteroids only. All patients attained remission after therapy. (**B**) Outcomes of Group B patients and (**C**) Group C patients at study end. CYP, cyclophosphamide-based treatment; Steroids, corticosteroids only; MMF, mycophenolate mofetil; CyA, cyclosporine; NS; nephrotic syndrome.

Group C: Patients not fulfilling criteria for immunosuppressive treatment and not given immunosuppressive treatment

We categorized 30 patients into this group; 27 of these patients (90%) received ACEIs and/or ARBs. Mean follow-up was 87 ± 7 months (range 53–162). Nineteen patients had proteinuria (measured as albumin excretion in urine) ≤4 g/day, eight patients

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4–8 g/day and three patients had proteinuria ≥8 g/day at the time of renal biopsy.

The outcomes of Group C patients are presented in Figure 3C. At the end of follow-up, 23 patients had attained and sustained CR and 3 had attained PR. One patient had persistent low-grade proteinuria (<2 g/day) during the follow-up period, despite treatment with ACEI and ARB. In addition, three patients who initially attained CR subsequently relapsed and were under follow-up with conservative management prior to the study end. Four patients in this group relapsed during the follow-up period (Table 2). The three patients with heavy proteinuria received a combination of ACEIs and ARBs and experienced a decline in proteinuria and a stable serum creatinine, and they all reached and sustained CR without relapses during the studied time period.

Discussion

In this retrospective study, 75% of the 73 patients attained CR or PR and 14% developed ESRD during follow-up time. Recent studies report a better cumulative outcome and fewer cases of ESRD despite a higher proportion of nephrotic patients [3]. Furthermore, even in non-nephrotic patients, none of whom were given immunosuppressive therapy, outcome is reported to be better [17]. In our study, 42% of the patients presented with proteinuria ≤4 g/day, and 51% of all patients received immunosuppressive treatment. Eighty-eight per cent of the patients in our study received supportive treatment, which is a high rate compared with other reports [18], and renal survival could therefore have been expected to be better. Thus, this result raises questions of how to implement scientific findings and guidelines in clinical practice.

The most favourable outcomes were seen among patients with low-grade proteinuria at presentation, and/or a declining proteinuria and stable serum creatinine during the follow-up time, Group C. A majority of these patients achieved remission (23 CR and 3 PR), and there were no cases of ESRD, a result consistent with previous studies [2]. Even the outcomes of Group B patients were excellent; CR was attained in 14 of 15 patients. A larger proportion of patients had heavy proteinuria in this group compared with Group C patients, but the short time from kidney biopsy to specific therapy (0–2 months) and/or subnephrotic proteinuria at the time of initiation of therapy may have influenced the total outcome of this group. Moreover, since almost a third of the patients with idiopathic MN attain remission without specific treatment, and low-grade proteinuria indicates less severe disease [2], according to our definitions and current guidelines [9], 21% of the patients in this study were over-treated with immunosuppressive therapy.

The least favourable clinical outcomes were seen in the group of patients in whom conservative therapy was ineffective and/or combined with other features suggestive of a poor prognosis, in this study, the patients in Group A. Six patients were not given a specific therapy, and in four cases this was due to ESRD or low eGFR at the time of biopsy, or comorbidity contraindicating this kind of heavy medication. However, two patients had progressive decline of eGFR during the follow-up period and they eventually developed ESRD. Hence, they might have benefited from immunosuppressive treatment, but the medical records did not provide any information why specific therapy was withheld.

The choice of specific therapy in this study varied, both within and between the different nephrology clinics in the region. The frequent use of corticosteroids only is an interesting finding that might be explained by the fact that some earlier studies suggested that 2–3 months of alternate-day prednisone decreased proteinuria. However, a long-term benefit has never been confirmed [14, 19–21], and as far as we can tell, it has not been recommended, at least not after the year 2000, i.e. the study period.

In 11 patients, subcutaneous injections of synthetic ACTH were administered. This compound is not recommended as first- or second-line treatment [9], but some patients in this retrospective study participated in a randomized controlled trial of ACTH treatment, which may explain the high proportion of this therapy. The results of that study have been presented as a poster at the American Society of Nephrology [22], but not yet as a paper in a peer-reviewed journal.

This study highlights two difficulties in the management of patients with idiopathic MN in normal clinical practice. First, the decision of whom to treat tends to be a challenge. Since the discovery that a majority of patients with idiopathic MN have autoantibodies directed towards the PLA_2R in their glomeruli, we now have one more tool to use in the differentiation between idiopathic and secondary cases [23]. The PLA_2R antibodies have further been shown to follow the clinical course of the disease [24], and recent published data have suggested the autoantibodies to be a prognostic marker for outcome [8].

Secondly, when the decision to start treatment is made, the choice of specific therapy gives rise to uncertainty. Treatment recommendations in Sweden during the studied time period were based on international guidelines [14] that were readily available in a Swedish textbook from 1997 [13] and have indeed remained the same for two decades [9]. However, our study shows that implementation of guidelines in clinical practice constitutes a major challenge. The choice of treatment seems to be influenced by local traditions or 'hospital cultures', which could explain the large differences observed between the clinics. Furthermore, even within clinics the choice of therapy differed, probably reflecting personal preferences of the individual nephrologist. It is likely that this situation exists in many parts of the world; the same pattern has for example been shown in a study from the USA [18]. Moreover, a recent report from Canada showed an incomplete usage of KDIGO guidelines 2 years after publication [25]. There were several explanations for the large variability in treatment, such as lack of standardized care tools and treatment protocols, lack of physician access to educational glomerulonephritis rounds and also lack of insurance coverage for immunosuppressive medications. The last issue is not applicable everywhere in the world, but the rest probably are. Alternatively, patients with rare diseases such as glomerulonephritides should be managed with guidance from (or in collaboration with) specialized centres of excellence to ensure high quality of treatment for better outcome.

To conclude, in order to implement current guidelines, minimize over-treatment and improve the best-practice management in patients with idiopathic MN, we suggest a collegial board for treatment discussion, and further education and support of the treating physician, as well as initiation of more randomized controlled trials in order to be able to conclude best-practice therapy.

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Conflict of interest statement

None declared.

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