Introduction of a cyclophosphamide-based treatment strategy and the risk of ESRD in patients with idiopathic membranous nephropathy: A nationwide survey in the Netherlands

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Abstract

Background. The efficacy of immunosuppressive therapy in preventing ESRD in patients with idiopathic membranous nephropathy (iMN) is debated. From 1991 onwards, we have advocated a restrictive treatment strategy in our university hospital and regional referring hospitals. We advised the use of immunosuppressive therapy, consisting of a combination of steroids and oral cyclophosphamide for 12 months, in patients with iMN at high risk for ESRD.

Methods. Primary renal diagnosis of all patients who start renal replacement therapy in the Netherlands is registered in the RENINE database. We studied the incidence of ESRD due to iMN in the Netherlands in the period 1991–2005. We mailed a questionnaire to all nephrology centres that entered a patient with ESRD and iMN in the RENINE database after 2000.

Results. The introduction of the cyclophosphamide-based treatment strategy in the Nijmegen region resulted in a significant 70% reduction in the incidence of ESRD in patients with iMN as compared to an unchanged incidence in other parts of the Netherlands. The response rate to the questionnaire was 65%. There were 45 patients (34 M, 11 F) with a mean age of 49 ± 17 years at diagnosis and a median serum creatinine of 138 µmol/l (range 60–1798). Overall, only 22 patients (49%) had been treated with immunosuppressive therapy, consisting of prednisone monotherapy in 7.

Conclusions. Our data suggest that the introduction of a cyclophosphamide-based restrictive treatment policy has reduced the risk of ESRD in iMN. The questionnaires reflect the differences in opinion on the optimal treatment of high-risk patients with iMN.

Keywords: cyclophosphamide; ESRD; immunosuppression; membranous nephropathy

Introduction

Idiopathic membranous nephropathy (iMN) is one of the most common causes of the nephrotic syndrome in adults. If left untreated, 14–56% of patients develop a spontaneous remission whereas 34–62% of patients develop renal insufficiency [1]. Whether patients with iMN should be treated with immunosuppressive therapy has been heavily debated in the past decades. Several therapeutic measures have been studied, including corticosteroids, cyclosporine, alkylating agents, mycophenolate mofetil, anti-B-cell antibodies (rituximab) and synthetic adrenocorticotropic hormone. In a randomized controlled trial, Ponticelli et al. showed a treatment benefit when treating all patients with iMN and a nephrotic syndrome with methylprednisolone and chlorambucil [2]. In two cohort studies we and others also demonstrated that alkylating agents increased remission rate and improved renal survival [3,4]. However, some authors still doubt the efficacy of this therapy, pointing to a Cochrane meta-analysis that could not document a beneficial effect of alkylating agents on total mortality or risk of ESRD [5]. Many authors therefore argue against the use of immunosuppressive treatment with alkylating agents in patients with iMN and a nephrotic syndrome.

We have developed a restrictive treatment strategy, limiting immunosuppressive treatment to patients at highest risk for ESRD [1,6]. From 1991 onwards immunosuppressive therapy was advised only in patients with renal insufficiency or a severe intolerable nephrotic syndrome. Treatment consisted of a combination of steroids and cyclophosphamide for 12 months.

To evaluate the effects of this treatment strategy we studied the incidence of ESRD due to iMN in the Netherlands in the period from 1991 to 2005. In addition, we have retrieved information on the use of specific immunosuppressive therapy in patients with iMN who developed ESRD from 2000 onwards.

Subjects and methods

From 1991 onwards we used a combination of oral cyclophosphamide and steroids in our hospital for the
treatment of patients with IMN [7]. Our treatment regimen has been described in detail before [3,7]. Briefly, cyclophosphamide was administered orally during 1 year in a target dose of 1.5–2 mg/kg body weight per day. In addition, patients received intravenous pulses of methylprednisolone, 1 g each on 3 consecutive days at the beginning of the first, third and fifth month, and oral prednisone 0.5 mg/kg body weight every other day for 6 months. Treatment was restricted to patients at highest risk for ESRD, i.e. patients with established renal insufficiency (defined as a serum creatinine of >135 µmol/l or an increase in serum creatinine >50%). In addition, a few patients were treated because of a severe, intolerable nephrotic syndrome. This restrictive treatment strategy was used in our university hospital and in six regional referring hospitals (the study region: Hospital Gelderse Vallei, Ede; Canisius Wilhelmina Hospital, Nijmegen; Jeroen Bosch Hospital, Den Bosch; Hospital Rijnstate, Arnhem; Maxima Medical Center, Veldhoven; St Elisabeth Hospital, Tilburg).

The primary renal diagnosis of all patients who start renal replacement therapy (RRT) in the Netherlands is registered in the RENINE database. This database is an initiative of the Dutch societies of nephrologists and transplantation specialists, and data are available to all researchers after anonymization of patient characteristics. We have studied the incidence of ESRD due to IMN in the Netherlands and separately in our region in the period from 1991 to 2005. In the RENINE database IMN is by definition a biopsy-proven diagnosis (ERA-EDTA PRD-code 14). We have analysed the data for periods of 5 years, which are 1991–1995, 1996–2000 and 2001–2005. For comparison, we have studied the incidence of ESRD due to focal segmental glomerulosclerosis and histologically examined glomerulonephritis (ERA-EDTA PRD-codes 17 and 19).

To estimate changes in the overall incidence of IMN in the study period we used data from PALGA, the nationwide registry and network of histopathology and cytopathology in the Netherlands. In the PALGA database all histological diagnoses made by pathologists are entered after anonymization of patient characteristics. Results of second biopsies and biopsies in transplant kidneys are included; therefore, the data will somewhat overestimate the true incidence of IMN.

The databases of RENINE and PALGA are unrelated and cannot be linked. The regions defined by the participating dialysis facilities and pathology laboratories do not match. Therefore, to analyse the incidence of IMN in the Nijmegen region we used the PALGA data of the pathology department of the University Medical Center. This department serves three hospitals and ~50% of the population in the inner circle of the Nijmegen region.

A questionnaire was mailed to all nephrology centres that entered a patient with the diagnosis IMN in the RENINE database since 2000. We chose to evaluate only those patients who started RRT since 2000, because of the time lag between diagnosis and/or treatment of IMN and the occurrence of ESRD. Several studies have shown that most cases of ESRD due to IMN occur within 10 years [3,8]. Thus, we started the evaluation of patients 10 years after the introduction of our cyclophosphamide-based treatment strategy (in 1991).

Fig. 1. (a) Number of patients with ESRD caused by idiopathic membranous nephropathy (IMN) in the Nijmegen region (open bars) versus the other parts of the Netherlands (black bars) over time. The \( \chi^2 \)-test for trend \( P = 0.012 \). (b) Number of patients with ESRD caused by FSGS and histologically examined glomerulonephritis (ERA-EDTA codes 17 and 19) in the Nijmegen region (open bars) versus the other parts of the Netherlands (black bars) over time. The \( \chi^2 \)-test for trend \( P = 0.89 \).

The questionnaire included questions about patient characteristics such as sex, age at diagnosis and start of RRT, serum creatinine and use of specific immunosuppressive therapy.

Data are presented as means (±SD) or medians (range) when appropriate. Pearson’s chi-square test was used for comparison of proportions. Poisson regression was used to compare per capita incidence rates. Statistics were performed with SPSS software, version 12.0.1 (Chicago, IL, USA) and SAs software, version 8.2 (Cary, NC, USA). Differences were considered significant with \( P \)-value < 0.05.

Results

We have analysed the incidence of ESRD for periods of 5 years. As expected the incidence of patients needing RRT increased over this time period. In our region 1038 patients started RRT in the period 1991–1995, increasing to 1152 in the period 1996–2000 and 1215 in the period 2001–2005. For the Netherlands (after exclusion of the Nijmegen region) these figures are 5118, 6292 and 7190, respectively.

In the Nijmegen region the number of patients with ESRD due to IMN decreased by 70% when comparing the periods 1991–1995 and 2001–2005. In contrast, the number of patients with ESRD due to IMN in the other parts of the Netherlands did not change (Figure 1a, \( \chi^2 \)-test for trend \( P = 0.012 \)). We next evaluated the incidence of ESRD due to IMN on a per capita rate (Table 1). Poisson regression
Table 1. Incidence rates

<table>
<thead>
<tr>
<th></th>
<th>Nijmegen region</th>
<th>The Netherlands (Nijmegen excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence ESRD due to iMN&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>5.78</td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td>3.15</td>
<td>3.30</td>
</tr>
<tr>
<td>Incidence of histopathological diagnosis of MN&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>46.15</td>
<td>49.23</td>
</tr>
<tr>
<td></td>
<td>30.20</td>
<td>29.21</td>
</tr>
<tr>
<td>Corrected incidence of ESRD due to iMN&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.125</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>0.111</td>
<td>0.116</td>
</tr>
<tr>
<td>Incidence ESRD due to glomerular diseases (EDTA codes 17 + 19)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>16.25</td>
<td>14.80</td>
</tr>
<tr>
<td></td>
<td>14.45</td>
<td>12.91</td>
</tr>
</tbody>
</table>

ESRD: end-stage renal disease; iMN: idiopathic membranous nephropathy; EDTA codes 17 + 19: focal segmental glomerulosclerosis and histologically examined glomerulonephritis.

<sup>a</sup>Incidence rates are given as number per million per period of 5 years.

<sup>b</sup>Data from the RENINE registry.

<sup>c</sup>Data from the PALGA database.

<sup>d</sup>The corrected incidence was calculated from the RENINE data and the PALGA data.

<sup>e</sup>P-value given for Poisson regression for trend (period<sup>c</sup> region).

<sup>f</sup>P-value given for Poisson regression for difference between regions.

Table 2. Characteristics of patients with ESRD due to iMN<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands questionnaire</th>
<th>Nijmegen cohort</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n = 45)</td>
<td>Untreated (n = 23)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>34/11</td>
<td>19/4</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>49 ± 17</td>
<td>50 ± 17</td>
</tr>
<tr>
<td>Serum creatinine at diagnosis (µmol/l)</td>
<td>138 (60–1798)</td>
<td>120 (78–1072)</td>
</tr>
<tr>
<td>Proteinuria at diagnosis (g/24 h)</td>
<td>10.0 (0.6–20.2)</td>
<td>9.6 (3.0–20.2)</td>
</tr>
<tr>
<td>Age at the start of RRT (years)</td>
<td>60 + 15</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Serum creatinine at the start of treatment (µmol/l)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

RRT: renal replacement therapy.

Data are presented as mean ± SD or median (range).

<sup>a</sup>Data derived from the questionnaire with information on patients with ESRD. For comparison patient characteristics are given of patients at high risk for ESRD in the Nijmegen region who were all treated with cyclophosphamide and prednisone.

<sup>b</sup>Only four patients started RRT after 51 (5–125) months of follow-up.

revealed a significant difference in the change in incidence rates between the regions (P = 0.004).

Of note, in the first period (1991–1995) the incidence rate of ESRD due to iMN was higher in the Nijmegen region than in the other parts of the Netherlands. We therefore questioned if there might be differences in the overall incidence of iMN. From the PALGA database we retrieved the total number of the histological diagnosis membranous nephropathy for the study period. In the Nijmegen region the diagnosis MN was indeed encountered more often than in the other parts of the Netherlands (Table 1). Most importantly, the incidence of membranous nephropathy based on the PALGA database did not change in either region.

Although the PALGA database overestimates the number of patients with iMN (see the Subjects and methods section), the data provide the best estimate for the overall (change in) incidence of iMN. If we compare the incidence rate of ESRD due to iMN with the rates of the histopathological diagnosis of membranous nephropathy, the difference between the regions can be even better appreciated (Table 1, corrected incidence of ESRD).

We next questioned if the observed decreased incidence of ESRD due to iMN in the Nijmegen region was indeed specific for iMN. We therefore analysed the incidence of ESRD due to FSGS and histologically proven glomerulonephritis (EDTA codes 17 and 19). The results are depicted in Figure 1b and Table 1. It is evident that there are no differences between the Nijmegen region and the other parts of the Netherlands for these diagnoses.

Overall 81 questionnaires were mailed to nephrology centres that entered a patient with the diagnosis iMN in the RENINE database since 2000. We received 53 responses (65%). Eight patients were excluded because of a wrong diagnosis (n = 4) or missing data (n = 4). Our analysis thus included 45 patients (34 M, 11 F) with a mean age of 49 ± 17 years at diagnosis and a median serum creatinine of 138 µmol/l (range 60–1798). Other characteristics are shown in Table 2. For comparison we have added the characteristics of 65 patients from the Nijmegen region who were identified as high risk for progression to ESRD and received treatment in the period from 1991 to 2002. There were no significant differences between the groups.

Of the 45 patients included in our analysis, 22 patients (49%) have received some form of immunosuppressive therapy. There were no major differences with respect to age, serum creatinine concentration and proteinuria at diagnosis between treated and untreated patients (Table 2). The median serum creatinine concentration was 214 µmol/l (range 60–1798) at the start of treatment. Many different treatment strategies have been applied (Table 3). Eight of
Our epidemiological survey demonstrates a significant decrease in the incidence of ESRD due to iMN in the Nijmegen area compared to the other regions of the Netherlands. The decrease paralleled the introduction in our region of a restrictive treatment strategy [6]. Using this strategy we observed high renal survival rates, which were better than in historical controls [3]. The present data extend our observations and support the efficacy of our treatment strategy. Admittedly, epidemiological data can be biased and the observed differences may be unrelated to differences in treatment protocols.

We have performed additional analyses that support our conclusions. First, we have excluded variations in the overall incidence of membranous nephropathy as a cause of our findings. Data retrieved from the PALGA database clearly indicated that there was no change in the reported incidence of MN between the time periods. Therefore, the decreased incidence of ESRD due to iMN in the Nijmegen region cannot be explained by changes in the epidemiology of MN. Of note, the reported incidence of membranous nephropathy was consistently and ∼1.5-fold higher in the Nijmegen region. Differences in the characteristics of the populations are the most likely explanation for this finding. The Nijmegen region, located in the Southeast of the Netherlands, has more native inhabitants and fewer immigrants than the Western part of the Netherlands.

To document that the decreased incidence of ESRD due to iMN in the Nijmegen region was specific for iMN, we have also analysed the incidence of ESRD due to other glomerular diseases (EDTA codes 17 and 19). Here, we did not observe differences between the Nijmegen region and other parts of the Netherlands.

To further explore the explanatory role of immunosuppressive therapy we have mailed questionnaires to all nephrologists who have registered a patient with ESRD due to iMN in the RENINE database since 2000. The response rate was good and amounted to 65%. Most patients had not been treated or only had received prednisone monotherapy, which is ineffective [9,10]. Thus, the data clearly show that only 33% (15/45) of the patients who developed ESRD due to iMN received a potentially effective immunosuppressive agent such as cyclophosphamide, chlorambucil, cyclosporine or mycophenolate mofetil.

Admittedly, the 35% non-response rate could have biased our conclusions. However, since the use of immunosuppressive therapy and its relationship with outcome was the leading study question, we feel that it is unlikely that non-responders have preferentially used immunosuppressive therapy. However, even if all non-responding doctors (35%, n = 28) had treated their patients with immunosuppressive agents, still only 59% of the high-risk patients would have received potentially effective therapy.

In our previous study we have shown that in our region >90% of high-risk patients received immunosuppressive therapy with an alkylating agent [6]. Thus, the observed differences between the Nijmegen region and other parts of the Netherlands in the incidence rate of ESRD due to iMN are likely explained by the differences in the use of immunosuppressive therapy. Admittedly, although unlikely, we cannot exclude that other factors such as a change in supportive therapy or earlier detection of iMN could explain the differences between the regions.

Obviously, one could speculate that death from immunosuppressive related causes in the Nijmegen region could have led to the lower number of patients with iMN needing RRT. Our previous studies clearly argue against this idea. We have described a cohort of 65 patients with iMN treated according to our restrictive cyclophosphamide-based treatment strategy [3]. Patient survival was 84% after 7 years of follow-up. No patient died from renal failure. Out of the five patients who have died, in one patient, who died from bladder carcinoma, death may have been related to treatment. The other patients died after the end of treatment, most frequently from cardiovascular disease. We are not informed about the survival rates in the other regions in the Netherlands. However, if theoretically, patient survival would have been 100% in those regions; the

### Table 3. Immunosuppressive therapy used in 22 treated patients

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Rescue therapy 1</th>
<th>Rescue therapy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 22</td>
<td>n = 9</td>
<td>n = 3</td>
</tr>
<tr>
<td>Prednisone (8)</td>
<td>CsA (1)</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (5)</td>
<td>C (1)</td>
<td>MMF (1)</td>
</tr>
<tr>
<td>Azathioprine (1)</td>
<td>CP (1)</td>
<td></td>
</tr>
<tr>
<td>Chl (1)</td>
<td>CsA (2, 3)</td>
<td></td>
</tr>
<tr>
<td>Chl (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chl (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (5)</td>
<td>CP (1)</td>
<td></td>
</tr>
<tr>
<td>CsA (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CP: cyclophosphamide; Chl: chlorambucil; CsA: cyclosporine; Az: azathioprine; MMF: mycophenolate mofetil.

Number of patients treated with the given immunosuppressive drug. Alkylating agents and cyclophosphamide were mostly given in combination with steroids. MMF was used only as rescue therapy. All treatment given after the first period of immunosuppressive therapy is considered rescue treatment. Some patients have received a second rescue therapy. See the Results section for explanation.

the 22 treated patients received prednisone monotherapy as the initial treatment. During the follow-up, only one of these patients received rescue treatment (cyclosporine). Thus, seven patients received prednisone monotherapy as only treatment. In 14 patients the initial treatment consisted of another immunosuppressive agent (Table 3). Eight of these patients received rescue treatment afterwards, three of them with two different agents. Thus, overall 15 patients (33%) were treated with non-steroidal immunosuppressive agents in the course of their disease. In sum, four patients received prednisone and chlorambucil according to the original Ponticelli protocol. Eight patients received cyclophosphamide, two patients were treated with azathioprine and three received mycophenolate mofetil. Seven patients received cyclophosphamide: five of them as initial treatment and two of them as rescue therapy. Of these seven patients treated with cyclophosphamide, two patients were treated for a period of 3 and 8 weeks, three patients for 3 months and only two patients received cyclophosphamide for 12 months.

### Discussion

Our epidemiological survey demonstrates a significant decrease in the incidence of ESRD due to iMN in the Nijmegen area compared to the other regions of the Netherlands. The decrease paralleled the introduction in our region of a restrictive treatment strategy [6]. Using this strategy we observed high renal survival rates, which were better than in historical controls [3]. The present data extend our observations and support the efficacy of our treatment strategy. Admittedly, epidemiological data can be biased and the observed differences may be unrelated to differences in treatment protocols.

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difference of 16% can still not explain why the incidence of ESRD due to iMN has decreased by 70% in our region, compared to a stable incidence in the other regions.

Our treatment regimen consists of cyclophosphamide and prednisone. Our data thus support the findings of the randomized controlled trial of Ponticelli et al., and the cohort studies of Torres et al. and DuBuf-Vereijken et al. that demonstrated the efficacy of an immunosuppressive regimen consisting of a combination of steroids and an alkylating agent [2, 4, 6]. A recent study provided additional evidence. Jha et al. conducted a randomized controlled trial [8]. Forty-seven patients with iMN and a nephrotic syndrome were treated with a 6-month course of alternating prednisolone and cyclophosphamide. Outcome was compared to the control group of 46 patients that received only supportive treatment. In this study, immunosuppressive therapy more often induced a remission, arrested progression of renal insufficiency and improved quality of life compared to supportive treatment. Based on these data, we feel that it is no longer justified to withhold treatment to patients with iMN who are at risk for ESRD.

Admittedly, our data do not prove that cyclophosphamide is more effective than other immunosuppressive agents. Several trials have evaluated calcineurin inhibitors, mycophenolate mofetil, ACTH or rituximab and reported short-term efficacy [1].

From our questionnaire it is evident that many physicians are reluctant to use immunosuppressive therapy in patients with iMN. Almost all reported patients presented with renal insufficiency and thus must be considered at highest risk for ESRD. Often, further deterioration of renal function is awaited, and immunosuppressive treatment is started at a time point when renal function is even more impaired. Of note, immunosuppressive therapy may be less effective and more toxic when used in patients with more severe renal insufficiency.

The answers to the questionnaire are not unexpected. There is still an ongoing debate on the optimal treatment of patients with iMN, with discussion on the type of agent and the duration of therapy. Although alkylating agents are considered effective, many physicians and patients fear their side effects. The ongoing debate apparently often results in a wait and see policy. In our view this must be a concern since many patients unnecessarily develop ESRD and are thus exposed to the morbidity and mortality risks associated with dialysis and transplantation. Although side effects of alkylating agents are a major problem, our studies have shown high patient survival rates in treated patients. Of note, in the study of Jha et al. side effects occurred at comparable rates in patients treated with cyclophosphamide or supportive treatment [8].

In conclusion, our data suggest that the introduction of a cyclophosphamide-based restrictive treatment policy has reduced the risk of ESRD in Dutch patients with iMN. The questionnaires reflect the differences in opinion on the optimal treatment of high-risk patients with iMN. Implementation of treatment guidelines for patients with iMN seems indicated.

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Conflict of interest statement. None declared.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

References


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