Idiopathic membranous nephropathy and nephrotic syndrome: outcome in the era of evidence-based therapy

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Abstract
Background. Contemporary studies analysing the long-term outcomes of patients with idiopathic membranous nephropathy and nephrotic syndrome in the era of evidence-based antiproteinuric and immunosuppressive therapies are sparse. Controversy also persists regarding which immunosuppression (IS) regimen to use. In this retrospective cohort study, we aimed to characterize time to partial remission (PR), complete remission (CR), requirement for renal replacement therapy (RRT) or death. We aimed to assess which factors predicted RRT or death and determine the impact of IS on outcome.

Methods. Ninety-five consecutive adult patients attending two centres between 1997 and 2008 were identified. Baseline demographics and subsequent treatment and outcome were recorded.

Results. Ninety-five percent of patients were prescribed angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blocker (ACEI/ARB) therapy, 78% statin therapy, 70% antiplatelets and 38% IS. The 5-year actuarial rates for PR, CR, RRT and death were 76.4, 24.4, 11.9 and 16.8%, respectively. In patients achieving at least one PR, the 5-year actuarial risk of relapse was 32.8%. Using multivariate survival analysis, achievement of remission was the factor most strongly associated with reduced risk of RRT or death. There was no significant difference in outcomes between patients who did or did not receive IS, although patients receiving IS had more severe disease. Contrary to published findings, 81.8% of patients treated with the Ponticelli regimen (6 months of alternating prednisolone and cyclophosphamide or chlorambucil) suffered significant treatment-related complications compared with 19% of patients prescribed the Cattran regimen (prolonged combined low-dose prednisolone and cyclosporine).

Conclusions. Using an approach of widespread ACEI/ARB treatment and targeted IS, 76% of patients can expect to achieve PR by 5 years. Achievement of remission is the factor most strongly associated with reduced risk of RRT and death. Treatment with IS is associated with significant treatment complications.

Keywords: death; glomerulonephritis; proteinuria; remission; RRT

Introduction

Idiopathic membranous nephropathy (IMN) remains the commonest primary glomerulopathy associated with nephrotic syndrome in Europe [1, 2] and is second to focal segmental glomerulosclerosis in North America [3, 4]. Data relating to the prognosis of patients with nephrotic syndrome secondary to membranous nephropathy in the modern era are scarce [5]; however, outcomes are known to be worse than in those presenting with subnephrotic proteinuria [6, 7]. Studies from the early 1990s are often quoted [8, 9], but these relate to a time before lowered blood pressure targets, the establishment of general antiproteinuric therapeutic strategies such as renin–angiotensin system blockade with angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockade (ACEI/ARB) and evidence-based immunotherapy strategies. It would seem reasonable to postulate that treatment in the modern era would be associated with an improved outcome.

We aimed to characterize baseline demographics, renal survival and patient death in patients with IMN and nephrotic syndrome, diagnosed over the last 10 years in two renal units serving a population of ~1.5 million people. We aimed to assess the impact of immunosuppression (IS) on these outcomes, comparing two regimens with proven effect in previous randomized controlled trials: six alternating months of corticosteroid and alkylating agent (Ponticelli regimen) [10, 11] and low-dose corticosteroid and cyclosporine (Cattran regimen) [12]. Lastly, we aimed to assess the side effects associated with these two regimens.

Materials and methods

Inclusions

The adult renal electronic patient records for Greater Glasgow and Clyde were searched to identify consecutive patients diagnosed with membranous nephropathy between 03 January 1997 and 09 January 2008. Outcomes were censored at 09 January 2009 to ensure a minimum of 1-year follow-up. Only patients with nephrotic syndrome [urine protein to
creatinine ratio (uPCR) > 300 mg/mmol and serum albumin < 35 g/L on at least two consecutive occasions[1] were included for further analysis.

Exclusions

Patients were excluded if their membranous nephropathy was secondary to an established causative factor. Patients are routinely screened for hepatitis and systemic lupus erythematosus (hepatitis serology and antinuclear factor levels are analysed) at presentation. They also undergo detailed history, examination and chest radiography to exclude underlying malignancy.

Treatment

Standard local practice is to treat all patients with ACEI/ARB unless contraindicated, to a target blood pressure of <125/75 mmHg, with the addition of other antihypertensives as necessary. Patients were considered to have been treated with these agents if they had received them at any point during follow-up. IS is considered for patients with prolonged nephrotic syndrome (>6 months), serious complications of nephrotic syndrome including venous thromboembolism and intractable oedema or rapidly deteriorating renal function. Choice of immunosuppressive regime has been physician led, with no fixed unit policy but treatments adhered to published protocols [11, 12]. Eight patients had immunosuppressive choice randomized as part of the MRC trial of IS for membranous nephropathy (ISRCTN99959692), one of whom was randomized to no IS. For the present study, these patients were analysed within the appropriate treatment groups along with patients receiving the same regimen outside of a clinical trial.

Outcomes

Partial remission (PR) was defined as uPCR <300 mg/mmol and >50% decline in uPCR from baseline, and complete remission (CR) was uPCR <30 mg/mmol and relapse as uPCR >300 mg/mmol. To be classified as a PR or CR, the uPCR target had to be reached on at least two consecutive occasions. Time to death or starting renal replacement therapy (RRT) for chronic renal failure was also analysed. Renal function was assessed by the four variable Modification of Diet in Renal Disease formula to estimate glomerular filtration rate (eGFR). Blood pressure control was assessed by clinic blood pressure at time of biopsy and, in patients alive and not on RRT, glomerular filtration rate (eGFR). Blood pressure control was assessed by clinic blood pressure at time of biopsy and, in patients alive and not on RRT, blood pressure at 1- and 2-year follow-up.

Comparisons and statistical tests

Baseline demographic factors were compared using Student’s t-test, Mann–Whitney U-test or chi-square test as appropriate. Time to first PR, first CR and first relapse were compared by Kaplan–Meier analysis with log-rank test comparison. Factors associated with risk of requiring RRT for chronic renal failure and death were established using correlations (Spearman’s or Pearson’s as appropriate) and significant factors assessed further using multivariate Cox regression analysis. The impact of IS on outcome was assessed by comparing patients who received the Ponticelli regimen, Catran regimen and no IS, respectively.

Ethics

The Scottish Renal Biopsy Registry has research ethics approval for data collection and analysis with informed patient consent.

Results

Baseline demographics

One hundred and forty-six patients were identified, of whom 24 had secondary membranous nephropathy (15%). Of the remaining 124 patients, 95 were nephrotic at time of diagnosis (78%) and only these patients are included in the analysis.

Mean age at presentation was 61.4 (SD 14.0) years and 74.7% of patients were male. Renal function was relatively preserved at baseline with mean eGFR of 59.4 (SD 25.8) mL/min/1.73m². Median uPCR was 917 [interquartile range (IQR) 606–1331] mg/mmol and mean serum albumin 23.5 (SD 6.9) g/L. Table 1 describes the baseline demographics. Median follow-up was 1179 (IQR 552–2188) days. During follow-up, ACEI/ARB was prescribed in 94.7% of patients, HMG Co-A reductase inhibitors (statins) in 77.9% and 69.5% were prescribed antiplatelet agents or anticoagulation. It was not possible to ascertain retrospectively whether patients achieved the pre-determined blood pressure target. Thirty-nine percent received IS with either the Ponticelli or Catran regimens (see below).

Outcomes

The 1- and 5-year actuarial death rates were 9.6 and 16.8%, RRT rates were 1.1 and 11.9%, PR rates were 21.3 and 76.4% and CR rates were 0 and 24.4%, respectively. Of the patients who developed PR or CR, the actuarial risk of relapse within 5 years was 32.8% (Table 2). Only one patient died whilst receiving RRT. Median time to PR was 1.4 years and CR was 3.5 years.

Predictors of outcome—RRT or death

In order to determine which factors predict the outcome of requirement for RRT or death, multiple factors were entered into a correlation matrix (Spearman’s or Pearson’s as appropriate). These were age, sex, proteinuria, eGFR and serum albumin at baseline and any remission, CR, PR, ACEI/ARB treatment, statin treatment, antiplatelet treatment and immunosuppressive therapy.

Of these, factors associated with a significantly reduced risk of requirement for RRT or death, multiple factors were entered into a correlation matrix (Spearman’s or Pearson’s as appropriate). These were age, sex, proteinuria, eGFR and serum albumin at baseline and any remission, CR, PR, ACEI/ARB treatment, statin treatment, antiplatelet treatment and immunosuppressive therapy.

The effect of type of IS on outcome

Thirty-nine patients received IS. Treatment choice was largely determined by the attending nephrologist and was not randomized, although seven were randomized to IS as part of the UK MRC trial. Eleven patients received a
Outcomes of idiopathic membranous nephropathy MGN

maximum of six alternating months of corticosteroid and chlorambucil/cyclophosphamide (Ponticelli regimen) and 26 received cyclosporin (usually with low-dose prednisolone) (Cattran regimen). Eight patients were treated with both IS regimens successively. The median time from diagnosis to starting IS was 244 (IQR 135–435) days. Two patients received azathioprine as first immunosuppressive therapy and were excluded from further analyses of IS effect due to small numbers.

Patients who received IS were a selected group. They were significantly younger than those who did not (56.4 versus 64.6 years, P = 0.005) and had significantly better-preserved renal function at baseline (66.6 versus 54.8 mL/min/m², P = 0.013). However, they also had more aggressive disease with eGFR at 6 months declining significantly in the IS group (66.6 versus 54.9 mL/min) compared with the non-IS group (54.8 versus 54.5 mL/min), had a higher baseline uPCR (1065 versus 840 mg/mmol; P = 0.031) (Table 1) and had lost an average of 18.9 mL/min of eGFR from baseline by the time immunosuppressive treatment was commenced. At time of starting IS, median eGFR was 47.7 mL/min (IQR 39.4–60.5) and median uPCR was 913.5 mg/mmol (IQR 502.5–1333).

### Table 1. Baseline demographics of whole cohort and stratified by use of IS

<table>
<thead>
<tr>
<th></th>
<th>Nephrotic</th>
<th>Immunosuppressed</th>
<th>Not immunosuppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>95</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.4 (14.0)</td>
<td>56.4 (47.3–64.0)*</td>
<td>64.6 (14.8)</td>
</tr>
<tr>
<td>% Male</td>
<td>74.7</td>
<td>75.7</td>
<td>74.1</td>
</tr>
<tr>
<td>Mean baseline eGFR (mL/min/1.73m²)</td>
<td>59.4 (25.8)</td>
<td>66.6 (20.7)*</td>
<td>54.8 (27.8)</td>
</tr>
<tr>
<td>Mean eGFR at 6 months (mL/min/1.73m²)</td>
<td>54.6 (25.1)</td>
<td>54.9 (16.6)</td>
<td>54.5 (30.5)</td>
</tr>
<tr>
<td>Median sCr (micro mol/L)</td>
<td>109.0 (93–143)</td>
<td>106.0 (88–119)</td>
<td>112 (95–181)</td>
</tr>
<tr>
<td>Mean serum albumin (g/L)</td>
<td>23.5 (6.9)</td>
<td>22.9 (7.0)</td>
<td>23.9 (6.9)</td>
</tr>
<tr>
<td>Mean uPCR (mg/mmol)</td>
<td>917 (606–1331)</td>
<td>1065 (620–1354)*</td>
<td>840 (592–1210)</td>
</tr>
<tr>
<td>% Nephrotic</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>% Prescribed ACEI/ARB during follow-up</td>
<td>94.7</td>
<td>91.9</td>
<td>96.6</td>
</tr>
<tr>
<td>% Prescribed statin during follow-up</td>
<td>77.9</td>
<td>83.8</td>
<td>74.1</td>
</tr>
<tr>
<td>% Prescribed antiplatelet agent during follow-up</td>
<td>69.5</td>
<td>70.3</td>
<td>69.0</td>
</tr>
<tr>
<td>Median follow-up (days)</td>
<td>1179 (552–2188)</td>
<td>1543 (719–2413)</td>
<td>896 (440–2159)</td>
</tr>
</tbody>
</table>

*Data are presented as means (SD) or median (IQR). Factors are compared using t-test, Mann–Whitney U-test or chi-square test as appropriate. Items in bold are significant differences between groups. *P < 0.05.

### Table 2. Outcomes for the whole cohort and stratified by whether the patient received IS and if so, which type [Cattran or Ponticelli (Pont) regimen]

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>IS</th>
<th>No IS</th>
<th>Cattran</th>
<th>Pont</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>95</td>
<td>37</td>
<td>58</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Any PR (%)</td>
<td>76.4</td>
<td>79.2</td>
<td>69.6</td>
<td>66.7</td>
<td>77.3</td>
</tr>
<tr>
<td>Any CR (%)</td>
<td>24.4</td>
<td>22.3</td>
<td>24.3</td>
<td>32.8</td>
<td>48.2</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>32.8</td>
<td>47.4</td>
<td>22.3*</td>
<td>48.2</td>
<td>49.1</td>
</tr>
<tr>
<td>Dead (%)</td>
<td>16.8</td>
<td>11.5</td>
<td>19.7</td>
<td>13.5</td>
<td>14.3</td>
</tr>
<tr>
<td>RRT (%)</td>
<td>11.9</td>
<td>8.2</td>
<td>13.6</td>
<td>14.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Data reported as the actuarial probability (%) of an event at 5 years using Kaplan–Meier analysis. Comparisons made using log-rank test. Items in bold are significant differences between groups. *P < 0.05.

### Table 3. Correlation matrix for the requirement for RRT or death (Spearman’s or Pearson’s as appropriate)

<table>
<thead>
<tr>
<th></th>
<th>RRT</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.036</td>
<td>0.723</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.088</td>
<td>0.385</td>
</tr>
<tr>
<td>uPCR (mg/mmol)</td>
<td>−0.158</td>
<td>0.121</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>−0.038</td>
<td>0.712</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>0.244 (0.016)</td>
<td>0.242 (0.017)</td>
</tr>
<tr>
<td>Any remission</td>
<td>−0.347</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR</td>
<td>−0.396</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>−0.121</td>
<td>0.232</td>
</tr>
<tr>
<td>ACEI/ARB treatment</td>
<td>−0.319</td>
<td>0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>0.124</td>
<td>0.22</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>−0.018</td>
<td>0.862</td>
</tr>
<tr>
<td>IS</td>
<td>−0.007</td>
<td>0.942</td>
</tr>
</tbody>
</table>

*Items in bold are significant values.
In IS patients, 1- and 5-year actuarial PR rates were 18.4 and 79.2% and CR rates were 0 and 22.3%, respectively. One- and 5-year patient death rates were 2.6 and 11.5%, respectively, and 1- and 5-year RRT rates were 0 and 8.2%, respectively. In IS patients who achieved PR, the probability of suffering a relapse within 5 years of PR was 47.4% (compared with 22.3% in those not immunosuppressed).

There were no significant differences in outcome comparing the patients who received IS with those who did not, although groups differed at baseline (Table 1), with the IS group having more severe disease in terms of rate of decline in eGFR and higher baseline proteinuria. There was a trend to higher 5-year actuarial PR rates in the IS group (79.2 versus 69.6%) and a higher 5-year actuarial death rate in the non-IS group (13.6 versus 8.2%) (Table 2). In patients who were not immunosuppressed, it can be seen that there was an early increase in mortality and more patients commenced RRT (Figure 2) but this was not statistically significant over the whole follow-up period. This may be explained by the fact that patients who did not receive IS were older and had more advanced renal failure at baseline (Table 1).

The outcomes of the Ponticelli and Cattran regimens were compared using an intention to treat approach based on first IS regimen. There were no significant baseline differences between patients who received the different regimens in terms of patient age, baseline eGFR, serum albumin, serum creatinine, protein:creatinine ratio or time to IS. Five patients progressed to RRT [Ponticelli = 2 (18%); Cattran = 3 (11%)] and five patients died [Ponticelli = 1 (9%); Cattran = 4 (15%); see below]. Median time from diagnosis to RRT was 1862 days (1662–2044) in patients who received RRT. The type of immunosuppressive regimen had no significant impact on incidence or time to PR or CR, requirement for RRT or death (Figure 3).

There was no significant difference in relapse rates between the two immunosuppressive regimens.

Complications of IS

Of the 11 patients who commenced the Ponticelli regimen, 81.8% (n = 9) developed a significant complication including infection (n = 2, 18%), leucopenia (n = 3, 27%), drug intolerances (n = 3, 27%), steroid-induced diabetes (n = 1, 9%) and other medical problems (n = 1, 9%). Twenty-seven percent (n = 3) of patients required a dose reduction and the regimen was discontinued in a further 36% (n = 4) of patients. Only 18% (n = 2) completed the regimen without complication.

Table 4. Multivariate Cox regression analysis of the factors significantly predictive of the requirement for RRT (a) or death (b)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Time to RRT. Chi square for Model 34.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB treatment</td>
<td>0.67</td>
<td>0.13–3.30</td>
<td>0.618</td>
</tr>
<tr>
<td>Any remission</td>
<td>0.02</td>
<td>0.00–0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>1.01</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>b. Time to death. Chi square for Model 37.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03</td>
<td>0.99–1.08</td>
<td>0.187</td>
</tr>
<tr>
<td>Any remission</td>
<td>0.07</td>
<td>0.02–0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>0.98</td>
<td>0.95–1.003</td>
<td>0.086</td>
</tr>
<tr>
<td>Antiplatelet/anticoagulant treatment</td>
<td>7.36</td>
<td>0.95–56.9</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Fig. 1. One-survival plot for time to RRT (A) or death (B) stratified by the presence (interrupted line) or absence (solid line) of any remission during follow-up. Comparison by log-rank test.
Of the 26 patients prescribed the Cattran regimen as first line, 5 (19%) developed a significant complication, with 1 patient requiring temporary haemodialysis for rhabdomyolysis secondary to the interaction between cyclosporine and a statin. The remaining four had difficulties with hirsutism, hypertension and renal impairment. All five patients had treatment discontinued. The majority of patients prescribed the Cattran regimen had multiple cyclosporine dose adjustments in response to serum trough levels or changes in the level of proteinuria or renal function. The Cattran regimen was associated with a longer duration of treatment than the Ponticelli regimen (median 425 versus 122 days).

As described above 5 (13.7%), patients prescribed IS died (Cattran n = 4, Ponticelli n = 1), although none died while receiving IS. Median time from stopping IS to death

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**Fig. 2.** Kaplan–Meier one-survival plot of outcome stratified by use of IS (interrupted line) (n = 37) and no IS (solid line) (n = 58). Outcome judged from time of starting IS. (A) Time to requiring RRT; (B) time to death. Comparison by log-rank test.

**Fig. 3.** Kaplan–Meier one-survival plots of outcomes by type of IS. (A) Cattran regimen (cyclosporine) (interrupted line); (B) Ponticelli regimen (solid line). Comparison by log-rank test.
in these five patients was 351 days (IQR 207–499). One of these patients died while receiving RRT. None of these patients had achieved CR with IS, only one had achieved PR and the nephrotic syndrome relapsed 133 days later in this patient.

Blood pressure control

Mean systolic blood pressure (SD) at time of biopsy, at 1 and at 2 years (in patients alive and not on RRT), was 143.7 (20.7), 141.2 (22.2) and 135.4 (22.1) mmHg, respectively. Mean diastolic blood pressure (standard deviation) at time of biopsy, at 1 and at 2 years, was 78.5 (13.8), 76.2 (13.3) and 75.7 (13.0) mmHg, respectively. The proportion of patients with systolic blood pressure target of <125 mmHg at time of biopsy, at 1 and at 2 years, was 18.9, 27.3 and 33.8%, respectively.

Discussion

In this retrospective cohort study of consecutive patients with IMN and nephrotic syndrome, we aimed to assess patient outcomes using our current therapeutic strategy of ACEI/ARB for all and targeted IS. We have shown that the conventionally accepted prognostic rule of thirds (one-third will have spontaneous remission, one-third will have progressive renal failure and one-third will stay the same) should be modified for the modern era. Now, 75% of patients can expect to have achieved at least one PR in the 5 years after diagnosis and 25% will have required RRT or died. Achievement of remission is the factor most strongly associated with a reduced risk of RRT and death, with subsequent relapse appearing not to have a negative impact.

Comparison with historical published data

Our knowledge of the natural history of membranous nephropathy is largely derived from historical data, where antiproteinuric therapies such as renin–angiotensin blockade and statin therapy were largely not available or used, blood pressure control was less tightly defined and IS not widely used. There are potential difficulties in comparing remission rates between published studies because some studies report the prevalence of remission at defined follow-up time points, while others report actuarial incidence. We chose to analyse actuarial incidence of remission, even if there was subsequent relapse, as published data suggest that achieving any remission is important for determining the risk of progression and renal survival even if the remission is not sustained [13].

Similarly, comparison between studies is difficult because of differing baseline cohorts. Our cohort differed from other published studies in that 95% of patients received ACEI/ARB, fewer patients were immunosuppressed, our patients were older, more likely to be male, had poorer baseline renal function and higher levels of proteinuria, which may explain some of the reported differences in outcomes.

The most contemporaneous study with which to compare our data is a multicentre study from Spain [5] including patients with nephrotic IMN and largely preserved renal function, diagnosed between 1975 and 2007. In that study, 66.7% received ACEI/ARB treatment and 53.7% received IS. The probability of a spontaneous CR or PR at 5 years was 31.7%, with a 5.7% relapse rate after 11 years. The probability of spontaneous remission was significantly higher in patients treated with ACEI/ARB. This rate of remission is below that seen in our cohort where 69.6% of patients can be expected to achieve at least a PR at 5 years; however, our cohort had a higher probability of relapse (22.3% at 5 years) in those who achieved spontaneous remission. In older prevalence studies, Schieppati et al. [8] found that at 5 years, 35% would remain nephrotic, 40% would be in PR and 20% in CR. Their findings were confirmed by other investigators [7, 14]. The control arm of the Ponticelli study, which only included nephrotic patients, reported a 40% CR or PR rate at 5 years [10], again in younger patients with better-preserved renal function.

Factors which predict progression of membranous nephropathy have been well characterized and include male gender (at higher levels of proteinuria), impaired renal function at presentation and the severity of proteinuria at diagnosis [7, 13, 15]. We extend these findings by reporting that if nephrotic age at presentation has no impact on renal outcome. Similarly, impaired eGFR at baseline increased the risk of requiring RRT but had no apparent impact on the chance of remission, although eGFR was relatively preserved at baseline.

Utilization of ACE inhibition in patients with significant proteinuria has been adopted as the antihypertensive approach of choice. It should, however, be noted that data relating to the definitive role for these agents in reducing proteinuria in patients with nephrotic range proteinuria secondary to IMN and improving outcomes are scarce and conflicting [16, 17]. Further prospective study is required to clarify this issue.

Immunosuppression

Significant advances in immunosuppressive therapy for membranous nephropathy [18] have been seen in the last 20 years with the establishment of the Ponticelli regimen [10, 11, 19] and Cattran regimen [12]. Alkylating agents (cyclophosphamide or chlorambucil) and corticosteroids form the Ponticelli regimen and the benefits have been confirmed in different populations [20, 21], with studies reporting improved remission rates and reduced RRT requirements, largely in patients with relatively preserved renal function at enrolment. The Cattran regimen (cyclosporine and low-dose prednisolone) has a better evidence base for patients with renal impairment. Drawbacks known to be encountered with cyclosporine use include dependency, whereby withdrawal of the drug results in relapse of the nephrosis [22], the long duration of treatment required to attain remission [23] and resistance to treatment. This is in addition to the recognized side effects of hypertension and renal impairment (although these are usually reversible on dose reduction or discontinuation). These regimens have been an important advance but high spontaneous remission rates and side effects associated with IS have limited its use to selected patients.

No randomized controlled trials have compared the two regimens; however, Goumenos et al. [24] also retrospectively compared outcomes in 77 patients with nephrotic syndrome and preserved renal function from a single centre treated with
either the Catran \( n = 46 \), treated 2000–2005) or Ponticelli \( n = 31 \), treated between 1995 and 2000) regimens. Contrary to our findings, remission rates were higher with the Catran regimen (85%) with only 55% of patients achieving any remission with the Ponticelli regimen, despite no difference in drug discontinuation rates, which were very low. Differences in remission rates were not associated with any difference in rates of doubling of serum creatinine or requirement for RRT between the two groups. The inclusion of only patients with preserved renal function may explain some of the findings. Interestingly, in a recently published randomized controlled trial in 42 patients with lupus membranous nephropathy, the cumulative probability of remission at 1 year was 60% with six alternate monthly doses of IV cyclophosphamide and 83% with 11 months of CyA [25]. Both of these study regimens were combined with prednisone and the probability of remission at 1 year with prednisone alone was significantly lower at 27%. The UK MRC-funded trial of treatment for IMN, comparing no additional IS against treatment with cyclosporine or chlorambucil for patients with deteriorating renal function (ISRCTN99959692), is currently undergoing follow-up and should provide information to further guide management.

Our retrospective analysis of patients who received IS versus those who did not should be interpreted in the context that these groups of patients differed at baseline. Those receiving IS were younger with more severe disease, as evidenced by significantly higher baseline proteinuria and rapid decline in eGFR over the first 6 months after diagnosis, with patients having lost on average 11.7ml/min/1.73m\(^2\) eGFR within 6 months. It is therefore difficult to draw firm conclusions about the impact of IS on disease outcome. In patients who did receive IS, our non-randomized retrospective comparison of the two evidence-based IS regimens showed no significant difference in achievement of PR, CR, progression to RRT or patient death between the Ponticelli and Catran regimens. The comparison must be interpreted with caution as numbers were small and this was not undertaken as part of a prospective clinical trial.

The significant number of side effects seen in our cohort, where 82% of those treated with the Ponticelli regimen experienced at least one significant side effect, supports the notion that this regimen is not without burden but is contrary to published studies that imply the regimen is well tolerated [11, 20]. The discrepancy may relate to differences in baseline renal function and older age in our cohort but should be interpreted with caution as only 11 patients were treated with the regimen as first-line IS. The Catran regimen was better tolerated, perhaps reflecting better evidence for use in patients with renal impairment [26].

The relatively low number of patients undergoing IS in our cohort and the relatively long observation period prior to commencing IS (median 244 days) suggest physician reluctance to embark on an intensive immunosuppressive regimen, perhaps due to witnessing the high number of side effects in our population. There is a need for better methods of identifying the high-risk patients most likely to benefit from IS and it may be that stratifying patient risk based on measurement of urinary biomarkers, e.g. IgG and beta 2-microglobulin excretion [27] or established predictive models based on proteinuria excretion [15], will have the utility to guide physicians to institute IS at a timely stage in the disease course.

The drawbacks and inadequacies of conventional therapies have prompted the search for better tolerated more effective treatments, of which rituximab appears to be the forerunner due to relatively improved tolerability and ease of administration. As both a first and second line treatment approach it appears to be associated with a significant reduction in proteinuria [28–31]. As yet no directly comparative trial has been undertaken. Further to this, with the identification of the M-type phospholipase A2 receptor as an antigen, there is hope that a more targeted therapeutic approach may yet be possible [32, 33].

**Mortality**

The morbidity associated with nephrotic syndrome is well documented and includes the complications of fluid overload, increased risk of venous thromboembolism [34], hyperlipidaemia, accelerated coronary artery disease [35], potentially progressive renal dysfunction and the risks of therapy. Membranous nephropathy is also associated with an elevated malignancy risk, which persists long after diagnosis [36]. Despite this, the mortality risk associated with IMN has been largely overlooked. The 5-year actuarial mortality rate of 16.8% in our cohort is worth comparing with the 5.5% five-year standardized mortality rate for the Scottish population aged 55–64 years [37] (http://www.gro-scotland.gov.uk/files1/stats/01t5_1.pdf). This elevated risk seems to be linked to the underlying disease pathogenesis in that the only significant predictor of death was the absence of a remission and only one death occurred after starting RRT. This suggests an added incentive to attaining remission. Similarly, whether remission was obtained spontaneously or following IS had no impact on risk of death in our cohort. The positive correlation between death and the prescription of antiplatelets or anticoagulants raises the possibility that these medicines might be harmful in IMN but it seems more likely that either these patients had a higher risk of death because of co-existent cardiovascular disease or previous thromboembolic events.

**Limitations of the study**

The retrospective nature of this study limits the interpretation of results. It is difficult to be clear about the impact of IS in a non-randomized retrospective study and also to assess the impact of different immunosuppressive regimens when patient numbers are small. However, the data were collected in a real-time electronic patient record and the number of patients studied compares favourably with previous studies. More extensive follow-up would be helpful to strengthen the findings in this chronic condition.

**Conclusions**

With our current approach to management of IMN and nephrotic syndrome with widespread ACEI/ARB usage and selective IS, 76.4% of patients can expect to achieve at least one remission, 11.9% will require RRT and 16.8% will die in the 5 years after diagnosis. Attaining any remission is the most important factor associated with reducing...
the risk of requiring RRT and of death. Type of IS used did not have an impact on outcome but the Ponticelli regimen was associated with a higher incidence of side effects than the Cattran regimen. These findings should help inform physician and patient treatment choice while awaiting the results of the ongoing UK MRC randomized controlled trial of immunosuppressive regimens in patients with IMN.

Conflict of interest statement. None declared.

References