## ORIGINAL ARTICLE

# Intravenous cyclophosphamide and oral prednisolone is a safe and effective treatment option for idiopathic membranous nephropathy

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## Abstract

**Background.** Idiopathic membranous nephropathy (IMN) is one of the most common causes of nephrotic syndrome in adults. A proportion of patients will experience spontaneous remission and the decision to offer immunosuppression is guided by the presence of adverse prognostic features. Data relating to the efficacy of different immunosuppressive protocols is lacking, in particular there are little data available on the efficacy or benefits of an intravenous (IV) cyclophosphamide-based regimen. Since 2010, our unit has been using a treatment regimen based on IV cyclophosphamide and oral prednisolone for patients with IMN associated with adverse prognostic features. The outcomes of these patients were compared with a historic cohort of similar patients who did not receive immunosuppressive therapy.

**Methods.** Between January 2010 and 2014, a total of 41 patients were treated with pulse IV cyclophosphamide and oral prednisolone. The historical comparator group included 47 similar patients diagnosed between 2006 and 2010 who did not receive immunosuppression. Two-year follow-up data were collected. The primary outcome measure was time to remission of nephrotic syndrome (defined as normalization of serum albumin). Secondary outcomes included rate of progression of kidney disease as well as incidence of treatment-related adverse events.

**Results.** As compared with supportive care alone, treatment with IV cyclophosphamide and oral prednisolone was associated with a significantly higher number of patients achieving remission. Within 18 months of therapy, 74% of treated patients had achieved a normal serum albumin level. Though there was a trend towards a more rapid decline in estimated glomerular filtration rate in the untreated cohort, this did not reach statistical significance. The IV cyclophosphamide-based regimen was well tolerated, with few significant treatment-associated side effects.

**Conclusion.** IV cyclophosphamide is a safe and effective treatment for IMN.

Key words: albumin, glomerulonephritis, immunosuppression, membranous nephropathy, nephrotic syndrome

## Introduction

Idiopathic membranous nephropathy (IMN) is one of the most common causes of nephrotic syndrome among adults, accounting for up to one-third of cases [1, 2]. Although spontaneous remission is said to occur within 2 years in up to one-third of patients, there are well-documented risk factors that are associated with progressive disease, including male sex, heavy proteinuria (> 8 g/24 h) and renal impairment at presentation [3].

There is increasing evidence that IMN is an autoimmune disease. A number of target autoantigens have been described, with antibodies most frequently being directed against the phospholipase A2 receptor (PLA2R), highly expressed in glomerular podocytes [4–6]. The optimal treatment approach to patients with IMN is controversial given the relatively high rate of spontaneous remission; however, the clarification of an autoimmune aetiology has led to renewed interest in the role of immunosuppressive treatment for patients with IMN.

Although multiple therapeutic regimens have been studied in patients with IMN, most studies have used treatment protocols based on the Ponticelli regimen [7, 8]. More recently, a randomized controlled trial undertaken in the UK demonstrated that a regimen of prednisolone plus chlorambucil was superior to ciclosporin and supportive therapy [9]. The most recent (2012) Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines advocate an initial therapy consisting of a 6-month course of alternating monthly cycles of corticosteroids and oral alkylating agents. In spite of the evidence for chlorambucil, KDIGO guidelines recommend using oral cyclophosphamide for initial therapy. This most likely reflects both a lack of familiarity and concerns about the side effects of chlorambucil within the nephrology community [10, 11].

There are also concerns relating to the use of oral cyclophosphamide, in particular relating to patient adherence and the unpredictability of potentially severe neutropaenia. These concerns have led to an increased use of intravenous (IV) cyclophosphamide in the treatment of other immune-mediated glomerular diseases. For these conditions, the use of IV cyclophosmide has been proven to be effective, with the additional benefit of a lower cumulative dose [12–15].

Data on the role of IV cyclophosphamide to treat IMN are limited and conflicting. A study by Reichert et al. [16] suggested that monthly IV cyclophosphamide was not as effective as oral chlorambucil in terms of preserving renal function. In contrast, a retrospective analysis by Yuan et al. [17] suggested that IV cyclophosphamide may be an effective alternative therapy for IMN. Given the increasing evidence for the use of IV cyclophosphamide in the treatment of other glomerular diseases, we hypothesized that this would be an appropriate regimen for patients with IMN.

Since 2010, our unit has been using an IV pulse cyclophosphamide-based treatment regimen for patients with IMN. Patients are stratified according to the severity of their disease at presentation. Patients deemed at high risk of progression and unlikely to achieve spontaneous remission by recognized criteria are treated with a 6-month course of IV cyclophoshamide together with a tapering course of oral prednisolone and appropriate supportive treatment. The IV cyclophosphamide dose was based on the published protocol used for the treatment of antineutrophil cytoplasmic antibody–associated vasculitis [18].

In the current analysis, we describe the outcomes of patients who presented with nephrotic syndrome related to IMN who were treated according to this regimen. We compared their outcomes with a previous era where the decision whether or not to treat was based on individual physician preference, so that a proportion of similar patients with nephrotic syndrome were not treated with immunosuppression.

## Materials and Methods

### Patient population

This was a retrospective analysis of prospectively collected data from a large tertiary referral renal unit (catchment population 1.4 million). All patients diagnosed with IMN and nephrotic syndrome who had been treated according to the units IV cyclophosphamide protocol (Supplementary data, Figures S1 and S2) between January 2010 and 2014 were identified. Patients with secondary MN (based on clinical/histological or serological evidence) were excluded from analysis. The median cumulative dose of IV cyclophosphamide was 7200 mg [interquartile range (IQR), 5270–9600 mg]. Prednisolone was commenced at a dose of 1 mg/kg and the dose was reduced at 2-week intervals so that steroid therapy was stopped at 6 months. During this period, a total of 41 patients received immunosuppression. The historical comparator group included all similar patients with IMN and nephrotic syndrome who had been diagnosed between 2006 and 2010 but had not received immunosuppressive therapy ($n = 47$).

### Data collection

Clinical and laboratory data were collected from both case notes review and review of our renal unit's electronic database. The local laboratory uses the bromocresol green albumin assay and a modified Jaffe reaction-based assay is used to measure serum creatinine. The laboratory routinely reports estimated glomerular filtration rate (eGFR) determined using the Modification of Diet in Renal Disease equation. Two-year follow-up data were collected from all patients. Baseline was defined as the time of renal biopsy.

### Outcome

The primary outcome measure was time to remission of nephrotic syndrome (defined as normalization of serum albumin). Secondary outcomes included the rate of progression of kidney disease (time to 30% decrease in eGFR) and incidence of treatment-related adverse events.

### Statistical analysis

Statistical analysis was done using SPSS version 23 (IBM, Armonk, NY, USA). Where data were normally distributed, the mean and standard deviation are shown; for skewed data, the median and IQR were used. Log-rank test analysis was used to compare the time to remission and the time to further 30% decrease in eGFR between groups.

## Results

### Patient demographics

The patient demographics were similar in both groups, although as shown in Table 1, there was a non-significant trend for more severe disease in those patients who received immunosuppression (lower eGFR, higher level of proteinuria).

**Table 1.** Patient demographics

| | Treated ($n = 41$) | Untreated ($n = 47$) | P-value |
|---|---|---|---|
| Gender (male), % | 59 | 60 | 0.51 |
| Age (years), median (IQR) | 65 (57–75) | 63 (48–72) | 0.31 |
| Baseline albumin (g/L), median (IQR) | 19 (16–24) | 20 (15–25) | 0.8 |
| Baseline eGFR (mL/min), median (IQR) | 55 (34–76) | 72 (47–89) | 0.07 |
| Baseline urine protein:creatinine ratio (mg/mmol), median (IQR) | 835 (791–835) | 700 (450–905) | 0.06 |
| Percentage on angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker | 58 | 59 | 0.286 |
| Percentage on statins | 39 | 40 | 0.59 |
| Percentage with each histological stage of IMN | | | |
| Stage 1 (sparse small deposits without thickening of the glomerular basement membrane (GBM)) | 36 | 30 | 0.83 |
| Stage 2 (more extensive subepithelial deposits with formation of basement membrane spikes between the deposits and thickening of the GBM) | 53 | 49 | |
| Stage 3 (combination of stage 2 along with deposits completely surrounded by basement membrane) | 5 | 13 | |
| Stage 4 (incorporation of deposits in the GBM and irregular thickening of the GBM) | 0 | 0 | |
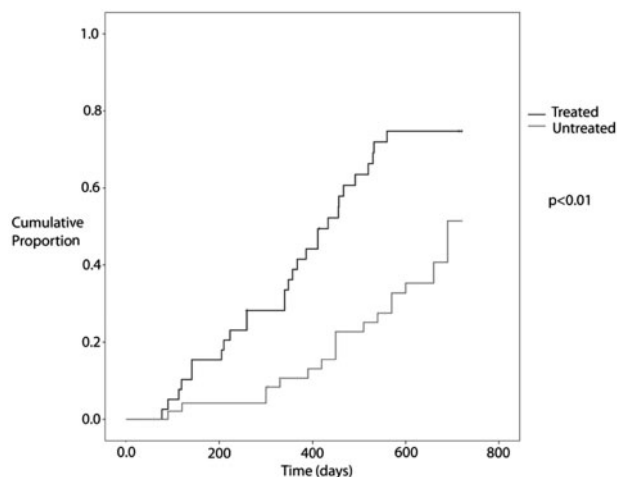


**Fig. 1.** Kaplan–Meier curve showing time to normalization of serum albumin (albumin ≥35 g/L) in treated and untreated patients.
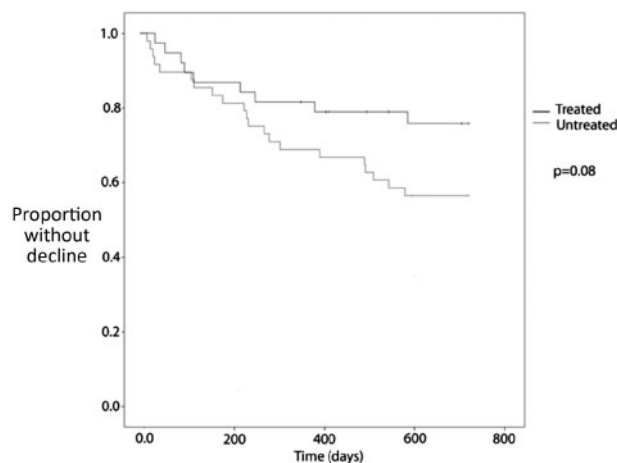


**Fig. 2.** Kaplan–Meier curve showing time to a further 30% decrease in eGFR from the time of biopsy in treated and untreated patients.

## Remission of nephrotic syndrome

Time from biopsy to normalization of serum albumin was analysed in the treatment group and compared with the historical untreated cohort of patients. As shown in Figure 1, there was a statistically significant difference between the groups, with the treated group achieving remission of nephrotic syndrome more quickly.

## Rate of decline in eGFR

Although there was a trend towards a more rapid decline in eGFR in the untreated cohort, this did not reach statistical significance (Figure 2). Within the groups, three patients progressed to end-stage renal disease within 2 years of biopsy, of which two were in the untreated group and one in the treated group.

## Time from treatment to remission of nephrotic syndrome

The median time from biopsy to treatment was 6 months, so that analysing time from biopsy to remission may

underestimate the effect of therapy. To better assess the temporal changes in albumin after treatment, the time from treatment (rather than the time from biopsy) to remission was assessed in the treated group. Immunosuppression was associated with a rapid rise in serum albumin so that within 6 months of treatment the mean rise in albumin was 10 g/L. The improvement was sustained beyond the 6-month period of treatment and by 18 months post-therapy, 74% of treated patients had achieved a normal serum albumin level. The increased serum albumin was maintained at the 2-year follow-up period (Figures 3 and 4). The medium- to long-term clinical condition of the treated cohort is shown in Supplementary data, Table S1.

## Adverse events

Four patients developed cyclophosphamide-related leucopaenia (white cell count nadir $<3 \times 10^9$ g/L). Of these, two patients were managed by dose reduction and two were switched to mycophenolate mofetil (MMF). Both of the patients who switched to MMF achieved a normal serum albumin by 12 months. None of the patients developed treatment-related infections that required
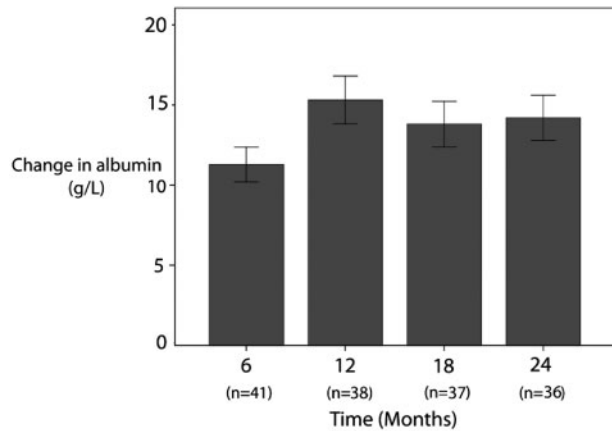
**Fig. 3.** Change in albumin (g/L) from baseline (mean ± standard error) post-treatment.
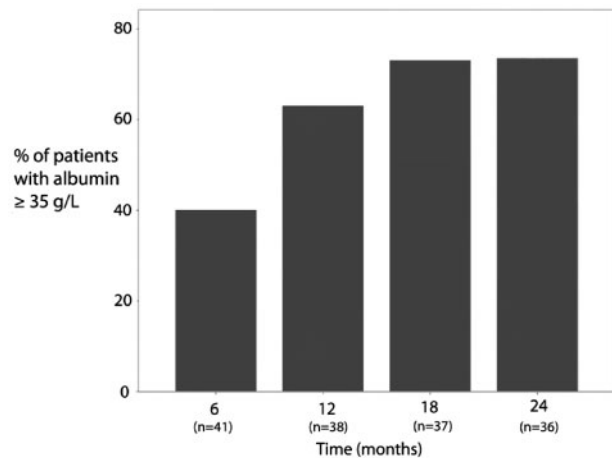


**Fig. 4.** Percentage of patients with normal serum albumin (>35 g/L) post-treatment.

hospitalization. There were four deaths within the 2-year follow-up period, two in the treated cohort (myocardial infarction, sepsis) and two in the historical cohort (congestive cardiac failure, pneumonia).

## Discussion

IMN remains one of the most common causes of nephrotic syndrome in adults [2]. The high incidence of spontaneous remission has justifiably dampened clinician enthusiasm for universal immunosupression and hampered recruitment to and interpretation of therapeutic clinical trials. The 2012 KDIGO guidelines suggest that defined groups of patients deemed at risk of progression should be treated with immunosuppression. The majority of studies assessing the role of cytotoxic therapy have focused on either chlorambucil or oral cyclophosphamide. These treatments are hindered by concerns about potential side effects [10, 11].

Based on the strong evidence base for using IV cyclophophamide in other immune-mediated glomerular diseases, our unit has been using an IV treatment regimen for IMN. The IV regimen coupled with oral prednisolone has several potential benefits, including a lower cumulative dose of cyclophosphamide

(80–120 versus 180 mg/kg with the modified Ponticelli treatment), fewer side effects and the avoidance of high-dose IV steroids [7].

Our data suggest that for patients with nephrotic syndrome due to IMN at high risk for progressive disease, a 6-month treatment regimen consisting of IV cyclophosphamide and oral corticosteroids every 3 weeks seems to be safe and effective. Within 12 months of therapy the majority of patients had entered clinical remission, with this maintained at 24 months. As compared with a historical untreated cohort, a significantly higher proportion of patients achieved remission of nephrotic syndrome within 2 years of biopsy. Our remission rates are comparable to those described in patients treated with methyl-prednisolone and oral cyclophosphamide [19].

Treatment appeared to slow progression of eGFR decline; however, this did not reach statistical significance. This may be related to the fact that in order to compare the treated and untreated groups, time zero was defined as the time of biopsy (rather than time of treatment commencement). In some patients there was a significant delay in commencement treatment so that the median time to treatment post-biopsy was 6 months. It is likely that a longer follow-up period would be required to accurately assess the impact of treatment on renal decline. Relatively few treatment-related side effects were seen as compared with previous studies with oral cyclophosphamide [10, 11].

Our study has a number of limitations; in particular, this was not a randomized controlled trial, so selection bias may have influenced the treatment of patients in the historical cohort. This seems unlikely, however, since in our unit prior to the introduction of a treatment protocol, the decision whether or not to treat IMN with immunosuppression varied according to physician preference, with some clinicians choosing not to treat patients based on a lack of robust evidence. Additionally, baseline characteristics were similar between the groups.

Another drawback of the study is the use of albumin as a surrogate marker of remission. We had initially intended to use urine protein levels to define remission; however, it became apparent that (other than early in the course of disease) laboratory quantification of proteinuria was not undertaken at every clinic visit. This was particularly true in the historical cohort and in patients who had achieved clinical remission of nephrotic syndrome. Again, this reflects the fact that this was a retrospective analysis of real-world data rather than a controlled study where proteinuria would be quantified on a regular basis. The limited urine protein data that were available suggested that remission was more frequent in the treated group (data not shown). Further review of the clinical notes confirmed that albumin was a reasonable surrogate marker of remission since all patients in the treated group who achieved normal serum albumin levels also had resolution of peripheral oedema.

In conclusion our data suggest that pulsed IV cyclophosphamide together with a tapering course of oral prednisolone is an effective treatment option for patients suffering from nephrotic syndrome due to IMN. Longer-term follow-up is required to assess the impact of treatment on disease progression.

## Supplementary data

Supplementary data are available online at http://ckj.oxford journals.org.

## Conflict of interest statement

None declared.

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