Brief Report

Treatment of idiopathic membranoproliferative glomerulonephritis with mycophenolate mofetil and steroids

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Abstract

Background. Treatment of adults with idiopathic membranoproliferative glomerulonephritis (IMPGN) is often unrewarding with ~60% of patients progressing to end-stage renal failure within 10 years. Although children with IMPGN may respond to steroid therapy, there is no significant benefit to treating adult IMPGN patients with immunosuppression.

Methods. Outcome measures in five patients with IMPGN who were treated with oral prednisolone and mycophenolate mofetil (MMF) (treatment group) were compared with six patients with IMPGN who did not receive immunosuppression (control group).

Results. There was no significant difference between either group in baseline clinical characteristics or systolic and diastolic blood pressure during observation. In the treatment group, there was a significant reduction in proteinuria from a baseline of 5.09 to 1.97 g/24 h ($P=0.003$) at 6 months, 1.96 g/24 h ($P=0.003$) at 12 months and 2.59 g/24 h ($P=0.015$) at 18 months. There was no significant change in proteinuria over 18 months in the control group. Serum creatinine concentration and creatinine clearance did not change significantly over 18 months in the treatment group. In the control group, there were significant changes in serum creatinine and creatinine clearance over 18 months [baseline 103 to 159 µmol/l ($P=0.004$) and baseline 108 to 67 ml/min ($P>0.001$), respectively] when compared to baseline, although the differences were not significant when the two groups were compared directly.

Conclusions. This preliminary study suggests that in the short term, the combination of MMF and prednisolone can significantly reduce proteinuria and may preserve renal function in patients with IMPGN.

Keywords: membranoproliferative glomerulonephritis; mycophenolate mofetil; proteinuria

Introduction

Idiopathic membranoproliferative glomerulonephritis (IMPGN) is an uncommon renal disease which accounts for only 6.4–7.3% of all primary glomerulopathies [1,2] and 0.4% of patients starting renal replacement therapy (USRDS data, personal communication). The renal outcome in patients with IMPGN is poor, with a 10 year renal survival of 32–40% [3–5] and only 5–7.6% of patients achieving remission [4,5]. Treatment strategies have included both immunosuppression and antiplatelet regimes and although treatment of proteinuric children with high dose alternate day steroids has been shown to improve renal survival [6], reviews of the immunosuppressive trials in adults have not revealed any significant benefit [7]. Trials using anti-platelet therapy alone in proteinuric adults have resulted in differing outcomes, with one study suggesting a reduction in proteinuria but little alteration in renal function [8] and another showing a reduction in the progression of renal disease but no change in proteinuria [9].

Over the last decade, a number of newer, non-nephrotoxic and more predictable immunosuppressive agents have become available prompting our unit to investigate whether mycophenolate mofetil (MMF) in combination with prednisolone could improve renal outcomes in IMPGN.

Subjects and methods

We performed a retrospective analysis of five patients with IMPGN who were treated with oral prednisolone and MMF (treatment group) and compared their outcome measures to six patients with IMPGN who did not receive immunosuppressive therapy for their glomerular disease (control group).
Data were collected from medical records, electronic patient databases and electronic pathology resources. The data was recorded from the time of initiation of treatment, for the treatment group, or at diagnosis in the control group (baseline data). Subsequent data was recorded from follow-up visits approximately 6, 12 and 18 months after the initial time point.

Patients with a known secondary cause for MPGN were excluded and all patients were hepatitis B, C and HIV negative and had negative serology for a panel of autoantibodies; including double-stranded DNA, ANA and extractable nuclear antigens. All patients were over the age of 17 at baseline.

Four patients had received previous treatment for their glomerular disease and were entered into the study at the time of repeat renal biopsy. In the control group, a single patient had received prednisolone and azathioprine followed by prednisolone and cyclophosphamide, with a partial remission of proteinuria on each occasion. In the treatment group, two patients had been treated unsuccessfully with prednisolone only. None of these three patients were taking immunosuppression at baseline. A further patient in the treatment group had achieved a full remission of proteinuria with azathioprine and prednisolone but relapsed during reduction of immunosuppression. This patient restarted her steroids and increased the dose of azathioprine but failed to respond and was converted to MMF.

Immunosuppressive therapy in the treatment group was initiated with 60 mg of oral prednisolone, tapering to 20 mg within 2 months and withdrawn by 1 year. MMF was started at 500 mg/day and increased gradually, depending on patient tolerance, either to achieve remission of proteinuria or to a maximum of 2 g daily. If patients achieved remission of proteinuria and had stopped prednisolone, the dose of MMF was slowly reduced. The average maintenance dose of MMF was 1.1 g/day. All patients in the treatment group received omeprazole 20 mg daily, co-trimoxazole 480 mg daily and nystatin suspension 1 ml four times daily up to at least 6 months, as prophylaxis for gastric irritation and infection.

Statistical analysis was performed by repeated measures ANOVA for inter- and intra-group differences. The change in mean values between baseline and 18 months was analysed by r-test.

### Results

The baseline demographics and clinical characteristics of both groups are recorded in Table 1. All patients in the treatment arm and four out of six patients in the control arm received angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blocking agents (ARB) from the baseline time point. At the 12 month observation point, all patients in the control and treatment groups were taking either ACE-I or ARB. There was no significant change in the systolic and diastolic blood pressures in either group.

#### Serum albumin concentration and proteinuria (Figure 1)

In the treatment group, there was a significant reduction in proteinuria from a baseline of 5.09 to 1.97 g/24 h (P = 0.003) at 6 months, 1.96 g/24 h (P = 0.003) at 12 months and 2.59 g/24 h (P = 0.015) at 18 months. There was no change in proteinuria over 18 months in the control group; baseline 5.98 g/24 h, 6 months 4.77 g/24 h (P = 0.57), 12 months 6.61 g/24 h (P = 0.625) and 18 months 6.34 g/24 h (P = 0.13). When the control and treatment groups were compared by repeated measures ANOVA, there was a significant difference in proteinuria between the two groups (P = 0.03). The reduction in proteinuria in the treatment group was associated with a non-significant increase in serum albumin concentration from 29 g/l at baseline to 36.6 g/l at 6 months, 38.2 g/l at 12 months and 37 g/l after 18 months. There was a small but insignificant change in serum albumin concentration in the control

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Figures expressed as mean with SD in parenthesis.

**Fig. 1.** Change in proteinuria over time in control and MMF treated patients. Graphs are expressed as average ±SE. Overall difference between treatment and control by repeated measures ANOVA, P = 0.03.
group, from 30.8 g/l at baseline to 33.7 g/l at 6 months, 34.5 g/l at 12 months and 33.5 g/l after 18 months.

**Creatinine**

The serum creatinine concentration did not change significantly over 18 months in the treatment group; baseline 101.4 μmol/l, 6 months 86.4 μmol/l \((P = 0.4)\), 12 months 92.8 μmol/l \((P = 0.65)\) and 18 months 103 μmol/l \((P = 0.9)\). In the control group, the creatinine was stable during the first 12 months but rose significantly from baseline at 18 months; baseline 103.2 μmol/l, 6 months 132.3 μmol/l \((P = 0.17)\), 12 months 133.7 μmol/l \((P = 0.08)\) and 18 months 155.8 μmol/l \((P = 0.004)\). There was no significant difference between the control and treatment groups when the data were compared by repeated measures ANOVA \((P = 0.19)\).

**Measured creatinine clearance (Figure 2)**

Creatinine clearance did not change significantly in the treatment group; baseline 105.3 ml/min, 6 months 112.4 ml/min \((P = 0.51)\), 12 months 106.4 ml/min \((P = 0.92)\) and 18 months 99.04 ml/min \((P = 0.6)\). In the control group, the creatinine clearance was significantly reduced from baseline at 6, 12 and 18 months; baseline 108.4 ml/min, 6 months 80.3 ml/min \((P = 0.02)\), 12 months 81.31 ml/min \((P = 0.02)\) and 18 months 66.83 ml/min \((P > 0.001)\). When the treatment and control groups were compared by repeated measures ANOVA, the difference did not reach statistical significance \((P = 0.06)\).

**Adverse events**

There was one serious pulmonary infection in the treatment group, which required temporary withdrawal of MMF and was associated with an increase in proteinuria. A further patient in the treatment group had the dose of MMF reduced due to leukopenia. There were no serious complications in the control group.

**Discussion**

IMPGN is an uncommon renal disease with poor long-term kidney survival, for which there is little evidence for a specific treatment to improve outcome in adult patients. The aetiology of IMPGN is unclear but the finding of immune complexes with an associated mesangial inflammatory cell infiltrate would suggest that the disease should be amenable to immune modulation. The use of steroids in children has been reported to improve renal outcomes [6] but data in adults is less compelling. The addition of an alkylating agent to steroids in a non-controlled study of adults reduced proteinuria and may have stabilized renal function but required large doses of steroids \(15.7 \text{ g}\) and cyclophosphamide \(35.0 \text{ g}\) over an average period of \(9.5 \text{ months}\) [10]. There were few reported immediate side effects in the trial but one patient developed a cerebrovascular accident due to hypertensive crisis and 40% of the patients developed azoospermia or ovarian failure. A further controlled trial of cyclophosphamide, coumadin and dipyridamole for 18 months in adult patients did not show any significant benefit of treatment in the progression of renal disease or reduction of proteinuria [11]. In addition, 22% of patients could not tolerate the full course of therapy due to side effects. The results of these studies suggest that immunosuppressive treatment of IMPGN with steroids and alkylating agents is probably not beneficial and the side effects outweigh any small benefit in improving outcome.

MMF is a newer and more specific immunosuppressive agent than treatments previously used for glomerular disease. The active metabolite, mycophenolic acid, is a selective inhibitor of purine metabolism and leads to a reduction of T- and B-lymphocyte proliferation, primary and secondary antibody response and cellular adhesion molecule expression [12]. In addition, MMF also has antiproliferative effects on endothelial [12] and mesangial cells and is non-nephrotoxic, which makes it an ideal agent for treating glomerular disease. In patients with a number of primary glomerular diseases, MMF as monotherapy or with steroids has been shown to reduce proteinuria and maintain serum creatinine concentrations [13]. MMF and steroids have also been used to treat lupus nephritis, another immune complex mediated disease, with a similar efficacy and slightly better side effect profile than a steroid and cyclophosphamide/azathioprine combination [14]. Therefore, the use of MMF in patients with IMPGN might be expected to reduce proteinuria and improve renal survival, without the side effects associated with other immunosuppressive agents.

Proteinuria is the best predictor of renal outcome in non-diabetic kidney disease [15] and a reduction

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**Fig. 2.** Change in creatinine clearance over time in control and MMF treated patients. Graphs are expressed as average ±SE. Overall difference between treatment and control by repeated measures ANOVA, \(P = 0.06\).
of proteinuria in response to treatment predicts a better long-term renal survival [15]. Our study shows a significant reduction in proteinuria after 6 months of treatment with MMF and prednisolone, which was maintained for the period of observation. This finding compares well with other immunosuppressive studies in adults, which either did not show any reduction in proteinuria with treatment [11] or had a reduction in proteinuria at the expense of intense immunosuppressive regimes and their associated side effects [10]. The serum creatinine concentration and creatinine clearance remained unchanged in the treatment group, compared to a significant reduction in creatinine clearance and increase in serum creatinine concentration within the control group, suggesting that MMF and steroid treatment may reduce the decline in renal function in proteinuric IMPGN.

Only one patient received an anti-platelet agent. The low dose of aspirin (75 mg daily) used in the treatment group patient without other anti-platelet agents or anticoagulants is unlikely to have affected outcome. ACE-I have been shown to reduce proteinuria and effect the outcome of proteinuric renal disease. All patients in the treatment group and four out of six patients in the control group were on ACE-I at baseline but at the 12 month analysis point, all patients were taking ACE-I. Differences in ACE-I treatment are unlikely to have caused the disparity in proteinuria between groups and any patients starting on ACE-I in the control group would have benefitted by a reduction in proteinuria. In addition to ACE-I, improved blood pressure control can reduce the progression of renal disease and proteinuria [15]. There were no significant differences in blood pressure, number or type of antihypertensive agents used between groups and these factors are unlikely to have affected the outcome.

IMPGN is uncommon and this is reflected by the low number of patients in this study. Although the treatment and control groups in our study were similarly matched at the start of the study (Table 1), there were some differences between the groups. The patients in the control group had a wider range of proteinuria, with some patients only having just over 1 g/24 h compared with the predominantly nephrotic group in the treatment arm. In addition, the wider range of some other clinically predictive parameters within the control group may have created a more heterogeneous outcome, therefore reducing the significance of changes in clinical endpoints between the groups. Lead time bias is a further confounding factor in any study where the rarity of the disease necessitates the inclusion of patients being observed some time after the initial diagnosis. The control and treatment groups did differ, although not significantly, in the time from initial diagnosis to inclusion into the study; 78.6 (±82.9) and 11.7 (±13.9) months, respectively. It is therefore possible that the control group of patients were further into the natural progression of their glomerular disease, accounting for their worse outcome. However, this group of patients were included after a repeat renal biopsy, at which time there were no differences in the major histological or clinical prognostic indicators between the groups. Lastly, the patients were not randomized or followed prospectively and these factors will have weakened the power of the analysis further.

This study was not intended to be a definitive answer to the treatment of IMPGN and large, randomized prospective trials are needed to answer whether MMF and steroid treatment definitely improves outcomes in IMPGN. This study does, however, give an insight into a further treatment option for this rare glomerular disease and suggests that in the short term, the combination of MMF and prednisolone can significantly reduce proteinuria and may preserve renal function in patients with IMPGN.

Conflict of interest statement. Dr Paul Sweny and Dr Aine Burns wish to declare they have previously received sponsorship for attending international meetings from Roche pharmaceuticals and have provided advice and educational input to Roche pharmaceuticals. Dr Gareth Jones and Dr Edward Kingdon have previously received sponsorship for attending international meetings from Roche pharmaceuticals. The remaining authors declare that they have no conflict of interest in the publication of the submitted material.

References


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