

# Outcome of Therapy with Mycophenolate Mofetil in Membranoproliferative Glomerulonephritis in pediatric age group

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## ABSTRACT

**Background:** Membranoproliferative Glomerulonephritis (MPGN) is an uncommon glomerulopathy in pediatric age group which progresses gradually to chronic kidney disease (CKD) despite long-term treatment with corticosteroids.

**Aim:** To determine the efficacy of Mycophenolate mofetil (MMF) in patients of biopsy-proven MPGN regarding (1) maintenance of remission and (2) delay in progression to CKD.

**Methods:** A prospective, interventional case-control study was carried out on forty children with idiopathic MPGN who received steroids with and without MMF. The follow-up was done for  $\geq 3$  years for every child during which the drugs were tapered in case of complete remission and discontinued if failure of response occurred after 3 months of therapy.

**Results:** The serum creatinine was normal in Group A (steroids alone) and deranged at the time of presentation in Group B (steroids+MMF) with a mean value of  $0.91 \pm 0.42$  and  $1.07 \pm 0.49$  mg/dl respectively. Among group A patients 55% achieved complete and sustained remission for  $\geq 3$  years as compared to 60% children in group B, while partial remission was seen in 25% and 30% respectively. CKD was found to develop in 40% children in group A and 25% patients in group B.

**Conclusion:** The response to MMF in combination with steroids was found to be better than steroids alone in terms of achieving and maintaining remission with less progression to CKD in biopsy-proven patients of MPGN. However, the study was underpowered to show statistical significance.

**Keywords:** Corticosteroids; Membranoproliferative Glomerulonephritis; Mycophenolate mofetil

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## INTRODUCTION

Idiopathic MPGN is one of the least common types of glomerulopathies accounting for only 4% of secondary nephrotic syndrome in children and adolescents<sup>1</sup>. It was first described by Habib et al<sup>2</sup> carrying an unfavorable prognosis in children and typically resulting in CKD during late childhood or early adolescence<sup>3</sup>. Morphologically, it is classified into three types – immune complex-mediated (IC) MPGN, complement mediated (C) MPGN, and non-IC non-C mediated MPGN<sup>4</sup>, characterized by presence of sub-endothelial, intra-membranous and sub-epithelial deposits on immunofluorescent and electron microscopy respectively. The various types of MPGN cannot be distinguished based on clinical manifestations as patients present with nephritic / nephrotic syndrome, recurrent episodes of gross hematuria or asymptomatic proteinuria/micro-hematuria detected on routine urinalysis. It often progresses gradually to end-stage renal disease with a tendency of recurrence after renal transplantation. Long-term therapy with steroids has been found to be effective in children although improvement in renal

outcome relies on evaluation of more selective agents like MMF. The efficacy of this drug depends on the combination of its immunosuppressive properties and other mechanisms of action<sup>5</sup>. Mycophenolic acid (MPA), the pharmacologically active metabolite, inhibits T and B lymphocytes proliferation, B cell antibody production as well as glycosylation and expression of adhesion molecules besides inhibiting mesangial cell proliferation and preventing fibrosis<sup>6</sup>. One or another, these actions are likely to be operative in the amelioration of inflammation / structural remodeling characteristic of glomerulopathies.

Over the last decade, a number of newer non-nephrotoxic and more predictable immunosuppressive agents have become available prompting us to explore the response of our patients to MMF with and without steroids regarding maintenance of prolonged remission and delay in progression to CKD in children with biopsy-proven idiopathic MPGN.

## METHODS

Forty children with newly diagnosed idiopathic MPGN (biopsy-proven) were selected at the Nephrology clinic of The Children's Hospital & The Institute of Child Health Lahore Pakistan between January 2005

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- December 2013. They were divided into 2 groups- A=those with normal serum creatinine received steroids alone (40mg/m<sup>2</sup> single dose on alternate days) and B=those with deranged serum creatinine were administered MMF (1200mg/m<sup>2</sup>/day in 2 divided doses) in addition to steroids. The male: female ratio was 1:1.7 and 1.4:1 and the mean age of presentation was 10.11±1.98 and 10.53±2.07 years in Groups A and B respectively. Angiotensin converting enzyme inhibitors (ACEIs) were prescribed to all the individuals for anti-proteinuric effect as well as for control of hypertension in some. The various histological types of MPGN could not be differentiated due to lack of immunofluorescence and electron microscopic facilities. Those diagnosed as secondary MPGN and with estimated GFR <60 ml/min/1.73m<sup>2</sup> were excluded from the study. The ethical committee of the hospital approved the study protocol and informed consent was obtained from the parents following provision of verbal information.

The treatment protocol was uniform for all patients – they were maintained on steroids for 5 years in case of response (complete/partial) which were tapered by 5 mg decrements every 6 months. In patients with failure of response, steroids were tapered after 6 months of initiation and finally discontinued with prescription of conservative management in the form of ACEIs and / or diuretics. Administration of MMF to Group B continued for 2 years along with steroids in case of response with 50% dose reduction done after 12 months of commencement of therapy. MMF was stopped in individuals showing failure of response after 3 months of therapy or those with progressive deterioration of renal functions. The drug was decreased by 50% / withheld temporarily in presence of serious infection, leucopenia, deranged liver function or severe diarrhea although dose adjustment was not based on MMF trough levels.

Response to treatment was defined as (1) complete remission – clinical disappearance of edema and hematuria ( if present ) with control of hypertension; resolution of proteinuria ( nil/traces on dipstick or spot urine protein : creatinine = < 0.2 ) and micro-hematuria; normal serum creatinine, albumin and complement levels

(2) partial remission – clinical presence / absence of edema with / without blood pressure control; persistent proteinuria ( ++ or more on dipstick or spot urine protein: creatinine =0.2–3.0 ) and / or micro-hematuria; low / normal serum albumin with worsened / normal serum creatinine levels; and presence of hypocomplementemia

(3) development of CKD – progressive deterioration of serum creatinine concentration and / or eGFR = <

60 ml/min/1.73m<sup>2</sup> estimated by Schwartz formula or DTPA (diethylenetriaminepenta acetate ) renal scan.

The follow-up of each subject was done ≥3 years for both the groups, initially fortnightly and then monthly for 6 months followed by 3-monthly visit thereafter. Each patient was assessed for clinical improvement at every appointment, with measurement of blood pressure and adjustment of dose of ACEIs in hypertensive subjects in an attempt to achieve BP <90<sup>th</sup> percentile for age, sex and height of the individual. Laboratory parameters regularly monitored on out-patient basis included (a) urinalysis for estimation of proteinuria and micro-hematuria (b) complete blood count for evidence of infection (c) biochemical panel for serum albumin level with renal and liver functions and (d) serology for serum complement levels. All the subjects underwent ophthalmological examination on an annual basis for detection of cataract occurring as a complication of long-term steroid therapy. Counseling sessions were arranged for the parents / guardians of the patients regarding the details and guarded prognosis of the disease.

The statistical analysis was performed using SPSS version 17.0. The Student t test and the Fisher exact test were utilized for estimation of p value.

## RESULTS

The 40 selected patients with idiopathic MPGN were divided into 2 groups with their baseline characteristics summarized in Table I. The time elapsed from the onset of illness and initiation of treatment in all the patients was ≥6 months. On analysis of biochemical parameters and estimation of proteinuria during the trial period, nephrotic range proteinuria (spot urine protein: creatinine >3.0/24 hours urine protein excretion >1g/m<sup>2</sup>) was documented in 9(45%) Group A patients and 10(50%) Group B subjects. Hypoalbuminemia and hypercholesterolemia were documented in all the children and hypocomplementemia was present in 16(80%) Group A and 18(90%) Group B patients. Among Group A patients 11(55%) achieved complete / sustained remission for ≥3 years as compared to 12(60%) children in Group B; while partial remission was seen in 5(25%) and 6(30%) individuals respectively (Table 1).

The mean serum creatinine level at the time of presentation was 0.91±0.42mg/dl in Group A in comparison to Group B in which it was already deranged (mean=1.07±0.49mg/dl) before the administration of MMF. CKD was seen to develop in 8(40%) children of Group A and 5(25%) patients in group B.

However, the differences observed by the Fisher exact test did not attain statistical significance regarding both the achievement of complete remission and risk of developing CKD, we observed a trend towards a lower chance of progression to CKD in Group B which had a higher potential of resulting in renal failure in contrast to Group A with comparatively normal mean serum creatinine level at the beginning of the study. But the differences between the 2 groups did not reach statistical significance (p value=0.232) (Table 2).

We did not observe undesirable effects requiring discontinuation of MMF in any patient as the adverse effects of MMF therapy were generally mild, and most patients tolerated the drug well except 2 children who experienced a bout of severe pulmonary infection following leucopenia while 1 had protracted diarrhea that remitted on 50% dose reduction of the drug. The dose modification was not necessary in subjects with complaints of a slight increase in frequency of stools. The pharmacokinetic profile of MPA could not be determined due to unavailability of this facility.

Table 1: Baseline patient characteristics

Patient characteristics	Group A	Group B	P value
Number of patients	20	20	
Age (years)	10.11±1.98	10.53±2.07	0.365
Male:Female ratio	1:1.7	1.4:1	0.073
Serum Creatinine (mg/dl) at onset	0.91±0.42	1.07±0.49	0.126
Low serum C3 level	16 (80%)	18 (90%)	
Treatment	Steroids	Steroids+MMF	

Table 2: Development of Chronic Kidney Disease.

Treatment		Total	CKD	Fisher exact test
Steroids	MMF+ Steroids			
8(40%)	5(25%)	13	Yes	
12(60%)	15(75%)	27	No	0.232

## DISCUSSION

This study focuses on our experience with MMF in children with MPGN which is an uncommon renal disease for which there is paucity of data in the literature regarding optimal treatment to improve renal outcome in pediatric age group. Histological detection of immune complexes within the glomeruli would suggest that the disease should be amenable to immune modulation. MMF is a newer and more specific immunosuppressive agent which has been

used in other glomerulopathies in children commonly lupus nephritis. Hence, the use of MMF might also be expected to reduce proteinuria and improve renal outcome in pediatric patients with MPGN.

A prospective multicenter double-blind trial by The International Study of Kidney Disease in Children (ISKDC) randomized 80 children with idiopathic MPGN to steroids and placebo with a mean follow-up of 41 months<sup>7</sup>. Treatment failure was found to be lower in the steroid-treated group in contrast to the placebo group (40% versus 55%) although these results were not statistically significant. The renal survival rate at 130 months was 61% and 12% among the treatment and non-treatment groups respectively, with the conclusion made by the authors that steroids improved renal survival in pediatric MPGN.

The favorable treatment for MPGN was considered to be only steroids with some investigators introducing use of immunosuppressive agents like azathioprine, cyclophosphamide, cyclosporin and tacrolimus. Janette et al assessed the prognosis of 53 children with MPGN who were administered steroids, azathioprine and cyclophosphamide<sup>8</sup>. The analysis showed that there were no significant differences in outcome measured by eGFR, hypertension and proteinuria between the treatment and non-treatment groups.

On the other hand, Haddad et al<sup>9</sup> described the advantage of induction of rapid and complete remission by tacrolimus (calcineurin inhibitor) in 2 children with idiopathic MPGN in whom the drug was continued for 20 months. A similar response was seen by Cansick et al in terms of complete remission with the same dose<sup>10</sup> as compared to partial remission achieved in 1 child reported by Xia et al<sup>11</sup>. Cyclosporin, also a calcineurin inhibitor has also been experienced by some authors to be efficacious in the treatment of MPGN<sup>12,13</sup>, but is associated with intolerable side effects.

Jones G et al reported that 5 patients with idiopathic MPGN had significant reduction in proteinuria over an 18-month period when they were treated with oral prednisolone and mycophenolate mofetil relative to a control group of 6 patients who did not receive immunosuppression. No significant change occurred in serum creatinine or creatinine clearance in the treatment group; however, in the control group, serum creatinine and creatinine clearance deteriorated significantly<sup>14</sup>. De S reported a case of a 12 years old boy with MPGN I who remained in remission for twelve months following the introduction of MMF into his therapeutic regimen, suggesting the potential benefit for use of MMF in pediatric MPGN<sup>15</sup>. A similar case was encountered by Shuichi et al who also showed a prompt response

after 2 months of initiation of therapy with steroids along with MMF<sup>16</sup>.

The above-mentioned MMF trials support the results of our study which indicate that treated patients achieved benefits with MMF therapy in terms of a decrease in exposure to steroids, achieving and maintaining prolonged, complete and sustained remission along with a decline in the rate of progression to CKD as compared to those receiving steroids alone. An added advantage of MMF was seen in halting the progression to CKD in 75% Group B patients in whom serum creatinine level was already deranged at the time of presentation. In general, MMF was very well tolerated by all our subjects except 1 patient experiencing severe diarrhea and 2 individuals developing pulmonary infection for which the drug dose had to be reduced by 50% temporarily.

Given the lack of nephrotoxicity and adverse hemodynamic and metabolic effects, MMF can be a suitable alternative to alkylating agents and calcineurin inhibitors which have been used by investigators for treatment of MPGN in the past.

## CONCLUSION

MPGN is a difficult renal disease associated with significant morbidity and mortality in pediatric age group for which MMF can be an insight into a further treatment option in combination with steroids. Although the response to MMF in conjunction with steroids was found to be better in our study than steroids alone (in terms of achieving and maintaining prolonged, complete and sustained remission with less progression to CKD and a benign side-effect profile), the study was underpowered to show statistical significance. However, larger randomized multicenter prospective trials with therapeutic drug monitoring are warranted with a longer follow-up period to answer whether MMF and steroids definitely play a role in improvement of short- and long-term outcome in children with idiopathic MPGN.

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