# Mycophenolate Sodium for Children with Frequently Relapsing or Steroid Dependent Nephrotic Syndrome

In this retrospective study, patients with idiopathic frequently-relapsing nephrotic syndrome (FRNS) (*n*=27) and steroid dependent nephrotic syndrome (SDNS) (*n*=13) who received enteric coated mycophenolate sodium (ECMS) for at least 6 months, were included for analysis. Primary outcome was response to ECMS, which was defined as complete if there were no relapses, partial response if there was 1 relapse and no response if there were 2 or more relapses within 6 months of initiation. The mean (SD) dose of ECMS was 985.24 (190.82) mg/m$^2$/day. Thirty patients(75%) had complete response, eight (20%) had partial and two (5%) patients did not respond at 6 months. ECMS seems to be a safe and effective as steroid sparing agent in children with FRNS/SDNS.

**Key Words:** *Minimal change disease, Proteinuria, Refractory, Treatment.*

Enteric coated Mycophenolate sodium (ECMS) is an advanced formulation that delivers active moiety mycophenolic acid (MPA), and is associated with less gastrointestinal side effects [1]. There is paucity of reports on efficacy and side effects of mycophenolate sodium in nephrotic syndrome in children.

In this retrospective study, we included frequently-relapsing (FRNS) and steroid-department nephrotic syndrome (SDNS), patients aged 1-16 year who received ECMS for at least 6 months with or without other immunosuppressive agent in past were included. Children were diagnosed and treated according to consensus guidelines of Indian Society of Pediatric Nephrology (ISPN) [2]. ECMS was started at a dose of 600-1200 mg/m$^2$/day of MPA equivalent in two divided doses after remission was attained with 2 mg/kg of prednisolone if there was failure of other immunosuppressive agent or as first line agent. Relapses were treated with short courses of prednisolone as per standard relapse protocol [2], and ECMS dose was optimized to a maximum of 1200 mg/m$^2$/day of MPA equivalent (max 1440 mg/day of ECMS or 2000 mg /day of MPA equivalent). Relapse rate was defined as number of relapses in 6 month period. Primary outcome was response to ECMS, which was defined as 'complete' if there were no relapses, 'partial'if there was 1 relapse and 'no'if there were 2 or more relapses within 6 months of initiation. Steroid-free period was the period in which patient was off-prednisolone and suffered no relapse. The study was conducted according to the institutional guidelines and informed consent was obtained from the patients.

Forty children with idiopathic FRNS/SDNS fulfilled the inclusion criteria, of which 27 were frequent relapsers while 13 were steroid dependent. Mean (SD) age at initiation of ECMS was 7.52 (3.38) years. ECMS was initiated at mean (SD) dose of 795.63 (156.85) mg/m$^2$/day of MPA equivalent. Dose was increased in 19 patients when they suffered relapse on initial dose while remaining 21 patients received mean (SD) dose of 869.8(164.3) mg/m$^2$/day of MPA equivalent. Mean (SD) maximum dose was 985.2 (190.8) mg/m$^2$/day of MPA equivalent. Nineteen patients had received other immunosuppressive agents before ECMS (levamisole 10, cyclophosphamide 4, both levamisole and cyclophosphamide 3, CNI + cyclophosphamide 1) while in 21 patients it was used as first line alternate immunosuppressive agent. Median (IQR) duration of treatment with ECMS was 1.62 (1.00, 2.08) years. Thirty (75%) patients had complete response, eight (20%) had partial and two (5%) patients did not respond at 6 months (***Table* I**). Seventeen patients received ECMS for more than 2 years, and did not have any side effects. In twenty patients, steroids were stopped for median (IQR) period of 8.75 months (1.5, 24 months) and there was no relapse. There were no major side effects except severe sepsis in one patient in whom ECMS was discontinued.

We found that the mean relapse rate decreased to more than 70% after 6 months of ECMS therapy. Relapse rate improved from one episode every three months before ECMS to one episode every 14.6 months after ECMS therapy. There was 46% reduction in cumulative dose of steroids 6 months after initiation of ECMS, and in 50% of them we were able to discontinue steroids. We observed that patients who were initiated ECMS at dose of ≥800 mg/m$_2$/day in comparison to those in whom initial dose was lower had decreased number of relapses and time to first relapse was delayed but results were not statistically significant.

The present study shows similar results as reported earlier [4,7] but we used enteric-coated mycophenolate sodium (ECMS) formulation. Bagga, *et al.* [4]

**TABLE I** RESPONSE TO MYCOPHENOLATE SODIUM IN PRESENT SERIES

| | |
|---|---|
| Time to first relapse(mo); *n*=29* | 7 (5,11) |
| Time to 2nd relapse (mo) | 11.5 (3, 24) |
| Steroid-free period (months); *n*=20 | 8.75 (1.5, 24) |
| Duration of ECMS administration (*y*) | 1.62 (1.00, 2.08) |
| Relapse rate before MMF(*n*=40) | 2 (2,2.09) |
| Relapse rate after MMF$(*n*=40) | 0.41 (0, 0.62) |
| Cumulative dose of steroids 6 months before initiation of MMF (mg/kg) (*n*=35) | 100.4 (49.7) |
| Cumulative dose of steroids 6 months after initiation of MMF (mg/kg)$(*n*=35) | 54.2 ( 25.28) |

**11 patients had no relapse, values are expressed in median (IQR) or $mean (SD) P <0.001.*

prospectively studied 19 SDNS patients who received MMF for 12 months duration and reported 70% reduction in 6 and 12 monthly relapse rates. Enteric coated mycophenolate sodium (ECMS) releases mycophenolic acid in duodenum where pH is about 5,and thus has lesser gastrointestinal side effects. A multicenter phase III randomized double blind parallel-group trial with 423 *de novo* kidney transplant recipients evaluated therapeutic equivalence of MMF and ECMS and found similar treatment failure rates between therapies (25.8% *vs*. 26.2% for ECMS and MMF, respectively). Fewer patients on ECMS (15%) required dose reductions when compared to individuals on MMF (19.5%), but no statistically significant differences were observed in the incidence of adverse gastrointestinal events [8]. Mycophenolate has been found safe even when given for 12 months [4,5]; 40% of our patients received ECMS for more than 2 years without experiencing any major side effects.

Our study had limitations of being retrospective, and we did not include therapeutic drug monitoring. Obtaining a pharmacokinetic profile, drawing MPA-AUC and comparing them among patients with initial dose of ECMS<800 mg/m$^2$/day with those who received higher and correlating it with occurrence of relapse would have been imperative. In conclusion, findings of this study suggest that enteric coated mycophenolate sodium is effective as steroid sparing agent. Extending the therapy beyond 12 months appear to be safe and free of renal, hemodynamic and metabolic toxicity.

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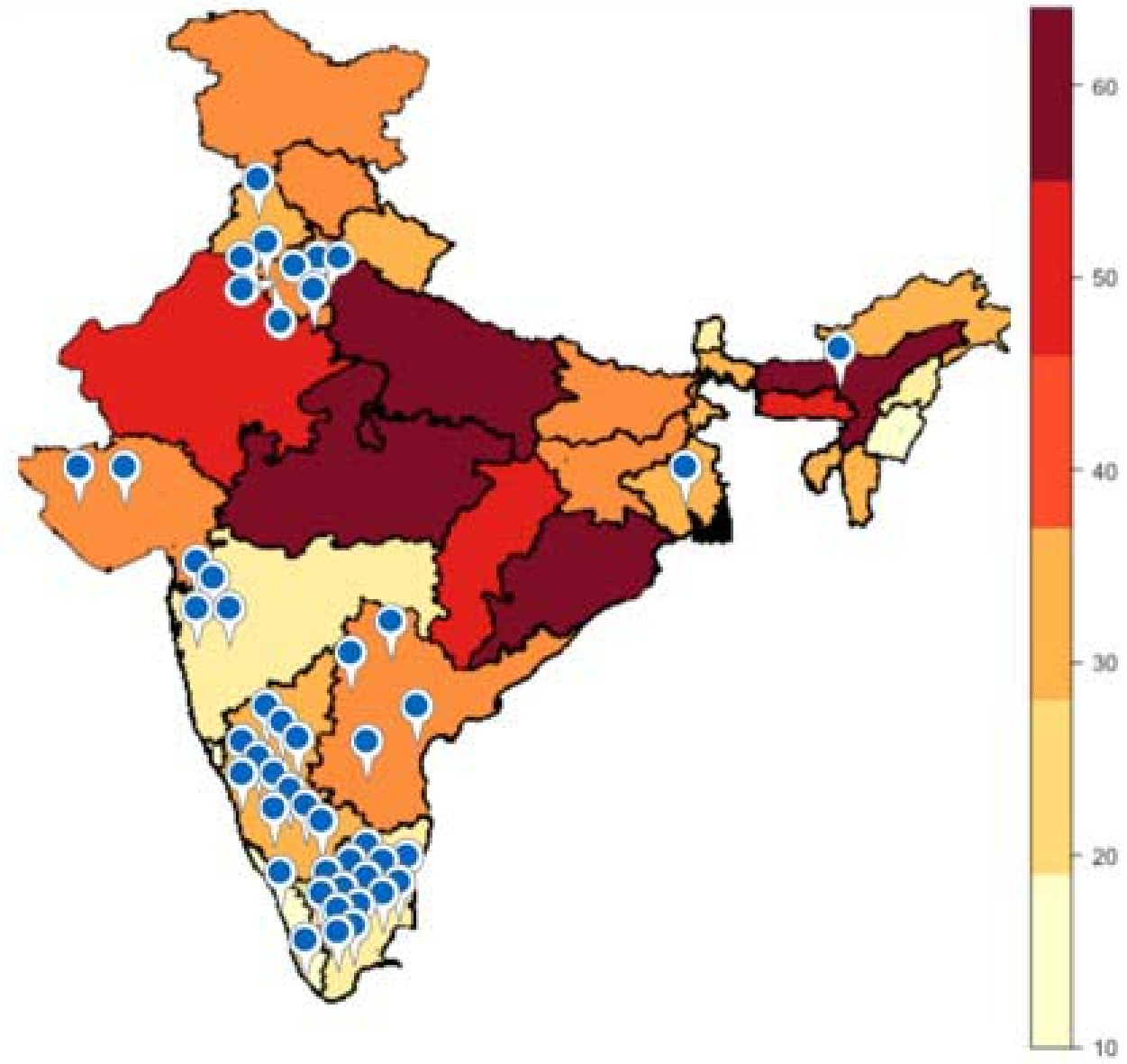
**REFERENCES**

1. Ransom JT. Mechanism of action of mycophenolate mofetil. Therap Drug Monit. 1995;17:68-84.
2. Zolezzi M. Mycophenolate sodium versus mycophenolate mofetil: A review of their comparative features. Saudi J Kidney Dis Transplant. 2005;16:140-5.
3. Indian Pediatrics Nephrology Group, Indian Academy of Pediatrics Management of steroid sensitive nephrotic syndrome: Revised guidelines. Indian Pediatr. 2008; 45:203-14.
4. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. Am J Kidney Dis. 2003; 42:1114-20.
5. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. Pediatr Nephrol. 2013;28:93-7.
6. Afzal K, Bagga A, Menon S, Hari P, Jordan SC. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2007; 22:2059-65.
7. Hogg RJ, Fitzgibbons L, Bruick J, Bunke M, Ault B, Baqi N, *et al*. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: A Report from the southwest pediatric nephrology study group. Clin J Am Soc Nephrol. 2006;1:1173-8.
8. Salvadori M, Holzer H, de Mattos A, Sollinger H, Arns W, Oppenheimer F, *et al*. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renaltransplant patients. Am J Transplant. 2004;4:231-6.




**WEB FIG. 1** *Distribution of the hospitals offering cooling therapy (blue circle), superimposed on a heat map of infant mortality rates.*