Review Article

Efficacy of Mycophenolate Mofetil in Nephrotic Syndrome in Children: A Systematic Review and Network Metaanalysis

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Received: 05-08-2021 / Revised: 17-09-2021 / Accepted: 16-10-2021

Abstract

This Systematic review and meta-analysis compare efficacy of Mycophenolate mofetil (MMF) to other second line drugs levamisole, cyclosporine and Tacrolimus in Nephrotic syndrome in children and adolescents. Major databases Pubmed, Embase, Scopus, Web of Science, Cochrane and clinical trial registry platforms CENTRAL, WHO ICTRP etc. along with recent pediatric and nephrology journals with cross references from articles were searched. Protocol was registered at international registry platform PROSPERO **as** CRD42021236056. PRISMA guideline and PICO format was followed, GRADE analysis was done. Available studies in full text in English language were included in analysis. Population was Nephrotic syndrome in children and adolescents, Intervention as MMF, comparator as other second line drugs. KIDGO definitions were followed. Over all 10 studies were included and 3 groups meta-analyzed. MMF versus Levamisole 2 studies 191 subjects, MMF versus Cyclosporine 4 studies 256 subjects, MMF versus Tacrolimus 3 studies 196 subjects. Primary outcomes were frequency of relapse, achievement of complete remission and post treatment steroid dose. Efficacy of MMF, Levamisole, Cyclosporine, Tacrolimus, all 4 drugs was found to be almost similar, and the differences were not statistically significant. The overall effect size diamond either did not cross the central line or the effect was not persistent for all outcomes. Therefore, other factors like easy availability, cost, side effects and long-term safety should guide clinician as well as patients for an informed choice. Sample data is limited and follow up time is also limited to a median length of 12 months; therefore, generalizability of findings is also limited, considering the fact that it is meant for a disease like nephrotic syndrome where categorizing definition itself takes 12 months. More robust studies across the globe are still needed for gathering further evidence to either support or refute the findings.

Keywords: Mycophenolate Mofetil, Nephrotic Syndrome, Children, Cyclosporine, Tacrolimus, Levamisole.

Introduction

Nephrotic syndrome (NS) is the most common kidney disease occurring in pediatric population in age group of 1-18 years. Incidence varies with region and ethnicity ranging from 1.15 to 16.9 per 100,000 children[1]. Roelans in 1484 initially described it, although edema and proteinuria were a recognized entity for more than 2000 years. Henry Christian coined the term Nephrotic syndrome 1929[2]. It had a high mortality of ~67% before introduction of corticosteroids and antibiotics. Mortality fell to ~35% with sulphonamides and penicillin's in ~ 1940. and further decreased to ~ 9% with introduction of steroids in 1950s[3]. Since then modifications and standardization have been emerging globally further reducing mortality and end stage disease[4]. 70 years of rapid scientific advancements worldwide have taken place but the picture of Nephrotic syndrome in children has not changed much since then. Theoretically speaking we still do not know what will be the future of a child when he lands up at with an initial attack.

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Even with standard therapy, the only expected outcome is that 80-90% of children who respond to 8-12 weeks of Prednisolone will relapse[5], whereas the desired outcome for a clinician as well as patient will be that no relapse occurs.

Label of NS paints a gloomy picture in a child's life at the outset. Impact on quality of life and health becomes a challenge due to its relapsing course, long term complications, frequent hospitalizations, monitoring system, drug side effects. Impact on body image, school days lost, emotional stress, economic burden are immense. Scarce data exists on health-related quality of life in nephrotic children, but when checked their scores have been found to be lower on quality scores[6]. The need of hour is to think and plan about modifying the initial treatment to modify the future course of disease and not to wait till relapses occur. Instead of sequential introduction of drugs like alkylating agents, calcinuerin inhibitors, repeat steroid courses. etc. focus should shift to identification of early predictors for relapse[7] and early introduction of second line drugs or combination therapy in initial attack itself. Current treatment outcome is definitely far from satisfactory from a clinician's as well as a patient's point of view in this age of rapid scientific advancement and statistical excellence.

As regards etiopathogenesis of NS, 95% are primary idiopathic type and rest 5% are secondary to glomerular involvement in a variety of conditions like Systemic lupus, HSP, amyloidosis etc[8]. Many gene mutations have been noted but the primary problem identified so far is confined to effacement of foot processes of podocytes in MCNS (minimal change) and more severe podocytopathies in others. Primary pathology is heavy proteinuria leading to manifestations of edema

hypoalbuminemia and hypercholestolemia. Evidence of immune dysfunction has been identified in form of diminished cellular immunity, low serum IgG levels, abnormalities of T lymphocytes etc. A role of B cells is also suggested due to beneficial effect of rituximab. Rapid precipitation of relapses following infections point towards involvement of innate immunity. Response to immunosuppression induced by steroids and beneficial role of immunomodulators in later stage of diseases point towards rethinking our approach for management of initial episode. A direct effect of immunomodulatory agents on podocytes in immune mediated glomerular diseases[9]. Amelioration of Podocyte injury may be the target of therapeutic intervention. Podocytes are terminally differentiated cells with very little or no proliferative ability, their loss results in permanent glomerular dysfunction. Input of immunological stress is achieved by systemic immunosuppression which is an indirect way achieved with steroids. It has been established that immunomodulator agents directly act on podocytes in an agent independent manner, therefore therapeutic efficacy of immunomodulatory agents is in part delivered by direct action on podocytes, this may be of clinical significance and the knowledge may be utilized not only in management of relapses but also in initial management of NS, because proteinuria is the signature of podocyte injury clinically.

Mycophenolate mofetil is a purine synthesis inhibitor, it modifies ATP depletion by inhibiting podocyte inosine 5'-monophosphate dehydrogenase and helps in restoration and maintenance of podocyte homeostasis leading to stabilization of actin cytoskeleton. It also avoids accumulation of unfolded and misfolded proteins that lead to endoplasmic reticulum stress with further podocyte injury. In the background of above knowledge, we systemically reviewed the existing evidence for efficacy of MMF in NS in children with a possibility of earlier introduction of MMF in course of disease and its possible use in the first episode itself.

Materials and methods

The study protocol was prepared and registered at PROSPERO, the International prospective register for systematic reviews platform vide registration number CRD42021236056. PRISMA 2020 guidelines were followed. Protocol was prepared taking guidance from library internet sites further strengthened by consulting Cochrane handbook. No formal Institutional review board /Institutional Ethics committee permission was taken as it was not necessary for systematic review and meta-analysis of published data, however institutional authorities were kept informed about the study. The Zotero software was used along with end note for collection and sorting of data and selection of studies. A data dictionary was prepared data was extracted into MS excel and MSword. Data analysis was done in Cochrane RevMan 5.4 by entering relevant data for noncochrane review. GRADE analysis was done by using GRADEpro software GDT. Risk of Bias assessment was judged using Cochrane risk of Bias tool.

Search Strategy

PICO search model (Population, Intervention, Comparator, Outcome) was designed for PubMed. It was modified for different databases as per availability of options in their advanced search features. Outcome was omitted from search as its inclusion gave zero search results. Comprehensive search results were obtained by using PI in Title abstract keyword search, which was then manually screened for selection of relevant studies for full text retrieval of published articles. Human filter was used wherever available. Keywords, controlled vocabulary, subject terms, entry terms, text words, MeSH terms and Emtree terms considering major headings, subheadings, supplementary concept and explode feature were used. All synonyms MeSH term or Emtree terms were included. Both simple and complex searches were done for identifying any missing data. Search was limited to English language databases as per protocol, focusing on latest articles. Initial Search was performed in month of march and search rerun was done in month of May 2021. Two authors performed search independently and matched their results later.

We searched major databases PubMed, Embase, Google scholar along with Scopus and Web of Science citation databases

Cochrane central registry of controlled trials (CENTRAL) & Clinical trial registry platforms, WHO ICTRP, Cochrane database were searched for systematic reviews and meta-analysis for their reference lists and Grey literature at OpenGrey. Indian studies were searched at Indian medical databases, CTRI and ICMR compendium of research papers, Shodhganga and Shodhgangotri. Hand searching in reference list of cited and citing articles, Journal search for nephrology/Urology related journals and pediatric journals with Cross ref was also performed. (Figure 1)

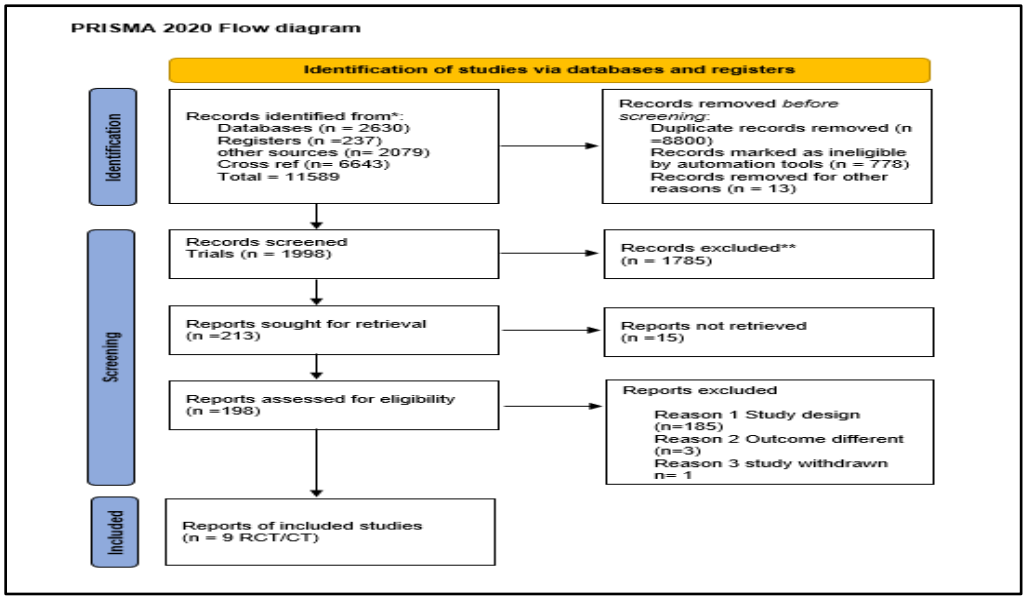


Fig. 1: Identification of studies via databases and registers

Our Inclusion criteria for population was children 0-18 years with nephrotic syndrome at initial onset. Age > 18 at initial onset were excluded. Inclusion criteria for intervention was use of Mycophenolate mofetil (MMF) therapy with or without prednisolone

or with any other drug /immunosuppressant at any stage of disease excluding ayurvedic, herbal or any other Chinese local drug. For comparator standard therapy or any other immunosuppressant drug alkylating agent /calcineurin inhibitor/rituximab/levamisole. with exclusion criteria as with or without prednisolone three or more immunosuppressant drug use. No setting restriction was applied because of the nature of disease itself where setting keeps changing from specialized indoor care to home care with near normal life. As for study design we included Randomized Controlled trials (RCT), clinical trial (CT) clinical study. exclusion criteria were Case reports, case series, cross sectional studies, Cohort studies, case control studies, reviews etc. Our research question was "How effective is Mycophenolate mofetil (MMF) in preventing relapse in children suffering from Nephrotic syndrome as compared to standard therapy of Prednisolone/ Prednisone alone with or without other immunosuppressive drugs/ immunomodulator drugs in use? and included nine studies[10-18].We did not come across any RCT with published results where MMF was used in initial attack while results of INTENT trial are eagerly awaited[19].Directly comparing study of rituximab versus MMF was terminated early for unexpectedly high relapse rates in one arm[20]. Other studies had too many drugs and did not meet our all inclusion criterias.

Main Outcomes: (Standard KDIGO Definitions)

1. Frequency of relapse after initial attack, (Relapse defined as urinary protein 3+ or more for 3 consecutive days) upto the last follow up period described in study.
2. Achievement of remission (complete or partial remission) as measured by urinary protein <+ for 3 consecutive days or decrease from baseline to be stratified by complete or partial remission if described separately in study.
3. Reduction in maintenance dose of steroid being given during remission (Remission defined as protein
negative /traces /4mg/m2/hr for 3 consecutive days) following introduction of intervention MMF) up to the last follow up period described in study

Additional Outcomes

1. Response time from intervention to achievement of complete or partial remission
2. Duration of remission
3. Dose of MMF being given

Measure of Effect

Relative risk for dichotomous data and mean difference for continuous data.

Data Extraction and Data Synthesis

After critical appraisal and discussion among authors, data was extracted and entered in a standard format, pooling of data was done together for study characteristics (Table 1) and for analysis purpose the studies were grouped as per comparator arm drug (Table 2) Size of effect and consistency of effect across studies along with strength of evidence were analyzed and results were combined for meta-analysis where at least two studies were available. Random effect model was used and P value of 0.05 was considered statistically significant at 95% confidence interval. Cochrane software RevMan version 5.4 was utilized for analysis. Heterogeneity was assessed by visualizing data in Forest plot. I^2 test statistic and Cochran Q test were applied.

Results

PubMed n= 687, Google Scholar n= 269, Embase n= 1713, Scopus n= 1637, Web of science (5 years) n= 195, Database total n= 2630

Clinical Registers CENTRAL n= 119, fda n= 70, WHO ICTRP n= 28, CTRI n= 20, Shodhganga & Gangotri n=0, Registers total n= 237

Scirus n=690, Journal search n= 98 + 186 + 171 + 453+ 478, Open Gray n= 3, Others total n= 2079, Cross ref n= 6643

We had two studies comparing MMF with Levamisole (LEV) four comparing MMF with Cyclosporine (CsA), three comparing MMF with Tacrolimus (TAC), 1 comparing MMF with CsA versus (vs) CsA with Prednisolone (Pred)

Study characteristics are described in Table 1, and as the methods and outcomes were similar enough, we synthesized the results and meta-analysis was done. Main Outcomes one and two are described in Table 2 for frequency of relapse and for achievement of complete sustained remission for study duration which was 12 months for all except one study where it was 6 months.

Table 1: Study characteristics of all included studies in systematic review

Study Author Year Location Reference	Singh 2020 India (10)	Sinha 2019 India (11)	Rahman 2018 Bangla desh (12)	Gellermann 2013 Germany (13) 1st year	Gellermann 2013 Germany (13) 2nd year	Shah 2016 Pakistan (14)	Dorresteijn Netherland 2008 (15)	Sinha India 2017 (16)	Wang China 2016 (17)	Nikibakhsh 2011 Iran (18)
Study type	RCT Parallel	RCT parallel	RCT	RCT Cross over	RCT Cross over	NRCT	RCT	RCT	RCT	RCT
Intervention / Comparator	MMF/ LEV	MMF / LEV	MMF/ CsA	MMF/ CsA	MMF/ CsA	MMF/ CsA	MMF/ TAC	MMF/ TAC	MMF/ TAC	MMF+CsA/ CsA +Pred
Population N	42	149	60	60	60	105	24	60	72	60
Arms n/n	21/21	76/73	30/30	30/30	30/30	43/38/21 /3	12/12	29/31	34/72	60 ?
Age group	2-14	6-18	<18	<18	<18	1-12	<18	1-18	1-10	<18
Male/Female	25/17	125/24	30/23	48/12	48/12	63/42	21/3	44/16	51/21	22/15
Steroid Response	FRNS SDNS	FRNS SDNS	FRNS SSNS	FRSS	FRSS	SRNS	FRNS	SRNS	SDNS	SRNS
Available Histopathology rest not done	Not done	Not done	15 MCD 12MesPGN 2 NonSp	60 MCD	60 MCD	20 FSGS 11 MCD 74 MesPGN	15 MCD 12 MesPGN 2 NonSp	34 MCD 26 FSGS	40 MCD 16IgMN	11 DMP 10 FSGS 16 MCD
Withdraw I/C	0/0	12/17	6/1	2/0	2/0	0/0/0/0	2/0	16/3	0/0	0/0

Lost to Follow	1/0	0/0	0/1	0/0	2/0	0/0	0/0	0/1	0/0	0/0
Analyszed I/C	21/21	76/73	24/29	28/30	26/30	43/38/21/3	12/12	29/31	34/38	23/37
Study months	12	12	12	12	12	6	12	12	12	12
Age at onset (mean in years)	4.5/5.0	4.4 /4.0	5.09 /4.0	4.4/3.92	4.4/3.92	NA	5.6/ 4.0	3.5/ 4.3	3.6/4.2	NA
Age at Trial (mean in years)	10.0/5.0	5.4/5.6	8.99/7.69	10 /9.5	11/10.5	6.5 /6.5	10.9 /9.2	5.6/5.5	64.1/ 72.1	NA
Previous therapy Standard or with others	Standard Toxicity in 22	with/ without CYP	Standard therapy	LEV, CYP, CsA, MMF, CMB	Standard with CsA or MMF	Standard	Standard with TAC	Standard	NA	NA
MMF Dose given in two divided doses	1000 mg /m2(850 - 1100	750-1000	1200 mg/m2	1000-1200 mg/m2 max 1gm	1000-1200 mg/m2 max 1gm	Standard dose	1200 mg/m2 max 1gm	750-1000 mg/m2	20-30 mg/kg/day	30 mg mg/kg/day + Pred ?
Comparator dose	LEV 2.5 mg/kg daily	LEV 2.5 mg/kg alternate day	CsA 3-5 mg/kg/day	CsA 150 mg m2 /day	CsA 150 mg m2 /day	Standard dose	CsA 4-5 mg/kg/day TAC ?	TAC 0.1-0.15 mg /kg/day	TAC 0.05-0.15 mg /kg/day	CsA 5 mg /kg/day i + MMF 30mg /kg/day
Drug monitoring & dose adjustment	Not done	Not done	MMF: Nil CsA : Trough levels	MPA predose 1.5- 2.5 µg/ml CsA to 80-100 ng/ml trough level	Nil	MPA area under curve by limited sampling CsA not done	MPA area under curve by limited sampling CsA not done	I)MMF =Nil (C)TAC trough levels 4-7ng/ml	MMF =Nil (C)TAC trough levels 5-10 µg/L	Nil

MCD: Minimal change disease; FSGS: Focal segmental glomerulosclerosis; MeSPGN: Mesangial Proliferative glomerulonephritis; IgMN: Immunoglobulin M nephropathy; NonSp: nonspecific findings; ND: Not done

Table 2: Main Outcomes, Frequency of relapse MMF versus alternate drugs & Achievement of complete remission

Study ID	**Comparison**	**Number Analyzed**	**Number MMF arm**	**Number alternate drug arm**	**Outcome 1 Frequency of relapse MMF versus alternate drugs**					**Outcome 2 Achievement of complete sustained remission**		**Grade Analysis certainty of evidence**
					Number relapsed MMF arm	**Number relapsed alternate drug arm**	**Risk with MMF**	**Risk with Alternate drug**	**Relative risk**	**Complete remission achievers MMF**	**Complete remission achievers alternate drug**	
Singh 2020	MMF Vs LEV	42	21	21	16	15	762/1000	714/1000	1.07	5 (23.80 %)	6 (28.57 %)	⊕⊕⊕◯ MODERATE
Sinha 2019	MMF vs LEV	149	76	73	45	48	592/1000	658/1000	0.90	31 (40.79 %)	25 (34.25 %)	
Rahman 2018	MMF vs CsA	53	24	29	16	9	666/1000	310/1000	2.15	8 (33.33 %)	20 (68.96 %)	⊕⊕◯◯ LOW
Gellerman 2013	MMF vs CsA	120	60	60	21	9	350/1000	150/1000	2.0	38 (64.40 %)	50 (84.74 %)	
Shah	MMF vs	59	21	38	3	2	143/	53/100	2.69	18	36	

2016	CsA						1000	0		(85.71 %)	(94.73 %)	
Doorestejin 20008	MMF vs CsA	24	12	12	5	1	416/1000	83/1000	5.01	7 (58.33 %)	11 (91.66 %)	
Sinha 2017	MMF vs TAC	60	29	31	18	15	621/1000	484/1000	1.28	11 (37.93 %)	16 (51.61 %)	⊕⊕◯◯ LOW
Wang 2016	MMF vs TAC	72	34	38	13	20	382/1000	526/1000	0.72	13 (38.23 %)	20) (52.63 %	
Shah 2016	MMF vs TAC	81	21	43	3	3	143/1000	70/1000	2.04	18) (85.71 %	40 (93.03 %)	
Nikibakhsh 2011	MMF + CsA vs CsA +Pred	60	23	37	12	25	522/1000	675/1000	0.77	11 (47.82 %)	12 (32.43 %)	⊕⊕◯◯ LOW

Regarding outcome 3, statistically significant post treatment reduction in steroid dose was observed in all studies by the pretreatment values and comparisons were not reported for all. Both studies in MMF vs LEV group and two studies in MMF vs TAC. group by Wang and Sinha reported it. None of the studies reported statistically significant difference between MMF, Levamisole and Tacrolimus. (P = 0.22, P= 0.88). Nikabaksh study did not report that outcome.

Outcomes 4. Response time to urinary remission of protein data was available in only one study, Rahman 2018 which was reported as as 12.20 ± 4.80 days in MMF group and 11.58 ± 5.77 days in cyclosporine group (P=0.676) and there was no statistically significant difference.

Outcome 5 : Data for complete stoppage of Steroid was available in two studies only, in MMF versus LEV group. It was not available in other studies. Singh 2020. reported achievement of complete stoppage of steroids in 38% cases with MMF therapy and 28.5 % cases with Levamisole therapy. Similar observation was made by Sinha 2019 where 40.7% cases achieved complete stoppage of steroid with MMF therapy and 34.2 % achieved it with Levamisole therapy. On combining the results overall higher rates (40.2%) were observed achieved of with MMF as compared to Levamisole (32.9%).

Outcome 6 : Effect of drug dose and drug monitoring was analyzed in two studies only Gellerman2013 monitored MPA levels and divided them into higher and lower groups based on MFA - AUC < 50 µg.h/ml and MFA - AUC > 50 µg.h/ml, both subgroups being otherwise comparable for age and dose of MMF, the group with lower MPA –AUC exposure (mean 37.6 µg.h/ml) experienced significantly more relapses than those with a higher MPA exposure (mean 74.0 µg.h/ml) with a (P <0.05). Receiver operating characteristic (ROC) for MPA exposure was considered a predictor of relapse, a MFA - AUC level of 57.1 µg.h/ml depicted a sensitivity of 80.0 % and a diagnostic specificity of 63.0 % to discriminate relapsing from nonrelapsing patients. Patients with high MPA exposure were also noted to have significantly longer time without relapse. In the high MPA exposure subgroup and CsA group there was no significant difference. MPA trough levels also had a linear co-relation with relapse rate. Such analysis was not done in CsA group due to low Relapse rate. Doorestejin 2008 also described lower MPA trough levels as 3.4 mg/l in relapsers as compared to those without relapse as 3.6 mg/l (P=0.48), however Wang 2016 described lack of correlation between drug dose and serum levels of MMF and stated that lower doses of MMF were also effective in maintaining remission and reducing relapse rate .In other studies and for other drugs either the drug levels were not monitored or dose related outcome was not studied.

Meta-analysis for main outcome is given in figure 2, 3, and 4 for levamisole, cyclosporine and tacrolimus respectively and are self-explanatory, Outcome to synthesis and meta-analysis has been done together in table 3 for ease of understanding.

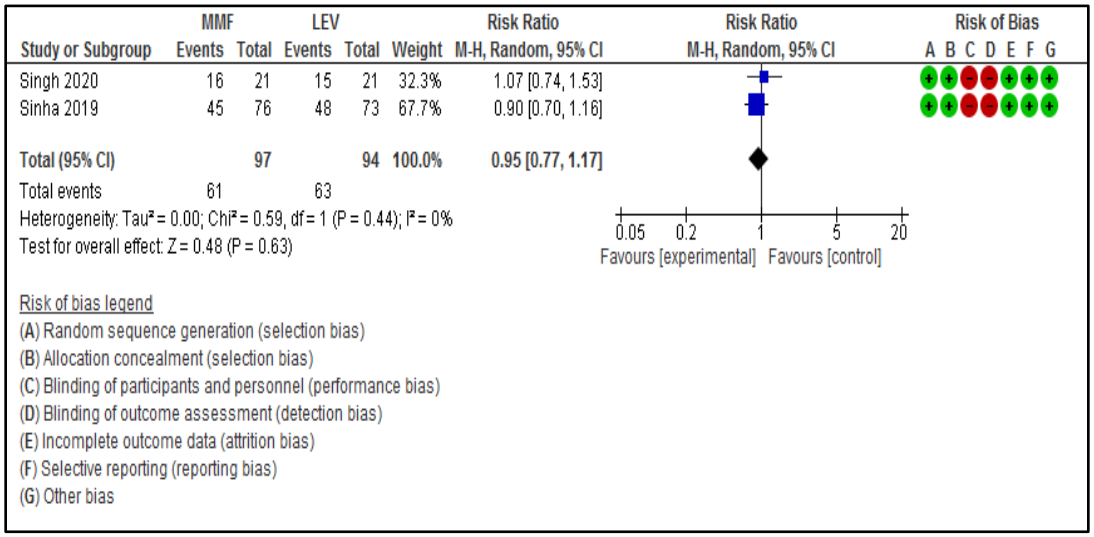


Fig. 2: Outcome 1.1; Frequency of relapse Mycophenolate mofetil Versus Levamisole

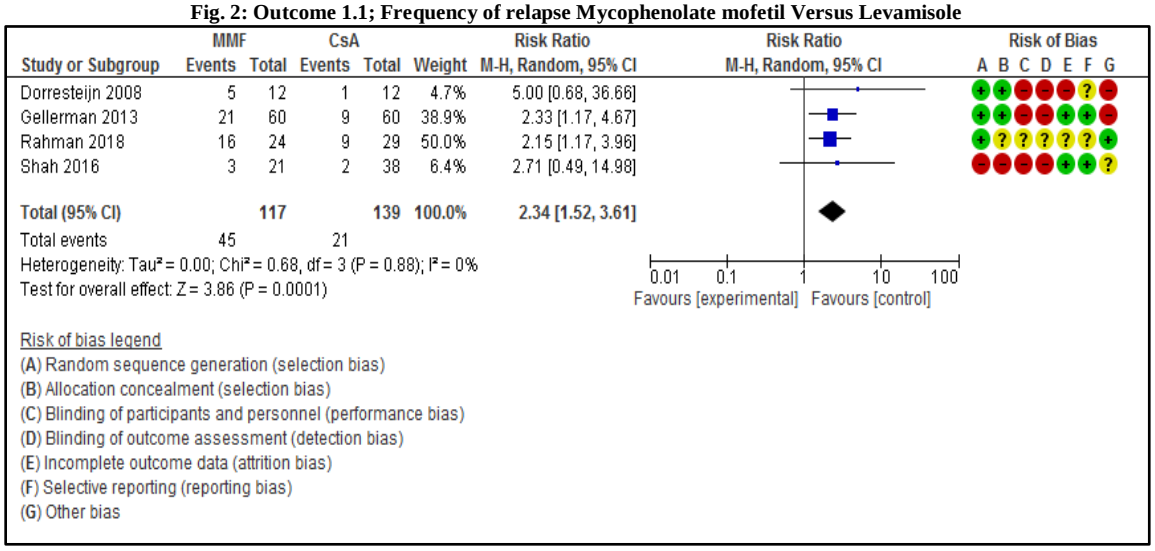


Fig. 3: Outcome 1.2; Frequency of relapse Mycophenolatemofetil versus Cyclosporine

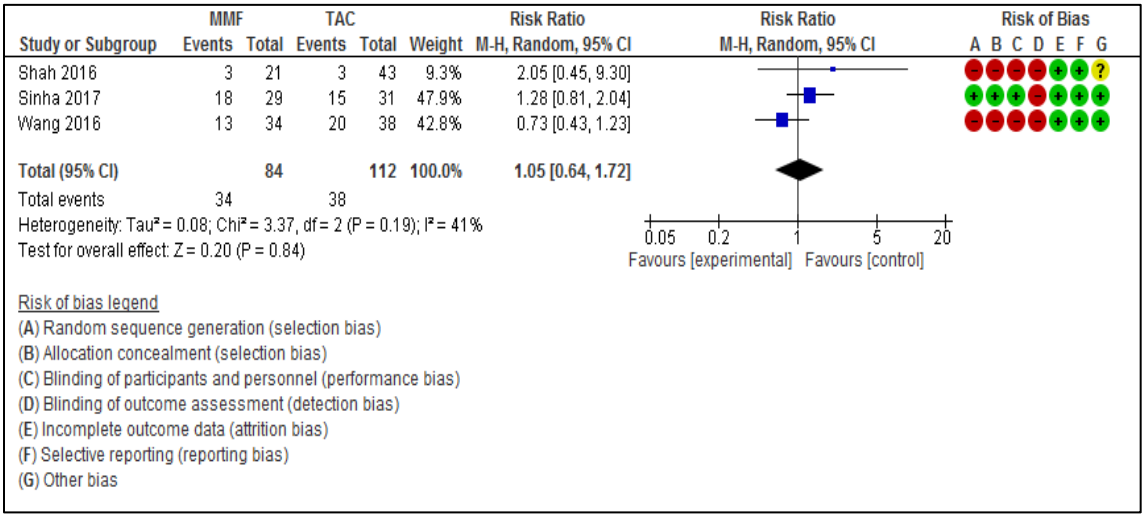
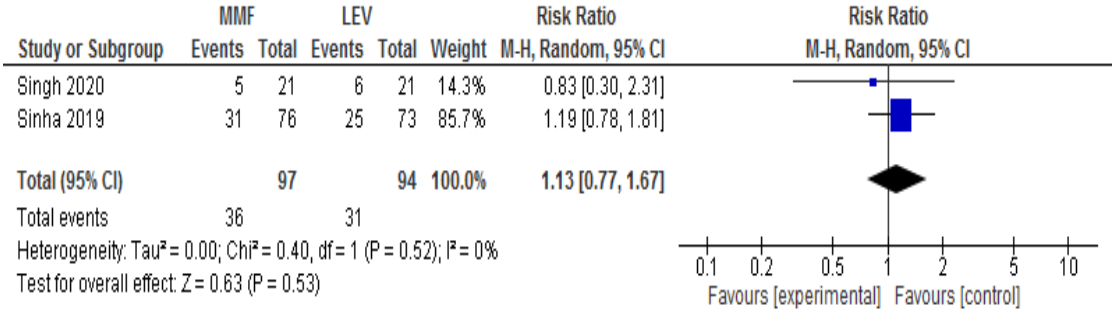


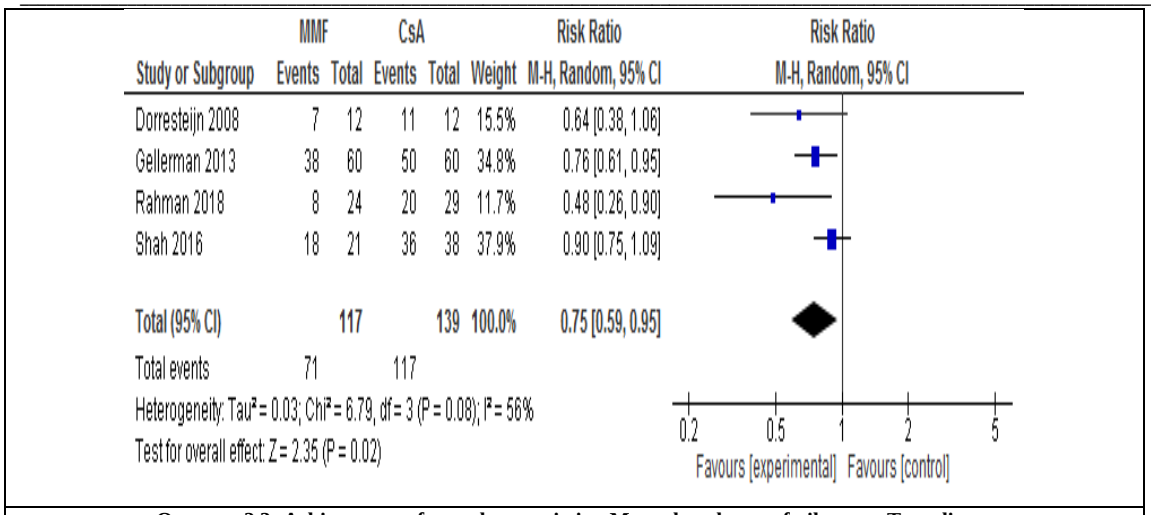
Fig. 4: Outcome 1.3; Frequency of relapse Mycophenolate mofetil versus Tacrolimus

Table 3: Outcome 2 (Meta-analysis): **Achievement of complete remission MMF versus** alternate drug

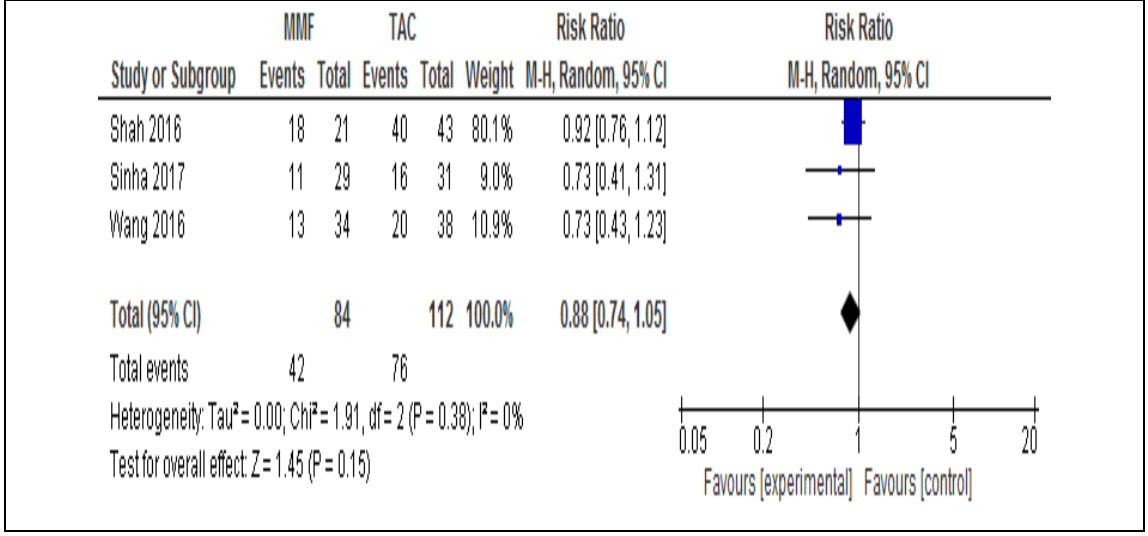
Outcome 2.1: Achievement of complete remission MMF versus Levamisole



Outcome 2.2: Achievement of complete remission Mycophenolate mofetil versus Cyclosporine



Outcome 2.3: Achievement of complete remission Mycophenolate mofetil versus Tacrolimus



Discussion

In the last two decades following a number of studies few drugs have gained popularity among clinicians either for their undisputed efficacy or for their undisputed safety especially in developing world where drug monitoring and investigative facilities are limited, cost effectiveness and economic burden are an issue both as a family and as a nation. Amongst them four popular drugs are MMF, Cyclosporine, tacrolimus and levamisole. In this systematic review we compared efficacy of MMF with other three to help clinicians in decision making for a choice. On one hand Nephrotic syndrome in children is a unique problem recognized easily at outset, but future course of disease is filled with uncertainties, relapses, complications, drug toxicities etc. Early introduction of second line drugs may change the course of disease and life of child significantly. In our systematic review and meta-analysis we were able to include 9 studies with a data analysis for 703 subjects, because only few clinical trials published in English exist in this field and that too with only a short follow up period of 12 months, therefore results are generizable only to a limited extent. Levamisole has been established as second line drug in preventing relapse as an alternate day or daily therapy[21]. Cochrane Systematic review had similar observation based on one study of MMF vs LEV[22]. We have included two studies and results of both are similar raising our confidence level in results. One was a non-inferiority trial for levamisole and other states superiority about MMF. MMF gives slightly better results, but the difference is not statistically significant. The effect size remains in center and sensitivity analysis does not change the picture. This translates into consideration of other factors in clinical decision like consideration of cost, side effects, feasibility drug monitoring availability etc. MMF is available throughout the world but Levamisole in Asian countries like India with a huge difference in cost, moreover these studies are also from India, therefore they can go for Levamisole first, and if it fails than shift to MMF, for others MMF remains the choice. however robust studies with larger sample size and blinding from different Asian and other geographical areas are needed for greater generalizability of results. Cyclosporine was found better than MMF in reducing relapses, the effect size clearly favored cyclosporine as it moved away from central line. Geng et.al 2018 also found CsA efficacy superior to MMF [23], not included due to language barrier for full text. When outcome of complete sustained remission was considered, it clearly favored MMF, but for third outcome reported by only two studies did not favor any, as diamond remained over central line. We can deduce that both MMF and Cyclosporine gave comparable results. Clinical decision will be guided by adverse effects and costs. MMF will be chosen first because of persisting fear of Cyclosporine induced nephrotoxicity [24,25,26]. Sensitivity analysis did not change the picture much. Sample size limitation, inclusion of non-randomized clinical trials and other risks of bias were present, therefore generalizability of results is limited. As regards MMF versus Tacrolimus, three studies data on 196 subjects

were analyzed. Effect size diamond remained in center and confidence intervals of all studies crossed the midline. Therefore, we can say that there was no statistically significant difference between MMF and Tacrolimus. As regards achievement of complete remission MMF fared better, but for steroid dose the effect size diamond remained in center. Decision for a clinician will again be guided by other factors also. Go first for MMF and if it fails then Tacrolimus line may be adopted as it has been found successful when both MMF and CsA have failed[27]. Sensitivity analysis did not change the picture much. Studies had similar design, execution and generalizability limitations. Combination therapy with a sequential design was done by Nikabaksh, no other similar study was found. Combined MMF CsA results were better and results statistically significant, this combination may provide a good choice for non-responders, but issue of CsA nephrotoxicity will be there in the long run, Further studies are needed. Regarding additional outcomes response time to complete urinary remission, a measure of quickness of effect, was available in one study only where MMF and levamisole had comparable results without any statistical significance, Achievement of complete stoppage of steroid was measured in first group and the results favored levamisole but had no statistical significance as in both studies confidence intervals crossed the central line when meta analyzed. Outcome 6 was important regarding dose, drug levels and its relationship over outcomes. It has been observed in different studies that mycophenolate levels are affected by kidney condition, age of child, immune status and nephrotic state, hence treatment is individualized[28,29]. Fixed dose without blood drug level monitoring may not give good results, moreover the picture may change overtime in the same individual. Drug levels in MMF vs LEV were not available for both. In MMF vs CSA group MMF dose was adjusted in some studies. Gellerman measured both CSA and MMF drug levels, and concluded that relapse rate was less in higher MPA group and monitoring matters[30]. Doorestejin also had the same conclusion for MPA although they did limited sampling for MM, but concluded that relapsers had lower MPA trough levels. In the third group MMF versus TAC, MMF and Tac both trough levels were measured but dose was not adjusted, the dose given by them was not similar (20-30 mg/kg) and they concluded that lower dose was also effective. Language barrier was the main limitation, as we could not include studies available in other languages. Mix of Steroid resistant /dependent/sensitive/ frequent relapsers together was another limitation. Response analysis according to biopsy diagnosis was also not possible due to lack of data. We found a median 12 months follow up period in studies, a limitation for a disease like nephrotic syndrome where categorization itself is defined after 12 months. A longer follow up data of 3-5 years is desired.

Conclusion

Efficacy of all four drugs was found to be similar statistically, therefore other factors fitting on AFASS criteria should guide the choice of drug for a clinician. They all can be used sequentially. Developing nations like India may choose either levamisole as first, second line drug and developed word with facilities should go for MMF. Second in order comes MMF. Tacrolimus and cyclosporine will come at third place.

Weakness

The results had the limitation of sample size, mixture of randomization and non-randomization, blinding issue and few without allocation concealment as well. Risk of bias cannot be ruled out, therefore results should be interpreted in context to that. Properly planned randomized trials with allocation concealments and triple blinding with good sample size are needed to support or refute the derived clinical inferences.

Strength

No such clinically useful Systematic review is available

Future

Introduction of combination therapy at initial attack and prevention of first relapse itself to change the doomed characteristic of 80 -90 % relapse. MMF or Levamisole may be a good choice for combination therapy trials.

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Conflict of Interest: Nil Source of support: Nil