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Original Article

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A single-centre retrospective study of the safety and efficacy of mycophenolate mofetil in children and adolescents with nephrotic syndrome

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Abstract

Background. The aim of the study was to investigate the efficacy and side effect profile of mycophenolate mofetil (MMF) therapy in children with nephrotic syndrome (NS).

Methods. A retrospective case note review was performed on all patients with NS who were commenced on MMF between 1 January 2000 and 31 December 2009 and were followed up for a minimum of 1 year.

Results. The sample size was 73 patients. The duration of follow-up was for a median of 3.2 years, interquartile range (IQR) (1.7–4.7 years). The median age at diagnosis was 3.2 years, IQR (2.3–5.7 years). The median age of MMF commencement was 11 years, IQR (7.9–13.6 years). There were more boys (67%) than girls. The majority were Caucasian (77%), with 18% Asian 4%, Black Africans and 1% other ethnicities. At initial diagnosis, 61 (84%) were steroid sensitive, 9 (12%) steroid resistant, 3 (4%) steroid dependent (SD). Forty-five (74%) of the 61 steroid-sensitive patients became SD, 4 (7%) of them became steroid resistant, 1 (1%) remained steroid-sensitive and 11 (18%) became frequent relapsers. As to the previous use of second-line immunosuppressants, none were used in 5 (7%) patients, one agent in 17 (23%), two in 27 (37%) and three or more agents were used in 23 (32%) patients. MMF was effective in 45 (62%) patients. Of these, 38 (52%) of them were in remission for >2 years; and in 7 (10%) MMF worked for 1 to 2 years (MMF therapy electively stopped/ongoing). MMF therapy allowed 27 (37%) patients to wean steroids completely and 8 (11%) to achieve complete steroid and immunosuppressant withdrawal. A further 8 (11%) had steroids partially weaned. MMF failures were seen in 13 (18%) within the first year and 5 (7%) in the second year. MMF was stopped due to side effects in 4 (6%) and non-compliance in 4 (6%). The majority of patients had no side effects [51 (70%)]. Seven (9%) had gastrointestinal side effects (diarrhoea/abdominal pain); 5 (7%) had immunological side effects (leucopenia/infections); 3 (4%) had both immunological and gastrointestinal side effects; and 2 (3%) suffered arthralgia.

Conclusions. MMF is well tolerated and effective as a second-line agent in treating steroid-sensitive NS. The drug permitted prolonged remission and steroid weaning or other second-line agent withdrawal in a majority of cases.

Keywords: steroid sensitive; steroid sparing; relapse

Introduction

Steroid-sensitive nephrotic syndrome (NS) remains the predominant type of NS during childhood with 90–95% children being responsive to steroids, of whom a large proportion have minimal change disease following renal biopsy [1]. Following initial remission, 80–90% of these patients with steroid-sensitive NS (SSNS) have clinical relapses of their NS [2]. The clinical course is variable, with up to 60% having frequent relapses or becoming dependent on steroid therapy to maintain them in remission [3]. 'Steroid sparing' immunosuppressive agents are used for reducing the use of steroids and to maintain remission in patients with frequently relapsing/steroid–dependent (SD) NS (FRNS/SDNS). Patients with steroid-resistant NS (SRNS) also benefit from second-line immunosuppressive therapy. These agents have potentially significant adverse effects, and there is a lack of evidence base or consensus opinion on their use for clinicians to manage children with difficult NS [2].

Mycophenolate mofetil (MMF), a steroid-sparing agent, introduced over the past decade is a selective reversible inhibitor of inosine monophosphate dehydrogenase that inhibits *de novo* synthesis of purines. MMF exerts a cytostatic effect specifically on lymphocytes as they are unable to use salvage pathways to synthesize purines [4].

Table 1. Demographics of all patients who received MMF therapy

Age at initial diagnosis of NS	3.2 years (IQR 2.3–5.7 years)
Age at initiation of MMF therapy	11 years (IQR 7.9–13.6 years)
Duration of treatment with MMF	2.1 years (IQR 0.8–3.2 years)
Duration of follow-up after commencement of MMF therapy	3.2 years (IQR 1.7–4.7 years)

All data are shown as median (IQR).

It's use in the management of childhood NS alone or in combination with other immunosuppressive agents such as prednisolone has been demonstrated in several small studies, but there remain limited data on its safety and efficacy.

Our objective in this retrospective study was to evaluate the safety and efficacy of MMF in children with NS. This retrospective analysis of 73 patients, of different racial backgrounds, is the largest such study so far published in children, furthermore we report over a prolonged follow-up period (median of 3.2 years). Most patients had difficult-to-treat disease refractory to multiple therapies (Table 1).

Patients and methods

This is a single-centre retrospective study including all children presenting with NS who were treated with MMF at the Evelina Children's Hospital, London, UK. Patients were identified from an electronic database and their clinical case notes were reviewed. All children on MMF between 1 January 2000 and 31 December 2009 were included in the study.

This was a service evaluation audit that was designed as a retrospective case note review and did not require any local Ethics Committee permissions.

Seventy-three children, aged 1–19 years, who were treated for NS between 1 January 2000 and 31 December 2009 with a follow-up of at least 1 year were included in this review. Children on MMF for indications other than idiopathic NS (e.g. lupus nephritis; renal transplant) were excluded.

The following widely accepted International Study of Kidney Disease in Children definitions were used

(i) Steroid-sensitive NS: patients who enter into remission in response to corticosteroid treatment are referred to as having steroid-sensitive NS.
(ii) Remission: urinary protein excretion <4 mg/m^2/hr or urine dipstick nil/trace for three consecutive days.
(iii) Relapse: urinary protein excretion >40 mg/m^2/hr or urine dipstick +++ or more for three consecutive days.
(iv) Frequent relapses: two or more relapses within 6 months of initial response or four or more relapses within any 12-month period.
(v) Steroid dependence: two consecutive relapses occurring during the period of steroid taper or within 14 days of its cessation.
(vi) Steroid resistance: failure to achieve remission in spite of 4 weeks of standard prednisolone therapy.

As a tertiary referral centre patients may present to us at different stages of their disease following referral from colleagues in primary or secondary care. These include (i) new patients—in whom steroid sensitivity or steroid resistance would be defined following the initial standard definition; and (ii) previously known NS—who may be frequently relapsing/ SD or steroid resistant at the time of referral to us. Steroid sensitivity and steroid resistance at initial presentation was defined similarly in all patients following a review.

During the period of MMF treatment, all patients received intermittent prednisolone therapy for relapses. Treatment of relapse was with daily oral steroids until early morning urine specimens were negative or trace on dipstick testing for three consecutive days; subsequently various steroid weaning regimes were followed.

Patients were commenced on MMF if they had failed to respond to other steroid-sparing therapies or if they had adverse effects as a result of their usage, such as calcineurin inhibitors (CNIs) or steroids. MMF was stopped electively due to the length of treatment or changed following drug failure (frequent relapses), the patient having side effects or being non-compliant.

The therapeutic dose of MMF was 600 mg/m^2 per dose twice daily in most patients. Those with gastrointestinal side effects took the medication in three divided doses. Full blood count was monitored before and after starting the medication (weekly until 2 weeks following full dose and subsequently 3–6 monthly). The following clinical data were recorded: age at the onset of disease, ethnicity, gender, history of prior treatment and age at initiation of MMF therapy, biopsy findings, duration of treatment and the reason for stopping treatment. If a patient was non-compliant, it was explicitly mentioned in the notes by the clinician.

Statistics

All values were expressed as medians and interquartile ranges (IQRs). A chi-square test was used to evaluate the relation between biopsy categories and steroid responsiveness. Mann–Whitney *U*-test was used to compare relapse rates before and during MMF therapy. All P-values were two sided and considered statistically significant at a value of <0.05.

Results

Demography

Of the 73 children, 49 (67%) were males and 24 (33%) were females. The majority were Caucasians, 56 (77%), the remainder were Asians, 13 (18%)—4 Bangladeshi, 3 Chinese, 3 Indians, 2 Sri Lankans, 1 Pakistani—Black Africans 3 (4%) and other mixed ethnicities 1 (1%). This racial mix reflects the normal distribution of children seen at our unit.

Course of the disease

The median age at first presentation of NS was 3.2 years (IQR 2.3–5.7 years).

The median age at referral to Evelina Children's hospital, Guy's and St Thomas' NHS trust was 4.7 years (IQR 3.0–7.7 years).

As shown in (Figure 1), at initial presentation the majority, 61 (84%), were steroid sensitive, 9 (12%) were steroid resistant and 3 (4%) were SD from the time of first presentation with NS.

Forty-five (73%) of the 61 steroid-sensitive patients became SD and 4 (7%) of them became steroid resistant at the time of commencement of MMF. One percent

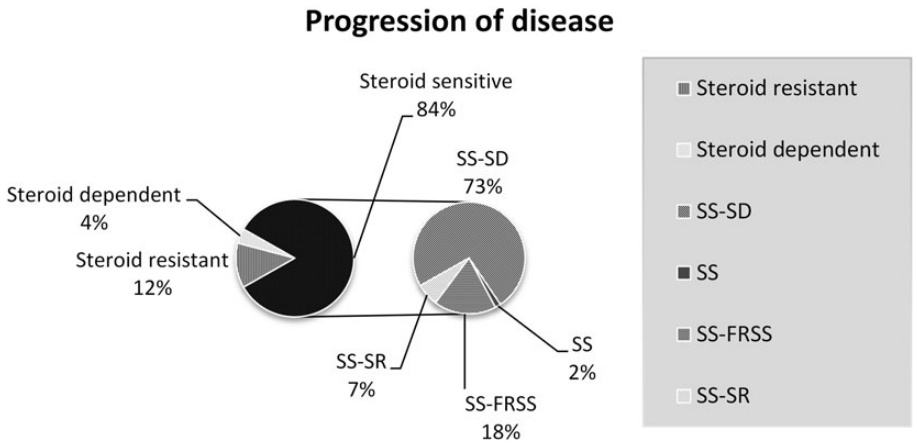

Fig. 1. Nature of disease at first presentation and progression of disease in SSNS at the point of MMF commencement. SS—steroid sensitive, SD—steroid dependent, SR—steroid resistant, FRSS—frequently relapsing steroid-sensitive NS.

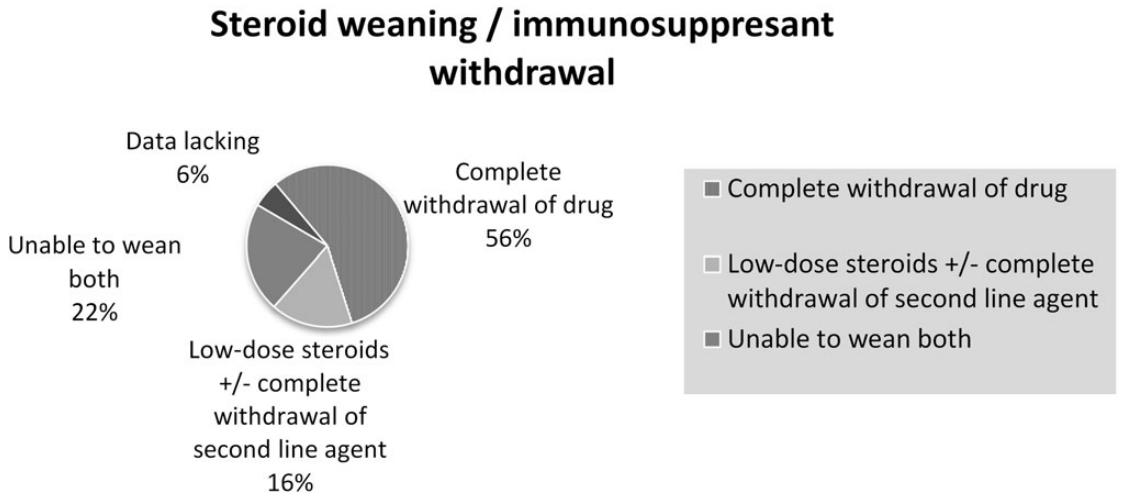

Fig. 2. Withdrawal of steroid/other second-line immunosuppressants.

remained steroid sensitive, and 11 (18%) became frequent relapsers.

Indications for commencing MMF were failure of other second-line immunosuppressants in 52 (71%) patients, CNI toxicity in 14 (19%) patients and steroid toxicity in 2 (3%) patients.

Most patients had previously used other second-line agents, i.e. alone/a combination of any of the following medications [cyclosporine (37)/cyclophosphamide (23) and a few had tried mustine (15) and levamisole (15) before commencing MMF]. Seventeen (23%) patients had previously been prescribed a single agent, 27 (37%) had two agents and 23 (32%) had previously been prescribed three or more agents prior to starting MMF. Only 5 (7%) patients were prescribed MMF as the first second-line agent.

Non-compliance was an issue in four patients. In the rest of the patients, the clinicians were fairly sure of compliance.

Efficacy

MMF was deemed to be efficacious if it permitted all of the following (i) prolonged remission (remission for more than a year), (ii) withdrawal of steroid/other steroid-sparing immunosuppressants and (iii) reduction in relapse rates (per year) from the period before starting MMF.

Overall, MMF was effective in 45 of 73 (62%) patients.

Of the total population,

(i) Complete remission was seen in 36 children (49%) for >2 years. In these patients, the previous second-line agent and steroids were completely withdrawn or they were on low-dose steroids.
(ii) Partial remission (with complete steroid withdrawal) was seen in 2(3%) children for >2 years.
(iii) Complete remission for 1 to 2 years was seen in 7 (10%) children. In these patients, second-line agents/steroids were withdrawn completely or they were on low-dose steroids. (MMF therapy was electively stopped or was still ongoing at the time of the study).

A further nine (~12%) achieved complete remission, but MMF was withdrawn due to various reasons: non-compliance in four (5.5%), side effects four (5.5%) and the drug was stopped due to infrequent relapses in one (1.3%) patient.

As shown in Figure 2, nearly one in five patients (22%) did not demonstrate a positive response to MMF therapy.

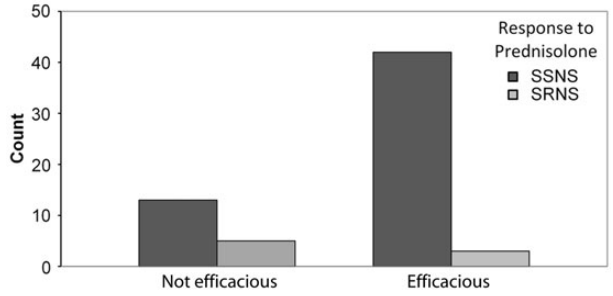

Fig. 3. Relationship between the nature of disease and the response to MMF.

Complete withdrawal of the drug was possible in 41 (56%) patients, which include patients with either steroid withdrawal 38% or second-line agent withdrawal 8% or both 11%. Some patients 12 (16%) were on low-dose steroids, and this included 8 (11%) on low-dose steroids and 4 (5%) who were on low-dose steroids and also had the second-line agent withdrawn. MMF was used in conjunction with cyclosporine A ($n = 2$), tacrolimus ($n = 3$) and rituximab ($n = 1$) for a prolonged period of time and proved effective with regard to steroid withdrawal.

Of the 45 patients in whom MMF was efficacious we obtained detailed data regarding relapse rates in 41. There was a significant fall in relapse rates while on MMF therapy; median relapse rate per year prior to MMF was 1.5 (1.2–2.3) compared with only 0.5 (0–0.87) in those who responded to MMF (P = 0.001).

In which patient group is MMF most effective as a second-line agent?

Figure 3 demonstrates that MMF, as expected, was much more likely to be efficacious in patients with SSNS compared with those with steroid resistance (χ^2 P = 0.023).

Biopsy

A majority of the patients, 64 (88%), had a renal biopsy at some point in their disease course. Of the 64 patients who had a renal biopsy, 37 (58%) had minimal change disease (mixture of steroid-sensitive and steroid-resistant patients). Of the 45 patients in whom MMF was efficacious for more than a year, 27 (56%) had minimal change disease.

Table 2 shows that children who were steroid sensitive and had minimal change disease were much more likely 27 (87%) to respond to MMF (Table 2, P = 0.01); MMF was efficacious in 8 (50%) of the patients with steroid-sensitive NS and any other biopsy category.

In the rest of the patients where MMF was efficacious, seven did not have a biopsy and three were steroid resistant.

MMF therapy failed in six out of the nine steroid-resistant patients. Of the six steroid-resistant patients, MMF failed in five patients who had FSGS on biopsy.

MMF failures

MMF failures (frequent relapses whilst on MMF) were seen in 10 (14%) within first 6 months. Seven were SD and three were steroid-resistant patients. A further three (4%) patients failed MMF therapy within 6 month–1 year of starting the drug. MMF was stopped in five (7%) patients 1 to 2 years after therapy because they started to have frequent relapses.

Table 2. Renal biopsy categories and relation to steroid responsiveness

	MMF efficacious	MMF failed	Total
Steroid sensitive with minimal change disease	27 (87%)	4	31
Steroid sensitive with any other biopsy category	8 (50%)	8	16
Total	35	12	47

Safety and tolerability

Side effects were generally mild, and most patients tolerated MMF well. The majority of patients had no side effects, 51 (70%). Gastrointestinal side effects of diarrhoea and abdominal pain were observed in seven (9%); five (7%) had side effects of leucopenia/infections; three (4%) had both immunological and gastrointestinal side effects and two (3%) suffered arthralgia.

One patient developed abdominal pain, and MMF was stopped at 11 months of therapy. Another patient developed shingles within 6 weeks of treatment and had to discontinue it. A third patient had arthralgia for which the drug was stopped at 6 months of treatment.

MMF was stopped due to side effects in four (6%) and non-compliance in four (6%). Of the non-compliant group, one patient refused to take steroids when he relapsed after 6 months of MMF therapy and hence, MMF treatment was stopped.

Discussion

We present the largest paediatric series so far published investigating the safety and efficacy of MMF in paediatric NS. When compared with all previous studies, our series had a mixture of patients: frequent relapsers; SD and steroid resistant. This gave us an opportunity to look at the response of all categories of nephrotic patients to this medication.

Most of our patients had minimal change disease on biopsy, and although the majority of patients were steroid sensitive to start with, a large proportion of them had become SD at the time of MMF commencement. A large proportion of our patients had NS for several years and were treated with other second-line immunosuppressants during this period (cyclosporine (37)/cyclophosphamide (23) or few had been treated with mustine (15) and levamisole (15) before commencing MMF. The history of multiple drug usage, steroid dependence and age at starting MMF implies that many of these patients were particularly 'difficult to treat'. Despite this, MMF permitted prolonged remission and steroid and/or other second-line agent withdrawal in a majority of cases (2/3rds).

Our median duration of treatment with MMF was 2.1 years which is one of the longest described so far in such cohorts—other published studies describe relatively shorter, 6–12-month periods of MMF therapy [5–8]. Furthermore, we describe the longest patient follow-up in the literature so far, with a median duration of 3.2 years, demonstrating the long-term efficacy of MMF in some patients. An important limitation of this study was the absence of a control group, with patients serving as their own controls.

There are several studies that have suggested that there is a beneficial effect of MMF as adjunctive therapy in childhood NS and following is a discussion of the published studies with the largest sample numbers. Novak *et al*. [5] looked at 21 patients with SDNS. Hogg *et al*. [6] studied 32 frequently relapsing steroid-sensitive NS patients. Afzal *et al*. [7] reported their experience on 42 SDNS patients. Baudouin *et al*. [8] in 2011 studied 23 SDNS patients. Banerjee *et al*. most recently reported the long-term outcome of MMF therapy in 46 patients who remained SD despite previous treatment with levamisole and cyclophosphamide [9]. Our study has the largest sample size (73 patients) when compared with the ones published so far but is a mixture of steroid-sensitive / dependent / resistant patients. Though the majority of them (61) were steroid sensitive at presentation, interestingly, over the ensuing years, 45 became SD, the number of SDNS patients being comparable with that of Banerjee *et al*.'s most recent publication in 2012.

Our median length of therapy of 2.1 years (IQR 0.8–3.2 years) was longer than others and is comparable with Banerjee *et al*., where 14 stopped MMF after a mean 2.4 SD +0.9 years and 11 were continuing on MMF for a median of 2.25 years (range 1.33–7.75 years [9]). Whereas the mean duration of MMF treatment by Novak *et al*. was 1.0 ± 0.5 years (range 0.2 –2.0 years) [5]. In Hogg *et al*. [6], the duration of therapy was 6 months and Afzal *et al*. [7] 14.3 months (6–45 months).

With regard to dosage, Novak and Hogg used the same regimen as the current study; patients received 600 mg/m^2 twice daily (maximum 1 g twice daily) [5, 6]. However, Baudouin *et al*. in 2011 gave their patients 600 mg/m^2 BSA/day of MMF during the first 7 days then increased it to 1200 mg/m^2 BSA/day for a year [8] whereas Afzal *et al*. administered MMF at a mean daily dose of 26.5 mg/kg (16.6–31.3) mg/kg for 14.3 months (6–45) [7].

Most of the published efficacy data are reasonably consistent including the current data. Novak *et al*. showed overall that the relapse rate decreased from 9.6 ± 4.92 to 5.64 ± 5.16 relapses/year ($P < 0.02$) [5]. Hogg *et al*. showed that 24 of 32 (75%) patients stayed in remission throughout the 6 months of MMF therapy, and the relapse rate reduced from 6 relapses/year before MMF to 0.84 relapses/year after treatment [6]. Afzal *et al*. showed that the relapse rates pre-MMF was 6 ± 2.2 episodes/year; during MMF therapy this decreased to 2.2 ± 2.4 episodes/year ($P < 0.001$). Prednisolone sparing was also seen in [7]. Baudouin *et al*. showed that MMF in combination with low-dose alternate-day prednisone was effective in maintaining a long-term remission (relapse probability during the first 6 months of treatment being 17.6%) and allowed steroid dose reduction (50% of the pre-MMF threshold dose at 3 months and 25% at 6 months [8]). In the study by Banerjee *et al*., at a follow-up of a mean of 3.56 (SD +1.76) years, 25 of 46 (54%) children required no further alternative immunosuppression (IS), having infrequent or no relapses. In the same study, 1 year after initiation of MMF, 32 (70%) patients had reduced steroid requirement: 12 with decreased threshold dose and 20 were able to stop steroids [9]. Our study shows similar results to the ones mentioned above; we demonstrated that in the efficacious group, MMF therapy significantly lowered the relapse rates from 1.5/year to 0.5/year ($P = 0.001$). MMF is most efficacious in steroid-sensitive patients with minimal change disease on biopsy. Also, we demonstrated that MMF ± low-dose alternate-day prednisolone is effective in maintaining long-term remission and allows decreasing/withdrawal of prednisolone dose in a heterogeneous population of children who were predominantly SD. MMF therapy failed in six out of the nine steroid-resistant patients. Of the six steroid-resistant patients, MMF failed in five patients who had FSGS on biopsy. The reduced efficacy in steroid-resistant patients with FSGS is consistent with data from Gargah *et al*., which was a single-centre study, where a therapeutic response to MMF was obtained in only one third of the patients. Four out of the six steroid-resistant patients had FSGS on biopsy and were non-responders [10].

With regard to the side effect profile, our findings are similar to those of others. Novak *et al*. found a mild side effect profile and therapeutic benefit in 76% (16 of 21) of patients and argued in favour of using MMF as the first-line adjunctive therapy for SDNS as a steroid-sparing agent [5]. Hogg *et al*. [6] showed that only 2 of 33 (6%) had adverse side effects; 1 patient had a neutrophil count of 0.3 and another patient developed varicella. Side effects in the study by Afzal *et al*. were limited to mild abdominal pain which resolved spontaneously. The absence of diarrhea, serious infections and haematological adverse effects in their study was attributed to a lower but therapeutically effective dosage of medication [7]. Baudouin *et al*. [8] showed that side effects were scarce and reversible compared with those observed with CNIs and cyclophosphamide. No serious adverse effects were seen. Banerjee *et al*. described only one patient having a psoriasis flare, following which MMF was stopped. No other patient required permanent drug withdrawal due to side effects [9]. In our study, we found that MMF was a well-tolerated drug with a mild reversible side effect profile. Only four (6%) had adverse side effects due to which the drug was stopped (one developed shingles, two had abdominal pain and one had arthralgia).

Our data substantiate other smaller retrospective data that MMF could be considered as a second-line agent after steroids; this should be confirmed with randomized controlled trials. We suggest that MMF could be tried before CNIs considering its similar efficiency and its lack of nephrotoxicity.

Conclusion

MMF is well tolerated and relatively effective as a second-line agent in treating steroid-sensitive NS, even when other second-line agents have been previously used.

These data concur with other smaller series in terms of efficacy and suggest that MMF is an appropriate medicine to add to the clinician's armamentarium for treating NS. We believe that a randomized controlled trial is needed to determine the role of MMF more precisely and in particular to compare and contrast all currently used second-line immunosuppressants.

Conflict of interest statement. None declared.

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