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ORIGINAL ARTICLE

Efficacy of mycophenolate treatment in adults with steroid-dependent/frequently relapsing idiopathic nephrotic syndrome

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Abstract

Background: This study assessed the efficacy of therapy with mycophenolate (MF) and reduced doses of steroids in adults with steroid-dependent/frequently relapsing idiopathic nephrotic syndrome (SD/FR-INS).

Methods: Twenty-nine nephrotic patients (including 16 males and 13 females; mean age: 40 years, range: 18–74) were treated. Starting doses of MF were 2000 mg/day for mofetil MF (1500 mg/day in one patient) or 1440 mg/day for sodium MF. The initial prednisone (PDN) dose was 10 mg/day in 14 patients, 5 mg/day in two patients and no steroids in one patient. In the remaining 12 patients, moderate initial doses of PDN were administered (mean: 23.7 mg/day, range: 15–40), tapering to 10 mg/day after 1 month.

Results: Nephrotic syndrome remission was achieved in 27/29 cases (93.1%) (25 complete, 2 partial). Two patients showed resistance to the prescribed schedule. The first cycle of MF therapy was concluded in 20 patients after a mean (range) of 16.9 months (12–49). Maintenance of remission was observed in 11 of these 20 cases (55%) after a mean follow-up of 32.8 months (12–108). In nine patients with nephrotic syndrome relapse after tapering of MF (MF dependency), the same MF-PDN schedule was restarted, leading again to remission in all nine. The remaining seven MF-sensitive patients are still receiving their first therapeutic cycle. To date, the mean time under therapy in the 27 MF-sensitive patients is 38 months (4–216). Regarding complications, only minor digestive disorders and a slight decrease in blood haemoglobin levels were observed in a few patients.

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Conclusions: MF plus reduced doses of PDN is an effective and well-tolerated therapy for adult SD/FR-INS. Though MF dependence is observed, its low toxicity could allow long periods of therapy if it is required to maintain nephrotic syndrome remission.

Key words: immunosuppresion, minimal change disease, mycophenolate mofetil, nephrotic syndrome, steroids

Introduction

The clinical problem of steroid dependency/frequent relapses in idiopathic nephrotic syndrome (SD/FR-INS) has been only partially resolved to date. While INS very often responds to steroids (80% in classic reports), up to 75% of responders have one or more episodes of relapsing disease when therapy is tapered [1, 2]. In these cases, alternatives to steroids are employed in order to avoid cumulative steroid toxicity. Among these, cyclophosphamide, cyclosporine and tacrolimus are the most frequently administered according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines [3]. Although these drugs are both effective and steroid sparing, dependence is frequently observed, which may once more lead to important undesirable side effects. Thus, further alternatives are sought to improve the efficacy/toxicity balance.

Mycophenolate (MF) therapy was added to the KDIGO 2012 recommendations for cases of relapsing INS showing intolerance or toxicity to classic immunosuppressive drugs. Available in two formulations, mofetil mycophenolate (MMF) and sodium mycophenolate (SMF), MF is transformed after its digestive absorption into mycophenolic acid, a selective and reversible inhibitor of inosine monophosphate dehydrogenase. The latter is needed for *de novo* synthesis of purines by lymphocytes, which, unlike other cells, are unable to use other salvage pathways to synthesize them. Therefore, MF exerts a specific and reversible cytostatic effect on lymphocytes; furthermore, it displays a low toxicity profile [4, 5].

MF has an established role as an immunosuppressive agent in renal transplantation [6] and has also been employed in the treatment of a variety of immunologic diseases, including systemic lupus erythematosus [7, 8] and Antineutrophil Cytoplasmatic Antibody (ANCA)-mediated vasculitis [9, 10]. In recent years, MF has been reported to be capable of inducing remission of SD/FR-INS in children [11, 12], but very little experience in adults has been reported [13].

Here, we report our retrospective experience regarding the use of MF in 29 adult patients with SD/FR-INS.

Materials and methods

Patients

Adult patients having a nephrotic syndrome relapse in the setting of SD/FR-INS.

Definitions

Definitions were based on the KDIGO 2012 guidelines [3]:

Idiopathic nephrotic syndrome: This diagnosis is applied to patients with nephrotic syndrome (pure in most cases) that is sensitive to steroid therapy and shows, in most cases, minimal change disease (MCD) on renal histopathology, but also mesangial proliferative glomerulonephropathy—with or without diffuse mesangial IgM deposits on immunofluorescence (IF) studies—or scarce lesions of focal segmental glomerulosclerosis (FSGS) [14, 15]. Slight mesangial IgA deposits have been described in rare cases in which no apparent clinical or evolutive differences from conventional INS were evident [16].

Complete remission of INS: Denotes the decrease in proteinuria after therapy to values lower than 300 mg/day or 200 mg/g creatinine, with subsequent normalization of serum albumin values.

Partial remission of INS: Indicates a reduction in proteinuria of 50% with absolute values higher than 300 mg/day or 200 mg/g creatinine, with normalization of serum albumin values in response to therapy.

Steroid dependent: Designates nephrotic syndrome that, after remission under steroid treatment, reappears during the tapering phase of treatment or within 2 weeks after discontinuation of therapy.

Frequent relapsers: Designates those patients who present two or more relapses within a period of 6 months.

Prior to MF-PDN therapies

All patients had received previous standard first-line therapy with prednisone (PDN) at 1 mg/kg/day over a minimum period of 1 month and, when remission was achieved, further slow tapering over a total period of up to 6 months, in accordance with the KDIGO 2012 guidelines. If a relapse occurred after tapering of the standard PDN schedule, a new course of steroid therapy was started at a dosage of 1 mg/kg/day with a further slower tapering phase and, in an empirical way, a low-moderate dosage (10–15 mg/day) of PDN was maintained for more than 6 months, until the moment at which a new tapering of the steroid dosage was implemented.

This 'long-term maintenance of low-moderate steroid dosage' has been the steroid schedule that we have most frequently employed in cases of repeated relapsers, before the introduction of MF for this disease.

In six patients, prior to MF, therapy had included conventional immunosuppressants (cyclophosphamide, $n = 3$; cyclosporine, $n = 3$), because of significant steroid toxicity (Cushing syndrome or diabetes) (See Tables 1–4).

MF-PDN therapeutic schedule

Patients who experienced SD/FR-INS were treated with a starting dose of 1000 mg/12 h for the MMF form or 720 mg/12 h for the SMF form. Concomitant medication with PDN was given at a dose of 10 mg/day. For the purposes of this study, moderate starting doses (up to 40 mg/day) of PDN were allowed and were tapered to 10 mg/day at the end of the first month of therapy. Diuretics and prophylactic heparin were administered according to the established criteria at each hospital.

Clinical controls

General biological parameters were monitored at routine visits, with special attention to daily proteinuria excretion and albumin, urea, creatinine, cholesterol and serum immunoglobulin levels in addition to haemoglobin and coagulation blood tests.

Duration of MF-PDN therapy

After nephrotic syndrome remission, MF was progressively reduced to a maintenance dose of 500 mg/12 h (MMF) or 360 mg/12 h (SMF). The duration of MF treatment was not predetermined, but treatment for at least 12 months was mandatory

Table 1. Patients in complete remission with therapy and no posterior relapse

Cases	Gender/age (years)	Pathologic diagnosis	Urine protein (g/day)	Previous IS	Starting MMF or SMF dose (mg/day)	Starting PDN dose (mg/day)	Complete remission with MF-PDN	Duration of first MF-PDN cycle (months)	First MF cycle was ended?	PDN dose (mg/day)	Relapse	Time in remission after MF withdrawal (months)	Remission in last control
1	F/ 39	MCD	5.1	No	1440[a]	10	Yes	12	Yes	0	NO	18	Yes
2	F/55	MCD + IgA	3.8	No	2000	15	Yes	15	Yes	0	NO	108	Yes
3	M/72	FSGS	4.3	No	1440[a]	30	Yes	49	Yes	0	NO	12	Yes
4	F/34	Mes. IgM[b]	3.2	No	2000	20	Yes	12	Yes	0	NO	20	Yes
5	F/26	MCD	5.9	No	2000	20	Yes	18	Yes	0	NO	20	Yes
6	M/41	MCD	4.7	No	1440[a]	10	Yes	12	Yes	5	NO	12	Yes
7	F/35	MCD	4.6	No	2000	20	Yes	18	Yes	0	NO	15	Yes
8	F/37	FSGS	3.8	No	2000	20	Yes	12	Yes	10	NO	12	Yes
9	F/68	MCD	3.7	No	1440[a]	10	Yes	19	Yes	0	NO	43	Yes
10	F/50	Mes. NegIF[c]	3.1	No	1440[a]	10	Yes	36	Yes	0	NO	76	Yes
11	F/31	MCD	5.1	No	1440[a]	20	Yes	14	Yes	0	NO	25	Yes

[a]SMF.
[b]Mes. Immunoglobulin M (IgM): mesangial proliferative Glomerulonephritis (GN) with diffuse IgM deposits in immunofluorescence.
[c]Mes. Neg.Immunofluorescence (IF): mesangial proliferative GN without deposits in immunofluorescence.
IS: immunosuppression.

Table 2. Patients in complete remission with therapy, followed by posterior relapse/MF dependence

Cases	Gender/ age (years)	Pathologic diagnosis	Urine protein (g/day)	Previous IS	Starting MMF or SMF dose (mg/day)	Starting PDN dose (mg/day)	Complete remission with MF-PDN	Duration of first MF-PDN cycle (months)	First MF cycle was ended?	PDN dose (mg/day)	Relapse	Restarted MF-PDN	Second complete remission	MF dependence	Total time under MF-PDN (months)	Remission in last control
12	F/40	Mes. NegIF[a]	4.3	No	2000	10	Yes	12	Yes	0	Yes	Yes	Yes	Yes	216	Yes
13	M/27	Mes. NegIF[a]	3.8	CYC	2000	10	Yes	12	Yes	0	Yes	Yes	Yes	Yes	72	Yes
14	M/20	FSGS	3.3	CsA	2000	20	Yes	12	Yes	10	Yes	Yes	Yes	Yes	72	Yes
15	F/40	MCD	3.9	No	2000	10	Yes	16	Yes	10	Yes	Yes	Yes	Yes	48	Yes
16	M/18	MCD	4.7	CsA	2000	10	Yes	12	Yes	10	Yes	Yes	Yes	Yes	36	Yes
17	M/76	FSGS	4.4	No	2000	10	Yes	16	Yes	10	Yes	Yes	Yes	Yes	30	Yes
18	M/26	Mes. NegIF[a]	3.8	No	1440[b]	10	Yes	15	Yes	10	Yes	Yes	Yes	Yes	27	Yes
19	F/59	MCD	3.9	No	1440[b]	10	Yes	15	Yes	10	Yes	Yes	Yes	Yes	48	Yes
20	M/28	MCD	5.7	CYC	1440[b]	10	Yes	12	Yes	10	Yes	Yes	Yes	Yes	31	Yes

[a]Mes. NegIF: mesangial proliferative GN with no deposits in IF; FSGS, cFocal and Segmental Glomerulosclerosis; CYC, dCyclophosphamide.
[b]SMF.
IS: immunosuppression.

Table 3. Patients sensitive to therapy that remains under its first MF-PDN cycle

Case	Gender/age (years)	Pathologic diagnosis	Urine protein (g/d)	Previous IS	Starting MMF or SMF dose (mg/day)	Starting PDN dose (mg/day)	Complete remission with MF-PDN	Time under first MF-PDN cycle (months)	First MF cycle was ended?	PDN dose (mg/day)	Remission in last control
21	M/ 73	MCD	3.8	No	2000	20	Yes	8	No	10	Yes
22	M/30	MCD	4.7	No	1500	5	Yes	4	No	5	Yes
23	M/37	MCD	3.9	CYC	2000	40	Yes	17	No	0	Yes
24	M/20	MCD	5.7	No	1440[a]	0	Yes	14	No	0	Yes
25	M/30	MCD	5.5	No	1440[a]	5	Yes	48	No	0	Yes

[a]SMF.
IS: immunosuppression.

Table 4. Patients in partial remission or resistance in front of MF-PDN therapy

Case	Gender/age (years)	Pathologic diagnosis	Urine protein (gr/day)	Previous IS	Starting MMF or SMF dose (mg/day)	Starting PDN dose (mg/day)	Response to therapy	Time under first MF-PDN cycle (months)	First MF cycle was ended?	Maintenance PDN dose (mg/day)	Remission in last control
26	M/48	Mes. IgM[a]	5.5	No	2000	10	Partial remission	60	Yes	0	Yes
27	M/48	MCD	3.7	No	1440[b]	10	Partial remission	79	No	5	Yes
28	F/24	FSGS	3.2	No	2000	30	Resistance	8	Yes	0	No
29	M/40	MCD	3.9	CsA	1440[b]	30	Resistance	5	Yes	0	No

[a]Mes. IgM: mesangial proliferative GN with diffuse IgM deposits in immunofluorescence.
[b]SMF.
IS: immunosuppression.

before its withdrawal. Further progressive reduction in the MF dose was implemented before discontinuation. The duration of administration of the maintenance dose of PDN (10 mg/day) was similarly not predetermined. If a relapse occurred, the initial MF-PDN schedule was restarted. If no response to therapy was observed within 5–8 months, MF and PDN were withdrawn.

Results

Patients

The patient population comprised 29 adult nephrotic patients diagnosed with SD/FR-INS at five nephrology units in the Barcelona and Girona areas. Sixteen patients were males and 13 were females, and their mean age was 40 years (range: 18–74 years).

All 29 patients included here were in nephrotic syndrome relapse, with normal serum levels of creatinine (70–90 μmol/L). The mean time since the initial diagnosis of nephrotic syndrome was 96 months (range: 16–228 months), indicating a long period of relapsing disease in most patients. Renal biopsy, performed upon appearance of renal disease (several months or years before MF therapy in all cases) showed MCD in 17 cases and mesangial proliferative GN in six cases, including two with diffuse mesangial IgM deposits on IF studies and four with no deposits on IF. Five patients showed scarce lesions (in $<$20% of glomeruli) of FSGS and one case presented slight diffuse mesangial Immunoglobulin A (IgA) deposits on IF studies, with minor mesangial proliferative lesions visible on light microscopy (see Tables 1, 2 and 4).

Therapeutic MF-PDN schedule

Fourteen patients received MMF at a starting dosage of 1000 mg/12 h, and one case received 750 mg/12 h. The remaining 14 patients received SMF at a dosage of 720 mg/12 h.

The initial PDN dosage was 10 mg/day in 14 patients, 5 mg/day in 2 patients and no steroids in 1 patient. In the remaining 12 patients, moderate initial doses of PDN were administered (mean: 23.7 mg, range: 15–40) and tapered to 10 mg/day after 1 month.

Clinical response

'Complete remission' was achieved in 25 of the 29 cases (86.2%) (see Figure 1 and Tables 1–3: Cases 1 to 25).

'Partial remission' was observed in two patients (Table 3, Cases 26 and 27). Both had shown complete remission with only PDN in the previous therapeutic cycle, with histologic diagnosis of MCD. Patient 26 had developed diabetes during his previous steroid therapy, and a possible diabetic glomerulopathy component may have been the cause of the non-severe residual proteinuria (1.1 g/day). Patient 27 had, prior to the nephrotic syndrome, a clinical profile compatible with 'benign' nephrosclerosis, (i.e. overweight, hyperlipidaemia and essential hypertension), which could explain his residual proteinuria (0.8 g/day).

'Lack of clinical response to therapy (MF-PDN resistance)' was observed in two patients (Cases 28 and 29) after 8 and 5 months of therapy, respectively. One of them had responded only partially to a previous PDN-cyclosporine schedule, having histologic diagnosis of FSGS. The second resistant case was in a patient who had shown complete remission in response to PDN during the previous therapeutic cycle, with histologic diagnosis of MCD. No repeat biopsy was performed.

No relation appeared to exist between clinical response to MF therapy for nephrotic syndrome relapse and histologic diagnosis at the time of the first episode of renal disease. Furthermore, in some cases, the renal lesions may have changed during the months or years of clinical follow-up.

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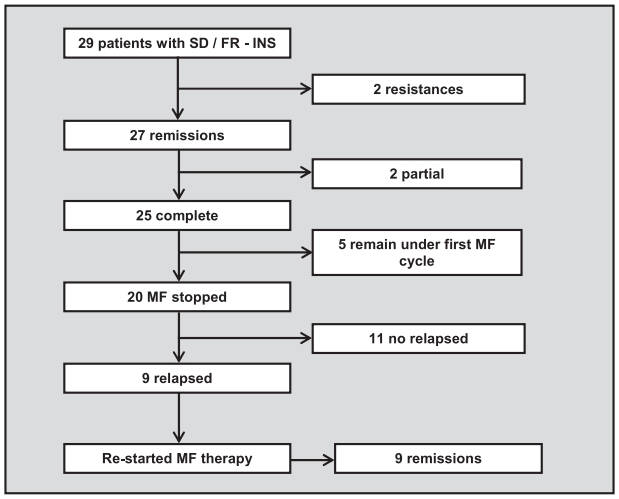

Fig. 1. Schema of clinical outcome after MF-PDN therapy in 29 adult patients diagnosed of SD/FR-INS.

Termination of the first MF cycle

The first MF cycle was terminated in 20 sensitive patients (Cases 1–20) after a mean of 16.9 months (range: 12–49). The remaining seven MF sensitive patients are currently still receiving their first therapeutic cycle.

In the two resistant cases (nos. 28 and 29), MF and PDN were stopped after 5 and 8 months of therapy, respectively.

Therapy has also been terminated in Case 26 (presenting partial remission) due to an intercurrent problem (a diagnosis of colorectal carcinoma, see below: 'Adverse events' and 'Discussion' sections).

Clinical outcome after MF withdrawal

Maintenance of remission was observed post-MF withdrawal in 11 out of 20 cases (55%) after a mean follow-up of 32.8 months (range: 12–108 months; Table 1, Cases 1–11). Nine of them now receive no drug treatment while two are receiving 5 and 10 mg/day of PDN, respectively. Nephrotic syndrome relapse after MF discontinuation (MF dependency) occurred in 9 of the 20 cases (45%). In these cases, the same MF-PDN schedule was restarted and remission was again observed in all patients (see Figure 1 and Table 2, Cases 12–20).

The clinical outcome of the two MF-PDN-resistant patients was the following: Case 28 (a 24-year-old female with steroid-dependent Focal and Segmental Glomerulosclerosis (FSGS)) and Case 29 (a 40-year-old male with steroid-dependent and Cyclosporine A (CsA)-dependent MCD) received further therapy with tacrolimus at doses of 1 mg/12 h plus 10 mg/day of PDN. In both cases, a decrease in proteinuria but no remission of nephrotic syndrome was observed. Overall, all treated patients maintained normal serum creatinine (70–90 μmol/L) levels during clinical follow-up.

Time under therapy

Until the time of data analysis for this study, the mean time for which the 27 sensitive patients had been receiving therapy was 38 months, ranging between 4 months in a patient who had just started therapy (Table 3, Case 22) and 216 months in one patient in therapy who experienced multiple relapses following attempts to taper MF but is currently in complete remission without any treatment (Table 2, Case 12).

Adverse events

Assessment of intolerance and toxicity data identified only minor digestive disorders (abdominal pain and/or soft faeces) in four patients; this improved after modifying the MF schedule from twice to thrice daily administration. No cases of leucopaenia or significant infectious episodes were registered. Slight decreases in blood haemoglobin levels were observed in some patients (data not shown).

One male patient aged 48 years who developed diabetes during first-line steroid therapy for INS subsequently progressed to the SD/FR form (Case 26). Upon starting MF (without associated steroids), he responded partially, presenting multiple relapses following attempts to taper MF therapy. After 60 months of discontinued MF monotherapy, he was diagnosed with a colorectal carcinoma, and MF was stopped. The patient remained in nephrotic partial remission 6 months later and is under oncologic therapy.

Discussion

Dependency or frequent relapses after steroid therapy, alone or in combination with cyclophosphamide or calcineurin inhibitors (CNI), continues to represent a significant problem in patients with INS. Nephrotic relapse is a grave clinical situation that must be quickly reversed, given the metabolic and renal consequences and the thromboembolic and immunologic risks. Furthermore, the reintroduction of these standard therapies in response to recurrences entails a risk of severe adverse effects, including, most importantly, diabetes and cardiovascular disturbances in the case of steroid therapy, bone-marrow depression and carcinogenicity in the case of cyclophosphamide and hypertension or renal failure in the case of CNI. Thus, more effective and safer therapies are needed.

MF is an immunosuppressive drug that exerts a specific and reversible cytostatic effect on lymphocytes, having the additional advantage of a low toxic profile. This drug has an established role in solid organ transplantation [6] and has also been employed in the treatment of a variety of immunologic diseases such as systemic lupus erythematosus [7, 8] and ANCA-mediated vasculitis [9, 10]. In recent years, MF has been reported to be able to induce remission of SD/FR-INS in children [11, 12], though experience in adult patients is limited [13].

Here, we have reported on our experience in the use of MF and low doses of steroids in 29 nephrotic adult patients diagnosed as having SD/FR-INS. The results suggest that MF is effective and safe when applied to this renal disease.

Twenty-seven patients (93.1%) showed nephrotic remission (complete in 25 and partial in two patients: a diabetic and a previously hypertensive patient who showed mild proteinuria after therapy).

The first therapeutic MF-PDN cycle was terminated in 20 patients after a mean of 16.9 months under therapy. Unfortunately, in line with findings in children treated with MF, nephrotic syndrome relapse after drug discontinuation was observed in almost half of our MF-sensitive patients (MF dependence), including some in whom 5–10 mg/day was retained with the aim of avoiding relapse. Nevertheless, in these MF-dependent cases, a new remission was achieved when the drug was restarted. Overall, up to the last control, MF-sensitive patients had remained on this therapy for a mean of 38 months, and in many cases, this maintenance or chronic phase of therapy did not include steroids. Therefore, the chronic use of MF in SD/FR-INS seems to be of value. In fact, the KDIGO

2012 guidelines advise the use of MF in this clinical setting for 1–2 years [3].

The only registered adverse events were minor digestive disorders (abdominal pain or soft faeces) in four patients; however, it is difficult to assess the true prevalence of adverse events in a retrospective study such as this. In any case, symptoms improved after the MF schedule was modified from twice to thrice daily administration.

In one diabetic, 48-year-old, MF-dependent patient who had suffered multiple relapses of nephrotic syndrome, a colorectal carcinoma was diagnosed after 5 years of discontinued MF monotherapy. We have considered the possibility that MCD revealed the existence of a 'hidden' carcinoma as described [17–19], although in our case, the renal diagnosis would have preceded that of neoplasia by almost 6 years. Another possibility is that the appearance of the neoplastic disease was related to prolonged administration of immunosuppressive therapy, as has also been described [20]. Nevertheless, this association has most frequently been observed in the field of solid organ transplantation, in which the possible carcinogenic effects individual agents are difficult to assess because most patients are treated with a combination of different drugs, resulting in further severe immunosuppression. In this setting, post-transplant lymphoproliferative disorders and skin cancers are more prevalent. Diverse prospective registry-based observational cohort studies have demonstrated that MF is not associated with an increased risk of malignancies in renal transplant patients and may even be associated with a lower risk in some populations when compared with no-MF groups [21, 22]. Reported data indicate that the incidence of colorectal cancer after immunosuppression in patients undergoing solid organ transplantation is 0.25%, which is similar to the incidence in immunocompetent individuals of corresponding age [23]. Furthermore, it has been reported that the incidence of colorectal cancer was not elevated in kidney recipients treated with tacrolimus and MF [24]. Consequently, while an influence of MF on the development of the malignancy in our patient could not be absolutely excluded, this seems unlikely.

In recent years, another immunosuppressive therapy that has been proposed for diverse immune-mediated diseases and also for SD/FR-INS is rituximab (RTX), a B-cell-depleting monoclonal antibody that targets CD20 [25]. This drug induces nephrotic remission in many of these patients as well, and its effect can persist over months, although nephrotic relapses are also frequently described, in some instances coinciding with B-cell population recovery [26]. Predictive factors for response, long-term outcomes and tolerance of RTX in patients with SD/FR-INS are under study [26, 27].

This work has the limitations of a retrospective study. The low incidence of INS in adult patients made it necessary to combine data from five nephrology units in our geographic area in order to analyse the role of MF in this disease.

In conclusion, pending further experience with MF or better therapeutic options, it can be considered that MF therapy in combination with reduced doses of steroids offers good effectiveness in adult SD/FR-INS patients. Furthermore, given its low toxicity profile, prolonged MF therapy seems feasible in cases of dependence on this drug.

Conflict of interest statement

None declared.

References

1. Hogan J, Radhakrishnan J. The treatment of minimal change disease in adults. *J Am Soc Nephrol* 2013; 24: 702–711
2. Canetta PA, Radhakrishnan J. The evidence-based approach to adult-onset idiopathic nephrotic syndrome. *Front Pediatr* 2015; 3: 1–8
3. Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 139–274
4. Ransom JT. Mechanism of action of mycophenolate mofetil. *Ther Drug Monit* 1995; 17: 681–684
5. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). *Clin Transplant* 1996; 10: 77–84
6. Halloran P, Mathew T, Tomlanovich S *et al*. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double blind, clinical studies in prevention of rejection. *Transplantation* 1997; 6: 39–47
7. Zhu B, Chen N, Lin Y *et al*. Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2007; 22: 1933–1942
8. Henderson L, Masson P, Craig JC *et al*. Treatment for lupus nephritis. *Cochrane Database Syst Rev* 2012; 12: CD002922
9. Silva F, Specks U, Kalra S *et al*. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement–a prospective, open-label pilot trial. *Clin J Am Soc Nephrol* 2010; 5: 445–453
10. Draibe J, Poveda R, Fulladosa X *et al*. Use of mycophenolate in ANCA-associated renal vasculitis: 13 years of experience at a university hospital. *Nephrol Dial Transplant* 2015; 30 (Suppl 1): i132–i137
11. Baudouin V, Alberti C, Lapeyraque AL *et al*. Mycophenolate mofetil for steroid-dependent nephrotic syndrome: a phase II Bayesian trial. *Pediatr Nephrol* 2012; 27: 389–396
12. Afzal K, Bagga A, Menon S *et al*. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2007; 22: 2059–2065
13. Day CJ, Cockwell P, Lipkin GW *et al*. Mycophenolate mofetil in the treatment of resistant idiopathic nephrotic syndrome. *Nephrol Dial Transplant* 2002; 17: 2011–2013
14. A Report of the International Study of Kidney Disease in Children. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. *Kidney Int* 1981; 20: 765–771
15. Trachtman H, Carroll F, Phadke K *et al*. Paucity of minimal-change lesion in children with early frequently relapsing steroid-responsive nephrotic syndrome. *Am J Nephrol* 1987; 7: 13–17
16. Lai KN, Lai FM, Chan KW *et al*. An overlapping syndrome of IgA nephropathy and lipoid nephrosis. *Am J Clin Pathol* 1986; 86: 716–723
17. Gandini E, Allaria P, Castiglioni A *et al*. Minimal change nephrotic syndrome with cecum adenocarcinoma. *Clin Nephrol* 1996; 45: 268–270
18. Martinez-Vea A, Panisello JM, García C *et al*. Minimal-change glomerulopathy and carcinoma. Report of two cases and review of the literature. *Am J Nephrol* 1993; 13: 69–72
19. Meyrier A, Delahousse M, Callard P *et al*. Minimal change nephrotic syndrome revealing solid tumors. *Nephron* 1992; 61: 220–223

20. Vial T, Descotes J. Immunosuppressive drugs and cancer. *Toxicology* 2003; 185: 229–240
21. Dantal J, Pohanka E. Malignancies in renal transplantation: an unmet medical need. *Nephrol Dial Transplant* 2007; 22 (Suppl 1): i4–i10
22. Robson R, Cecka JM, Opelz G *et al*. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. *Am J Transplant* 2005; 5: 2954–2960
23. Aigner F, Boeckle E, Albright J *et al*. Malignancies of the colorectum and anus in solid organ recipients. *Transplant* 2007; 20: 497–504
24. Safaeian M, Robbins HA, Berndt SI *et al*. Risk of colorectal cancer after solid organ transplantation in the United States. *Am J Transplant* 2016; 16: 960–967
25. Evans R, Salama AD. Update on rituximab: an established treatment for all immune-mediated kidney diseases? *Nephron Clin Pract* 2014; 126: 97–109
26. Bruchfeld A, Benedek S, Hilderman M *et al*. Rituximab for minimal change disease in adults: long-term follow-up. *Nephrol Dial Transplant* 2014; 29: 851–856
27. Guitard J, Hebral AL, Fakhouri F *et al*. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. *Nephrol Dial Transplant* 2014; 29: 2084–2091

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