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Clinical experience with mycophenolate mofetil in systemic autoimmune conditions refractory to common immunosuppressive therapies

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Summary

Objectives: Standard therapies against inflammatory rheumatic diseases consist of immunosuppressive drugs with high toxicities and many side-effects. Except in the treatment of systemic lupus erythematosus with renal involvement, controlled studies with mycophenolate mofetil (MMF) are lacking in other autoimmune and inflammatory systemic diseases. Here we describe our clinical experience with MMF in several unusual indications.

Methods: We collected data including serological findings, adverse events and response to treatment in eleven patients with autoimmune diseases including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), polymyositis (PM), diffuse systemic sclerosis that were treated in our rheumatology unit.

Results: Our results show remission in ten patients with minimal side effects and reduced prednisone dosage. The median dose of MMF was 2 g per day. Adverse events were limited, with one case of leucopenia, one tachycardia and one colitis. One patient definitively stopped the treatment because of side effects.

Conclusions: MMF seems to be a very powerful and attractive alternative medication in the treatment of immune-mediated inflammatory diseases. The good tolerance and safety profile makes it an excellent therapeutic option permitting a global reduction of corticosteroids doses.

Key words: mycophenolate mofetil; immunosuppressant; autoimmune rheumatic diseases

Introduction

Mycophenolate mofetil (MMF, Cellcept®) is an immunosuppressive drug used in organ transplantation with the aim of reducing acute rejection episodes. Mycophenolate mofetil has immunomodulating effects by inhibiting de novo purine synthesis, which leads to decreased proliferation of activated lymphocytes, thus resulting in reduction of antibody production, changes in the recruitment and induction of apoptosis [1].

More recently, MMF has also been used as a novel therapy for systemic lupus erythematosus (SLE) with renal involvement [2, 3], essentially in refractory cases and patients intolerant to conventional immunosuppressive regimens [4–6]. In addition, some studies reported encouraging results regarding MMF as an alternative therapy for treating SLE with and without renal involvement as well as other immune-mediated rheumatologic diseases such as polymyositis, systemic vasculitis and autoimmune haemolytic anaemia [7–12]. However, the literature supporting the efficacy of MMF in the treatment of inflammatory rheumatic diseases is scarce, with only few prospective studies and case reports. Therefore, we decided to collect and describe our clinical experience on all patients with different immune-mediated rheumatic diseases treated with MMF, and to compare our results with a review of the literature.

No conflict of interest to declare.

Patients and methods

We retrospectively studied eleven consecutive patients with inflammatory rheumatic diseases who were followed in our unit from the start of MMF treatment until December 2007, and who received at least one dose of MMF. All data were collected from clinical chart reviews and interviews with the different specialists involved in the follow up of the patients.

The diagnosis of SLE was based on the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE [13]. The diagnosis of polymyositis was based upon the criteria of Bohan and Peter [14, 15]. The diagnosis of mixed connective tissue disease (MCTD) was established according to Alarcon-Segovia's criteria using serologic (anti-RNP antibodies) and clinical findings [16]. We have used the ACR criteria for the diagnosis of systemic sclerosis [17].

All the data included details regarding initial presentation and global evolution of disease activity up to December 2007. We documented all the treatments prior to the introduction of MMF as well as concomitant treatments in combination with MMF. We examined all significant changes following the initiation of MMF. Patient's records were also studied for details on the occurrence of adverse events. We also collected laboratory results on autoantibody tests. Similarly to previous studies, we operationally defined a successful therapeutic response as a complete resolution of clinical symptoms, a normalisation of biological markers of inflammation and a reduction of concomitant anti-rheumatic therapies particularly corticosteroids.

Autoantibody determinations were performed in the Clinical Immunology and Allergy Laboratory of the Geneva University Hospitals. Anti-nuclear antibody (ANA) detection was performed by indirect immunofluorescence (IFI) technique using Hep-2 substrate slides and FITC anti-human IgG conjugates (Nova Lite™ Inova Diagnostics, San Diego, USA). Anti-neutrophil cytoplasmic antibody (ANCA) detection was performed by IFI technique using ethanol-fixed human neutrophil and formalin-fixed human neutrophil substrate slides and FTIC anti-human IgG conjugate (Nova Lite™ Inova Diagnostics). Anti-double-stranded DNA antibody detection was performed by IFI technique using Crithidia luciliae slides and FTIC anti-human IgG conjugate (Nova Lite™ Inova Diagnostics). Anti-nucleoproteins detection and quantification were performed using specific ELISA kits (Quanta Lite™ ENA 6, Inova Diagnostics; Quanta Lite™ SS-A / SS-B / RNP / Sm / Jo-1 / Scl-70). Anti-MPO and PR3 detection and quantification were performed using specific ELISA kits (Quanta Lite™ MPO / PR3, Inova Diagnostics).

Results

Patient description

Nine of the eleven patients were female and the median age was 41 years (range 16–68) at the time of MMF initiation. The following diseases were treated with MMF and reviewed in this article: SLE (six patients), polymyositis (two patients), MCTD (two patients), systemic sclerosis (one patient). The median disease duration before the start of MMF was 38 months (rang 17–114), the median age at time of diagnosis was 36 years (range 13–63). In table 1 we describe the list of previous treatments and disease characteristics.

All diagnoses were already established at the start of MMF therapy. One patient with SLE had concomitant psoriatic arthritis, a further SLE patient also suffered from multiple sclerosis and a third SLE case exhibited features of Evans syndrome, including the combination of autoimmune haemolytic anaemia and thrombocytopenia. All these concomitant manifestations were present before the start of MMF therapy.

Previous treatments

Patients received a median of three anti-inflammatory or immunosuppressive drugs (range from two to five drugs) to treat their respective diseases, including prednisone, colchicine, methotrexate, azathioprine, cyclosporin A, cyclophosphamide, hydroxychloroquine, intravenous immunoglobulins, interferon beta, etanercept, infliximab, and rituximab (see details in table 1). Among the six SLE patients, MMF was initiated because of incomplete or poor response to previous treatments in four cases, whereas the two others promptly received MMF because of the presence of renal involvement. Two patients with polymyositis had refractory active disease despite a combination of prednisone and methotrexate. Two MCTD patients had inadequate disease control despite immunosuppressive treatment and, in addition, one of them had to stop azathioprine as a consequence of digestive intolerance. Azathioprine was discontinued in the patient with systemic sclerosis because of cutaneous allergy.

MMF treatment

The dosages of MMF, treatment duration and clinical evolution are shown in table 2. The median daily dose of MMF was 2 g (range 1–3 g) and median treatment duration was 29 months (range 4–67). Patients took a median of two concomitant medications (range 1–3).

Follow-up

Among the six patients with SLE, three had renal involvement. Other manifestations included psoriatic arthritis, multiple sclerosis, Evans syndrome and more classical lupus symptoms such as alopecia, fever or aphtosis. The SLE disease activity index (SLEDAI) [18] was determined according to clinical and biological manifestations before the start of MMF and ranged from 12 to 21 (median = 17). The median prednisone dosage was 37.5 mg (range 10–60). The median MMF treat-

Table 1

Baseline data.

Case no	Diagnosis	Date of diagnosis	Age at time of diagnosis (years)	Sex	Initial manifestations	Autoantibodies	Previous treatments*	Prednisone dosage before MMF start (mg/d)	Other clinical/ biological parameters measured before MMF start	Indication for MMF treatment
1	SLE	2001	37	F	Arthralgia, aphtosis, cutaneous vasculitis, GN	ANA + Anti-dsDNA +	MTX PDN	15	SLEDAI = 20	Polyarthralgia, aphtosis, vasculitis, GN
2	Polymyositis	2003	56	F	Asthenia, weakness, arthralgia, erythema	ANA + Anti-SSA + Anti-Jo1 +	MTX PDN RTX	10	CK 1587 (U/L)	Active myositis
3	MCTD	2005	33	F	Synovitis, myalgia, livedo	ANA + Anti-U1-RNP +	PDN HCQ MTX-AZA INF	20	CK 1184 (U/L)	Asthenia, myalgia, arthralgia
4	Diffuse systemic sclerosis	2003	63	F	Raynaud, cutaneous ulcers, diffuse scleroderma	ANA +	AZA PDN	20	Diffuse skin involvement, no other organ involvement	AZA allergy
5	SLE + psoriatic arthritis	2004	30	M	Arthritis	ANA + Anti-dsDNA +	PDN MTX ETN	10	SLEDAI = 21	Arthralgia, GN
6	SLE + multiple sclerosis	2005	41	F	Asthenia, arthralgia	ANA + Anti-dsDNA + Anti-U1-RNP +	PDN IFN-β	30	SLEDAI = 16	Active polyarthritis, serositis and digital necrosis
7	SLE + Evans syndrome	1999	13	F	Polyarthritis, asthenia, headache, anemia, thrombocytopenia	ANA + Anti-dsDNA + Anti-U1-RNP +	PDN AZA-HCQ	50	SLEDAI = 17	Evans syndrome, polyarthralgia
8	MCTD	2002	28	F	Myositis, asthenia, scleroderma	ANA + Anti-U1-RNP +	CYC PDN	20	CK 1220 (U/L)	Myositis, dyspnea, asthenia
9	Polymyositis	1993	54	M	Weakness, myositis	ANA +	PDN AZA-MTX-CSA IVIg	15	CK 600 (U/L)	Active myositis
10	SLE	2002	26	F	Asthenia, arthralgia, rash, GN	ANA + Anti-dsDNA +	PDN HCQ NSAID	60	SLEDAI = 16	Arthralgia, GN
11	SLE	2005	13	F	Arthralgia, alopecia, aphtosis	ANA + Anti-dsDNA +	PDN HCQ MTX	60	SLEDAI = 12	Arthralgia, alopecia, fever

ANA: antinuclear antibodies; anti-ds DNA: anti-double stranded DNA; AZA: azathioprine; CK normal range: 47–222 U/L; CSA: cyclosporin A; CYC: cyclophosphamide; ETN: etanercept; GN: glomerulonephritis; HCQ: hydroxychloroquine; IFN-β: interferon beta; INF: infliximab; IVIg: intravenous immunoglobulins; MCTD: mixed connective tissue disease; MMF: mycophenolate mofetil; MTX: methotrexate; NSAID: non steroidal anti inflammatory drug; PDN: prednisone; RTX: rituximab; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

* treatments were frequently combined

ment duration was 30 months (range 4–67) up to December 2007. At the last follow-up visit all patients exhibited clinical and biological signs of improvement. The median SLEDAI score was 4 (range 0–7). In addition the dosage of prednisone could be reduced in five of six patients to values under 10 mg/day (mean 6 mg, range 0–20).

The two patients with polymyositis exhibited clinical and biological signs of active disease prior to starting therapy with MMF. CK values were 1587 (U/L) and 600 (U/L), respectively. At the end of the follow-up period both patients achieved total remission, the CK values dropped to 82 and 142 (U/L) and prednisone dosages to 15 and 2.5 mg per day, respectively.

In the two cases of MCTD, one patient had severe and refractory disease that did not respond to previous treatment with methotrexate, azathioprine, hydroxychloroquine, or concomitant immunotherapy with infliximab. Remission was only achieved when the MMF dosage reached 2 g/d. In addition, CK levels decreased from 1184 (U/L) to 238 (U/L) after one year. The other patient with MCTD had symptoms of dyspnoea, asthenia and myalgia with elevated CK levels reaching 1220 (U/L) at the start of the MMF treatment. After

Table 2
Follow-up data.

Case no	MMF treatment initiation	MMF dosage (g/d)	Other concomitant treatments	MMF total treatment duration (month)	MMF side effects	Prednisone dosage at the end of the follow-up (mg/d)	Other clinical/ biological parameters measured at the end of the follow-up
1	06/2004	3	PDN MTX RTX	43	None	2.5	SLEDAI = 6
2	06/2005	2	PDN MTX	22 + 5 (stopped in April 07 and started again in August 07)	Diarrhea, colitis	15	CK 82 (U/L)
3	07/2006	2	PDN MTX RTX - INF	18	Transient leucopenia	0	CK 238 (U/L)
4	06/2005	2	PDN	4 (stopped in October 05)	Tachycardia	5	/
5	11/2006	1.5	PDN ETN	14	None	5	SLEDAI = 7
6	07/2006	3	PDN IFN-β	18	None	20	SLEDAI = 4
7	07/2006	1	PDN RTX	18	None	3	SLEDAI = 2
8	03/2004	2	PDN	46	None	10	CK 174 (U/L)
9	06/2002	2	PDN IVIg	67	None	2.5	CK 142 (U/L)
10	10/2002	2	PDN HCQ	63	None	0	SLEDAI = 2
11	10/2007	1	PDN HCQ	7	None	5	SLEDAI = 4

CK normal range: 47–222 (U/L); ETN: etanercept; HCQ: hydroxychloroquine; IFN-β: interferon beta; INF: infliximab; IVIg: intravenous immunoglobulins; MMF: mycophenolate mofetil; MTX: methotrexate; PDN: prednisone; RTX: rituximab; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

one year of therapy, we observed an improvement in clinical and biological parameters (CK levels at 174 U/L) allowing the prednisone dosage to be reduced from 20 to 10 mg daily. MMF treatment was prescribed to one patient with diffuse systemic sclerosis who had no organ involvement. However, MMF had to be stopped four months later due to symptomatic tachyarrhythmia confirmed by 24h-Holter measurement and attributed to the medication. Cardiological investigations including echocardiography, thyroid hormone dosage and specialist consultation were normal and reassuring. The arrhythmia resolved after treatment discontinuation. Her condition remained stable on low dose prednisone.

Side effects

One patient with polymyositis developed active colitis with major weight loss 22 months after starting MMF leading to treatment discontinuation and resolution of digestive symptoms. However, the polymyositis relapsed after four months and MMF therapy was resumed with good clinical response and no intestinal problems after a follow-up of ten months. One patient had transient leucopenia that resolved without treatment discontinuation.

Discussion

Mycophenolate mofetil is an immunosuppressant used since the early nineties to reduce the occurrence of allograft rejection in renal transplantation. More recently it has also been prescribed to induce and maintain remission of severe lupus nephritis and thereafter to treat various other immune-mediated inflammatory diseases. In our case review, we observed that MMF alone or in combination with other immunosuppressive therapies was effective in controlling disease activity in patients with SLE, MCTD, and polymyositis. Furthermore, MMF was generally well tolerated and adverse events were relatively mild and reversible. These encouraging findings further suggest that MMF may be very useful in the treatment of connective tissue diseases refrac-

tory to other treatments or requiring more toxic medications such as cyclophosphamide. All the patients were followed in the same centre and considerations whether the treatment was useful were based upon global evaluation from the physicians confirmed by biological parameters. In all the patients who responded favourably to MMF therapy we also noticed that the dosage of corticosteroids was progressively tapered, suggesting a possible steroid sparing effect of MMF.

The beneficial effect of MMF in the treatment of lupus nephritis has been reported in randomised controlled clinical trials in comparison with cyclophosphamide [2, 19]. In their review concerning 86 patients with SLE, Pisoni et al found a substantial benefit of using MMF on the reduction of steroid dosage as well as on clinical and biological markers of disease activity, including ECLAM, erythrocyte sedimentation rate, and anti-double stranded DNA antibody titre in SLE patients with renal involvement or refractory disease activity [4]. In addition, some studies in SLE patients suggested that MMF is effective in controlling non-renal manifestations. Gaubitz et al showed significant improvement in ten patients with moderate and severe SLE after three months of MMF [6]. Furthermore, the clinical benefit on skin erythema, musculoskeletal symptoms, and cytopenia persisted up to 16 months leading to a reduction in steroid dosage. Karim et al reported encouraging results in 21 refractory SLE patients with clear benefit on disease activity allowing a significant reduction of oral corticosteroid doses with minimal side-effects [5]. In contrast, Pisoni et al reported poor results in their review of seven patients with skin manifestations refractory to multiple treatments [20].

Considering the use of MMF in other immune-mediated rheumatologic diseases, promising results were observed in the control of idiopathic inflammatory myopathy in a small prospective study [8]. Six of seven patients had a marked improvement of muscle weakness and all of them demonstrated an impressive response regarding serum levels of muscle enzymes as well as a reduction in prednisone dosage. Similarly, there are other reports of significant improvement in patients with severe refractory polymyositis treated with MMF [21]. These results are consistent with our observation. Furthermore, MMF discontinuation in one of our polymyositis patient resulted in a disease flare despite treatment with methotrexate (15 mg weekly) suggesting that MMF played a critical role in maintaining the remission. In a small prospective open-label trial, Liossis et al obtained encouraging results treating five patients with systemic sclerosis and interstitial lung disease with MMF and low-dose prednisolone [22]. Nihtyanova et al reported that systemic sclerosis was adequately controlled in 109 patients during five years with a significantly lower frequency of clinically significant pulmonary fibrosis and better five year survival [9]. Good results were observed in 28 rheumatoid arthritis (RA) patients with reduced numbers of painful and swollen joints and positive investigator and patient evaluation [23]. A multicentre, 36-week, randomised, dose escalating, placebo controlled clinical trial including 217 patients with severe refractory RA showed a modest clinical improvement with the highest dose (MMF 1 g twice daily) [24]. In a subsequent 9-month, randomised double-blind trial including 356 RA patients comparing two doses of MMF, the results showed that MMF 1 g twice daily was as effective and better tolerated than MMF 2 g twice daily [25]. To further examine the effect of MMF on disease control, the patients included in this 9-month study were re-randomised either to continue MMF (1 g or 2 g twice daily) or to receive a placebo. The proportion of patients experiencing a RA flare was lower in those treated with MMF than in placebo groups [26]. A three-year open label clinical trial in RA showed that MMF was well tolerated and that the main side effects were non serious gastrointestinal events [27]. All together, the results of clinical trials suggest that MMF exerts a modest beneficial effect on RA disease activity. Unfortunately, none of these studies has provided any data on the prevention of structural damage by MMF.

In our group of patients, there was one case of diarrhoea with major weight loss. MMF discontinuation resulted in the complete resolution of symptoms. In addition, this treatment was resumed after a few months without any further adverse event. We observed one case of transient leucopenia, but no case of superimposed serious infection.

There are some limitations to this study. Retrospective case studies, such as this one, are prone to selection bias and missing data. We addressed this by making every effort to include all patients in our unit who had received MMF. All rheumatologists within the unit where personally encouraged to review their patients for cases treated with MMF and data were reviewed for completeness with their help. In addition, it is difficult to analyse the effect of MMF alone as this treatment was used in combination with corticosteroids and other immunosuppressive drugs in several patients. Thus, it is important to consider the possible positive effect of drug combinations in the treatment of autoimmune systemic diseases.

In conclusion, MMF is an interesting alternative for the treatment of several immune mediated inflammatory diseases. It appears to be especially effective in autoimmune connective tissue diseases including SLE, polymyositis and MCTD. Drug tolerance and safety profile seem good compared to other immunosuppressive agents. However, further prospective studies are needed to compare benefits of MMF with other classical immunosuppressive drugs.

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