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PAPER

Mycophenolate mofetil and neurological diseases

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We describe experience with the use of mycophenolate mofetil (MMF) in neurological diseases. Although only small series of patients or case reports were described, MMF is promising in immune-mediated neuromuscular disorders. MMF has been used for the treatment of polymyositis, chronic inflammatory demyelinating polyradiculoneuropathy, and multifocal motor neuropathy. These studies showed that MMF is well tolerated and may be useful in some patients. MMF can be effective alone but mainly as an adjuvant therapy by reducing steroid requirements or the frequency of infusions of IVIg. MMF has also been tested alone as a single drug treatment or in combination with immunomodulatory drugs in multiple sclerosis in open surveillance trials or in phase II studies. None of these studies have been designed to demonstrate a clinical efficacy but preliminary results are very promising. *Lupus* (2005) **14,** s42–s45.

Key words: chronic inflammatory demyelinating polyradiculoneuropathy; multifocal motor neuropathy; multiple sclerosis; mycophenolate mofetil; polymyositis

Introduction

Immune mediated neuromuscular diseases are currently treated with several immunosuppressive agents including azathioprine, cyclophosphamide, methotrexate or cyclosporin and with glucocorticoids. Other conditions such as multiple sclerosis (MS) require immunomodulatory agents such as interferon β or glatiramer acetate or in some cases mitoxantrone. Even though the physician is armed with these choices, the risk–benefit ratio of these medications and their efficacy are highly variable and often need searching for alternatives.

Mycophenolate mofetil (MMF), the prodrug of mycophenolic acid, is a selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase. Its mechanism of action has been reviewed in details by Allison in this issue.[1] MMF is well tolerated and has proved to be relatively safe causing only minor bone marrow suppression.

We describe experience with the use of MMF in neurological diseases. The experience in myasthenia gravis is described elsewhere in this issue.

MMF in neuromuscular disorders

Although only small series of patients or case reports are described, MMF is promising in immune-mediated neuromuscular disorders. MMF has been used for the treatment of polymyositis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MNN).[2–7]

MMF in CIDP

CIDP is an autoimmune disorder caused by an attack on peripheral nervous system myelin. The exact pathophysiologic mechanisms are not known. CIDP is marked clinically by the subacute onset of weakness or sensory less, evolving progressively or in a stepwise fashion. There is no definite consensus in choosing the best therapy for a given patient. Randomized, placebo-controlled trials have demonstrated the individual efficacy of prednisone, plasmapheresis and IVIg.[8–10] In 2001, Chaudry *et al.* and Mowzoon *et al.* reported their experiences with MMF in CIDP.[2,3] MMF was given in three and two patients, respectively. In all cases MMF was begun at a dose of 0.5 g/day and increased to 1 g twice daily over two to three weeks. In one case in Mowzoon *et al.*'s study, the patient, aged 72 was in a severe condition and almost unable to walk despite receiving intravenous immunoglobulins (IVIg) five days every three weeks. Their second patient, aged 83, was also in a severe condition, unable to walk, unresponsive to prednisone and IVIg, improved on plasma exchange once every four weeks. In both cases, considerable improvement was noted shortly after onset of MMF as adjunct therapy. The three patients

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treated by Chaudry *et al.* were aged between 60 and 64-years old. One patient only benefited from the treatment after four months, with an improved functional status and a reduction of steroid dosage. No significant side-effects was noted in these five cases. Recently, Benedetti *et al.* (2004) treated two patients with MMF as add on therapy with IVIg and azathioprine.[5] Without deterioration of the disability scores after 12 months, IVIg dosage was reduced by 50% and azathioprine was discontinued after three months. Gorson *et al.* (2004) reviewed retrospectively the efficacy of MMF in 12 patients with CIDP.[7] All patients failed to improve or relapsed after treatment with conventional immune therapies and four were dependent on periodic infusions of IVIg. Most of them were severely disabled. The average duration of MMF treatment was 15 months. After treatment with MMF, no significant changes of the median scores were observed on the medical research council (MRC) and the Rankin scales. However, three patients had a treatment response, defined as improvement by one or more points on the Rankin scale or $\geq 25\%$ increase in the interval between IVIg infusions.

MMF in IgM neuropathy

A few cases have been published of MMF in demyelinating neuropathy associated with osteosclerosis myeloma or with monoclonal gammopathy of unknown significance. Gorson *et al.* (2004) treated eight patients with an IgM neuropathy, six were men and two were women, with an average age of 67 years and duration of symptoms of six years (range, 2.5–12 years).[7] Four had a slowly progressive, predominantly large fibre sensory neuropathy throughout their course, whereas the remainder also had mild to moderate leg weakness. Four had elevated anti-MAG antibodies and all had only slight or no improvement with conventional therapies and one was dependant on infusions of IVIg. After treatment with MMF, there were no significant changes of the median MRC and Rankin scores compared with baseline. The average amount of the M-protein decreased slightly from 456 mg/dL to 356 mg/dL (22%, $P = 0.09$). One patient, who had a moderate sensory ataxic neuropathy, reported a significant treatment response with improved balance and sensory after nine months of MMF therapy. The lack of efficacy of MMF in most of their patients may be explained by the population included. Indeed, many patients had a long course and may have had severe deficits because of axonal loss. They were also selected because they were refractory or relapsed after treatment with other therapies and therefore may have been less likely to improve with MMF. The one patient who improved had a 62% reduction of the IgM protein after treatment. This result suggested that a reduction of 22% may be insufficient to induce a clinical response.

MMF in multifocal motor neuropathy (MMN)

The findings in five patients have been published.[4,5] Benedetti *et al.* (2004) treated four patients with possible, probable or definite MMN according to Van den Berg-Vos *et al.*'s criteria.[5,11] All were on large dose of IVIg and two of them were on immunosuppressive drugs (azathioprine and cyclophosphamide) when MMF was introduced. The objectives were to reduce or withdraw IVIg while maintaining a satisfactory and stable clinical state. In patients 1 and 2, IVIg was reduced by 50% after two months and discontinued after four months. After one year of therapy with MMF, IVIg treatment remains discontinued. In patient 4, the addition of MMF allowed a reduction in IVIg dose to 50% after four months. In patient 3, IVIg was reduced by 25% but only for four months, symptoms relapsed and required a return to the previous IVIg schedule. Azathioprine and cyclophosphamide were stopped after three months of combined IVIg and MMF treatment. Two patients reported loss of appetite, weight loss and abdominal pain (grade 1 in both cases).

MMF in inflammatory myopathies

The inflammatory myopathies are a diverse group of disorders ranging from focal varieties confined to a single muscle or group of muscles, to diffuse forms in which there is a widespread involvement of the skeletal muscles. The most common varieties encountered in clinical practice are dermatomyositis (DM), polymyositis (PM) and inclusion-body myositis (IBM). The treatments are largely empirical as there is only limited data from controlled clinical trials to allow an evidence-based approach. In DM and PM, treatment has traditionally relied upon the use of corticosteroids and immunosuppressive agents with a satisfactory response in a majority of the patients whereas resistance to treatment is one of the characteristic features of IBM.[12] Although most patients respond to steroids, in a high percentage of cases, the response is incomplete or dependent upon a high dose and it is then necessary to introduce second-line agents usually in combination with steroids such as methotrexate, azathioprine, cyclosporine or cyclophosphamide. Treatment of inflammatory myopathies with MMF are anecdotal. Schneider *et al.* described a patient with severe refractory polymyositis associated with pleuritis, who also suffered from ulcerative colitis and HLA-B27 positive spondylitic arthritis, and who showed marked

benefit from MMF therapy.[13] In the Chaudry *et al.*'s study, three patients, who were unresponsive to other immunosuppressive agents, were treated with MMF.[1] Among the three patients, one patient, who had PM improved. No significant response was observed in the two other patients, who had IBM. Mowzoon *et al.* treated two patients with MMF, one with PM secondary to limb girdle muscular dystrophy and one patient with IBM.[3] The first improved from being wheelchair-bound to being able to stand and take four steps within one month of starting MMF. Abdominal cramps and the cost of the medication forced her to stop the drug after three months, and she became wheelchair-bound again within one month. The latter had a five years history of progressive weakness of grip, difficulty in getting up from sitting and going up stairs and dysphagia. Treatment with prednisone (30 mg/day) and MMF (1500–2000 mg/day) resulted in a progressive and dramatic increase strength of grip and tibialis anterior muscle. Strength and function began to deteriorate three months after discontinuation of prednisone and MMF therapy.

These studies showed that MMF is well tolerated and may be useful in some patients with autoimmune neuropathies. MMF is useful as an adjuvant therapy by reducing steroid requirements or the frequency of infusions of IVIg. MMF appears to be an addition to the armamentarium of immunosuppressants for treatment of inflammatory myopathies. Randomized controlled trials are warranted to further clarify the role of this immunosuppressant in the therapy of dysimmune neuropathies.

MMF in multiple sclerosis

MS is an autoimmune disease stimulated by activated lymphocytes, and the entry of T and B cells into the central nervous system (CNS). Over the last decade, several immunomodulatory therapies have been introduced for the treatment of relapsing-remitting (RR) form of the disease, providing for the first time a possibility to modify the course of this progressively disabling disease. These include three interferon β (IFNβ) preparations and an activator of anti-inflammatory T-cells, glatiramer acetate. The overall impact of these drugs may be defined as modest. Mitoxantrone can also be used in a few specific conditions. Treatment failure occurs in a large number of patients and there is an ongoing need for rescue therapy. Because of its properties and safety, MMF is a good candidate for therapy in MS. MMF has a potent cytostatic effect not only on T lymphocytes but also on B lymphocytes, which play also a major role in the pathogenesis of MS.[14] Others mechanisms may contribute to the efficacy of the mycophenolic acid (MPA), the active metabolite of MMF, in MS. MMF can induce apoptosis of activated T-lymphocytes, which may eliminate clones of cells responding to antigenic stimulation. By depleting guanosine nucleotides, MMF suppresses glycosylation and the expression of some adhesion molecules like VCAM-1, thereby decreasing the recruitment of lymphocytes and monocytes into the CNS.[15] MPA also depletes tetrahydrobiopterin, a co-factor for the inducible form of nitric oxide synthase (iNOS), MPA therefore suppresses the production of nitric oxide by iNOS.[16] Evidence is accumulating that induction of iNOS and peroxynitrite formation contribute to tissue damage in MS suggesting that MMF may act at least partially as a neuroprotective agent. This protective effect of MMF has already been demonstrated in several animal models of brain and renal injuries. Treatment of experimental allergic encephalomyelitis (EAE) with MMF at the onset of the clinical symptoms results in more rapid recovery from EAE than in control or CsA-treated rats. MMF-treated rats had also less infiltration of T cells, B cells, macrophages and dendritic cells and cytokine production in the brainstem than either controls or CsA-treated rats. Oral treatment with MMF from the day of immunization significantly delayed both the development of active EAE and reduced the antibody response to myelin basic protein.[17]

Ahrens *et al.* treated seven patients in an open surveillance trial.[18] All had disease-progression despite established treatment. The administration of MMF at a dose of 2 g/day led to improvement or stopped progression in five cases. Three of the five showed improved movement. One had to reduce the dose from 2 to 1.5 g/day because of frequent infections, one discontinued the treatment owing to uncontrolled nausea. Two larger series were recently reported, one evaluating MMF as a single drug treatment, the other as adjunctive therapy in most of the cases.[19,20] Vukusic *et al.* retrospectively reviewed data on 42 consecutive patients, secondary progressive or primary progressive patients.[19] In one half of the patients, MMF was given as relay therapy after mitoxantrone. Mean follow-up duration after treatment onset was 14.5 months. Nineteen patients experienced side-effects but only three of them definitively stopped MMF because of a clinical adverse event: two because of asthenia and one because of increased spasticity. The neurological conditions improved slightly or stabilized in almost all cases. In Frohman *et al.*'s study, MMF was added to conventional therapy in 64 patients [either IFNβ ($n = 44$) or glatiramer acetate ($n = 20$)] or given as a monotherapy in 15 patients.[20] Most of them had secondary progressive MS and the mean disease duration was 17.6 years. Seventy percent

of the patients continued MMF treatment after an average of 12 months. Eight patients discontinued therapy because of side-effects, seven patients continued to exhibit clinical deterioration and four were denied insurance coverage. Biological abnormalities were rare. One patient had an elevation of liver enzymes that resolved upon drug discontinuation. Two other patients experienced a mild and transient elevation of liver transaminases. Most of the patients stabilized their neurological condition. In 12 patients, clinical improvements were evident with reduction or absence of relapses, improvements in activities of daily living or greater exercise tolerance.

In a prospective phase II study, we also determined the safety of a combination of MMF and IFNβ-1a (Avonex®) in RRMS.[21] Secondary objectives were evolution of the relapse rate, disability assessed on the expanded disability status scale (EDSS) and magnetic resonance imaging (MRI) data.

Thirty patients were recruited. The inclusion criteria were patients, treated by Avonex® for at least six months, with at least two relapses during the last two years with at least one during the last six months. The EDSS score needed to be lower than 6.0 at baseline. MMF at a progressive dose of 2 g per day orally was added to Avonex® for a duration of six months. MRI data were taken at baseline and at the end of the study.

At baseline, the prestudy annual relapse rate was 2.0 ± 0.7 (mean $\pm$ standard deviation) and the mean EDSS score was 2.9 ± 1.3. Eleven patients had gadolinium-enhanced lesions at baseline for a total number of 35 lesions. Two patients disrupted the combination, one after the first dose for personal reasons and the other for diarrhea. A few patients reported nausea or abdominal pains. Adverse events included infections, insomnia, and dizziness. No significant biological abnormalities were noted. At the end of the study the annual relapse rate was 0.57 ± 0.3 ($P < 0.001$) and the mean EDSS score was 2.6 ± 1.5. We observed a dramatic effect on MRI because no gadolinium-enhanced lesions were detected at the end of the study. Even considering the limitations of the design, this open-label pilot study suggests also a clinical efficacy with a low relapse rate and very few patients with disability progression. Even considering a placebo effect and a regression to the mean, such a result with a complete disappearance of gadolinium-enhancing lesions has not been previously described in pivotal or open MS therapeutic studies.

All these studies demonstrated that MMF is safe and well tolerated in MS. None was designed to demonstrate treatment effects. However the preliminary data are promising. Randomized controlled trials with MMF alone or in combination are warranted.

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