Eur J Med Res (2009) 14: 364-366

Mycophenolate Mofetil as Second Line Immunosuppressant in Myasthenia gravis - A Long-term Prospective Open-label Study

F. Hanisch, M. Wendt, S. Zierz

Klinik und Poliklinik für Neurologie, Martin-Luther-Universität Halle-Wittenberg, Halle/Saale, Germany

Abstract

Background: The preferred immunosuppressive drug for long term treatment of myasthenia gravis (MG) is azathioprine (AZA). Mycophenolate mofetil (MMF) was suggested as an effective and safe second line alternative to AZA.

Methods: In a prospective open-label study, 11 patients with acetylcholine receptor antibody (AChR-ab) positive MG (n = 4 ocular MG, n = 7 generalized MG) were treated with MMF which replaced AZA. Reasons for the change of immunosuppressant therapy were side effects (n = 9) or unresponsiveness under AZA (n = 3).

Results: Mean duration of MMF treatment was 16.9 months (6-46 months). During MMF treatment AZA side effects resolved in 8/9 patients, concomitant therapy could be discontinued in 4 patients and reduced in 5 patients, and 5 patients remitted and 3 remained in remission. One MMF-refractory patient required add-on IVIG therapy and another with ocular MG showed signs of generalization after 20 months of MG treatment. One patient was diagnosed with bronchial carcinoma after 10 months of MMF treatment.

Conclusion: Due to its favourable spectrum of side effects compared to AZA MMF might serve as a second-line immunosuppressant in those MG patients who have not tolerated AZA.

Key words: mycophenolate mofetil, myasthenia gravis

Introduction

Steroid-sparing immunosupressants such as azathioprine (AZA) for the long-term course of myasthenia gravis (MG) are the preferred first-line treatment for generalized and severe ocular AChR-ab positive MG. However, 10-20% of MG patients treated with AZA do not respond sufficiently to AZA and side effects occur frequently (nausea, elevated liver enzymes, leuco- or thrombocytopenia).

Methods

In the present prospective open-label study we replaced AZA by MMF in eleven patients with AChR-ab positive MG and analysed the effect and safety of MMF for a mean duration of 16.9 months ±11.1 (6-46). Four patients with pure ocular and seven patients with generalized MG were included. AChR-ab titer, QMGS, MGFA postintervention status, and concomitant drugs were assessed before the beginning and during MMF treatment (Table 1).

Results

The reasons for the exchange from AZA to MMF were gastrointestinal (liver enzyme increase n = 4, nausea/vomiting n = 2, increase of pancreatic enzymes n = 1) and haematological adverse effects (leuco- or pancytopenia n = 3), peripheral edema (n = 1), unresponsiveness to AZA (n = 3). According to the QMGS treatment resulted in complete (pat. 8) and incomplete (pat.6, 7, 10, 11) pharmacological remission, three patients remained in complete pharmacological remission (pat. 1, 5) or with minimal manifestation (pat. 2). Clinical improvement was seen after a period of 2-9 months. In two patients clinical improvement along with decreasing AChR-ab occurred after more than six months on MMF (pat. 7, 11). Patient 3 with disabling unilateral ptosis was refractory despite a combined therapy of prednisolone, high dose pyridostigmine, and MMF. Symptoms improved during a concomitant therapy of intravenous immunoglobins. Patient 4 showed signs of generalization (head lifting weakness) after 20 months on MMF. Patient 2 with mild unilateral ptosis discontinued MMF after sixteen months due to its fear of side effects. Concomitant medication (prednisolone, pyridostigmine) could be discontinued in 4 patients (pat. 1, 2, 5, 7) and reduced in 5 patients (pat. 4, 6, 8, 10, 11). Laboratory parameters which had led to the change from AZA to MMF normalized in all patients affected (n = 8) except pat. 9. In the latter patient MMF treatment had to be discontinued due to persistent increase of pancreatic enzymes and recurrent gastrointestinal problems. One patient was diagnosed with bronchial carcinoma after 10 months of MMF treatment (pat. 5). The daily MMF dosage ranged from 0.5 to 2.5 g and had to be reduced in three patients due to gastrointestinal problems (pat. 3), and persistent leucopenia (pat. 10).

Dicussion

Anecdotic reports, uncontrolled open label and retrospective studies with MMF had shown clinical improvement and steroid dose reduction in patients with

Table 1. AChR-ab titer, quantitative MG score, MGFA postintervention status, and concomitant drugs were assessed before and after the beginning with MMF treatment in 11 patients with AChR-ab positive MG.

nr./sex age	MGFA score	medication before MM treatment (mg)	reason for drug exchange	MMF duration (months)	dose	serum level (µg/ml)	concomitant treatment (mg)	MGFA postintervention status during MMF	change in status	QMGS		AChR-ab (nmol/l)	
										before	after[1]	before	after[1]
1. m/67	I	PR 20 AZA 150 CH 360	gGT increase (15-fold)	46	2.0 g	2.26	none	complete pharmacologic remission	unchanged	0/24	0/24	21	17
2. m/52	I	PR 40 AZA 150 CH 240	gGT increase (13-fold)	16	2.0 g	2.15	none	minimal manifestations (mild ptosis)	unchanged	3/24	3/24	3.6	10.4
3.m/59	I	PR 20 CH 330 AZA 150	gGT increase (5-fold) drug resistancy	7	2.0 g	2.43	PR (7.5)	severe right ptosis CH (480)	unchanged	3/24	3/24	5.0	2.3
				36	1.5 g	(GI-problems)	CH (20) IVIG 10g/month	minimal manifestation mild ptosis	improvement		1/24		2.9
4.f/33	I	PR 5 CH 270 AZA 150	nausea, vomiting	20	2.0 g	2.97	CH (180)	incomplete pharmacol. remission after 20 mo generalization	exacerbation	1/24	5/24	0.21	0.44
5.m/77	IIa	PR 20 AZA 150 (13-fold) CH 240	gGT increase pancyopenia	20	2.0 g 1.0 g	n.a. (flatulence)	none	pharmacologic remission	unchanged	0/24	0/24	1.6	6.7
6.f/64	IIa	PR 20 AZA 200 CH 240	exacerbation	36	2.0 g 2.5 g	2.18	CH (150)	complete pharmacologic remission	improvement	7/24	3/24	31	39
7.f/20	IIb	CH120 AZA 50	edema (hand, feet)	20	1.5 g	0.72	CH (240)	complete pharmacol. remission	improvement	6/24	4/24	43	22
8.f/43	IIIa	PR 25 CH 240 AZA 150	lymphopenia	21	1.5 g	1.90	CH (240)	complete pharmacol. remission	improvement	4/24	0/24	44	34
9.m/64	IIIa	PR CH AZA MTX	amylase/ 8 lipase increase nausea, vomiting	2.0 g	n.a.		CH (345)	therapyresistancy	unchanged	11/24	11/24	17	21
10.f/33	IIIb	CH 330 AZA 50	recurrent 14 pancytopenia persistent sympt.	1.0 g	0.50 0.5 g		CH (270)	incomplete pharmacol. remission remission leucopenia	improvement	5/24	1/24	7.5	11.5
11.m/59	V	PR 40 CH 540 AZA 150	persistant sympt.	26	2.0 g	3.05	PR (7.5) CH (480)	incomplete pharmacol. remission	improvement	11/24	4/24	200	24

AchR-ab – acetylcholine receptor antibody, AZA – azathioprine, CH – choline esterase inhibitor, IVIG – intravenous immunoglobulins, MGFA – myasthenia gravis foundation association, MMF – mycophenolate mofetil, PR – prednisolone, QMGS, - quantitative myasthenia gravis score for disease severity

[1] i.e. at the end of the observation period

severe refractory MG [2, 4]. The time to improvement in that trials was highly variable and ranged from 2 weeks to 12 months [6, 7]. A small double-blind, placebo-controlled pilot trial of MMF with concomitant prednisolon and/or cyclosporine A medication in MG showed a significant improvement of MMF compared to placebo [3]. However, two recent randomized, double blind, placebo-controlled studies with larger cohorts failed to show a benefit for MMF in generalized MG using quantiative MG scores during a treatment period of 12 and 36 weeks, respectively [5, 6]. It is unclear whether this was due to the short duration of the follow-up period, the effect of the add-on steroid therapy, or the insufficient effect of MMF in MG itself. Consistent with our study side effects of MMF are often transitory and mild, including mostly gastrointestinal symptoms as nausea and diarrhoea or headache [4, 5]. However, severe side effects as an increased risk of lymphoproliferative disorders [7] and severe skin reactions might also be associated with MMF therapy. It remains open whether the bronchial cancer diagnosed in one of our patients was related to MMF.

The present study shows that MMF led to the reduction of concomitant medication and of AZA induced side effects in the majority of patients.

References

1. Hauser RA, Malek AR, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. Neurology 1998; 51: 912-913
2. Schneider C, Gold R, Reiners K, Toyka KV. Mycophenolate mofetil in the therapy of severe myasthenia gravis. Eur Neurol 2001; 46: 79-82
3. Meriggioli MN, Ciafaloni E, Al-Hayk KA et al. Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. Ann N Y Sci 2003; 998: 949-499
4. Ciafaloni E, Massey JM, Sanders DB. Preliminary results of an open label trial of cellcept in myasthenia gravis. Neurology 2001; 56: 97-99
5. Sanders DB, Hart IK, Mantegazza R, Shukla SS, Siddiqi ZA, De Baets MH, Melms A, Nicolle MW, Solomons N, Richman DP. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 2008; 71(6): 390-1
6. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 2008; 71(6): 394-9
7. Vernino S, Salomao DR, Habermann TM, O'Neill BP. Promary CNS lymphoma complicating treatment of myasthenia gravis with mycophenolate mofetil. Neurology 2005; 65: 639-41

Received: May 29, 2009 / Accepted: June 8, 2009

Address for correspondence:
Dr. med. Frank Hanisch
Klinik und Poliklinik für Neurologie
Martin-Luther-Universität Halle-Wittenberg
Ernst-Grube Str. 40
06097 Halle/Saale
Telefon: ++49(0)345/557-2934
Fax: ++49(0)345/557-2935
E-mail: frank.hanisch@medizin.uni-halle.de