Cyclosporine A and mycophenolate mofetil as second choice immunosuppressants in myasthenia gravis

P.E. Alboini; V. Damato; R. Iorio; A. Evoli

Istituto di Neurologia, Università Cattolica del Sacro Cuore – Roma

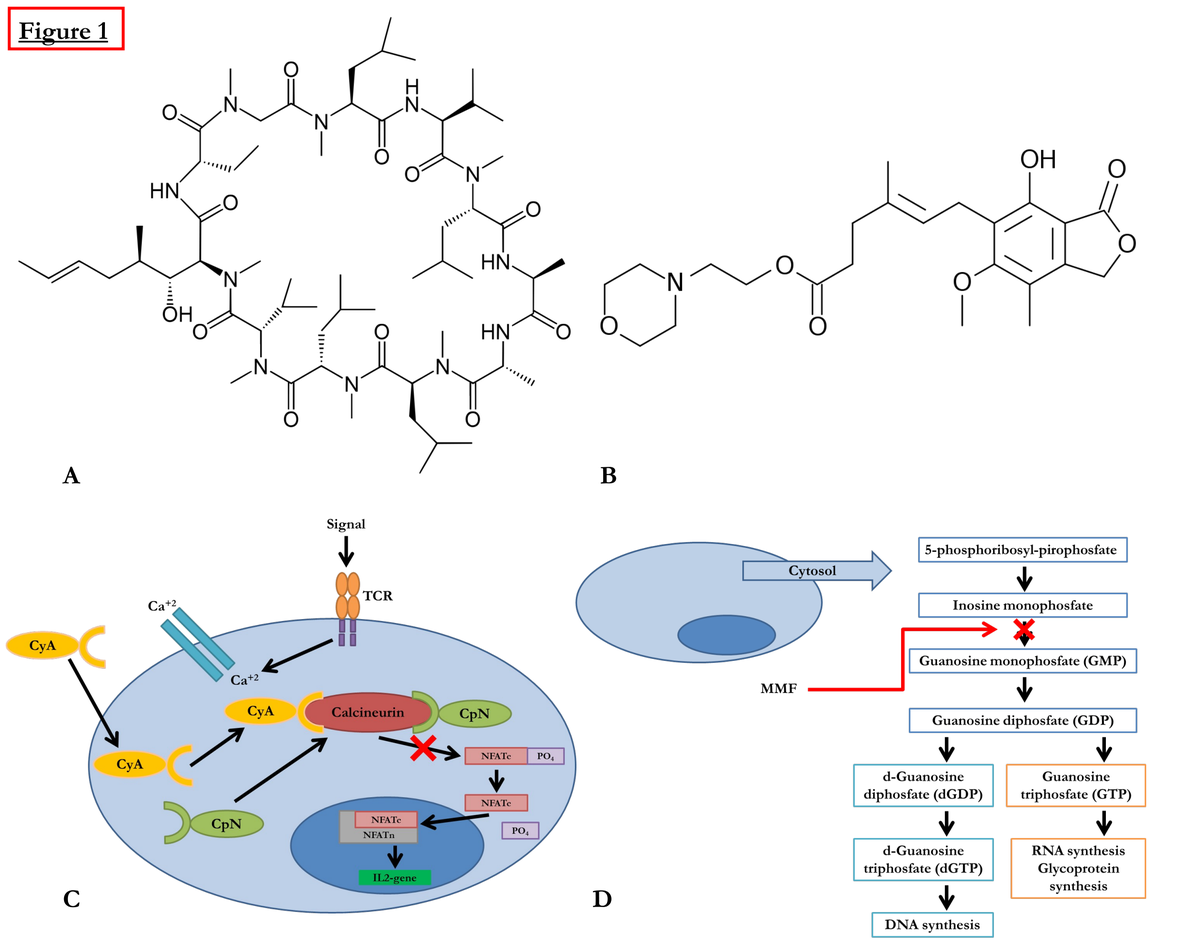
Introduction

Immunosuppression is the mainstay of treatment for myasthenia gravis (MG), as it produces a marked and sustained improvement in those patients where steroids or thymectomy have not brought benefits.

Different classes of immunosuppressants, such as cytostatic drugs, alkylating agents and calcineurin inhibitors, are currently used in MG treatment.

Azathioprine (AZA), a cytostatic drug, is the main steroid-sparing agent in the long-term treatment of MG. It is used in patients who developed steroid side effects, when steroid dosage cannot be reduced or when the response to prednisone alone has not been satisfactory. In some cases, AZA treatment can be unsuccessful: patients could develop either an untoward reaction, characterized by a flu-like syndrome, or side effects, such as hepatic toxicity or leukopenia, leading to a second choice immunosuppressant treatment. Cyclosporine A (CyA), a calcineurin inhibitor, and mycophenolate mofetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase, are the most used second choice immunosuppressants (Figure 1).

Figure 1



Legend. Chemical structure of CyA (A) and MMF (B). Mechanism of action of CyA (C) and MMF (D)

Objective

The aim of our study was to evaluate the clinical response, rate of steroid reduction and tolerance of CyA and MMF as second choice immunosuppressants in seropositive MG patients.

Materials and methods

Eighty seropositive MG patients, followed in our department, were treated with CyA or MMF. Of these, 29 patients were excluded form this study as:

- they received both CyA and MMF as MG treatment for at last one year;
- CyA and MMF were administered as first choice treatment (due to pre-existent diseases, AZA was not indicated);
- they received CyA of MMF for other autoimmune diseases, developed after MG symptoms remission.

The remaining 51 patients were treated, for at last one year, either with CyA (31) or with MMF (20).

CyA subgroup was composed by 29 females and two males with a mean age of onset of 37.1 years. Twenty-two patients were acetylcholine receptor (AChR) antibodies (Abs) positive; nine were muscle-specific kinase (MuSK) Abs positive.

MMF subgroup was composed by 15 females and five males with a mean age of onset of 32.3 years. Thirteen patients were AChR Abs positive; seven were MuSK Abs positive.

During periodic follow up visits, changes in disease severity and post-intervention status (PIS) were evaluated according to Myasthenia Gravis Foundation of America (MGFA) recommendations; variations in prednisone dosage and side effects were recorded.

Statistical analysis was performed by Chi-square test with Yates correction and Student's t-test.

Results

At the start of CyA administration, nine patients (29%) had mild symptoms (MGFA classes I to IIb) and 22 (71%) had moderate to severe disease (MGFA IIIa to V). On the other hand, of patients shifted to MMF, nine (49%) were affected by mild symptoms and 11 (51%) by moderate to severe symptoms (Figure 2). Disease severity was not different between the two subgroups (p=0.387).

Thirteen patients under CyA (41%) and five under MMF (25%) achieved a good PIS (minimal manifestation/pharmacological remission/complete stable remission) (p=0.349). In the remaining patients, all those treated with CyA achieved at least some improvement, while nine patients receiving MMF (49%) were unchanged at the last control (Figure 3).

In 26 patients (84%) of the CyA subgroup and in seven (35%) of the MMF subgroup, the prednisone dosage at the last visit was reduced by 25% or more (p=0.0011) (Table 1). The mean prednisone daily dosage was significantly lower in the CyA subgroup (p=0.0003).

A total of nine CyA patients (29%) complained of side effects, that were serious in four cases (immunosuppression-related tumors, severe infections); side effect rate (15%) and severity (a single serious complication) were recorded in MMF treated patients.

Figure 2

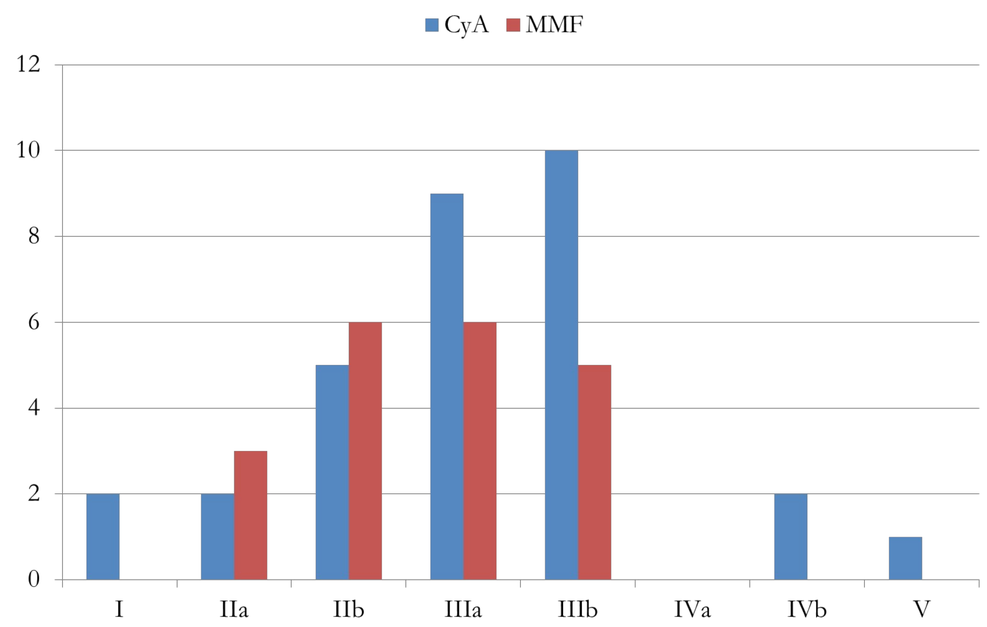
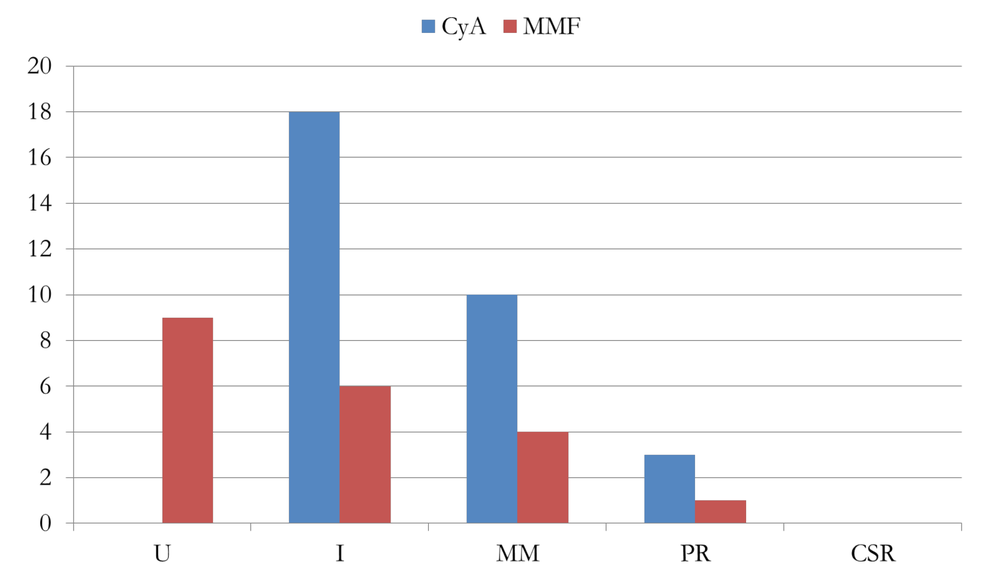


Figure 3



Legend. PIS of patients trated with CyA or MMF. U: unchanged; I: improved; MM: minimal manifestation; PR: pharmacological remission; CSR: complete stable remission

Table 1

	>25%	≤25%
CyA	26	5
MMF	7	13

p=0.0011

Conclusions

Our retrospective study shows notable differences between CyA and MMF in the treatment of MG. In comparison with MMF, CyA showed a higher efficacy and a stronger steroid-sparing effect, associated, however, with a worse safety profile. It cannot be excluded that some unwanted effects, in our population, were caused by the previous treatment with AZA or the concomitant administration of steroids.

References

Gilhus NE, Verschuuren JJ. Lancet Neurol. 2015 Oct;14:1023-1036

Jaretzki A 3rd et al. Ann Thorac Surg. 2000 Jul;70:327-334

Sanders DB, Evoli A. Autoimmunity. 2010 Aug;43:428-435

Gotterer L, Li Y. J Neurol Sci. 2016 Oct 15;369:294-302

Sin

XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA

WebPoster