Clinical Neurology and Neurosurgery 173 (2018) 70–76

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Efficacy and safety of tacrolimus in Osserman grade III and Osserman grade IV Myasthenia Gravis

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ARTICLE INFO

Keywords:
Myasthenia Gravis
Tacrolimus
Immunosuppressive agents
Drug-related side effect and adverse reactions

ABSTRACT

Objective: A retrospective observational cohort study was conducted to evaluate the efficacy and safety of tacrolimus in Osserman grade III and Osserman grade IV myasthenia gravis (MG) patients.

Patients and methods: MG patients admitted to the First Affiliated Hospital of Guangzhou University of Chinese Medicine between June 2011 and January 2017 with grade III and grade IV according to the modified Osserman scale were recruited and received a telephone follow-up in September 2017. Patients treated with tacrolimus plus prednisone were compared with those treated without tacrolimus. The efficacy of tacrolimus was assessed using MG-activities of daily living (MG-ADL) score, Osserman classification, Myasthenia Gravis Foundation of America (MGFA) post intervention status (PIS), the number of hospitalizations, the number of myasthenic crises and deaths. The adverse drug effects of tacrolimus were monitored.

Results: A total of 124 patients were included. The tacrolimus group had a significantly lower MG-ADL score than the control group at follow-up (1.90 ± 2.27 *vs* 2.97 ± 2.78, $p = 0.029$). The difference of MG-ADL score between baseline and after follow-up was significantly greater in the tacrolimus group than the control group (-7.20 ± 2.95 *vs* -5.52 ± 2.91, $p = 0.003$). Fewer patients were hospitalized in the tacrolimus group ($p = 0.011$). The Osserman classification, MGFA PIS, the number of myasthenic crises and deaths did not differ significantly between the two groups. Nineteen patients in the tacrolimus group had adverse drug reactions, but no severe adverse effects appeared.

Conclusion: Our study suggested that tacrolimus could be an effective and safe treatment for Osserman grade III and Osserman grade IV MG patients.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease generally mediated by antibodies against the acetylcholine receptor (AChR) targeting the neuromuscular junction and characterized by weakness of skeletal muscle [1]. A rare portion of MG cases is mediated with muscle specific kinase (MUSK) antibodies, low-density lipoprotein receptor related protein 4 (LPR4) antibodies and agrin antibodies. Titin and ryanodine receptor antibodies could be detected with a high frequency in thymoma-associated MG [2,3]. The production of AChR antibodies in B cell depends on AChR specific T cells and T-cell proliferation and activation induced by interleukin-2 (IL-2), particularly in severe cases of MG [4,5]. The symptoms of MG are fluctuating and include easy fatigability, ptosis, diplopia, weakness of limbs, dysphagia and so on [6]. But for some cases, especially for Osserman grade III and Osserman grade IV MG, they may rapidly deteriorate and even experience myasthenic crisis which can cause respiratory failure and even death [7,8]. Thus, their treatment remains a big challenge.

The main treatment for MG includes acetycholinesterase inhibitors, thymectomy, corticosteroids, non-steroidal immunosuppressive agents, and potential immunotherapies. Acetycholinesterase inhibitors are the first-line drugs for MG, but they are only symptomatic treatment and could not induce remission [9]. Being the most commonly used immunosuppressive agent, corticosteroids are often associated with adverse effects, such as Cushingoid appearance, osteoporosis, hypertension, weight gain, hyperglycemia and increased risk for infection [10]. What's more, approximately 5–20% of MG patients have a poor therapeutic response to corticosteroids, particularly MUSK-MG patients

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https://doi.org/10.1016/j.clineuro.2018.07.023
Received 14 May 2018; Received in revised form 17 July 2018; Accepted 29 July 2018
Available online 30 July 2018

[10–12]. Nowadays, non-steroidal immunosuppressive agents such as azathioprine, cyclophosphamide, cyclosporine and tacrolimus are available for the treatment of MG. Azathioprine is the first-line immunosuppressant for MG. But its initial improvement is usually seen in 3–10 months after administration while the peak effect will reach 1–2 years [7], which, with such a relatively long onset time, makes it less favorable for severe MG patients with significant weakness [13]. As for cyclophosphamide and cyclosporine, potential serious side effects limit their use in treatment of MG. New potential immunotherapies, such as rituximab and eculizumab, have been used to treat MG, especially for refractory MG patients in recent years, but more evidence is needed for their efficacy and safety [7,14,15]. Therefore, an immunosuppressive agent with a quick onset and less serious side effects is needed for treating MG, especially for those Osserman grade III and Osserman grade IV MG.

Tacrolimus, a calcineurin inhibitor usually used for preventing rejection after organ transplantation, has been administered to treat MG [16]. As a non-steroidal immunosuppressive agent, tacrolimus suppresses antigen-simulated interleukin-2 [IL-2] production by T-cells and IL-2 receptor expression on T cell and reduces T-cell proliferation [1,17–20]. In addition, tacrolimus can improve excitation-contraction coupling in skeletal muscle by enhancing ryanodine receptor related sarcoplasmic calcium release [13,21,22]. Tacrolimus with a rapid onset around 2 weeks after administration has been suggested to have corticosteroids sparing effect in treatment of MG [23–26]. Recently, several studies showed that tacrolimus could be effective and well tolerated as an immunosuppressive agent in MG patients [19,27,28]. However, to our knowledge, MG patients enrolled in these studies most were classified as Myasthenia Gravis Foundation of America (MGFA) class I, MGFA Class II or Osserman grade I and Osserman grade II. Therefore, we conducted a retrospective cohort study to evaluate the efficacy and safety of tacrolimus in Osserman grade III and Osserman grade IV MG patients.

2. Material and methods

2.1. Patients

MG patients admitted to the First Affiliated Hospital of Guangzhou University of Chinese Medicine between June 2011 and January 2017 aged between 18 and 70 with grade III and grade IV according to the modified Osserman scale were recruited and received a telephone follow-up in September 2017. Our department is a well-known tertiary referral center for MG. Patients' clinical and laboratory data were collected retrospectively. Diagnosis of MG was based on their history, clinical symptoms, positive outcomes of pharmacological and electrophysiological tests and antibody tests [7]. Diagnosis of MG was confirmed by assessing serum AChR-Ab titers in most cases. Patients with elevated levels of liver enzymes, renal insufficiency, impaired glucose tolerance, malignant tumor, severe infection, patients undergoing thymectomy within one year, pregnant and lactating women at baseline were excluded. All subjects were contacted and received information about the aim of this study and written consents were obtained. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine.

2.2. Treatment

Patients were divided into two groups. The tacrolimus group was treated with prednisone plus tacrolimus and the control group was treated with prednisone alone or prednisone plus azathioprine or prednisone plus cyclosporine. Tacrolimus was administered orally at a daily dose of 2 mg and adjusted according to physician's judgment based on patients' condition. Prednisone was orally administered at an initial dose of 5–15 mg and gradually increased to 40–60 mg per day as the maximum maintaining dose if needed. After the clinical symptoms improved, the dose of prednisone was tapered gradually. Pyridostigmine was permitted within the dosage of 360 mg per day if required. Cyclosporine was taken 50–100 mg daily and adjusted according to the blood level of cyclosporine. Azathioprine was administered 50–100 mg daily initially and increased every 2 weeks up to 2–3 mg/kg/day according to patients' tolerance toward azathioprine.

2.3. Clinical evaluation

Clinical classification was performed according to the modified Osserman scale [29]. Disease severity was graded according to the MG-activities of daily living (MG-ADL) score [30]. Clinical classification and MG-ADL score were compared between the two groups at baseline and after follow-up. Differences of MG-ADL score between baseline and after follow-up were calculated. The number of hospital admissions related to MG, episodes of myasthenic crisis and the number of deaths were recorded. The MG-ADL score and Osserman scale at baseline were acquired by reviewing the charts of MG patients when they were admitted to our hospital. The MG-ADL score, Osserman scale and Myasthenia Gravis Foundation of America (MGFA) post intervention status (PIS) at follow-up were obtained mostly by clinic visits and supplemented by telephone calls. The number of hospitalization, the episodes of myasthenia crisis, the number of death were collected by reviewing the clinical charts of patients and telephone calls. The physicians who participated in clinic visits and making phone calls were not aware of the patients' treatment status.

2.4. Safety evaluation

To assess safety, unfavorable events occurring after the administration of tacrolimus were collected by reviewing the clinic records of patients and telephone calls.

2.5. Statistical analysis

The statistical analyses were performed using SPSS version 19.0 for Windows. Continuous data were analyzed by *t*-test or Mann-Whitney *U* test depending on the data distribution. Categorical data were estimated by Chi-square test or Mann-Whitney *U* test. Two-way analysis of variance (two-way ANOVA) was applied to examine the interaction effects of treatment groups and thymectomy history, using the difference of MG-ADL score between baseline and after follow-up, the MG-ADL score after follow-up and the number of hospital admissions as dependent variables. Comparisons between the four different treatments groups were used one-way ANOVA followed by the S-N-K post-hoc method or the non-parametric Kruskal-Wallis test followed by the Dunn's post-test depending on the data distribution. All the tests were two-tailed. A p value < 0.05 was considered to be statistically significant. The number of adverse drug reactions and the number of the affected patients were described.

3. Results

3.1. Clinical features of MG patients at baseline

One hundred and thirty-two patients were enrolled in this study. Two patients were excluded from the study due to their short treatment periods (less than 2 months). Six patients were lost during the follow-up and excluded because of insufficient clinical data. The final analysis was performed for a total of 124 patients (55 in the tacrolimus group and 69 in the control group). In the tacrolimus group, 28 patients chose tacrolimus plus prednisone treatment due to insufficient response that patients relapsed after a stable condition or their symptoms could not be relieved after a sufficient dose and time of medications to their previous treatments and 19 patients chose tacrolimus plus prednisone treatment due to intolerable side effects associated with their previous