Rituximab in refractory myasthenia gravis: a prospective, open-label study with long-term follow-up

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Abstract

We examined the clinical effectiveness of rituximab in fourteen patients with refractory myasthenia gravis (MG). Manual muscle testing (MMT) score was recorded at baseline and followed during the course of the study. Steroid dose, frequency of intravenous immunoglobulin (IVIG) infusions, and plasma exchange (PLEX) were also monitored throughout the duration of the study. All patients responded dramatically to rituximab, as measured by a change in MMT score, prednisone dose, or the frequency of IVIG infusions or PLEX. Rituximab appears safe and effective for the treatment of refractory MG. It should be considered as a therapeutic option in refractory patients.

Introduction

Myasthenia gravis (MG) is an autoimmune condition of the neuromuscular junction, characterized by weak and fatigable skeletal muscles. Approximately 80–85% of MG patients respond favorably to available immunosuppressive therapies, which include steroids, azathioprine (Az), mycophenolate mofetil (MM), cyclosporine (Cy), intravenous immunoglobulin (IVIG), plasma exchange (PLEX), or tacrolimus. The remaining 15–20% of MG patients are refractory to treatment, demonstrating suboptimal responses to multiple immunosuppressive therapies, periodically requiring IVIG infusions or PLEX, or are unable to reduce their steroid dose without clinical relapse. The discovery and development of novel therapeutics for the treatment of refractory MG is thus critical, in particular those with an optimal side effect profile and steroid sparing effect.

Rituximab is a monoclonal antibody that targets the CD20 antigen found on all mature B cells, initiating complement-dependent cytolysis or antibody-dependent cell-mediated-cytotoxicity. It depletes B cell populations but does not affect B cell recovery or antibody production. It is part of the standard therapeutic regimen for non-Hodgkin’s lymphoma and has been successfully used in the treatment of a number of autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia. To date, a number of case reports and a small number of case series’ (the large majority of which are retrospective) have demonstrated the potential benefit of rituximab in treatment-refractory MG. In the present study, we describe the clinical follow-up of fourteen patients with refractory MG treated with rituximab.

Methods

A prospective, open-label study examining rituximab in refractory MG was performed at the University of Alberta between 2012 and 2016. The study was approved by the Research Ethics Board at the University of Alberta. All patients provided informed, written consent to participate in the study. Rituximab was provided on a compassionate basis, through Alberta Health Services’ Short-Term Exceptional Drug Therapy program. A total of fourteen patients were enrolled in the study (Table 1). MuSK- and AChR-positive, in addition to seronegative patients were included in the study. Seronegative patients were diagnosed through established clinical and electrodagnostic criteria (data not available).
Results

Fourteen patients with refractory MG (eight females and six males) were treated with rituximab between 2012 and 2016. The mean age for all participants in the study was 50.9 ± 3.7 years (Table 1). In total, six patients had MuSK-positive MG, five had AChR positive-MG, and three had seronegative MG (Table 1). The mean time between disease onset and initiation of rituximab was 47.1 ± 15.0 months (range = 1–216 months). Rituximab infusions were well tolerated, with only three patients complaining of post-infusion headaches. Headaches resolved with standard anti-inflammatory drugs.

All fourteen patients demonstrated a marked improvement in clinical status by the end of the follow-up period (22.6 ± 2.4 months). Eleven of the fourteen patients underwent a single cycle of rituximab, while the remaining three patients received two or more cycles (Table 1). In patients treated with a single cycle of rituximab, MMT score was significantly reduced from a baseline of 13.1 ± 1.9 (range = 5–27) to 3.5 ± 0.8 (range = 0–5) at the end of the study (Fig. 1A, \( P < 0.001 \)). The time to peak response in these eleven patients was 4.5 ± 1.0 months (Fig. 1B). Eight of the fourteen patients were taking prednisone at study initiation (Fig. 1C, 27.2 ± 6.0 mg), a value that was significantly reduced by the end of the follow-up period (Fig. 1C, 4.7 ± 1.7 mg, \( P = 0.02 \)). In the eleven patients treated with a single cycle of rituximab, some were actively being treated with intermittent IVIG infusions (Fig. 1D, \( n = 7 \)) and/or PLEX (Fig. 1E, \( n = 4 \)). At the end of the follow-up period, the frequency of both IVIG infusions (2.2 ± 0.8–0.0 ± 0.0, \( P = 0.01 \)) and PLEX (1.3 ± 0.3–0.0 ± 0.0, \( P = 0.02 \)) were significantly reduced.

In the three patients treated with multiple cycles of rituximab, one (P12, Table 1) was treated with three cycles, while the other two (P13, P14, Table 1) were treated with two cycles. At the end of the follow-up period, P12’s MMT score decreased from a baseline of twelve to
Moreover, PLEX frequency markedly decreased from eighteen to one by cycle three. P13 initially responded to the first cycle of rituximab, with the patient’s MMT score falling from fourteen to six at the two-month follow-up. By 4 months, the patient began to relapse, necessitating an additional cycle of rituximab. As with P12, the frequency of P13’s IVIG infusions and PLEX also decreased by the end of the study. Lastly, P14 initially demonstrated a modest response to rituximab: MMT decreased from fourteen at baseline to a nadir of eight at 6 months; however, at twenty-one months a second cycle of rituximab was initiated, as P14’s clinical status drastically worsened. By the end of the follow-up period, P14’s MMT score was four and he was no longer requiring intermittent PLEX.

**Discussion**

Zeja et al. were the first group to demonstrate the utility of rituximab in treating MG, in a patient who developed MG after bone marrow transplantation. The largest study (retrospective) of rituximab and MG to date, demonstrated a significant decrease in the annualized relapse rate (ARR) and the Myasthenia Gravis Foundation of America (MGFA) scores in twenty patients with either refractory or nonrefractory MG. Lebrun et al., in
the first prospective series investigating rituximab in the treatment of MG, showed that the Osserman score was improved in six refractory patients. In a prospective study with long-term follow-up of seventeen patients with refractory MG (eleven AChR- and six MuSK-positive), Díaz-Manera et al. demonstrated improvement in MGFA scores after rituximab. Subgroup analysis from that study further revealed that MuSK-positive patients achieved higher rates of disease remission and did not require repeat infusions, as opposed to their AChR-positive counterparts.

In the present study, all fourteen treatment-refractory patients markedly improved after rituximab, as demonstrated by significantly improved MMT scores, lower steroid dose, and a decreased need for IVIG infusions or PLEX. This is the first prospective study to demonstrate the effectiveness of rituximab in treating refractory, seronegative MG patients. All three patients demonstrated a sustained clinical response (mean follow-up for this group = 17.7 ± 4.4 months) after a single cycle of rituximab. One AChR- and two MuSK-positive patients relapsed during the course of the study, necessitating further cycles of rituximab. Repeat cycles were effective, with all three patients demonstrating a marked clinical response at the end of the follow-up period (MMT for this group = 2.7 ± 1.3).

In general, rituximab was well tolerated, with the only documented side effect being post-infusion headache. Serial monitoring of lymphocyte counts revealed that CD19/CD20-positive cells were depleted early in the course of treatment. CD19/CD20 counts recovered along an anticipated time-course in the majority of patients; however, the re-emergence of CD19/CD20-positive B cells did not foretell disease relapse, highlighting the importance of treating refractory patients based on clinical status alone.

The current study represents one of the largest prospective studies investigating rituximab in the treatment of refractory MG, adding to the growing body of evidence that rituximab appears to be both a safe and effective treatment for MG. A phase II trial (NCT02110706), currently in the recruitment phase, should further help clarify rituximab’s role in MG treatment.

**Author Contributions**

DA analyzed data and wrote the manuscript. CP performed clinical assessments and edited the manuscript. WSJ performed clinical assessments and edited the manuscript. ZAS designed the study, performed clinical assessments, and wrote the manuscript.

**Conflicts of Interest**

Drs. Anderson, Siddiqi, Phan, and Johnston declare no conflicts of interest.

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