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Resistant myasthenia gravis and rituximab: A monocentric retrospective study of 28 patients

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Abstract

This retrospective study evaluated the efficiency and tolerance of rituximab in the management of resistant myasthenia gravis (MG). All patients who received rituximab for the treatment of MG between 2004 and 2015 at Pitié-Salpétrière University Hospital (Paris, France) were included. The efficacy of rituximab was evaluated every 6 months by the myasthenic muscle score (MMS), the Myasthenia Gravis Foundation of America – Clinical Classification (MGFA-CC), the MGFA Therapy Status and the Postintervention Status (PIS). All rituximab-related side effects were noted. Twenty-eight patients were included: 21 with anti-acetylcholine receptor antibodies, 3 with anti-muscle-specific tyrosine kinase antibodies and 4 seronegatives. The mean age at day 1 of RTX was 50.6 ± 12.0 years. Patients previously received 1–4 immunosuppressants. The mean follow-up was 27.2 months (range: 6–60 months). The mean total dose of rituximab was 4.8 ± 2.5 g. The initial median MMS (58.8 points) improved significantly at M6 (74.5 ± 15.0 points; $p < 0.0001$) and remained stable thereafter: at M12: 75.9 ± 14.0 points ($p = 0.00014$), at M36: 72.5 ± 13.1 points ($p = 0.0013$). Among 16 patients with initial severe symptoms (MGFA-CC class IV), 14 improved. The PIS showed efficacy in about 50% of patients: at M6, 12/28 (43%) patients were considered improved. This benefit remained stable thereafter: at M12: 12/24, at M24: 7/17, at M36: 6/12. One patient developed a delayed progressive multifocal leukoencephalopathy. Based on the PIS, rituximab may be efficient in 50% of patients with MG resistant to immunosuppressants.

Keywords: Resistant myasthenia gravis; Rituximab; Retrospective cohort; Progressive multifocal leukoencephalopathy

1. Introduction

Resistant (or refractory) myasthenia gravis (MG) is usually defined as a chronic condition in which patients are not relieved of severe MG symptoms despite an optimal use of prednisone and/or other second or third line drugs, such as immunosuppressants (IS) (azathioprine, mycophenolate mofetil, cyclosporin, cyclophosphamide, methotrexate, tacrolimus. . .), intravenous immunoglobulins (IVIg), or plasma exchanges (PE). Resistant MG reduces quality of life, may require hospital management of potentially lethal exacerbation and comes with a heavy financial burden.

Rituximab (RTX) is a genetically engineered chimeric murine/human monoclonal antibody that targets B-lymphocyte antigen CD20, initially developed and approved for the treatment of B-cell lymphoma [1]. In the field of autoimmune disorders, RTX is today approved for the treatment of rheumatoid arthritis [2] and ANCA vasculitis [3].

The efficacy of RTX in MG was first observed in patients suffering from both B-cell lymphoma and MG [4,5] where the treatment of the hematological condition with RTX improved MG symptoms. The interest of RTX in MG has limited evidence-based data support. All previous studies had a retrospective design with relatively small series, the greatest including only 22 subjects [6].

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The main objective of this study is to assess the efficacy and the tolerance of RTX in the management of resistant MG in a monocentric retrospective cohort.

2. Patients and methods

2.1. Patients

This retrospective monocentric study (Department of Internal Medicine and Clinical Immunology, Myology Institute, Department of Neurology, Pitié-Salpétrière Hospital, Paris, France) included all patients who had a resistant MG and who received RTX, from January 1, 2004, to August 1, 2015. Indications of RTX use were

- patients with severe MG symptoms (Myasthenia Gravis Foundation of America – Clinical Classification (MGFA-CC) class IV or V) despite an optimal use of prednisone and at least of one IS during at least 6 months; or
- patients with a past history of severe MG symptoms and now stabilized (MGFA-CC class I to III) at the price of a chronic treatment with IVIg and/or PE with regular programmed hospitalizations or with prednisone and IS but with side effects necessitating their withdrawal.

The MG diagnosis was established on the basis of the clinical presentation; the presence of serum anti-acetylcholine receptor (anti-AchR) antibodies (Abs) or anti-muscle-specific tyrosine kinase (anti-MuSK) Abs; and/or a decrement of more than 10% in compound muscle action potential after repetitive nerve stimulation during an electromyographic test.

We reviewed patients' charts, letters, laboratory and electrophysiological results.

2.2. Outcome measures

The following standardized outcome measures were tested every 6 months during the follow-up: The myasthenic muscle score (MMS), the MGFA-CC and the MGFA Therapy Status (number of anti-myasthenic treatments) [7]. The daily dose of prednisone was also reported at each visit.

In order to integrate all the clinical data in the evaluation of the patients, we used the Postintervention Status (PIS) as described by Jaretzki et al. [7] with a minor modification. The PIS evaluates the patient's status (complete stable remission, pharmacologic remission, minimal manifestations) and the change of status since the initiation of treatment (improved (I), unchanged (U), worse (W), exacerbation (E) and died of MG (D)) as described previously [7]. The minor modification was to define *Exacerbation (E)* status as an acute worsening of myasthenic symptoms that needed hospital management.

The follow-up visits were performed every 6 months from the first RTX infusion (day 1). Twelve out of 28 patients (43%) were followed for 36 months (M36).

2.3. Tolerance of RTX

The tolerance of RTX was evaluated by assessing all the side effects presented in the Summary of Product Characteristics. Moreover, we noted all other side effects that could be related to RTX use.

2.4. Rituximab protocol

The treatment with RTX consisted of an induction treatment using either the "rheumatologic disease-like" protocol, i.e. 1000 mg on day 1 (D1) and D15, or the "lymphoma-like" protocol, i.e. 375 mg/m^2 on D1, D7, D15 and D21.

The induction treatment was followed by a maintenance treatment, 1000 mg or 375 mg/m^2 infusion, with a 6 months periodicity. The maintenance infusions were administered either *systematically* every 6 months (regardless of the clinical evolution of the MG symptoms) or *as needed* (in case of worsening MG symptoms), depending on the clinical experience of RTX of each clinician. The blood CD20 + B cell counts were rarely checked during the follow-up of the patients and did not influence the decision of RTX reinfusion in the "as needed" group, severity of MG symptoms being the major decision criterion.

2.5. Statistical analysis

Statistical analyses for comparisons were performed using the t-test for quantitative values.

2.6. Ethics approval

Informed consent was obtained from all patients. In accordance with French regulations, no other ethical committee approval was required for this retrospective study.

3. Results

3.1. Cohort characteristics

From January 1, 2004, to August 1, 2015, 28 patients (sex ratio male/female: 13/15) received RTX for a resistant MG (Table 1). The majority had anti-AchR Abs (21/28, 75%), 3 patients had anti-MuSK Abs and the 4 remaining were seronegative for anti-AchR and anti-MuSK. Among these 4 seronegative patients, MG was diagnosed on the basis of clinical phenotype and the presence of one decrement of more than 10% in compound muscle action potential after repetitive nerve stimulation during an electromyographic test. The anti-LRP4 (lipoprotein-related protein 4) Abs [8,9] and the anti-AchR Ab of low affinity [10] were not assessed.

The mean age at the onset of MG was 39.1 ± 14.6 years. The mean period of MG evolution before first RTX infusion was 11.4 ± 7.6 years.

The mean age at D1 of RTX was 50.6 ± 12.0 years. The mean follow-up duration was 27.2 ± 16.6 months (range: 6–60 months).

Before RTX, half of the patients were hospitalized for a myasthenic crisis: 4 patients had one ICU admission, 7 patients had two ICU admissions and 3 other patients had, respectively, 3, 4 and 10 ICU admissions.

Twenty-one patients (71%) had a thymectomy. Among those, the histopathological analysis found 8 thymomas, 10 follicular