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Original article

Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost–utility analysis

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ABSTRACT

Introduction: Myasthenia Gravis is a humoral autoimmune disorder affecting the neuromuscular junction. Its treatment is based on immunosuppressive agents. Rituximab has shown efficacy in refractory and severe Myasthenia Gravis. We evaluate the potential pharmacoeconomic and quality of life benefits of its use.
Methods: A retrospective analysis of Myasthenia Gravis patients treated with Rituximab was performed. Clinical charts were reviewed and scales for assessment of quality of life were applied. Health care costs were estimated based on the average of each treatment and daily charge of hospitalization.
Results: Six patients were treated. Rituximab use lead to the reduction of relapses and to a lesser use of immunosuppressive agents. An overall decrease in healthcare costs after treatment was observed along with an evident clinical improvement.
Discussion: Rituximab is a clinical effective treatment for B cell-related diseases like MG and seems to be a cost–saving intervention. Its use is associated with a decrease in the need for other immunosuppressive treatments whilst improving quality of life and reducing health costs.

Introduction

Myasthenia Gravis (MG) is a rare autoimmune disorder affecting the neuromuscular junction caused by antibodies (Abs) against postsynaptic membrane proteins, thus preventing an effective neurotransmission at the synaptic terminal.

The most important membrane antigen is the muscle acetylcholine receptor (AchR) as AchR-Abs are present in the serum of 85–90% MG patients. About 40% of the remainder AchR-negative patients have Abs directed against the muscle-specific tyrosine-kinase (MuSK). In some patients with a generalized form of MG, antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) may be present. MuSK and LRP4 are not directly involved in the neuromuscular transmission, but in the end-plate maturation. The clinical phenotype of anti-MuSK is associated with a poorer response to standard therapies compared to AChR-positive patients, whilst the LRP4 subset resembles closely that of anti-AChR-positive MG. Recently a new epitope antibody was identified in patients with MG, Anti-agrin.[1,2] Even with 4 antibodies identified, a small proportion of patients remain seronegative.

The goal of MG treatment is to induce and then maintain disease remission. Current treatment options include acetylcholinesterase inhibitors, short-term immune therapies (plasmapheresis or intravenous immunoglobulin), and long-term treatment with corticosteroids and classic immunosuppressive agents, namely azathioprine, mycophenolate mofetil and cyclosporine, among others.[3]

Treatment with immunosuppressors has reduced mortality and significantly improved the prognosis of these patients. However, a subset of patients has refractory disease or requires high doses of immunosuppressive agents with multiple side effects.[3]

Recently, several authors have described the role and efficacy of Rituximab (RTX), a chimeric mouse/human monoclonal antibody that targets CD20 B lymphocytes in the treatment of drug-resistant MG.[4–7]

Abbreviations: Abs, antibodies; AchR, muscle acetylcholine receptor; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA-PIS, myasthenia gravis foundation of America-post interventional status; MGCS, myasthenia gravis composite scale; MuSK, muscle-specific tyrosine-kinase; PEX, plasma exchange; QALY, quality-adjusted life years; RA, rheumathoid arthritis; RTX, rituximab; SLE, systemic lupus erythematous.

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RTX was first used for the treatment of haematological malignancies, mainly non-Hodgkin's lymphoma and in this context was found useful for patients with lymphoma-associated MG.[8,9] It is also used for the treatment of several autoimmune diseases in which B cells have a predominant pathogenic role such as systemic lupus erythematosus and rheumatoid arthritis.[10]

MG is an "antibody associated disease" with B cells having an important role in its pathogenesis. Therefore, the use of RTX in MG has been increasingly suggested, but reports are still restricted to minor series or individual cases.[1]

To our knowledge, no studies have described the impact of this new therapeutic approach in the quality of life, nor have been determined its economic implications. Having different therapeutic options makes it essential to establish the costs and benefits of this new treatment in comparison with the former available options. The quality-adjusted life year (QALY) is an outcome measure that merges quality and duration of life and is crucial to cost–effectiveness analysis.[11]

We performed a cost–utility analysis regarding the treatment of six MG patients with RTX, taking into account major aspects such as clinical and serologic characteristics, objective evaluation of quality of life and overall treatment costs.

Material and methods

The use of rituximab (RTX) in MG in our centre is confined to patients with refractory[4] and/or severe[1] MG or with a concomitant autoimmune disease in which rituximab therapy has proven efficacy such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). Refractory patients are defined when they cannot lower their steroid therapy without clinical relapse, are not clinically controlled on their immunotherapy regimen, or have severe side effects from immunosuppressive treatments. Severe MG was defined as a classification of MGFA $\geq$ IIIb.

Our protocol of administration consists of a course of treatment that is composed of 2 infusions of 1000 mg given 15 days apart. Retreatment is decided in a multidisciplinary team (neurology and internal medicine specialists, with experience in autoimmune diseases) and based on disease activity, CD19 lymphocyte plasma count and serum immunoglobulin levels, with a minimum interval between infusions of 4 months.

Six patients with generalized MG were treated with Rituximab, since February 2010, and followed in the Neurology clinic and Autoimmune Diseases Unit of our Hospital. We performed a retrospective study and collected data from the clinical records of those patients since the beginning of their follow up in our hospital until September 2015.

The patients fulfilled the diagnostic criteria for MG on the basis of clinical history, neurological examination and evidence of electrophysiologic neuromuscular transmission defect.

We assessed clinical data, quality of life and economic costs before and after treatment with RTX. Clinical data included (a) prednisone dose, (b) number of imunossupressors, (c) IVIg and plasmapheresis treatments used for myasthenic crisis, (d) Myasthenia gravis composite scale (MGCS),[12] (e) Myasthenia Gravis Post interventional status (MGFA-PIS) 15,[13] and (f) safety data/side effects. We used paired *t*-test analysis to evaluate differences; results were considered significant when $p < 0.05$.

Quality of life was assessed applying a generic (EQ-5D-3L, Portuguese version, which includes a questionnaire and a visual analogic scale),[14] and a disease specific (MG-QOL 15) quality of life instrument.[15]

EQ-5D is an instrument developed by EuroQol which allows the measure of health-related quality of life to be used in cost–utility economic evaluations. It defines health status in terms of domains or dimensions, which are convertible to a numeric value associated with the health status described (health utilities). Health utilities can be used to compare improvement or decrease in quality of life status, and using a time factor (for example the time between two evaluations) it can be used to calculate QALY's. The higher the numeric value, the higher is the quality of life measured with EQ-5D. MGQOL-15 is a disease specific MG quality of life measurement that uses 15 questions to evaluate the 4 domains, namely mobility (9 items); MG symptoms (3 items); general contentment (1 item); and emotional well being (2 items). The higher the total score, the lower is the quality of life related to MG.

These instruments were applied after the collection of the clinical information. Patients were asked to complete the abovementioned questionnaires referring to the moment before starting treatment with RTX and to their current status. To assess the convergent validity between values obtained from the general quality of life instrument (validated to Portuguese language (EQ-5D), but not for MG), and the quality of life instrument specifically developed and validated to Myasthenia Gravis (MG-QOL-15), we used Pearson correlation test.

Pharmacoeconomic methods

Health state utilities were transformed into quality adjusted life years (QALYs) by using the time of follow up, and assuming a linear evolution over time as commonly suggested.[16]

Estimated healthcare costs were calculated based on the average cost of RTX, plasmapheresis session, human immunoglobulin, the daily charge of hospitalization on a Neurology ward and in an Intensive care unit. All costs are expressed in Euros (€). Appendix 1 can be visualized for further detail.

The cost–utility analysis was performed making a direct comparison between the cost/patient in the year before and the year after RTX treatment, and using as utility marker the calculated QALY/patient/year, value.

Statistics were performed using IBM SPSS Statistics version 21.

Results

A total of 6 patients (5 females and 1 male) with a mean age of 65 years (standard deviation (SD) 15.9 years) were studied. The mean age of disease onset was 51.2 years (SD 19.8 years), and time between diagnosis and treatment with rituximab was 10.8 years (SD 12.8 years). Patients mean follow up time after starting rituximab was 39 months (ranging from 11 to 67 months).

All patients were diagnosed with generalized MG, 4 of them were AChR-IgG+ and 2 were seronegative. The majority of patients started rituximab due to refractory MG, yet 2 patients initiated treatment in order to control a concurrent autoimmune disease (SLE and RA).

Clinical response to treatment

A summary of the clinical response is expressed in Tables 1 and 2.

We observed a decrease in the MGCS mean score after the first cycle of RTX and an even more relevant decrease at the final evaluation, 36% and 53% ($p = 0.028$) respectively.

All our 6 patients were on treatment with several immunosuppressors (average of 2.2 drugs). After the first cycle of RTX therapy that number was reduced in 33%, to a mean of 1.5 drugs per patient and had a further reduction of 47% to a mean of 1.2 ($p = 0.012$) at the final evaluation.

Five out of 6 patients were on oral corticosteroids. None of them was able to completely taper off prednisone after starting rituximab treatment; however, there was a significant reduction of 53%, from an average dose of 23.5 mg/day to 13 mg/day ($p = 0.047$).

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