Original manuscript

Rituximab in the Treatment of Refractory Myasthenia Gravis : Studying the Outcomes using MMT Score and Need for Plasmapheresis in Baghdad Teaching Hospital

Abeer Abdulhadi Rashid[1], Sarmad Abdulrasool Almashta[2], Rana Ali Hussein[3], Ahmed khaleel Mashaallah*[4]

[1]Lecturer, department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah university,Iraq, [2]Consultant neurologist, Baghdad teaching hospital, Iraq, [3]Clinical pharmacy specialist, Intensive care unit,Baghdad teaching hospital, Iraq, [4]Bactriologist, Baghdad Health Directorate - Al-Karkh,Iraq.

Abstract

Introduction: Myasthenia gravis (MG) is an uncommon autoimmune disease that is caused by acetylcholine receptor antibodies (AChRA) at the neuromuscular junction. Its pathogenesis involves complement fixing antibodies directed against acetylcholine receptors, muscle-specific tyrosine kinase or low density lipoprotein receptor–related protein.

Method: A descriptive case series study investigating rituximab in refractory MG was conducted in Baghdad teaching hospital .Patients who were included in the study had received a regimen of rituximab that was deemed appropriate by their treating physician.

Results: A total of 24 patients with mean disease duration of 6.3 years ±3.6 standard deviation were included in this study. The results showed that the average age of patients was 33.3 ,years ±10.1 SD and 62.5% was females. All twenty four patients showed an obvious improvement in clinical status after finishing the follow-up period. The results demonstrated from all patients that enrolled in our study, only one patient that who was on 14 sessions of plasmapheresis was in need for plasmapheresis after induction of rituximab and this difference was statistically significant.

Conclusion: There were a great clinical improvement as shown with MMT score in addition to discontinuation of plasma exchange treatments fallowing treatment with rituximab.

Keywords*: Rituximab, Myasthenia gravis, Refractory, plasmapheresis*

Introduction

Myasthenia gravis(MG) is an uncommon autoimmune disease that is caused by acetylcholine receptor antibodies (AChRA) at the neuromuscular junction[1]. Its pathogenesis involves complement fixing antibodies directed against acetylcholine receptors, muscle-specific tyrosine kinase or low density lipoprotein receptor–related protein[2].Muscle weakness, with abnormal fatiguability, and improvement after rest, characterize myasthenia gravis. Symptoms tend to be worse at the end of the day, and after repetitive use of muscles for a particular task[3]. Commonly, MG affects the ocular muscles first and this results in ptosis and diplopia[4]. Many studies was done to clarify the meaning of refractory myasthenia gravis and use specific standards like failed response to standard duration and doses of traditional treatment with immunosuppressive drugs, undesirable adverse reactions to conventional therapy, the need for frequent use of short period therapies such as IV Immunoglobulin and plasmapheresis,and /or suffering patients from repeated myasthenic crises[5]. It can occur at any age but most commonly affects women under the age of 40 and men over the age of 60[6].There are only a few studies on the epidemiology of myasthenia gravis based on complete populations[7] prevalence rates have increased to about 20 per 100,000 in the US population[8] . There are a deficit in epidemiological data on MG in Arab countries. The incidence rate reported from Libya is similar to the worldwide incidence rate of 5.3 per million person-years estimated in a systematic

review of population-based studies, and showed a higher incidence rate of MG in young women and older men[9]. The neuromuscular abnormalities in MG are thought to be an autoimmune response related to specific anti-AChR antibodies,but how the autoimmune response is started and preserved in MG is not fully understood[10]. AChR antibodies mostly belong to the IgG1 and IgG3 subclasses, which stimulate the complement cascade to destruct the postsynaptic membrane,which may lead to up regulation of inflammatory cytokines[11]. The ultimate goal of treatment is to achieve complete stable remission, defined as no myasthenic symptoms or signs without any ongoing treatment for at least 1 year[12]. Therapies in MG should therefore eliminate patients' symptoms within the boundaries of adverse events associated with treatment itself[13].

Patients and Method

A descriptive case series study examining rituximab in refractory MG was performed in Baghdad teaching hospital .Patients who were included in the study had received a regimen of rituximab that was deemed appropriate by their treating physician. total of twenty four patients identified with refractory generalized MG were enrolled in the study. Physical tests were estimated before and after treatment with rituximab.MMT score is used to show clinical improvement. MMT is a procedure for the evaluation of strength of individual muscle or muscles group based upon the effective performance of movement relation to the forces of gravity or manual resistance.

There were no specific criteria used to stage clinical response against no clinical response. The main outcome of the study was the improvement in MMT score and symptoms of patients ,with the other outcomes being the change in the frequency of plasma exchange which were done at the estimation of the clinician.patients that are included in the study are 13 to 90 years old that must have refractory MG, that not respond to glucorticoid and other immunsupressive therapy,Subjects must be on a stable standard immunosuppressive regimen with no history of thymoma, tumor, infection, or interstitial lung disease on chest CT, MRI, or chest x-ray.patient that are excluded from the study are patients with history of chronic degenerative, psychiatric, or neurologic disorder other than MG that can produce weakness or fatigue,Female subjects who are premenopausal who are pregnant,breast feeding or not use effective method for contraception.Protocol for Rituximab was administered in a standard dose of 1g. Every cycle is estimated as one infusion for two weeks. The space between cycles was adjusted as 6 months.To see the safety and adverse events, we collected notes from the infusion center and also, a complete blood count and, liver function test profiles present in patient's medical records. SPSS version 22 was used for data entry and analysis. Mean and standard deviation was used to represent the numerical data while the frequency and percentage for categorical data. Independent student T test and the test chi-square (Fischer exact test if not applicable) ,were used to confirm significance $p < 0.05$ was considered significant.

Results

A total of 24 patients with mean disease duration of 6.3 years ±3.6 SD were included in this study. The results showed that the mean age of patients was 33.3 years ±10.1 SD and 62.5% was females. All twenty four patients showed a marked improvement in clinical status by the end of the follow-up period. Five of the patients underwent a single cycle of rituximab, two received two cycles of rituximab while the remaining received either three or more cycles of rituximab.The results indicated there was no significant difference ($p=0.5$) in plasmapheresis session that as needed after induction of rituximab when compared according to number of cycle of rituximab in term of < 4 or ≥ 4 cycles, where the results showed that only one patient was in need for plasmapheresis session of those who received less than 4 cycles of rituximab while no one in need for plasmapheresis session of those who received more than 4 cycles of rituximab as seen in table 1.

Table.1. Association between no. of cycles of treatment and number of pl. exchange session

cycle of treatment with rituximab		plasmapheresis session				p-value
	Yes		No			
	No.	%	No.	%		
	<4	1	7.1%	13	92.9%	0.5
	≥4	0	0.0%	10	100.0%	

The results demonstrated from all patients that enrolled in our study, only one patient that who was on 14 sessions of plasmapheresis was in need for plasmapheresis after induction of rituximab and this difference was statistically significant(p=0.03) as seen in table 2.

Table.2: Associations between plasmapheresis sessions pre and post treatment with rituximab

Plasmapheresis session-pre rituximab/no.of patients		plasmapheresis session/post rituximab				p-value
	Yes		No			
	Count	Row N %	Count	Row N %		
	No sessions(1 patients)	0	0.0%	1	100.0%	0.03
	1 session(1 patients)	0	0.0%	1	100.0%	
	2 session(2 patients)	0	0.0%	2	100.0%	
	3 sessions(5 patients)	0	0.0%	5	100.0%	
	4 sessions(6 patients)	0	0.0%	6	100.0%	
	5 sessions(3 patients)	0	0.0%	3	100.0%	
	6 sessions(1 patients)	0	0.0%	1	100.0%	
	7 sessions(1 patients)	0	0.0%	1	100.0%	
	8 sessions(1 patients)	0	0.0%	1	100.0%	
	10 sessions(1 patients)	0	0.0%	1	100.0%	
	12 sessions(1 patients)	0	0.0%	1	100.0%	
	14 sessions(1 patients)	1	100.0%	0	0.0%	

Regarding MMT score the results indicated that the highest frequency (50%) of patients was in score 2 of MMT score before using the rituximab followed by score 3(33.3%) and lastly the score 1(16.7%) as seen in table 3.

Table 3. Frequency of patients according to MMT scores before using rituximab.

	No. of patients	%
Score-2	12	50.0
Score-3	8	33.3
Score-1	4	16.7
Total	24	100.0

After using the rituximab; the highest frequency of patients 12(50%) was improved to score 5 of MMT followed by score 4 (33.3%) and only 16.7% was in score 3 as seen in table 4.

Table.4. Frequency of patients according to MMT scores post using rituximab.

	No. of patients	**%**
Score-5	12	50.0
Score 4	8	33.3
Score 3	4	16.7
Total	24	100.0

The finding revealed that from 4 patients who was with score one before treatment with rituximab;3 patients was improved to score 4 and 1 to score 5.From 12 patients who were in score 2 before using of rituximab;4 patients were improved to score 3,3 patients improved to score 4 and 5 patients to score 5.From 8 patients who were in score 3 before treatment with rituximan;2 patients were improved to score 4 and 6 patients to score 5. So the results revealed that the frequency of patient who had pretreatment high score of MMT ,who were reach the highest score after treatment with rituximab was higher than those who were already had low score before using the rituximab but this difference was non-significant as seen in table 5.

Table 5:Association of MMT pre and post using of rituximab

		MMT/after					**p-value**
	Score-3		**Score-4**		**Score-5**		
	No.	%	No.	%	No.	%	
MMT/ before	Score-1(n=4)	0	0.0%	3	75.0%	1	0.8 25.0% 41.7% 75.0%
	Score -2(n=12)	4	33.3%	3	25.0%	5	
	Score-3(n=8)	0	0.0%	2	25.0%	6	

Discussion

In this study of 24 patients that present with refractory generalized myasthenia gravis ,we see that rituximab result in a sustained clinical improvement as demonstrated by immproved MMT score in addition to reduce frequency or lack of need for plasma exchange treatments as shown with Anderson et al study[14]. At time of this study, all patients were followed for1 year following infusion with rituximab. The results of this analysis favor the theory that rituximab can be effective for treatment of refractory MG which is compatible with small reports that were done previously as in Zebardast et al and other studies[15,16]. Most patients may need two or more cycles of rituximab for obvious decrease and discontinuation of other immunsupressant ,in addition to the attainment of disease remission.As there is no fixed protocol for rituximab use in myasthenia gravis, retreatment is decided based on disease activity and clinical improvement , with a minimum interval between infusions of 6 months which is similar to Peres et al[17].A perfect protocol has not yet been confirmed, however, some studies used peripheral B-cell count as a guide for retreatment with rituximab and to decrease toxicity and side effects [18,19]. An additional studies are required to recognize the best objective clinical indicators and to fix pharmacokinetics in this kind of patients. Immunoglobulin levels,B-cell counts, titers for antibody would seem the most helpful objectives at this time but in our study we depend on symptoms improvement and MMT score. All patients in this study can tolerate rituximab with no severe hematologic derangements[20,21]. The patients in this study were monitored clinically for rituximab adverse effects while in the infusion center as well as with CBC and LFTat baseline and after each infusion. All patients in this study can tolerate rituximab with no severe hematologic derangements. Infusion reaction is the most common side effect reported in general[22]. There is a need for a larger prospective controlled trial to gain more definitive conclusions about the efficacy of rituximab in the treatment of refractory MG.The strong effect of rituximab in patients with refractory MG in our center as well as in similar studies is promising and suggests that further investigation of this agent in MG is warranted [23,24].

Conclusion

There were a great clinical improvement based on MMT score, in addition to decrease or cutting the use of plasma exchange fallowing treatment with rituximab. Rituximab is an attractive treatment because of its mechanism of action that result in targeting CD20-positive B cells which are engaged in the production of antibodies . Most patients in this study can tolerate rituximab with no sever hematologic derangements and mild infusion reactions were the most common side effects associated with our study.

Conflict of Interest :Nil

Source of Funding:self

Ethical Clearance: Ethical Clearance: verbal consents were obtained from the all patients before their enrollment in the study.

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