Exp Biomed Res 2023; 6(2): 99-105 **DOI: 10.30714/j-ebr.2023.173**

Experimental Biomedical Research *Original article*

Effect of mirabegron on overactive bladder symptoms in patients with myasthenia gravis disease

Burak Onal[1], Kenan Sabuncu[2], Bahadır Ermec[2], Erdal Abay[2], Mehmet Gokhan Culha[2]

[1]Biruni University Medical Faculty, Medical Pharmacology Department, Istanbul, Türkiye
[2]University of Health Sciences, Prof. Dr. Cemil Taşçioğlu City Hospital, Urology Clinic, Istanbul, Türkiye

ABSTRACT

Aim: Overactive bladder (OAB) is a chronic, bothersome disease that decreases the quality of life and can be treated with antimuscarinic or β(3)-adrenergic agonist drugs, such as mirabegron. Myasthenia gravis (MG) is an autoimmune disease, in which neurotransmission is blocked by antibodies. Mirabegron is recommended as the first-line medical treatment for OAB compared with antimuscarinic drugs, which have several severe side effects. In this study, we assessed the efficacy of mirabegron in patients with MG and OAB.

Methods: A total of 57 MG patients with OAB were included in this study. The participants received 50 mg mirabegron once daily and were followed up for 4 weeks. Subsequently, patients were evaluated using the International Consultation on Incontinence-Short Form and the "Overactive Bladder Symptom Score" (OABSS) and tasked to complete a 3-day micturition diary.

Results: According to the 4-week follow-up results, the decrease in the OABSS scores following mirabegron administration was statistically significant ($p<0.001$). In addition, the frequency of daily micturition, nocturia, and need for a daily pad decreased dramatically ($p=0.001$, $p=0.002$, and $p<0.001$, respectively). In contrast, the average voiding volume increased significantly ($p=0.001$).

Conclusions: Although they induce several side effects, antimuscarinic drugs are commonly used for OAB treatment. However, only a few autoimmune response-inducing drugs, with minimal side effects, are favored in MG comorbidity treatments. Thus, mirabegron is a promising candidate drug for the treatment of this type of comorbidity.

Key words: Overactive bladder, Myasthenia gravis, mirabegron, comorbidity.

✉ *Dr. Burak Onal*
Biruni University, 10. Yil Cad. Protokol Yolu No: 45 Zeytinburnu, Istanbul, Türkiye
E-mail: burakonal@yandex.com
Received: 2022-12-28 / Revisisons: 2023-01-15
Accepted: 2023-01-25 / Published online: 2023-03-15

Introduction

Overactive bladder (OAB) is a chronic multi-symptom complex with a high global prevalence of approximately 12% [1]. The International Continence Society and International Urogynecology Association define OAB as “urinary urgency, usually accompanied by frequency and nocturia with or without urinary incontinence in the absence of pathologic or metabolic conditions that might explain these symptoms” [2]. Nocturia is defined as one or more voids that disturb sleep whereas urinary frequency corresponds to more than seven voids

during the daytime. Urinary incontinence is an uncontrollable leakage of urine induced by an urgent need to void [3]. The number of pads used, impact on quality of life, and/or use of validated questionnaires can all be used to measure the severity of OAB symptoms [4].

According to the American Urological Association OAB treatment guidelines, treatment should be performed at three levels of care [5]. Primary treatment involves a change in the lifestyle of the patient. This behavior-modified therapy includes pelvic floor physical therapy, Kegel exercises, bladder training, weight loss, and bowel regulation. Secondary treatment is focused on medical treatment, and neuromodulation of the nerves mediating bladder function is the third-line therapeutic option. Among the US Food and Drug Administration-approved neuromodulation therapies, sacral neuromodulation (approved in 1997) is used to treat fecal incontinence and non-obstructive urinary retention in addition to refractory OAB, whereas other classes of neuromodulation therapies, such as peripheral tibial nerve stimulation (approved in 2005) or the injection into the bladder of a chemo-denervation agent like botulinum toxin A (approved in 2013), are limited to refractory OAB treatment only [6].

The physiology of OAB depends on the degree of impairment of muscarinic acetylcholine receptors, including M3, which is responsible for normal micturition contraction, and M2, which controls detrusor contractions [7]. Due to detrusor overactivity induced by the stimulation of bladder muscarinic receptors by acetylcholine, the detrusor muscle contracts involuntarily during the filling phase of the micturition cycle, resulting in the OAB phenotype [8].

Antimuscarinic drugs, including solifenacin, oxybutynin, darifenacin, and trospium are currently available with grade A recommendations [9], level 1 evidence [10], and similar efficacy and safety profiles. However, due to intolerable side effects such as dry mouth and eyes, blurred vision, and constipation owing to the non-selective anticholinergic mechanism of action of antimuscarinic drugs, current OAB treatment is now dominated by β(3)-adrenoceptor agonists, such as mirabegron [11]. Mirabegron as the first β(3)-adrenoceptor agonist, currently dominates the market and functions by targeting β(3)-adrenoceptors in the detrusor muscle and urothelium. Its metabolism is controlled by the cytochrome P450 system and is mainly excreted in the urine and feces [12]. After oral administration, mirabegron increases bladder storage capacity while maintaining bladder contractions during voiding [13]. In addition, since the expression of target receptor β(3) is limited to the bladder, the inherent cardiovascular safety profile of mirabegron contributes to its superiority in comparison to antimuscarinic drugs [14].

Myasthenia gravis (MG) is a chronic, autoimmune and neuromuscular transmission disease characterized by an autoantibody reaction to the structures of the neuromuscular junction, resulting in impaired synaptic transmission and the consequent fatigability and weakness of skeletal muscles [15]. The disease's prevalence is higher in women (approximately 70%), and the varying severity of symptoms and degree of muscular involvement directly impact the patient's quality of life [16]. The existing standard of care for the management of mild symptoms of MG entails the use of acetylcholine esterase inhibitors; however, immunosuppressors such as eculizumab (FDA approved), zilucoplan (FDA orphan drug approval), rozanolixizumab, and efgartigimod are used for long-term treatment [17].

This study aimed to clarify the efficacy of mirabegron in patients with MG and OAB.

Materials and metods

Study sampling

A total of 57 female MG patients, receiving 50 mg mirabegron (Astellas Pharma, Japan) once daily for OAB symptoms and followed up in Prof. Dr. Cemil Tascioglu City Hospital in Istanbul between November 2018 and June 2019, were enrolled in the study. The study participants were requested to answer the International Consultation on Incontinence-Short Form (ICIQ-SF) and Overactive Bladder Symptom Score (OABSS) questionnaires and complete a 3-day micturition diary. After the administration of 50 mg of mirabegron, the patients were then subsequently followed up for 4 weeks. Improvement in the OAB symptoms of the patients was evaluated according to the OABSS survey, daily pad number, and 3-day micturition diary notes. The study was approved by the Clinical Research Ethics Committee of Prof. Dr. Cemil Tascioglu City Hospital (approval number: 361). Written informed consent was obtained from all the patients.

Statistical Analysis

Data analysis was performed using SPSS 25.0 (IBM Corp, Armonk, NY, USA). The distribution of cases was tested for goodness-of-fit using the Kolmogorov-Smirnov test. The dependent samples *t*-test and Wilcoxon test were used to compare data before and after treatment. Statistical significance was set at <0.05.

Results

Patient clinical history and demographic data are presented in Table 1. The patients were requested to answer the OABSS and ICIQ-SF to collect OAB and incontinence data, such as daily micturition and nocturia, average voiding volume, and pad usage before and after the treatment. According to the 4-week follow-up results, the decrease in the OABSS scores was statistically significant (p<0.001). Additionally, the frequency of daily micturition and nocturia decreased dramatically (p=0.001 and p=0.002, respectively). However, the average voiding volume increased significantly (p=0.001). Moreover, the need for daily pads decreased after treatment (p<0.001) (Table 2).

Table 1. The demographic evaluation of the participants.

Parameters	**Patient n (%)**	
Constipation	28/57 (49.1)	
Smoking	38/57 (66.7)	
Alcohol Usage	52/57 (91.2)	
OAB-Dry	25/57 (43.9)	
OAB-Wet	32/57 (56.1)	
	Mean±SD	**Min-Max**
Age	47.25±11.26	23-76
BMI	27.65±8.61	20.12-35.71

OAB, overactive bladder; BMI, body mass index; SD, standard deviation

Table 2. Changes in OABSS, ICIQ-SF scores, and pad usage between pre-and post-treatment.

	Pretreatment	**Posttreatment**	***p*-value**
OABSS	7.12±4.54	2.18±2.89	<0.001
Pad/day	3.25±0.81	0.98±0.62	<0.001
Micturition/day	9.12±3.65	6.30±2.22	0.001
Nocturia/day	1.62±0.77	0.67±0.35	0.002
Mean Voiding Volume	127.02±62.03	185.56±71.90	0.001

OABSS, Overactive Bladder Symptom Score; ICIQ-SF, International Consultation on Incontinence-Short Form

Some patients reported side effects such as hypertension, constipation, dry mouth, and headache; however, the percentage of these side effects was low (Table 3).

Table 3. The side effects of post-mirabegron treatment

Side effects	Patient n (%)
Hypertension	5/57 (8.8%)
Constipation	3/57 (5.3%)
Dry mouth	2/57 (3.5%)
Blurred vision	1/57 (1.8%)
Headache	1/57 (1.8%)

Discussion

Overactive bladder (OAB) syndrome is a detrusor overactivity and/or ureterovesical dysfunction that adversely affects the quality of life in both sexes [18]. Although the overall pathophysiology of OAB has not yet been uncovered, for several decades, the antagonism of muscarinic receptors through antimuscarinic agents has been a significant milestone in the management of overactive bladder symptoms [19]. However, due to the lack of specificity of these antimuscarinics, several side effects may emerge during treatment [20]. Owing to interindividual differences and symptoms, there is no standard treatment protocol for OAB management [14]. Moreover, the presence or absence of side effects due to oral medication is found to be a crucial factor in the management of OAB tolerability results [21].

The discovery of mirabegron, a β(3)-adrenoceptor agonist, is an important breakthrough in the management of OAB, owing to its lack of anticholinergic side effects and its effectiveness in patients with hypersensitivity to antimuscarinic treatment [11].

MG is an autoimmune disease characterized by the accumulation of self-antibodies at the neuromuscular junction, resulting in the attenuation of neuromuscular transmission. Immunotherapies are used to manage the symptoms [22,23]. This study focused on mirabegron-associated overactive bladder symptom improvement in patients with myasthenia gravis disease.

According to our results, mirabegron administration to MG patients with OAB has significantly contributed to their quality of life, as micturition, nocturia, and the required pad numbers have dramatically decreased during the post-treatment period.

The first-line treatment for mild MG is acetylcholinesterase inhibitors. However, in more severe conditions, broad-based, long-term immunosuppressants, including azathioprine, corticosteroids, and tacrolimus, may be applied [22]. However, for a remarkable number of patients with MG, these broad-range therapies are ineffective and/or lead to serious adverse effects [24]. Thus, owing to their non-selective anticholinergic mechanism of action, antimuscarinic administration in MG patients with OAB must be carefully monitored. Accumulating evidence suggests that an alternative antimuscarinic-free treatment protocol should be applied in patients with MG and OAB. In contrast to the established side effects of antimuscarinic drugs, such as increased constipation, blurred vision, dry mouth and eyes [13], mirabegron administration resulted in the alleviation of the aforementioned side effects in the present study.

It is critical to note that OAB therapy should be based on a bother score. In cases with a low bother score and a high OAB total score, lifestyle changes without medical treatment should be recommended to the patient. In the presence of a high bother score, the effect of well-known conditions, such as diabetes or obesity, that exacerbate OAB should be considered as much

as possible [25]. In addition, an autoimmune response based on the MG profile may elevate these conditions. Thus, a well-designed conservative therapy, such as weight loss and pelvic floor exercise, should be the first-line therapy for MG patients with OAB. However, due to the accompanying symptoms of OAB, MG patients should be supported with medical treatment employing the β(3)-adrenoceptor agonist, mirabegron, but not an antimuscarinic drug.

This study has certain limitations. First, this study was inherently limited by its small sample size. Second, there was a lack of healthy participants in the control group. Finally, we only reported on the patients' short-term outcomes and were unable to gather long-term data. However, it is important to note that the effect of mirabegron at the end of the 4th week was still significant in some studies [26,27].

Conclusions

The underlying causes of OAB are not well known, and its symptoms can vary among individuals. A complete cure is still undiscovered and managing an OAB with concurrent MG comorbidity is difficult for the physician. As these are preliminary findings, new studies should be conducted to evaluate the effects of present OAB therapies for each diverse OAB subpopulation with different comorbidities, leading to a more individualized medical approach in the era of personalized pharmacotherapy.

Funding: *The authors received no financial support for the research, authorship, and/or publication of this article.*

Conflict of interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *The study was approved by the Clinical Research Ethics Committee of Prof. Dr. Cemil Tascioglu City Hospital (approval number: 361).*

References

[1]Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50(6):1306-1314.

[2]Bo K, Frawley HC, Haylen BT, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. Int Urogynecol J. 2017;28(2):191-213.

[3]Raju R, Linder BJ. Evaluation and Treatment of Overactive Bladder in Women. Mayo Clin Proc. 2020;95(2):370-377.

[4]Gormley EA, Lightner DJ, Faraday M, et al. American Urological Association; Society of Urodynamics, Female Pelvic Medicine. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol. 2015;193(5):1572-1580.

[5] Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019;202(3):558-563.

[6] Willis-Gray MG, Dieter AA, Geller EJ. Evaluation and management of overactive bladder: strategies for optimizing care. Res Rep Urol. 2016;8:113-122.

[7] Braverman AS, Luthin GR, Ruggieri MR. M2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. Am J Physiol. 1998;275(5):R1654-60.

[8] Robinson D, Cardozo L. Managing overactive bladder. Climacteric. 2019;22(3):250-256.

[9] Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323(7308):334-336.

[10] Hadorn DC, Baker D, Hodges JS, et al. Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol. 1996;49(7):749-754.

[11] Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. J Urol. 2019;202(3):558-563.

[12] Shaw C, Gibson W. Assessing quality-of-life of patients taking mirabegron for overactive bladder. Ther Clin Risk Manag. 2023;19: 27-33.

[13] Chapple CR, Cardozo L, Nitti VW, et al. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. Neurourol Urodyn. 2014;33(1):17-30.

[14] Pratt TS, Suskind AM. Management of overactive bladder in older women. Curr Urol Rep. 2018 ;19(11):92.

[15] O'Connell K, Ramdas S, Palace J. Management of juvenile myasthenia gravis. Front Neurol. 2020 ;11:743.

[16] Mantegazza R, Baggi F, Antozzi C, et al. Myasthenia gravis (MG): epidemiological data and prognostic factors. Ann N Y Acad Sci. 2003;998:413-423.

[17] Menon D, Barnett C, Bril V. Novel treatments in myasthenia gravis. Front Neurol. 2020 Jun 30;11: 538.

[18] Abrams P, Cardozo L, Fall M, et al. Standardisation Sub-committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167-178.

[19] Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. J Urol. 2014;191(4):1003-1008.

[20] Pindoria N, Malde S, Nowers J, et al. Persistence with mirabegron therapy for overactive bladder: A real life experience. Neurourol Urodyn. 2017 ;36(2):404-408.

[21] Brubaker L, Fanning K, Goldberg EL, et al. Predictors of discontinuing overactive bladder medications. Br J Urol Int 2009;105: 1283-1290

[22] Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol. 2015;15(3):199-206.

[23] Koneczny I, Herbst R. Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture. Cells. 2019;8(7):671.

[24] Silvestri NJ, Wolfe GI. Treatment-refractory myasthenia gravis. J Clin Neuromuscul Dis. 2014;15(4):167-78.

[25] Zacche MM, Giarenis I, Thiagamoorthy G, et al. Is there an association between aspects of the metabolic syndrome and overactive bladder? A prospective cohort study in

women with lower urinary tract symptoms. Eur J Obstet Gynecol Reprod Biol. 2017;217:1-5.

[26] Khullar V, Amarenco G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol. 2013;63(2):283-295.

[27] Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol. 2013;63(2):296-305.