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Journal of Urology and Research

Research Article

Long Term Follow Up of Mirabegron - A Real Life- Pragmatic Experience

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Submitted: 04 June 2016

Accepted: 22 August 2016

Published: 24 August 2016

ISSN: 2379-951X

Keywords

- Mirabegron
- Beta-3 agonist
- Overactive bladder syndrome
- Long term

Abstract

Objectives: To evaluate the efficacy and tolerability of Mirabegron for the treatment of overactive bladder symptoms in a real life, long term follow up study conducted in a tertiary referral centre.

Methods: A structured telephone questionnaire of patients was conducted in order to evaluate the efficacy and tolerability of Mirabegron. Patients who were initially prescribed and responded to Mirabegron 50mg once daily between 6/2013 and 9/2013, were interviewed to see if they were compliant with treatment, continue to respond to treatment and if they discontinued treatment.

Results: Follow-up was for a mean of 11.7 months. At short-term follow-up, 20/39 patients responded to treatment. In the long term follow-up, 18/20 patients were still using Mirabegron. 2/20 patients discontinued because of lack of efficacy. Overall, the main reasons for discontinuation of Mirabegron after trying it for a mean of 5.3 months, was lack of efficacy and adverse events. The majority of AEs were mild in severity and few were serious. Other reasons include the lack of further prescription from general practitioners.

Conclusion: Mirabegron is an efficacious new treatment for OAB with a favorable tolerability profile over 1-year period. The treatment led to a noticeable improvement in patients' symptoms. The incidence of AEs was low; the majority was mild in severity and few were serious.

ABBREVIATIONS

OAB: Overactive bladder; UTI: Urinary Tract Infections; LUTS: Lower Urinary Tract Symptom; ICS: International Continence Society; AEs: adverse events; cAMP: cyclic Adenosine Monophosphate; NICEHTA: National Institute for Health and Clinical Excellence Health Technology Assessment; CTCAE: Common Terminology Criteria For Adverse Events; MMSE: Mini-Mental State Examination

INTRODUCTION

Overactive bladder (OAB) is defined as a condition with characteristic symptoms of urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection s (UTI) or other obvious pathology [1]. Using the standardized International Continence Society (ICS) definition of OAB, the EPIC study reported the prevalence of OAB in four European countries and Canada, as 11.8%, in the context of a prevalence of 64.3% for at least one lower urinary tract symptom (LUTS) [2]. Initial treatment of OAB involves life style interventions such as avoidance of dietary irritants and cessation of smoking, bladder training and pelvic floor muscle exercises followed by medications. Antimuscarinic agents have become the most widely used pharmacologic agents for the treatment of OAB symptoms. These agents elicit their effects by blocking muscarinic M2 and M3 receptors, thereby inhibiting involuntary detrusor contractions.

However, because detrusor contractions are also required for voluntary voiding, antimuscarinic agents have the potential to impair bladder emptying and may even cause urinary retention, particularly where there is coexisting bladder outlet obstruction [3]. Other common and bothersome adverse events (AEs) associated with antimuscarinics are dry mouth, constipation, dry or itchy eyes, blurred vision and UTIs [4]. In a considerable proportion of OAB patients, such side effects are sufficiently detrimental to quality of life that patients choose to discontinue treatment. Hence, these agents are associated with poor treatment compliance. The discontinuation rate is about 24.5%. The most commonly reported reason for discontinuing antimuscarinic agents was lack of efficacy (46.2%), followed by switching to a new medication (25.1%), patients managed to

get on by without medication (23.3%), and 21.1% discontinued because of experiencing adverse events [5].

Mirabegron is the first approved drug in a new class of compounds with a mechanism of action that is different from that of antimuscarinic agents [6]. It acts as an agonist at the beta3-adrenoceptor, which has been proposed to play a role in promoting urine storage in the bladder. The release of norepinephrine from sympathetic nerves induces the beta3-adrenoceptor to stimulate production of adenylcyclase, in turn increasing levels of intracellular cyclic adenosine monophosphate (cAMP) and thereby inducing detrusor relaxation [7]. Pharmacological studies support the conclusions that modest β1-adrenoceptor agonism occurs at high mirabegron exposures, with the potential for increases in pulse rate. However, its effects on cardiac electrophysiology are limited. Moreover, the effect of mirabegron on pulse rate in humans was less than in animals because of a higher cross sensitivity of mirabegron for the β1-adrenoceptor in animals, compared with humans at similar exposure levels. Tissue distribution studies in animals show that mirabegron is distributed to all tissue except the brain. Thus, mirabegron has a low propensity to cross the blood–brain barrier, suggesting that mirabegron has an acceptable central nervous system safety (CNS) safety profile for the treatment of patients with OAB [8–10]. However, this still needs long term randomized controlled studies in human to be proven.

Mirabegron was launched in the United Kingdom in February 2013 and had National Institute for Health and Clinical Excellence Health Technology Assessment (NICE HTA) approval in June 2013. The aim of this study is to assess the efficacy and tolerability of Mirabegron in a pragmatic clinical setting outside the context of a clinical trial in a secondary and tertiary care centre.

MATERIALS AND METHODS

An open label prospective observational study was conducted to assess the compliance, tolerability and efficacy of Mirabegron. Local ethical committee approval was granted before carrying out this study. Patients were prospectively recruited between 6/2013 and 9/2013. These patients had a clinical diagnosis of refractory OAB or urodynamic diagnosis of detrusor overactivity and have failed antimuscarinic therapy previously after a trial of at least two months except for one patient who had Sjogren's disease with dry eyes and mouth. 72 patients were prescribed 50mg Mirabegron.

Patients were informed about the study in a specialized functional urology clinic and had the right to refuse to participate as well as withdraw from the study at any point without giving reasons. Patients were also informed about the nature of follow up and that it will entail a telephone interview at a short term follow up of around 6 weeks and a long term follow up at around 12 months. Several trials were made to contact the patients before they were deemed un-contactable. The structured telephone questionnaire of patients was conducted by an independent researcher to assess compliance, tolerability and efficacy of Mirabegron.

The questions asked were:

1. Are you still on the medication?
2. How long have you been on the treatment in months?
3. If you stopped the medication, why did you?
4. Did you encounter any side effects from treatment? If yes, what side effects?
5. Did the medication improve your symptoms? If yes, in what way?
6. Are you taking other anticholinergics with Mirabegron?

RESULTS AND DISCUSSION

Results

39 patients were included in the trial with 30 female patients and 9 male patients; median age of 62 years (range 22 - 84). 33 patients were excluded from the study for various reasons. All of the recruited patients had a clinical diagnoses of OAB and 64% (n=25/39) had urodynamics (Figure 1). 38/39 patients (97.4%) had been on previous antimuscarinics; 14 (35.9%) tried 1; 10 (25.6%) tried 2 and 14 (35.9%) tried 3 or more antimuscarinics. There was no statistical difference between the number of previous antimuscarinics tried and response to Mirabegron (Chi^2 0.23).

At short term follow up of a median of 6 weeks (range 2-16), 51.3% of patients (n=20/39) responded to treatment and had symptomatic improvement of OAB symptoms in the form of a reduction in the 24 hour incontinence episodes, decrease in daily pad usage and a reduction in the micturition frequency episodes. The response rate at 1-3 weeks was 2.6%, at 4 weeks was 12.8% and at 6-16 weeks was 35.9% (Chi^2 0.03). Having idiopathic or neurogenic detrusor overactivity did not significantly affect the response to Mirabegron (Chi^2 0.15).

The most reported adverse events (AEs) observed are in Table 1. 12.8% of patients (n=5/39) stopped their treatment because of AEs which included dry eyes and mouth, worsening Parkinson's and palpitations. All the patients who had palpitations were less than 65 years old. The AEs were of grades 1 and 2 based on the common terminology criteria for adverse events v4.0 (CTCAE).

20 patients were included in the long-term follow-up of a mean of 11.7 months. 18/20 patients were still using Mirabegron due to an improvement in their symptoms. 2/20 patients discontinued because of lack of efficacy. The beneficial effects of Mirabegron started to gradually fade away after 24 weeks in one patient and after 30 weeks in the other patient. Only 1 patient had AEs in the form of bladder pain. 9/18 patients were using a combination of Mirabegron and 1 other antimuscarinic medication. The other antimuscarinics used were solifenacin, trospium and fesoterodine. Those patients were on a combination of Mirabegron and other antimuscarinic agents from the start of the study.

Discussion

Antimuscarinic therapy is the current standard first-line pharmacotherapy for OAB. However, although these agents are generally effective, nearly a quarter of the patients experience a suboptimal response to treatment or experience frequent, bothersome AEs, the most common of which is dry mouth.

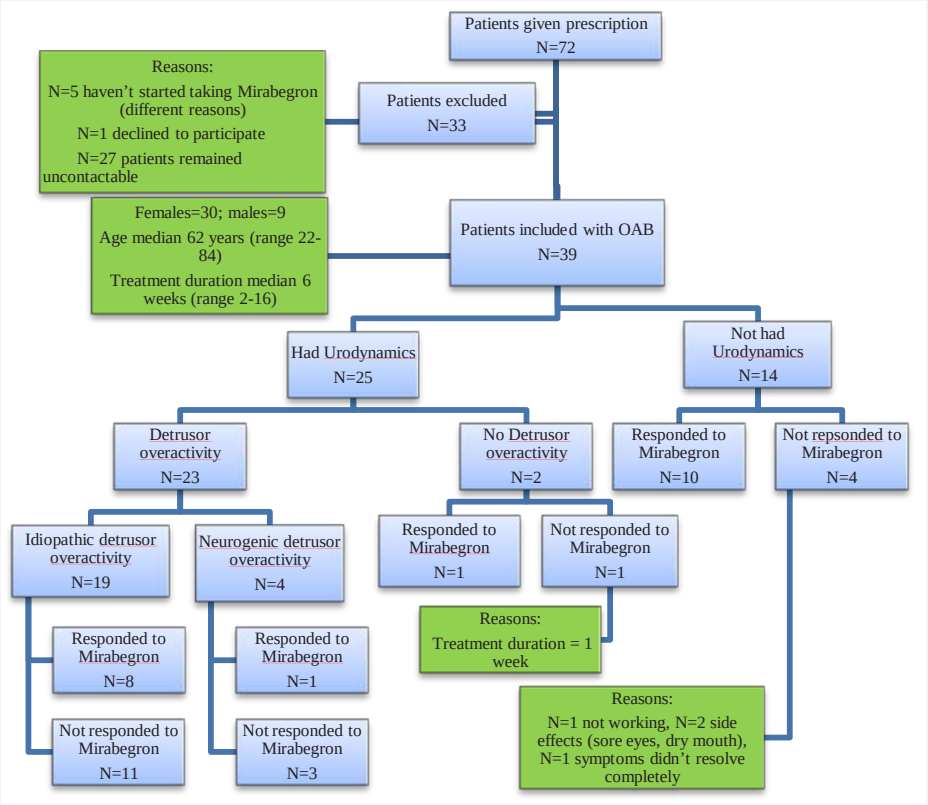

Figure 1 All of the recruited patients had a clinical diagnoses of OAB and 64% (n=25/39) had urodynamics.

Table 1: Adverse Events of Mirabegron.

Adverse Events (AEs)	Number (%)
Rash / itchy	2 (5%)
Palpitations	2 (5%)
Dry mouth	1 (2.6%)
Dry eyes	1 (2.6%)
Sore eyes	1 (2.6%)
Headache	1 (2.6%)
Dizziness	1 (2.6%)
Bloated/puffy legs/tiredness	1 (2.6%)
Abdominal pain	1 (2.6%)
Worsening Parkinson's	1 (2.6%)
Total	10/39 (25.6%)

Abbreviations: AEs: Adverse Events

Patients with suboptimal responses to antimuscarinic treatment or who are unwilling to continue treatment due to the associated AEs have no other oral drug available as a treatment option [11]. However, mirabegron is the first drug in the class of β 3 adrenoreceptor agonists to have completed phase 3 registration studies and approved for the treatment of OAB [10].

In the current study, mirabegron 50mg once daily showed clinical efficacy in the treatment of symptoms of OAB including; urgency, frequency and urgency incontinence that is comparable to phase III trials. Phase III trials showed a mean reduction in the mean number of incontinence episodes and micturation episodes per 24 hours form baseline to final visit (-1.48 (+0.15) and -1.74 (+0.16) respectively) [12]. This was supported by the data collected from the structured telephone questionnaire of patients. Mirabegron was well tolerated by the patients recruited in this study. The majority of AEs were mild in severity and few were serious. Only 1% of our patients suffered from dry mouth, which is reported to be an important factor in determining persistence with antimuscarinic agents [5,13]. Thus, the tolerability profile of mirabegron is higher than that of antimuscarinics offering the potential to improve persistence with treatment for OAB.

Another phase III trial comparing the effects of mirabegron, tolterodine and placebo conducted by Yamaguchi et al., [14] showed similar results as regards to improvement in the quality of life, compliance and AEs to this study. Treatment for 12 weeks was implemented in the phase III trial. The majority of AEs in the mirabegron group were mild in severity with constipation (3.4%) and dry mouth (2.6%) - excluding those on antimuscarinics - being the most predominant. The overall incidence of treatment-related AEs was similar in the mirabegron (24.5%) and placebo (24.0%) groups, but higher in the tolterodine group (34.9%). Still the main reason for withdrawal from the trial was AEs. 72% of patients on the mirabegron group were using concomitant medications to control their bladder symptoms.

A 12 months phase III trial was conducted to demonstrate the safety and tolerability of mirabegron [15]. The safety profile of mirabegron was similar to that seen in 12 weeks phase III studies [12,14]. Most AEs were mild or moderate in severity. The most frequent AEs included hypertension, dry mouth, constipation,

and headache. The reasons for discontinuing mirabegron were AEs (6.4%) and lack of efficacy (4.2%).

Wagg et al., [13] conducted a study to analyze the persistence patterns for different anti-muscarinics prescribed for OAB symptoms across the UK over a 12 months period. Persistence was defined as the mean number of days that a patient remained on therapy [16]. At 12 months, the persistence for anti-muscarinics ranged from 35% for solifenacin to 13.5% for flavoxate. Thus, sub-optimal persistence is therefore a major challenge for the successful management of OAB [17]. Medications with anti-cholinergic properties recognized by the anti-cholinergic cognitive burden (ACB) scale have been recently correlated with an additional 0.33 point decline in Mini-Mental State Examination (MMSE) score over 2 years [18]. There is a significant decline in cognitive ability with increasing anti-cholinergic load [19]. Not having anti-cholinergic properties, Mirabegron is not included in the anti-cholinergic risk scale and doesn't seem to have an effect on the cognitive abilities in the short term results so far [20]. Further research is needed to establish whether a relationship is present or not.

A phase III trial was conducted to assess the efficacy of mirabegron in patients with and without prior antimuscarinic therapy for OAB [21]. This trial concluded that mirabegron had a numerically positive treatment effect on incontinence and micturition frequency in patients who were treatment-naïve as well as in those who had received, but discontinued, prior antimuscarinic therapy, regardless of whether they had discontinued due to insufficient efficacy or poor tolerability. They also concluded that prior antimuscarinic users who discontinued due to insufficient efficacy, mirabegron showed numerical improvements in both outcomes whereas re-treatment with the antimuscarinic, tolterodine, produced an effect size similar to placebo.

Given the fact that the monthly cost of treatment for Mirabegron is £29 and the equivalent for solifenacin 10 mg is £35.91, Mirabegron may be the first line therapy for treatment of OAB symptoms being more cost effective with fewer side effects.

We acknowledge that this study has limitations. Firstly, the study population is small with a high initial exclusion numbers. Also, there is a lack of a placebo control group. However, this is the first study which aimed to be pragmatic and assess Mirabegron in the 'real' world outside the context of a clinical trial following approval and registration. After all, the majority of patients seen in outpatient clinics are not included in clinical trials and hence this study is very important in establishing whether the results seen in randomized clinical trials apply to the 'real' world.

CONCLUSION

Mirabegron is an efficacious new treatment for OAB with a favorable tolerability profile over a one year period. The treatment led to a noticeable improvement in patients' symptoms. The incidence of AEs was low; the majority was mild in severity and few were serious.

The efficacy and tolerability profile of mirabegron suggest that it may represent a valuable therapeutic option for patients with OAB who experience insufficient benefit from antimuscarinic therapy and in those who are intolerant of the associated AEs of antimuscarinics. It may even become first line medical therapy instead of antimuscarinics.

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Cite this article

Abdelmoteleb H, Yassin M, Hashim H (2016) Long Term Follow Up of Mirabegron - A Real Life- Pragmatic Experience. J Urol Res 3(6): 1068.