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Mirabegron: the review of current knowledge of safety and efficacy in the relief of overactive bladder symptoms

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abstract:

Mirabegron has been registered as the first strong and selective agonist of the β3 receptor. It is currently used for relief of symptoms of overactive bladder (OAB). That onerous illness involving urgency and detrusor overactivity, that may be accompanied by incontinence, affects approx. 16% of the population. Before registration of Mirabegron, the main

pharmacological and non-surgical therapeutic method was the treatment with anti-muscarinic drugs, associated with burdensome adverse effects. Clinical trials on over 10,000 participants demonstrated efficacy and safety of Mirabegron. Besides monotherapy, attempts are being made to use Mirabegron in combined therapy of OAB. The innovative mechanism of action of the drug makes it an attractive option not only in treatment of conditions of the urinary system, but also of metabolic disorders and diseases of the cardiovascular system. This article provides a review of the current knowledge and recent reports regarding Mirabegron - an alternative in treatment of the common and onerous disease of overactive bladder.

key words:
mirabegron, overactive bladder, review,

1. Introduction

Mirabegron is the first drug in the class of β3-adrenomimetics, that on December 20, 2012 was approved by the European Medicines Agency for treatment of symptoms of overactive bladder (OAB) in adults [1]. The need for a new strategy of OAB treatment is demonstrated in the Canadian study, in which over 91% of more than 30,000 participants with the disease discontinued the treatment with antimuscarinic drugs over the 4-year follow-up period. Additionally, majority of those patients received no second line treatment [2].

The OAB widespread in the general population is notable. According to Tubaro et al. the morbidity is 16.5%, and increases with age [3].

In clinical trials of over 10,000 patients, Mirabegron proved safe and equally effective as antimuscarinic drugs used before. Table 1. The innovative mechanism of action - the first potent and selective β3 receptor agonist - makes it, that: a) numerous studies are under way on the use of Mirabegron in treatment of other diseases, e.g. carbohydrate metabolism disorders [4] and heart failure [5], and b) Mirabegron is considered a valuable component of the new approach to OAB involving a combined therapy with Solifenacin - an antimuscarinic drug [6, 7].

The purpose of this article is to provide a review of literature regarding the use of Mirabegron in treatment of overactive bladder.

2 Overactive bladder

Overactive bladder (OAB) is the disease manifested by: urgency, frequent urination, nocturia, and incontinence. There is also a variant of the disease not associated with incontinence [8]. The diagnosis of OAB requires exclusion of other similarly manifesting diseases. Those diseases are: metabolic disorders (e.g.: diabetes, etc.) and local pathologies of the urinary system and of nearby structures (e.g.: UTI, prostatic hyperplasia, etc.). Depending on presence of episodes of incontinence, OAB is divided into OAB-wet (associated with incontinence) and OAB-dry (absence of incontinence) [10].

The aetiology of OAB remains unclear. It is believed that the principal role in that disease is played by overactivity of the detrusor muscle, resulting in abnormal function of the bladder (e.g.: contraction of the bladder at the stage of accumulation of urine). There are also premises indicating a significant role of exaggerated response of the cerebral cortex to the urinary stimulus [9].

It is estimated that OAB morbidity increases with age of the population [9]. A tendency for morbidity increasing with age is notable, particularly in women [10].

The strategy of OAB treatment is composed of three types of actions. Behavioural treatment is the first line. It is often combined with pharmacotherapy. According to literature reports, that strategy brings a significant improvement of the patient's quality of life [11]. Pharmacotherapy with antimuscarinics and β3 agonists is the second line. Surgical methods constitute an additional and separate attempt for treatment of OAB.

3 Mirabegron

According to MDA recommendations Mirabegron is a drug used for treatment of the following symptoms of OAB: urgency, increased frequency of urination (pollakiuria), incontinence. The drug has been registered by the EMA in two doses: 25 mg and 50 mg, in form of delayed release tablets. The recommended dosage is 50 mg once a day [1].

Using Mirabegron some clinical situations have to be considered in which the drug is not indicated, such as grade III arterial hypertension [1]. It was demonstrated that Mirabegron at the dose of 50 mg may increase the blood pressure by approx. 1 mmHg in patients treated for OAB [12]. Other clinical circumstances in which Miragebron is not indicated are: dysfunction of the liver classified as Child-Pugh category C and terminal kidney failure (dose

reduction down to 25 mg at the stage 4). The drug is also contraindicated for the juvenile population of under 18, because of insufficient body of data confirming safety and efficacy of the drug [1].

Mirabegron is also contraindicated during pregnancy and breastfeeding, because human milk is one of the drug's elimination routes, which may unfavourable affect breastfed children [13].

Theoretically there are three important metabolic pathways on which Mirabegron may interact with other drugs. They are: CYP2D6, CYP3A4 and the P glycoprotein transporter, where the drug acts as an inhibitor [1].

The most significant interactions of Mirabegron with other drugs occur in association with CYP2D6 inhibition [1]. The inhibition leads to increased levels of drugs being substrates for that isoenzyme. Examples of those drugs are: class I anti-arrhythmic drugs, tricyclic antidepressants and Metoprolol. Concomitant use of Mirabegron and Metoprolol resulted in a significant increase of the β-blocker maximum level, and extension of its half-life time. A similar correlation was observed for concomitant use of Mirabegron and desipramine (and active metabolite of imipramine)[14]. As for CYP3A4 that in patients using strong inhibitors of the enzyme (e.g. Ketokonazole) concomitantly with Mirabegron, and showing a moderate renal failure (eGFR 30-89 ml/min.) or hepatic failure (grade A), a dose reduction of the latter drug down to 25 mg is recommended. However, in case of grade 4 kidney failure and a concomitant use of a CYP3A4 inhibitor, Mirabegron is contraindicated [1]. As for the P glycoprotein transport pathway, a possible interaction with drugs, such as nitroglycerin, should be considered [1].

The effect of Mirabegron overdose was empirically studies on a selected group of patients who received a single dose of 300 mg or 400 mg over a period of 10 days. The patients presented symptoms of palpitation and tachycardia. Additionally, in case of an overdose lasting for 10 days, the blood pressure was increased [1]. Overdose should be treated symptomatically, as no specific antidote has been developed so far.

4 Mirabegron in other indications, besides OAB

Mirabegron is a relatively novel drug, and its field of application has not been clearly defined yet. There are premises of other possible use of the drug, besides OAB. One interesting possibility is a potential slimming and antidiabetic effect of Mirabegron. The effect could be based on the drug-induced increase of the resting metabolism by activation of cells of the brown adipose tissue (BAT). An attempt to confirm this theory was made by

Aaraon M. Cypess et al. on a group of selected healthy and young males. Although promising, results of that study indicated also a high (significant) rate of cardiovascular complications in form of hypertension and increased HR [4].

There are premises suggesting a positive effect of Mirabegron on patients with heart failure and reduced left ventricular ejection fraction (40 %). The positive effect would involve a clinically significant increase of LVEF [15]. Animal studies demonstrated that the mechanism could involve expression of the B-3 receptor, damping the hypertrophic response to factors such as angiotensin II [5].

5 Mechanism of action

Urine storage is under the control of the sympathetic nervous system. In opposition, micturiction is under control of the parasympathetic nervous system. Hence it may seem that both of these processes are independent of consciousness. However the storage of urine is also under control of consciousness because the external sphincter is sensory innervated. [16] The sympathetic impulses are conducted to bladder through the hypogastric nerves which is releasing noradrenalin (NA) from hypogastric nerve endings. Sympathetic impulse promote urine storage in two mechanisms. First, noradrenalin activates β3-adrenoreceptors localized in urinary bladder wall which cause relaxation of the detrusor muscle. Secondly noradrenalin activates α1A –adrenoreceptors localized in urethra what causes contraction of urethral smooth muscle. [16] In Summary of Product Characteristic published by European Medicines Agency mirabegron has been registered as selective and potent β3 agonist.[1] Therefore, mirabegron promotes the urine storage by stimulating the β3-adrenoreceptor which causes detrusor relaxation. This mechanism of action can be found in scientific databases. However, recent study shows that mechanism of mirabegron action in treatment of overactive bladder symptoms is not as clear as it seemed to be.

Alexander et al. in 2015 published interesting results of the research, which shows that the action of mirabegron in the urethra, in addition to β3- adrenoreceptors agonism, it is also α1-adrenoreceptors antagonism. [17] From a clinical point of view mirabegron compared to placebo showed significantly better results at primary endpoints (mean number of incontinence episodes/24 h, micturitions/24 h, and mean vo lume voided/micturition (MVV)) [18]

6 Safety and adverse events

The multicentre TAURUS study by Chapple et al. was designed to assess safety of the therapy with Mirabegron. Table 1 [19]. The follow-up in the study was 12 months, 812 patients received Mirabegron 50mg, 820 - Mirabegron 100 mg, and 812 - Tolterodine 4 mg extended release. The primary endpoint was the number of participants with treatment-emergent adverse events (TEAEs) and their severity. The study confirmed safety of Mirabegron in comparison to Tolterodine, in terms of number of TEAEs and their severity: (Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, respectively.) Additionally, the TAURUS study indicated a statistically lower incidence of mouth dryness episodes in the Mirabegron group compared to Tolterodine [19].

The clinical studies carried out so far show that dry mouth as a side effect of the mirabegron is comparable to placebo.[20,21,22] In comparison to antimuscarinic, the risk of dry mouth for mirabegron is significantly lower. [23] Hence mirabegron therapy compared to antimuscarinic therapy has lower percentage of discontinuation. [24] Warren et al. in her review also confirmed that there was significantly less dry mouth incidence in the mirabegron groups. Constipation, hypertension and tachycardia were comparable to anticholinergic medication. [25] Due to the presence of β3-adrenoreceptors in cardiovascular tissue the using of mirabegron can cause hypertension, tachycardia, palpitations and atrial fibrillation. Rossa et al. performed a systematic literature search to provide a summary of cardiovascular effects of β3-adrenoceptor. Conlusion of these study is that cardiovascular safety of the mirabegron is acceptable and comparable to antimuscarinic. [26] An additional common side effect is urinary tract infection. This is due to the mechanism of action by promote the storage of urine. This side effect is not serious enough to stops β3- adrenomimetic treatment. [27]

7 Clinical trials of Mirabegron in OAB

Many clinical trials were conducted that confirmed safety and efficacy of Mirabegron in treatment of OAB symptoms. The need for such extensive clinical research, especially on the safety of the medicine, resulted from its novel mechanism of action. Authors of this article focused on the analysis of 11 reports. Four of them were phase II clinical trials and other seven were phase III clinical trials [19-22; 28-34] Table 1. The total number of randomised patients was 13,458, including 7,643 participants receiving Mirabegron. Follow-up of those studies was 12 weeks, except for the BLOSSOM study [20] (4 weeks; proof-of-concept

study) and the TAURUS study [19] (12 months; the assessment of safety). All studies involved a control arm of: placebo (9 of 11; 2,656 patients) and/or antimuscarinics: Tolterodine 4 mg extended-release (6 of 11; 2,212 patients) and Solifenacin 5 mg (1 of 11; 944 patients). Inclusion criteria were: men and women at least 18 years of age; OAB symptoms lasting for at least 3-6 months. In studies 19; 21; 22; 28-32 there were some additional inclusion criteria regarding recorded micturition within a period of three days: an average ≥8 micturitions per 24h with an average 1 episode of urgency or urgency with incontinence per 24h. All studies demonstrated effectiveness of Mirabegron in treatment of symptoms of OAB. Table 1. Studies with primary endpoints of the change from baseline in mean number of micturitions per 24 hours and/or the change from baseline in mean number of incontinence episodes per 24 hours demonstrated a statistically significant improvement, compared to placebo, for doses: 25 mg; 50 mg; 100 mg; 200 mg once daily [21; 22; 28-32], and 100 mg and 150 mg twice daily [20].

For studies in which patients in the control arm received Tolterodine 4 mg extended release or placebo, it was demonstrated that the efficacy of Tolterodine in respect to the above mentioned endpoints was not statistically different to placebo [20-22]. Despite the use of a double control with Tolterodine and placebo, Yamaguchi et al. failed to report the statistical analysis of Tolterodine efficacy [31].

Secondary endpoints considered in studies were: changes from baseline to end-of-treatment in mean volume voided per micturition; mean number of urinary incontinence and urgency urinary incontinence episodes, and urgency episodes per 24 hr; severity of urgency; nocturia. Also for those endpoints the efficacy of Mirabegron was demonstrated [19-22; 28-33].

The aim of this work is reviewing effectiveness of Mirabegron. Hence, this publication does not contain any statistical analysis. For more insightful readers the authors recommend the meta-analysis and the systematic review on the efficacy and tolerance of Mirabegron published by Sebastianelli et al. in 2018 [27].

	study	study phase	participans (n)*	follow up (weeks)	experimental arms (n)**	active or placebo comparator (n)**	adverse events- overall (n; %)**	Primary efficacy endpoint and safety
1	BLOSSOM Chaplle et al. 2013 [20]	II	262	4	1) MIR 100mg TD (n=65) 2) MIR 150mg TD (n=65)	1) PBO (n=66) 2) TOL ER 4mg OD (n=64)	PBO 16/66 (24.2) - MIR 100mg 12/65 (18.5) MIR 150mg 16/65 (24.6) - TOL 4mg 17/64 (26.6)	1) Statistically significant improvement in micturition frequency. MIR 100mg TD and 150mg TD vs PBO; p≤0.01 for both comparisons). 2) A reduction noted for Tolterodine was not statistically significant versus placebo. 3) The incidence of AEs (overall) in each mirabegron doses was comparable with placebo
2	DRAGON Chaplle et al. 2013 [21]	II	928	12	1) MIR 25mg OD (n=169) 2) MIR 50mg OD (n=169) 3) MIR 100mg OD (n=168) 4) MIR 200mg OD (n=167)	1) PBO (n=169) 2) TOL ER 4mg OD (n=85)	PBO 26/169 (15.4) - MIR 25mg 34/169 (20.1) MIR 50mg 38/169 (22.5) MIR 100mg 36/168 (21.4) MIR 200mg 37/167 (22.2) - TOL 4mg 13/85 (15.3)	1) Statistically significant improvement in micturition frequency. MIR 50mg, 100mg and 200mg vs PBO; p≤0.05 for every comparsion. There was no statistical significance for the 25 mg dose per day. 2) A reduction noted for Tolterodine was not statistically significant versus placebo. 3) The incidence of AEs (overall) in each mirabegron doses was comparable with placebo.
3	Yamaguchi et al. 2015 [28]	II	842	12	1) MIR 25mg OD (n=211) 2) MIR 50mg OD (n=208) 3) MIR 100mg OD (n=209)	1) PBO (n=214)	PBO 40/212 (18.9) - MIR 25mg 49/210 (23.3) MIR 50mg 51/208 (24.5) MIR 100mg 54/208 (26.0)	1) Statistically significant improvement in micturition frequency. MIR 25mg, 50mg, 100mg vs PBO; p<0,001 for every comparison. 2) The incidence of AEs (overall) in each mirabegron doses was comparable with placebo.
4	ARIES Nitti et al. 2013 [29]	III	1329	12	1) MIR 50mg OD (n=442) 2) MIR 100mg OD (n=433)	1) PBO (n=454)	PBO 9/453 (1.99)^ - MIR 50mg 11/442 (2.49)^ MIR 100mg 14/433 (3.23)^ - ^ - Total, Serious Adverse Events	1) Statistically significant improvement in micturition frequency and incontinence episodes. MIR 50mg and 100mg vs PBO; p<0,05 for both comparisons. 2) The incidence of AEs in each mirabegron doses was comparable with placebo.
5	CAPRICORN Herschorn et al. 2013 [30]	III	1306	12	1) MIR 25mg OD (n=433) 2) MIR 50mg OD (n=440)	1) PBO (n=433)	PBO 217/433 (50.1) - MIR 25mg 210/432 (48.6) MIR 50mg 208/440 (47.3)	1) Statistically significant improvement in micturition frequency (MIR 25mg and 50mg vs PBO; p<0,005 for both comparsions) and incontinence episodes (MIR 25mg and 50mg vs PBO; p<0,005 and p<0,001; respectively.) 2) The incidence of AEs in each mirabegron doses was comparable with placebo.
6	Yamaguchi et al. 2014 [31]	III	1139	12	1) MIR 50mg OD (n=380)	1) PBO (n=381) 2) TOL ER 4mg OD (n=378)	PBO 91/379 (24.0) - MIR 50mg 93/379 (24.5) - TOL 4mg 131/375 (34.9)	1) Statistically significant improvement in micturition frequency. MIR 50mg vs PBO; p<0,001 2) Tolterodine group was not testing. 3) The incidence of AEs in mirabegron dose was comparable with placebo.
7	SCORPIO Khullar et al. 2013 [32]	III	1987	12	1) MIR 50mg OD (n=497) 2) MIR 100mg OD (n=498)	1) PBO (n=497) 2) TOL ER 4mg OD (n=495)	PBO 214/494 (43.3) - MIR 50mg 211/493 (42.8) MIR 100mg 199/496 (40.1) - TOL 4mg 231/495 (46.7)	1) Statistically significant improvement in micturition frequency (MIR 50mg and 100mg vs PBO; p < 0.05 for both comparisons) and incontience episodes (MIR 50mg and 100mg vs PBO; p < 0.05 for both comparisons) 2) A reduction noted for Tolterodine was not statistically significant versus placebo. (p=0.11) 3) The incidence of AEs (overall) in each mirabegron dose was comparable with placebo.
8	TAURUS Chaplle et al. 2013 [19]	III	2452	12 months	1) MIR 50mg OD (n=815) 2) MIR 100mg OD (n=824)	1) TOL ER 4mg OD (n=813)	MIR 50mg 485/812 (59.7) MIR 100mg 503/820 (61.3) - TOL 4mg 508/812 (62.6)	1) The incidence of TEAEs was similar across mirabegron doses and tolterodine. 2) Improvement in micturition frequency and incontience episodes was comparable to teltoridine.
9	Kuo et al. 2015 [22]	III	1126	12	1) MIR 50mg OD (n=372)	1) PBO (n=377) 2) TOL ER 4mg OD (n=377)	PBO 214/366 (58.5) - MIR 50mg 191/366 (52.2) - TOL 4mg 260/371 (70.1)	1) Statistically significant improvement in micturition frequency (MIR 50mg vs PBO; p < 0.05) 2) A reduction noted for Tolterodine was not statistically significant versus placebo. (p=0.895) 3) The incidence of TEAEs for mirabegron dose was lower than for placebo and tolterodine but not statistically significant.
10	BEYOND Batista et al. 2015 [33]	III	1887	12	1) MIR 50mg OD (n=943)	1) Solifenacin (n=944) 5mg	MIR 50mg 274/936 (29.3) - SOLIFENACIN 5mg 282/934 (30.2)	1) No inferiority of mirabegron therapy compared to solifenacin therapy. (MIR 50mg vs SOLIFENACIN 5mg; 95% CI) 2) The incidence of AEs (overall) for mirabegron was comparable with with solifenacin
11	Nitti et al. 2013 [34]	II	200	12	1) MIR 50mg OD (n=70) 2) MIR 100mg OD (n=65)	1) PBO (n=65)	PBO 28/65 (43.1) - MIR 50mg 28/70 (40.0) MIR 100mg 34/65 (52.3)	1) No inferiority of mirabegron therapy compared to placebo for maximum urinary flow and detrusor pressure at maximum urinary flow. (MIR 50mg and MIR 100mg vs PBO; 95% CI, respectively) 2) The incidence of AEs (overall) in each mirabegron doses was comparable with placebo.
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	LEGENDA				ER, extended release; TD, twice-daily; OD, once-daily	*number of participants who were randomized **number of participants who were treated	MIR- Miraberon; TOL- Tolterodine; PBO- placebo; AEs- adverse events; TEAEs- treatment-emergent adverse event;	

Table 1. Data from clinical trials on the safety and efficacy of the mirabegron. MIR- miraberon; TOL- tolterodine; PBO- placebo; AEs- adverse events; TEAEs- treatment-emergent adverse event; ER- extended release; TD- twice-daily; OD- once-dail; *- number of participants who were randomized; **- number of participants who were treated;

8 Recent studies of Mirabegron

Currently, studies are conducted on the efficacy and safety of the use of the combined therapy with Mirabegron and Solifenacin in the treatment of overactive bladder. Abrams et al. [7] conducted the SYMPHONY trial comparing the effectiveness of the combined therapy to the monotherapy with Solifenacin, and underlined the correlation between the applied dose and safety in the placebo and monotherapy groups. Total 1,306 patients with symptoms of OAB participated in the study. The combined treatment with Solifenacin and Mirabegron was statistically superior to the monotherapy with Solifenacin at the dose of 5 mg. All combinations were well tolerated, with no significant additional safety issues compared to the monoterapy or placebo [7].

Herschorn et al. in the SYNERGY trial also studied the combined therapy of superior efficacy compared to corresponding monotherapies. Morover, the authors observed that majority of effects of the combined therapy lasted until the week 4, compared to the monotherapy [6].

In their study Wollner et al. reported that Mirabegron could be an alternative to antimuscarinics in patients with neurogenic bladder. The assessment of efficacy of Mirabegron in patients with neurogenic bladder indicated a significant reduction of voiding frequency and reduced incidence of incontinence. Increased capacity of the bladder was also observed [35].

Mirabegron as a potent and selective β3-adrenomimetic, has no adverse effects typical for anticholinergic drugs. Kinjo et al. attempted an answer to the question of that fact could translate to a lower number of cases of discontinuation of Mirabegron compared to Solifenacin. Women with OAB symptoms were randomised into two groups: 76 treated with Mirabegron (25-50 mg) and 72 treated with Solifenacin (2.5-5 mg) for 12 months. The ratio of patients continuing their therapies was assessed after a year. For the Mirabegron group the ratio was 12.2%, and for Solifenacin it was 20.1% (not statistically significant difference). The main cause of discontinuation in the Mirabegron group was the lack of efficacy (36.8%

vs. 5.6%). And the main cause of discontinuation in the Solifenacin group was the presence of adverse effects (27.3% vs. 7.9%) [36].

9 Conclusion

It seems that with its innovative mechanism of action Mirabegron has become an answer to the need for a novel therapeutic strategy of a common and troublesome disease of overactive bladder. Clinical trials confirmed safety and efficacy of the drug comparable to the "old" therapeutic strategy with antimuscarinics burdened with the main disadvantage of adverse effects. Vouri et al. noted that the main reason for discontinuation of anticholinergic drugs were side effects - mostly oral dryness [37]. Unfortunately, despite absence of burdensome adverse effects, Mirabegron is characterised by a high discontinuation ratio [36].

Some recent studies on combined therapy of OAB with Mirabegron and Solifacin - two drugs demonstrating different mechanisms of action - give a positive signal for patients and their doctors.

Despite favourable results of clinical trials of Mirabegron, new and more effective therapies of OAB are sought, so that the condition could be treated causatively, and not only symptomatically. It should be definitely stated that the approval for the first potent and selective β3-adrenomimetic drug is a step in the right direction for OAB patients. Scientific studies suggest that Mirabegron may be also used for therapy of other diseases.

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