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Platinum Priority – Editorial

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Mirabegron as a New Class of Oral Drug for Overactive Bladder Syndrome: Many Positive Perspectives, Some Concerns

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Overactive bladder (OAB) syndrome is a highly prevalent condition characterized by the presence of urgency with or without incontinence, frequency, and nocturia. Epidemiologic data suggest that OAB is present in about 12% of all adult men and women, although prevalence rates increase with aging in both sexes [1].

Antimuscarinic receptors antagonists (ie, darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) are the standard first-line drug therapy for OAB. Antimuscarinics act by competitively inhibiting the effects of acetylcholine at postjunctional muscarinic M3 receptors on detrusor muscle cells. It has been suggested they may reduce detrusor activity and improve bladder capacity via additional mechanisms including direct inhibition of bladder afferent signaling at the level of the urothelium and suburothelium where acetylcholine receptors have been demonstrated on urothelium, suburothelial interstitial cells, and afferent nerves [2].

Antimuscarinic drugs are quite effective in improving urgency episodes, number of micturitions, and number of urgency incontinence episodes per 24 h both in idiopathic and neurogenic OAB [3,4]. However, many patients do not get sufficient relief from symptoms or they experience intolerable adverse events (AEs), with dry mouth and constipation usually among the most bothersome. The strategy for treatment of those patients who are unresponsive and/or intolerant to antimuscarinic drugs is currently not well standardized, but detrusor injections of onabotulinumtoxinA or abobotulinumtoxinA are often used with good results [5].

In the present issue of *European Urology*, two very relevant randomized controlled trials (RCTs) on mirabegron use in OAB patients were reported [6,7]. Mirabegron is the first drug of a new class of oral therapy for OAB (ie, a β-3 agonist) to be approved by the US Food and Drug Administration. It also received a recommendation for the granting of a marketing authorization from the European Medicines Agency's Committee for Medicinal Products for Human Use in October 2012.

A β3-agonist acts on a totally different molecular pathway. Three subtypes of β-adrenoreceptors (β-1, β-2, and β-3) have been identified in the detrusor muscle and the urothelium, with the β-3 subtype the most common in the human detrusor. Specifically, it has been shown that stimulation of human β-3 adrenoreceptors results in direct relaxation of detrusor smooth muscle via activation of G proteins and adenyl cyclase, and increases in the levels of cyclic adenosine monophosphate, contributing to urine storage [8]. Although results of phase 3 RCTs have been extensively discussed at several international meetings in the last few years and a phase 2 study on another β-3 agonist, solabegron, was recently published in *European Urology* [9], the results of the two phase 3 RCTs presented in the current issue of the journal may change current clinical practice with OAB patients.

In the first RCT, Khullar et al. reported the European and Australian phase 3 registrational study that enrolled >2300 adult patients with micturition frequency of eight or more times per 24-h period and at least three episodes of urgency, with or without incontinence [6]. After placebo run-in, about 2000 patients were randomized to receive mirabegron 50 mg (n = 497), mirabegron 100 mg (n = 498), or tolterodine extended release (ER) 4 mg (n = 495) orally once daily for 12 wk or placebo (n = 497). Coprimary efficacy end

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points were changed from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 h, with the primary comparison mirabegron versus placebo and the secondary comparison tolterodine versus placebo. About 50% of the patients randomized were treatment naive, whereas the other 50% were previously treated with anticholinergic drugs. As compared with placebo, patients in both mirabegron arms experienced statistically significant reductions in the mean number of incontinence episodes per 24 h from baseline to final visit (−1.57, −1.46, and −1.17 for mirabegron 50 mg, mirabegron 100 mg, and placebo, respectively; $p < 0.05$ for either mirabegron 50 mg or mirabegron 100 mg vs placebo).

Similarly, a statistically significant reduction in the mean number of micturitions per 24 h was observed (−1.93, −1.77, and −1.34 for mirabegron 50 mg, mirabegron 100 mg, and placebo, respectively; $p < 0.05$ for either mirabegron 50 mg or mirabegron 100 mg vs placebo). Consistent improvements were also found in a broad set of secondary end points. With regard to safety, the incidence of treatment-emergent AEs was similar in all study arms, with mirabegron patients failing to experience more cardiovascular AEs than placebo (as well as all the typical adverse events of anticholinergics) [6].

Long-term safety and efficacy issues were further explored in the second RCT included in the current issue of the journal. Specifically, Chapple et al. randomized >2400 patients to receive mirabegron 50 mg ($n = 812$), mirabegron 100 mg ($n = 812$), or tolterodine ER 4 mg ($n = 812$) orally once daily for 12 mo, with the primary end point to evaluate the incidence and severity of treatment-emergent AEs [7]. Notably, about 81% of the patients included in the study were not treatment naive but had previously been included in the two US [10] and European-Australian [7] registrational phase 3 RCTs. The prevalence of AEs was about 60% in each study arm, with most AEs mild to moderate. Discontinuations due to AEs were about 6% in each arm over the 12-mo treatment, and only minimal and not clinically significant changes in systolic blood pressure, diastolic blood pressure, and pulse rate were observed in the patients receiving mirabegron. Finally, efficacy data demonstrated that improvements in OAB symptoms were maintained throughout the 12-mo treatment [8]. Taken together, the data of the available studies suggest that mirabegron is the first exponent soon available on the market of a new category of oral drugs for OAB, with good efficacy in improving symptoms (at least until the tested 12-mo time frame) and a favorable placebo-like profile of AE.

On the whole, the two studies are far from being perfect and have some limitations. For example, urgency, the key symptom of OAB, is not the primary end point of the 12-wk phase 3 RCT; about 50% of the patients included in the 12-wk phase 3 RCT were pretreated with anticholinergic drugs, which makes any comparisons with tolterodine unfair; about 80% of the patients included in the 12-mo phase 3 RCT were previously enrolled in two other phase 3 registrational studies, representing a superselected cohort of patients.

Practically speaking, mirabegron is another symptomatic treatment for OAB symptoms (so far no data are available on the long-term effect of the drug on the natural history of OAB, but there is no evidence to suppose any impact on that). Although statistically significant over placebo, the observed benefit on efficacy end points was not very large. In other words, we may assume that in most of the patients, symptoms will be only partially improved, as happens also with antimuscarinics. Despite that, mirabegron may represent a revolution in the treatment of patients with OAB, and it is supposed to quickly become a standard treatment for OAB due to its favorable AE profile. However, the available data cannot allow us to identify the most appropriate role for the drug as either first- or second-line therapy after anticholinergics, and RCTs aiming at identifying the best sequences of treatments are eagerly awaited as well as cost-effectiveness analyses. The availability for the first time of a second class of oral drug may open the door to the combination of mirabegron and an anticholinergic, which, considering the different mechanism of actions, might be effective. Patients with neurogenic lower urinary tract symptoms (LUTS) might also theoretically benefit from mirabegron. Finally, considering the high prevalence of storage symptoms in men with voiding LUTS suggestive of benign prostatic enlargement, mirabegron might also be a valuable option in combination or sequential treatments with α-blockers, considering the lack of effects on postvoid residual volume. All these future scenarios for mirabegron use should be assessed in specific RCTs that Astellas, the manufacturer of mirabegron, should be strongly encouraged to undertake.

Postmarketing pharmacovigilance will be of extraordinary importance because we are evaluating a totally new class of drug. Although the observed cardiovascular effects were minimal and not clinically relevant as far as we know from the large number of patients included in RCTs, even such minimal modifications of heart rate and blood pressure could have some impact on individuals with significant cardiovascular risk factors or concomitant cardiovascular disease, as often found in elderly patients with OAB.

Conflicts of interest: Giacomo Novara is an advisory board member, consultant, researcher, and speaker for Astellas, GSK, Lilly, Pierre Fabre, Recordati, and Takeda. Jean-Nicolas Cornu has nothing to disclose.

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