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European Association of Urology

Platinum Priority – Voiding Dysfunction
Editorial by XXX on pp. x–y of this issue

Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE)

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Article info

Article history:
Accepted February 8, 2016

Associate Editor:
James Catto

Keywords:
Add-on therapy
Incontinence
Mirabegron
Overactive bladder
Solifenacin

Abstract

Background: Incontinence has a greater detrimental effect on quality of life than other symptoms of overactive bladder (OAB) and is often difficult to treat with antimuscarinic monotherapy.
Objective: To evaluate the efficacy and the safety and tolerability of combination (solifenacin 5 mg and mirabegron 50 mg) versus solifenacin 5 or 10 mg in OAB patients remaining incontinent after 4 wk of solifenacin 5 mg.
Design, setting, and participants: OAB patients remaining incontinent despite daily solifenacin 5 mg during 4-wk single-blind run-in were randomised 1:1:1 to double-blind daily combination or solifenacin 5 or 10 mg for 12 wk. Patients receiving the combination were initiated on mirabegron 25 mg increasing to 50 mg after week 4.
Outcome measurements and statistical analysis: The primary end point was a change from baseline to end of treatment (EOT) in the mean number of incontinence episodes per 24 h (stratified rank analysis of covariance [ANCOVA]). Key secondary end points were a change from baseline to EOT in the mean number of micturitions per 24 h (ANCOVA) and number of incontinence episodes noted in a 3-d diary at EOT (mixed-effects Poisson regression). A trial (BESIDE) comparing combination treatment (solifenacin plus mirabegron) with one treatment alone (solifenacin) tested the superiority of combination versus solifenacin 5 mg, noninferiority (and potential superiority) of combination versus solifenacin 10 mg (key secondary end points), and the safety and tolerability of combination therapy versus solifenacin monotherapy.
Results and limitations: A total of 2174 patients were randomised to combination ($n = 727$), solifenacin 5 mg ($n = 728$), or solifenacin 10 mg ($n = 719$). At EOT, combination was superior to solifenacin 5 mg, with significant improvements in daily incontinence ($p = 0.001$), daily micturitions ($p < 0.001$), and incontinence noted in a 3-d diary

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http://dx.doi.org/10.1016/j.eururo.2016.02.030

Please cite this article in press as: Drake MJ, et al. Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.02.030

($p = 0.014$). Combination was noninferior to solifenacin 10 mg for key secondary end points and superior to solifenacin 10 mg for improving daily micturitions. All treatments were well tolerated.

Conclusions: Adding mirabegron 50 mg to solifenacin 5 mg further improved OAB symptoms versus solifenacin 5 or 10 mg, and it was well tolerated in OAB patients remaining incontinent after initial solifenacin 5 mg.

Patient summary: In this 12-wk study, overactive bladder patients who remained incontinent despite initial solifenacin 5 mg treatment received additional treatment with mirabegron 50 mg. Combining mirabegron 50 mg with solifenacin 5 mg was superior to solifenacin 5 mg alone in improving symptoms of incontinence and frequent urination, and it was well tolerated.

Trial registration: ClinicalTrials.gov NCT01908829.

1. Introduction

Overactive bladder (OAB) syndrome is a symptom complex defined as urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [1,2]. Urgency incontinence is present in approximately one-third of OAB cases [3]. Compared with other OAB symptoms, it has the greatest impact on quality of life (QoL), with higher rates reported for depression, psychological and emotional distress, and social isolation [4]. Incontinence is associated with significantly higher health care resource utilisation and lower productivity [5]; consequently, incontinence has a major socioeconomic impact.

Oral pharmacotherapies consist of antimuscarinics (eg, solifenacin) and mirabegron, the β_3-adrenoceptor agonist. Both classes of drugs share similar efficacy, but mirabegron is not associated with anticholinergic adverse events (AEs; eg, the incidence of dry mouth is comparable with placebo) [6]. In current clinical practice, patients are often initiated on antimuscarinics; however, symptom improvement is often insufficient [7], leading to dissatisfaction, particularly if incontinence persists. Increasing the antimuscarinic dose often exacerbates anticholinergic AEs that can lead to treatment discontinuation [7,8]. If oral therapy fails, intravesical onabotulinumtoxinA can be used to treat OAB symptoms [9,10], but it is associated with urinary tract infections, fluctuating response, and may require intermittent self-catheterisation [11]. Other invasive alternatives include percutaneous tibial nerve stimulation and sacral nerve stimulation [12,13], but their penetrance in clinical practice is limited.

A trial (BESIDE, NCT01908829) comparing combination treatment (solifenacin plus mirabegron) with one treatment alone (solifenacin) tested the superiority of a 12-wk combination (solifenacin 5 mg and mirabegron 25 mg increasing to 50 mg after week 4) versus solifenacin 5 mg in OAB patients remaining incontinent after 4 wk of solifenacin 5 mg. The primary objective was to evaluate the efficacy of combination versus solifenacin 5 mg. Secondary objectives were to evaluate the safety/tolerability of combination versus solifenacin 5 or 10 mg, and the noninferiority of combination versus solifenacin 10 mg. Initial experience with the combination, based on the results from an open-label postmarketing Japanese study, suggest good efficacy and tolerability with add-on mirabegron 25 or 50 mg to solifenacin 2.5 or 5 mg compared with solifenacin monotherapy [14].

2. Patients and methods

2.1. Study design and participants

In this randomised double-blind parallel-group multicentre phase 3B study, patients aged ≥18 yr with OAB symptoms for ≥3 mo, including an average of two or more incontinence episodes per 24 h, entered a 2-wk screening/washout period (visit 1) to remove the effects of previous OAB medication and familiarise themselves with the electronic micturition diary. After 4 wk of single-blind daily solifenacin 5 mg, patients remaining incontinent at baseline (one or more episodes during the 3-d diary), were eligible for double-blind treatment (Fig. 1).

Patients who satisfied inclusion and did not meet exclusion criteria (Supplementary Table 1) were randomised 1:1:1 to 12 wk of daily double-blind treatment with combination (solifenacin 5 mg and mirabegron 25 mg increasing to 50 mg after week 4), solifenacin 5 mg, or solifenacin 10 mg (Supplement 1).

2.2. Efficacy and safety assessments

During the double-blind period, efficacy was assessed using a 3-d diary prior to each study visit. The primary efficacy end point was change from baseline to end of treatment (EOT) in mean number of incontinence episodes per 24 h. Key secondary efficacy end points were change from baseline to EOT in mean number of micturitions per 24 h and the number of incontinence episodes noted in the 3-d diary at EOT. In the full analysis set (FAS; randomised patients who received one or more doses of double-blind treatment, one or more micturitions at baseline and after baseline, and one or more incontinence episodes at baseline), the primary comparison was combination versus solifenacin 5 mg; combination versus solifenacin 10 mg was a secondary analysis. A noninferiority comparison between combination and solifenacin 10 mg was performed for the key secondary end points in the per protocol set (PPS; FAS patients without major protocol violations). If noninferiority was demonstrated, the superiority of combination versus solifenacin 10 mg would be investigated.

Other secondary end points included change from baseline to weeks 4, 8, 12, and EOT in the mean number of urgency episodes (grade 3/4 on the Patient Perception of Intensity of Urgency Scale per 24 h [15]) mean volume voided micturition, mean number of urgency incontinence episodes per 24 h, mean number of pads per 24 h, mean number of nocturia episodes, Patient Perception of Bladder Condition score [16], and the percentage of patients (“responders”) achieving zero

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