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Platinum Priority – Editorial

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What Is the Current Role of β_3-Adrenergic Receptor Agonists and How Do They Work?

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The β-adrenergic receptor (βAR) family, which can be divided into the subtypes β_1, β_2, and β_3, was first described more than 60 yr ago [1]. The efficacy of a β_3AR agonist in clinical practice for the treatment of overactive bladder symptom complex (OAB) with the introduction of mirabegron has been well recognised by the European Association of Urology guidelines as an effective alternative to an antimuscarinic agent (after failure of antimuscarinic therapy) and with fewer side effects [2,3], a conclusion supported by a recent network meta-analysis of 64 studies (n = 46 666) [4]. A recent publication of the first phase 3 trial with vibegron, a new selective β_3AR agonist, confirmed the efficacy and tolerability of this second-in-class compound [5]. In this study a small group of patients were also treated with the anticholinergic imidafenacin as an active comparator. While the number of patients studied did not allow a robust statistical analysis between vibegron and imidafenacin, efficacy was similar between the active agents, with better tolerability for the β_3AR agonist.

In this issue of *European Urology* Mitcheson et al. [6] report results from a phase 11b placebo-controlled study with vibegron. This study is novel in a number of ways and included a combination arm of vibegron plus the anticholinergic agent tolterodine at an early phase in a drug evaluation programme. There were two separate active treatment periods: part 1 was for 2 mo and part 2 was for 1 mo, and bladder diaries were used for ≥7 d before each visit rather than 3 d. Of 1395 randomised patients (part 1, 987; part 2, 408), 1393 (part 1, 985; part 2, 408) received the study medications, and 1324 (94.9%; part 1, 936; part 2, 388) completed the trial. Vibegron dose selection for part 2 was based on the interim results from part 1. In part 2, patients were randomised 2:2:2:1 to receive once-daily vibegron 100 mg (V100), tolterodine extended release 4 mg (TER4), V100 + TER4, or placebo for 4 wk. The mean patient age was 58.6 yr (standard deviation 9.3); 89.7%of the patients were women, 80.6% were OAB-wet, and 63.3% had never received anticholinergic therapy for OAB. No clinically meaningful between-group differences in baseline characteristics were noted. Overall, I think that this is an interesting and innovative study design, trying to break the mould of conventional trials, although it can be criticised for the short treatment period (2 mo, albeit with a 1-yr extension phase), the complexity of the design, and potentially trying to answer too many questions at once. Nevertheless, it has several strengths: it used a multiregional global recruitment strategy; a randomised, double-blind design; a wide vibegron dose range; and a large and diverse group of OAB patients.

While the trial was not designed to allow direct statistical comparison of the magnitude of the effect seen for vibegron versus TER4, it did demonstrate a clear dose-response effect for vibegron for the clinical endpoints in patients both with and without incontinence. However, surprisingly and in contradiction to the body of evidence seen for the combination of mirabegron and solifenacin, it did not show an additional benefit of combination therapy. The improvement with V100 monotherapy reported was comparable to the improvement seen with V100 + TER4 combination therapy (despite anticholinergic-related adverse events). Clearly this requires adequate further assessment in the future.

Bearing in mind the better tolerability and comparable efficacy of β_3AR agonists, why do we still suggest that this is

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second-line therapy? With the potential for impairment of bladder contractility in men, this is an important potential benefit in clinical practice (although we do not have adequately powered placebo-controlled studies in male patients).

There is now an extensive body of evidence to support the view that all therapies for OAB exert their principal benefit via action on the afferent system; after all, urgency (a sensation) is the driving symptom. In addition, only a proportion of patients with OAB have demonstrable detrusor overactivity (DO), but the efficacy of therapy is present irrespective of whether DO is present or not. Sacral neuromodulation acts on neural sensorimotor pathways. Both anticholinergics and botulinum toxin in sufficient doses certainly inhibit the motor function of the detrusor muscle, but is this not a bystander effect? Cholinergic receptors are present on both sensory nerves and in the urothelium, and botulinum toxin when used in many clinical scenarios has its positive therapeutic effects by inhibiting sensory mechanisms. Capsaicin, which acts principally on sensory nerves when instilled in the bladder, causes retention for a prolonged period. It is clearly confusing to envisage that β_3AR agonists act principally on the bladder to cause it to "relax", but do not impair bladder contractility.

Vibegron has been studied in rhesus monkeys and led to an increase bladder capacity in a dose-dependent fashion, with a reduction in micturition pressure and improved bladder compliance leading to an increase in bladder capacity [7]. Autoradiography of bladder sections incubated with [^{3}H]MRL-037 revealed β_3AR expression in the urothelium, with less intense β_3AR expression in detrusor muscle. A similar observation was made in female human bladder specimens, where β_3AR expression was more intense in urothelium than in detrusor muscle [8], while studies with a selective β_3AR agonist confirmed potent action on isolated human detrusor muscle strips [9]. Aizawa et al. [10] studied the effect of mirabegron on primary bladder mechanosensitive single-unit afferent activity (SAA) in the female rat bladder. They used 74 single-unit afferent fibres isolated from 55 rats (Aδ-fibres: $n = 34$; C-fibres: $n = 40$). Mirabegron administration significantly diminished SAA in both Aδ-fibres and C-fibres during bladder filling in a dose-dependent manner, and was more marked for the Aδ-fibres. These data suggest that mirabegron can inhibit mechanosensitive bladder afferent activity, in particular in Aδ-fibres. β_3AR activation in the bladder represents a powerful mechanism for increasing bladder capacity without affecting bladder contraction, as evidenced by the absence of an increase in post void residual volume when using a β_3AR agonist in clinical practice. It does therefore seem likely that β_3AR agonists act principally via sensory mechanisms rather than via a direct action on the detrusor muscle.

Conflicts of interest: The author is a consultant for Allergan, Astellas, Pfizer, Recordati, Targis, Urovant, and Symimetic; and a researcher, speaker, and trial participant for Allergan, Astellas, Pfizer, and Recordati.

References

[1] Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948;153:586–600.
[2] Nambiar AK, Bosch R, Cruz F, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol 2018;73:596–609.
[3] Maman K, Aballea S, Nazir J, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol 2014;65:755–65.
[4] Kelleher C, Hakimi Z, Zur R, et al. Efficacy and tolerability of mirabegron compared with antimuscarinic monotherapy or combination therapies for overactive bladder: a systematic review and network meta-analysis. Eur Urol 2018;74:324–33.
[5] Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a novel potent and selective β_3-adrenoreceptor agonist, for the treatment of patients with overactive bladder: a randomized, double-blind, placebo-controlled phase 3 study. Eur Urol 2018;73:783–90.
[6] Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase IIb, randomized, double-blind, controlled trial. Eur Urol 2019;75:274–82.
[7] Di Salvo J, Nagabukuro H, Wickham LA, et al. Pharmacological characterization of a novel beta 3 adrenergic agonist, vibegron: evaluation of antimuscarinic receptor selectivity for combination therapy for overactive bladder. J Pharmacol Exp Ther 2017;360:346–55.
[8] Limberg BJ, Andersson KE, Aura Kullmann F, Burmer G, de Groat WC, Rosenbaum JS. β-Adrenergic receptor subtype expression in myocyte and non-myocyte cells in human female bladder. Cell Tissue Res 2010;342:295–306.
[9] Michel MC, Korstanje C. β_3-Adrenoceptor agonists for overactive bladder syndrome: role of translational pharmacology in a repositioning clinical drug development project. Pharmacol Ther 2016;159:66–82.
[10] Aizawa N, Homma Y, Igawa Y. Effects of mirabegron, a novel β_3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. Eur Urol 2012;62:1165–73.