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European Association of Urology

Letter to the Editor

Re: Christian Gratzke, Rob van Maanen, Christopher Chapple, et al. Long-term Safety and Efficacy of Combined Mirabegron and Solifenacin Compared with Monotherapy in Patients with Overactive Bladder: A Randomised, Multicentre Phase 3 Study (SYNERGY II). Eur Urol 2018;74:501–9

Gratzke et al. [1] report on the long-term safety and efficacy of mirabegron monotherapy and of mirabegron and solifenacin combination therapy. Mirabegron, the only clinically approved β3-adrenoreceptor agonist, is known to have a better tolerance profile because of fewer adverse events such as dry mouth, blurred vision, and constipation. One remaining concern was possible long-term cardiovascular adverse events, which was shown not to be an issue by this study [1] confirming the long-term safety of mirabegron.

Although the cardiovascular safety of mirabegron has been proven in the study by Gratzke et al. [1] and in a systematic review [2], among the possible cardiovascular adverse events is a negative inotropic effect on ventricular tissue. Increases in heart rate and decreases in stroke volume due to mirabegron were attributed to acute baroreflex activation caused by short-term hypotensive effects or positive inotropic effects in human atrial tissue, and negative inotropic effects in ventricular tissue [3]. Moreover, β-adrenoreceptor cross-reactivity was observed: mirabegron showed intrinsic activation from β_1- to β_3-adrenoreceptor expression in transfected cell lines.

However, this negative inotropic effect of mirabegron was not observed in a trial of a higher therapeutic dose. In an exploratory study among healthy males to prove the cardiovascular effects of a fourfold dose (200 mg) there were increases in heart rate and decreases in stroke volume, but cardiac output and diastolic blood pressure remained unchanged [4].

Moreover, mirabegron is expected to play a positive role in the treatment of structural heart disease via a number of mechanisms. Mirabegron is expected to activate β_3-adrenergic receptors in adipocytes, endothelial cells, and cardiac monocytes, which could result in increases in adipocytes with decreasing insulin resistance, improvements in endothelial function, vasodilation, and coronary perfusion, an antioxidant effect, and a cGMP-mediated protective effect with improved relaxation [5]. The first randomised controlled trial of mirabegron in heart failure patients (ejection fraction <40%) showed that it increased the contractility of the left ventricle and was safe, with no prolongation of the QT interval in this patient population [6].

The safety of mirabegron in terms of cardiovascular effects has been established in overactive bladder patients both without and with heart failure, and even those with severe structural heart disease. Moreover, mirabegron has a possible positive role in adiopocytes, endothelial cells, and cardiac myocytes, representing possible clinical targets not only in heart-compromised disease but also in metabolic disease. Although drug interactions with other β-adrenoreceptor agonists and antagonists and the cardiovascular safety of mirabegron in uncontrolled hypertension have to be further explored, particularly in real settings for cardiovascular disease patients, the drug is a promising medication for more than just overactive bladder.

Conflicts of interest: The authors have nothing to disclose.

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