

# Personalized therapeutics of $\alpha_1$ -blockers in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

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## Dear editor

We read with great interest the multicenter, prospective, comparative cohort study by Zhang et al<sup>1</sup> who suggested that patients with uncontrolled or untreated hypertension and lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS) should be warned about a decrease in blood pressure on initiation of alfuzosin 10 mg therapy alone or concomitantly with antihypertensive medication. Here we discuss and share our perspectives on this issue.

$\alpha_1$ -blockers are the most frequently prescribed medical therapy in the treatment of BPH/LUTS. A number of  $\alpha_1$ -blockers (alfuzosin, doxazosin, terazosin, tamsulosin, naftopidil, silodosin) have been approved for the treatment of BPH throughout the world; however, they exhibit different selectivity toward  $\alpha_1$ -adrenoceptor (AR) subtypes. Three types of  $\alpha_1$ -AR subtypes ( $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_{1D}$ ) are found in human tissue. The  $\alpha_{1A}$  subtype is located in the human prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra, and mediates contraction of the smooth muscle in these tissues. In addition to  $\alpha_{1A}$ -ARs,  $\alpha_{1D}$ -ARs are also present to a significant extent in the human prostate, and  $\alpha_{1B}$ -ARs are thought to mediate contraction of human arteries.<sup>2</sup>

The early  $\alpha_1$ -blockers (alfuzosin, doxazosin, terazosin) were nonselective for subtype and were associated with blood pressure-related adverse effects, such as orthostatic hypotension.<sup>3</sup> Sato et al compared the binding affinity of tamsulosin for human  $\alpha_1$ -AR subtypes with that of other  $\alpha_1$ -blockers, ie, silodosin, terazosin, alfuzosin, and naftopidil.<sup>4</sup> Tamsulosin has relative selectivity for the  $\alpha_{1A}$ -subtype and  $\alpha_{1D}$ -subtype ( $\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$ ), and naftopidil has relative selectivity for the  $\alpha_{1D}$ -subtype ( $\alpha_{1D} \geq \alpha_{1A} > \alpha_{1B}$ ). The affinity of tamsulosin for the human  $\alpha_{1A}$ -AR was, respectively, 5-fold, 120-fold, 280-fold, and 400-fold higher than that of silodosin, terazosin, alfuzosin, and naftopidil, respectively. However, the  $\alpha_{1B}$ -AR binding affinity of silodosin was shown to be much lower than that of tamsulosin in vitro.<sup>5</sup> The selectivity of silodosin towards the  $\alpha_{1A}$ -AR subtype versus the  $\alpha_{1B}$ -AR subtype ( $\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$ ) was reported to be 38-fold higher than that of tamsulosin in studies using transgenic Chinese hamster ovary cells.<sup>6,7</sup> The selectivity ratio ( $\alpha_{1A}/\alpha_{1B}$ ) for terazosin, doxazosin, alfuzosin, tamsulosin, and silodosin was 0.3, 0.4, 0.5, 6.3, and 166, respectively.<sup>8</sup> The unique AR selectivity profile of silodosin minimizes the propensity for blood pressure-related adverse effects caused by  $\alpha_{1B}$ -AR blockade.<sup>9</sup> Regarding the efficacy of subtype-selective  $\alpha_1$ -blockers in the management of BPH, expression of  $\alpha_1$ -AR subtype mRNA was observed as a predictor. Tamsulosin hydrochloride was more effective in patients with dominant

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expression of the  $\alpha_{1A}$ -AR subtype, whereas naftopidil was more effective in those with dominant expression of the  $\alpha_{1D}$ -AR subtype.<sup>10</sup>

With respect to the indications for  $\alpha_1$ -blockers, doxazosin and terazosin are currently indicated for the treatment of both hypertension and BPH/LUTS, and are more likely to impair safety-relevant physiological blood pressure control in normotensives with LUTS than are tamsulosin and silodosin.<sup>11,12</sup> Alfuzosin is only indicated for treatment of BPH/LUTS. The study by Zhang et al demonstrated that alfuzosin 10 mg has no clinically important effects on blood pressure when used to treat BPH/LUTS in men who were physiologically normotensive or had hypertension controlled by antihypertensive medication. The relevance of their finding is that it provides reassurance for clinicians when prescribing alfuzosin 10 mg for a patient who is already on antihypertensive therapy, without the need to worry about the risk of hypotensive episodes. However, alfuzosin 10 mg significantly decreased blood pressure in patients with uncontrolled or untreated hypertension, indicating that such patients require careful evaluation before initiating alfuzosin therapy.<sup>1</sup> The study by Zhang et al further indicates that the clinical selectivity and cardiovascular safety of  $\alpha_1$ -blockers are related to patient-treatment interactions (comedication and comorbidity), and their finding will enrich our knowledge about the personalized therapeutics of  $\alpha_1$ -blockers in the treatment of BPH/LUTS.<sup>1</sup> However, the vasodilatory adverse events of alfuzosin are related to dose, dosage interval, and formulation, ie, they are less frequent with once-daily, sustained-release alfuzosin 10 mg than with the three times daily 2.5 mg formulation (6.3% versus 9.4%, respectively).<sup>13</sup> Therefore, clinicians should be cautious about extrapolating the finding of the study by Zhang et al to treatment of BPH/LUTS with an immediate-release formulation of alfuzosin.<sup>1</sup>

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## Disclosure

The authors report no conflicts of interest in this work.

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## Authors' reply

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## Dear editor

Alpha<sub>1</sub>-adrenergic receptor antagonists (α<sub>1</sub>-blockers) were initially developed as cardiovascular drugs for the treatment of arterial hypertension, but are no longer considered first-line antihypertensive drugs, with more favorable medications now available for use in clinical practice.<sup>1</sup> However, α-blockers have remained first-line agents in the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH), producing rapid and sustained symptomatic relief irrespective of prostate size.<sup>2</sup> The American Urological Association recommends α-blockers as safe and efficacious pharmacological treatment options for patients suffering from LUTS/BPH.<sup>3,4</sup>

Alpha<sub>1</sub>-receptors are abundant in the smooth muscle of the prostate and bladder, and α<sub>1</sub>-blockers produce a reduction in smooth muscle tone.<sup>5</sup> Of the three α-blocker subtypes (α<sub>1A</sub>, α<sub>1B</sub>, and α<sub>1D</sub>), α<sub>1A</sub> is considered to be the major regulator of smooth muscle tone in the prostate and bladder neck.<sup>6,7</sup> In contrast, the α<sub>1B</sub> subtype regulates blood pressure via arterial smooth muscle relaxation,<sup>7</sup> while the α<sub>1D</sub> subtype is associated with relaxation of the bladder muscle as well as innervation of the sacral spinal cord.<sup>7,8</sup>

The currently available α<sub>1</sub>-blockers (alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin) differ in their safety profiles but share similar efficacy.<sup>4,9</sup> Older α<sub>1</sub>-blockers (doxazosin and terazosin), which are used to treat both hypertension and LUTS/BPH, are associated with a greater incidence of symptomatic hypotension while silodosin is associated with a higher prevalence of anejaculation ascribed to its selectivity for the α<sub>1A</sub> adrenergic receptor at the seminal vesicle and vas deferens.<sup>4,9-11</sup> The orthostatic hypotension by α<sub>1</sub>-blocker was not frequently but diversely occurred, although the patient took the very low dosage of the medication, which had highly uroselectivity. As such, the concept of a uroselective α<sub>1A</sub> adrenergic receptor antagonist has been proposed to reflect the ratio of beneficial urinary effects versus cardiovascular adverse effects such as orthostatic hypotension. Alfuzosin, a novel uroselective antagonist devoid of cardiovascular adverse effects, have been successfully developed in recent years. It is presently available in three formulations: immediate-release alfuzosin 2.5 mg taken three times a day,<sup>12</sup> sustained-release alfuzosin 5 mg taken twice a day,<sup>13</sup> and prolonged-release alfuzosin 10 mg taken once a day.<sup>14</sup>

As early as 2000 years, the cardiovascular safety of alfuzosin 10 mg had never been investigated in patients aged older than 50 years.<sup>15</sup> In the current study, 335 patients were recruited for assessment in daily clinical practice, and it was found that antihypertensive comedication does not affect its cardiovascular tolerability when taken once daily. This more favorable safety profile is attributed to the pharmacokinetic properties of the 10 mg formulation because the time to peak plasma concentration is 9 hours versus 1 hour for alfuzosin 2.5 mg and 3 hours for alfuzosin 5 mg, as reviewed in Oelke et al.<sup>16</sup> Therefore, this novel formulation implied the uroselectivity of alfuzosin 10 mg, which is clinically effective in the treatment of LUTS without adverse cardiovascular events.

## Disclosure

The authors report no conflicts of interest in this work.

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