available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial and Reply from Authors

*Referring to the article published on pp. 342–352 of this issue*

# Does the Use of Silodosin to Treat Benign Prostatic Hyperplasia Really Offer Something New?

*Giuseppe Morgia* *

*Department of Urology, University of Catania, Via S. Sofia 78, 95100 Catania, Italy*

Benign prostatic hyperplasia (BPH) is the most common progressive disease in men and obviously correlated with the age of the patient. It tends to develop after 40 yr of age and affects >90% of men >85 yr. The two main medications used today for the management of BPH are α-blockers and 5α-reductase inhibitors (5-ARIs), although in some cases and in particular in some countries, phytotherapy is also used. α-Blockers are certainly the therapy of choice recommended by all the international guidelines and are the most used and prescribed, as Cornu et al found in his study of 19 European countries. Of a total of 11.6 million prescriptions, between 11% and 41% were for α-blockers; the percentage for 5-ARIs varied between 2% and 20% and for phytotherapy varied between 0% and 20% in different countries [1].

It is well known that α-blockers have different levels of selectivity, and, from this perspective, tamsulosin is the only α1-receptor antagonist that has demonstrated a pronounced preferential selectivity for the α1A-receptor rather than the α1B or α1D receptors (some 10–15 times more selective). In October 2008, the US Food and Drug Administration approved the use of silodosin, a new α-blocker, for treating BPH. This new antagonist seems to be superselective and thus to have an even more efficacious link with the α1A-receptors than with the α1B or α1D receptors (some 50–100 times more selective). Thus one can hypothesize that it is more efficacious in treating the urinary symptoms and has fewer side effects on the cardiovascular system, which is mainly regulated by the α1B receptors [2]. This has also been confirmed by studies on animals, where the selectivity for α1-receptors resulted in an improvement in the urodynamic voiding parameters [3], although these tests on animals also found that prolonged treatment with silodosin caused an upregulation in the mRNA of the α1A-receptors in the seminal vessels responsible for negative events in the ejaculatory functions [4].

Studies have already been published that show there is an improvement in the parameters of the International Prostate Symptom Score (IPSS) and the peak urinary flow rate ($Q_{max}$) when compared with placebo. Marks et al analyzed two randomized phase 3 studies of 923 patients half a week after beginning treatment and found a statistically significant improvement in the IPSS ($-1.9$; $p < 0.0001$) compared with the placebo, and further improvement after 12 wk ($-2.9$; $p < 0.0001$). The $Q_{max}$ was also already better than the placebo both 2–6 h after starting treatment (+1.3; $p < 0.0001$) and after 12 wk (+1.1; $p = 0.0007$). However, his work was based on studies that only provided information on the short-term efficacy of the treatment [5]. A further study of 435 patients found that the improvement in the IPSS was still significant after 40 wk but only for newly treated patients rather than those who continued the treatment ($-4.5$; $p < 0.0001$ vs $-1.6$; $p < 0.01$). It must be emphasized that the study was designed to highlight and have adverse effects (AEs) not efficacy as its end point [6]. Many studies have confirmed that silodosin is safe, above all in terms of cardiovascular tolerability, It appears that silodosin does not have statistically significant clinically important effects on heart rate, PR segment, QRS complex, or morphologic electrocardiogram (ECG) data [7]. An analysis of several works on silodosin found that the adverse effects were upper respiratory tract infection (2.6–18.9%), diarrhea (2.6–6.9%), dizziness (3.2–5.1%), and orthostatic hypertension (2.6%).

It is obvious, however, that the most important adverse effects are alterations in ejaculatory functions (5–28.1% with a median value of about 20%). It seems that silodosin therapy is still widely used even when this adverse effect is

DOI of original article: 10.1016/j.eururo.2010.10.046
* Tel. +39095351816; Fax: +390953782373.
E-mail address: gmorgia@policlinico.unict.it.

present, and in only 2.8–2.9% of cases is it seen as a reason to discontinue the therapy. In contrast, Furuya et al found that the continuance rate for the drug was only 12% after 1 yr, and it was precisely the adverse effect just mentioned that seemed to be the reason for the low rate of continuing the therapy for a long period [8]. Thus it seems that silodosin can be used in association with a phosphodiesterase type 5 (PDE5) without causing an increase in side effects, above all cardiovascular ones. However, it does seem strange that the same study reports that ejaculatory disturbances are only 5% when silodosin and PDE5 inhibitor (PDE5-I) are administered in conjunction (this may be due to the small number of subjects: only 22) [9].

A new randomized multicenter double-blind study was recently published in Europe that compared patients treated with silodosin with others treated with tamsulosin or a placebo for 12 wk [10]. This well-conducted study involved 1228 patients (955 randomized at a relationship of 2:2:1) at 72 hospital clinics and inpatient units in 11 countries.

The study investigated whether silodosin was not inferior to tamsulosin and superior to the placebo. The first end point was the evaluation of the IPSS; the secondary ones were a subanalysis of urinary storage and voiding symptoms, quality of life (QoL), and $Q_{max}$.

The patient responders (<25% of the baseline IPSS) were 66.8% for silodosin, 65.4% for tamsulosin, and 50.8% for the placebo (with $p < 0.001$ for the first two when compared with the latter). The same results were obtained from the analysis of the subgroup of urinary system storage and voiding symptoms when compared with the placebo. Only in the nocturia did silodosin have an advantage over tamsulosin, which was not statistically significant ($p = 0.095$ for tamsulosin and the placebo; $p = 0.314$ for silodosin vs tamsulosin; $p = 0.013$ for silodosin vs placebo). There was no significant difference, however, between the two molecules and the placebo in terms of $Q_{max}$ (responders 46.6% silodosin, 46.5% tamsulosin, and 40.5% placebo; responders had reduction >30% from baseline). There was also no difference between the two α-blockers for the QoL parameter, whereas both were better than the placebo. The AEs for the three groups were 34.9% for silodosin, 28.9% for tamsulosin, and 24.2% for the placebo, and the disturbances to the ejaculatory function were significantly higher in the group treated with silodosin (14.2%) than in that treated with tamsulosin (2.1%) or the placebo (1.1%). When analyzing cardiovascular AE, no statistically significant differences were found in laboratory parameters, vital signs, and ECGs for silodosin and tamsulosin when compared with the placebo. There were significant greater variations in blood pressure and heart rate for silodosin than tamsulosin when compared with the placebo.

What we can learn from this study is there is not much difference between the two molecules. There are, indeed, no significant differences between silodosin and tamsulosin for IPSS or for storage and voiding symptoms. What is striking, however, is the lack of a significant difference in $Q_{max}$ when the two molecules are compared with the placebo. However, in terms of side effects, the percentage of absent ejaculation when silodosin was used was much higher than the results for the other molecules that are currently employed, which other studies have confirmed. This is particularly important when we bear in mind that some 40% of the patients were relatively young (50–64 yr of age). This can be partially explained by the fact that 16% of the patients suffered from ejaculatory disorders. Silodosin had better results for cardiovascular side effects than tamsulosin, but neither differed significantly from the results using the placebo.

Thus the objective of the study was achieved: It was shown that silodosin is not inferior to tamsulosin and that both were superior to the placebo.

However, because at present silodosin is a new form of treatment for BPH, I believe it would be useful to investigate certain of our findings more fully. Why, unlike in other studies, was there no significant reduction in $Q_{max}$ when compared with the placebo? Why was there not an easily understandable increase in these values that was not present in other studies? A study should be carried out to establish the superiority of silodosin compared with tamsulosin and the results evaluated. A long-term evaluation of the molecule should be carried out that could answer the questions posed in our introduction here, with regard to possible reductions in episodes of acute urinary retention or upper urinary tract dilation. A study should be carried out on other patients who did not respond to treatment with other α-blockers to establish whether silodosin may be useful as a possible ''second line'' of treatment for BPH.

Finally, the higher percentage of abnormal ejaculation when silodosin was used can be explained by the superselectivity of the molecule, which may be an advantage in terms of cardiovascular AE, especially when one bears in mind, as reported in the study, that adherence to the therapy was good.

Thus we can welcome the arrival of this new molecule while waiting for further and definitive proof that it finally offers something new in the treatment of BPH.

***Conflicts of interest:*** The author has nothing to disclose.

## References

[1] Cornu J-N, Cussenot O, Haab F, Lukacs B. A widespread population study of actual medical management of lower urinary tract symptoms related to benign prostatic hyperplasia across Europe and beyond official clinical guidelines. Eur Urol 2010;58:450–6.

[2] Montorsi F. Profile of silodosin. Eur Urol Suppl 2010;9:491–5, Corrigendum. Eur Urol 2011;59:315.

[3] Yazaki J, Aikawa K, Shishido K, et al. Alpha1-adrenoceptor antagonists improve bladder storage function through reduction of afferent activity in rats with bladder outlet obstruction. Neurourol Urodyn. In press. doi:10.1002/nau.20984.

[4] Yono M, Yamamoto Y, Imanishi A, Fucagawa A, Latifpour J, Yoshida M. Short and long-term effects of silodosin, a selective α1A-adrenoceptor antagonist, on ejaculatory function in rats. BJU Int 2009;103:1680–5.

[5] Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective α1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol 2009;181:2634–40.

[6] Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. Urology 2009; 6:1318–22.
[7] Morganroth J, Lepor H, Hill LA, Volinn W, Hoel G. Effects of the selective α1A-adrenoceptor antagonist silodosin on ECGs of healthy men in a randomized, double blind, placebo- moxifloxacin-controlled study. Clin Pharmacol Ther 2010;87:609–13.
[8] Furuya R, Masumori N, Furuya S, et al. Investigation of adverse events and the continuance rate of silodosin in all patients who received silodosin for lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Nippon Hinyokika Gakkai Zashi 2010;101: 13–7.
[9] MacDiarmid SA, Hill LA, Volinn W, Hoel G. Lack of pharmacodynamic interaction of silodosin, a highly selective α1A-adrenoceptor antagonist, with the phosphodiesterase-5 inhibitors sildenafil and tadalafil in healthy men. Urology 2010;75:520–5.
[10] Chapple CR, Montorsi F, Tammela TLJ, Wirth M, Koldewijn E, Fernández Fernández E, on behalf of the European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol 2011;59:342–52.

doi:10.1016/j.eururo.2010.11.023

## Platinum Priority

### Reply from Authors re: Giuseppe Morgia. Does the Use of Silodosin to Treat Benign Prostatic Hyperplasia Really Offer Something New? Eur Urol 2011;59:353–5

*Christopher R. Chapple*[a,*], *Francesco Montorsi*[b], *Teuvo L.J. Tammela*[c], *Manfred Wirth*[d], *Evert Koldewijn*[e], *Eldiberto Fernández Fernández*[f] *on behalf of the European Silodosin Study Group*

[a] *Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK*
[b] *Department of Urology, Università Vita Salute San Raffaele, Milan, Italy*
[c] *Department of Urology, Tampere University Hospital, Tampere, Finland*
[d] *Department of Urology, University Hospital Carl Gustav Carus, Dresden, Germany*
[e] *Department of Urology, Catharina Hospital, Eindhoven, The Netherlands*
[f] *Department of Urology, University Hospital Ramón y Cajal, Madrid, Spain*

As co-authors of the article published in the current issue of *European Urology* [1] reporting the results of the randomised, multicentre, double-blind study in Europe comparing silodosin with placebo and tamsulosin in patients with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH), we have read with great interest the comments by Professor Morgia [2]. The key issue is that it would appear that despite much higher selectivity for silodosin over tamsulosin, we have reached the top of the dose response curve and it does not seem possible with an α-blocker to achieve a greater effect than that with the existing selective α-1a antagonist.

Post hoc analyses suggest that there may be differences in certain subgoups of patients in favour of silodosin, but clearly one should be aware of the methodological limitations of these analyses [3]. Failure of ejaculation does occur and is a consequence of the high selectivity of the compound. It is interesting to note that although failure of ejaculation was reported by quite a number of patients treated with silodosin, only a small minority eventually dropped out of treatment; this may be correlated to the fact that ejaculatory abnormalities per se are quite common in patients with BPH and related LUTS [4]. In addition, it is interesting to note that recent evidence suggests that patients experiencing ejaculatory abnormalities are those who enjoy the best effects on LUTS [5].

The most important feature of this compound is that as a consequence of the high selectivity for α-1a receptors, there is a much lower likelihood of cardiovascular side effects. This is particularly relevant with an ageing population, a significant proportion of which takes cardioactive medication, whether phosphodiesterase inhibitors or antihypertensives [6].

We feel that there is no ground on which to define a particular α-1 blocker as first-line or second-line treatment for patients with LUTS due to BPH. Every practising physician must know in detail the pharmacologic features of all available compounds and tailor the treatment to the patient's profile and needs.

***Conflicts of interest:*** The authors have nothing to disclose.

### References

[1] Chapple CR, Montorsi F, Tammela TLJ, Wirth M, Koldewijn E, Fernández Fernández E, on behalf of the European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol 2011;59:342–52.
[2] Morgia G. Does the use of silodosin to treat benign prostatic hyperplasia really offer something new? Eur Urol 2011;59:353–5.
[3] Montorsi F. Profile of silodosin. Eur Urol Suppl 2010;9:491–5, Corrigendum. Eur Urol 2011;59:315.
[4] Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). Eur Urol 2003;44:637–49.
[5] Yukio H, Kazuki K, Masayuki T, Masaki Y. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. Urology 2010;76:1446–50.
[6] MacDiarmid SA, Hill L, Volinn W, Hoel G. Lack of pharmacodynamic interaction of silodosin, a highly selective α1a-adrenoceptor antagonist, with the phosphodiesterase-5 inhibitors sildenafil and tadalafil in healthy men. Urology 2010;75:520–5.

doi:10.1016/j.eururo.2010.12.026

DOIs of original articles: 10.1016/j.eururo.2010.10.046, 10.1016/j.eururo.2010.11.023
* Corresponding author. The Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Glossop Road, Sheffield S10 2JF, United Kingdom. Tel. +44 74 271 2559; Fax: +44 74 279 7841.
E-mail address: c.r.chapple@shef.ac.uk (C.R. Chapple).