

**HYPOTHESIS / AIMS OF STUDY**

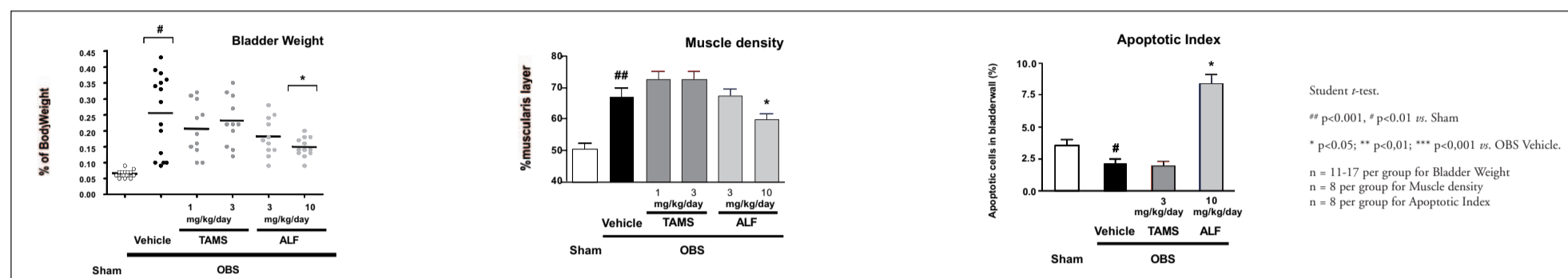
A pro-apoptotic effect on bladder wall<sup>(1)</sup> and prostatic tissue<sup>(2)</sup> was reported in BPH patients treated with  $\alpha_1$ -adrenoceptor blockers ( $\alpha_1$ -AR). The aim of the present study was to evaluate the effects of a chronic treatment with alfuzosin (ALF, 3 and 10 mg/kg/day), a quinazoline derivative, and tamsulosin (TAMS, 1 and 3 mg/kg/day), a sulphonamide derivative, on bladder hypertrophy induced by bladder outlet obstruction (BOO).

**STUDY DESIGN, MATERIALS AND METHODS**

In female rats a ligature was tied around the urethra leaving a 1 mm diameter lumen. Six weeks later, Alzet<sup>®</sup> osmotic pumps filled with ALF, TAMS or vehicle were implanted subcutaneously in the obstructed (OBS) rats. After 7 days-treatment rats were sacrificed and bladders were collected. Bladders were weighted (BW) and histomorphometric analyses were performed on Sirius red colorations to determine muscularis layer thickness (MLT) and muscle density (MD). TUNEL assay and PCNA staining were used to evaluate apoptotic index (AI) and proliferation in the bladder wall, respectively.

**RESULTS**

OBS vehicle-treated rats displayed a significant increase in BW, MLT and MD as compared with sham rats as well as a significant decrease in AI. At the highest dose tested, ALF significantly decreased BW, MD towards quasi-normalization *vs* sham-operated animals, and increased AI. ALF was devoid of significant effect on MLT and proliferation. TAMS had no significant effect on any parameter studied. (Figure)



**INTERPRETATION OF RESULTS**

In contrast to TAMS, one-week treatment with ALF, at non-hypotensive doses<sup>(3)</sup>, relieves the bladder hypertrophy associated with BOO. This effect is not due to a decreased obstruction at the urethral level since the urethral ligature was present during  $\alpha_1$ -AR administration. The decreased bladder hypertrophy observed with ALF at 10 mg/kg correlates with the decreased MD in the bladder wall and the increased AI.

**CONCLUDING MESSAGE**

These results suggest that ALF counteracts the bladder hypertrophy induced by BOO in rats, and that these effects appear already after one week treatment. Since TAMS was devoid of such effects, we conclude that this effect of ALF could be related to its quinazoline structure. This could have clinical significance in the management of LUTS associated with BOO.

References : (1) *Scand J. Urol. Nephrol* 2002, 36; 188-93. (2) *Urol.* 2003, 169; 1520-1525. (3) *Eur. Urol.* 2006, 5; 121 (abstract 396).

ICS 2007

37<sup>th</sup> Annual Meeting of the International Continence Society  
Rotterdam, The Netherlands. 20<sup>th</sup> - 24<sup>th</sup> August 2007

**Alfuzosin, but not tamsulosin, relieves bladder hypertrophy in rats despite a persistent bladder outlet obstruction**

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# Alfuzosin, but not tamsulosin, relieves bladder hypertrophy in rats despite a persistent bladder outlet obstruction

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UROsphere This work was supported by sanofi-aventis

## INTRODUCTION

- Pathophysiology of lower urinary tract symptoms (LUTS) is complex. LUTS severity and bladder outlet obstruction (BOO) are only weakly correlated<sup>1</sup>. Prostatectomy may not always result in symptom relief in men with LUTS suggestive of BOO, especially when storage symptoms predominate<sup>2</sup>.
- It has been hypothesized that  $\alpha_1$ -adrenoceptor ( $\alpha_1$ -AR) blockers could improve LUTS via extra prostatic actions. Based on preclinical experiments, the role of  $\alpha_1$ -AR at the level of the bladder, the spinal cord or on the efferent pathway has been postulated. Till now, no definitive conclusion could be drawn.
- A pro-apoptotic effect on bladder wall and prostate was reported in benign prostatic hyperplasia (BPH) patients treated with  $\alpha_1$ -AR blockers<sup>3-4</sup>.
- In rats, BOO induces cystometric modifications associated with bladder hypertrophy<sup>5</sup>.

## AIMS OF THE STUDY

- The aims of the study were to evaluate, in rats with BOO, the effects of a chronic treatment with alfuzosin (3 and 10 mg/kg/day), a quinazoline derivative, and tamsulosin (1 and 3 mg/kg/day), a sulphonamide derivative, on bladder hypertrophy while maintaining BOO.

## MATERIALS & METHODS

### Animals

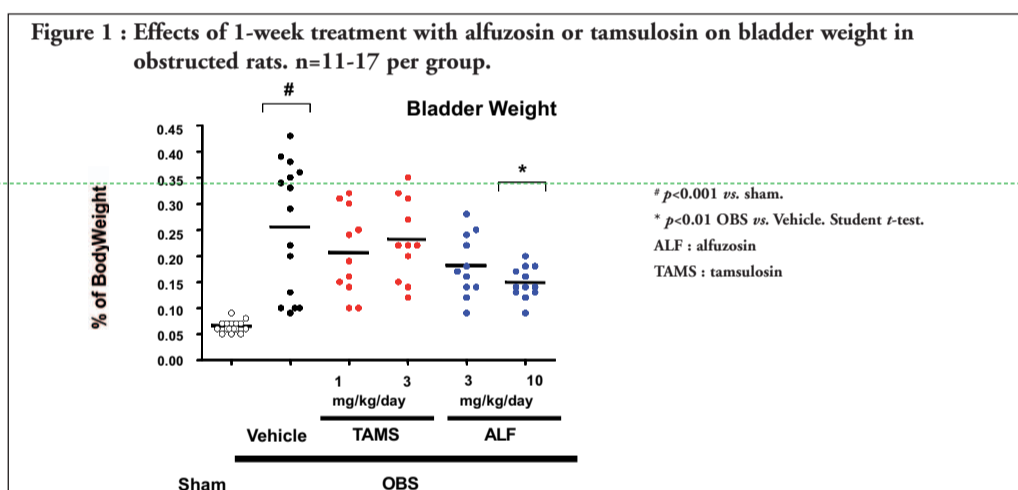
- BOO was performed as previously described<sup>5</sup>. Briefly, in female Wistar rats under isoflurane anesthesia, a ligature was tied around the urethra leaving a 1 mm diameter lumen.
- 6 weeks later, Alzet<sup>®</sup> osmotic pumps filled with alfuzosin (ALF), tamsulosin (TAMS) or vehicle were implanted subcutaneously in obstructed rats (OBS).
- After 7 days treatment, rats were sacrificed and bladder collected and weighted.

### Histology and immunocytochemistry

- Bladders were fixed in 10% formalin. After paraffin embedding, transverse 5  $\mu$ m thick histological sections were performed in two distinct regions of the bladder body.
- Sections were stained with Hematoxylin-Eosin and Orcein (HEO) for qualitative assessment of the general structure and elastic fibres.
- Sirius Red (SR) coloration was performed for histomorphometric analyses of muscularis layer thickness ( $\mu$ m) and its muscle proportion (% of the muscularis layer).
- TUNEL (Terminal deoxynucleotidyl transferase-mediated dUTP Nick-End Labeling, Promega kit) assay was used to detect apoptotic cells in the bladder wall.
- PCNA (Proliferating Cell Nuclear Antigen) immunostaining was performed for the proliferating cell detection in the bladder wall.

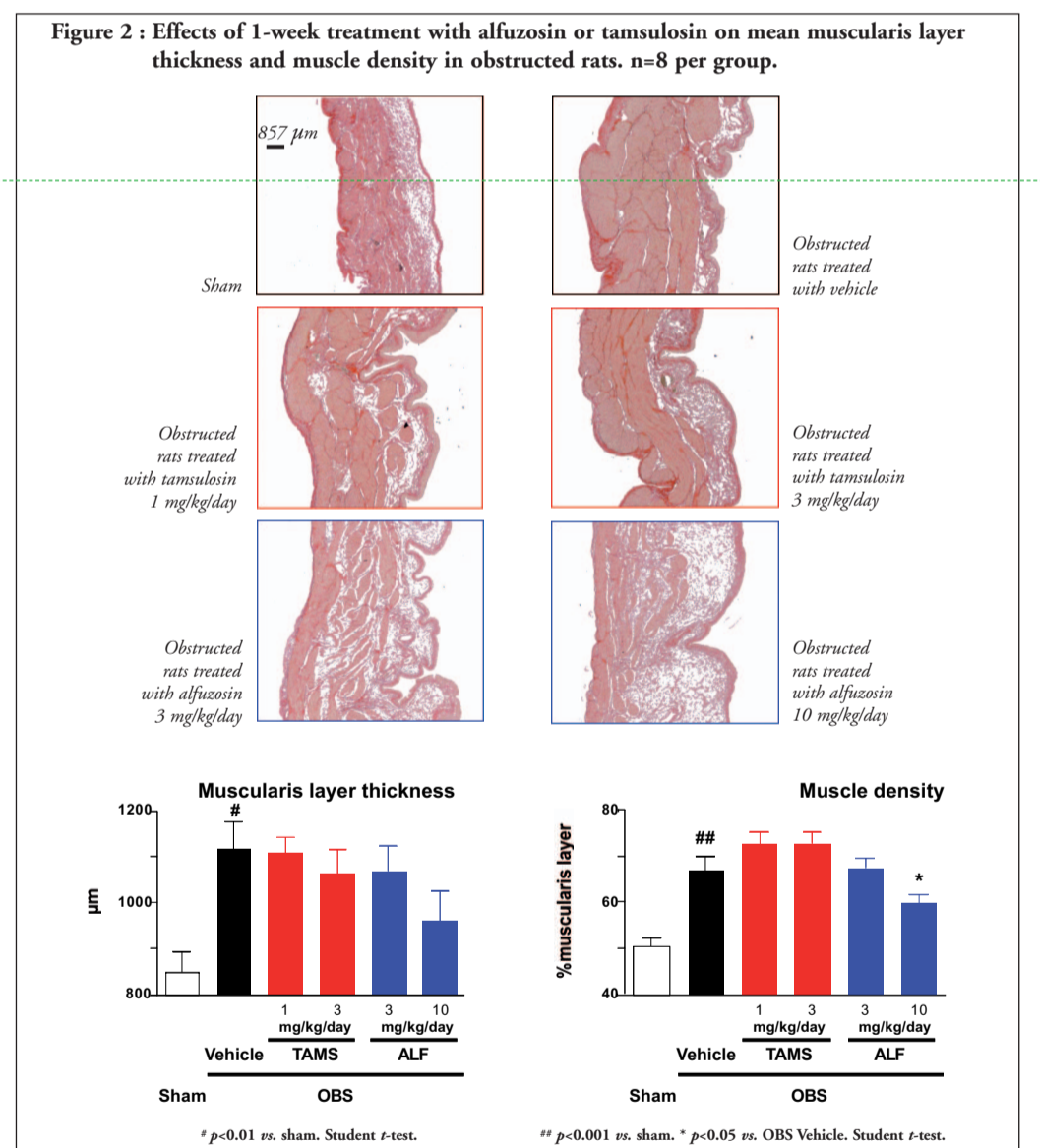
## RESULTS

### Effects on bladder weight



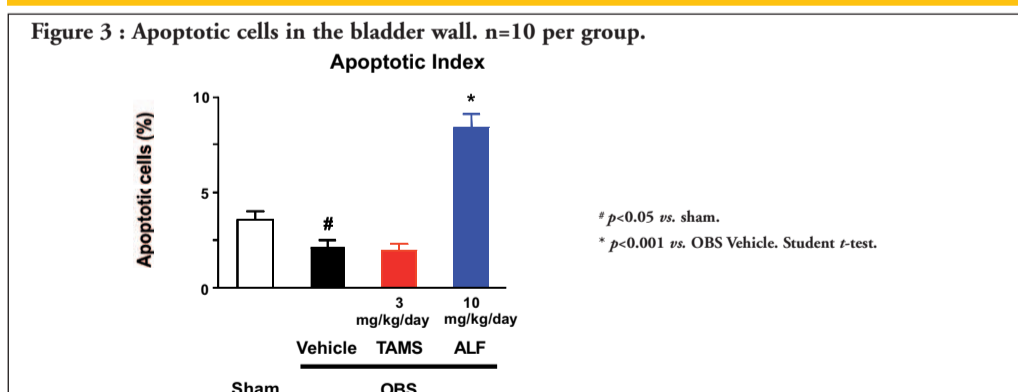
- As previously described<sup>5</sup>, rats with BOO displayed a significant increase in bladder weight compared with sham-operated animals.
- In alfuzosin-treated rats, a dose-dependent decrease in bladder weight was observed as compared to obstructed vehicle-treated rats. At the dose of 10 mg/kg/day, bladder weights were statistically lower from those of vehicle-obstructed rats.
- Tamsulosin had no effect on bladder weight, with the 2 studied doses.

### Effects on muscularis layer thickness and muscle density



- BOO induced a significant increase in both muscle layer thickness and muscle density.
- At the highest dose tested (10 mg/kg/day), alfuzosin tended to decrease muscularis layer thickness and significantly decreased muscle density.
- Tamsulosin had no effect on these parameters, even at the highest dose tested.

### Effects on apoptotic index



- BOO induced a significant decrease of the apoptotic index. No effect on proliferation was observed.
- At the highest dose tested (10 mg/kg/day), alfuzosin induced a significant increase in apoptotic index while tamsulosin had no effect on it.
- No effect on proliferation was observed with both compounds.

## CONCLUSIONS

- One-week treatment with alfuzosin, at non-hypotensive doses<sup>6</sup>, relieves bladder hypertrophy associated with BOO in rats. This effect is not due to a decreased BOO since the urethral ligature was present during chronic administration of  $\alpha_1$ -blockers.
- The decreased bladder hypertrophy observed with alfuzosin at 10 mg/kg correlates with a decrease in muscle density and an increase in the apoptotic index in the bladder wall.
- Since tamsulosin was devoid of such effects, we conclude that this effect of alfuzosin could be related to its quinazoline structure, in analogy with a similar effect described in human prostate for this class of compounds<sup>4</sup>.
- This counteracting effect of alfuzosin on bladder hypertrophy induced by BOO could have clinical significance in the management of LUTS due to BOO.