93

Robinson D[1], Cardozo L[1], Terpstra G [2], Bolodeoku J[2]
1. Dept of Urogynaecology, Kings College Hospital, 2. Astellas Pharma Europe BV

A RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED STUDY TO EVALUATE THE EFFICACY OF TAMSULOSIN OCAS IN THE MANAGEMENT OF WOMEN WITH OVERACTIVE BLADDER.

Hypothesis / aims of study

Antimuscarinics are the most commonly used drugs in the management of Overactive Bladder (OAB) although are associated with troublesome side effects. Consequently compliance and efficacy remain a problem; in women taking oxybutynin just 5.5% were cured of their urinary symptoms and only 18.2% continued therapy for over 6 months (1). Persistence rates of 44% are little better for the newer extended release preparations of tolterodine and oxybutynin (2). The lower urinary tract is innervated by the parasympathetic and sympathetic nervous system. During the storage phase continence is maintained by parasympathetic inhibition and sympathetic activation, which by acting on β_2 and α adrenergic receptors, lead to bladder relaxation and urethral sphincter contraction respectively. Bladder neck receptors are α_1 adrenergic (α_{1A}, α_{1B} and α_{1D}) whilst those in the bladder are α_{1A} and α_{1D}. It is postulated that the α_{1D} receptor may mediate OAB symptoms while the α_{1A} receptor subtype mediates obstructive symptoms (3).
Tamsulosin is a potent, specific and selective α_1 adrenoceptor antagonist with greater specificity for α_{1A} and α_{1D} receptors than for α_{1B} and may have a role in the management of OAB in women. Whilst there is little evidence supporting the efficacy of tamsulosin in OAB anecdotal evidence has demonstrated that it may improve urinary symptoms secondary to detrusor overactivity in men and for some time it has been used 'off label' in women with OAB. The primary aim of this study was to evaluate the efficacy of tamsulosin OCAS (oral controlled absorption system) compared to placebo in OAB whilst the secondary aims were to evaluate the safety and tolerability of once daily dosing with tamsulosin OCAS and to compare the efficacy and safety with tolterodine ER.

Study design, materials and methods

This was a parallel group, multicentre, multinational study with a single blind placebo run in period of 2 weeks followed by a randomised, double blind, double dummy active and placebo controlled treatment period of 6 weeks. Women (18-70 yrs) with OAB for ≥ 3 months were recruited. Exclusion criteria included stress incontinence, stress predominant mixed incontinence and women with neurogenic detrusor overactivity.
Following screening women entered a 2 week single blind placebo run in and completed a 3 day voiding diary. At randomisation women must have recorded an average of >/= 8 micturitions/ 24 hrs in the previous 3 days and one or more of the following: at least 3 episodes of urinary urge incontinence or at least 3 episodes of urgency. Patients were randomised to receive 1 of 4 doses of tamsulosin OCAS (0.25mg, 0.5mg, 1.0 mg or 1.5mg), 4mg of tolterodine extended release (ER), or placebo od for 6 weeks.
The primary efficacy variable was change in mean number of micturitions/24 hours. Secondary efficacy variables included change from baseline in; mean volume voided per micturition, mean number of incontinence episodes/24 hours, mean number of urgency episodes/24 hours and in Quality of Life (QoL) as assessed using the Kings Health Questionnaire (KHQ). Assuming a dropout rate of upto 20% 360 women had to be randomised in order to have 300 evaluable patients (50 patients per treatment arm). With 50 patients in each arm it would be possible to detect a difference of 0.56 standard deviations between the changes in mean number of micturitions per 24 hours of a tamsulosin OCAS dosing group and the placebo group with 80% power at a two sided significance level of 0.05. Changes from baseline to endpoint in mean number of micturitions per 24 hours were subjected to Analysis of Variance (ANOVA). A hierarchical test procedure was performed. Comparison of tamsulosin OCAS 1.5mg to placebo was tested at the two-sided significance level 0.05 by means of the corresponding contrast. If there was statistical significance then comparison of the lower doses was planned.

Results

Overall 364 women were randomized in the study. The Safety Population (SP) included 364, Full Analysis Set (FAS) 352 and the Per Protocol Set (PPS) 324. The results of the primary efficacy analysis showed that the difference from placebo in the mean number of micturitions/24 hours was not statistically significant for tamsulosin OCAS 1.5mg (p=0.189) **[Table 1]**. Consequently, based on the hierarchical testing procedure adopted, the differences for the lower tamsulosin OCAS dose groups were not tested. In addition there was no statistically significant difference observed for tolterodine 4mg od compared to placebo in the mean number of micturitions per 24hrs (p=0.353) suggesting a lack of efficacy.

	Placebo	**Tamsulosin OCAS**				**Tolterodine 4mg**
		0.25mg	**0.5mg**	**1.0mg**	**1.5mg**	
Number of patients	59	57	63	62	51	60
Baseline mean	11.90	12.20	11.09	12.96	12.46	13.22
Endpoint change from baseline	-1.81	-1.60	-1.01	-1.38	-1.18	-2.59
Estimated difference from placebo		0.28	0.65	0.66	0.73	-0.50
p value					0.189	0.353

Table 1: Primary Efficacy Analysis: Micturitions /24hrs

Similarly, when considering the secondary outcome parameters of mean volume voided, incontinence episodes/24 hrs, urgency episodes/24hrs and episodes of nocturia/24hrs there was no statistically significant difference between

tamsulosin and placebo. In addition, although women taking tolterodine 4mg od demonstrated a consistently greater increase in mean voided volume voided and consistent decreases in incontinence episodes/24 hrs, urgency episodes/24 hrs and episodes of nocturia/24 hrs this was not statistically significant. In addition there was no significant improvement in QoL scores across the treatment groups. Tamsulosin OCAS was well tolerated and the proportion of women that discontinued because of adverse events was low (4.7%) and did not differ across treatment groups.

Interpretation of results

The results of this study did not indicate a clinically relevant or statistically effect of tamsulosin OCAS 0.25mg – 1.5mg od versus placebo on any of the primary or secondary efficacy variables, nor on QoL assessment, indicating that it is not effective for the treatment of OAB in women. Whilst tolterodine 4mg od exhibited a consistent trend towards improvement of symptoms there was no indication of efficacy although the study was not powered appropriately for this outcome measure and thus no firm conclusion can be made.

Concluding message

Tamsulosin, a selective α_1 adrenoceptor antagonist, is not effective in the treatment of OAB in women and the evidence from this study does not support its use on an empirical basis. However, whether there may be a synergistic role when used concomitantly with an antimuscarinic agent remains to be elucidated. Combination therapy may allow reduced dosing and lead to an improvement in tolerability and compliance with therapy.

Although negative in its conclusion we believe this study is important to report in order to adopt a more evidence based approach to the clinical management of OAB.

References

1. A medium term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. Br J Obstet Gynaecol 1997; 104: 988-993.
2. Persistence with overactive bladder pharmacotherapy in a Medicaid population. Am J Manag Care 2005; 11: S121-129.
3. Novel role for alpha 1-adrenergic receptor sub-types in lower urinary tract symptoms. BJU Int 2000; 86: Suppl 2: 11-20.

FUNDING: **Astellas Pharma Europe Ltd**

DISCLOSURES: **Bolodeoku J and Terpstra G are employees of Astellas Pharma Europe Ltd**

CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**

HUMAN SUBJECTS: **This study was approved by the South East Multicentre Research Ethics Commitee, London,UK and followed the Declaration of Helsinki Informed consent was obtained from the patients.**