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CLINICAL EFFICACY AND SAFETY OF TOLTERODINE EXTENDED RELEASE FOR TREATMENT OF OVERACTIVE BLADDER. A PHASE III, 12-WEEK, RANDOMISED, DOUBLE-BLIND, PLACEBO- AND ACTIVE (OXYBUTYNIN)-CONTROLLED STUDY IN JAPAN AND KOREA

Aims of Study

Tolterodine extended release (ER) is effective in reducing symptoms of bladder overactivity in Caucasian populations[(1)]. The present study was conducted to compare the efficacy and tolerability of tolterodine ER 4 mg once daily (q.d.) versus oxybutynin 3 mg (t.i.d.) and placebo in Japanese and Korean patients with overactive bladder.

Methods

The study was conducted at 57 centres. Suitable patients completed a wash-out/run-in period (14 days total) where eligibility was confirmed using a 7-day micturition chart (eligibility and baseline assessment). Patients who qualified for the study with urge incontinence (≥ 5 episodes/week), and urinary frequency (≥ 8 micturitions/24 hours) were randomized to receive tolterodine ER 4 mg q.d., oxybutynin 3 mg t.i.d., or placebo in a 2:2:1 ratio for 12 weeks. Micturition charts were completed during the 7 days prior to the end of treatment (Week 12 or withdrawal). The primary efficacy variable was relative change from baseline to Week 12 in the number of urge incontinence episodes as determined from the micturition charts. Other micturition chart endpoints included: micturitions/24 hrs, pads used/24 hrs, and mean volume voided/micturition). Other secondary endpoints were patient perception variables (bladder condition, urgency).

Results

A total of 608 patients (293 Japanese and 315 Korean) were randomized into the study. The intent to treat (ITT) population was comprised of 239 patients treated with tolterodine ER, 244 treated with oxybutynin and 122 treated with placebo. About 70% of the study population was female, and age ranged from 25.9 to 88.2 years. The groups were well balanced at baseline. The efficacy analysis was conducted on the ITT population. Efficacy results are shown below. Tolterodine ER treatment resulted in significantly greater decreases in both urge incontinence episodes and micturitions/24 hrs than placebo (-78.6%, p = 0.0027, -2.0 micturitions/day, p = 0.0008, respectively). The percent decrease obtained with tolterodine ER was comparable to that obtained with oxybutynin. In addition, Tolterodine ER resulted in a significantly greater increase in volume voided per micturition than placebo (17.2 mL, p = 0.0086). Further, greater proportions of patients on both active treatments than on placebo had improvement in their perception of both bladder condition and urgency, and significantly greater proportions reported treatment benefit at the end of the study.

Summary of efficacy results

Endpoints	Placebo (n = 122)	Tol ER (n = 239)	Oxy (n = 244)	P values Tol ER vs Placebo	Oxy vs Placebo	Tol ER vs Oxy
% change from BL to Wk 12 (Median)						
Urge incontinence	-46.4	-78.6	-76.5	0.0027	0.0168	0.4469
Change from BL to Wk 12 (Median)						
Micturitions/24 hrs	-1.1	-2.0	-2.1	0.0008	0.0114	0.3132
Mean vol voided (ml/mic)	6.6	17.2	22.3	0.0086	<0.0001	0.0290

BL = baseline, Wk = week, Tol ER = tolterodine extended release, Oxy = oxybutynin

Safety results: Overall, patients on oxybutynin reported more adverse events than those on tolterodine ER or placebo. The most common adverse events included dry mouth, constipation, dyspepsia, difficulty in micturition, and headache. Dry mouth was by far the most frequently reported adverse event, and both its

incidence and severity were greater among oxybutynin (53.7%) than tolterodine ER-treated patients (33.5%). The incidence of urinary retention was similar among tolterodine ER and placebo-treated patients (1.7% and 1.6% respectively) while more frequent among oxybutynin-treated patients (9.4%). Although patients in Korea reported fewer adverse events overall, they had more reports of difficulty in micturition, urinary retention and urinary hesitation than did patients in Japan, particularly if on oxybutynin.

Conclusion:

This study demonstrated that tolterodine ER significantly improved micturition chart and patient perception variables compared with placebo in Asian patients with overactive bladder. The improvements with tolterodine ER were similar to those obtained with oxybutynin, but treatment with tolterodine showed fewer adverse events compared to treatment with oxybutynin. Treatment with tolterodine ER proved to be safe, and no new safety concerns were evident in this patient population.

Reference:
1. Van Kerrebroeck PEVA, et al. Urology, 2001, 57, 414-21