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EFFICACY AND SAFETY OF COMBINATION OF TOLTERODINE AND PILOCARPINE IN OVERACTIVE BLADDER PATIENTS: A RANDOMIZED DOUBLE-BLIND MULTICENTER PHASE 3 STUDY

Hypothesis / aims of study

Antimuscarinics are the mainstay treatment for overactive bladder (OAB), however, therapeutic potential is limited by side effects such as dry mouth. We aimed to determine the efficacy and safety of combination of tolterodine immediate-release (IR) 2mg and delayed-release pilocarpine 9mg (tolterodine/pilocarpine (2/9mg)) compared with tolterodine IR 2mg monotherapy for OAB.

Study design, materials and methods

This study was a 12-week, multicenter, randomized, double-blind, parallel, active control study. Patients≥20 years with OAB symptoms were recruited to a 2-week, single-blind, placebo run-in. Those with ≥8 micturitions and ≥2 urgency episodes per 24 hours and a total OABSS of 6 or more points were randomized 1:1 to tolterodine/pilocarpine (2/9mg) (n=193) or 2mg tolterodine (n=191) twice-daily for 12 weeks. Co-primary endpoints were the change from baseline in the mean number of daily micturitions and cumulative incidence of dry mouth at the end of the 12-week. Secondary endpoints included other OAB symptoms, xerostomia inventory total score and visual analogue scale (VAS) for dry mouth overall at the end of treatment period.

Results

Baseline characteristics were similar across the treatment groups. In the per protocol set, tolterodine/pilocarpine (2/9mg) combination treatment was noninferior to tolterodine 2mg monotherapy. Change from baseline in the mean number of daily micturitions was -1.49 ± 2.20 of tolterodine/pilocarpine (2/9mg) combination group and -1.74 ± 1.99 of tolterodine 2mg group, for a difference of -0.26 ± 2.09 between two groups. The 95% confidence limits on the difference (-0.79 to 0.27) was above the prespecified noninferiority threshold of -1.0 (Figure1). In the safety analysis set, incidence of dry mouth was lower in tolterodine/pilocarpine (2/9mg) combination group than tolterodine monotherapy group, significantly (57 of 190 or 30.0% for combination group vs 82 of 191 or 42.93% for monotherapy group, p=0.009) (Figure1). All secondary and other efficacy outcomes related to OAB symptoms were improved in both groups while no statistically differences between two groups at the end of the 12-week. The change from baseline in the xerostomia inventory total score and VAS for dry mouth was significantly lower in tolterodine/pilocarpine (2/9mg) combination group than tolterodine 2mg group (Table1). The incidence of adverse events was similar between two groups.

Interpretation of results

This randomised, double-blind phase 3 study showed that tolterodine/pilocarpine (2/9mg) combination treatment effectively reduced the incidence of dry mouth compared with tolterodine monotherapy while maintaining antimuscarinic efficacy in OAB. The safety of combination drug was consistent with the known safety profiles of these agents when administered individually.

Concluding message

A combination of tolterodine and pilocarpine effectively reduced incidence of dry mouth compared with tolterodine alone while preserving treatment efficacy in OAB and it was well tolerated.

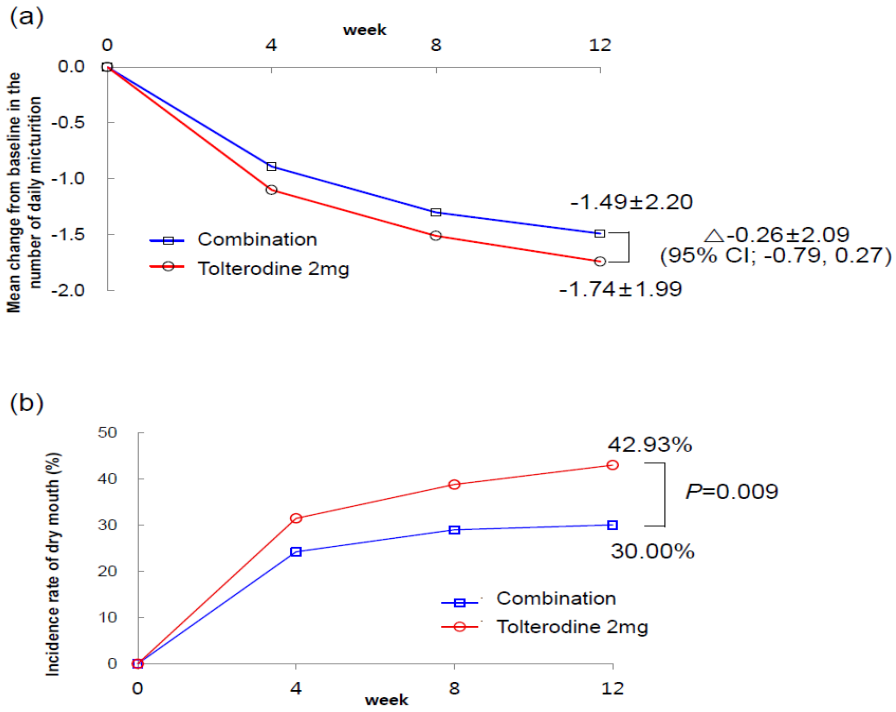

Figure1. Primary end points at end of treatment: (a) change from baseline in the mean number of micturition per day (per protocol set); (b) incidence of dry mouth (safety analysis set).

Table1. Changes in efficacy variables and questionnaires from baseline to 12 weeks (full analysis set)

	Tolterodine/pilocarpine (2/9mg) combination	**2mg tolterodine**	*p*
N (Full analysis set)	162	176	
Mean daily incontinence episodes			
Change from baseline to 12-weeks	-1.15 ± 2.74*	-1.21 ± 2.03*	0.986
Mean daily urgency episodes			
Change from baseline to 12-weeks	-2.55 ± 3.04*	-2.54 ± 2.59*	0.986
OABSS			
Change from baseline to 12-weeks	-4.72 ± 3.53*	-4.98 ± 3.08*	0.533
VAS for dry mouth			
Change from baseline to 12-weeks	7.75 ± 30.49 †	16.45 ± 34.12*	0.014
Xerostomia inventory total score			
Change from baseline to 12-weeks	1.39 ± 7.93 ‡	3.39 ± 8.56*	0.027

OABSS; overactive bladder symptom score, VAS; visual analogue scale
*** P<0.0001, † p=0.002, ‡ p=0.027**

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