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A 12-WEEK OPEN-LABEL EXTENSION STUDY TO ASSESS THE EFFICACY AND SAFETY OF COMBINATION OF TOLTERODINE AND PILOCARPINE IN THE TREATMENT OF PATIENTS WITH OVERACTIVE BLADDER AFTER 12-WEEK RANDOMIZED CONTROLLED STUDY

Hypothesis / aims of study

The aim of this study was to evaluate the safety and efficacy of 12 weeks of open-label extension study with combination of tolterodine/pilocarpine (2/9mg) following the completion of a blinded randomized controlled trial of acute treatment for overactive bladder (OAB).

Study design, materials and methods

Patients completing 12 weeks of randomized, double-blind treatment with either tolterodine/pilocarpine (2/9mg) or 2mg tolterodine twice daily were continued in the 12 weeks, open-label, uncontrolled extension study. Double-blind study medication was discontinued, and patients were started, open-label, on tolterodine/pilocarpine (2/9mg) twice daily. Efficacy analysis consisted of a comparison of the change from baseline in the mean number of daily micturitions, incontinence episodes, and urgency episodes at the end of the 24-week. The incidence of dry mouths and other adverse events were monitored and were evaluated for severity, duration, outcome, and relationship to the study drug. Overactive bladder symptom score(OABSS), xerostomia inventory total score, visual analogue scale (VAS) of dry mouth symptoms were also administered at each of the study visits.

Results

Of completers of randomized control study, 256 patients continued the extension study; 124 from tolterodine/pilocarpine (2/9mg) combination treatment (extended group) and 132 from the 2mg tolterodine monotherapy group (changed group). In the full analysis set, change from baseline in the mean number of daily micturitions was -1.78 ± 2.39 ($p<0.0001$) of extended group and -1.61 ± 2.32 ($p<0.0001$) of changed group. Other efficacy outcomes including the change from mean number of daily incontinence episodes and urgency episodes were improved in both groups while no statistically differences between two groups at the end of the 24-week (Table1). During the 12 weeks of randomized study period, incidence of dry mouth was lower in tolterodine/pilocarpine (2/9mg) combination group than tolterodine monotherapy group, significantly (33.06% vs 45.45%, $p=0.0427$). By the end of the 12-week period of the extension study, the incidence rate of dry mouths was 4.03% (95% confidence interval; 1.32-9.16) of extended group and 0.00% (confidence interval; 0.00-2.76) of changed group. The other adverse events were not significantly different between two groups.

Interpretation of results

The long-term administration of tolterodine/pilocarpine (2/9mg) combination for 24 weeks resulted in an additional increase in efficacy and it was tolerable for safety results. It has been confirmed that the efficacy is maintained and there was no occurrence of dry mouths during the extension period when tolterodine 2mg monotherapy is replaced with the tolterodine/pilocarpine (2/9mg) combination treatment. Changes in the subjective symptoms of dry mouth also improved to baseline levels after 24-week long-term treatment. Especially in changed group, VAS for dry mouth and xerostomia inventory total score was decreased dramatically after conversion to combination treatment during extension period.

Concluding message

In this 12-week, open-label extension study, a combination of tolterodine and pilocarpine demonstrated a favourable safety and tolerability profile. The efficacy and safety remained excellent even though 2mg tolterodine monotherapy was changed to tolterodine/pilocarpine (2/9mg) combination treatment. Patients demonstrated sustained improvement in OAB symptoms for up to 24 weeks of combination treatment.

Table 1. Changes in efficacy variables and questionnaires from baseline to 24 weeks (full analysis set)

	Combination → Combination (extended group)	Monotherapy → Combination (changed group)	p
N (Full analysis set)	121	123	
Mean daily micturitions			
Change from baseline to 24-weeks	-1.78 ± 2.39*	-1.61 ± 2.32*	0.5807
Change from 12-weeks to 24-weeks	0.15 ± 1.51*	0.15 ± 1.51	0.0259
Mean daily incontinence episodes			
Change from baseline to 24-weeks	-1.46 ± 3.11*	-1.39 ± 1.86*	0.8251
Change from 12-weeks to 24-weeks	-0.23 ± 0.88*	0.04 ± 0.99	0.0359
Mean daily urgency episodes			
Change from baseline to 24-weeks	-3.33 ± 3.29*	-3.26 ± 3.04*	0.8782
Change from 12-weeks to 24-weeks	-0.52 ± 1.42*	-0.34 ± 1.84	0.4220
OABSS			
Change from baseline to 24-weeks	-4.72 ± 3.53*	-4.98 ± 3.08*	0.5330
Change from 12-weeks to 24-weeks	-0.82 ± 2.52*	-0.33 ± 2.75	0.1455
VAS for dry mouth			
Change from baseline to 24-weeks	0.04 ± 25.36	1.82 ± 30.71	0.6218
Change from 12-weeks to 24-weeks	-8.54 ± 24.10*	-13.12 ± 20.94*	0.1331
Xerostomia inventory total score			
Change from baseline to 24-weeks	-0.73 ± 8.72	-0.09 ± 8.46	0.5625
Change from 12-weeks to 24-weeks	-2.41 ± 6.42*	-2.63 ± 6.62*	0.8001

Combination; tolterodine/pilocarpine (2/9mg) combination treatment, monotherapy; 2mg tolterodine treatment, OABSS; overactive bladder symptom score, VAS; visual analogue scale
*** P<0.05**

Disclosures
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