145

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DARIFENACIN IN THE TREATMENT OF OVERACTIVE BLADDER: DOSE–RESPONSE EFFECTS ON URINARY SYMPTOMS IN PHASE III TRIALS

Hypothesis / aims of study

Darifenacin is a muscarinic M_3 selective receptor antagonist, which has demonstrated marked selectivity for M_3 receptors (ranging from 9-fold to 59-fold) relative to other muscarinic receptor subtypes. In a pooled analysis of fixed dose, 12-week, phase III studies in 1,059 patients with overactive bladder (OAB) and urinary urge incontinence, darifenacin 7.5 mg once daily (qd) and 15 mg qd were associated with significant reductions, compared with placebo, in the median number of incontinence episodes per week. Significant decreases compared with placebo were also observed in micturition frequency and urgency episodes (1).

The aim of this study was to determine whether the efficacy of darifenacin in treating symptoms of OAB displays significant dose–response trends at doses up to 15 mg qd (the maximum marketed dose), based on combined (averaged) data from two fixed dose, placebo-controlled, 12-week, phase III studies.

Study design, materials and methods

Data were considered from the only two darifenacin fixed-dose, placebo-controlled, 12-week, phase III studies that evaluated both marketed darifenacin doses (7.5 and 15 mg qd).The two studies recruited male and female patients aged ≥18 years with OAB for ≥6 months prior to study entry. Study 1 assessed darifenacin 3.75, 7.5 and 15 mg qd and Study 2 assessed darifenacin 7.5 and 15 mg qd. Efficacy was determined using patients' OAB symptom electronic diaries. The primary efficacy endpoint was the median change from baseline in number of incontinence episodes (IEs)/week. Secondary endpoints included micturition frequency and urgency episodes/day. Each endpoint was compared with placebo within each study, and tested for dose–response using the one-sided Jonckheere test. Tolerability and safety were also assessed based on combined (averaged) data from the two studies.

Results

In both studies, treatment with darifenacin 7.5 and 15 mg qd was associated with significant improvements compared with placebo in reducing the number of IEs/week (Table). Significant improvements were also noted in frequency and urgency with darifenacin 15 mg qd in both studies, and with darifenacin 7.5 mg qd in one study. Significant dose–response trends were observed with darifenacin in both studies for the major efficacy endpoints: reduction in IEs, micturition frequency and urgency episodes (Table).

Table. Dose–response effect for IEs, micturition frequency and urgency episodes with darifenacin 3.75, 7.5 and 15 mg qd.

			Median (%) decrease from baseline			Median difference from placebo		
	Dose (mg)	**N**	**IEs**	**Freq.**	**Urg.**	**IEs**	**Freq.**	**Urg.**
Study 1	Placebo	163	7.6 (55.9)	0.8 (8.0)	0.9 (12.8)	-	-	
	3.75	53	8.6 (58.8)	1.7 (13.8)	1.8 (21.1)	–0.8	–0.6	–0.5
	7.5	228	9.0 (67.7)	1.6 (16.3)	2.0 (28.8)	–1.7*	–0.8*	–0.9*
	15	115	10.4 (72.8)	1.7 (15.3)	2.0 (28.7)	–2.0*	–0.9*	–0.9*
Dose–response trend, p value[a]						0.002	<0.001	<0.001
Study 2	Placebo	108	5.9 (46.0)	1.1 (9.6)	1.2 (15.7)	-	-	
	7.5	107	8.1 (68.7)	1.7 (16.7)	1.8 (29.2)	–2.8*	–0.5	–0.5
	15	106	10.4 (76.5)	1.9 (17.9)	2.3 (26.9)	–4.3*	–0.7*	–1.1*
Dose–response trend, p value[a]						<0.001	0.011	0.007

IEs = incontinence episodes/week; Freq. = micturition frequency; Urg. = urinary urgency episodes/day

*p<0.05 vs placebo, stratified Wilcoxon test; [a]one-sided test based on the Jonckheere's analysis.

The most common adverse events (AEs) were dry mouth (occurring in 13.2%, 20.2%, 35.6% and 7.7% of patients receiving darifenacin 3.75, 7.5 and 15 mg qd and placebo, respectively) and constipation (occurring in 5.7%, 14.8%, 19.4% and 6.2%, of patients, respectively), showing a dose-related trends (statistical significance not assessed). AEs were mostly mild to moderate and infrequently led to discontinuation.

Interpretation of results

Marketed doses of darifenacin show significant benefit and clear dose–response trends in treating symptoms of OAB patients. There was a corresponding increase in antimuscarinic class adverse events, further supporting the dose-dependent pharmacological action of the drug.

Concluding message

These data, together with results of a randomised voluntary dose-titration study (2), suggest that darifenacin provides an effective, flexible dosing treatment option for OAB, with the potential for individualised dosing according to patients' needs.

References

1. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M_3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int 2005:95(7):993–1001

2. An investigation of dose titration with darifenacin, an M_3 selective receptor antagonist. BJU Int 2005;94:580–6.

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