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THE EFFICACY, TOLERABILITY AND SAFETY OF DARIFENACIN GIVEN BY A FLEXIBLE TITRATION DOSING REGIMEN

Hypothesis / aims of study

Darifenacin is a muscarinic M_3 selective receptor antagonist for the treatment of overactive bladder (OAB). At fixed, once-daily doses of 7.5 mg and 15 mg, darifenacin provides effective symptom relief and is well tolerated in patients with OAB [1]. In routine clinical practice, however, flexible dosing may represent a more desirable approach. The aim of the present study was to determine the efficacy, tolerability and safety of a flexible dosing strategy with darifenacin, in which dose-escalation from 7.5 mg to 15 mg once daily (qd) was permitted if additional efficacy was required by the patient and physician.

Study design, materials and methods

This multicentre, double-blind, placebo-controlled study randomised 395 patients (aged 22–89 years; 84% female) with OAB for ≥6 months to receive darifenacin controlled-release tablets 7.5 mg qd (n=268) or matching placebo (n=127) for 12 weeks. After 2 weeks of double-blind treatment, efficacy, tolerability and safety were assessed and the dose increased to 15 mg qd (pseudo-increase for placebo recipients) if additional efficacy was required. Thereafter, dose adjustment was not permitted. Patients recorded incontinence episodes (primary efficacy endpoint) and secondary efficacy parameters in an electronic diary at weeks 2, 6 and 12. Severity of urgency was assessed using a visual analogue scale (VAS) (from 0=mild to 100=severe).

Results

Table 1 summarises efficacy results at week 12 for the full study population (patients who stayed on 7.5 mg [darifenacin, 41%; placebo, 32%] and those who dose-escalated to 15 mg [darifenacin, 59%; placebo, 68%]) as median (%) changes from baseline to week 12.

Table 1.

Parameter	Darifenacin	Placebo
Incontinence episodes/week	–8.2 (–62.9%)*	–6.0 (–48.1%)
Micturition frequency/day	–1.9 (–18.9%)***	–1.0 (–10.0%)
Bladder capacity (mean volume voided; mL)	+18.8 (10.5%)*	+6.6 (5.4%)
Frequency of urgency/day	–2.3 (–28.2%)***	–0.9 (–11.0%)
Severity of urgency (100 mm VAS)	–9.1 (–16.8%)*	–3.2 (–5.6%)

*p<0.05, ***p≤0.001 using Wilcoxon rank-sum test stratified by baseline severity for treatment difference versus placebo.

The most common adverse events were constipation (darifenacin, 21%; placebo, 8%) and dry mouth (darifenacin, 19%; placebo, 9%). These were mainly mild to moderate and infrequently led to discontinuation (<3.0% with darifenacin, <1% with placebo). CNS and cardiac safety was comparable between groups (treatment-related CNS event rates 3.7% darifenacin vs 1.6% placebo, and 1.5% darifenacin vs 0.8% placebo for cardiac events).

Table 2 summarises findings of a sub-analysis of darifenacin-treated patients by dose escalation status. Subgroups did not differ in mean age or weight. Secondary efficacy variables showed similar trends by sub-group, both in terms of the median change in episodes/week, and in response rates. There were few discontinuations due to treatment-related adverse events (3.1% in those who dose escalated, 9.3% in those who did not).

Table 2.

	Patients who did not dose-escalate (7.5 mg to 7.5 mg)		Patients who dose-escalated at week 2 (7.5 mg to 15 mg)	
Efficacy	Week 2	Week 12	Week 2	Week 12
Median (%) change in incontinence episodes/week[a]	–6.0 (–49.2)	–8.0 (–61.3)	–5.3 (–35.7)	–8.3 (–64.8)
Responders[a,b] (%)	49.0	59.6	37.4	62.8
All-causality adverse events	Week 2	Week 2–12	Week 2	Week 2–12
Constipation (%)	18.5	3.7	6.3	14.4
Dry mouth (%)	17.6	3.7	7.5	10.6
Headache (%)	3.7	1.9	4.4	5.0

[a]n=104 at weeks 2 and 12 for patients who did not dose escalate; n=156 at week 2 and n=157 at week 12 in those who dose-escalated; [b]Proportion of patients achieving ≥50% reduction in incontinence episodes/week at week 2 or 12.

Interpretation of results

Darifenacin demonstrated significant efficacy, as seen by the median reduction from baseline in the number of incontinence episodes/week, paralleled by significant improvements in other diary variables versus placebo.

The sub-analysis suggested that a subpopulation of patients (requiring dose escalation) exhibit lower sensitivity to darifenacin than those who continued on 7.5 mg darifenacin. This is supported by the following findings:

- Efficacy outcomes improved with dose escalation, to levels comparable to those in the 7.5/7.5 mg group
- Dose escalation increased the response rate by 25.4% (from 37.4% to 62.8%)
- Adverse events in the 15 mg group were lower at week 2 and remained lower at week 12, compared with the 7.5 mg group

Therefore, varying sensitivity to anticholinergic agents has been shown to exist, suggesting that dose flexibility is essential for optimal patient management.

Concluding message

Darifenacin offers an efficacious, well tolerated and flexible approach to the treatment of OAB. Dose adjustments can be made, with increased efficacy and minimal effects on tolerability.

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References

1. European Urology Supplement 2004;3(2):A512.

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