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CONSTIPATION AND ASSOCIATED INTERVENTION IN PATIENTS WITH OVERACTIVE BLADDER TREATED WITH DARIFENACIN OR TOLTERODINE

Hypothesis / aims of study

Darifenacin is a muscarinic M_3 selective receptor antagonist for the treatment of patients with overactive bladder (OAB), recently approved for use in both Europe and the USA. Besides dry mouth, one of the most frequently reported adverse events with all antimuscarinic agents is constipation. The side effect profile of darifenacin, including constipation rates, was evaluated in three multicentre, double-blind, placebo-controlled studies in patients with OAB. A pooled analysis of these studies was undertaken to determine whether constipation reported by patients treated with darifenacin 7.5 mg and 15 mg once daily (qd) and tolterodine 2 mg twice daily (bid) resulted in intervention and/or was associated with treatment withdrawal.

Study design, materials and methods

A pooled analysis of the data was possible as inclusion and exclusion criteria for the three studies were almost identical. Two of the studies included a darifenacin 7.5 mg treatment group, all three included a darifenacin 15 mg group, and one study included tolterodine. After a 2-week washout and 2-week placebo run-in, a total of 1,282 patients (age range 19–93 years, 85% female) who had suffered from OAB for more than 6 months were randomised to 12 weeks' treatment with darifenacin 7.5 mg qd (n=337), darifenacin 15 mg qd (n=334), tolterodine 2 mg bid (n=223) or matching placebo (n=388). Patient-reported constipation rates and the number of patients taking non-dietary intervention for management of constipation were evaluated for the purpose of this analysis.

Results

The reported incidence of constipation at any time during the study was 14.8% with darifenacin 7.5 mg, 21.3% with darifenacin 15 mg, 12.6% with tolterodine and 6.2% with placebo (see Table). Most cases required no action or only dietary modification. At baseline, a comparable proportion of patients was already taking treatments for management of constipation, including the use of stool softeners/fibre supplements or laxatives (see Table). During the study period, the increase in patients taking constipation treatments (whether or not constipation was reported as an adverse event) was comparable for the darifenacin 7.5 mg and placebo groups (3.3% and 2.3%, respectively) and for the darifenacin 15 mg and tolterodine groups (5.7% and 6.7%, respectively; see Table). This increase in the darifenacin 15 mg and placebo groups was comparable to that observed for these groups in the single study that included tolterodine, thereby supporting the validity of the pooled analysis. Discontinuation associated with constipation in the pooled analysis was also comparable for darifenacin 7.5 mg (2 patients; 0.6%) and placebo (1 patient; 0.3%) and for darifenacin 15 mg (4 patients; 1.2%) and tolterodine (4 patients; 1.8%).

	Darifenacin 7.5 mg qd (n=337)	Darifenacin 15 mg qd (n=334)	Tolterodine 2 mg bid (n=223)	Placebo (n=388)
Constipation (%)	50 (14.8)	71 (21.3)	28 (12.6)	24 (6.2)
Taking constipation treatments at baseline (%)	9 (2.7)	13 (3.9)	8 (3.6)	15 (3.9)
New-onset use of constipation treatment during study (%)	11 (3.3)	19 (5.7)	15 (6.7)	9 (2.3)
Discontinuation due to constipation (%)	2 (0.6)	4 (1.2)	4 (1.8)	1 (0.3)

Interpretation of results

The potential clinical relevance of adverse events reported in clinical trials of new therapies can be assessed by evaluating the need for treatment intervention. The extent to which an adverse event is 'bothersome' to the patient may be evaluated by looking at associated discontinuation rates. This pooled analysis of three randomised controlled trials of darifenacin indicates that constipation is unlikely to be a significant issue in clinical practice; the need for patients or physicians to manage constipation by non-dietary intervention was comparable to tolterodine. Furthermore, constipation should not be troublesome to the majority of darifenacin-treated patients, as indicated by the low discontinuation rates which, at the higher dose, were comparable to tolterodine.

Concluding message

Most cases of constipation reported by patients receiving darifenacin or tolterodine treatment are easily tolerated. The higher incidence of constipation reported with the higher dose of darifenacin compared with tolterodine did not translate into higher intervention rates and led to a similar withdrawal rate. This suggests that many self-reports reflect changes in bowel habits and may not correspond to standard definitions of constipation (Rome II criteria) (1). Therefore, use of an M_3 selective agent appears not to be associated with a greater incidence of bothersome constipation than a nonselective agent such as tolterodine.

References

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