ORIGINAL ARTICLE

Therapeutic benefit in patients switching tolterodine to other novel antimuscarinic agents

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KEYWORDS
Overactive bladder; Treatment benefit; Fesoterodine; Solifenacin

Abstract
Objectives: To explore in the daily clinical practice setting that antimuscarinic, fesoterodine or solifenacin, provides a greater clinical benefit after changing the prior overactive bladder (OAB) therapy with tolterodine extended release (ER) to other novel antimuscarinic agents.

Material and methods: A post hoc analysis of data from an observational multicenter, cross-sectional, retrospective study. Adult patients of both sexes, with OAB and OAB-V8 score ≥ 8, who switched to fesoterodine or solifenacin within the 3–4 months before study visit from their prior tolterodine-ER-based therapy due to poor response were included. 92 patients were selected for each treatment group, matched (1:1) according to conditioned probability using the propensity score. Benefit of treatment change perceived by the physician and patient was evaluated by means of the Clinical Global Impression of Improvement subscale (CGI-I) and Treatment Benefit Scale (TBS), respectively. Degree of worry, bother and interference with daily living activities due to urinary symptoms, level of satisfaction, and preference for current treatment were also assessed.

Results: Fesoterodine provided a significantly greater improvement than solifenacin in terms of therapeutic benefit perceived by the physician according to ICG-I. 96.7% of the patients on fesoterodine treatment vs. 81.6% of the solifenacin group showed a score of improvement in TBS (p < 0.05). Fesoterodine was also better rated than solifenacin with regard to satisfaction and preference for the new treatment (93.4 vs. 78.2%, p < 0.05).

Conclusions: In daily clinical practice the switch from tolterodine LP to fesoterodine seems to provide greater benefits both from the physician’s and the patient’s point of view compared with those provided by solifenacin.

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**Introduction**

Overactive bladder (OAB) is a syndrome of the lower urinary tract characterized by urgency with or without urge incontinence, usually accompanied by increased frequency during the day and nocturia.\(^1\)\(^-\)\(^3\) In Spain, the published prevalence data indicate that 5% of men aged 50–65 years and 10% of women aged 25–65 years suffer from OAB or urinary incontinence.\(^4\)\(^-\)\(^7\) The symptoms associated with OAB syndrome significantly affect the social, sexual, occupational, and psychological spheres of the patients.\(^8\) All this has a negative impact on both quality of life and personal relationships of those affected.\(^9\)\(^-\)\(^7\)

Antimuscarinic drugs are the first line of pharmacological treatment for OAB.\(^2\) However, many patients discontinue therapy within a year.\(^8\) For a patient to persist under treatment, he must be satisfied with it, so a proper balance between tolerability, efficacy, and cost is required.\(^10\) Therefore, the lack of adequate response to treatment in many patients is mainly due to breach thereof or lack of efficacy or intolerance.\(^11\) In these cases, the change of treatment\(^12\)\(^-\)\(^15\) and behavioral therapy techniques can improve the symptoms of these patients.\(^4\)

Fesoterodine and solifenacin are antimuscarinic agents that have proven effective, safe, and with a good tolerability profile for the treatment of patients with OAB.\(^16\)\(^-\)\(^19\) Different clinical studies have also confirmed that patients dissatisfied with the treatment of extended-release tolterodine (ER) showed an improvement after switching to fesoterodine\(^12\)\(^,\)\(^21\) or solifenacin.\(^13\)\(^,\)\(^15\) However, there have been no comparative data published between these latest generation antimuscarinics. The aim of this post hoc analysis was to explore in daily clinical practice which of these latest generation antimuscarinics provides greater benefit, both in the clinic and from the point of view of the patient after changing the first treatment with ER tolterodine. As secondary objectives, we also assessed satisfaction with the new treatment and the inconvenience that the urological symptoms cause to the patient.

**Materials and methods**

We conducted a post hoc analysis of the data from the IMPACTA study,\(^2\) a retrospective, cross-sectional, observational, multicenter study whose objective was to determine in clinical practice the factors influencing the change in treatment for OAB and the level of satisfaction with the change. In the original study, patients of both sexes were included, older than 18 years of age, diagnosed with OAB by a clinician and with a score on the OAB-V8 scale ≥ 8, whose treatment had been modified in the 3–4 months prior to the visit of the study and who gave their written informed consent. In the analysis shown in this article, only those patients who met the above-mentioned criteria and who had changed the previous treatment with ER tolterodine, first administered by fesoterodine or solifenacin at usual doses in routine clinical practice, were included. The study was approved by the ethics committee of the General University Hospital of Valencia, and was conducted in compliance with the principles outlined in the Declaration of Helsinki for studies in humans.

In the only visit of the study, demographic data, concomitant diseases, clinical history of the OAB, previous and current treatment for the OAB, reason for change, and therapeutic compliance were collected by means of the Morisky–Green Questionnaire.\(^2\) The benefit of the change
in treatment was assessed, defined as improvement in the symptoms of the OAB perceived by the physician and the patient. The doctor determined the benefit by means of the Clinical Global Impression Improvement Scale (CGI-I). The patient rated his improvement by means of the Treatment Benefit Scale (TBS). We also assessed, by means of a patient questionnaire, the concern, discomfort, and impact that the symptoms of the disease cause on daily life, as well as the degree of satisfaction with the current treatment and preference for the current or previous medication.

Measuring instruments

The CGI scale consists of 2 items, the first one (CGI-S) assesses the current severity of the disease. The second item (CGI-I) allows for assessment, from the point of view of the physician, of the clinical benefit of treatment change for the patient. The score ranges from 1 to 7 (1 = much better, 7 = much worse).

The TBS scale is a self-administered questionnaire which makes it possible to assess the benefit perceived by the patient after the change in treatment, when comparing the current and previous status of urinary problems. The score ranges from 1 to 4 (1 = significantly improved, 2 = improved, 3 = unchanged, 4 = worse). The addition of responses in categories 1 and 2 represents the patients who obtained improvement with the treatment as perceived by the patients.

In the patient questionnaire, we assessed using a 5-point scale (1 = no, 2 = a little, 3 = somewhat, 4 = considerable, 5 = much) the degree of concern by symptoms of increased daytime frequency, urinary incontinence during sex, nocturia, frequent urinary tract infections, urinary urgency, bladder pain, urinary incontinence, difficulty starting urination, and urinary stress incontinence; the degree of discomfort due to increased urinary frequency during the day, urinary urgency, and urge urinary incontinence, the degree of interference that the OAB symptoms cause with regard to daily life activities (leisure, professional and domestic work); and the satisfaction with the current treatment. The current treatment preference was also assessed according to the options: I definitely prefer the current one, certain preference for the current one, no preferences, certain preference for the previous one, I prefer the previous one without a doubt.

Statistical methodology

In this post hoc analysis, we used the Propensity Score methodology or propensity score for the selection of patients for statistical analysis. The Propensity Score methodology was developed as a way to reduce the selection biases and confusion of cohort studies. Later, it has been widely used in epidemiological studies, bringing them closer in accuracy and reliability to randomized studies. The term propensity score is defined as the conditioned probability of each individual in the sample to be assigned to the treatment group, given the other covariates. The Propensity Score method consists in building on the set of confounding variables a function of all of them to estimate the probability that patients have to be assigned to each treatment group, to later stratify or match by the values of this function. Thus, in each stratum or partner, the patients have the same probability of being assigned to each group, and therefore randomization is simulated. For each individual in the sample, the propensity score will be a function depending on the observed covariates. The Propensity Score was calculated by means of logistic regression using as covariates age, sex, time since the diagnosis, duration of antimuscarinic therapy, score on the OAB-V8 scale, and compliance according to the Morisky–Green test. The patients treated with fesoterodine were matched to those treated with solifenacin (1:1) according to the propensity score. Homogeneity of the 2 groups was guaranteed in the variables prior bladder retraining and presence of comorbidities.

The statistical analyses included the description of all the variables using central and dispersion-tendency statistics for continuous variables, and absolute and relative frequencies for categorical variables. We used a univariate general linear analysis model (ANCOVA) in which the propensity score was included as a covariate for the analysis of continuous variables. The categorical variables were analyzed using the Chi-square test with Yates correction for linear trend when appropriate. Logistic regression with propensity score was used for comparisons of categorical variables.

The statistical tests were performed with a 5% significance level and they were bilateral. The version 19 SPSS statistical package was used.

Results

In the IMPACTA study, a total of 3,365 patients were recruited, of whom 2,038 were considered evaluable (Fig. 1). A total of 842 patients changed their first ER tolterodine treatment; 92 did so by fesoterodine and 748 by solifenacin (Fig. 1). Among the latter, in this analysis, a sample of 92 patients was selected (1:1) matched to those treated with solifenacin depending on the Propensity Score. The mean (95% CI) of this index was 0.494 (0.508–0.480) for the fesoterodine group and 0.512 (0.525–0.499) for the solifenacin one. Table 1 shows the demographic and clinical characteristics of the 2 groups of patients analyzed. Both treatment groups were homogeneous; no statistically significant difference was observed for any of the variables analyzed. Most of the population were women, aged around 60 years and recently diagnosed. Hypertension was the most common concomitant disease (50%), followed by urinary tract infections and diabetes mellitus. 69.6% of the patients treated with fesoterodine and 65.2% of those treated with solifenacin were receiving some type of concomitant medication.

In both groups, the main reason for the change was the lack of effectiveness of previous treatment with ER tolterodine followed by adverse effects, with no significant differences between the 2 treatment groups being observed. The mean (SD) duration of treatment at the time of the study visit was also similar between the 2 groups: fesoterodine 253.6 (261.7) days vs. solifenacin 212.3 (207.3) days; p = 0.238. Regarding the doses used, the proportion of patients receiving the highest dose (8 mg/10 mg) was higher among those treated with fesoterodine than with solifenacin: 62 vs. 37%; p < 0.001. Regarding therapeutic
adherence to the new treatment, no significant differences were observed between both groups.

**Benefit after treatment change**

The substitution of ER tolterodine by any of the 2 latest generation antimuscarinics analyzed, fesoterodine, or solifenacin, provided a benefit perceived both by the doctor and the patient (Fig. 2). However, the improvement perceived by the doctor after the change of treatment was significantly higher among patients treated with fesoterodine than with solifenacin (average CGI-I score [95% CI] 2.20 [2.41–1.98] vs. 2.60 [2.81–2.38]; p = 0.012) (Fig. 2A). Fig. 2B shows the benefit that the treatment change meant from the point of view of the patient according to the TBS scale. Almost all the patients treated with fesoterodine (96.7%) compared to 81.6% of the solifenacin group perceived an improvement after the change (1–2 TBS score) (p < 0.05). Meanwhile, the proportion of patients who did not perceive any benefit or whose condition worsened with the change (3–4 TBS score) was significantly higher in the group treated with solifenacin (18.4%) than in the fesoterodine one (3.3%).

**Table 2** shows the assessment that the patients gave to their urinary symptoms. In most of the variables

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of the patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fesoterodine N (92)</td>
</tr>
<tr>
<td>Women, %</td>
<td>82.6</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>60.2 (11.9)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>27.0 (3.5)</td>
</tr>
<tr>
<td>Time since diagnosis, mean (SD), days</td>
<td>396.5 (517.2)</td>
</tr>
<tr>
<td>OAB-V8 score (0–40), mean (SD)</td>
<td>18.2 (6.9)</td>
</tr>
<tr>
<td>CGI-I score (1–7), mean (95% CI)</td>
<td>3.2 (3.4–2.9)</td>
</tr>
<tr>
<td>Bladder retraining, %</td>
<td>69.6</td>
</tr>
<tr>
<td><strong>Concomitant diseases</strong></td>
<td></td>
</tr>
<tr>
<td>HBP, %</td>
<td>50.0</td>
</tr>
<tr>
<td>Urinary tract infections, %</td>
<td>22.8</td>
</tr>
<tr>
<td>DM, %</td>
<td>20.7</td>
</tr>
<tr>
<td>Depression, %</td>
<td>16.3</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²), %</td>
<td>14.1</td>
</tr>
<tr>
<td>Ictus, %</td>
<td>2.2</td>
</tr>
<tr>
<td>Parkinson, %</td>
<td>0.0</td>
</tr>
<tr>
<td>Concomitant medication, %</td>
<td>69.6</td>
</tr>
</tbody>
</table>

DM: diabetes mellitus; HBP: high blood pressure; BMI: body mass index; OAB: overactive bladder.
Table 2  Assessment of urinary symptoms with the new treatment according to the patients.

<table>
<thead>
<tr>
<th>Symptoms (nothing/no=0 to considerable = 5)</th>
<th>Fesoterodine N (92)</th>
<th>Solifenacin N (92)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>3.10 (3.3–2.9)</td>
<td>3.34 (3.54–3.14)</td>
<td>0.107</td>
</tr>
<tr>
<td>Urinary incontinence during sexual intercourse</td>
<td>2.06 (2.32–1.8)</td>
<td>2.24 (2.49–1.98)</td>
<td>0.361</td>
</tr>
<tr>
<td>Nocturia</td>
<td>3.03 (3.24–2.82)</td>
<td>3.18 (3.4–2.97)</td>
<td>0.312</td>
</tr>
<tr>
<td>Frequent infections</td>
<td>2.44 (2.69–2.19)</td>
<td>2.42 (2.67–2.18)</td>
<td>0.934</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>3.17 (3.39–2.95)</td>
<td>3.49 (3.71–3.27)</td>
<td>0.047</td>
</tr>
<tr>
<td>Bladder pain</td>
<td>2.37 (2.61–2.13)</td>
<td>2.43 (2.67–2.2)</td>
<td>0.726</td>
</tr>
<tr>
<td>Urge urinary incontinence</td>
<td>3.03 (3.26–2.81)</td>
<td>3.26 (3.48–3.03)</td>
<td>0.177</td>
</tr>
<tr>
<td>Difficulty urinating</td>
<td>2.09 (2.33–1.85)</td>
<td>2.11 (2.34–1.87)</td>
<td>0.931</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>2.14 (2.38–1.91)</td>
<td>2.07 (2.3–1.84)</td>
<td>0.681</td>
</tr>
<tr>
<td>Discomfort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>3.09 (3.28–2.91)</td>
<td>3.33 (3.52–3.15)</td>
<td>0.085</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>2.33 (3.43–3.03)</td>
<td>3.59 (3.79–3.39)</td>
<td>0.014</td>
</tr>
<tr>
<td>Stress urinary urgency</td>
<td>2.93 (3.17–2.70)</td>
<td>3.31 (3.54–3.07)</td>
<td>0.032</td>
</tr>
<tr>
<td>Interference with daily life activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily life activities</td>
<td>2.91 (3.12–2.69)</td>
<td>3.01 (3.22–2.79)</td>
<td>0.524</td>
</tr>
<tr>
<td>Leisure</td>
<td>3.01 (3.22–2.79)</td>
<td>3.13 (3.35–2.91)</td>
<td>0.432</td>
</tr>
<tr>
<td>Work/household activities</td>
<td>2.33 (2.57–2.09)</td>
<td>2.53 (2.77–2.29)</td>
<td>0.249</td>
</tr>
<tr>
<td>Satisfaction with the treatment</td>
<td>3.58 (3.78–3.38)</td>
<td>3.25 (3.44–3.05)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Values given as mean (95% CI).

Figure 2  Benefit perceived by the doctor and the patient after change from ER tolterodine to fesoterodine or solifenacin.

analyzed, there were no significant differences between the 2 treatments (Table 2). Only those variables related to the symptoms of urgency, such as the concern for the symptom of urinary urgency, the discomfort caused by the symptoms of urinary urgency and urge incontinence, were found to be significantly lower among patients treated with fesoterodine than with solifenacin.

Both groups of patients rated more favorably the new treatment than ER tolterodine, although fesoterodine was significantly better assessed than solifenacin (Table 2 and Fig. 3). Satisfaction with the new treatment was significantly higher in the group of patients treated with fesoterodine (Table 2) (p < 0.05). As to the preference for the new treatment, the proportion of patients who preferred or had a certain preference for fesoterodine was also significantly higher than that observed in the group of solifenacin (93.4 vs. 78.2%, p = 0.029) (Fig. 3).

Discussion

This is a post hoc analysis of a study conducted in routine clinical practice, in which patients with OAB were included with inadequate response to previous treatment with ER tolterodine, mainly due to lack of efficacy and tolerability.2

The change from ER tolterodine to any of the 2 antimuscarinic agents tested provided benefits both from the clinical point of view and that of the patient. The data presented also show that the change to fesoterodine appears to provide greater benefits to a greater number of patients, compared with the one that solifenacin provides.
Therapeutic benefit in patients switching tolterodine to other novel antimuscarinic agents

Different clinical studies had already confirmed that dissatisfied patients, previously treated with ER tolterodine, had an improvement after switching to fesoterodine or solifenacin. There are no comparative data published between solifenacin and fesoterodine. Several randomized clinical trials in which the efficacy of 8 mg fesoterodine vs. 4 mg ER tolterodine showed the superiority of fesoterodine regarding, among other variables, the reduction of episodes of urge urinary incontinence (UUI), urgency, and number of urinations. However, between solifenacin and ER tolterodine, the data from published studies are not totally conclusive, not directly comparing both treatments or just demonstrating the non-inferiority of solifenacin vs. ER tolterodine.

A retrospective study has recently been published, which aimed to assess the effect of the use of fesoterodine as a rescue from a previous failed antimuscarinic treatment due to ineffectiveness or intolerance. Of the 158 patients analyzed, the majority (74%) received solifenacin (26% 10 mg; 47% 5 mg) and the rest (26%) 4 mg tolterodine. After replacement of these treatments with 8 mg fesoterodine, we observed a significant improvement in the symptoms of urinary urgency, inadequate voiding, and stress urinary incontinence, as well as a significant reduction in the incidence of dry mouth and constipation. Such data would come to support our results to a certain extent, showing that the therapeutic benefit perceived by both physicians and patients after the change was significantly greater with fesoterodine than with solifenacin. We also observed that the concern or discomfort due to some of the main urinary symptoms (urgency, UUI) was significantly lower among the patients who switched to fesoterodine than among those treated with solifenacin. However, it is true that the concern/discomfort with regard to the rest of the symptomatology assessed did not differ between both treatment groups.

Another aspect to consider in this study is the higher proportion of patients treated with the highest dose in the fesoterodine group compared to the solifenacin group, with no differences in the degree of severity of the OAB. In this sense, although the recommended starting dose of the treatment with fesoterodine is 4 mg, some authors, in order to obtain a greater therapeutic result, recommend using 8 mg in individuals from a previous failed treatment. The possibility of using higher doses according to the patient’s needs can help achieve the desired efficacy-tolerability balance. Several studies have confirmed that increased doses of fesoterodine are associated with a significant increased clinical benefit of urinary symptoms. Khullar et al., in an analysis with data from 2 studies with similar inclusion/exclusion criteria, blind, fixed dose, demonstrated that 8 mg fesoterodine significantly improved more than the dose of 4 mg all the variables in the patient diary (UUI episodes/24 h, voided volume, urgency episodes), except for the frequency of urination.

However, the dose–response relation observed with fesoterodine failed to be clearly demonstrated with all antimuscarinics offering the use of higher doses. Several parallel dose studies with 5 and 10 mg solifenacin did not show that increase of doses entails a significant increased clinical benefit. Data from a randomized comparative study between 5 and 10 mg solifenacin have recently been published. In that study, no significant differences were observed between the two doses of solifenacin regarding the main efficacy variable (number of episodes of severe urgency with or without incontinence) or relative to other secondary variables such as number of episodes of urgency and incontinence; 10 mg solifenacin did provide significant improvements in urinary frequency variables, total urgency score, and greater intensity of urgency.

One possible explanation for the possible greater effectiveness of fesoterodine observed in routine clinical practice could be based on the different metabolic pathways employed by these drugs. Fesoterodine is converted by plasma esterases into its active metabolite, 5-hydroxymethyl-tolterodine (5-HMT). These esterases do not seem to be involved in any drug interaction, unlike the hepatic cytochrome P450 3A4 (CYP3A4), through which solifenacin becomes its primary active metabolite, 4R-hydroxy solifenacin. In this study, about 70% of the patients received some kind of concomitant therapy. CYP3A4 is employed by many drugs, including antidepressants and macrolides, so there could be an effect of substrate competition that delayed or diminished the effect of solifenacin, while this would not happen with fesoterodine.

The different metabolic pathways employed could account for the differences in the effect of each of the molecules, both on overactive bladder symptoms and the appearance of unwanted symptoms. Following this hypothesis, we should go on moving in order to define the groups of patient candidates for a specific antimuscarinic treatment based on the etiology, concomitant diseases, and treatment of each patient, and it should also help us predict which patients will benefit from a higher dose of antimuscarinics, or even a combination of different antimuscarinics.
In this study, both groups of patients rated more favorably the new treatment than ER tolterodine. However, both satisfaction with the treatment and the proportion of patients who preferred the new treatment were significantly higher in the group of fesoterodine (93.4%) than in the group of solifenacin (78.2%). The opinion that a patients show regarding their satisfaction with the treatment reflects the benefit it provides. Likewise, satisfaction with the medication received may help the medical personnel make decisions to provide better care to the patient.

Along with the small sample size, this analysis could present some other limitations inherent in the nature of its design. Observational studies, such as the one presented, lacking the strict selection criteria of the randomized studies, make it possible to analyze a closer population to that treated in actual clinical practice. However, in order to give more reliability to this type of studies, it is necessary to use some tools which make it possible to reduce the limitations and biases of observational studies. In this analysis the propensity score methodology was used for selection of patients, in order to avoid possible differences between the 2 treatment groups due to possible selection bias or confounding factors. In this analysis, the 2 treatment groups were found to be homogeneous in all the analyzed variables that could induce some kind of bias.

The results observed in this study carried out in daily clinical practice enable us to conclude that the change of ER tolterodine to fesoterodine seems to provide from the point of view of the physician and the patient a greater improvement in urinary symptoms, and greater satisfaction with the treatment compared with the one provided by solifenacin.

However, the results shown are from an observational study, whose design was not focused to test differences between the 2 drugs analyzed. We would require a prospective comparative study with a larger sample size to corroborate the results observed in the present study.

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Conflict of interest

Drs. I. Lizarraga and J. Rejas work for Pfizer, S.L.U.

Dr. Daniel Arumi works for Pfizer Europe.

Drs. F. Sánchez-Ballester and P. Miranda declare that they have no conflict of interest.

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