Persistence and adherence of solifenacin treatment for Japanese women with overactive bladder

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Abstract

Persistence and adherence of overactive bladder (OAB) medication have reported to be generally lower in real-world setting as compared with those in clinical trials. However, this information in Japanese population has not been well addressed. Medical records were reviewed for solifenacin as an initial treatment for 172 women with OAB symptom to examine medication persistence, switching, adherence, and the reasons for discontinuation. The associations between persistence and the reasons for discontinuation as well as concomitant conditions regarded as OAB-related risk factors were assessed. The 6-month and 1-year persistence rate of solifenacin were 39.8% and 27.8%, respectively. Consequently, 121 patients (70.3%) discontinued solifenacin, of whom 18 (14.9%) patients switched to other OAB drugs and 9 (7.4%) patients restarted solifenacin. Thus, the adherence rate was 66.8%. More women discontinued solifenacin owing to symptom resolution (41.3%) rather than unfavorable outcomes such as adverse effects (12.4%) and lack of efficacy (21.5%). However, such reason for discontinuation was not the determinant of persistence of solifenacin. There was a non-significant trend towards higher persistence for those with OAB-related risk factors. Japanese women discontinued solofenacin treatment with various reasons in real-world practice, resulting in much lower persistence as compared with clinical trials. A further prospective study in a larger cohort of patients is awaited to better assess their persistence and adherence and understand exact efficacy and tolerability of antimuscarinics for Japanese patients with OAB.

Introduction

Overactive bladder (OAB) is a common and chronic condition, characterized by urinary urgency, frequency, or nocturia with or without urinary incontinence.[1] The use of antimuscarinic drugs has been the mainstay of conservative therapy for OAB for the last decades. These drugs suppress bladder muscle contraction mediated by the muscarinic receptors (primarily M3), thereby increasing bladder capacity and reducing the number and severity of urgency episodes.[2] However, as muscarinic receptors are widespread in the body, including the central nervous system, eyes, salivary glands, and gastrointestinal tract, concomitant blockade of these functions with antimuscarinic drugs can lead to undesirable adverse effects.[3]Patients' adherence and persistence during pharmacotherapy is a major issue in treating chronic diseases, however, persistence of long-term medication is typically low (about 50%) in a number of chronic disease areas,[4,5] and OAB is likely to be one of them.[6-21] To overcome such concerns, drugs with extended-release formations and greater M3 selectivity, such as darifenacin and solifenacinwere developed. Indeed, these drugs yielded high adherence over 80% with minimum discontinuation rate (5 -10%) due to the low incidence of adverse effects in the clinical trials.[22,23] However, trial subjects may not be representative of real-world situation since they were under intensive follow-up and incentives which encourage adherence.

Since solifenacin was introduced in Japan in 2006, it has gained the most popularityin a competitive domestic market of antimuscarinic drugs for OAB. However, little is known about the consequence of adherence and persistence in Japanese population treated with antimuscarinic drugs for OAB. Thus, we addressed such issues by retrospective review of medical records of women having lower urinary tract symptoms suggestive of OAB, who were treated with solifenacin.

Materials and Methods

The study cohort consisted of consecutive 172 women, 20 years and older who were prescribed 5 mg/day of solifenacin as an initial treatment for OAB symptom from April 2006 to August 2011 in Jichi Medical University Hospital. OAB definition was based on urgency and eight or more episodes urination per day. Most prescriptions given to patients were at 30-day intervals. Medication status such as persistence, switching, adherence and the reasons for discontinuation were examined. Persistence was measured by the length of continuous medication with OAB drugs. Patients were considered to discontinue their treatment if they failed to refill OAB drugs within 30 days after the expected end date of the previous prescription.[10] Time to discontinuation was defined as the number of days between the first dispense date and the expected end date of the last refill. Medication switch was defined as drug alternation from solifenacin to other OAB drugs. Medication possession ratio (MPR) was defined as the total days of medication dispense except for the last refill divided by the number of days between the first dispense date and the last refill date of any OAB drugs.[10] Adherence rate was measured as the proportion of patients with an MPR of at least 80%.[10,18]

The cumulative incidence of medication persistence was estimated using Kaplan-Meier method. Patients who remained on treatment until the end of the follow-up were regarded as censored data, and the length of follow-up period was assigned as the time of persistence. The proportion of persistence was compared according to several risk factors for OAB including advanced age and concomitant conditions related to OAB, as well as the reason for discontinuation, using the log-rank test. The reason for solifenacin discontinuation was mainly identified by chart review. Those who suspended hospital visits were inquired by mail whether they continued medication with solifenacin and why they discontinued treatment. Several conditions including aging, diabetes, diuretic use, depression and sleep disturbance were extracted as OAB-related risk factors from previous reports.[10,18,19,24-28]

Results

The mean age of women prescribed solifenacin as an initial treatment for OAB was

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62.3±14.7. The mean follow-up period of the whole patients was 246±260 days. Figure 1 shows the cumulative incidence of persistence of solifenacin treatment. The 6-month and 1-year persistence rate were 39.8% and 27.8%, respectively. The median time to solifenacin discontinuation was 117 days. As a consequence, 121 patients (70.3%) discontinued solifenacin for various reasons including symptom resolution (51, 41.3%), adverse effects (15, 12.4%), or lack of efficacy (26, 21.5%), leaving 30 (24.8%) not specified. Among these patients, 18 (14.9%) patients switched to other OAB drugs due to adverse effects in 6 and lack of efficacy in 12 patients. On the other, 9 (7.4%) patients restarted solifenacin treatment, and of these, 7 patients asked for retreatment once they discontinued solifenacin owing to symptom relief. To examine overall persistence, the Kaplan-Meier curve was reconstructed to indicate the cumulative incidence of persistence of any OAB drugs, including 18 patients who switched drugs (Figure 1). The 6-month and 1-year overall persistence rate were 45.3% and 34.8%, respectively. The median time to overall discontinuation was 154 days. The mean MPR was 0.73 and the adherence rate (MPR≥0.8) was as high as 66.8%. Persistence of solifenacin was compared according to the reason for discontinuation (Figure 2). There was no difference in persistence of solifenacin among the groups stratified by the reason for discontinuation (P=0.969). Namely, patients discontinued solifenacin regardless of treatment outcomes in terms of persistence, although more women discontinued medication owing to symptom resolution rather than adverse effects and lack of efficacy. Figure 3 depicts overall medication persistence estimated by Kaplan-Meier method stratified by age divided by median value (64 or elder *vs* 63 or younger) and the presence of any OAB-related risk factors including diabetes, diuretic use, depression and sleep disturbance. There was a statistical difference in persistence duration by age with a longer time to discontinuation in elder women (P=0.027). We found a tendency but not a significance towards higher persistence for those with other conditions regarded as OAB-related risk factors in this study (P=0.09). At the end of follow-up, 56 women discontinued treatment owing to symptom resolution, majority of whom (43, 77.8%) did not have OAB-related risk factors, implying that such concomitant condition may render OAB symptom more unresolved.

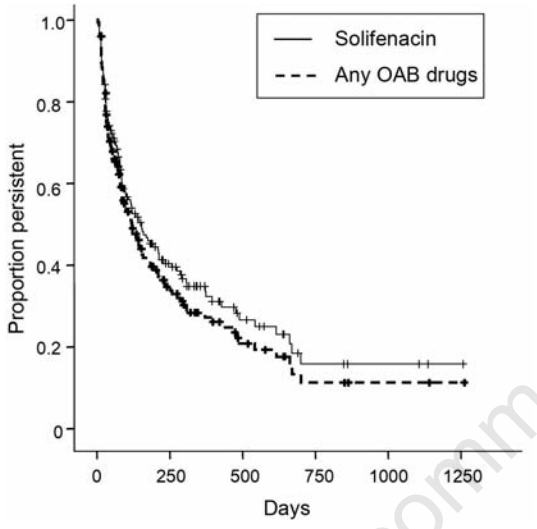

Figure 1. Kaplan-Meyer plots of persistence of solifenacin and any antinuscarinic drugs for overactive bladder (OAB) treatment.

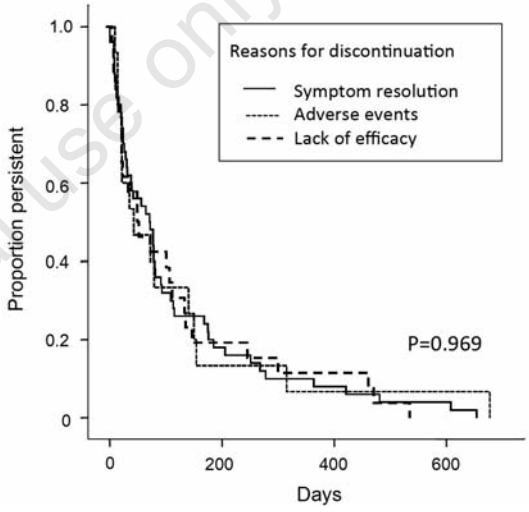

Figure 2. Kaplan-Meyer plots of persistence of solifenacin treatment stratified by the reasons for discontinuation.

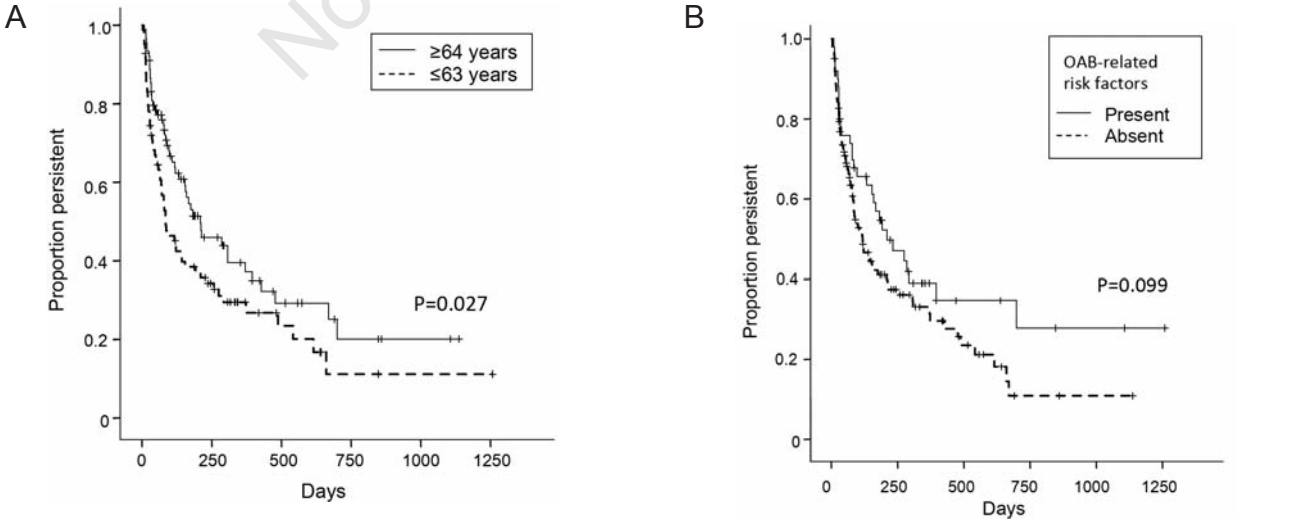

Figure 3. Kaplan-Meyer plots of persistence of any antinuscarinic drugs for overactive bladder (OAB) by the group dichotomized by median age (A), and OAB-related risk factors (B).

Discussion

The efficacy of drug therapy depends on a patient's ability to take the prescribed medication for an appropriate period, especially when it is a chronic disorder such as OAB. According to results from the 12-week randomized clinical trials for OAB drugs, varied rates of discontinuation mainly due to adverse events, ranging from 4% to 31% were reported. Similar rates were found in open-labeled studies, with substantially higher rates for studies with longer follow-up period.[29] However, several features of clinical trials make them inappropriate for assessing long-term persistence and adherence, including short follow-up period, inclusion criteria of patients not representative of the general population, and use of incentives. Thus, clinical trials were liable to underestimate the extent of treatment discontinuation observed in real-world setting, in which rates of discontinuation were substantially higher. Such lower persistence may result from mixed conditions in real-world practice in terms of patient factors (race, gender, age, life habit, co-morbidity, and symptom severity)[8,10-12,14,18,19] as well as treatment factors (cost, dosing frequency, efficacy and adverse effects).[12,14,18,21,24,27,28] Considering treatment factors as an OAB drug, solifenacin may be favorable drug to ensure good persistence for once-daily dosing and better tolerability owing to a greater selectivity to M3 over M2 receptor and apparent functional selectivity to the bladder over salivary gland.[30] However, no study has assessed persistence and adherence of this novel antimuscarinic drug for OAB treatment in Japanese population in real-world practice, which prompted us to address this issue. In the present study, we focused on female patients because male patients with OAB symptom are likely to have benign prostatic hyperplasia and therefore be treated together with α_1-blockades, rendering OAB symptom change by treatment more complicated than women.[31,32]

Surprisingly, we found higher overall persistence and adherence rates compared with previous reports in real-world setting (12-25% and 5-53%, respectively),[6-22] with our 1-year persistence rate of 34.8% and adherence rate of 66.8%. Such favorable adherence of antimuscarinic treatment observed in our study may in part derive from the characteristics of our study cohort as well as the use of solifenacin, since persistence specific to solifenacin in the previous reports (1-year persistence rate of 9-18%)[19,20] was lower than our result (27.8%). Some studies indicated that women were more likely to persist with their treatment than men.[10,19,21] Other reports demonstrated that health insurance coverage was important attribute to OAB medication compliance.[21,25] Our cohort was consisted of only women in Japan where the national health insurance system provides nation's entire population with medical services at a low cost, which may have largely contributed to high persistence and adherence. This assumption could be supported by the most recent report based on UK National Health Service prescription data showing that solifenacin achieved high levels of persistence (1-year persistence rate of 35%), in which 88% of all prescriptions are free to the patients.[33]

There is currently a paucity of data on the reason for poor adherence or persistence with antimuscarinics for OAB. Several studies demonstrated that lack of efficacy (35-46.2%) and adverse effects (21.1-39.8%) were main drivers of discontinuation.[27,28,34,35] On the other, some did not need medication because they were cured (14.5%) or learned to get by without drugs (23.3%).[28] Of note, one study showed that most frequent reason for discontinuation was that medication *didn't work as expected* (45.5%),[35] implying that unrealistic treatment expectation may contribute to low adherence, therefore underscoring the requirement of setting appropriate patient expectations about degree of possible symptom control by medication itself. Namely, an important message to convey is that OAB is a treatable, but not curable condition, which should be treated with a multidimensional intervention including behavior techniques as well as medication, when OAB drugs do not work sufficiently. The use of a bladder diary may facilitate the awareness of OAB symptom reduction, addressing the unmet treatment expectations. Indeed, it has been shown that patient support such as behavioral therapy and life style change through external programs helped to improve and maintain persistence with solifenacin therapy with much higher rate of 76% of patients remaining on medication.[33] On the other, a larger proportion of women discontinued treatment owing to symptom resolution (41.3%) rather than unfavorable reasons such as lack of efficacy (21.5%) and adverse effects (12.4%) in the present study. Such profile, contrasting to previous reports,[27,28,34,35] seems to reflect an acceptable balance between tolerability and efficacy of solifenacin that could decrease an early treatment failure and may be another contributory factor to high persistence. Actually, according to the same report discussed above, solifenacin was associated with the highest rate of persistence compared with the other available antimuscarinics in UK.[33]

We further investigated the effect of clinical risk factors on persistence of OAB treatment. Several morbidities including, urinary tract infection (UTI), skin infection, fall/fracture, diabetes, diuretic use, sleep disturbance and depression were listed as OAB-related comorbidities in the previous series,[7,18,19,24-28] although there is no definitive criteria as OAB-related comorbidities. Among these conditions, we considered UTI, skin infection, and fall/fracture inappropriate conditions to be counted as risk factors, since UTI is one of the conditions that should be excluded before the diagnosis as OAB and the latter two are obviously the result of OAB symptoms. Consequently, we focused on the following conditions such as diabetes, diuretic use, depression and sleep disturbance as possible OAB-related risk factors, which were often treated as separate entities from OAB. However recent studies revealed clear association between OAB and these conditions,[36-39] prompting us to know how such conditions impact on OAB treatment. Patients with OAB-related risk factors were less likely to discontinue treatment owing to symptom resolution compared with those without such conditions, resulting in non-significant trend towards higher persistence with antimuscarinic treatment. Therefore, such patients should be treated specifically for each morbidity and/or need alternative forms of treatment (fluid modification, bladder training, and pelvic floor exercise) to enhance the efficacy of antimuscarinic treatment for OAB. Also, concurrent with previous reports, elder patients significantly stayed on treatment for a longer time than younger patients.[11,14,18,19] When considering the methodology of this study, there are some possible weaknesses. First, the retrospective nature of our study did not permit complete data collection and follow-up in some cases, *i.e.* the reason for treatment discontinuation was not determined in a quarter of the whole patients. We feel that non-response bias is a common problem of postal surveys, which is unable to be avoided without profitable incentives for patients. Second, the sample size of 172 consecutive women is relatively small, although this sample size is representative of the local population attending the urology clinic. Third, we did not completely follow the subsequent course of patients who resolved OAB symptoms and discontinued solifenacin. However, a low retreatment rate of 13.7% in patients who discontinued treatment owing to symptom relief implies that OAB may remit in not a few patients.

In summary, the use of solifenacin achieved higher persistence and adherence in OAB medication for Japanese women. Nevertheless, a third of patients were still obliged to discontinue solifenacin treatment due to unfavorable outcomes such as adverse effects and lack of efficacy. Since persistence and adherence to treatment are important markers of the success of pharmacotherapy in controlling OAB symptoms, close assessment of efficacy and adverse events along with patient support including life style change and behavioral training are required. We believe that the present findings certainly mirrors the outcomes of OAB pharmacotherapy in real-world practice and encourages further stud-

ies in larger prospective series to complement existing evidence on exact efficacy and tolerability of antimuscarinics for Japanese population.

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