

COMPARATIVE EVALUATION OF THE SAFETY AND EFFICACY OF LONG-TERM USE OF IMIDAFENACIN AND SOLIFENACIN IN PATIENTS WITH OVERACTIVE BLADDER: A PROSPECTIVE, OPEN, RANDOMIZED, PARALLEL-GROUP TRIAL (THE LIST STUDY)

Hypothesis / aims of study

Anticholinergics are commonly used for treatment of overactive bladder (OAB). OAB is a chronic disease, but comparative trials of anticholinergics have generally been performed up to 12 weeks. There is no comparative study of a long term efficacy and tolerability of two anticholinergics.

Study design, materials and methods

We conducted a 52-week prospective randomized comparative study to evaluate the efficacy and tolerability of the anticholinergics imidafenacin and solifenacin. The subjects were male and female patients aged ≥ 50 and < 80 years old who were diagnosed with OAB based on their overactive bladder symptom score (OABSS: 0-15 range, with a higher score indicating a severer condition) and untreated with any anticholinergics. Patients with a score for urinary urgency of ≥ 2 points and a total OABSS of ≥ 3 points were enrolled in the study. The other inclusion criteria were symptoms for at least 4 weeks and untreated OAB. Forty-two Japanese patients with untreated OAB were randomly assigned to groups receiving 0.1 mg imidafenacin tablets twice a day after breakfast and supper or a 5 mg solifenacin tablet after breakfast. Random assignment to groups was performed by the central registration system in the pharmacy and age and sex were used as factors in the assignment. Efficacy was evaluated using OABSS and KHQ scores at the end of the observation period and after 4, 12, 28, 40 and 52 weeks of treatment. The incidence of adverse events of dry mouth, constipation and blurred vision during the study was evaluated in a safety analysis set of 41 patients (one patient met the exclusion criteria). The severity of dry mouth was evaluated on a 3-point scale: mild, barely noticeable; moderate, tolerable after drinking water; severe, intolerable after drinking water, leading to discontinuation of the investigational drug.

Results

Short-term efficacy was evaluated in 35 patients (imidafenacin: 17, solifenacin: 18) who took the drug for at least 12 weeks. The total OABSS in both groups show a significant improvement at 4 and 12 weeks in comparison with baseline. The extent of improvement of the total OABSS at 4 and 12 weeks did not differ between the two groups. Long-term efficacy was evaluated in 25 patients (imidafenacin: 11, solifenacin: 14) who were continuously treated with the drug for 52 weeks. Changes in the total OABSSs in the long-term efficacy analysis set of 25 patients are shown in Fig.1.

The tolerability of imidafenacin and solifenacin was good. Adverse events occurred in 76.2% of patients in the imidafenacin group and 95.0% in the solifenacin group. One patient discontinued solifenacin due to severe dry mouth. The incidences of adverse events caused by the drugs for 52 weeks are shown using Kaplan-Meier curves in Fig. 2. The severity and incidence of adverse events caused by the anticholinergics differed more between the two groups with time. There was also no difference in the incidence of constipation between the two groups in patients who took imidafenacin or solifenacin for at least 12 weeks (Log Rank test: $p=0.0621$). However, the incidence in patients who took either drug for 52 weeks was significantly higher in the solifenacin group (Log Rank test: $p=0.0017$). There was no significant difference in the incidence of blurred vision in patients who took the drug for at least 12 weeks (Log Rank test: $p=0.3749$) or continuously for 52 weeks (Log Rank test: $p=0.0686$). The incidence of constipation over 52 weeks was significantly lower in the imidafenacin group (14.3 % vs. 65.0 %). The incidence of blurred vision for 52 weeks did not differ significantly between the groups (9.5% vs. 35.0%) and there were no adverse events related to blood pressure and pulse rate in the two groups. Significant increases in the residual urine volume occurred in both groups at 12 weeks compared to baseline. No increase in the residual urine volume from baseline occurred in the imidafenacin group at 52 weeks, but a significant increase was found in the solifenacin group. There was no significant difference between the two groups and no patient had more than 100 mL of residual urine volume in either group. No significant change in QTc was observed throughout the study period in either group.

Interpretation of results

This study is the first long-term trial to show differences in the properties of anticholinergics that could not be detected in short-term studies. A limitation of the study was the number of dropout patients, since 35 patients who were took either drug for at least 12 weeks were included in the efficacy analysis set, but only 25 of these patients took a drug continuously for 52 weeks. Of the 10 patients who dropped out, 6 were in the imidafenacin group and 4 in the solifenacin group. However, the reason for discontinuation was remission of OAB symptoms in 3 patients in the imidafenacin group, reflecting a positive effect of the drug. The other 3 patients in this group discontinued the trial due to onset of neurogenic bladder caused by cerebral infarction (a causal relationship between the onset of cerebral infarction and imidafenacin was excluded) in 1 case and frequent visits for another disease in 2 cases; thus, none of the patients who discontinued imidafenacin did so for negative reasons associated with the drug. In contrast, two patients discontinued solifenacin due to the absence of an effect and a third patient discontinued due to a severe adverse reaction to solifenacin; thus, 3 patients discontinued solifenacin for negative reasons. The 6 patients who took imidafenacin or solifenacin for less than 12 weeks and were not included in the efficacy analysis did not discontinue for negative reasons. There was no difference in the percentage of patients who received continuous treatment in the two groups, and these data rule out the possibility that the apparent efficacy in the 52-week analysis was due to dropout of patients in whom the drugs were ineffective.

Concluding message

Imidafenacin and solifenacin were both effective for OAB, but the incidence of adverse events with imidafenacin was significantly lower than that with solifenacin. There were also time-dependent differences in the severity and incidence of adverse events. Since OAB is a chronic disease, we conclude that treatment with imidafenacin is preferable to solifenacin from a perspective of efficacy and safety.

Figure.1 Efficacy

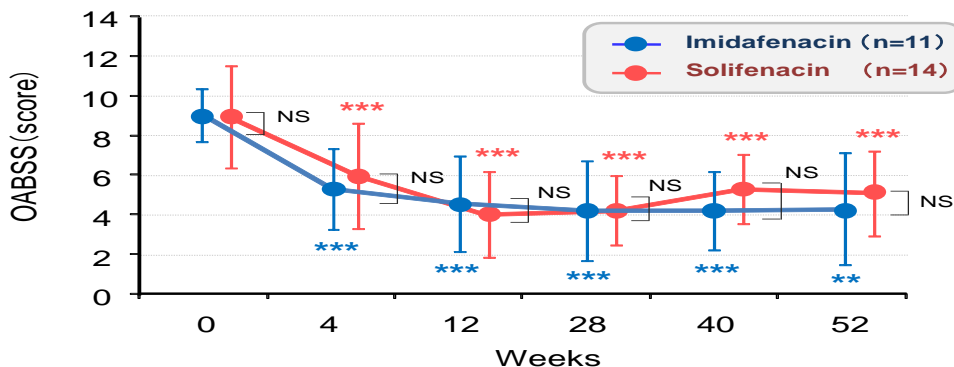
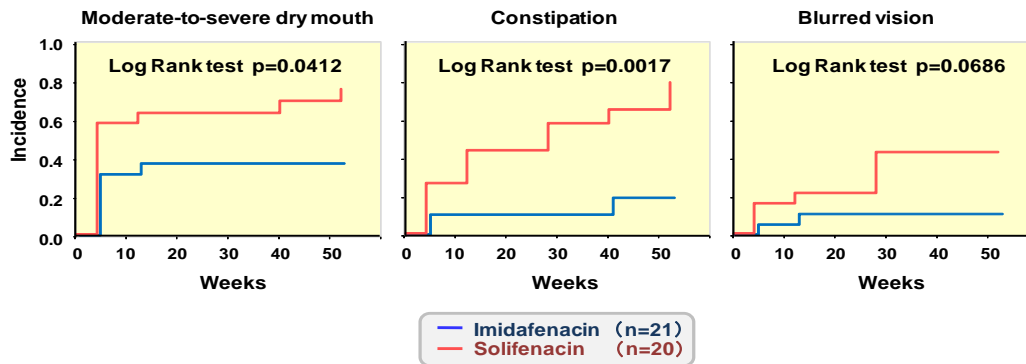


Figure.2 Safety



Specify source of funding or grant	No Funding was received
Is this a clinical trial?	Yes
Is this study registered in a public clinical trials registry?	Yes
Specify Name of Public Registry, Registration Number	UMIN, 000004354
Is this a Randomised Controlled Trial (RCT)?	Yes
What were the subjects in the study?	HUMAN
Was this study approved by an ethics committee?	Yes
Specify Name of Ethics Committee	the Kanto Rosai Hospital Ethics Committee
Was the Declaration of Helsinki followed?	Yes
Was informed consent obtained from the patients?	Yes