Comparative evaluation of the safety and efficacy of long-term use of Imidafenacin and Solifenacin in patients with overactive bladder: A prospective randomized parallel-group trial (the LIST study)

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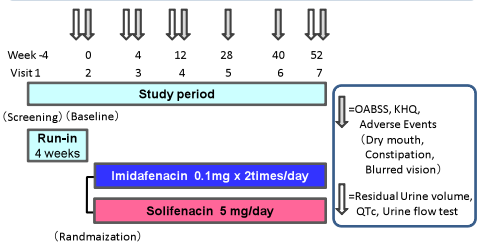
Background

Anticholinergics are commonly used for treatment of OAB. Comparative trials of anticholinergics have generally been performed up to 12 weeks. There is no comparative study of a long term efficacy and tolerability.

objective

To compare the long-term (52-week) efficacy and tolerability of imidafenacin and solifenacin as novel anticholinergics for OAB.

Material & Method



Forty-one patients were enrolled in a 52-week prospective randomized comparative study from January to December 2009 and followed up to December 2010
(Trial Registration: UMIN000004354).

Including criteria:

✶Male and female patients with untreated OAB.
✶Aged ≥50 and <80 years old.
✶A score for urinary urgency of ≥2 points and a total score of ≥3 points in OABSS (OABSS; overactive bladder symptom score: 0-15 range, with a higher score indicating a severer condition).
✶Symptoms for at least 4 weeks.

Exclusion criteria:

✶Residual urine volume ≥100 mL (by abdominal sonography).
✶Complications contraindicated for anticholinergics.
✶High possibility of prostate and bladder cancer.
✶Acute active urinary tract infection.
✶A patient judged not to be eligible by an investigator in charge.

Randomization:

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.

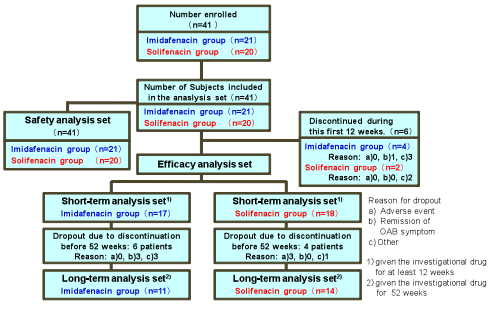
Imidafenacin group: 0.1 mg imidafenacin tablets twice a day after breakfast and supper.
Solifenacin group: 5 mg solifenacin tablet once daily after breakfast.

Efficacy:

OABSS and KHQ scores at the end of the observation period and after 4, 12, 28, 40 and 52 weeks of treatment.

Adverse events:

Dry mouth, constipation and blurred vision during the study.
Severity of dry mouth: a 3-point scale
Mild; barely noticeable
Moderate; tolerable after drinking water
Severe; intolerable after drinking water, leading to quit drugs



Results

Demographics	Imidafenacin	Solifenacin	P-value
Short-term analysis set			
Subjects	17	18	
Age (Years)	70.2±6.5	69.8±7.7	0.8697[a]
Gender			
Male , n (%)	10 (58.8%)	12 (66.7%)	0.7332[b]
Female , n (%)	7 (41.2%)	6 (33.3%)	
OABSS (total score)	8.0±2.0	8.7±2.4	0.2989[c]
Postvoid residual volume (mL)	14.2±15.1	13.5±11.4	0.8814[a]
Each urination volume (mL)	141.7±109.9	187.9±160.8	0.3312[a]
Urination time (second)	28.3±19.8	27.4±9.9	0.8749[a]
Qmax (mL/s)	12.1±7.4	14.2±10.6	0.4925[a]
In male			
Prostate volume (mL)	22.7±11.6	25.3±9.4	0.5661[a]
Use of α1 blocker, n (%)	10 (100%)	11 (100%)	1.0000[b]
Long-term analysis set			
Subjects	11	14	
Age (Years)	69.9±6.7	71.4±6.0	0.5560[a]
Gender			
Male , n (%)	7 (63.6%)	10 (71.4%)	1.0000[b]
Female , n (%)	4 (36.4%)	4 (28.6%)	
OABSS (total score)	9.0±1.3	8.9±2.6	0.8453[c]
Postvoid residual volume (mL)	15.1±14.7	13.4±11.0	0.7487[a]
Each urination volume (mL)	125.3±85.0	203.8±179.8	0.1654[a]
Urination time (second)	29.1±23.0	26.1±10.7	0.6939[a]
Qmax (mL/s)	11.2±8.8	14.8±11.8	0.4120[a]
In male			
Prostate volume (mL)	21.0±9.1	27.8±8.2	0.1302[a]
Use of α1 blocker, n (%)	6 (85.7%)	9 (90.0%)	1.0000[b]

Severity of OAB was defined as total OABSS score ≤5: mild; 6 to ≤11: moderate; ≥12: severe.
a:Unpaired t-test, b: Fisher Exact test, c: Mann-Whitney U-test, two-sided.
Mean±SD, SD: standard deviation.

Efficacy: Changes in the total OABSSs

Short-term analysis set

	Imidafenacin (n=17)	P value vs.0W	Solifenacin (n=18)	P value vs.0W	P value vs. intergroup
0W	8.0±2.0		8.7±2.4		0.2989
4W	4.9±2.2	***	5.7±2.6	***	0.2789
12W	4.1±2.4	***	3.9±2.1	***	0.8535

Long-term analysis set

	Imidafenacin (n=11)	P value vs.0W	Solifenacin (n=14)	P value vs.0W	P value vs. intergroup
0W	9.0±1.3		8.9±2.6		0.8543
4W	5.3±2.1	***	5.9±2.7	***	0.3910
12W	4.6±2.4	***	4.0±2.2	***	0.5599
28W	4.2±2.0	***	4.2±1.8	***	0.8459
40W	4.2±2.5	***	5.3±1.7	***	0.2870
52W	4.3±2.8	**	5.1±2.1	***	0.6384

Intragroup comparison (vs. the end of the observation period) by Wilcoxon test,**p<0.01, ***p<0.001.
Intergroup comparison by Mann-Whitney U-test, NS, not significant.

★KHQ were almost equal between two groups in short-term and long-term analysis sets.

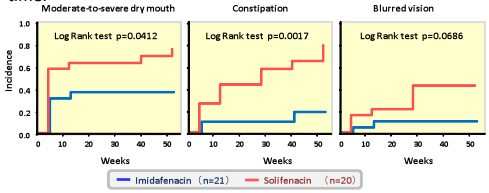
Adverse events:

Variable, n (%)	Imidafenacin	Solifenacin	P-value
N (Safety population)	21	20	
Dry mouth	15 (71.4%)	18 (90.0%)	0.2379[b]
Mild	8 (38.1%)	4 (20.0%)	
Moderate	7 (33.3%)	10 (50.0%)	0.0092[a]
Severe	0 (0%)	4 (20.0%)	
Constipation	3 (14.3%)	13 (65.0%)	0.0013[b]
Blurred vision	2 (9.5%)	7 (35.0%)	0.0670[b]

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
a: Mann-Whitney U-test, b: Fisher Exact test, two-sided.

Kaplan-Meier curves for time to first adverse events caused by anticholinergics:

The severity and incidence of adverse events caused by the anticholinergics differed more between the two groups with time.



Constipation:
12 weeks: No difference (Log Rank test: p=0.0621).
52 weeks: Significantly higher in the solifenacin group (Log Rank test: p=0.0017).

Blurred vision:
12 weeks: No difference (Log Rank test: p=0.3749)
52 weeks: No difference (Log Rank test: p=0.0686)

★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.
★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. No adverse events related to blood pressure and pulse rate.

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 shortterm studies. The reason why there were difference in the incidences of adverse events with imidafenacin and solifenacin might be due to differences in pharmacokinetics between the two drugs. In mouse and rat, Yamada et al. found that anticholinergics had different organ-specific affinity for muscarinic receptors. Solifenacin has a long half-life and binds to muscarinic receptors in not only the bladder but also the salivary gland and colon for an extended period, which reduces salivation and intestinal peristaltic movement and results in severe dry mouth and constipation. In contrast, imidafenacin has a short half-life and does not bind to muscarinic receptors in the colon , accounting for the low incidence of constipation. However, imidafenacin binds to muscarinic receptors in the bladder for a relatively long time, despite the short blood half-life. These properties of imidafenacin and solifenacin may account for the significantly higher incidence of constipation and the greater severity of dry mouth in patients who took solifenacin in this study.
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 neffective. One limitation of this study is the small-scale singlecenter design. However, conducting the study at a single institution also excludes interobserver variability and variation between institutions, and this improves the reliability of the results.

Conclusion

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.