

SUBGROUP ANALYSES OF TRIPLE THERAPY WITH TAMSULOSIN, DUTASTERIDE, AND IMIDAFENACIN FOR BENIGN PROSTATIC HYPERPLASIA PATIENTS WITH OVERACTIVE BLADDER SYMPTOMS REFRACTORY TO TAMSULOSIN (24-WEEK RANDOMIZED COMPARATIVE STUDY: DIRECT STUDY)

Hypothesis / aims of study

In the previously reported Direct Study, tamsulosin + dutasteride + imidafenacin therapy (triple therapy group) demonstrated significantly superior efficacy to tamsulosin + dutasteride therapy (dual therapy group) for the primary endpoint of overactive bladder symptom score (OABSS). Subgroup analyses were performed to explore factors affecting the difference in improvement of overactive bladder (OAB) symptoms between the two therapy groups.

Study design, materials and methods

The Direct Study was a 24-week, multicenter, randomized, open-label, comparative study conducted at a total of 33 sites in Japan: 2 university hospitals, 11 general hospitals, and 20 urology clinics. Patients between 50 and 89 years of age with benign prostatic hyperplasia (BPH), remaining OAB symptoms despite at least 8 weeks of tamsulosin therapy (OABSS urgency score ≥ 2 and OABSS total score ≥ 3) and a prostatic volume of 30 mL or more were enrolled in the study. Patients who consented to participate in the study were centrally randomized to receive either dutasteride 5 mg/day and imidafenacin 0.2 mg/day (triple therapy group) or dutasteride 5 mg/day (dual therapy group) for 24 weeks, in addition to preexisting tamsulosin 0.2 mg/day. Patients were allocated using site-stratified minimization method with a random factor. Subgroup analyses were performed to evaluate the superiority in efficacy assessed with OABSS of triple therapy over dual therapy between the subgroups divided according to age, International Prostate Symptom Score (IPSS), quality of life (QOL) index, OABSS, benign prostatic hyperplasia impact index (BII), prostate specific antigen (PSA), prostatic volume, maximum urine flow rate (Qmax), residual urine volume, or duration of pre-study tamsulosin therapy at baseline. In addition, similar analyses were performed for the following secondary endpoints: IPSS, QOL index, and residual urine volume. For each factor, patients were divided into two subgroups based on the median, and statistical analysis using the mixed-effects model including an interaction term between the variables indicating treatment group and subgroup was performed. A two-sided $p < 0.05$ was considered as statistically significant.

Results

Of the 163 enrolled subjects, 81 and 82 were randomly assigned to the dual therapy group and triple therapy group, respectively. Of these subjects, primary endpoint data were collected from a total of 150 subjects: 71 in the dual therapy group and 69 in the triple therapy group. The baseline characteristics of patients were similar between the dual therapy group and triple therapy group. The effects of age (≥ 75 years, < 75 years), IPSS (≥ 14 , ≤ 13), QOL index (severe [≥ 5], moderate [$2-4$]), OABSS (≥ 8 , ≤ 7), BII (≥ 5 , ≤ 4), PSA (≥ 2.7 ng/mL, < 2.7 ng/mL), prostatic volume (≥ 40 mL, < 40 mL), Qmax (≥ 10 mL/s, < 10 mL/s), residual urine volume (≥ 20 mL, < 20 mL), and duration of tamsulosin therapy (≥ 26 weeks, < 26 weeks) on OABSS were analyzed between two subgroups, and showed no significant difference regarding the superiority of triple therapy over dual therapy in terms of the improvement in OABSS ($p = 0.87$ to $p = 0.46$ for the interaction term). As for the secondary endpoints, no significant difference in superiority of efficacy for triple therapy was observed regarding the improvement in IPSS or QOL index between two subgroups stratified for any factor, however the difference in superiority of triple therapy was observed for residual urine volume in the subgroup that received tamsulosin for 26 weeks or more compared with those who received tamsulosin for less than 26 weeks ($p = 0.002$ for the interaction term). Adverse events possibly related to the study drug were reported in 5 subjects in the triple therapy group, with none reported in the dual therapy group. These adverse events were blurred vision in 2 subjects, dizziness on standing up in 1 subject, numbness of the tongue in 1 subject, palpitations/dizziness in 1 subject, and erectile dysfunction in 1 subject.

Interpretation of results

Factors affecting the improvement in OABSS from tamsulosin + dutasteride + imidafenacin therapy compared to tamsulosin + dutasteride therapy in BPH patients with an enlarged prostate and OAB symptoms refractory to tamsulosin were explored. No significant difference was observed regarding the superiority of improvement in OABSS by triple therapy over dual therapy between two subgroups stratified by any factor (age, IPSS, QOL index, OABSS, BII, PSA, prostatic volume, Qmax, residual urine volume, and duration of tamsulosin therapy), suggesting that none of the factors may affect the superiority in efficacy of triple therapy over dual therapy. Residual urine volume, a secondary endpoint, differed between subgroups regarding superiority of triple therapy over dual therapy; however, the study was conducted in an exploratory manner, meaning that further studies are required. In addition, the increased α error from multiple analyses (testing multiplicity) and decreased power from subgroup division should be taken into consideration.

Concluding message

Triple therapy with tamsulosin, dutasteride, and imidafenacin is suggested to be a therapeutic option for BPH patients with remaining OAB symptoms refractory to tamsulosin, regardless of age or severity of OAB symptoms.

Disclosures

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