A Randomized, Double-Blind, Solifenacin Succinate versus Placebo Control, Phase 4, Multicenter Study Evaluating Urinary Continence after Robotic Assisted Radical Prostatectomy

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Purpose: Bladder dysfunction influences recovery of urinary continence after radical prostatectomy. We performed a multicenter, randomized, double-blind study evaluating solifenacin vs placebo on return to continence in patients who were still incontinent 7 to 21 days after catheter removal after robot-assisted radical prostatectomy.

Materials and Methods: A wireless personal digital assistant was given to patients the day of catheter removal. Encrypted answers were transmitted daily to dedicated servers. After a 7 to 21-day treatment-free washout period, patients requiring 2 to 10 pads per day for 7 consecutive days were randomized (1:1) to 5 mg solifenacin daily or placebo. The primary end point was time from first dose to continence defined as 0 pads per day or a dry security pad for 3 consecutive days. Secondary end points included proportion of patients continent at end of study, average change in pads per day number and quality of life assessments.

Results: A total of 1,086 screened patients recorded personal digital assistant information. Overall 640 patients were randomized to solifenacin vs placebo and 17 failed to take medication. There was no difference in time to continence (p=0.17). Continence was achieved by study end in 91 of 313 (29%) vs 66 of 309 (21%), respectively (p=0.04). Pads per day change from baseline was −3.2 and −2.9, respectively (p=0.03). Dry mouth was the only common adverse event seen in 6.1% and 0.6%, respectively. Constipation rates were similar. The overall rate of continence in the entire population from screening to end of study was 73%.

Conclusions: There was no effect on primary outcome but some secondary end points benefited the solifenacin arm. The study provides level 1B clinical evidence for continence outcomes after robot-assisted radical prostatectomy.

Key Words: prostatic neoplasms, robotics, prostatectomy, treatment outcome, urinary incontinence

Abbreviations and Acronyms

AUASS = American Urological Association symptom score

FAS = full analysis set

ICIQ-SF = International Consultation on Incontinence Questionnaire-Short Form

PDA = personal digital assistant

PPD = pads per day

QOL = quality of life

RARP = robot-assisted radical prostatectomy

RP = radical prostatectomy

SAF = safety analysis set

UDS = urodynamics

WPAI = Work Productivity and Activity Impairment questionnaire

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Urinary continence is a pivotal end point of the desired "trifecta" outcome (continence, potency, and cancer control) after radical prostatectomy.[1,2] While cancer control outcomes are robust, prolonged or permanent urinary incontinence remains a significant problem.[3–6] Recovering postoperative

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continence after RP is largely a balance between the viability and strength of the external sphincter and the impact of bladder compliance and detrusor instability.[7–9] Rodriguez et al reported a strong association between preoperative detrusor instability and delayed return of continence after RARP.[10] Their findings echoed investigations showing detrusor instability as a cofactor in prolonged incontinence and that anticholinergics might shorten time to continence.[11–13] A phase I trial evaluating solifenacin in the post-RARP setting demonstrated that 1) there were no significant safety issues with solifenacin after RARP and 2) the prediction of severely delayed return of continence could not be established by standard baseline preoperative assessment (AUASS, prostate weight etc).[14]

Significant research has revealed that the degree of leakage in the first few days after catheter removal after RP may be the best predictor of prolonged incontinence,[15–17] as 95% become pad-free by 90 days if they only required zero or 1 pad 4 to 7 days after catheter removal.[16]

For patients with post-prostatectomy incontinence with mixed urinary incontinence symptoms and/or those with an urgency component, EAU (European Association of Urology) guidelines recommend a trial of antimuscarinics. However, the guidelines rank the evidence as C, noting the weakness of the evidence.[18] We conducted a randomized clinical trial that assessed efficacy and safety of 12 weeks of treatment with solifenacin vs placebo in patients with early moderate to severe incontinence (2 to 10 PPD) after RARP. The trial included a run-in period that eliminated those men from randomization who had minimal or no incontinence after catheter removal.

MATERIAL AND METHODS

Study Objectives and Duration

The trial was a phase 4, multicenter, randomized, double-blind, placebo controlled study to evaluate the efficacy of solifenacin[19,20] vs placebo in the recovery of urinary continence after RARP in those patients who are still incontinent 7 to 21 days after catheter removal. The purpose of the study was to assess the efficacy and safety of 12 weeks of treatment of solifenacin vs placebo in patients whose urinary incontinence required 2 to 10 PPD for 7 consecutive days after RARP catheter removal. The primary objective was the continuous assessment of time to continence during 12 weeks of treatment with solifenacin vs placebo. The secondary objectives were to assess (categorically) the treatment effect on the proportion of patients who gained continence at 4, 8 and 12 weeks and at the end of treatment, the change from baseline to average daily pad use per month, changes in QOL as measured by AUASS, ICIQ-SF, the WPAI and finally time to work resumption. The protocol received institutional review board approval (Shulman Associates IRB 905-UC-050) and was registered on clinicaltrials.gov (NCT01371994).

Study Design

Men with newly diagnosed clinically localized prostate cancer who underwent RARP were invited to participate in the study at the time of Foley catheter removal. Participants received a PDA, which is a smartphone-like device (DiaryPRO®, Invivo Data/eResearchTechnology Inc., Philadelphia, Pennsylvania). The PDA evaluated daily pad use and drug intake. The PDA was programed to ring nightly at 7 pm until the patient provided the required information regarding medication compliance and pad use. Answers were digitally encrypted and the uneditable data were securely transmitted to designated servers. No economic incentive was provided. However, all patients were given standardized pads free of charge.

There was a 7 to 21-day treatment-free screening and washout period. Those recording 2 to 10 PPD for 7 consecutive days and meeting the baseline criteria were eligible for the treatment phase of the trial, and randomized 1:1 to 5 mg solifenacin or placebo. At week 4, based on efficacy and safety, and in agreement with the investigator, the dose could be doubled to 10 mg once daily. Screening and end of treatment/week 12 visits were conducted onsite. Baseline and week 4 and 8 visits were telephone contact visits. Subjects completed the PDA survey daily during the study duration. In addition, subjects were asked to complete the AUASS with bother score, the ICIQ-SF and the WPAI at baseline and week 12 visits.

Primary and secondary end points. The primary efficacy end point was the time from the date of first dose of study drug to the date of urinary continence (defined as the date of the first of 3 consecutive days in which the subject used 0 pads or a pad for security which remained completely dry) during the 12-week study.

Secondary end points included 1) proportion of patients who gained continence at the end of 12 weeks, 2) change from baseline to each month in average daily pad use, 3) change from baseline to end of study in QOL measured by AUASS and ICIQ-SF, 4) change from baseline to end of study on work productivity as measured by the WPAI and 5) time from baseline to the first day of returning to work.

Sample size, power estimations and statistical analyses. All safety analyses were based on the safety analysis set. The SAF consists of all randomized patients who receive at least 1 dose of double-blind study medication. All efficacy analyses were based on the full analysis set. The FAS consists of SAF patients who had at least 1 post-baseline assessment in the primary efficacy variable. The primary efficacy variable is summarized by treatment group and cumulative incidence of continence over time is displayed using the Kaplan-Meier estimate. The treatment difference in time to continence was tested using a log rank test stratified by center and baseline pad use (3 or more and less than 3 PPD) at a 2-sided significance level of 0.05. Patients who did not gain continence during the study were censored at the end of 12 weeks. The number