Efficacy and Safety of Luteinizing Hormone-Releasing Hormone Antagonist Cetrorelix in the Treatment of Symptomatic Benign Prostatic Hyperplasia

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ABSTRACT
As the life expectancy for men increases, more cases of benign prostatic hyperplasia (BPH) will be expected. Symptomatic BPH causes morbidity and can lower the quality of life. We investigated whether short-term administration of the LH-releasing hormone antagonist cetrorelix could provide an improved treatment for men with BPH. Thirteen patients with moderate to severe symptomatic BPH were treated with cetrorelix (5 mg, sc, twice daily for 2 days followed by 1 mg/day, sc, for 2 months). Patients were evaluated at baseline, during treatment, and up to 18 months after therapy. We determined the effects of cetrorelix on the International Prostate Symptom Score (IPSS), Quality of Life score, sexual function, prostate size, uroflowmetry, and hormonal levels. Treatment with cetrorelix produced a decline of 52.9% (P < 0.0001) in IPSS, a 46% improvement in the Quality of Life score (P < 0.001), a rapid reduction of 27% (P < 0.006) in prostatic volume, and an increase in peak urinary flow rates by 2.86 mL/s. Serum testosterone fell to castrate levels on day 2, but was inhibited only by 64–74% during maintenance therapy, and after cessation of treatment returned to normal. During long-term follow-up, most patients continued to show a progressive improvement in urinary symptoms (decline in IPSS from 67% to 72% at weeks 20 and 85, respectively) and an enhancement of sexual function, and prostatic volume remained normal. Our study demonstrates that in patients with symptomatic BPH, treatment with cetrorelix is safe and produces long-term improvement.

BENIGN prostatic hyperplasia (BPH) is a condition that will affect most men should they live long enough (1–5). Symptomatic BPH is a frequent cause of morbidity among elderly men and can produce a great decline in general well-being (1–6). The annual medical costs of BPH are enormous ($2–5 billion in the U.S. alone) and present an economic burden on the public health systems (2–8). The pathogenesis of BPH is incompletely understood (4, 9–11). Aging and chronic exposure to dihydrotestosterone (DHT) are required for the development of BPH (4, 5, 9–11). However, the actions of androgen alone do not explain the hyperplastic process (11) or the progression of the disease from pathological to clinical BPH (4, 5, 11). Several peptide growth factors have also been implicated in the development of BPH (11–15). Thus, the overall disease process that leads to the production of symptomatic BPH is very complex. Improvement in urinary symptoms and the quality of life is an important issue for decision making on the treatment of patients with BPH (2, 3, 6, 7, 10, 16). Medical therapy is usually recommended first because of the probability of clinical improvement and the patients’ concern about surgery or other invasive treatments. Inhibitors of 5α-reductase or α1-adrenergic receptor antagonists do not offer long-term remission of urinary symptoms after discontinuation and should be used only in a selected population of patients (16, 17). Cetrorelix [(Ac-d-Nal(2), d-Phe(4Cl))2, d-Pal(3), d-Cit(6), d-Ala(10)]LH-releasing hormone (LHRH) is a highly active modern LHRH antagonist that induces an immediate inhibition of the pituitary-gonadal axis (18–20). Previously, responses to cetrorelix have been evaluated in normal subjects and in patients with advanced prostate cancer, leiomyomas, and other conditions (19–23). In view of favorable clinical results, we decided to evaluate the response to 2-month administration of cetrorelix in 13 men with moderate to severe symptomatic BPH.

Subjects and Methods

Study design and selection criteria

Fourteen men with BPH were initially enrolled in this open phase I/II study. These patients and others who were unsuitable for prostatectomy or refused surgery were first interviewed and screened. Patient 3 was withdrawn from the study during week 1 because he was unable to comply with the schedule of follow-up. Thirteen patients, aged 57–75 yr (mean, 66.1 yr), with a mean weight of 92.4 kg and moderate to severe BPH (mean International Prostate Symptom Score (IPSS), 21.85) completed the study. Each patient gave written consent to the study, which was approved by the committee on use of human subjects of Tulane University and the research and development committee of the V.A. Medical Center in New Orleans. The criteria for eligibility were: age 50–80 yr with no evidence of prostate cancer, previously untreated BPH and a total IPSS of 18 or more; an enlarged prostate estimated by digital rectal exam (DRE); serum prostate-specific antigen (PSA) below 10 ng/mL; peak urinary flow rate less than 15 cc/s on a voided volume of 150 cc or more measured by uroflowmetry; and a postvoid residual volume (PVR) of less than 300 cc estimated by bladder scan. Patients who had taken medications with antiandrogenic properties or α-adrenergic drugs during the previous 3 months were not enrolled in the study. The


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patients were not remunerated for participation in this clinical trial. Each subject acted as his own control. Clinical, laboratory, and radiological evaluations were carried out 1–2 weeks before initiation of cetrorelix therapy to establish baseline values. Clinical evaluations consisted of complete history, physical examination including DRE, and three patient self-administered questionnaires before each clinic visit for the assessment of urinary symptoms (IPSS), quality of life (QoL) due to urinary symptoms, and sexual function. The IPSS includes seven questions that assess urinary symptoms (10, 24, 25). The total score can range from 0–35. The severity of the urinary symptoms was estimated according to the American Urological Association Symptom Index: scores of 1–7, mild; 8–19, moderate; and, 20–35, severe (10, 24, 25). The questionnaire recommended by the international consensus committee was used to assess quality of life (26). Sexual function was assessed based on self-administered questionnaire developed by Reynolds et al. (27).

**Clinical, laboratory, and radiological evaluation**

Baseline laboratory and radiological studies consisted of determinations of hematology; chemistry (SMA16); urinalysis; serum levels of PSA, LH, FSH, testosterone (T), DHT, cetrorelix, and growth factors [insulin-like growth factors (IGF-I and IGF-II), transforming growth factor (TGFβ2), and basic fibroblast growth factor (bFGF)]. Serum concentrations of PSA, LH, FSH, T, and DHT were measured by specific RIA as described previously (18, 20–28, 29). Cetrorelix was determined by RIA using a highly specific antibody developed in our laboratory (20). All hormone estimations were performed as a batch in the same assay. Intraassay variation was less than 10%, and interassay variation was less than 15%. IGF-I and IGF-II were measured by RIAs after acid-extraction (29). TGFβ2 and bFGF were measured by Quantikine enzyme-linked immunosorbent assay kits. Additional studies included uroflowmetry, which was performed with a URODYN 1000 machine (Dantec Medical, Santa Clara, CA), estimation of PVR by a portable ultrasound device (bladder scanner ultrasound; Diagnostic Ultrasound, BVI-2000, Diagnostic Ultrason Corp., Kirkland, WA), Measurements of prostate volume (PV) were carried out by transrectal ultrasound (TRUS) with Dianosics SPA-1000, System ID 504–588 DUL-1 using the formula: the greatest sagittal measurement (in centimeters) divided by 2. The patients are listed according to duration of the study.

**TABLE 1.** The individual percentage of improvements in urinary symptoms in patients with BPH at week 4, on the last day of treatment with Cetrorelix and at the end of follow-up

<table>
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<th>Patient no.</th>
<th>Age (yr)</th>
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<th>Decrease in IPSS score compared to baseline</th>
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| P value b   | 0.001   | <0.001  | <0.001  | <0.001  | <0.001  |

a The patients are listed according to duration of the study.

b Determined by Wilcoxon signed rank test.

EFFECTS OF CETRORELIX ON BPH

Statistical methods

The data are expressed as the mean ± SEM unless indicated otherwise. Statistical analyses of the data were performed with use of Student’s t test (two-tailed) and Wilcoxon signed rank test. Differences were considered statistically significant at P < 0.05. Unless stated otherwise, the P values listed were determined by Student’s t test.

**Results**

Thirteen men with moderate to severe BPH completed 2 months of treatment with cetrorelix. The number of patients that were followed-up by visits to the clinic was 13 between weeks 8–16, 11 at week 20, 7 between weeks 21–32, 5 between weeks 33–60, and 3 between weeks 61–85. Five patients had moderate urinary symptoms, and 8 patients had severe...

Center of Tulane, Charity, and Louisiana State University for 32-h in-hospital monitoring of vital signs and any occurrences of adverse experiences. They were also instructed about preparation of the cetrorelix solution, dosage, and self-administration.

Clinical, laboratory and radiological reevaluations were carried out on all subjects during maintenance therapy and up to 18 months after completion of treatment. Clinical evaluations were performed at weeks 1, 4, 8, 12, 16, and 20 and periodically thereafter. Evaluations included progress notes, questions about adverse events, physical examination, DRE exam, and assessment of IPSS, QoL, sexual function, and uroflowmetry. In uroflow studies, some patients, on different occasions, could not void a total volume of 150 mL or more and in certain cases voided even less than 125 mL. Only the samples with a voided volume of 125 mL or more, the minimal voided volume recommended by Lepor et al. (24), were used for the evaluations of peak urinary flow rates. Measurements of PVR were made immediately after uroflowmetry and repeated at weeks 4, 8, 12, and 20 and later if considered necessary. TRUS was repeated at weeks 2, 4, 8, 12, 16, and 20 and thereafter at irregular intervals during the long duration of the study. Adherence to treatment was assessed by counting the number of vials unused at each clinic visit and by measurements of serum levels of LH, T, and cetrorelix. Hematology, urinalysis, and serum PSA levels were evaluated at baseline and weeks 4, 8, 12, and 20, and subsequently at irregular intervals. Serum levels of LH, FSH, T, DHT, IGF-I, IGF-II, TGFβ2, and bFGF were determined at baseline and weeks 1, 4, 8, 12, 16, and 20, and thereafter periodically during the long-term follow-ups.

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symptoms. Table 1 also shows the patients’ ages and the individual percentages of improvements in the IPSS during the study. Figures 1, 2, and 3 illustrate the long term effects of administration of cetrorelix on total IPSS, QoL, and PV determined by TRUS. There was an improvement in total IPSS, QoL scores, and prostatic size by TRUS during and after therapy. The mean basal value for total IPSS was 21.8 ± 5.8 (±sd; range, 13–30). The decrease in IPSS after 1 week of therapy was not statistically significant, but after 4 weeks of cetrorelix administration, the IPSS was significantly reduced by 8.5 ± 6.1 (P < 0.001, by Wilcoxon’s test). Symptom scores decreased significantly in all patients at the end of treatment period by 52.9 ± 23.9% (mean ± sd; P < 0.001, by Wilcoxon’s test). Interestingly, symptom scores continued to improve after discontinuation of therapy (Table 1 and Fig. 1). The decline in total IPSS ranged from 67% (P < 0.0001) to 72% at weeks 20 and 85, respectively, in evaluable patients compared to the baseline value. In addition, as a commonly accepted response definition for BPH is a 30% improvement of IPSS (25), the IPSS improved by more than 30% in 10 of the 13 patients (76.9%) at the end of treatment and in 9 of the 13 patients (69.2%) at the end of observation compared to baseline values.

The mean basal QoL score was 3.8 ± 0.19 (range, 3–5). The improvement in the score during the study is shown in Fig. 2. The total QoL score decreased significantly at the end of the treatment period to 2.07 ± 0.29 (46% reduction; P < 0.001, by Wilcoxon’s test). QoL scores continued to decline after cessation of therapy, decreasing significantly to 1.7 ± 0.3 (55% reduction; P < 0.004, by Wilcoxon’s test) in 11 evaluable patients at week 20 and subsequently falling to 1.3 ± 0.33 (65% reduction) at week 85 in 3 evaluable patients compared to baseline values.

The mean basal PV estimated by TRUS was 33.8 ± 3.5 mL (range, 24–65 mL). Figure 3 shows that only 3 patients (no. 4, 11, and 13) had pretreatment PV values of 40 mL or more. After 2 weeks of therapy, the mean PV diminished to 28.7 mL, but the reduction of 15% was not statistically significant (P = 0.065). The mean PV decreased significantly at week 4 of therapy to 26.4 ± 2.7 mL (22% reduction; P = 0.002) and at week 8 to 24.7 ± 1.8 mL (27% reduction; P = 0.006; data not shown). The reduction in mean PV at the end of treatment was also significant by Wilcoxon’s test. After discontinuation of cetrorelix, the mean PV increased slightly and at the end of individual follow-up was 27.3 ± 2.3 mL (P = 0.013, by Student’s t test; P = 0.004, by Wilcoxon’s test), being below basal values in 10 of 13 men (Fig. 3). In the remaining 3 cases (no. 7, 9, and 10), enlargement of the prostate above baseline

**Fig. 1.** Mean IPSS values in men with symptomatic BPH before, during, and after treatment with cetrorelix. Error bars indicate the SEM. The numbers above error bars show the number of evaluable patients. Asterisks designate a statistically significant decrease compared with the baseline (by Student’s two-tailed t test, P < 0.05). During the follow-up, some evaluations were performed in the combined range of weeks as indicated.

**Fig. 2.** Mean QoL scores in men with symptomatic BPH before, during, and after treatment with cetrorelix. Other designations are explained in Fig. 1.

**Fig. 3.** Individual PVs estimated by TRUS at baseline and at the time of the last evaluation of 13 men with symptomatic BPH treated with cetrorelix. The dashed line represents the normal prostatic volume. The time of the last evaluation is indicated in brackets.

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was minimal (Fig. 3). The mean basal prostatic size determined by DRE was 32 ± 1.4 g, and the reduction of prostate size determined by DRE and after cetrorelix therapy was similar to that determined by TRUS.

The mean basal peak urinary flow rate (PFR) of 13 patients who had voided 125 mL or more was 10.37 mL/s (not shown). The mean increase in the PFR at the end of treatment in these 13 patients was 2.86 mL/s ($P = 0.084$); 12 weeks after completion of therapy it was 1.88 mL/s ($P = 0.128$, both by Wilcoxon’s test) in 11 patients. PFR remained at this increased level during long term follow-up (not shown). On the basis of the $P$ value determined by the Wilcoxon signed rank test ($P < 0.026$), this trend toward increased flow rates was even more pronounced at the end of individual follow-up. Analyses of PFR and PVR based on a voided volume of 150 mL were similar to those in which 125 mL was used. The basal mean PVR in 13 men who had voided 125 mL or more was 107.8 mL. At the end of treatment, PVR decreased to 99.3 mL. Large variations in PVR were documented during long term follow-up, and although PVR values remained low, they were not significantly different from the basal level.

Serum levels of FSH and LH decreased by 54–59% during therapy, but later returned to normal (not shown). The effects of cetrorelix treatment on $T$ levels are shown in Fig. 4. Serum $T$ fell to castrate levels (90.6% inhibition) on day 2, but $T$ was inhibited only by 64–74% during maintenance therapy up to week 8. After completion of treatment, $T$ returned to normal levels.

The changes in DHT during treatment were not significant. After the loading dose of cetrorelix, serum levels of this antagonist rose to 153 ± 9.2 ng/mL, and during maintenance therapy, the values ranged from 25.1–35.8 ng/mL (Fig. 4). Serum PSA was maximally suppressed at week 8 of treatment when the levels decreased from a basal mean of 1.6 ± 0.35 to 0.8 ± 0.27 ng/mL ($P < 0.019$; not shown). PSA levels continued below basal values throughout the follow-up period. There were no significant changes in the serum levels of IGF-I, IGF-II, TGF-$\beta_2$, or bFGF during and after treatment with cetrorelix.

Evaluation of satisfaction with sexual life before, during, and after treatment with cetrorelix is shown in Table 2. Before therapy, 5 of 13 men (39%) were completely or moderately satisfied with their sexual lives. During the treatment, the patients’ complete or moderate satisfaction with their sexual lives varied from 62% at week 1 to 23% at week 8. Initially, 8 men (61%) perceived their libido as normal, and 6 (46%) had normal nocturnal penile tumescence. The percentage of men with stated normal libido and normal nocturnal penile tumescence decreased to 46% and 38%, respectively, at week 1. Both values decreased to 23% at week 8. Seven patients who temporarily lost their libido during treatment were those with greater suppression of $T$ levels. After completion of therapy, there was an increase in the percentage of men with complete or moderate satisfaction with their sexual life, the values being 62% at week 16 and 64% at week 20 ($n = 11$). A similar trend was obtained for libido and nocturnal penile tumescence. Normal libido was reported by 69% of men at week 16 and 82% at week 20, and normal nocturnal penile tumescence was reported by 69% of men at week 16 and 64% at week 20.

No serious side-effects occurred during therapy with cetrorelix, and there were no significant changes in any of the standard blood tests during this trial. There were no compliance problems with cetrorelix treatment. No patient presented with acute urinary retention during long term follow-up. Five men reported slight to notable hot flashes during cetrorelix therapy, which subsided when the treatment was ended. One 66-yr-old patient had excellent response to cetrorelix but died from bleeding complications caused by non-Hodgkin’s lymphoma 14 months after therapy was completed. Patients 8, 10, and 11 were discontinued from the trial between weeks 16 and 32 because they continued to be dissatisfied with their QoL despite some improvement in urinary symptoms. Subsequent treatment of these three men with an $\alpha$-adrenergic antagonist (Cardura, Pfizer, Inc.; 2–4 mg/day) did not produce any clinical benefits. After failure of subsequent treatment with Cardura, patient 10 underwent TURP and was diagnosed to have histological evidence of prostatitis in addition to BPH. Thus, in a subpopulation of patients with BPH, a coexisting prostatic condition may decrease the effectiveness of medical therapies.

**Discussion**

The natural history of BPH is variable, but the disease is usually slowly progressive ($3, 4, 5, 30, 31$). Improvement in the quality of life of patients suffering from BPH is an important issue in the medical management of this condition. In this study, we demonstrated that administration of cetrorelix for 2 months was of great clinical benefit to patients with moderate to severe BPH. During treatment with cetrorelix, the high scores of urinary symptoms and quality of life due to urinary symptoms decreased significantly by week 8; there was a rapid decline in total PV and mean peak urinary flow rates increased by nearly 3 mL/s. Serum $T$ fell to castrate levels on day 2, but $T$ was inhibited by only 64–74% during maintenance therapy, and subsequently $T$ returned to normal levels. Before entering this study, our patients were quite symptomatic. The reduction in high scores of IPSS and QoL due to urinary symptoms was not limited to the duration of the treatment period, and these scores continued to decline significantly in most patients during long term follow-up. After therapy, there was also an improvement in overall sexual function. The mean PV remained below basal in most
patients, and peak urinary flow rates continued above baseline. The severity of urinary symptoms at baseline and the improvement in symptomatology through the study showed only a weak correlation with the findings of uroflowmetry and postvoiding residual urine measurements. This weak association between symptoms and urinary flow rates has been previously observed by others (30, 32). Uroflowmetry is not a perfect test for monitoring the effects of treatment because of a considerable coefficient of variation between voided volumes created by a great susceptibility to straining artifact (33). In addition, many patients are not able to relax and produce their normal urinary flow in the clinic (34).

Several relevant findings were made in the course of this trial. The improvement in the sexual function of some patients was unexpected, and it is possible that the relief of urinary symptoms can have a major impact on the quality of sexual life. Initially, all men enrolled in this study had clinically significant urinary symptoms despite a mean basal PV of only 33.8 mL by TRUS. When prostate size was estimated clinically, and the individual PV stayed below basal in 10 of 13 men. It is also known from double blind, placebo-controlled trials that volume increases continuously in the placebo group despite some temporary improvement in the degree of symptomatology, and DRE tends to underestimate the size of the prostate. The decrease in PV was not limited to the prostates with volumes in excess of 40 mL. In addition, despite the return of serum T to normal levels after the discontinuation of cetrorelix, the patients continued to improve clinically, and the individual PV stayed below basal in 10 of 13 men. It is also known from double blind, placebo-controlled trials that volume increases continuously in the placebo group despite some temporary improvement in symptomatology (24, 31, 35). It has been suggested that androgen suppression with finasteride (an inhibitor of 5α-reductase) is more efficacious in men with prostates larger than 40 mL because of promoting regression primarily of the hyperplastic epithelial elements (16, 24, 31, 36, 37). Previously, a reduction of 44% in PV was observed after treatment with cetrorelix in BPH patients with a mean basal PV of 67.8 mL (28). In the present study, patients with relatively small prostates had a long lasting therapeutic response to cetrorelix although the percent reduction in PV was smaller. These findings can also be contrasted with the results of the studies on the administration of agonistic analogues of LHRH for 4–6 months to men with BPH (38, 39). The outcome of these trials with nafarelin and leuprolide was disappointing, as medical castration induced by prolonged administration of these analogues caused shrinkage of the prostate and improved urinary symptoms, but after the therapy was discontinued, these effects were reversed (38, 39). Interestingly, finasteride suppresses prostatic DHT but increases the concentration of T in the prostate (40). This may explain in part the slow onset of action of finasteride (16, 24, 25, 31, 36, 40). In contrast to the rapid effects of the LHRH antagonist cetrorelix, the improvement in symptoms after finasteride takes place over 6 months, and PV is reduced by only 17–21% (24, 31, 36, 41). Finasteride significantly reduces acute urinary retention and need for surgery in men with symptomatic BPH (30, 33), but causes significant sexual dysfunction (25, 31, 41). A long acting α-adrenergic antagonistic drug such as terazosin can produce responses within weeks (24, 36, 41), but needs to be given chronically and may cause orthostatic hypotension and syncope, which create a potential risk for falls.

The etiology of BPH and the mechanism of progression from pathological to clinical BPH are incompletely understood (4, 5, 9–11). The mode of action of cetrorelix accountable for the improvement in clinical BPH is not clear. The transient suppression of T levels can only account in part for the beneficial effects of cetrorelix. Various growth factors may be involved in the pathogenesis of BPH (11–15). In our study, we found no changes in serum levels of IGF-I, IGF-II, TGFβ2, or bFGF in patients treated with cetrorelix. It is possible that alterations in growth factors after therapy with cetrorelix might be detectable only in hyperplastic prostate tissue and not in serum. Prostatic needle biopsies in future studies might determine possible changes in growth factors. Cetrorelix was shown to inhibit the growth of human prostatic, mammary, ovarian, and other cancers xenografted into nude mice with the induction of apoptosis (19, 20, 23). This tumor growth suppression was invariably linked to a major reduction in the levels of epidermal growth factor receptors

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<td>1 14.3</td>
<td>1 14.3</td>
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<td>1 14.3</td>
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<tr>
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<td>5 100.0</td>
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<td>2 100.0</td>
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<tr>
<td>&gt;74 weeks</td>
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<td>0 0 0 0</td>
<td>1 50.0</td>
<td>0 0 0 0</td>
<td>2 100.0</td>
<td></td>
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</table>

n, The number of patients.
on tumors (23). Cetrorelix can also interfere with the growth-stimulating effects of IGFs in mammary and endometrial cancer cells (19). The reduction in messenger ribonucleic acid levels for epidermal growth factor receptors in experimental tumor models after therapy with cetrorelix is the subject of intense investigations by our group (19). Thus, it is possible that cetrorelix, despite only a temporary submaximal suppression of T, may provide clinical benefits by induction of apoptosis, inhibition of prostatic growth factors, and disruption of interactions between epithelial and stromal elements.

In this study, the long term benefits of cetrorelix were documented by subjective and objective parameters. A short term administration of cetrorelix to men with symptomatic BPH appears to be safe, provides a rapid onset of action, and tends to have a beneficial effect on the disease process and overall health-related quality of life. Randomized double blind, placebo-control studies are required to confirm these preliminary findings. Long acting depot preparations of cetrorelix that are being presently perfected should greatly facilitate the treatment of BPH.

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References