Cetrorelix Shows Promise in Prostatic Hyperplasia

BY NANCY WALSH
New York Bureau

NEW YORK — A new treatment paradigm for benign prostatic hyperplasia is on the horizon, according to Dr. Herbert Lepor.

During the past 2 decades, there has been a shift in the management of benign prostatic hyperplasia (BPH) away from surgery and toward earlier medical intervention, but standard treatment with the α_1-adrenergic receptor antagonists and the 5α-reductase inhibitors leaves a significant cohort of nonresponders, Dr. Lepor said at a meeting on adult and pediatric urology sponsored by New York University.

Among the limitations for α-blockers are safety concerns in patients with low blood pressure and orthostatic hypotension. The α-reductase inhibitors also have a slow onset of action and undesirable side effects, including erectile dysfunction.

Moreover, compliance with daily regimens has been low, at 50% with the α-reductase inhibitors and 67% with the α-blockers, Dr. Lepor said.

A new approach to the medical management of lower urinary tract symptoms (LUTS) secondary to BPH involves using a gonadotropin-releasing hormone (GnRH) antagonist such as cetrorelix. Unlike the GnRH agonists that are commonly used for prostate cancer, GnRH antagonists lower serum testosterone only partially and in a dose-dependent manner.

The goal of using the GnRH antagonist is to reach a level of androgen suppression that will shrink the prostate and improve clinical symptoms without the side effects associated with complete testosterone suppression, explained Dr. Lepor, who is professor and Martin Spatz chairman of the department of urology at the university.

In phase II studies evaluating various doses, regimens, and two different formulations of cetrorelix, statistically significant differences from baseline and compared with placebo were seen on the primary end point of International Prostate Symptom Score (IPSS) at week 12.

In one of these trials, 140 patients were randomized to receive cetrorelix acetate in four doses of 5 mg or 10 mg at 7-day intervals, two doses of 10 mg at 14-day intervals, or placebo.

"Even by week 4, there was a trend toward improvement in symptoms," Dr. Lepor said. "In patients taking the active drug, there were improvements on IPSS of three to four symptom units, which is equivalent to, if not greater than, the results seen in the best of the α-blocker studies."

Moreover, flow rates improved rapidly with a response "far greater than anything we see with medical therapy," he said.

The mean baseline flow rate was about 9 ng/mL, and it increased to about 13 ng/mL in the patients in the active treatment groups.

With regard to prostate size, the results were not significant, although there was a trend to decrease in prostate volume. Testosterone levels during the 4-week injection period showed decreases of about 25%. After the last injection, testosterone levels promptly returned to baseline, and there was no effect on erectile function.

A second phase II trial randomized 250 patients to placebo or cetrorelix pamoate in two doses of 30 mg, three doses of 30 mg, one dose of 60 mg followed by another of 30 mg, or 60 mg followed by 60 mg. All of the doses were given at 14-day intervals.

The results were similar to those in seen in the previous trial, with statistically significant dose-related improvements reported on the IPSS and on urinary flow rates, and with responses persisting out to 120 days. In none of the groups were castration-level testosterone suppression or associated adverse effects seen, Dr. Lepor said.

In a recent review of GnRH antagonists for BPH, Dr. Lepor wrote, "The fact that an intermediate level of testosterone suppression can achieve prostate volume reduction without causing hot flashes, erectile dysfunction, and other adverse events associated with castrate levels of testosterone suggests that there are different androgen thresholds mediating these events. Another possible explanation may be that cetrorelix mediates prostate volume reduction via its effects on other hormones and growth factors" (Rev. Urol. 2006;8:183-9).

Compliance has not been a problem in the clinical trials thus far, with patients having two to three long-lasting treatments a year, he said.

Dr. Lepor, the principal investigator for the phase III trial, disclosed that he serves as a consultant to Æterna Zentaris Inc., the study sponsor. ■