Panel: Prostate Cancer Therapy Trials Needed

BY JESSICA BYLANDER

GAITHERSBURG, MD. — Developers of targeted prostate cancer treatments should conduct randomized clinical trials with "watchful waiting" as a control, according to the Food and Drug Administration's Gastroenterology and Urology Devices Panel.

Active surveillance may be an appropriate control for studies of whole-gland therapies that treat or remove the entire prostate, as well as for studies of targeted therapies in which only the known cancerous regions are treated (focal treatments); however, the panel reached consensus only on the focal-treatment study controls.

There is a growing interest in developing new therapies, as current treatments may pose risks disproportionate to the risk of the disease itself.

The primary end point for active surveillance studies would measure the impact of therapy on disease progression. Because prostate cancer progresses so slowly, survival rates are not a feasible end point, the panel said.

"A win in the active surveillance arm is not needing treatment, and a win in the treatment arm is [cancer] not recurring after treatment," said panel member Dr. Peter Scardino of Memorial Sloan-Kettering Cancer Center in New York.

There is a growing interest in developing new, minimally invasive device therapies, as current treatments may pose risks disproportionate to the risk of the disease itself, according to the panel.

New treatment methods include high-intensity focused ultrasound, radiofrequency ablation, lasers, microwave devices, and photodynamic therapy.

Current prostate cancer treatments rely on the radical, whole-gland approach in which the entire prostate is removed or irradiated, and they are associated with significant morbidity. The FDA asked the panel whether nonrandomized study designs for new prostate cancer treatments could be considered, and to identify appropriate control groups, patient selection criteria, and effectiveness end points.

The panel agreed that randomized trials were necessary, despite the many challenges of conducting them, and that outcomes from focal treatments, at least, should be compared with outcomes from a watchful-waiting (or active surveillance) approach.

Few randomized studies comparing different prostate cancer treatment modalities have been completed, the panel noted. The Southwest Oncology Group study of prostatectomy vs. external-beam radiation treatment, for example, was terminated after enrolling only 6 of 1,000 planned subjects.

According to Dr. Scardino, it would be easier to enroll patients in a trial with an active surveillance control. He pointed to non-U.S. randomized studies that were successfully completed by using an active surveillance control.

Quality of life measurements and complication rates are also important, the panel said, but they disagreed on which data elements to collect and whether quality of life should be a primary or secondary end point. Additionally, the panel did not reach consensus on the appropriate length of follow-up for randomized studies.

Janine Morris, acting director of the Division of Reproductive, Abdominal, and Radiological Devices in the FDA's Center for Devices and Radiological Health, said that although the panel was able to answer the FDA's most important questions, she was disappointed that there was not time for further discussion.

"We will have to address this in another format," such as another advisory panel meeting, a public workshop, or a meeting with industry stakeholders, she said in an interview. "We have unanswered questions."

Prostate disease is the second leading form of cancer among men in the United States, with 192,000 cases expected to be diagnosed this year. It is also the second leading cause of cancer deaths. The disease generally affects men older than the age of 60 years. ■

Jessica Bylander is with "The Gray Sheet," which like this newspaper, is published by Elsevier.

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Erectile Dysfunction

BY NEIL S. SKOLNIK, M.D., AND EVAN E. NEFT, M.D.

Erectile dysfunction is a common primary care complaint. With leading ED risk factors such as obesity, diabetes, hyperlipidemia, vascular disease, and advanced age becoming increasingly common, many more than the estimated 152 million men worldwide who suffered from the affliction in 1995 will do so in the coming decades.

Men experiencing ED for more than 3 months warrant evaluation and possible treatment. In addition to modifiable cardiovascular risk factors, hypogonadism and psychiatric disorders are common ED causes that are potentially amenable to diagnosis and treatment. Here is a look at a recent guideline from the American College of Physicians on the diagnosis and treatment of erectile dysfunction (Ann. Intern. Med. 2009;151:639-49).

Pharmacologic Treatment

Data from randomized controlled trials strongly support beginning phosphodiesterase (PDE-5) inhibitor therapy in men with ED. Analyzed studies compared the efficacy and safety of five oral PDE-5 inhibitors: sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), mirodenafil, and udenafil. Most trials analyzed included 12 months of data.

Across all studies, the mean percentage of improved erections with PDE-5 inhibitors ranged from 73% to 88%, compared with 26%-32% with placebo. Successful sexual intercourse occurred 68%-69% of the time with PDE-5 inhibitors and 33%-36% of the time with placebo. This improvement in sexual function held true both in studies excluding men with a variety of comorbid medical conditions as well as in studies limited to men with diabetes, depression, cardiovascular disease, multiple sclerosis, schizophrenia, prostate cancer, colorectal cancer, liver failure, and renal failure. Data are robust that PDE-5 inhibitor therapy is potentially successful for individuals with or without medical comorbidities.

Dose escalation of some PDE-5 inhibitors improved sexual function. Sildenafil was associated with greater improvements when the dose was increased from 25 mg to 50 mg, but not from 50 mg to 100 mg. Vardenafil showed dose improvement from 5 mg to 10 mg and from 10 mg to 20 mg. Other PDE-5 inhibitors were not associated with greater improvements at higher doses.

Hormonal Evaluation and Therapy

Treating obesity, hyperlipidemia, hypertension, and diabetes reduces the risk of end-organ damage and improves erectile dysfunction. The utility of identifying and addressing the other main organic cause of ED—hormonal deficiency—is less clear. Numerous studies suggest that there is insufficient evidence for or against measuring prolactin and testosterone levels as a cause of ED. It is unclear whether men with ED have higher rates of hyperprolactinemia or hypogonadism than individuals without ED. Physicians should make decisions to screen men for hormonal deficiencies based on clinical presentations that suggest hormonal abnormalities such as decreased libido, premature ejaculation, fatigue, testicular atrophy, and muscle atrophy.

There was no evidence to support the use of hormonal therapy in men with ED and hypogonadism. Comparisons of patch or gel testosterone to placebo did not show significant improvement in erectile function or successful sexual activity. Similarly, no additional effect was found when comparing a testosterone/PDE-5 inhibitor combination with a PDE-5 inhibitor plus placebo.

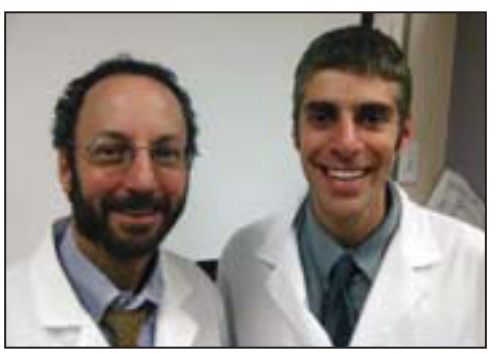
Side Effects of Therapy

The primary contraindication to PDE-5 inhibitor therapy is concurrent use of nitrates. Though serious side effects of PDE-5 therapies are rare with appropriate usage, treated men are more likely than controls to experience adverse events such as headache, flushing, rhinitis, dyspepsia, and less commonly, visual disturbances, myalgia, nausea, diarrhea, dizziness, and chest pain. Priapism has been infrequently reported in postmarketing surveillance.

The most serious adverse effect possibly attributed to PDE-5 inhibitors was nonarteritic anterior ischemic optic neuropathy (NAION). Low-quality evidence did not link PDE-5 inhibitors with an increased frequency of NAION (relative risk 1.02). The same low-quality trial evidence, however, did show an increased risk of possible NAION (defined as papillitis, optic neuritis, or both in the absence of temporal arteritis, polymyalgia rheumatica, and previous optic neuropathies). The relative risk of possible NAION with PDE-5 inhibitor use was 1.34, but the absolute risk remained a modest 2.4 cases in 10,000 men per year.

The Bottom Line

PDE-5 inhibitors are a safe, effective treatment for the common problem of erectile dysfunction. The choice of PDE-5 inhibitor therapy should be based on individual preference regarding factors such as ease of use, cost, and adverse effects. Titrating the dosage of sildenafil and vardenafil until the desired response is reached is likely beneficial; dose escalation of other PDE-5 inhibitors is not useful. No evidence-based role exists for hormonal testing or treatment for erectile dysfunction.



DR. SKOLNIK is an associate director of the Family Medicine Residency Program at Abington (Pa.) Memorial Hospital. DR. NEFT is a second-year resident in the program. A handheld computer version of this guideline is available at www.redi-reference.com.