EDITORIAL

Medical Management of Benign Prostatic Hyperplasia — Are Two Drugs Better Than One?

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The prostate is a complex organ composed of epithelial cells and fibromuscular stroma. Benign prostatic hyperplasia is a true hyperplastic process, with an increase in the number of cells arising initially in the transition zone of the gland. Complex stromal–epithelial interactions lead to benign prostatic hyperplasia in 50 percent of men by the age of 50 years. This process requires testicular androgens and progresses with age. Aging is accompanied by an increase in symptoms of bladder obstruction or irritation attributable to benign prostatic hyperplasia. A prospective study showed that 24 percent of men with moderate symptoms of benign prostatic hyperplasia who were randomly assigned to watchful waiting needed surgery within three years.[1] In addition, a community study showed that over 50 percent of men with benign prostatic hyperplasia had an impaired ability to perform daily activities, a problem that would potentially improve with medical management. The importance of this information is reflected by the fact that the 2000 U.S. Census included 14 million men over 65 years of age, with the number estimated to rise to 17 million by 2010.

Benign prostatic hyperplasia can lead to obstructive nephropathy, bladder decompensation, acute urinary retention, recurrent bacterial urinary tract infections, or bladder calculi. However, as early as 1989, a review of more than 3000 men undergoing surgery noted that over 80 percent had "bothersome" symptoms, in addition to the complications just listed.[2]

A major advance in the management of benign prostatic hyperplasia has been the development of the validated American Urological Association (AUA) symptom scale. This six-point scale grades the severity of symptoms in seven categories (frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency), with a total score of 35 indicating the most severe symptoms. There is also a six-point scale to assess the quality of life.[3] Accordingly, the recently published AUA guidelines recommend watchful waiting for patients with mild symptoms (symptom scores of 0 to 7). Medical management is generally the first recommendation for patients with symptom scores greater than 7, if they are bothered by symptoms.[4] In this issue of the *Journal*, McConnell et al.[5] use an inclusion criterion of an AUA symptom score of 8 to 30 in their study of the medical management of benign prostatic hyperplasia. The primary outcome was disease progression, defined by an increase in the symptom score of at least 4 points over the base-line score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.[5]

Medical management of benign prostatic hyperplasia with α-adrenergic–blocking agents was shown to be effective by Caine et al.,[6] who reported that phenoxybenzamine brought symptomatic relief to their patients. Alpha-blocker therapy is based on the demonstration of α_1-adrenergic–mediated innervation of the prostatic smooth muscle that controls contraction of the prostate and obstruction of the bladder outlet. All currently used alpha-blockers — doxazosin, tamsulosin, alfuzosin, and terazosin — block this process and are equally effective in reducing the AUA symptom score by 4 to 6 points.[4] These agents work rapidly and have caused few serious side effects in long-term studies. The α_{1a}-specific adrenergic blocker tamsulosin is now commonly prescribed because the dose does not have to be titrated and the incidence of systemic side ef-

fects is lower than with nonspecific alpha-blockers. However, none of these agents stop the progressive increase in prostatic size that characterizes benign prostatic hyperplasia and is correlated with such adverse events as acute urinary retention or the need for surgical intervention.[7]

The rationale for the second type of medical intervention — inhibition of 5α-reductase — is based on an "experiment of nature" in which men with an inherited deficiency of 5α-reductase were found to have small prostates. Subsequently, large, well-designed clinical trials showed that finasteride, a 5α-reductase inhibitor, reduced circulating dihydrotestosterone levels by approximately 80 percent, prostate-specific antigen levels by 50 percent, and prostatic size by about 20 percent and decreased the AUA symptom score by 3 points.[8] Side effects are related to sexual function and include decreased libido, ejaculatory dysfunction, and erectile dysfunction. In contrast to α-adrenergic–blocking agents, the 5α-reductase agents do not act rapidly and often require six months to a year to be effective. However, they do prevent prostatic growth, reduce the risk of acute urinary retention, and decrease the need for surgery related to benign prostatic hyperplasia.[9]

Since these two classes of agents have totally different modes of action and both have been shown to be of benefit in well-designed prospective trials, it is logical to hypothesize that giving the two types together would be more effective than giving either type alone. Thus, it was surprising when several earlier studies, up to one year in duration, failed to show that combination therapy was more effective in treating symptoms than alpha-blocker monotherapy.[10,11] McConnell et al., concentrating on the risk of disease progression, confirmed that combination therapy was no better than monotherapy at one year. But whereas there was disease progression in the placebo group over a four-year period, combination therapy reduced the risk of symptom progression by 66 percent, the risk of acute urinary retention by 81 percent, and the need for invasive therapy by 67 percent. The authors concluded that combination therapy with an alpha-blocker and a 5α-reductase inhibitor reduced the risk of overall clinical progression of benign prostatic hyperplasia significantly more than did treatment with either drug alone. Thus, two drugs are better than one.

Will this study change the medical management of benign prostatic hyperplasia? I will defer to health care economists to analyze the financial effect of lifetime dual therapy for the approximately 7 million men over 65 years of age who would be likely to benefit from therapy. Current therapy in most cases consists of an alpha-blocker initially. This practice is unlikely to change, since these agents rapidly relieve symptoms, are easily administered and tolerated, and have long-term efficacy, especially in the case of the α_{1a}-specific agents. In the current four-year study, clinical progression occurred in only 17 percent of men in the placebo group, and 80 percent of events were due to an increase of at least 4 points in the AUA symptom score. The study supports the use of dual therapy in men whose symptoms progress during monotherapy or men who are at a high risk for progression. Furthermore, the study identified a population of men with a high risk of undergoing invasive therapy who would benefit from initial combination therapy. Such high-risk men in the study had a serum prostate-specific antigen level of more than 4 ng per milliliter and a prostatic volume of more than 40 ml on transrectal ultrasonography, factors that predict prostatic growth in men with benign prostatic hyperplasia.[12]

Enthusiasm for the widespread use of dual therapy has, however, been dampened by the results of the Prostate Cancer Prevention Trial.[13] In this study, more than 18,000 men were randomly assigned to receive finasteride or placebo over a seven-year period. The finasteride group had an absolute reduction of nearly 25 percent in the prevalence of prostate cancer detected on prostatic biopsy, but tumors of Gleason grade 7 to 10 were more common in this group than in the placebo group. Recently, in the *Journal*, Ware cautioned us that when secondary analyses have unanticipated results, we should consider the finding to be hypothesis-generating rather than a definitive observation.[14] This advice may be applied to the unexpected finding of an increased risk of high-grade prostate cancer during finasteride therapy.

Currently, several hypotheses are being developed. The use of Gleason grading may be inaccurate because of a cellular effect of finasteride, although a small study did not identify such changes.[15] Polymorphisms of the 5α-reductase 2 (*SRD5A2*) gene may reduce the sensitivity of the prostate to finasteride.[16] In addition, there is decreased expression of the wild-type *SRD5A2* gene in prostate-cancer cells, which could limit the effectiveness of finasteride as a chemoprophylactic agent.[17]

Taken together, the encouraging results reported by McConnell and colleagues are a mandate for the development of appropriate studies to determine

the risks of finasteride therapy. In the meantime, the prudent physician needs to counsel men carefully before they begin combination therapy, weighing the benefit of preventing the progression of benign prostatic hyperplasia against the potentially increased risk of high-grade prostate cancer.

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