Androgen replacement and/or 5 alpha reductase inhibitors in aging men

Laurence H. Klotz, MD

Division of Urology, University of Toronto, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

KLOTZ LH. Androgen replacement and/or 5 alpha reductase inhibitors in aging men. The Canadian Journal of Urology. 2006;13(Supplement 1):44-45.

A case study of a typical 65 year old man with symptoms of both LUTS with established BPH, and andropause, is presented. The case for 5ARI therapy versus androgen replacement therapy is discussed, and the evidence for the use of these drugs in combination is reviewed.

Key Words: Andropause; prostate cancer prevention, 5 alpha reductase inhibitors, combination therapy

Case study

A 65 year old man is referred to you, a urologist, with several complaints. He has frequency, urgency, and nocturia three times per night. He complains of some decrease in libido, and erectile function is mildly diminished. He has mild depression and decrease in energy. He is otherwise healthy. His father was diagnosed with prostate cancer at age 75, and died at 87 of an MI. Physical exam is normal, except for a 55 cc benign feeling prostate. PSA is 3.5 ng/ml, and total serum testosterone is 12 (10-40 mMol/l).

Management of this type of patient has been discussed at several major international meetings which you have had the opportunity to attend. This included a symposium on BPH which discussed the results of the MTOPS and PCPT trials. You are aware that, in men with LUTS and large prostates, the combination of an alpha blocker and a 5 alpha reductase inhibitor produces improved results compared to either therapy alone. You are also aware that finasteride has been shown to reduce the likelihood of a prostate cancer diagnosis by 25%. You've concluded that the increase in high-grade cancers in the finasteride arm is almost certainly an artefact, and represents an acceptable level of risk. At this conference, key opinion leaders expressed the view that men with voiding symptoms and a large prostate benefit from a 5 alpha reductase inhibitor, particularly if they have risk factors for prostate cancer.

You also attended a symposium on andropause. You are aware that andropause is significantly underdiagnosed; that the symptoms can be vague and non-specific; that serum testosterone levels may be misleading, because a testosterone in the normal range may be lower than an individual's historical level. You are aware of the complexities of interpreting testosterone assays, including total, free, and bioavailable forms. You have been impressed by the favorable clinical response and improved quality of life which occurs with androgen replacement in aging men with hypogonadism. Speakers at the symposium opined that there was no evidence to date of an increased rate of prostate cancer associated with androgen replacement; although you have some concerns, you've decided that uncertainty regarding the prostate cancer issue represents an acceptable level of risk. At the symposium, key opinion leaders expressed the view that men with symptoms of andropause and a low normal testosterone benefit from androgen replacement.

Discussion

The clinical scenario described above is extremely common. Patients in the typical demographic of a urology practice fall into this age group, and have both LUTS, prostatic enlargement, and some decrease in libido and erectile function. Many are concerned about prostate cancer. It is ironic that in a given patient, a case can be often be made both for androgen

Address correspondence to Dr. Laurence H. Klotz, Division of Urology, Sunnybrook & Women's College Health Sciences Centre, 2075 Bayview Avenue #MG 408, Toronto, Ontario M4N 3M5 Canada

replacement and 5 alpha reductase inhibitor, depending on which symptom is prioritized. The available literature exclusively focuses on one or the other of these two approaches. For these very prevalent conditions which often co-exist in the same patient, there has been little attempt to mediate between these two therapeutic approaches, which are, at least at face value, contradictory.

There are two facets to this question. In a typical patient, such as the one described above, which should take priority—management of the hypogonadism, or management of the LUTS/BPH/prostate cancer risk? Secondly, is there a role in selected patients for using these drugs together?

Whether to treat the hypogonadism or the BPH is a typical risk/benefit dilemma which physicians are very familiar with. The lack of literature on this management question means that an evidence-based approach is not feasible. The approach involves determining which of the two complaints represents a greater health issue for a given patient; treating accordingly; observing the response, and adjusting the treatment. A pragmatic, empirical approach is warranted.

The second possibility, of using the drugs in combination, is intriguing. The hormonal consequences of 5ARI and androgen replacement used in combination are likely to be a marked increase in serum and cytoplasmic testosterone, and a decrease in intracellular DHT. This may result in a very favorable clinical outcome: an increase in skeletal muscle mass and a decrease in body fat (due to the increased T), accompanied by a reduction in prostatic volume (due to reduced DHT).

There is a single clinical trial in the literature that has addressed the impact of combining these two agents. This study randomized 70 men over age 65 with primary hypogonadism between three arms: Testosterone enthanate IM versus placebo versus Testosterone+ Finasteride for 3 years.[1] The study showed dramatic improvements in physical performance, hand grip strength, lean body mass, and total fat mass in the Testosterone and Testosterone-Finasteride groups compared to placebo. The Testosterone-Finasteride group had identical improvement in these parameters compared to the Testosterone alone group. A second publication on the same cohort reported that bone mineral density in the lumbar spine was increased about 10% in both the Testosterone and Testosterone-Finasteride groups, compared to placebo.[2] Prostate volume increased in all groups, but less so in the Testosterone-Finasteride group. Men treated with the combination of Testosterone and Finasteride reduced their DHT by 50%. Further, Testosterone plus Finasteride increased serum estradiol and testosterone levels more than testosterone alone, reflecting the increase in LH secretion due to inhibition of 5[alpha]-reductase in the pituitary. In observational studies, endogenous estradiol appears to be as important, or more important, than testosterone in bone maintenance.[3] Just how testosterone works to preserve bone is not clear, and some DHT may be required for bone benefit.

The concomitant administration of Finasteride with Testosterone appeared to attenuate the impact of Testosterone therapy on prostate size and PSA and might reduce the chance of benign prostatic hypertrophy or other prostate-related complications in older men on Testosterone therapy. The results of this study raise the possibility that a bone-sparing, muscle building, libido enhancing, prostate-sparing testosterone regimen may be feasible.

The question of the merits of 5ARI and androgen replacement in combination is a high priority and merits further study.

Urologists, as the 'male health experts', need to be very cognizant of the message that we transmit to primary care physicians. Physicians who advocate 5ARI therapy for its benefits on BPH and prostate cancer prevention must recognize that androgen replacement may also be indicated in selected patients with coexistent symptoms of andropause; and vice versa. Prioritizing these two quality of life related therapies in healthy, aging men with mild-moderate symptoms of both LUTS and andropause requires clinical judgement and a willingness to listen carefully to patients' concerns. Use of the two approaches in combination will require long term studies to ensure safety and efficacy before wide adoption takes place, although early results are promising. □

References

1. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrin Metab* 2005;90(3):1502-1510.
2. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89(2):503-510.
3. Barrett-Connor E, Mueller JE, von Mühlen DG, Laughlin GA, Schneider DL, Sartoris DJ. Low levels of estradiol are associated with vertebral fractures in older men, but not women: The Rancho Bernardo Study. *J Clin Endocrinol Metab* 2000;85:219-223.