REVIEW

The clinical applications of five-alpha reductase inhibitors

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Introduction: *Five-alpha reductase (5-AR) deficiency was first identified by Imperato-McGinley and Walsh as the cause of pseudohermaphroditism in two separate studies. The discoveries led to the development of finasteride (inhibitor of type 2 isoenzyme of 5-AR) and dutasteride (inhibitor of type 1 and type 2 isoenzymes of 5-AR.*
Both drugs have been proven effective for the treatment of benign prostatic hyperplasia and improve voiding symptoms, reduce the risk of urinary retention and the need for prostate surgery.
Five-alpha reductase inhibitors 5-ARIs have been demonstrated to be chemopreventive agents and reduce the risk of prostate cancer, although the risk of selecting out or mediating higher grade prostate cancer remains uncertain. A lower dose of finasteride has been shown to be effective in the treatment of male pattern baldness.
Materials and methods: *A Medline search was performed using mesh terms, benign prostatic hypertrophy, prostate cancer, male pattern baldness, female and 5-AR.*
Results: *The Prostate Long Term Efficacy and Safety Study (PLESS) was a randomized double-blind study that established that finasteride resulted in a 22% increase in maximum flow rate and a 19% decrease in prostate volume. Further studies demonstrated that finasteride caused a significant reduction in the risk of the need for surgery and urinary retention in a 4 year period. Additional studies showed similar beneficial results with dutasteride.*
The potential benefits of 5-ARIs as chemopreventive agents were examined in the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) studies. In the 7 year PCPT trial, 18.4% of the finasteride group developed prostate cancer compared to 24.4% in the placebo group. In the 4 year REDUCE trial, there was a 22.8% reduction of prostate cancer at the conclusion of the study.
Despite the reduction of prostate cancer in both the PCPT and REDUCE trials, each study showed an increased risk of prostate cancer in the treatment arms. The explanation for these observations remains an area of investigation.
Low dose finasteride has also been used successfully for the treatment of male pattern baldness.
Conclusions: *The use of 5-ARIs has been a major advance in urologic clinical practice. Urologists should be familiar with the underlying pharmacology of 5-ARIs as well as the clinical indications for their use.*

Key Words: five-alpha reductase inhibitors, benign prostatic hyperplasia, finasteride, dutasteride

History-the Guevedoces

In 1972, Julianne Imperato-McGinley was a young endocrinologist at Cornell Medical College in New York City who was interested in studying children with intersexuality and ambiguous genitalia. She investigated a cohort of children in an isolated village, Salinas, in southwestern Dominican Republic. These children appeared to be females at birth, but at puberty, these "girls" developed muscles, testicles and a penis. They were referred to locally as "Guevedoces"- penis at twelve. They then continued their lives as men.

Imperato-McGinley studied these children and identified their underlying defect as 5-AR deficiency, an inherited form of male pseudohermaphroditism.[1] That same year, Walsh et al identified the same defect in Texas.[2] Roy Vagelos was then the chief of research at Merck when he read the findings, " The prostate, however, remains small" and was struck by the possibility of drug development to impair the growth of benign prostatic hyperplasia (BPH).[3]

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5-ARIs: biochemistry, physiology and side effects

5-ARIs block the conversion of testosterone to dihydrotestosterone. There are three commercially available 5-ARIs in the United States. Finasteride (Proscar) is an orally active, competitive inhibitor of nicotinamide adenine dinucleotide phosphate, reduced from (NADPH) -dependent 5AR enzyme's type 2 isoenzyme.[4] Despite its steroid structure, it has no affinity for any steroid receptors, including androgens, estrogens and progesterone.[5] Finasteride has been shown to suppress serum DHT to approximately 70% of baseline levels in human males.[5-7] Propecia is a 1 mg formulation of finasteride used for male pattern hair loss.

Dutasteride (Avodart) is an inhibitor of both isoenzymes (type 1 and type 2) of 5-AR. Nonselective inhibition of both isoenzymes produces more than a 90% reduction in serum DHT.[4,8] Type 2 5-AR is the predominant isoenzyme within the prostate. Its inhibition by finasteride may lead to upregulation of type 1 5AR in extraprostatic sites (liver and skin) with consequent paracrine effects and elevated serum DHT on the prostate.[4,8] The half-life of finasteride is 5 to 8 hours, whereas the half-life of dutasteride is about 180 hours.[8,9]

Some investigators have reported increases in both or either serum testosterone and estrogens in patients receiving 5-ARIs.[10-12] However, a recent meta-analysis concluded that reported increases in T levels with finasteride or dutasteride in men with low baseline serum T may be attributed, in part, to increased trapping of T by unsaturated sex hormone binding globulin (SHBG) due to the dissociation of 5 alpha dihydrotestosterone. In men with high baseline T levels, there appears to be no change in serum T levels.[13] Ten studies reported LH, FSH, SHBG and estradiol values and none reported significant changes in these levels, suggesting that observed changes in serum T levels are unlikely mediated by gonadotropins or peripheral conversion of T to estradiol.[13]

The most common side effects of 5-ARIs include impotence, decreased libido, ejaculatory disorders and gynecomastia.[14] Less common side effects that have been reported include infertility, breast tenderness, depression, anxiety, dementia and suicide.[15-18] Finasteride has also been associated with intraoperative floppy iris syndrome and cataract formation.[19,20]

5-ARIs and PSA levels

It has been generally accepted that for men who have been on 5-ARIs for 6 months, that their measured serum PSA level should be doubled for proper interpretation.[21] However, there is some evidence that doubling of the PSA may actually be an underestimation. The Enlarged Prostate International Comparative Study (EPICS) reported similar median PSA suppression for both finasteride and dutasteride of approximately 55% at 12 months.[22] Finasteride treatment in the Proscar Long Term Efficacy and Safety Study (PLESS) trial resulted in a median change of 57% after 4 years.[23] Marks et al reported that dutasteride treatment resulted in a median change in PSA of 66% at 4 years[24] and proposed that a PSA increase from nadir of 0.3 ng/mL could represent an alternative to the doubling rule of PSA adjustment for patients on 5-ARIs.[24]

5-ARIs and BPH

Seminal studies were performed to examine the efficacy of treating the signs and symptoms of BPH with finasteride and dutasteride, respectively. The Prostate Long-Term Efficacy and Safety Study (PLESS) was a randomized double-blind study that evaluated the effect of two doses of finasteride (1 mg and 5 mg) and placebo each given once daily for 12 months in 895 men with prostatic hyperplasia.[7] Compared to men in the placebo group, the men treated with 5 mg of finasteride per day had a significant decrease in total urinary symptom scores ($p < 0.001$), an increase of 1.6 mL/second (22%, $p < 0.001$), in the maximal urinary flow rate and a 19 percent decrease in prostatic volume ($p < 0.001$). The men treated with 1 mg of finasteride per day did not have a significant decrease in total urinary symptom scores, but had an increase of 1.4 mL/second (23%) in the maximal urinary flow rate, and an 18% decrease in prostatic volume. The men who received placebo had no change in total urinary symptom scores, an increase of 0.2 mL/ second (8%) in maximal urinary flow rate and a 3 percent decrease in prostatic volume.[7]

Continuing the evaluation of finasteride for the treatment of BPH, McConnell et al published the effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with BPH.[25] In a double-blind, randomized, placebo-controlled trial they enrolled 3040 men with moderate to severe urinary symptoms and enlarged prostate glands who were treated daily with 5 mg of finasteride for 4 years. During the 4 year study period, 152 of the 1503 men in the placebo group (10%) and 69 of the 1513 men in the finasteride group (4.5%) underwent surgery for BPH for a 55% risk reduction for those men on finasteride. Acute urinary retention developed in 99 men (7%) in the placebo group and 42 men (3%) in the finasteride

group for a 57% risk reduction in those men receiving finasteride. Among those men who completed the study, the finasteride group had a 3.3 reduction in symptom score versus 1.3 in the placebo group ($p < 0.001$). In these men, there was an 18% decrease in prostate volume in the finasteride group versus a 14% increase in the placebo group at the end of 4 years.[25]

Dutasteride was examined in a similar manner to finasteride. The efficacy and safety of dutasteride was evaluated by a pooled analysis of three randomized, double-blinded, placebo-controlled, parallel-group clinical trials of 2 years duration followed by a 2 year open-label extension.[26,27] A total of 4235 patients were enrolled. At the conclusion of 2 years of follow up, the symptom score decreased by -4.5 in the dutasteride group compared to -2.3 in the placebo group. Prostate volume in the dutasteride group was decreased by 25.7% compared to baseline versus an increase in prostate volume of 1.7% in the placebo group. With 2 years of follow up, dutasteride therapy reduced the risk of BPH related surgery by 48% and acute urinary retention by 57% compared to placebo.[14,26] The FDA approved finasteride for the treatment of BPH in 1992 and dutasteride received FDA approval for BPH treatment in 2001.[27]

5-ARIs and prostate cancer

The next question to be addressed was whether 5-ARIs could serve as chemopreventive agents for prostate cancer. Two major trials, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) were undertaken to answer this question for finasteride and dutasteride, respectively.

The PCPT enrolled men who were 55 years old and above, were in good health and had no evidence of prostate cancer. The participants had to have a PSA of 3.0 ng/mL or less and a normal DRE at the time of entry into the study. Ultimately 18.882 men were recruited for the study. At the conclusion of the study period, each participant who had not been diagnosed with prostate cancer was asked to have a prostate biopsy. If during the study, a PSA screening value or DRE became abnormal, the man was recommended to undergo a prostate biopsy "for cause." At the conclusion of the 7 year study, 18.4% of the finasteride group developed prostate cancer compared to 24.4% in the placebo group for a 24.8% ($p < 0.001$) reduction in prevalence over the 7 year study period.[28] However, high grade disease (Gleason score 7-10) was more common in the finasteride group (6.4%) than in the placebo group (5.1%) ($p = 0.005$).[29] Although the study confirmed the potential for finasteride to serve as a chemopreventive agent for the development of prostate cancer, there was no obvious biological reason why finasteride would cause more high grade tumors. Subsequently, this apparent paradox has been extensively examined.

Several explanations for this observation have been proposed. First, 5-ARIs shrink prostate volume, thus making it more likely to find high grade disease when it is present.[29-31] Second, the 5-ARIs, by decreasing the confounding PSA from BPH, heighten the sensitivity of the PSA and DRE in the detection of high grade disease.[29,31,32] An analysis by Thompson et al revealed that the sensitivity and area under the receiver operating characteristic curve (AUC) of PSA for detecting prostate cancer was higher for men in the finasteride group at all PSA cutoffs matched by specificity.[32] It appears that a combination of cancer chemoprevention, PSA reduction from benign disease and an increased sensitivity of PSA for high grade prostate cancer may have resulted in the increased rate of detection of high grade cancer in the finasteride group, despite the overall reduction of the incidence of prostate cancer diagnosis.[4]

Long term follow up of the PCPT strongly suggests that any sequelae of potential risk for high grade cancer appears to be minimal, if at all. Thompson et al reported an 18 year follow up of patients in the PCPT.[33] Of the 18,880 men who underwent randomization, the prostate cancer rate was 10.5% in the finasteride group and 14.9% in the placebo group.[33] Of the men who were evaluated, the high grade cancer (Gleason score 7-10) was 3.5% versus 3.0% in the finasteride and placebo groups, respectively. The 10 year survival rates were 83.0% in the finasteride group and 80.9% in the placebo group for men with low grade prostate cancer and 73.0% and 73.6%, respectively, for those individuals with high grade cancer.

The REDUCE trial found results similar to those of the PCPT. In the REDUCE trial, 6279 men, aged 50-75 years, were treated with dutasteride 0.5 mg/day of placebo for 4 years. At the end of 4 years, there was a relative risk reduction of 22.8% ($p < 0.001$) in the dutasteride group. During the first 2 years of the trial, there were 141 more tumors with a Gleason of 5 to 7 in the placebo group than in the dutasteride group (558 of 3346 participants versus 417 of 3239 participants). The number of tumors with a Gleason score of 8-10 was similar in the two groups, 18 and 17 respectively. During years 3 and 4, however, there was only one tumor with a Gleason score of 8-10 detected among the 2343 men in the placebo group, whereas 12 high grade cancers were found in the 2447 men in the dutasteride group ($p = 0.003$). The authors speculated that if the men in the placebo group who had the 141 excess

tumors with a Gleason score of 5 to 7 during the first 2 years of the study had not been withdrawn as the trial protocol required, a proportion of the cancers might have been upgraded on biopsy during years 3 and 4.[34]

However, the controversy regarding the relationship between 5-ARIs and high grade prostate cancer is ongoing and unresolved. Kumar et al[35] used the Surveillance, Epidemiology and End Results Program-Medicare linked database and identified patients with stage I to IV prostate cancer known PSA level at diagnosis between January 1, 2008 and December 31, 2013. The final cohort included 30,313 patients with a median (interquartile range) follow up of 3.75 years. A total of 2373 patients (7.83%) were prescribed 5-ARIs at least 6 months before prostate cancer diagnosis with a median (interquartile range) treatment duration of 2.41 years. The 4 year cumulative incidence of death from prostate cancer was 5.3% in 5-ARI users and 2.8 % in nonusers. Compared with participants who did not receive ARIs, those who did were more likely to present with disease that was high grade (Gleason score 8-10) (18% versus 29%) respectively. No specific explanation was provided for these findings other than a need for increased awareness of 5-ARI induced PSA suppression and clearer guidelines for early prostate cancer detection.

5-ARIs and male pattern baldness

By the age of 30, 30% of white men have androgenetic alopecia; this increases to 50% by the age of 50. White men are four times more likely than black men to develop premature balding.[36,37] Hair loss does not actually start until after puberty and the rate of progression is extremely variable.[38] One study found an average rate of hair loss of about 5% per year.[37] The hair loss seen in androgenic alopecia is a result of stepwise miniaturization of the hair follicle and changes in hair cycle dynamics.[36,39] Androgenic alopecia is induced by activation of follicular androgen receptors by dihydrotestosterone.[38]

Finasteride at a dose of 1 mg/day (Propecia) was evaluated for the treatment of male pattern baldness. A group of 1879 men received oral finasteride, 1 mg per day. In men with vertex hair loss, global photographs showed improvement in hair growth of 48% of finasteride patients at 1 year and 66% at 2 years compared to 7% of placebo patients.[40] Side effects were observed and included decreased libido, ejaculatory disorders and erectile dysfunction. These events occurred in 3.8% of the finasteride patients and 2.1% of placebo patients. If the medication is stopped, hair loss will continue.[41] Propecia was approved in 1997 for the treatment of male pattern baldness.[27]

5-ARIs in females

At present, minoxidil is considered the first-line therapy for female pattern alopecia. However, finasteride and dutasteride are being more commonly used.[42] 5-ARIs should not be used in women who are pregnant or who may become pregnant as they can increase the risk of abnormal male external genital development including hypospadias.[40]

Conclusion

5-ARIs are a major component of the urological pharmacopeia. A knowledge of their mechanism of action, indications and potential side effects are essential to good urologic practice. □

References

1. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5-alpha reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 1974;186(4170):1213-1215.
2. Walsh PC, Madden JD, Goldstein JL, McDonald PC, Wilson JD. Familial incomplete male pseudohermaphroditism, type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *N Engl J Med* 1974;291(18):944-949.
3. Freudenheim M. Keeping the pipeline filled at Merck. NY Times 2/16/1992.
4. Hudak SJ, Hernandez J, Thompson IM. Role of 5-alpha reductase inhibitors in the management of prostate cancer. *Clin Interv Aging* 2006;1(4):425-431.
5. Stoner,E. The clinical effects of 5-alpha reductase inhibitor, finasteride, on benign prostatic hyperplasia. The Finasteride Study Group. *J Urol* 1992;147(5):1298-1302.
6. Rittmaster RS, Stoner E, Thompson et al. Effect of MK-906, a specific 5-alpha reductase inhibitor, on serum androgens and androgen conjugates in normal men. *J Androl* 1989;10(4):259-262.
7. Gormley GJ, Stoner E, Bruskewitz RC et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. *N Engl J Med* 1992;327(17):1185-1191.
8. Bramson HN, Hermann D, Batchelor KW et al. Unique preclinical characteristics of GC745, a potent dual inhibitor of 5 AR. *J Pharmacol Exp Ther* 1997;282(3):1496-1502.
9. Steiner JF. Clinical pharmacokinetics and pharmacodynamics of finasteride. *Clin Pharmacokinet* 1996;30(1):16-27.
10. Castro-Magano M, Angulo M, Fuentes B et al. Effect of finasteride on human testicular steroidogenesis. *J Androl* 1996;17(5):516-521.
11. Roehrborn CG, Lee M, Meehan A et al. Effects of finasteride on serum testosterone and body mass index in men with benign prostatic hyperplasia. *Urology* 2003;62(5):894-899.
12. Yao S, Till C, Kristal AR et al. Serum estrogen levels and prostate cancer risk in the Prostate Cancer Prevention Trial: a nested case-control study. *Cancer Causes Control* 2011;22(8):1121-1131.
13. Traish AM, Krakowsky Y, Duros G et al. Do 5-alpha reductase inhibitors raise circulating serum testosterone levels? A comparative review analysis to explaining paradoxical results. *Sex Med Rev* 2019;7(1):95-114.

14. Nickel JC. Comparison of clinical trials with finasteride and dutasteride. *Rev Urol* 2004;6(Suppl9):S31-S39.
15. 5-Alpha Reductase Inhibitor. Wikipedia. https://en.wikipedia.org/wiki/5%CE%B1-Reductase_inhibitor. Accessed 8/27/18.
16. Trust L, Saitz TR, Hellstrom WJ. Side effects of 5-alpha reductase inhibitors: A comprehensive review. *Sex Med Rev* 2013;1(1):24-41.
17. Welk B, McArthur E, OrdonM et al. Association of suicidality and depression with 5-alpha reductase inhibitors. *JAMA Intern Med* 2017;177(5);683-691.
18. Welk B, McArthur E, Ordon M et al. The risk of dementia with the use of 5- alpha reductase inhibitors. *J Neurol Sci* 2017;379:109-111.
19. Wong ACM, Mak ST. Finasteride-associated cataract and intraoperative floppy-iris syndrome. *J Cataract Refract Surg* 2011;37(7):1351-1354.
20. Issa SA, Dagres E. Intraoperative floppy-iris syndrome and finasteride intake. *J Cataract Refract Surg* 2007;33(12):2142-2143.
21. Guess HA, Heyse JF, Gormley GJ. The effect of finasteride and prostate specific antigen in men with benign prostatic hyperplasia. *Prostate* 1993;22(1):31-37.
22. Goldenberg L, So A, Fleshner N et al. The role of 5-alpha reductase inhibitors in prostate pathophysiology: Is there an additional advantage to the inhibition of type 1 enzyme? *Can Urol Assoc J* 2009;3(Suppl 2):S109-S114.
23. Andriole GL, Guess HA, Epstein JI et al. Treatment with finasteride preserves usefulness of prostate specific antigen in the detection of prostate cancer: results of a randomized, double-blind controlled clinical trial. PLESS Study Group, Proscar Long-term Efficacy and Safety Study. *Urology* 1998;52(2):195-201.
24. Marks, LS, Andriole GL, Fitzpatrick JM et al. The interpretation of serum prostatic antigen in men receiving 5-alpha reductase inhibitors: a review and clinical recommendations. *J Urol* 2006; 176(3):868-874.
25. McConnell JD, Bruskewitz R, Walsh PC et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical intervention among men with benign prostatic hyperplasia. *N Engl J Med* 1998;338(9):557-563.
26. Roehrborn CG, Boyle P, Nickel JC et al. Efficacy and safety of a dual inhibitor of 5-alpha reductase types 1 and 2(dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002;60(3):434-441.
27. https://www.drugs.com. Accessed 4/29/2019
28. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349(3);215-224.
29. Hamilton RJ, Freedland SJ. 5-alpha reductase and prostate cancer prevention : Where do we go from here? *BMC Med* 2011;9: 105-117.
30. Kulkarni GS, Al-Azab R, Lockwood et al. Evidence for a biopsy derived grade artifact among larger prostate glands. *J Urol* 2006; 175(2):505-509.
31. Thompson IM, Tangen CM, Goodman PJ et al. Finasteride improves the sensitivity of digital rectal examination for prostate cancer detection. *J Urol* 2007;177(5):1749-1752.
32. Thompson IM. Chi C, Ankerst DP et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006;98(16):1128-1133.
33. Thompson IM, Goodman PJ, Tangen CM et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med* 2013;369(7):603-610.
34. Andriole GL, Bostwick DG, Brawley OW et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010; 362(13):1192-1202.
35. Kumar A, Nalawade V, Riviere P et al. Association of treatment with 5 alpha reductase inhibitors and prostate cancer mortality among older adults. *JAMA Netw Open* 2019; 2(10):e1913612.
36. Sinclair R. Male pattern androgenic alopecia. *Brit Med J* 1998; 317:865-869.
37. Setty LR. Hair patterns of the scalp of white and Negro males. *Am J Phys Anthropol* 1970;33:49-55.
38. Rushton DH, Ramsay ID, Norris MJ et al. Natural progression of male pattern baldness in young men. *Clin Exp Dermatol* 1991; 16:188-192.
39. Curtois M, Loussouarn G, Horseau C et al. Hair cycle and alopecia. *Skin Pharmacol* 1994;7:84-89.
40. McClellan K, Markham A. Finasteride: a review of its use in male pattern hair loss. *Drugs* 1999;57(1):111-126.
41. Newman T. Everything you need to know about DHT. Medical News Today https://www.medicalnewstoday.com/articles/68082.php
42. Hirshburg JM, Kelsey PA, Therrien C et al. Adverse effects and safety of 5-alpha reductase inhibitors(finasteride, dutasteride): a systematic review. *J Clin Aesthet Dermatol* 2016;9(7):56-62.