

## CLINICAL PERSPECTIVE

# Proscar and Propecia—A Therapeutic Perspective

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The initial observation that the prostate could convert testosterone to dihydrotestosterone (DHT) (1), *e.g.* contained 5 $\alpha$ -reductase activity, was the first of a long succession of pieces of evidence that DHT might be important in the pathogenesis of benign prostatic hyperplasia (BPH). In 1980 it was hypothesized that: "Treatment directed at inhibiting 5 $\alpha$ -reductase activity (and consequently dihydrotestosterone formation). . . might inhibit further prostatic growth and/or induce regression of the prostate without causing impotence or other manifestations of hypogonadism" (2). This hypothesis was consistent with observations in a group of patients with a genetic deficiency of 5 $\alpha$ -reductase who had, among other phenotypic abnormalities, small prostates (3). A few years later it was demonstrated that the oral administration of a 5 $\alpha$ -reductase inhibitor prevented the testosterone-motivated increase in prostate size and weight in castrated dogs (4). Although BPH in dogs is an imperfect model for BPH in humans, it is probable that this proof of principle served as the impetus for human studies, which demonstrated the convincing efficacy of this drug for BPH (5, 6) and led to its (finasteride 5 mg, Proscar) approval for use by the Federal Drug Administration.

Two years after (1994) the approval of Proscar for BPH, a trial began to determine whether it could decrease the incidence of prostate cancer; the subjects were men 55 yr of age and older. The major result of the trial, a decrease in the incidence of low-grade prostate cancers accompanied by an absolute and relative increase in high-grade prostate cancers (Table 1), was surprising and led to discontinuation of the trial before its planned ending (7). *The New England Journal of Medicine* (NEJM) believed the results of the study to be of sufficient import to release them weeks before they appeared in print and to warrant the publication of both an accompanying editorial (8) and a perspective (9). The accompanying editorial by Scardino (8) concluded that Proscar probably should not be used for the prevention of prostate cancer, but

Abbreviations: BPH, Benign prostatic hyperplasia; DHT, dihydrotestosterone.

Proscar and Propecia are trade names for the same drug, finasteride. The difference between the two is in dosage and indication. Proscar is 5 mg of finasteride and is indicated for the treatment of BPH. Propecia is 1 mg of finasteride and is indicated for the treatment of male pattern baldness.

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that, based on his view of its risk to benefit ratio, it remained reasonable to use it for the treatment of BPH. Unlike Scardino, the authors of the article refrained from making specific recommendations on the use or nonuse of the drug. For a variety of reasons, the interpretation of the data is moderately contentious, as attested to by a series of letters in the NEJM (10–16) in October 2003, and a "News" article in the *Journal of the National Cancer Institute* (JNCI) (17) that swiftly followed the release of the results of the study.

Although the issue of using Proscar to treat BPH has been addressed, there remains the question of how to advise patients who take Propecia (finasteride, 1 mg) for the treatment of baldness. This concern was not raised in the article itself, in the NEJM editorial, in the discussion in the JNCI, or in the correspondence in the October issue of the NEJM. This is a most significant oversight because the effects of 1 and 5 mg of finasteride result in more or less equal changes in serum DHT and testosterone (Refs. 18 and 19 and Fig. 1A), prostatic DHT and testosterone (Ref. 19 Fig. 1B), and scalp DHT (Refs. 18 and 20 and Fig. 1C). A subsequent study (21) confirmed the lack of difference in blood, but found a significantly greater fall in prostate DHT for the 5-mg than the 1-mg dose (placebo, 18.6 nmol/kg; 1 mg, 3.8 nmol/kg; 5 mg, 1.0 nmol/kg;  $P = 0.049$  between the two doses of finasteride) after 6–8 wk of treatment. It is important to recall that these hormonal surrogates for clinical efficacy formed the most important basis for the early dose-ranging studies of this drug, which, in turn, led to the choice of the doses to be used in the large clinical trials addressing efficacy. The defining large trial (5) assessed efficacy in almost 900 men given placebo or 1 or 5 mg finasteride. At the end of 1 yr, 5 mg finasteride improved total urinary-symptom scores compared with placebo, whereas 1 mg did not. However, there was no difference between the doses in their effect on either prostate size or maximum urinary flow rate. Both were equally better than placebo. Thus, at least for purposes of this discussion, it is both conservative and reasonable to presume that the long-

**TABLE 1.** Gleason scores for prostate cancers detected and graded [adapted from Thompson *et al.* (7)]

	Placebo	Finasteride
Total cancers	1068 <sup>a</sup>	757
Grade 2–6 cancers	831 <sup>a</sup>	477
Grade 7–10 cancers	237 <sup>a</sup>	280

<sup>a</sup> Significantly different from finasteride,  $P < 0.001$ .

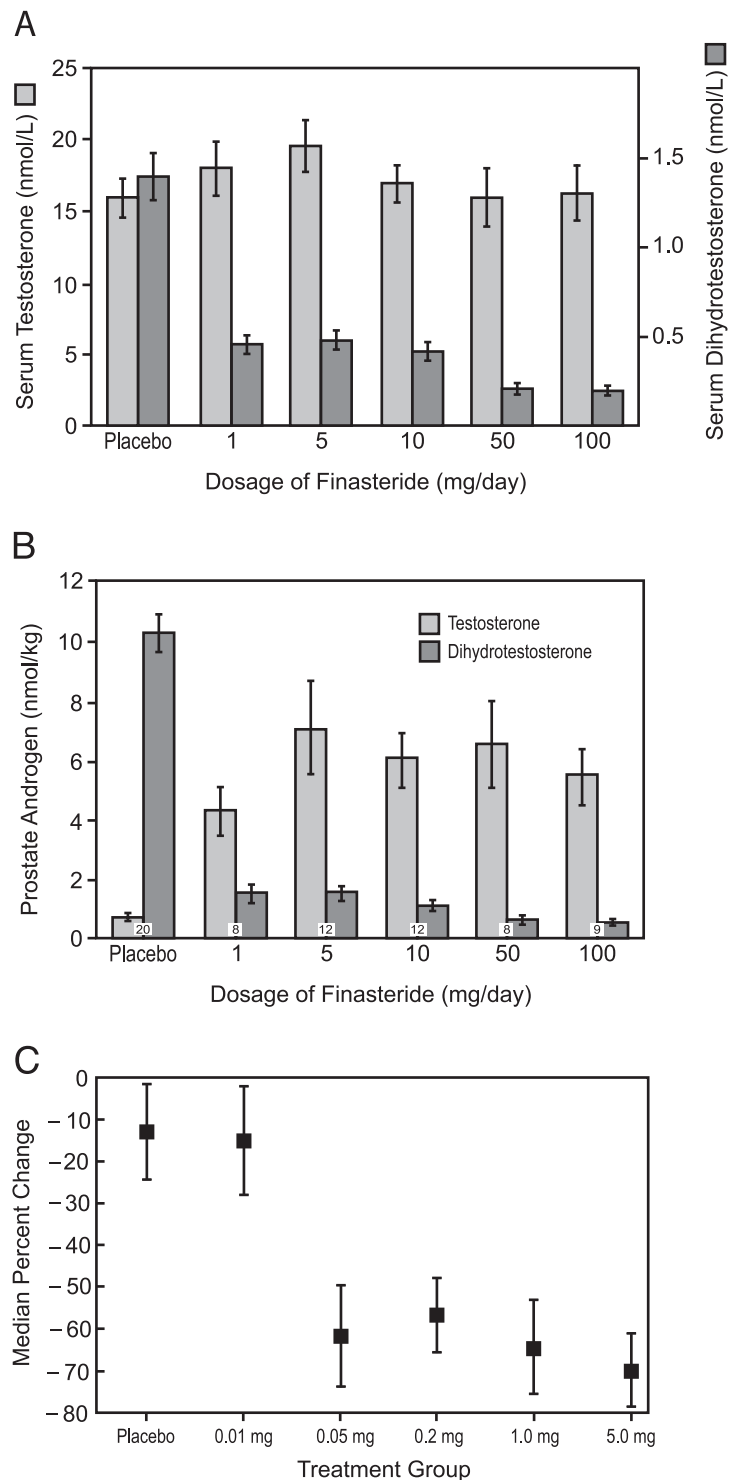


FIG. 1. A, Serum androgen levels in men treated with the indicated doses of finasteride for 7 d before prostate surgery. Serum was drawn on the day of surgery, and androgens were assayed by RIA. Each bar represents the mean  $\pm$  SEM. Figure (redrawn) and legend adapted from McConnell *et al.* (19). B, Men with benign prostatic hyperplasia who were scheduled for prostate resection surgery were treated orally with 1.5, 10.5, and 100 mg/d finasteride or placebo for 7 d immediately before surgery. Androgens were measured by RIA in samples removed at the time of surgery. Each bar represents the mean  $\pm$  SEM for the number of patients indicated. Figure (redrawn) and legend adapted from McConnell *et al.* (19). C, Median percent change from baseline in scalp skin DHT according to dose of finasteride. Figure (redrawn) and legend adapted from: Food and Drug Administration Approval Package for NDA 20-788 (Propecia Tablets, 1 mg); December 19, 1997, cited in Ref. 20.

term effects of 1 and 5 mg finasteride, in regard to prostate cancer, will not differ.

The biology of the relationship between testosterone, DHT, and the etiology of prostate cancer was—and is—less clear than the relationship between these steroids and BPH. Although the steroidal surrogates correctly predicted the efficacy of Proscar in BPH, its action on the prevention of prostate cancer appears mixed. This issue is now unsettled,

but raises concern for those in whom finasteride is used for a cosmetic rather than a moderately severe medical problem (BPH). This predicament resolves itself into two separate but related questions. First, is the observed decrease in low-grade prostate cancer worth the tradeoff for an increased risk of high-grade cancers in patients with BPH? Unfortunately, the data do not furnish an unambiguous answer to this question; furthermore, it is not an issue that has escaped the attention

of the medical community. For the moment anyway, it appears that the benefits of therapy with finasteride for BPH are probably worth the risk. Second, and more problematic, is the fact that there has been no open discussion of the potential danger in the long-term use of Propecia.

We need to think seriously about the large group of men, younger by far than those with prostate disease, who use finasteride for hair loss and not for symptoms arising from BPH. Bear in mind that the treatment of alopecia with finasteride is a lifelong commitment and that “lifelong” means a long time for young men. Will these patients be protected from prostate cancer, or are they at greater risk of serious disease? Whatever the answer, because of the prospect of many years of use, there should be a sense of urgency in sorting out this dilemma. In the interim, physicians and their patients should at least be aware of the potential risks and together should evaluate the use of Propecia for baldness. For my part, I will stay with the tried and true, “first do no harm.”

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