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Chemoprevention Strategies for Prostate Cancer: The Role of 5α-Reductase Inhibitors

Glenn J. Gormley, M.D., Ph.D.

Department of Endocrinology and Metabolism, Merck Research Laboratories, Rahway, New Jersey 07065

Abstract Prostate cancer is a major health problem for the aging male population. Despite hormonal dependence, the inevitable emergence of androgen insensitive tumors, which have a dismal prognosis, highlights the need to develop prevention strategies such as chemoprevention. An acceptable agent must interfere with either the process of carcinogenesis or tumor growth, and have minimal toxicity. In clinical studies, 5α-reductase inhibitors have been shown to suppress serum and intraprostatic levels of dihydrotestosterone, an important promoter of prostate cancer, leading to reduction in prostate size and suppression of glandular cell activity as measured by prostate specific antigen secretion. In addition, 5α-reductase inhibitors have demonstrated an excellent safety profile and tolerability in 12 month controlled clinical trials. No significant metabolic effects have been observed in gonadotropin secretion, spermatogenesis, serum lipids or glucose tolerance. The efficacy and safety of 5α-reductase inhibitors in studies to date, combined with the androgen dependence of tumor production, strongly supports investigating their use for chemoprevention of prostate cancer.

Key words: chemoprevention, finasteride, prostate cancer, 5α-reductase

Adenocarcinoma of the prostate has become the most common cancer found in men over the age of 40, accounting for more than 33,000 deaths each year [1,2]. The lifetime probability of developing prostate cancer among men in the United States has been estimated to be 5 to 10% depending on race and ethnic background [3]. Once the diagnosis has been established, treatment depends on clinical and pathologic staging. Patients with organ-confined tumors can potentially be cured with surgical resection of the prostate. However, pathologic staging at the time of surgery often reveals evidence of capsular penetration. For those patients with local or distant metastasis, systemic therapy is commonly employed, usually in the form of hormonal ablation [4,5]. The hormonal dependence of prostatic growth has been well established [5,6]. This has led to the understanding that medical therapies which deprive the tumor of androgens can significantly reduce tumor volume and delay progression of the disease. Unfortunately, many patients treated with medical or surgical castration eventually develop hormonally resistant disease which is rapidly progressive and usually fatal. The mechanism for developing hormonal independence is unknown but the two most frequently debated theories are:

1. Cellular adaptation of tumor cells due to growth in an androgen-depleted environment leading to progressive loss of androgen dependence [7];
2. Growth of a preexisting androgen-insensitive clone of tumor cells as the androgen-sensitive clone(s) are inhibited by the androgen-depleted environment [7].

The inevitable emergence of androgen-insensitive tumors, which are refractory to conventional chemotherapy, highlights the need to develop and test chemoprevention strategies for prostate cancer. There is little doubt that a therapy which can prevent prostate cancer, even in a relatively small proportion of the aging male population, will have a major impact on human health. A viable agent for chemoprevention must have the potential to interfere with a critical step in either the process of carcinogenesis or tumor growth. At the same time the toxicity of such an agent must be extremely small because those receiving it would be relatively young

TABLE I. Pubertal and Postpubertal Roles of Testosterone and Dihydrotestosterone

- Testosterone-Mediated

  Penile and Scrotal Enlargement
  Spermatogenesis
  Vocal Cord Enlargment
  Muscle Mass Increase
  Male Libido and Sexual Performance

- Dihydrotestosterone-Mediated

  Increase in Body and Facial Hair
  Acne
  Scalp Hair Recession
  Prostate Enlargement

TABLE II. Metabolic Effects of Finasteride

- Clinically Significant Reduction In:

  Serum and Intraprostatic DHT
  Serum and Intraprostatic PSA

- Significant Increase In:

  Intraprostatic Testosterone

- No Clinically Significant Change in Serum:

Testosterone	Thyroid Function
LH or FSH	Lipid Profile
Cortisol	Glucose Tolerance
Prolactin	Routine Biochemistry
Estradiol	or Hematology

and healthy. Indeed, a strategy for chemoprevention of prostate cancer would require exposing a large number of men to an agent over many years in order to benefit the 5 to 10% of men destined to develop the disease. In this context, a pure 5α-reductase inhibitor has the potential to remove an important promoter of prostate cancer, dihydrotestosterone (DHT) [8,9], with minimal toxicity. The rational and experimental evidence for this approach to chemoprevention are outlined below.

ANDROGEN DEPENDENCE OF THE PROSTATE

The prostate gland is dependent on androgen stimulation both for embryologic development and for maintenance of its size and function in mature men. The crucial role of DHT in this process was established when the genetic syndrome of 5α-reductase deficiency was described [10,11]. Affected men lack the enzyme 5α-reductase and are therefore unable to convert testosterone into the more potent androgen DHT. This defect results in ambiguous genitalia at birth, undescended testes and an underdeveloped prostate gland. With the onset of puberty, testosterone levels rise as the testes descend and at least partial masculinization occurs characterized by penile enlargement, scrotal rugae with hyperpigmentation, growth of male pubic hair, and increased muscle mass. Despite these androgen-mediated changes, the prostate glands from 15 post-pubertal men have remained underdeveloped [12,13], and prostate cancer has not been reported. These observations have led to the conclusion that in man, testosterone and DHT have separate functions (Table 1), with DHT actively modulating prostate growth.

The 5α-reductase enzyme is a membrane-bound NADPH-dependent protein which metabolizes testosterone to DHT [14] within androgen-dependent target cells (Figure 1). Although both steroids can bind to the androgen receptor and produce androgen-mediated effects, DHT has a greater affinity for the receptor [15]. In animals prostate growth appears to be controlled by a feed-forward mechanism mediated by DHT which induces 5α-reductase enzyme activity and 5α-reductase messenger RNA expression [16]. Two 5α-reductase inhibitors, finasteride [17] and SKF105657 [18], have been shown to significantly reduce prostate size in animals. In rats, finasteride treatment decreases prostatic DNA content without inducing testosterone-repressed prostate message (TRPM-2) expression which suggests that 5α-reductase inhibition leads to cell loss by mechanisms other than apoptosis [19]. In man both normal and hyperplastic prostate tissue contain significant amounts of 5α-reductase [20-22]. In addition, 5α-reductase has been observed in human prostate cancer and in several androgen-dependent tumor cell lines including the Dunning tumor and the Noble rat PR-129 adenocarcinoma [20,21]. Several studies have demonstrated a tumor-suppressing effect of 5α-reductase inhibition in animal models [23,24] and in man [25] but this has not been confirmed in all studies [26].

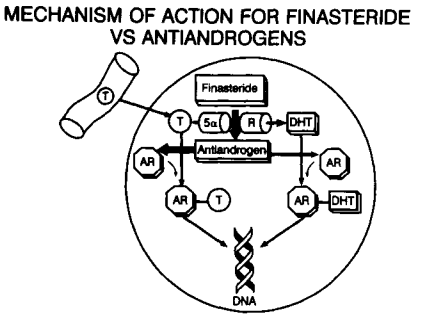

Fig. 1 Site of action of finasteride and antiandrogens. T = testosterone; DHT = dihydrotestosterone; AR = androgen receptor, 5α-R = 5α-reductase.

CLINICAL PHARMACOLOGY OF FINASTERIDE

Finasteride (MK-906, PROSCAR®) is a steroid analog of testosterone which inhibits 5α-reductase, blocking the conversion of testosterone to DHT without interfering with androgen receptor binding [14,27,28]. This allows testosterone-dependent functions (Table 1) to remain unaffected while DHT-mediated functions are suppressed. This is in contrast to the effects of antiandrogens which block both testosterone- and DHT-mediated functions by inhibiting androgen receptor binding (Figure 1). The known metabolic effects of pharmacologic 5α-reductase inhibition in man are summarized in Table 2, and are consistent with its selective mechanism of action.

Clinical studies in men with benign prostatic hyperplasia (BPH) have demonstrated that treatment with finasteride (5 mg daily) results in suppression of serum and intraprostatic DHT to castrate levels [29,30] resulting in a significant reduction in prostate size (Figure 2A). The magnitude of this effect is similar to reports in patients with BPH receiving LHRH analogs (24% reduction) [31] or surgical castration (31% reduction) [32]. The reduction in prostate size during treatment with finasteride was associated with a 40 to 50% reduction in prostate specific antigen (PSA) indicating suppression of prostate glandular cell activity (Figure 2B). These changes in prostate physiology resulted in progressive improvement in maximum urinary flow rates and improvement in the symptoms of BPH [33].

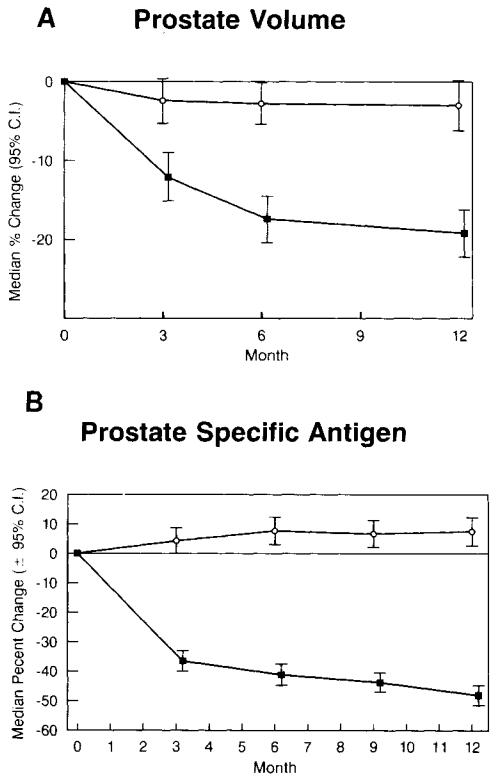

Fig. 2 Change in prostate volume (2A) and PSA (2B) during one year of treatment with placebo (---0---) or 5 mg finasteride (---• ---) [reproduced from Gormley (1991) with permission from the publisher].

In clinical studies involving more than 1600 patients with a mean age of 65 years [33], finasteride was well tolerated. Only 1.7% of patients dropped out due to drug-related adverse experiences. During 12 months of treatment only sexually-related adverse experiences were significantly different from placebo. These adverse experiences were reported in 10.8% of men taking 5 mg of finasteride and 5.2% of men taking placebo. The number of men diagnosed with prostate cancer (5 on 5 mg of finasteride and 4 on placebo) was not significantly different between the treatment groups. However, a measurable decrease in prostate cancer incidence would not be expected after only 12 months of treatment. A recently completed pilot study in men with Stage D prostate cancer [34] demonstrated that treatment with finasteride could significantly reduce PSA levels by 20% within 6 weeks with no significant adverse experiences.

SUMMARY

The high incidence of prostate cancer in men with normal-functioning testes compared to the virtual absence of this disease in pre-pubertally castrated men, men with 5α-reductase deficiency, and men with androgen insensitivity syndrome, supports the hypothesis that life-long exposure to androgens is a critical factor in the development of prostate cancer. A specific 5α-reductase inhibitor can suppress DHT and thus has the potential to remove an important promoter of prostate cancer leading to a protective effect against tumor formation and growth. This can be accomplished with minimal toxicity as demonstrated in the treatment of men with BPH. In addition, given the large number of men who might receive such a drug for prostate cancer chemoprevention, there are other potential benefits to the patient since the development of an enlarged, hyperplastic prostate during treatment is unlikely. It is therefore reasonable to consider 5α-reductase inhibitors in the search for chemoprevention strategies for prostate cancer.

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