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THE CLINICAL DEVELOPMENT OF A 5α-REDUCTASE INHIBITOR, FINASTERIDE

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Summary—Finasteride, a 4-aza steroid compound, is an orally active inhibitor of the 5α-reductase enzyme. 5α-Reductase is necessary for the metabolism of testosterone (T) to dihydrotestosterone (DHT) and is found in high levels only in certain tissues such as the prostate. Finasteride has been shown to markedly suppress serum DHT levels in man without lowering testosterone levels. In patients with benign prostate hyperplasia (BPH), finasteride was found to decrease prostate volume by a mean of 28% over a period of 6 months, without causing clinically significant adverse effects. DHT appears to be the primary androgen for prostatic growth. Selective inhibition of 5α-reductase by finasteride may provide a novel approach to BPH therapy by reducing prostate size without affecting T-dependent processes such as fertility, muscle strength, and libido. The clinical development of finasteride for the treatment of benign prostate hyperplasia is reviewed.

INTRODUCTION

Enlargement of the prostate gland, medically termed benign prostatic hyperplasia (BPH), is a common consequence of the normal male aging process. The majority of the men over the age of 55 (in the U.S. approx. 10,000,000 males) exhibit some degree of prostatic enlargement, and many show a resultant partial urinary obstruction. The current therapy for men with urinary flow obstruction is surgical resection of prostate tissue. BPH is presently the second leading indication for surgery in American men. Transurethral resection under spinal anesthesia is the usual procedure with a mortality of approx. 1% [1]. Although urinary incontinence and impotence are uncommon complications following surgery, recurrence of urinary obstruction can occur in up to 20% of patients. Therefore an effective medical treatment for BPH would be an important therapeutic advance.

The observation that androgen deprivation induces shrinkage of hyperplastic tissue in the human prostate provides the basis for treatment of BPH with hormonal modulation. During the last 20 years several drugs producing androgen deprivation have been developed. However, most of these agents successfully shrink the prostate by blocking testosterone; as a consequence, they cause undesirable side effects such as gynecomastia and impotence. Specific inhibition of androgen action in the prostate gland is possible by blocking the action of testosterone (T) to the more potent androgen dihydrotestosterone (DHT). DHT is formed from T in the prostate by the enzyme 5α-reductase. Inhibition of 5α-reductase provides a novel and selective approach to androgen deprivation [2].

Research chemists at Merck Sharp & Dohme Laboratories have synthesized a class of 4-aza steroid compounds that are potent *in vivo* 5α-reductase inhibitions [2]. Finasteride (MK-906, PROSCAR®) is one such compound (see Fig. 1). Inhibition occurs without affecting the binding of T or DHT to the androgen receptor. Finasteride in itself possesses no androgenic, antiandrogenic, or other steroid hormone-related properties.

In vivo pharmacologic experiments in rats and dogs treated with finasteride have demonstrated a marked decrease of the concentration of DHT in prostatic tissue without significant side effects. Clinical studies with finasteride in humans have demonstrated that inhibition of 5α-reductase activity results in marked suppression of DHT levels, while circulating levels of T are maintained. Therefore, those events that are mediated by T such as libido and muscular strength are not affected by this mechanism of action. Together the data suggest that finasteride may be useful in the treatment of several androgen-mediated conditions including benign prostatic hyperplasia (BPH) and prostate cancer. This report reviews the clinical development

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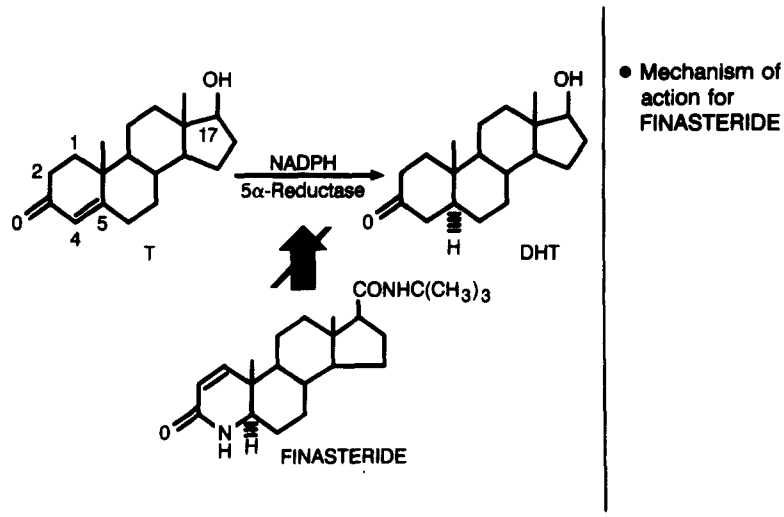

Fig. 1. The conversion of testosterone (T) to 5α-dihydrotestosterone (DHT) by the enzyme 5α-reductase. The structure of finasteride, an inhibitor of this enzyme, is illustrated.

of finasteride for the treatment of benign prostatic hyperplasia.

BACKGROUND—THE EFFECTS OF 5α-REDUCTASE INHIBITION IN MAN

In 1974, two independent groups, Walsh *et al.* [3] and Imperato-McGinley *et al.* [4], described an inherited disorder, transmitted by a recessive gene in which the external genitalia of the genetically male children were not normally virilized at birth. The patients of Imperato-McGinley *et al.* were confined to a single village in the Dominican Republic, where inbreeding was prevalent. These children were initially raised as girls until puberty when their voices deepened and characteristic male sexual features and gender identity developed. A systematic biochemical investigation was undertaken which led to the conclusion that these affected male children are genetically deficient in 5α-reductase and are therefore unable to metabolize T to DHT.

The clinical features which define the genetic syndrome of 5α-reductase deficiency have provided a model for predicting the biologic effects of chronic inhibition of this enzyme in the adult male. In patients with the genetic form of 5α-reductase deficiency, libido is normal, the prostate remains small during adulthood, beard growth is scanty, and neither acne nor temporal recession of the hair line occurs. 5α-Reductase is certainly necessary for normal development of the male external genitalia *in utero* and for the complete development of primary and secondary sexual characteristics at puberty, but it appears to have no other specific biologic function in the adult male.

Only certain tissues such as the prostate gland, genital skin, and frontal scalp contain high levels of 5α-reductase. T is converted to DHT by this enzyme in these androgen-targeted organs. DHT is further metabolized to androgen conjugates such as androstanediol glucuronide and androsterone glucuronide. While T is the major serum androgen, DHT is the active androgen in the skin and prostate.

Based on these observations, it has been postulated that distinct and specific physiologic processes are mediated by each of the androgenic hormones, T, and DHT. For example, spermatogenesis, libido, and muscular strength are mediated primarily by T, whereas growth of the prostate gland and male pattern baldness are processes primarily under the control of DHT. The specificity of these two enzymes may allow for the successful treatment of several DHT-mediated conditions, such as BPH, prostate cancer, baldness, hirsutism, and acne, without affecting functions such as T-dependent fertility or libido.

CLINICAL TRIALS

The objective of the clinical program at the Merck Research Laboratories over the last 3 years has been to demonstrate biochemical activity, safety, tolerability, and efficacy of the orally active 5α-reductase inhibitor, finasteride. Finasteride was first administered to man in March 1986. Approximately 350 patients/volunteers have completed clinical studies to

date. Some patients received up to 80 mg per day for 3 months, and of these, approximately 65 have now completed 12 months of therapy.

In phase I clinical studies it was demonstrated that a single oral dose of finasteride markedly reduced plasma levels of DHT in male subjects, thereby demonstrating the biochemical efficacy and potency of finasteride. In fact, a single oral dose of as little as 0.5 mg caused a 65% decrease in plasma DHT, which persisted for 5–7 days. Furthermore, androstenediol glucuronide and androsterone glucuronide were also suppressed, suggesting that finasteride suppresses formation of both conjugated and unconjugated 5α-reduced androgens in hepatic and extrasplanchnic tissues [5, 6].

In a blind, placebo-controlled trial, finasteride was administered to normal male volunteers at daily oral doses of 25, 50, and 100 mg for 11 days in the high-dose phase of the study and daily oral doses of 0.04, 0.12, 0.2, and 1.0 mg for 14 days in the low-dose phase [7]. Results from the high-dose study showed a significant reduction in DHT at all doses and a statistically significant increase in both T and Δ^4-androstenedione at the 50 and 100 mg doses. No change was seen in LH, FSH, cortisol, or estradiol levels. Serum lipids including total cholesterol, LDL, HDL, and triglycerides were not affected by treatment with finasteride. Results from the low-dose study again showed significant reduction in DHT at all doses. Patients taking 1.0 and 0.2 mg per day of finasteride had significantly lower baseline levels and maximum suppressions of DHT (see Fig. 2). DHT levels returned to pretreatment values within 14 days of discontinuing treatment.

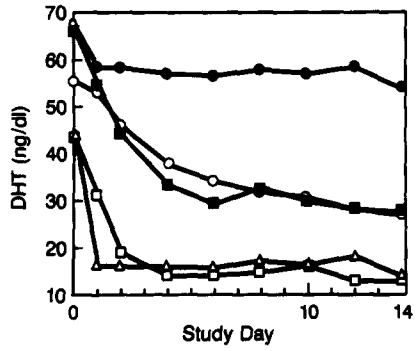

Fig. 2. The effect of finasteride on serum DHT during 14 days of treatment. Daily doses were 1.0 mg (△—△), 0.2 mg (□—□), 0.12 mg (■—■), 0.04 mg (○—○), and placebo (●—●). Values are expressed as the mean of 6 subjects per group.

Statistically significant, but clinically unimportant increases in T ($18.9 \pm 15.6\%$) were observed only in the 1.0 mg group and only during the first 8 days of treatment. The T/DHT ratio increased with all doses and returned to baseline when drug was discontinued. The DHT metabolites, androstenediol glucuronide and androsterone glucuronide, were significantly reduced at all doses. These data in normal volunteers clearly established that treatment with finasteride results in a significant decrease in the level of circulating DHT. This suppression is readily reversible upon withdrawal of treatment.

A placebo-controlled study in men awaiting definitive surgery with clinically significant BPH was undertaken to determine the ability of finasteride to suppress intraprostatic DHT levels [8]. After 7 days of treatment with 50 mg of finasteride daily, prostatic DHT decreased by 92%. Intraprostatic T levels increased from 0.26 ± 0.18 ng/g of tissue to 1.91 ng/g of tissue. This study demonstrated that finasteride causes significant inhibition of 5α-reductase activity in the hyperplastic human prostate, with a moderate, reciprocal increase in intraprostatic testosterone after 7 days of treatment.

Prostate-specific antigen (PSA) was measured in prostatic tissue obtained from BPH patients who had received finasteride (50 and 100 mg) for one week [9]. A marked decrease in PSA was observed and there was a significant correlation ($\gamma \pm 0.83$) between prostate PSA and prostate epithelial cell DHT levels [9]. The rise in intraprostatic T, appears to have little, if any biological effect on PSA an androgen-dependent protein.

In clinical studies where finasteride was administered for 6 months, a marked decrease in circulating DHT levels was observed, with 80% suppression of DHT at the 5 mg dose. These circulating levels of DHT are similar to those following castration. The effects of chronic finasteride on various hormonal parameters were examined and no clinically significant changes in circulating T nor any changes in serum luteinizing hormone, cortisol, prolactin, thyroxine, estradiol or on glucose tolerance were found.

Other clinical trials were performed specifically to evaluate the effect of finasteride on prostate volume. In patients with BPH, prostate volume decreased by a mean of 18% by 12 weeks. This decrease in the size of the prostate gland was found to continue throughout the initial 6 months of therapy. Shrinkage at the end

of the period was 28%. This suggests that to achieve the maximum therapeutic response at least 6 months of treatment is required. The effect of finasteride on the urinary flow rate in these patients was also determined. The mean increase in the maximum urinary flow rate was approximately 3 ml/s in the drug-treated group, compared to no change in the placebo group (Stoner, manuscript in preparation).

The effect of finasteride on other hormonal parameters was determined. Tenover *et al.* [10], reported no major changes in serum gonadotropins, free T, or sex-hormone binding globulin in a subgroup of the 6-month study. Imperato-McGinley *et al.* [11] demonstrated that the deficiency in 5α-reductase that is induced by finasteride is not specific for androgen metabolism. It is a general deficiency in steroid metabolism affecting C19 and C21 steroids, metabolized by both hepatic and extrasplanchnic 5α-reductase. Furthermore, this pattern is strikingly similar to that observed in male pseudohermaphroditism due to inherited 5α-reductase deficiency.

The metabolism of finasteride has now been defined in humans [12]. The parent drug is the major circulating component in the plasma. In addition, two monohydroxy metabolites have been identified in the blood. The metabolites also possess some activity as inhibitors of 5α-reductase.

In summary, there is strong evidence to support the hypothesis that prostatic hypertrophy is androgen-mediated. Administration of finasteride limits the amount of DHT available to the prostate and alleviates the symptoms of prostatic hypertrophy in a large number of patients. The first change observed in patients with BPH on finasteride therapy is a gradual decrease in prostate size. An improvement in the flow rate follows with a delayed perception of improved symptoms. Although the current studies clearly suggest the efficacy of finasteride, more extensive clinical trials will be needed to reach a full understanding of 5α-reductase inhibitors and their therapeutic potential in the treatment of benign prostatic hyperplasia.

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