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The Effect of 5 α-Reductase Inhibitors on Erectile Function

Review

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ABSTRACT: The 5 α-reductase inhibitors, which inhibit conversion of testosterone to dihydrotestosterone, are used for miscellaneous clinical applications, including the treatment of benign prostatic hyperplasia and male pattern hair loss, and for possible reduction of the risk of prostate cancer. Erectile dysfunction has been associated with 5 α-reductase inhibitors. Overall, reports in the literature suggest rates of erectile dysfunction to be between 0.8%–33% in men using these medications. However, randomized controlled studies report the rates of erectile dysfunction to be between 0.8%–15.8%. The possible risk association is that these medications impact androgen function, which is understood to contribute to normal erectile physiology. The 5 α-reductase inhibitors result in a drop in median serum dihydrotestosterone levels by 60%–93% within 2 years, but there is no major change in testosterone levels. In this review, we surveyed studies on erectile dysfunction in patients treated with 5 α-reductase inhibitors and critically examined the evidence that associates 5 α-reductase inhibitors and erectile dysfunction. We conclude that 5 α-reductase inhibitors do not lead to erectile dysfunction to a significant degree, and we support the position that dihydrotestosterone is less relevant than testosterone in erectile function.

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The 5 α-reductase inhibitors (5ARIs) have been successfully used for more than 20 years for treatments of benign prostatic hyperplasia (BPH) and male pattern hair loss, and lately they have been evaluated for reduction in prostate cancer risk. Presently available orally administered 5ARIs, finasteride and dutasteride, inhibit 5 α-reductase, an enzyme that catalyzes the irreversible reduction of testosterone (T) to dihydrotestosterone (DHT), with NADPH as the hydrogen donor (Russell and Wilson, 1994). There are 2 isoenzyme forms (types I and II). Type I is located predominantly in the skin, in both hair follicles and sebaceous glands, as well as in the liver, prostate, and kidney and is responsible for approximately one-third of circulating DHT (Thiboutot et al, 1995). Type II is found in the prostate, seminal vesicles, epididymis, hair follicles, and liver, and is responsible for the remaining two-thirds of circulating DHT (Thigpen et al, 1993a; Gisleskog et al, 1998). Finasteride inhibits type II, while dutasteride is an inhibitor of both types and may decrease circulating DHT to a greater extent than finasteride (Clark et al, 2004).

The sex steroidal influence in the physiology of the erectile response has been an issue of controversy for many years. Points of view have ranged from thought that the androgens offer an unneeded role in physiological mechanisms of penile erection (Handelsman and Zajac, 2004) to the view that these hormones critically influence structural and functional circumstances required for the erectile response (Gooren and Saad, 2006; Traish and Guay, 2006).

We are able to treat patients for prostatic or hair diseases by decreasing their DHT levels. Do we also lessen the quality of their sexual lives? In this review, we summarize information from animal models and clinical studies with regard to the effect of 5ARIs on erectile function. We begin with a description of 5 α-reductase deficiency (male pseudohermaphroditism) and continue with an overview of the role of T and DHT on erectile capability by highlighting the physiological properties and molecular interactions of the intriguing hormone DHT in general. Then, within the context of several specific studies, we explore the impact of currently available 5ARIs on erectile function in men.

Deficiency in 5 α-Reductase

The effect of androgens on the physiology of the penis has been a topic of discussion for many years. In 1974, Imperato-McGinley and colleagues (1974) discovered an autosomal recessive form of incomplete male pseudohermaphroditism, which was shown to result from 5 α-reductase deficiency. This disorder, also known as pseudovaginal perineoscrotal hypospadias, or type 2 familial male pseudohermaphroditism, is characterized

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by a 46,XY karyotype, ambiguity of the external genitalia (female phenotype at birth), and virilization at puberty. During fetal development, the decrease in DHT results in incomplete masculinization of the external genitalia. Later in puberty, affected individuals develop a muscular male habitus with growth of the phallus and scrotum, and their voices change into adulthood. In adulthood, they have decreased body hair, a scant to absent beard, no temporal hair line recession, and a small prostate. However, subjects have normal erections and ejaculations and a libido directed towards females (Imperato-McGinley et al, 1974).

Anatomic investigations have shown that mesonephric duct structures (ie, testis, epididymis, seminal vesicles, ejaculatory duct, and prostate) are developed, but that the external genitalia are incompletely masculinized. The mean plasma T levels in affected adults are significantly higher and the mean plasma DHT levels significantly lower when compared with those of normal subjects (Imperato-McGinley et al, 1974; Peterson et al, 1977). The plasma T:DHT ratios range from 35 to 84 compared with 8 to 16 in normal subjects. In affected subjects, the metabolic clearance rates of T and DHT are normal, but the conversion ratio of T (using radioactive T) to DHT is less than 1% (Peterson et al, 1977).

Imperato-McGinley and colleagues (1974) mentioned that T is required for differentiation of embryonic mesonephric duct structures, and that DHT is required for differentiation of the embryonic urogenital sinus and tubercle into male external genitalia. Male psychosexual development and virilization at puberty are mediated by T, while adult prostatic growth and male pattern baldness are mediated by DHT (Imperato-McGinley et al, 1974; Tarter and Vaughan, 2006).

Type 2 familial male pseudohermaphroditism, which features lack of prostate growth and male pattern baldness, provides a model for the development of 5ARIs. Some diseases (eg, BPH and androgenetic alopecia) are treated using these medications. However, these medications change serum levels of androgens, mainly DHT. If androgen levels affect erectile function, then it stands to wonder whether changes in DHT levels can affect erectile function as well.

Role of Androgens in Erectile Function

T is the major androgenic hormone produced by Leydig cells of the testes in response to stimulation by luteinizing hormone of the pituitary gland. T, regulated by the hypothalamic-pituitary-testis axis, is converted to DHT in the liver, skin, and organs that originate from the mesonephric duct, such as the prostate. The enzyme that is responsible for conversion of T to DHT is 5 α-reductase. T either directly or subsequent to its conversion into DHT exerts important physiological actions on muscle, bone, prostate, bone marrow, the central nervous system, and erectile function (Saad et al, 2007). T exerts both humoral endocrine and local paracrine effects, whereas DHT is largely a paracrine hormone and exerts effects in the tissues of origin (Tarter and Vaughan, 2006).

Although the role of androgens in erectile function in men is controversial, primary or secondary hypogonadism is considered key in the pathophysiology of erectile dysfunction (ED) (Korenman et al, 1990; Aversa et al, 2004; Yassin and Saad, 2007). Androgens exert not only genomic effects, for example, by stimulating the expression of the neuronal isoform of nitric oxide (NO) synthase (Reilly et al, 1997; Park et al, 1999), but also nongenomic effects, for example, by relaxing the smooth musculature of coronary arteries and the aorta (Yue et al, 1995; Deenadayalu et al, 2001). Criteria representing nongenomic effects include a rapid onset of action within seconds or minutes, effects elicited by androgens that do not enter the cytosol. An interesting matter is that androgenic actions associated with nongenomic effects are not blocked by inhibitors of the androgen receptor or by inhibitors of transcription (Yue et al, 1995; Deenadayalu et al, 2001). Waldkirch and associates (2008) demonstrated that T and DHT dose-dependently reversed the noradrenalin-induced tension of human cavernosal arteries and corpus cavernosum strips, indicating the clinical significance and supporting the concept of threshold levels.

T is important for modulating the central and peripheral regulation of ED. Erectile function depends on a normal penile anatomy and a functioning veno-occlusive mechanism, which implies integrity of the structural and cellular components. It was demonstrated that T deprivation causes apoptosis of cells from cavernosal and spongiosal tissues, which can be prevented by androgen administration (Podlasek et al, 2005).

Smooth muscle, a vital component of the penile anatomy, is a critical structure for tumescence. Using a rat model, investigators established that experimental castration caused significant reduction in trabecular smooth muscle and a significant increase in connective tissue deposition concomitant with loss of erectile function, indicating that T is vital for smooth muscle integrity (Traish et al, 2003). Further support for the androgenic requirement for penile erection derives from scientific knowledge of the molecular basis for NO function in the penis. It was shown that the NO pathway plays a critical role in initiation and maintenance of erectile function (Burnett, 2004). In animals, the expression of NO synthase (NOS) isoforms in the

corpus cavernosum is regulated by androgens. Researchers found that NOS activity is decreased in erectile tissues of castrated animals, as is the erectile response to pelvic nerve stimulation (Lugg et al, 1995; Park et al, 1999; Baba et al, 2000). These investigators further established that T restores the erectile response and normalizes NOS protein expression and activity.

On the whole, the mechanism of penile erection is a function of corporal smooth muscle relaxation required for blood filling and engorgement of the penis in response to sexual excitement, exerted at the molecular level by cGMP by way of its effector cGKI (Andersson, 2001). Type 5 phosphodiesterase enzyme (PDE5), the predominant phosphodiesterase expressed in the corpus cavernosum, has regulatory control of penile vasorelaxant actions. In the animal model, castration resulted in reduced protein expression and activity of PDE5, although androgen treatment up-regulated the expression of PDE5 activity (Morelli et al, 2004). In addition, the efficacy of PDE5 inhibitors to elicit erections induced by electrostimulation of the cavernous nerves following castration was decreased. After castrated animals were treated with T, the tissue relaxation caused by PDE5 inhibitors was successfully restored (Traish et al, 1999; Morelli et al, 2004).

Clinical studies also indicate the direct influence of androgens on erectile responses to PDE5 inhibitors. Investigators carrying out clinical trials in androgen-deficient men confirmed these observations and found that with androgen substitution these men displayed enhanced responses to the ED treatment (Aversa et al, 2004; Shabsigh et al, 2004; Morelli et al, 2007). These studies strongly suggest that T exerts vital physiological actions in erectile function.

Experimental Animal Models

Description of 5 α-reductase deficiency in male pseudohermaphroditism caused investigators to study the influence of 5ARIs on erectile function in animal models. To begin to unravel this issue, Bradshaw and associates (1981) designed a study in which they administered the 5ARI, 17-beta-testosterone carboxylic acid and T propionate or 5 α-DHT propionate, after castration of animals. The investigators observed significantly attenuated stimulatory effects of T propionate on penile erections. However, when they administered 5 α-DHT propionate to castrated rats, penile erections were preserved, implying the importance of DHT in erectile function (Bradshaw et al, 1981).

The work of Baum and colleagues (1983) suggested an opposite conclusion. These investigators implanted subcutaneous silastic capsules containing either the aromatase inhibitor androst-1,4,6-triene-3, 17-dione (ATD), the 5ARI testosterone-17-beta-carboxylic acid (17 beta C), or no hormone into male ferrets for 15 days beginning on the day of birth. All ferrets were gonadectomized when they were 11 weeks of age and were subsequently tested for masculine sexual behavior after a latin-square sequence of treatments with subcutaneous silastic capsules containing T, estradiol, or DHT. After T administration, control males displayed significantly more neck gripping, mounting, and pelvic thrusting than males treated neonatally with ATD. After DHT administration, little masculine sexual behavior was shown by any group. These consequences suggest that behavioral masculinization in the male ferret results primarily from the neonatal action of T itself in the brain, and not from its estrogenic or 5 α-reduced androgenic metabolites (Baum et al, 1983).

Lugg et al (1995) further investigated which androgen is vital for function of the penis with respect to erectile function. They performed a study to determine whether the T effects on erectile function are mediated via its conversion to DHT. In their study, castrated rats were implanted with silastic brand silicon tubing containing T or DHT with or without daily injections of the 5ARI finasteride. Orchiectomy reduced the electrical field stimulation-induced erectile response by 50% in comparison with intact rats, and T restored this decrease to normal. When finasteride was given to these T-treated castrated rats, erectile response was not restored. DHT was as effective as T in restoring response to stimulation in castrates, and this effect was not decreased by finasteride (Lugg et al, 1995). The results seem to corroborate the information of Bradshaw and associates (1981). The data suggested that DHT is the active androgen that prevents erectile failure in castrated rats.

With recent discoveries of PDE5 inhibitors as well NOS signaling in the penis, Park et al (1999) examined whether DHT influences the erectile response and the mRNA expressions of NOS isoforms in the penile corpus cavernosum of castrated rats. For this purpose, rats were separated into 5 groups: sham, castrated alone, and castrated receiving T, DHT, or T with the 5ARI finasteride. Both T and DHT effectively restored the erectile response to normal. NOS activity and the amount of neuronal NOS (nNOS) mRNA were also reduced in castrated rats but restored by both T and DHT replacement. Although there was no significant difference in NOS activity between the androgens, nNOS mRNA expression was higher in rats treated with DHT. Strikingly, there were no effects of T in rats treated with finasteride, since the ratio of maximum intracavernosal pressure to systolic blood pressure (ICPmax/SBP ratio), NOS activity, and amount of nNOS mRNA were decreased (Park et al, 1999).

Further evaluation of the role of DHT in the penis has been done at the penile morphologic level. Shen et al (2000) investigated the ultrastructural changes of the penile corpus cavernosum and tunica albuginea in rats representing 3 groups: sham control, castrated, and treated with finasteride. Four weeks later, blood samples were obtained for the determination of serum T and DHT levels, and penile tissues were taken for scanning electron microscopy. The T and DHT levels in castrated rats and the DHT level in finasteride-treated groups were significantly lower than those in the control group. In the castrated animals, there was a high degree of fibrosis in the corpus cavernosum with irregularly arranged collagenous fibers and a marked decrease in smooth muscle fibers, while in the DHT-inhibited group (finasteride-treated), the corpus cavernosum comprised a substantial amount of thick and irregularly arranged collagenous fibers, but the degree of fibrosis was less than that of the castration group (Shen et al, 2000). This work suggests that because finasteride inhibits the action of DHT but not T on the corporal cavernosal tissue, the degree of fibrosis was less in the DHT-inhibited group than in the castration group. In the castration group, the thickness of tunica albuginea decreased significantly and the elastic fibers were mostly supplanted by collagenous fibers, and in the DHT-inhibited group, the elastic fibers were replaced by disorganized and thick collagenous fibers. Since the tunica albuginea plays a major role in the erectile mechanism of the penis, the latter results offer an explanation for the presentation of ED in patients treated with 5ARIs.

Clinical Investigations

Clinical Studies Testing the Effect of DHT on Erectile Function—In order to evaluate the direct effect of 5ARIs on sexual life, investigators studied erectile function in patients taking these drugs. Cunningham and Hirshkowitz (1995) designed a sleep-related erection study, with the aim of measuring erectile function objectively during double-blind administration of finasteride or placebo. Their purpose was to find the answer to the question, ''Does finasteride impair erectile function?'' Sleep-related erection studies provide objective measures of erection physiology and pathophysiology. Naturally occurring, spontaneous episodes of nocturnal penile tumescence (NPT) occur with consistent regularity during rapid eye movement (REM) sleep in all sexually potent men. Twenty healthy, sexually active men were randomized to receive either placebo or 5 mg/day finasteride for 12 weeks according to a double-blind study design. Erection physiology was assessed by a polysomnography device. The investigators found that finasteride did not consistently suppress sleep-related erections compared with placebo (Cunningham and Hirshkowitz, 1995). They explained the most likely reason that finasteride did not impair erectile function was that it did not sufficiently inhibit 5 α-reductase activity in critical areas of the brain. They acknowledged that DHT involvement in the maintenance of libido and potency is not excluded.

Uygur and associates (1998) investigated the effects of finasteride on the serum levels of gonadal, hypophyseal, and adrenal hormones and the clinical significance of these effects. In this prospective clinical study, serum levels of T, DHT, dehydroepiandrosterone, and luteinizing hormone were determined, and erectile function was evaluated in 48 BPH patients using a brief sexual function questionnaire, which included a total of 11 self-administered questions (O'Leary et al, 1995). DHT levels decreased by 60%, and T levels increased by 15% after finasteride was given. Finasteride led to ED in 22% by month 3 and in 33% by month 6 (Uygur et al, 1998). Despite the suggestion of a high level of ED associated with finasteride use in this study, an accurate determination of this risk is precluded by the lack of a control group.

Anderson and colleagues (1999) compared the effects of 7 α-methyl-19-nortestosterone (MENT), a potent synthetic androgen (selective androgen receptor modulator), which can be converted by aromatase to an active estrogen, 7 α-methyl estradiol, but is resistant to 5 α-reductase actions, with T enanthate on erectile function in 20 hypogonadal men. It is worth emphasizing that DHT is not formed from MENT. Both MENT and T treatment resulted in significant increases in spontaneous erection (both by self-report and NPT measurement) and positive moods (Anderson et al, 1999). The study demonstrated that MENT is sufficient to restore androgen-dependent physiology in hypogonadal men, lending indirect evidence that DHT is not required for mediation of these responses in men (Anderson et al, 1999).

Clinicians counsel more or less on a drug's sexual side effects. Could this counseling trigger ED as a placebo effect? Mondaini et al (2007) investigated whether a discrepancy exists in finasteride-related sexual adverse effects between double-blind trials and clinical practice, and if the difference might be partially related to a placebo effect. The patients were asked to complete the International Index of Erectile Function (IIEF) and the Male Sexual Function-4 (MSF-4; contains questions about interest in sex, quality of erection, achievement of orgasm, and achievement of ejaculation) questionnaires (Mondaini et al, 2007). Finasteride was prescribed to 120 patients with or without counseling on the drug's sexual side effects. The estimation of side effects was conducted at 6 and 12 months using the MSF-4

questionnaire and a self-administered questionnaire. In this study, finasteride was associated with a significantly higher proportion of ED in patients informed of possible erectile side effects as compared with that in patients for whom the same information was withheld. The incidence of ED was 9.6% for the group without counseling and 30.9% for the group with counseling (Mondaini et al, 2007). The placebo effect demonstrated here has to be taken into account when managing finasteride-related EDs.

When the results of clinical studies are examined, it is not clearly evident that 5ARIs have a negative effect in men as seen in animal studies. This may be explained by the fact that in animals DHT levels were either zero or normal. It was shown that treatment with 5ARIs results in a reduction in median serum DHT levels in men by 60%–93% after 2 years (Imperato-McGinley et al, 1974; Uygur et al, 1998; Andriole and Kirby, 2003; Clark et al, 2004; Marberger et al, 2006). The 5ARIs cause a reduction in DHT levels but do not eliminate it completely from the circulation. For example, since finasteride inhibits only type II 5 α-reductase receptors, circulating DHT is only reduced by two-thirds (Thigpen et al, 1993a; Thigpen et al, 1993b; Gisleskog et al, 1998).

Clinical Studies for Benign Prostatic Hyperplasia—Mechanisms of BPH, the most prevalent disease of the prostate, are multifactorial and are not yet completely understood. Nevertheless, BPH is known to depend on androgens, especially on DHT, which also plays a crucial role in the early development and normal growth of the prostate. The 5ARIs finasteride and dutasteride are used to treat BPH and to prevent urinary complications according to randomized, controlled trials. Finasteride, an inhibitor of type II 5 α-reductase isozyme, was the first 5ARI used in men with BPH (Sudduth and Koronkowski, 1993). It has no binding affinity for androgen receptor sites, and it possesses no androgenic, antiandrogenic, or other steroid hormone-related properties. It is well-absorbed after oral administration, with absolute bioavailability in humans of 63% (range 34%–108%). The mean time to maximum concentration is 1–2 hours, and it is approximately 90% plasma protein-bound. The elimination half-life averages 6–8 hours. The agent is metabolized to a series of 5 metabolites, of which 2 are active and have less than 20% of the 5 α-reductase activity of finasteride (Sudduth and Koronkowski, 1993).

Concerns regarding the adverse metabolic side effects of finasteride emerged from the analysis of the Finasteride Study Group (Gormley et al, 1992). The Finasteride Study Group carried out a double-blind study on finasteride detailing the side effects resulting from the effect of 2 doses of finasteride (1 mg and 5 mg) and placebo, each given once daily for 1 year in men with BPH (Gormley et al, 1992). As compared with the men in the placebo group, the men treated with 5 mg of finasteride per day had a significant decrease in total urinary symptom scores, an increase of 1.6 mL per second in the maximal urinary flow rate, and a 19% decrease in prostatic volume. 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 per second in the maximal urinary flow rate and an 18% decrease in prostatic volume. There was also a higher incidence of ED in the finasteride-treated groups (12.5%, n = 297) compared with placebo (4.7%, n = 300). Unfortunately, the investigators did not assess patients' baseline sexual function nor use a questionnaire in this study; the side effects reported were those identified by the patients and considered by investigators to have some relation to treatment (Geller, 1993).

The Finasteride Study Group further assessed the long-term safety and efficacy of finasteride in the treatment of symptomatic BPH in patients treated with 5 mg finasteride for 36 months (Stoner, 1994). ED at the end of 1 year was reported by 3.7% of the men in the 5 mg finasteride-treated group compared with 1.1% of the men in the placebo-treated group. Interestingly, by the end of 3 years, 45% of adverse erectile effects had resolved in the group taking 5 mg finasteride. Finasteride was well-tolerated, and there was no evidence of increased adverse experiences with increased duration of treatment (Stoner, 1994). These data indicated that although there was a 3.7% incidence of ED at the beginning of treatment, ED declined to 2.1% at the end of 3 years (Table).

Nickel and colleagues (1996) reported the results of a 2-year double-blind, prospective, placebo-controlled randomized trial on efficacy and safety of finasteride (the PROSPECT study). Among 698 patients, adverse events related to ED were significantly higher in the finasteride-treated group than in the placebo-treated group (15.8% vs. 6.3%; Nickel et al, 1996). Although ED associated with finasteride was found to be much more prevalent than in other trials, it is likely that these estimations were high based on inclusive subjective reporting. Investigators subjectively assessed patients' well-being and the incidence of ED during an open-ended interview.

Additional evidence regarding the effects of finasteride on erectile function comes from the ALFIN Study, a randomized, double-blind, multicenter trial involving 1051 patients, which assessed the additive benefit of combining an α_1-blocker and a 5ARI (Debruyne et al, 1998). From the point of view of erectile function, Debruyne et al reported that the ratio of ED was 6.7%, which was higher in patients treated with finasteride,

Table. *Randomized controlled trials investigating the rates of erectile dysfunction associated with use of 5 α-reductase inhibitors*

Investigators	N	Age, y	Drug, Dosage	Duration of Treatment, y	ED Rate, % Drug/Placebo	*P* Value
BPH Trials						
Gormley et al, 1992	597	≥50	Finasteride, 5 mg/d	1	12.5/4.7	<.05
Stoner, 1994	1098	40–80	Finasteride, 5 mg/d	3	2.1/1.1	>.05
Nickel et al, 1996	698	45–80	Finasteride, 5 mg/d	2	15.8/6.3	<.01
Wessells et al, 2003	3040	45–78	Finasteride, 5 mg/d	4	5.0/5.0	>.05
McConnell et al, 2003	1505	≥50	Finasteride, 5 mg/d	4.5	4.5/3.3	<.05
McConnell et al, 2003	1493	≥50	Dutasteride, 0.5 mg/d	4.5	3.5/3.3	>.05
Andriole and Kirby, 2003	5655	~65	Dutasteride, 0.5 mg/d	2	0.8/0.9	>.05
Roehrborn et al, 2004	569	≥50	Dutasteride, 0.5 mg/d	2	1.3/1.3	>.05
Marberger et al, 2006	4254	≥50	Dutasteride, 0.5 mg/d	2	6.7/4.0	>.05
MPHL Trials						
Finasteride MPHL Study Group, 2002	1553	18–41	Finasteride, 1 mg/d	1	1.4/0.6	<.05
Tosti et al, 2004	186	19–43	Finasteride, 1 mg/d	0.5	Same IIEF scores	>.05

Abbreviations: BPH, benign prostatic hyperplasia; ED, erectile dysfunction; IIEF, International Index of Erectile Function; MPHL, male pattern hair loss.

alone or in combination, than with alfuzosin alone (Debruyne et al, 1998). A limitation of this study is that it was not placebo-controlled. The investigators also did not use any questionnaire for examining erectile function. The adverse events communicated spontaneously by patients or from notes taken by the investigator during examination were reported during the whole study.

A placebo-controlled study involving a large population evaluated over a long period may offer the best determination of outcomes associated with 5ARI treatment. The Proscar Long-Term Efficacy and Safety Study (PLESS), a 4-year, double-blind, placebo-controlled finasteride study of more than 3000 men with BPH, was designed to prospectively determine the efficacy of finasteride, as well as the incidence of erectile adverse effects over time (Wessells et al, 2003). The drug-related ED profile for finasteride was similar for men with and without a history of ED at baseline. Wessells et al reported that ED was a consistent side effect of finasteride in a maximum percentage of 12.6% (mild, moderate, or severe ED) after 1 year of therapy. However, the incidence of severe ED was 5% in the finasteride group and 5% in the placebo group during years 2–4 of treatment (Table). Wessels et al concluded that ED was mild to moderate in intensity and resolved in about half of men after discontinuation of either finasteride or placebo, consistent with the natural history of ED in this patient population and likely concurrent with a substantial placebo effect (Wessells et al, 2003).

McConnell and colleagues (2003) conducted a long-term, double-blind trial (mean follow-up, 4.5 years) involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combination therapy (doxazosin and finasteride; Table). The reduction in risk of overall clinical progression of BPH was associated with combination therapy to a significantly greater extent than that associated with doxazosin or finasteride treatment alone. McConnell and colleagues also demonstrated that long-term combination therapy was safe. On the other hand, ED occurred to a significantly greater degree in the finasteride-treated group than in the placebo-treated group (4.53 vs 3.32 incidents per 100 person-years; McConnell et al, 2003).

Dutasteride, a newer 5ARI available for the treatment of symptomatic BPH, is a dual inhibitor of type I and II human 5 α-reductase. It is possible that it may decrease circulating DHT to a greater extent than finasteride (Clark et al, 2004). Since it blocks both of the 2 known 5 α-reductase isozymes, does it cause a higher incidence of ED? Marberger and associates (2006) evaluated the results of 4254 men with BPH participating in 2-year, randomized, double-blind and placebo-controlled dutasteride (0.5 mg) trials. The Sexual Function Inventory (SFI) was administered at baseline and 1 year to assess perceptions of problems associated with sexual drive, erection, or ejaculation (3 items). In men with normal baseline serum T (≥300 ng/dL), drug-related ED occurred in 6.7% of the dutasteride-treated group, compared with 4.0% of the placebo-treated group (Marberger et al, 2006). In this study with a large population, an increased incidence of ED was generally not observed unless T levels were less than 225 ng/dL (Table).

In a 2-year, prospective, double-blind randomized, placebo-controlled trial with an additional 2-year open-label phase for BPH with dutasteride (0.5 mg/day), 6.1%

of dutasteride-treated subjects developed ED (control, 3.0%) in the first year (Roehrborn et al, 2004). The most commonly reported drug-related adverse events, including ED with new onset of these events, occurred primarily within the first year of treatment. Roehrborn and colleagues (2004) also showed that ED results diminished to 1.3% (control, 1.3%) at the end of 2 years.

Andriole and Kirby (2003) summarized the results of 4 large, randomized, double-blind clinical trials of dutasteride (n = 5655) and a comparator study of dutasteride and finasteride (n = 1630). The incidence of drug-related adverse events was not significantly different between dutasteride and finasteride. The investigators observed that the onset of the majority of possibly drug-related adverse events occurred within the first year of treatment, with a statistically significantly lower incidence of ED occurring in the placebo-treated group versus the dutasteride-treated group (1.7% vs 4.7%) from 0–6 months (Andriole and Kirby, 2003). Subsequently (7–12 months, 13–18 months, and 19–24 months), there were no significant differences with respect to ED between the dutasteride-treated (1.4%, 1.1%, and 0.8%, respectively) and placebo-treated (1.5%, 0.5%, and 0.9%, respectively) groups (Andriole and Kirby, 2003). Although suppression of both 5 α-reductase isoenzymes with dutasteride resulted in greater and more consistent suppression of serum DHT than that observed with the selective inhibitor of the type II 5 α-reductase finasteride, no significant difference in long term (19–24 months) erectile function was seen between dutasteride-treated and placebo-treated men (Andriole and Kirby, 2003; Clark et al, 2004).

Clinical Studies for Androgenic Alopecia—Androgens also have profound effects on scalp and body hair in humans. Scalp hair grows constitutively in the absence of androgens, while body hair growth is dependent on the action of androgens. Male pattern hair loss, known to depend on the presence of the DHT and on a genetic predisposition for this condition, affects approximately 50% of the male population (Otberg et al, 2007). Reduction in DHT results in a significant improvement in subjective and objective assessments of hair growth and density.

In clinical trials involving finasteride (1 mg for androgenic alopecia), ED has been reported from patients' assessments in 1.4% of patients treated with the active drug and in 0.6% of patients taking a placebo in the first year of treatment (Finasteride Male Pattern Hair Loss Study Group, 2002). There are some studies that showed adverse erectile effects using validated questionnaires while treating male pattern hair loss. In one of the earliest studies using validated questionnaires, Tosti et al (2001) evaluated the erectile function in subjects taking 1 mg finasteride compared with placebo using the International Index of Erectile Function (IIEF-5). Statistical analysis showed no differences between scores obtained with the IIEF in subjects taking finasteride and controls. In a multicenter study, 186 patients with androgenic alopecia were asked to complete the erectile function domain of the IIEF before (at baseline) and 4 to 6 months after beginning finasteride treatment (Tosti et al, 2004). In this study, erectile function of all patients remained stable after 4 to 6 months of treatment with 1 mg finasteride, and no statistically significant changes were noted between active drug and placebo (Table; Tosti et al, 2004).

Clinical Studies for Prostate Cancer Prevention—In order to prevent prostate cancer, one of the most common cancers in the world, 5ARIs have been investigated in clinical trials. In a large study population, Moinpour and colleagues (2007) assessed ED in 17 313 Prostate Cancer Prevention Trial (PCPT) participants during a 7-year period. In this randomized, double-blind, placebo-controlled study, the efficacy of finasteride in preventing prostate cancer was examined. Sexual Activity Scale (SAS) scores were developed and used to assess sexual dysfunction. SAS has 4 items, including erection when desired, satisfaction, sexual performance, and frequency of sexual activities. Response levels ranged from 4–7 and were transformed to a 0–100 scale. Self-reported patient measures were obtained at study baseline and annually for 7 years. Results were that finasteride increased the SAS scores relative to placebo by 3.21 points at the first assessment, although its impact diminished over time, and at the end of the study it had decreased by 2.11 points (Moinpour et al, 2007). These data demonstrate that the effect of finasteride on erectile functioning is minimal for most men and that finasteride can be prescribed or taken comfortably.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) is another continuing trial in which dutasteride has been assessed for prostate cancer prevention (Andriole et al, 2004). A total of 8000 men were randomized to receive dutasteride or placebo for 4 years. Although this study comprises a population half that of the PCPT, it is expected to characterize adverse events data of a younger population (by 5 years), which is particularly significant with respect to erectile function. REDUCE has included men older than 50 years, whereas the PCPT criteria included men older than 55 years (Andriole et al, 2004).

Conclusions

Finasteride and dutasteride are approved for use in the treatment of men with symptomatic BPH and andro-

genic alopecia and are also under study in ongoing prostate cancer prevention trials. It was shown that treatment with 5ARIs results in a reduction in median serum DHT levels by 60%–93% after 2 years (Imperato-McGinley et al, 1974; Uygur et al, 1998; Andriole and Kirby, 2003; Clark et al, 2004; Marberger et al, 2006). According to 13 randomized studies in which finasteride was used alone, erectile problems occurred in 3% of the men studied long term (AUA Practice Guidelines Committee, 2003). This percentage of ED would seem minimal, and it is also noteworthy that this adverse event diminished by half over time in men taking finasteride (Stoner, 1994; Roehrborn et al, 2004; Moinpour et al, 2007). Randomized controlled studies report the rates of erectile dysfunction to be between 0.8%–15.8% (Table). The placebo effect demonstrated by Mondaini and associates (Mondaini et al, 2007) has to be taken into account when relating the effects of 5ARIs to ED. On the other hand, ejaculation disorders (premature or retarded) related to the use of these inhibitors has not been reported in detail. This outcome should be better described in further studies.

Although there are controversial studies, as a best example we should look for 5 α-reductase–deficient men whose mean plasma DHT levels are significantly lower when compared with those in normal subjects. More remarkably, the subjects have normal erections directed towards females, although they have low DHT levels (Imperato-McGinley et al, 1974).

Previous studies have shown that there does not seem to be a strong cause-and-effect relationship between serum androgen concentrations and erectile function; even in severely hypogonadal men, the erectile response is not always lost, and T treatment of hypogonadal men with ED does not necessarily restore lost erectile function (Mills and Lewis, 1999). Studies also verified that MENT, which is resistant to 5 α-reductase, is able to provide physiological and behavioral androgen replacement in hypogonadal men and may provide indirect evidence that 5 α-reduction is not required for mediation of the influence of T on these behaviors in men (Andersson, 2001).

T and DHT perform vital functions in various organs in different ratios. DHT is more active in prostate than T. This may be due to the fact that DHT is largely a paracrine hormone and exerts effects in tissues of its origin. On the other hand, T is more relevant than DHT in erectile function, which requires central and peripheral androgenic activity. T exerts both humoral endocrine and local paracrine effects.

In this review, we summarized the effect of 5ARIs with respect to erectile function. It is likely that androgens are vital for the development, maintenance and function of penile tissue and regulation of erectile physiology. However, the critical androgenic substance for these effects is most likely T rather than DHT.

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