ORIGINAL RESEARCH—ENDOCRINOLOGY

Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients

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ABSTRACT

Introduction. 5α-reductase inhibitors (5α-RIs), finasteride and dutasteride, have been approved for treatment of lower urinary tract symptoms, due to benign prostatic hyperplasia, with marked clinical efficacy. Finasteride is also approved for treatment of hair loss (androgenetic alopecia). Although the adverse side effects of these agents are thought to be minimal, the magnitude of adverse effects on sexual function, gynecomastia, depression, and quality of life remains ill-defined.

Aim. The goal of this review is to discuss 5α-RIs therapy, the potential persistent side effects, and the possible mechanisms responsible for these undesirable effects.

Methods. We examined data reported in various clinical studies from the available literature concerning the side effects of finasteride and dutasteride.

Main Outcome Measures. Data reported in the literature were reviewed and discussed.

Results. Prolonged adverse effects on sexual function such as erectile dysfunction and diminished libido are reported by a subset of men, raising the possibility of a causal relationship.

Conclusions. We suggest discussion with patients on the potential sexual side effects of 5α-RIs before commencing therapy. Alternative therapies may be considered in the discussion, especially when treating androgenetic alopecia.

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Key Words. Finasteride; Dutasteride; Alopecia; Benign Prostatic Hyperplasia; Sexual Dysfunction Depression; Gynecomastia

Case Study

In 1999, a 24-year-old male was diagnosed with androgenetic alopecia (AGA). He had normal stature (height, 182 cm; weight, 80 kg), had no history of any medical illness, and was not taking any medications. He reported having a normal sex drive and normal erectile capacity. He started treatment with finasteride (Propecia™), 1 mg daily, and within 2–5 days experienced soreness of the testicles, total lack of sex drive, and complete inability to achieve an erection. He had difficulty concentrating and felt depressed. Expecting these initial side effects to be temporary, he continued treatment. Except for some improvement of the soreness in the testicles, he felt numbness and there was no improvement in his sex drive or erectile function. After a little more than 1 month, he

discontinued treatment and the side effects diminished to some degree, but sexual function never returned to normal. In the following months and years, the symptoms persisted with loss of libido and erectile dysfunction (ED). In 2003, the patient consulted a specialty clinic for sexual medicine in Boston, MA, USA, and went through extensive examinations. At this point, treatment with Viagra had been tried with only marginal success. Because of hopelessness and depression, two types of antidepressants (citalopram and bupropion) had been prescribed, which helped by "taking away the deepest lows," but with no improvement in either libido or erectile capacity. In addition, there were undesirable side effects to these drugs and treatment was discontinued after several months. In Boston, the patient had a psychological evaluation and underwent duplex Doppler ultrasonography.

Suffering from persistent symptoms of ED, loss of libido, and depression, the patient consulted a clinic in Copenhagen, Denmark, which specializes in testosterone treatment. The total testosterone (T) varied between 22.6 and 14.2 nmol/L (651 and 409 ng/dL) in the baseline state. The fluctuations were felt to be quite wide. No 5 α-dihydrotestosterone (5 α-DHT) measurements were available. The following baseline tests were all found to be normal: sex hormone binding globulin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, T3, T4, prolactin, estradiol, dehydroepiandrosterone sulfate (DHEA-S), and androstenedione. He is currently under no treatment, but 11 years later, he still suffers from ED and loss of libido.

Introduction

5α-reductase inhibitors (5α-RIs), finasteride and dutasteride (Figure 1), were developed to treat patients with symptoms of benign prostatic hyperplasia (BPH) and decrease the frequency and risk of BPH-related surgeries [1,2]. Finasteride was also approved for treatment of AGA, a male pattern hair loss which affects approximately 50% of the male population [3]. Long-term studies showed that finasteride and dutasteride reduced prostate size within 3 months to 2 years [1,2,4,5]. Recent studies suggested that 5α-RIs reduce the incidence of prostate cancer (PCa) [6], but this conclusion remains to be substantiated [7]. In this clinical trial [6], it was stated that "there was an unexpected imbalance in a composite event termed 'cardiac failure', which included conditions such as congestive heart failure, cardiac failure, acute cardiac failure, ventricular failure, cardiopulmonary failure, and congestive cardiomyopathy. Although there was no significant difference between the two groups in the overall incidence of cardiovascular events or deaths from cardiovascular events, there was a higher incidence of the composite event of cardiac failure in the dutasteride group than in the placebo group." Moreover, physiological levels of 5 α-DHT attenuated development of atherosclerosis in the animal model through the suppression of intimal foam cell formation of macrophage partly via the suppression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, suggesting the role of 5 α-DHT in atheroprotection of vascular health [8].

The potential widespread use of 5α-RIs for treatment of BPH, PCa and AGA may produce undesirable adverse side effects on overall health and in particular, vascular health [6] and sexual function in a subgroup of susceptible patients. Furthermore, treatment of AGA, a benign condition with 5α-RIs may produce persistent side effects in a number of young patients. To date, the adverse side effects of 5α-RIs on sexual function, gynecomastia, and the impact on the overall health have received minimal attention. However, in some patients, these side effects are persistent with regard to sexual function and with an emotional toll including decreased quality of life. The goal of this review is to discuss 5α-RIs therapy, the potential persistent side effects, and the possible mechanisms responsible for these undesirable effects.

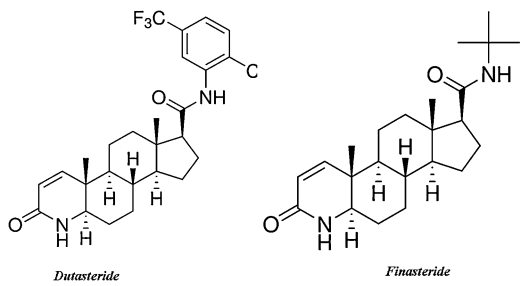

Figure 1 5α-reductase inhibitors.

Biochemistry and Pharmacology of 5α-Reductases (5α-R) and their Inhibitors

Two isozymes, namely, 5α-R type 1 (5α-R1) and 5α-R type 2 (5α-R2) have been well characterized [9]. They are potential targets for drug therapy. 5α-R enzymes reduce the double bond at the 4,5 position in C19 and C21 steroids. 5α-R enzymes