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Review

Androgenic alopecia; the risk–benefit ratio of Finasteride

David L. Rowland[1]*, Ion G. Motofei[2], Ioana Păunică[2], Petrișor Banu[2], Mihaela F. Nistor[2], Stana Păunică[3], Vlad D. Constantin[2]

[1]Valparaiso University, Department of Psychology, Valparaiso, Indiana, USA
[2]Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania
[3]Carol Davila University of Medicine and Pharmacy, Dan Theodorescu Hospital, Bucharest, Romania
#All authors contributed equally to this work and thus share first authorship.

Abstract

Finasteride is currently approved and largely used as a therapeutic option for androgenetic alopecia. Apparently a safe drug and effective at the onset of its application, several concerns have since appeared over the years regarding the frequency and magnitude of finasteride adverse effects, which in some cases appear irreversible even after drug termination.

This paper discusses the use of finasteride for androgenic alopecia from two distinct perspectives. On the one hand, androgenic alopecia is a condition that especially affects a person's self-image and esteem, aspects that are subjectively-constructed and thus relative and changeable. On the other hand, this condition involves a multifactorial etiology, with androgens being only partly responsible. Because androgens have important and unique physiological roles within the body, any procedure that results in androgenic suppression should be advised with caution. Furthermore, adverse effects induced by finasteride are neither fully documented nor easily treated. Finally, as alternative therapeutic approaches (such as topical finasteride) become available, the oral administration of finasteride for androgenic alopecia should, in our opinion, be reevaluated. Due to such concerns, a detailed and informed discussion should take place with patients considering therapy with finasteride for androgenic alopecia.

Keywords : androgenic alopecia, the risk–benefit ratio, finasteride, adverse effects, post-finasteride syndrome

Highlights

- ✓ Finasteride administration places the subjects with androgenic alopecia into an abnormal state, characterized by a low level of DHT
- ✓ Finasteride adverse effects persist in some men indefinitely after treatment cessation, the corresponding medical support being non-specific, namely symptomatic

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✉ *Corresponding author: David L. Rowland, Valparaiso University, Department of Psychology, Valparaiso, IN, 46383-6493, e-mail: david.rowland@valpo.edu

Introduction

Androgenetic alopecia (AGA) is not considered an effective disease, as it has minimal or no impact on body physiology. However, it is currently accepted as a relatively benign affection that not only has a psychological impact but also has variable psycho-social implications. Some individuals adapt well to AGA, while others seem to be severely disturbed, the condition being associated with decreased self-esteem, stress, and even depression (1). Depending on geographic region and culture, bald people are sometimes perceived by others as less attractive and older (2). Studies performed on patients with hair loss have shown that younger individuals and those with longer duration of AGA are generally more severely affected regarding self-esteem and social perception (3).

Various therapeutic approaches for AGA have been proposed and tested in clinical practice, with topical minoxidil and oral finasteride both currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as treatment options. Before beginning therapy, patients must be advised that ongoing administration is required in order to achieve and maintain therapeutic benefits on hair loss (4).

Other therapeutic strategies have been also tested, some positive results being observed with Alfatradiol (17-α-estradiol), latanoprost, bimatoprost, ketoconazole, and various topical reagents (5). Furthermore, recent studies with platelet-rich plasma (alone or in combination with minoxidil) seem promising in the management of AGA (6). A surgical approach toward AGA includes autologous hair transplantation using hair follicles especially from the occipital area. For both men and women, predicted results are generally considered acceptable; however this procedure can be performed only by an experienced surgical team. Moreover, implantation of prosthetic hair is associated with some (non-negligible) adverse effects (7). For women with AGA, the use of several drugs such as cyproterone acetate, spironolactone, and flutamide have been investigated. Such compounds have shown only modest results in ameliorating AGA, a better effect being obtained in women with hyperandrogenism (8).

All therapeutic solutions presented above have variable adverse effects and relatively limited results (which can be maintained only through ongoing administration of the drug), so that the choice of the most adequate therapy is not straightforward. This paper continues a series of articles focused on finasteride administration for androgenic alopecia that better evaluate the opportunity of long term use of an oral chemical compound for a biological condition having non-life-threatening implications.

Discussion

Inhibitors of the 5α-reductase enzyme such as finasteride and dutasteride are currently approved and administered for benign prostatic hyperplasia, while for androgenic alopecia these same compounds are the subject of controversy in the literature. Several studies suggest that finasteride should be used with caution for AGA due to the considerable adverse effects induced in some men (9). These adverse effects are the consequence of the action of finasteride in decreasing the conversion of testosterone into the more potent metabolite, dihydrotestosterone (DHT), a natural compound that plays a critical role in the process of growth and maintenance of several functions of tissues and organs (thereby modulating important biochemical signaling pathways of human physiology). In support of this idea, testosterone deficiency, for example, is a recognized medical condition with a specific symptomatology. Administration of exogenous testosterone in hypogonadal men leads to correction of the plasmatic level of testosterone, which often is followed by amelioration and subsequent disappearance of the symptomatology (10).

Inhibitors of 5α -reductase enzyme therefore have the potential to induce a veritable hypogonadal status, yet in turn, the same 5α -reductase inhibitors have the capacity to ameliorate androgenic alopecia. Accordingly, administration of finasteride and dutasteride for androgenic alopecia might be viewed in two very different ways. Taking into account only its therapeutic efficiency for AGA, several authors have demonstrated that dutasteride (a stronger inhibitor/ more potent antiandrogen than finasteride) produces superior results in ameliorating androgenic alopecia than finasteride, such that it should be preferred in clinical practice for AGA (11).

In contrast, from the perspective of drug safety and adverse effects, other authors have resisted the use of dutasteride and, further, suggest that *oral* finasteride should be replaced with *topical* administration. Studies have shown that both scalp and plasma DHT levels significantly decrease after topical application of finasteride, while no changes of testosterone levels were registered in plasma. In all studies investigating topical

finasteride, significant decreases in the rate of hair loss and increases in total and terminal hair counts (4) were noted.

1. Pharmacology of finasteride

Generally, inhibition of the 5α-reductase enzyme by this drug disrupts the conversion of testosterone to DHT, resulting in a decrease in serum DHT levels by about 65-70%. Thus, finasteride does not completely suppress DHT production because it lacks significant inhibitory effects on the 5α-reductase type I isoenzyme, the main inhibitory effect being on the type II and III isoenzymes. In fact, the action of the 5α-reductase enzyme is more complex, intervening in the metabolism of multiple neurosteroids within the brain (e.g., testosterone, progesterone, deoxycorticosterone, etc.), neuromodulators that further interfere with cerebral activation of $GABA_A$ receptors (12). By inhibiting the 5α-reductase enzyme, finasteride leads to several hormonal abnormalities and GABA disruption, with important implications on various neurophysiological processes of the brain. Such interference is encountered not only during finasteride administration but also after treatment cessation, which is clinically expressed as the post-finasteride syndrome. Men with post-finasteride syndrome present—at considerable periods of time after the therapy termination ranging from months to years—disturbed levels of specific neurosteroids in cerebrospinal fluid and plasma, including: increased testosterone, pregnenolone, 5a-androstane-3a, 17b-diol, and decreased progesterone, dihydroprogesterone, dihydrotestosterone, and allopregnanolone (13).

After finasteride administration, circulating levels of testosterone and estradiol slightly increase (by up to 15%), remaining however within the physiologic range, though qualified by the fact that testosterone is much less active than DHT, which decreases significantly. Similar variation has been observed for luteinizing hormone and follicle stimulating hormone, which increase by about 10% during finasteride administration though without exceeding physiological levels.

Finally, studies show that finasteride action is more complex than initially assumed, inhibiting not only 5α-reductase but also competitively inhibiting the 5β-reductase (AKR1D1) and other possible enzymes (14).

Oral administration of finasteride is not affected by food, having a good absorption and a bioavailability around 65%. The maximum plasmatic concentration is reached about 1-2 hours after administration, successive doses leading to a slow accumulation of the drug, with plasma protein binding of finasteride being about 90%. finasteride crosses the blood-brain barrier, this capacity of the drug being able to explain many finasteride side effects, like mental and sexual impairment.

Finasteride (administered orally) is extensively metabolized by cytochrome P450 in the liver, the resulting metabolites having (comparable to finasteride) no more than 20% inhibitory activity. Oral administration of finasteride produces a significant decrease of plasmatic DHT concentrations during the first 6-8 hours, and this effect persists for about 24 hours for a single dose, and longer for repeated administrations. Daily administration of finasteride suppresses the serum DHT level by about 65-70%, depending on the dose.

Excretion is largely realized as metabolites through urine (about 39%) and feces (57-60%). The mean terminal half-life of finasteride is about 7 hours, shorter in younger men and longer in men over 70 years (15).

2. Adverse effects of finasteride

Finasteride side effects are the consequence of cerebral interferences of this drug with sexual neuromodulators and $GABA_A$ receptors, although a direct action of finasteride on cerebral receptors cannot be excluded. Such adverse effects described in the case of finasteride can be absent or negligible (anhedonia, lack of mental concentration, insomnia, chronic fatigue, elevated body mass index), or in contrast, quite severe (depression, suicidal ideations, impotence, erectile dysfunction, decreased libido, ejaculation disorders) (16, 17).

Due to interference with $GABA_A$ receptors, finasteride seems to change tolerance to ethanol in some individuals, with former users of finasteride reporting a variable decreasing tolerance to alcohol (18). Other studies have reported possible connections (if not causal relationships) between finasteride administration and the occurrence of different forms of neoplasia, such as high-grade prostate cancers or male breast cancer (19, 20). If finasteride is administered to early pregnant women, contraception should be taken into account due to a potential embryoteratogenic effect, while in postmenopausal women finasteride seems to be effective only at high doses (21).

Finally, hormonal disturbances and GABA interferences from finasteride are encountered not only during the drug administration but also after treatment cessation in some patients, with corresponding clinical manifestations in the form of the so-called post-finasteride syndrome. The most frequent manifestations of post-finasteride syndrome are relatively similar with finasteride side effects occurring during drug

administration, being represented especially by mental/psychological impairments and sexual disorders.

3. Inconsistent adverse effects of finasteride

Recent studies suggest that the main (mental and sexual) side effects of finasteride would be encountered only in a subset of men, according to structural and informational dichotomies of the brain. These two neuro-physiological processes of the brain are presumably interrelated with hand preference and sexual orientation in both men and women (22-24).

Informational dichotomy of the brain is closely related to two distinct and opposite cerebral networks (task positive network and default mode network), sexual hormones acting on the concrete mind while sexual pheromones preferentially activating the abstract mind (25). *Structural* dichotomy of the brain results from the lateralization process of the brain, with androgens and female pheromones activating the left hemibrain, and estrogens and male pheromones activating the right hemibrain (26, 27).

According to this line of thinking, finasteride adverse effects would be encountered most strongly in right-handed persons who present a concrete-thalamic psycho-physiologic profile. In contrast, left-handed men with a concrete-thalamic profile would be less likely to develop side effects.

Thus, hand preference and psychological profile/ sexual orientation could be used as possible predictive factors for finasteride side effects, being therefore able to delineate, prior to treatment, patients having a lower risk for developing sexual side effects to the drug. For those men with androgenic alopecia having a lower predicted risk for adverse effects, the use of finasteride would be presumed safe (7).

4. The risk-benefit ratio of finasteride administration in androgenic alopecia

To appreciate the risk-benefit ratio of finasteride administration on patients with androgenic alopecia, it is first necessary to establish the major elements that influence the evaluation.

- First, male androgenic alopecia is a benign condition with a multifactorial etiology, being only in part induced/ supported by DHT. Other non-hormonal co-factors are also involved, as those with androgenic alopecia actually have a normal (non-elevated) level of DHT. Thus, finasteride administration places subjects with androgenic alopecia into an abnormal state, characterized by a low level of DHT.
- DHT, the most active androgenic compound, has its own (neuro-endocrine, metabolic, etc.) physiological roles within the body, and its suppression should be carefully advised. As an example, recent studies show that 5α-reductase-2 deficiency leads to reduced dominance-related and impulse-control behaviors (28). In addition, studies using functional magnetic resonance imaging show that men with post-finasteride syndrome (consisting of sexual dysfunctions and major depression) revealed abnormal function in brain connectivity (29).
- More importantly, adverse effects induced by finasteride are incompletely documented. In support of this point, mental and sexual functions, generally affected in tandem by finasteride, lead to specific disorders such as sexual dysfunctions and depression, which may potentiate one other and which do not respond well to established/ etiological treatments. Furthermore, the post-finasteride syndrome itself has yet to be fully elaborated (17).
- Adverse effects from finasteride have generally been investigated only over relatively short periods of time. Important additional data are needed to understand potential metabolic implications that might develop 5-10 years after finasteride cessation.
- Study design and procedures should also be revisited. For example, the frequency and magnitude of finasteride adverse effects strongly depend on the study protocol, being higher when patients are advised (before the therapy) of possible adverse effects, and lower (or ignored) when the patients are not advised (30).
- Alternative therapeutic approaches are becoming available, such as topical application of finasteride which bypasses the liver (toxicity) and which results in higher concentrations in the scalp skin at low doses than oral administration.
- Finally, androgenic alopecia is a condition that can affect one's self-image and esteem, aspects that are subjective/ relative and thus changeable over time. Contrary to this perspective, a possible post-finasteride syndrome could persist indefinitely in time, and subjects must be informed before therapy about these aspects.

Conclusions

Although not an exhaustive presentation, here we attempted to highlight the importance of patient informing and consent before commencing therapy with finasteride for androgenic alopecia. Generally, men who seek medical support for androgenic alopecia seem to be more emotionally distressed than others, while adverse effects occurring in those with post-finasteride syndrome can persist indefinitely in time.

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