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REVIEWS

Finasteride and Dutasteride for the Treatment of Male Androgenetic Alopecia: A Review of Efficacy and Reproductive Adverse Effects

Mariah C. Estill[1], Avery Ford[1], Ruba Omeira[1], Matthew Rodman[1]

[1] Georgetown University School of Medicine

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Finasteride and dutasteride are 5-α-reductase inhibitors (5-ARIs) used to treat androgenetic alopecia (AGA). This review evaluates the efficacy of 5-ARIs for treatment of men with AGA and the potential adverse effects on reproduction including sexual dysfunction, infertility, and teratogenicity. A broad literature review was conducted to search for publications on 5-ARI treatment in men with AGA. Hair counts, hair growth assessments, sexual adverse effects (erectile dysfunction, ejaculatory dysfunction, and decreased libido), change in sperm parameters (decreased sperm count, semen volume, sperm motility), and teratogenic drug concentration levels in semen were the measured outcomes of studies included in this literature review. Both finasteride and dutasteride are effective at treating hair loss in male AGA, with studies finding dutasteride was more efficacious than finasteride. Many studies reported sexual adverse effects of 5-ARIs that are uncommon and resolve spontaneously, although there remains no consensus with respect to the presence, severity, and duration of sexual adverse effects. 5-ARIs may have a negative impact on spermatogenesis although the clinical significance of this is unclear and discontinuation of these medications results in improved sperm parameters for most patients. Teratogenicity after paternal exposure is unlikely due to the low concentration of 5-ARIs absorbed in semen. Further research is needed to evaluate the effects of 5-ARI use on reproduction.

Introduction

Male pattern hair loss, also called male androgenetic alopecia or androgenetic alopecia (AGA), is the most common cause of hair loss in men.[1] AGA is a skin condition characterized by changes to hair cycle, follicular miniaturization, and inflammation that contribute to a pattern of progressive hair loss. AGA in men usually begins to manifest itself between adolescence and age 30 years, with a younger onset predicting a more severe form of the condition. By age 50 years, approximately 50% of men are affected to some extent by AGA.[2] AGA affects as much as 80% of the male population.[3] Hair loss from AGA has been correlated with decreased quality of life and psychological distress.[4] Given its high prevalence and psychosocial morbidity, there is a demand for treatment options.

AGA is a genetic disorder with an excessive response to androgens. Finasteride and dutasteride are 5-α-reductase inhibitors (5-ARIs) used in the treatment of AGA by preventing the conversion of testosterone to dihydrotestosterone (DHT) because suppression of circulating levels of DHT is thought to improve hair growth in men with AGA. During normal hair growth, activation of the androgen receptor shortens the anagen (growth) phase. It has been proposed that excessive activation of the androgen receptor by DHT leads to progressively shorter anagen phases and follicular miniaturization.[5] This

results in shorter and thinner hair follicles that are unable to reach the surface of the scalp creating the appearance of hair loss seen in patients with AGA. 5-ARIs are also used at higher doses to treat benign prostatic hyperplasia (BPH). There have been adverse sexual health effects reported with 5-ARI use including erectile dysfunction, decreased libido, and ejaculation disorders. There is also concern for teratogenicity and potential effects on spermatogenesis. This literature review provides an overview of published research on the efficacy of finasteride and dutasteride for treatment of AGA in men and the potential for adverse effects on reproduction.

Methods

PubMed/MEDLINE and Google Scholar were used to search for documented cases of sexual adverse effects in men treated with finasteride and dutasteride for AGA published in the literature. The following search terms used were: *finasteride*, *dutasteride*, *androgenetic alopecia*, *sexual dysfunction*, *erectile dysfunction*, *post-finasteride syndrome*, *infertility*, *spermatogenesis*, *sperm count*, and *teratogenicity*. References cited in the identified articles were analyzed for additional primary articles to review. The search was limited to articles written in the English language published until April 2023.

Treatment With 5-ARIs

5-ARIs are thought to improve hair growth in men with AGA by reducing the amount of circulating DHT and thus its potential impact on androgen receptors. There are two 5-ARIs used for the treatment of AGA: finasteride and dutasteride.

ORAL FINASTERIDE

Finasteride is a type II 5-ARI used to limit the conversion of testosterone to DHT. Oral finasteride, 1 mg, daily is the only 5-ARI that has received Food and Drug Administration (FDA) approval for AGA treatment. There have been multiple studies evaluating the effectiveness of finasteride in treating men with AGA, in which the use of finasteride has been shown to significantly reduce the progression of baldness, while also increasing new hair growth as measured by hair count and weight.[5-7]

In two 1-year trials, 1553 men with AGA were treated with oral finasteride, 1 mg, or placebo daily, and 1215 men continued in blinded extension studies for a second year. These trials showed that finasteride led to improvement in hair counts, patient/investigator assessments of hair growth, and panel review of photographs. Over a 2-year period, treatment with finasteride, 1 mg, daily slowed progression of hair loss and increased hair growth in men with AGA.[8]

In a systematic review that included 12 studies, 3927 men with AGA were randomized to receive either oral finasteride or placebo. In comparison with placebo treatment, finasteride therapy resulted in a greater increase in hair count and investigator/patient assessments of hair appearance.[9]

ORAL DUTASTERIDE

Dutasteride is a type I and II 5-ARI that is FDA approved for treatment of benign prostatic hyperplasia and is used off label to treat AGA.[5] Although dutasteride has not received FDA approval for AGA treatment in the United States, other countries, such as Japan, South Korea, and Taiwan, have approved oral dutasteride at 0.5 mg daily for treating male AGA.[10]

In a randomized, double-blind, placebo-controlled study, 153 men with AGA were randomized to receive dutasteride, 0.5 mg, daily or placebo daily for 6 months.[11] Researchers found that dutasteride over 6 months had a higher efficacy compared with placebo in hair counts, participants' self-assessments of hair growth, and investigator/panel photographic assessments of hair growth.[11]

In a multicenter, open-label, prospective outpatient study, 110 Japanese men with AGA completed 52 weeks of treatment with dutasteride, 0.5 mg, daily.[12] Hair growth, hair restoration, and global appearance of hair at 52 weeks improved from baseline in this study. The researchers concluded dutasteride, 0.5 mg, daily exhibited efficacy for treatment of AGA.[12]

COMPARISON OF ORAL FINASTERIDE AND DUTASTERIDE

Finasteride and dutasteride are used in clinical practice to treat men with AGA.[5] Both finasteride and dutasteride are considered efficacious at reducing male pattern hair loss by decreasing DHT levels and thus limiting their action of hair follicles.[13] Dutasteride is more potent than finasteride due to its ability to inhibit both 5-α-reductase types I and II, thus leading to a 90% reduction in DHT serum levels compared with finasteride with a reduction of only 70%.[14]

In a randomized, placebo-controlled study, researchers compared the efficacy of dutasteride to finasteride. This study had a large sample size of 917 men with AGA and participants were randomized to receive dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d), or placebo.[15] Dutasteride, 0.5 mg, significantly increased hair count and improved hair growth at week 24 compared with finasteride ($P = .003$, $P = .004$, and $P = .002$, respectively) and placebo (all $P < .001$). Dutasteride was more effective than finasteride and placebo in increasing hair count and results were dose dependent.[15]

Two different meta-analyses demonstrated that oral dutasteride was more effective than oral finasteride for the treatment of male AGA. In the first meta-analysis, 23 studies were included, with 2 studies being single-group observational studies and the remaining 21 studies being randomized trials.[16] This meta-analysis showed that taking oral dutasteride, 0.5 mg, daily led to a greater increase in total hair count after 24 weeks. When compared with finasteride, 1 mg, daily, the difference was found to be 7.1 hairs/cm^2, indicating that oral dutasteride was more effective.[16]

The other meta-analysis found that dutasteride provided better efficacy than finasteride in treating men with AGA during a 24-week treatment period.[17] Three articles with 576 participants were included in the meta-analysis. The researchers found a statistically significant difference in treatment results when comparing mean change in total hair count, investigator/panel's assessment of photographs, and the participants' assessments after treatment.[17] The finding that dutasteride was more efficacious than finasteride in treating AGA aligns with previous research indicating dutasteride was a more potent inhibitor of 5-α-reductase and a better suppressor of DHT.[18]

TOPICAL FINASTERIDE EFFICACY

In recent years, topical administration of finasteride has been studied. A systematic review, which included 7 studies, was performed to evaluate the treatment of AGA with topical finasteride.[19] Researchers found that in patients treated with topical finasteride for AGA, there was a significant reduction in the rate of hair loss, increase in total hair counts, and positive hair growth assessments in all studies.[19]

In a randomized, double-blind, double-dummy, parallel-group study conducted in men with AGA over a 24-week period, patients were randomized to the either receive topical finasteride, oral finasteride, or placebo. Compared with placebo, topical finasteride significantly increased hair count from baseline to week 24 (adjusted mean change, 20.2 vs. 6.7 hairs; $P < .001$), while being numerically similar between topical and oral finasteride.[20] Researchers concluded that topical finasteride improved hair count compared with placebo while having a similar effect to oral finasteride.[20]

TOPICAL DUTASTERIDE EFFICACY

Research published on topical dutasteride in treating AGA is limited to a few studies where topical dutasteride has been used as an agent in mesotherapy. Mesotherapy is a technique involving multiple intradermal injections of medication diluted in small doses into an area in which their effect is needed.

In a blinded, placebo-controlled study, participants were randomized to receive 7 intradermal mesotherapy injections of either 0.05% dutasteride containing solution or 0.9% saline over 12 weeks or receive placebo. The study found that those receiving dutasteride had a statistically significant increase in mean hair count when compared with placebo (Mean Density, 7.90 hairs [95% CI, 7.14-8.66]; $P \leq .001$).[21] There was a statistically significant improvement with dutasteride in independent observer assessment ($P = .001$) and participants' self-assessment ($P < .001$). Researchers concluded that mesotherapy with dutasteride was more effective than placebo in treating men with AGA.[21]

A recent randomized, double-blind, placebo-controlled trial evaluated the use of microneedling with topical 0.01% solution dutasteride compared with saline solution over a 20-week period in men with AGA. This study found that

microneedling with dutasteride produced a greater overall change in hair thickness, hair density, and ratio of vellus hair/terminal hair.[22] Researchers concluded that microneedling with topical dutasteride was an effective therapy for AGA and further research should include follow-up studies to establish the persistence of treatment efficacy over the long-term.[22]

We found only 1 study comparing topical and oral dutasteride in the treatment of AGA. A systematic review compared the findings of 5 studies with oral dutasteride and 3 studies with intralesional dutasteride.[23] None of the included studies directly compared oral vs intralesional dutasteride. Researchers compared the mean change in hair count between oral or intralesional dutasteride and placebo, although only 1 study reported hair count for intralesional dutasteride. The researchers concluded that although both interventions worked better than placebo, there are not enough data to reliably compare outcomes and that further studies are needed to assess the efficacy between topical and oral dutasteride.[23]

Sexual Dysfunction With 5-ARI Use

Although 5-ARIs are considered well-tolerated medications, adverse sexual effects have been reported including decrease or loss of libido, ejaculatory dysfunction, and erectile dysfunction.[24] Randomized clinical trials have demonstrated increased incidences of these adverse sexual effects in men taking finasteride and dutasteride.[25]

FINASTERIDE

The most common category of complications reported with finasteride use was sexual adverse effects. Erectile dysfunction is the most commonly reported followed by ejaculatory dysfunction and loss of libido.[26] Several studies have found that in patients treated with finasteride, 5 mg, daily, erectile dysfunction was reported in 3.4% to 15.8% of patients (compared with 1.7% to 6.3% with placebo), decreased libido in 2.36% to 10.0% of patients (1.2% to 6.3% of patients treated with placebo), and ejaculatory dysfunction in 0.9% to 5.7% of patients (compared with 0.5% to 1.7% treated with placebo).[27]

A recent systematic review evaluated sexual dysfunction in men taking systemic dermatologic medication. This review found that most studies with patients taking high-dose finasteride described relatively common sexual adverse effects of decreased libido, impotence, and ejaculation disorders.[28] However, high-dose finasteride at 5 mg daily is typically used to treat BPH and is rarely used in dermatology. It is also important to note that prostate disease itself is a risk factor for erectile dysfunction, which may contribute to the development of sexual dysfunction.[28] Among studies with men taking low-dose finasteride at 1 mg daily for AGA, there was less conclusive evidence of sexual adverse effects. Five studies included in the systematic review did not support increased risk of sexual dysfunction, while 10 studies provided evidence of increased rates of sexual adverse effects.[29] The researchers

acknowledged that this review included studies limited by sample size and methodology, with some studies not including any formal evaluation of male sexual function. These limitations may explain the inconsistency in findings among the included studies.

A meta-analysis examined the risk of adverse sexual effects in men treated with 5-ARIs for AGA. A subgroup analysis of 11 studies found that among men with AGA, there was a statistically significant increase in sexual dysfunction in those treated with finasteride, 1 mg, daily compared with placebo.[30] Finasteride, 1 mg, daily had a 1.66-fold risk of adverse sexual effects overall compared with placebo (95% CI, 1.20-2.30). The risk of erectile dysfunction was significantly increased at nearly 2-fold (95% CI, 1.10-3.60), while the risk of decreased libido and difficulty in ejaculation increased but not significantly.[30]

PERSISTENT SYMPTOMS

When sexual adverse events occur in patients taking finasteride, some studies have indicated that symptoms often resolve either while continuing treatment or with discontinuation of the medication. However, in recent years, there have been reports of persistent sexual (low libido, erectile dysfunction, and orgasmic dysfunction) and psychological (depression, anxiety, and suicidal ideation) symptoms that persist despite discontinuation of finasteride.[31,32] This led to the coining of the term *postfinasteride syndrome*. Increased reports of these symptoms resulted in the labeling update of finasteride to include the risk of depression and persistent sexual dysfunction by regulatory agencies including the FDA.[33] However, there has been criticism and doubts raised about the existence of postfinasteride syndrome due to the poor quality of the studies performed.[34,35]

In a retrospective study examining this topic, 71 men with a history of finasteride treatment and persistent sexual adverse symptoms underwent standardized interviews.[32] The participants reported new-onset sexual dysfunction (low libido, erectile dysfunction, and problems with orgasm) associated with finasteride use and these symptoms remained for at least 3 months despite discontinuation of the medication. It was reported that 96% continued to experience these effects when reassessed 9 to 16 months (mean, 14 months) later.[32] It is important to note that this study had selection bias because the participants had self-reported sexual dysfunction and were recruited from an online forum for individuals with unresolved adverse effects after the use of 5-ARIs.

This contrasts with the results of the Proscar Long-term Efficacy and Safety Study (PLESS), a 4-year, randomized, double-blind, placebo-controlled trial evaluating the incidence and resolution of sexual adverse effects in 3040 men, aged 45 to 78 years, treated with finasteride, 5 mg daily, for benign prostatic hyperplasia. Researchers found that in the first year, 15% of finasteride-treated patients reported sexual adverse effects compared with 7% in the placebo group

($P < .001$).[36] In the subsequent 3 years of the study, there was no difference between the finasteride and placebo groups in the incidence of new sexual adverse effects. The reported sexual adverse effects resolved while continuing therapy for 12% of the finasteride-treated patients and 19% of the placebo patients. Only 4% of the finasteride-treated patients and 2% of the placebo patients discontinued the study due to sexual adverse effects. In those who discontinued treatment, 50% in the finasteride group and 41% in the placebo group experienced resolution of their sexual adverse effects after stopping treatment.[36] Researchers concluded that there was a higher incidence of sexual adverse effects associated with finasteride use, but only during the first year of treatment. This study found that for participants who reported sexual dysfunction and stopped treatment, the continuation of symptoms in the finasteride group was less than in the placebo group.[36]

Furthermore, a systematic review found that most patients treated with finasteride had resolution of symptoms after discontinuation or while continuing finasteride therapy. However, there were some studies that described a subset of patients with persistent adverse effects after discontinuation of finasteride. Three studies included in this systematic review showed complete reversibility of sexual dysfunction in all patients, while 11 studies described persistent sexual dysfunction with irreversible symptoms including erectile dysfunction, decreased libido, decreased arousal, and problems with orgasm.[29] Although postfinasteride syndrome seems to be supported by some studies, it is not consistently characterized, and the poor quality of studies limits the findings.

DUTASTERIDE ADVERSE EVENTS

Similar to users of finasteride, there have been reports of sexual dysfunction among those using dutasteride. In a study examining dutasteride use in males with BPH, researchers found sexual adverse effects of erectile dysfunction in 7.3%, decreased libido in 4.2%, and ejaculation disturbances in 2.2% of patients.[37]

A meta-analysis of 3 randomized clinical trials found that the most common adverse effect reported with dutasteride compared with placebo for BPH was sexual dysfunction (odds ratio, 0.41 [95% CI, 0.31-0.54]; $P < .001$).[38] In the first year of treatment, dutasteride was found to cause a higher incidence of sexual dysfunction events compared with placebo (odds ratio, 2.68 [95% CI, 2.19-3.28]; $P < .001$).[38] The sexual adverse events reported included impotence, decreased libido, gynecomastia, and ejaculation disorder. Most of these events were transient and in the second year of treatment with dutasteride, the incidence of new occurrences of each event decreased, with no statistically significant difference compared with placebo.[38]

To evaluate the impact of dutasteride wh8en used at a lower dose to treat AGA, a randomized, double-blind study examined sexual dysfunction in participants.[39] In this study, 117 men with AGA were randomized to receive either dutasteride, 0.5 mg, or placebo once daily for 24 weeks, followed by open-label dutasteride, 0.5 mg, for 24 weeks.[39]

The sexual adverse events were 2-fold higher in the dutasteride group (16%) than in the placebo group (8%) during the double-blind period.[39] Although those taking dutasteride had a larger incidence of reported sexual dysfunction, the adverse events were reversible and resolved either during treatment or within 6 weeks after treatment discontinuation. Dutasteride was not associated with sexual dysfunction that persisted following treatment discontinuation.[39]

COMPARISON OF FINASTERIDE AND DUTASTERIDE

The half-life of dutasteride is 5 weeks compared with 6 to 8 hours for finasteride.[40] For this reason, it has been thought that the potential adverse effects of sexual dysfunction with dutasteride could be longer lasting and more challenging to reverse.[40-42] Despite this hesitancy about dutasteride use, sexual adverse effects in patients treated with dutasteride have been observed to be comparable with those treated with finasteride. Similar rates of sexual adverse effects have been reported in multiple studies and like finasteride, some studies reported that those treated with dutasteride showed improvement in symptoms over time.[27]

Recently, a meta-analysis examined the adverse effects of dutasteride compared with finasteride in treating men with AGA and included 3 randomized clinical trials that found that dutasteride and finasteride had similar rates of adverse sexual function reactions over 24 weeks of treatment.[17] There was no statistical difference in altered libido (P = .54), erectile dysfunction (P = .07), and ejaculation disorders (P = .58) when comparing finasteride and dutasteride use in the short-term.[17]

A meta-analysis evaluating the risk of sexual dysfunction in men treated with finasteride, 1 mg, daily or dutasteride, 0.5 mg, daily for AGA included 15 randomized, double-blind, placebo-controlled trials with 4495 participants.[30] The relative risk for sexual dysfunction was 1.66 (95% CI, 1.20-2.30) for finasteride and 1.37 (95% CI, 0.81-2.32) for dutasteride. Both finasteride and dutasteride were associated with an increased risk of sexual dysfunction, but the increase was not statistically significant for dutasteride.[30] Still, there was only a small number (n = 5) of relevant studies on dutasteride and further research into dutasteride is likely required to clarify the risk of sexual dysfunction.

TOPICAL FINASTERIDE ADVERSE EVENTS

The sexual adverse effects that develop in some patients treated with oral finasteride are thought to be related to the amount of circulating drug in plasma that is needed to attain an effective concentration at the scalp. It has been proposed that topical administration of finasteride may reduce systemic effects by preferentially inhibiting 5-α-reductase locally in the scalp and reducing the drug concentration present in plasma.[19,20]

A randomized, double-blind trial of men with AGA over 24 weeks compared the efficacy of topical finasteride, oral finasteride, and placebo. It found no significant differences between topical finasteride and placebo in mean scores on the Sexual Dysfunction Questionnaire at week 12 or 24.[20] This study also measured finasteride concentrations in plasma and DHT concentrations in serum. The maximum plasma concentration of finasteride was lower in men treated with topical finasteride compared with oral finasteride. This study suggested that topical finasteride had lower systemic exposure of finasteride and less impact on serum DHT concentrations, without significant development of adverse sexual effects compared with oral finasteride.[20]

TOPICAL DUTASTERIDE ADVERSE EVENTS

For patients who are concerned about systemic adverse effects of oral dutasteride, the possibility of using dutasteride locally could potentially minimize systemic adverse effects on reproduction. In a meta-analysis comparing sexual adverse effects with oral dutasteride and intralesional dutasteride vs placebo in AGA, there were no studies that reported sexual adverse effects with intralesional dutasteride treatment. This suggested that sexual adverse effects did not appear to be a serious concern with mesotherapy injections of dutasteride.[23]

Infertility With Finasteride and Dutasteride Use

The importance of DHT in spermatogenesis remains unclear and the potential impact of 5-ARIs use on fertility is controversial.

FINASTERIDE

There have been studies evaluating the effects of DHT suppression mediated by finasteride on spermatogenesis. In a multicenter, double-blind, placebo-controlled study, researchers demonstrated that treating healthy men with finasteride, 1 mg, daily for 48 weeks did not significantly affect sperm concentration, total sperm per ejaculate, sperm motility, or morphology.[43]

The effect of finasteride on spermatogenesis at a higher dose of 5 mg daily has also been examined. In a multicenter, randomized, double-blinded study, 21 healthy men completed treatment with finasteride, 5 mg, daily for 52 weeks and a 24-week follow-up phase.[44] There was a significant decrease in semen volume, sperm count, sperm concentration, and sperm motility. Sperm volume and concentration recovered comparable with baseline after 52 weeks of treatment,

while decrease in sperm motility persisted after treatment discontinuation.[44] One participant had a marked decrease in sperm count of less than 10% of baseline during treatment.[44]

The use of a higher finasteride dose at 5 mg daily compared with 1 mg daily could explain the differences seen in spermatogenesis in healthy men between these 2 studies. At 1 mg daily, there was no significant effect on spermatogenesis (concentration, sperm count, motility), while at 5 mg there was a significant reduction in volume, count, concentration, and motility. This suggests that the effect of finasteride on spermatogenesis is increased with dose administered. Furthermore, the finding of marked changes in sperm parameters in 1 participant indicated that there could be individual variability in the response to finasteride, with some patients being more sensitive to the effects of finasteride.

In contrast to the studies discussed in healthy individuals, there has been research assessing the impact of finasteride on individuals with a predisposition to infertility. In a multicenter database study investigating the characteristics and referral patterns of men presenting for male infertility assessments, 4287 men were given a standardized male infertility questionnaire to identify potentially reversible causes of infertility. Of 4287 men who sought treatment at infertility clinics, 37 (0.9%) reported using finasteride.[45]

Furthermore, in a retrospective study, 27 (0.6%) of 4400 men who presented for evaluation of infertility were found to be taking low-dose finasteride.[46] After discontinuation of the drug, there was a statistically significant increase in sperm counts (average 11.6-fold increase), with the most significant increase in men with severe oligospermia initially. Seven men had severe oligospermia (<5 million sperm/mL) with 4 (57%) having counts increase to more than 15 million sperm/mL after the discontinuation of finasteride.[46]

This study showed that finasteride, even at low doses, may have caused a decrease in sperm count in some men and cessation of the drug resulted in improvement. Researchers concluded that finasteride should be used with caution in men who desire fertility and discontinued in those with oligospermia.[46]

DUTASTERIDE

In a study comparing dutasteride vs placebo, 27 healthy men took dutasteride, 0.5 mg, daily for 52 weeks and completed 24 weeks of follow-up.[47] At 52 weeks, compared with placebo, dutasteride treatment resulted in a reduction in sperm count, semen volume, and sperm motility (23%, 26%, and 18%, respectively). There were 2 participants in the dutasteride group who had decreases in sperm count that were greater than 90% from baseline at 52 weeks.[47] At 24-week follow-up, all semen parameters were within normal range, except for sperm count, which remained decreased at 23% lower than baseline.[47]

In a multicenter, randomized, double-blinded, placebo-controlled trial where participants were randomly assigned to receive dutasteride, finasteride, or placebo, 28 healthy men completed treatment with 0.5 mg of dutasteride for 52 weeks and a 24-week follow-up phase.[44] There was a statistically significant decrease in total sperm count (-28.6%) at 26 weeks of treatment but not at 52 weeks of treatment (-24.9%) or at 24-week follow-up (-23.3%).[44] Two participants showed a significant decline in sperm count to less than 10% of their baseline with both participants showing recovery at the 24-week follow-up. There was a significant decrease in semen volume and sperm motility at all points during treatment and follow up, although these appeared to be recovering toward baseline.[44]

Both studies demonstrated a negative effect of dutasteride on spermatogenesis with decreased sperm count, semen volume, and motility, but the clinical significance of these effects of dutasteride on a patient's fertility is unclear and may be minimal or not impact fertility in most men. Furthermore, the finding that a small number of patients treated with dutasteride showed significant declines in sperm count during treatment suggested some patients may have a marked sensitivity to dutasteride and should be considered as a possible etiology when evaluating men for infertility.[44]

Teratogenicity

The use of finasteride and dutasteride in pregnant women or in women who may become pregnant is contraindicated due to increased risk of abnormal genital development in male fetuses.[5] Suppression of circulating levels of DHT is thought to inhibit the development of the external genital organs in male fetuses carried by a female exposed to finasteride or dutasteride. Similar outcomes have been reported in male infants with 5-α-reductase deficiency, further supporting the role that DHT suppression can have on fetal reproductive development.[48]

Because finasteride and dutasteride are detectable in the serum months after treatment discontinuation, males receiving 5-ARI treatment are recommended not to donate blood for a period following discontinuation of the medications. The blood donation deferral period for finasteride is 1 month after the last dose, while for dutasteride it is 6 months.[49] This recommendation is to prevent pregnant females from receiving a teratogenic drug concentration via blood transfusions, which may cause harm to male fetuses. Although the blood donation deferral period for finasteride is 1 month, a study analyzing stored blood specimens showed teratogenic drug concentration levels of finasteride in donor plasma at the time of donation and beyond the recommended drug deferral period. This may suggest a donor deferral period longer than 1 month is needed for finasteride.[50]

FINASTERIDE TERATOGENICITY

Studies have been able to measure finasteride levels in semen, demonstrating that finasteride taken by males can be secreted in semen.[48,51] The use of finasteride in reproductively active males has raised concerns about the potential for teratogenicity if females are exposed to finasteride through semen.[48,51]

In a study of 35 men taking 1-mg oral finasteride daily for 6 weeks, the highest measured semen finasteride level was 1.52 ng/mL. Assuming 100% vaginal absorption from a 5-mL ejaculate volume, this means that a female partner would be exposed to a maximum of 7.6 ng of finasteride per day, which is 650 times less than the dose of finasteride that has no effect on circulating DHT levels in men.[48] This level of finasteride is considered insignificant for the risk of causing developmental anomalies.[52,53]

In an animal study, no developmental abnormalities were observed in the offspring of untreated female rats mated with finasteride-treated male rats that received approximately 488 times the recommended human dose.[48] This suggests that finasteride teratogenicity through semen exposure was unlikely.

In other experimental studies, intravenous administration of finasteride to pregnant monkeys at high doses (up to 800 mg/d) resulted in no abnormalities in male fetuses. Although oral administration at higher doses (2 mg/kg/d) resulted in external genital abnormalities in male fetuses. No other abnormalities in male fetuses and no effects on female fetuses were observed.[52, 53]

Despite animal studies suggesting that finasteride teratogenicity after paternal exposure is unlikely due to the low concentration of finasteride absorbed in semen, there have been some reported cases of teratogenicity after paternal exposure and a possible association with spontaneous abortion.[54-57] For these reasons, it has been recommended by some researchers that males taking finasteride should avoid unprotected intercourse with a female partner who is or may be pregnant and discontinue finasteride before conceiving.[33,46,58] No mechanism has been elucidated for a finasteride-induced spontaneous abortion, although inadequate secretion of progesterone, uterine cervix stenosis, and sperm chromosomal abnormalities have been suggested as possible mechanisms.[56,57]

DUTASTERIDE TERATOGENICITY

Paternal dutasteride exposure is considered unlikely to be teratogenic because the concentration in semen is below the dose that could cause teratogenicity. Dutasteride, 0.5 mg/d, for 52 weeks would result in a maximum concentration of 14 ng/mL in semen, but the volume of semen required to cause teratogenicity is 186 mL (5 mL is an estimated volume per ejaculation).[41] If we assume complete absorption of dutasteride through vaginal contact from 5

mL of semen, at the highest measured concentration in a female weighing 50 kg, the expected dutasteride concentration in the blood would be about 0.0175 ng/mL. This concentration is approximately 100 times lower than the levels found to cause abnormalities in male genitalia in animal experiments.[47]

However, to our knowledge, there have been no clinical studies in humans to date on the teratogenic effect of paternal exposure to dutasteride. For this reason, barrier contraception during intercourse is recommended for female partners who are pregnant or may become pregnant.[33] There is no definitive guidance on when males should discontinue dutasteride before conceiving a child.[47]

Discussion

For the treatment of male AGA, finasteride is recommended to be dosed at 1 mg daily. Treatment should be given for at least 6 to 12 months to assess the drug's effects. The therapeutic effects disappear after therapy is stopped, so the drug must be continued to maintain efficacy. If finasteride therapy for 12 months is not effective, dutasteride at a dose of 0.5 mg daily can be considered.[59]

Both finasteride and dutasteride are efficacious at treating hair loss in patients with AGA. Studies have shown that compared with placebo, treatment with 5-ARIs can increase hair counts and improve assessments of hair growth. In studies comparing the efficacy of finasteride and dutasteride, dutasteride has been shown to be more effective than finasteride in increasing hair count and hair growth assessments. The finding that dutasteride is more efficacious than finasteride is consistent with previous research showing dutasteride is a more potent inhibitor of 5-α-reductase and a better suppressor of DHT.

The most commonly reported sexual adverse events with 5-ARIs are erectile dysfunction, ejaculatory dysfunction, and loss of libido, with similar rates found with both finasteride and dutasteride use. Multiple studies have found sexual adverse effects of 5-ARIs to be uncommon, significant compared with placebo, and often resolved spontaneously without discontinuing treatment, although some studies reported persistent symptoms after discontinuation of the medications. Persistent sexual dysfunction associated with finasteride, termed *postfinasteride syndrome*, remains controversial due to conflicting results between studies and poor quality of studies performed. Further research is needed to evaluate whether persistent sexual dysfunction is a potential risk of low-dose finasteride.

A direct link between sexual dysfunction and 5-ARIs has been challenging to establish. It has been suggested that the reports of sexual dysfunction may be a result of a "nocebo" effect. This is supported by a study that found significantly higher rates of sexual adverse effects among patients aware of the drug adverse effects compared with those blind to the drug adverse effects.[60] Furthermore, many of the studies evaluating sexual adverse effects with 5-ARIs

involve patients with BPH. BPH is much more common among men older than age 50 and is typically treated with higher doses of 5-ARIs than in AGA. It has been suggested that the association between sexual dysfunction and treatment with 5-ARIs could be partially related to drug dosage, duration of treatment, older age (>50 years), and history of sexual dysfunction compounding in patients with BPH.[24] This was supported by a meta-analysis that found a significantly increased risk of sexual dysfunction for men being treated for BPH with finasteride or dutasteride compared with placebo, but not in those treated for AGA.[61]

5-ARIs may negatively affect spermatogenesis, and discontinuation of these medications results in improved sperm parameters (such as sperm count, semen volume, and sperm motility) in most patients. For both dutasteride and finasteride, there seems to be a level of individual variability in response to treatment, with a small number of men having a measured response. It is possible that finasteride and dutasteride negatively impact spermatogenesis more profoundly in patients with preexisting conditions related to infertility.

As of April 2023, males receiving 5-ARI treatment are not permitted to donate blood and the use of 5-ARIs in pregnant women is contraindicated. This is due to increased risk of birth defects caused by the antiandrogenic effects of 5-α-reductase inhibition during the reproductive development of male fetuses carried by a female exposed to finasteride or dutasteride. Teratogenicity after paternal exposure through sexual intercourse is unlikely due to the low concentration of 5-ARIs absorbed in semen, although there have been some reported cases of teratogenicity in male fetuses after paternal exposure and a possible association with spontaneous abortion.

Further research is needed to evaluate the effects of 5-ARIs use on reproduction. Areas in need of investigation include (1) the potential mechanisms underlying how finasteride and dutasteride might affect sexual dysfunction, (2) the clinical significance of sperm parameter changes on a patient's fertility, (3) the potential for teratogenicity or spontaneous abortion if females are exposed to finasteride through semen, and (4) alternative administration options for 5-ARIs, such as topical application or mesotherapy injections, and whether their efficacy and decreased risk for sexual adverse effects are maintained in longer-term studies.

Conclusions

Both finasteride and dutasteride are effective at treating hair loss in male AGA, with studies finding dutasteride is more efficacious than finasteride. Overall, there remains no consensus with respect to the presence, severity, or duration of sexual adverse effects induced by 5-ARIs, although many studies suggest sexual adverse effects are uncommon and resolve spontaneously. Furthermore, it has been suggested that the reports of sexual dysfunction may be a result of a nocebo effect, drug dosage, duration of treatment, or disease process. For patients concerned about systemic adverse effects of oral 5-ARIs, topical

administration may be effective at treating AGA with less potential for sexual adverse effects. 5-ARIs may have a negative impact on spermatogenesis and discontinuation of these medications results in improved sperm parameters in most patients. Teratogenicity after paternal exposure is unlikely due to the low concentration of 5-ARIs absorbed in semen. Further research is needed to clarify the effects of 5-ARI use on reproduction.

It is important for physicians treating AGA to counsel patients about the efficacy of 5-ARIs and the potential adverse effects prior to starting treatment. It is reasonable to consider screening patients taking finasteride for sexual adverse effects, even when using a low dose. If patients experience adverse effects, discontinuation should be considered and patients should be monitored for recovery of sexual function. Finasteride and dutasteride should be used with caution in men who desire fertility and should be considered on the differential during infertility evaluations. Barrier contraception during intercourse is recommended for female partners who are pregnant or may become pregnant. Furthermore, topical application of finasteride and dutasteride may be considered as a treatment option if patients want to avoid systematic reproductive adverse effects.

Conflicts of interest

All authors have no conflict of interest to disclose.

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