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OPINION ARTICLE

Adverse Effects of 5-Alpha Reductase Inhibitor Therapy in Men With Androgenetic Alopecia: Is There Cause for Concern?☆



Efectos adversos de los inhibidores de la 5-alfa-reductasa en la alopecia androgenética masculina ¿hay por qué preocuparse?

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The 5-alpha reductase inhibitors finasteride and dutasteride are fundamental agents, along with minoxidil, for treating male androgenetic alopecia. Both inhibitors are approved for benign prostatic hyperplasia, but only finasteride has been designated (since 1997) for male androgenetic alopecia. Finasteride, a highly selective inhibitor of 5-alpha reductase type 2, lowers levels of 5-alpha-dihydrotestosterone. Dutasteride, however, is a potent inhibitor of 5-alpha reductase type 1 and 2 isoenzymes, and its antiandrogenetic effect is superior to finasteride's. These drugs have also been suggested for treating neuropsychologic disorders (Parkinsonism and Tourette syndrome) on the basis of the antidopaminergic activity of finasteride in certain regions of the brain.¹ A recent clinical trial comparing a 1-mg dose of finasteride to various doses of dutasteride and placebo showed that dutasteride at a dosage of 0.5 mg/d is more effective than the comparator dose of finasteride and of course far superior to placebo, with a similar safety profile.²

These drugs have traditionally been linked to a slightly increased risk of adverse sexual effects.³ Although the symptoms are generally minor and well tolerated, a post-finasteride syndrome was described a few years ago.⁴ This syndrome groups together sexual and nonsexual side effects that have appeared after treatment with this drug. The sexual effects have most often involved decreased libido, erectile dysfunction, and ejaculation disorder; erectile dysfunction has been reported to affect between 2% and 7% of patients on finasteride.⁵ Some authors have suggested that these same adverse effects appear more often in patients on dutasteride,⁶ and that the inhibition of nitric oxide synthase activity might be the mechanism that explains erectile dysfunction.⁷

Our clinical experience suggests that these adverse effects are reversible, resolving when the medication is stopped, or that they become less pronounced with long-term use of the drug; however, some have reported that the effects can be irreversible or persistent in susceptible patients and that they may even lead to suicidal ideation.^{8,9} These differences from our clinical experience may be due to selection biases and the absence of placebo in the cited studies. Another study recently demonstrated that patients with male androgenetic alopecia show signs of psychosocial changes due to an altered body image related to balding, potentially affecting changes in sexual desire and erectile function in ways that are not strictly related to the drugs

☆ Please cite this article as: Arias-Santiago S, Camacho-Martínez F. Efectos adversos de los inhibidores de la 5-alfa-reductasa en la alopecia androgenética masculina ¿hay por qué preocuparse?. Actas Dermosifiliogr. 2016;107:709–711.

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themselves.¹⁰ Adverse effects are said to be more common in persons who have received incorrect information about them, sometimes from relatives and friends, suggesting that the underlying mechanism is more psychological than pharmacologic. This phenomenon has been referred to as the placebo effect. Another consideration is that the most common reasons for abandoning finasteride therapy have nothing to do with the presence of adverse sexual effects but rather the lack of fulfillment of the clinical outcomes the patients expected.¹¹ In any case, well designed studies and adequate pharmacovigilance programs may provide us with more information in the future.

Men with androgenetic alopecia are at greater risk of benign prostatic hyperplasia¹² because both conditions share pathophysiologic mechanisms. A slight increase in the risk of prostate cancer has also been described for men with vertex baldness.¹³ It is therefore particularly important to consider the relation of finasteride therapy to this cancer. Although these drugs were initially thought to offer a chemoprotective effect against cancer, a study published in 2013 showed that while finasteride reduces the overall risk of low-grade prostate cancer, it nonetheless slightly increases the risk of high-grade prostate cancer (3.5%) in comparison with placebo (3%).¹⁴ However, no significant differences in overall survival or survival after the cancer diagnosis were observed. The increased risk associated with androgenetic alopecia itself and the use of finasteride justifies the pretreatment screening of these patients given that a finasteride dose of 1 mg reduces plasma levels of prostate specific antigen by 20%, especially in individuals under the age of 26 years.¹⁵

Although some studies have suggested an association between breast cancer in men and the use of 5-alpha reductase inhibitors, 2 large case-control studies recently reported no evidence of such risk with either short- or long-term therapy with either drug.^{16,17} However, unilateral gynecomastia in men has been shown to be a complication of finasteride treatment, though in many cases it reverses when treatment is suspended.¹⁸

The cardiovascular effects of 5-alpha reductase inhibitor therapy have been debated, but information is limited given that the relevant variables have not been analyzed in most clinical trials. Initial studies showed that treatment with a 1-mg dose of finasteride was associated with a decrease in glycated hemoglobin level and a slight increase in insulin resistance.¹⁹ These inhibitors have also been reported to alter cortisol concentrations and to be associated with higher insulin resistance and hyperglycemia in an animal model.²⁰ In a study of metabolic dysfunction in patients treated with finasteride and dutasteride in comparison with controls, the inhibition of both enzymes of 5-alpha reductase by dutasteride was associated with higher peripheral insulin levels.²¹ A preclinical study confirmed these data: the absence of the 5-alpha reductase type 1 isoenzyme in rats has been linked to hepatic steatosis, insulin resistance, and altered fat storage.²² Thus, the metabolic implications of treatment would be greater with dutasteride than finasteride. Although more clinical studies are needed to confirm these effects in patients treated with 5-alpha reductase inhibitors, it is important to screen for metabolic syndrome and insulin resistance when candidates are over the age of 35 years or have an Ebling grade higher than III,

which might be the case in up to half the patients we evaluate.²³

Altered bone metabolism is another recently described adverse effect. One case-control study showed that the risk of osteoporosis increased by a factor of 1.52 in patients taking finasteride for benign prostatic hyperplasia in comparison with controls.²⁴ Moreover, the risk was dose-dependent. The association between 5-alpha reductase type 1 inhibition and loss of bone density has also been demonstrated in an animal model.²⁵ These data are preliminary, however, and more studies are needed to analyze this risk in greater detail before recommending bone density studies for patients starting finasteride therapy for androgenetic alopecia.

An increased prevalence in symptoms of depression and anxiety unassociated with sexual dysfunction has also been reported in patients on finasteride, but symptoms resolved on suspending treatment.²⁶ We have not encountered this type of adverse effect in our clinical experience, but we note that lower levels of certain steroid hormones could explain such symptoms.

5-alpha reductase inhibitors—finasteride in particular—offer a safe, effective option for treating male androgenetic alopecia according to numerous studies. However, risk of adverse sexual effects have been reported in recent years, and they are potentially irreversible. We therefore believe that alternative safe, effective therapeutic targets should be investigated. Patients with androgenetic alopecia should be given complete information about the potential adverse effects of these medications so that they can make informed decisions, especially considering that the problem they seek treatment for is purely cosmetic. Starting finasteride treatment at a lower dose (0.5mg) in patients who are worried about adverse effects has also been suggested.²⁷

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