EDITORIAL

Hair Are the Rankings—5-α Reductase Inhibitors and Minoxidil in Male Androgenetic Alopecia

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Androgenetic alopecia (AGA) in men is the most common type of hair loss in the US, affecting 50% of men by age 50 and up to 90% of men in their lifetime.[1] AGA moderately impairs health-related quality of life and is associated with low self-esteem and depression.[1] Despite the outcomes associated with this condition and its high prevalence, treatment options remain limited, with topical minoxidil, oral finasteride 1 mg, and low-level light therapy being the only US Food and Drug Administration–approved therapies. In an attempt to increase therapeutic options for patients, off-label use of oral minoxidil, oral dutasteride, and higher doses of oral finasteride and topical minoxidil are increasingly reported in the literature.

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Finasteride is a 5-α reductase inhibitor (5-ARI) that inhibits the 5-α reductase type 2 enzyme, preventing conversion of testosterone to dihydrotestosterone, the main hormone contributor to AGA. At the 1 mg dose of finasteride, full efficacy for the treatment of AGA is seen at 12 months.[2] Finasteride use is associated with potential adverse events including decreased libido, erectile dysfunction, decreased ejaculatory volume, reduction in sperm count, testicular pain, depression, and gynecomastia.[2] While there seems to be a decreased risk for prostate cancer in AGA patients taking finasteride, patients receiving finasteride who develop prostate cancer may be diagnosed with higher grade prostate cancer, which might be related to tissue sampling artifact.[3] It also decreases prostate-specific antigen screening laboratory results, which could affect cancer screening. Further, 2 recent studies reported increased rates of suicide, depression, and anxiety in male patients receiving oral finasteride for AGA.[4,5]

Dutasteride is also a 5-ARI, but in contrast to finasteride, it blocks both type 1 and 2 of the 5-α reductase enzyme isoforms, and is a more potent inhibitor of dihydrotestosterone production than finasteride.[2] In the US, dutasteride is US Food and Drug Administration approved for the treatment of benign prostatic hyperplasia and has been approved in Japan and South Korea for male AGA.[6] The half-life of dutasteride compared with finasteride is also much longer (5 weeks vs 6 hours, respectively), allowing for less frequent dosing for patients who prefer it. While dutasteride has been shown to have greater efficacy in treating male AGA,[7] there are fewer studies evaluating its adverse event profile. Some studies suggest that the adverse event profiles of finasteride and dutasteride are comparable, but more research is needed to confirm these reports.[8]

Since 1998, topical minoxidil has been US Food and Drug Administration approved and widely used for the treatment of male AGA. The topical formulation was developed from the observation that men receiving oral minoxidil for hypertension had increased hair growth. High dose oral minoxidil as a treatment for severe hypertension is associated with a risk of pericardial effusion and cardiac tamponade, leading to a US Food and Drug Administration black box warning.[9] The topical formulation allowed for the treatment of AGA while avoiding undue cardiac risks. However, twice daily application of topical minoxidil may be a factor in decreased compliance because patients often report that topical minoxidil changes hair texture or causes skin irritation.[2] In recent years, the off-label use of low dose oral minoxidil (0.25 to 5 mg) has been reported as an effective treatment for AGA with minimal adverse events and better patient adherence.[10] Adverse events of low dose oral minoxidil include generalized hypertrichosis, tachycardia, postural hypotension, and edema.[10] While the minoxidil mechanism of action in treating alopecia is not fully understood, it is thought that vasodilation and upregulation of vascular endothelial growth factor leads to increased oxygen and growth factor production around the hair follicle.[9] Minoxidil is also thought to prolong the anagen growth phase of the hair follicle via activation of hair follicle potassium channels. As it is not a 5-ARI and does not affect dihydrotestosterone levels, sexual adverse events, depression, and gynecomastia are not seen with low dose oral minoxidil use.

When patients are presented with these treatment options, they frequently ask which option works best; unfortunately, comparative studies of these therapies in treating AGA are lacking. In this issue of *JAMA Dermatology*, Gupta and colleagues[11] use network meta-analyses to determine the relative efficacy of 5-ARIs and minoxidil in various dosing and administration routes in the treatment of male AGA. Based on their analysis of the change in total and terminal hair counts after 24 and 48 weeks of therapy, they propose a possible ranking in decreasing order as follows: dutasteride (oral) 0.5 mg, finasteride (oral) 5 mg, minoxidil (oral) 5 mg, finasteride (oral) 1 mg, minoxidil (topical) 5%, minoxidil (topical) 2%, and minoxidil (oral) 0.25mg.

A reviewing of the results of this study suggests that many of the comparisons are consistent with what we would expect and observe at Brigham and Women's Hospital and Massachusetts General Hospital. For example, it can be expected that 5% topical minoxidil works better than 2% topical minoxidil; 2% minoxidil is not recommended for male AGA for this reason. Although topical minoxidil ranked higher than the very low dose 0.25 mg oral minoxidil, our personal experience is

that oral minoxidil at doses of 1.25 mg to 5 mg are far superior to topical minoxidil for treating AGA.

Interpreting the difference between 1 mg finasteride, 5 mg finasteride, and dutasteride 0.5 mg is difficult in this study. As the authors explain, the relative efficacy should not be based on the surface under the cumulative ranking curve value because it does not incorporate statistical significance or quality of evidence, and a prior meta-analysis by Gupta et al[12] found no statistically significant difference in the relative efficacies of finasteride 1 mg, finasteride 5 mg, and dutasteride 0.5 mg. In addition, in the league tables, many of the differences between these treatments were not statistically significant. Therefore, even though this article ranks these therapies, the limitations of the surface under the cumulative ranking curve must be considered when interpreting the results.

Incorporating the study findings into clinical practice, we must remember to consider adverse event profiles, patient comorbidities, and patient preferences. Patients and physicians have different thresholds for risk in terms of adverse events, even when the frequency is low, as they may adversely affect quality of life, especially in the case of depressed mood and sexual adverse events associated with 5-ARIs. Although this study ranked dutasteride highest with regard to AGA efficacy, the adverse event profile is not as well studied as that for finasteride 1 mg, and patients should be counseled regarding the adverse event profile being not well studied. As more direct-to-consumer companies treating male AGA emerge, it is especially important that the potential risks of these medications be made clear to patients.

While the findings of Gupta et al[11] help us understand the relative efficacy for available AGA treatments, it also highlights the paucity of therapeutic options for this condition. Well-designed studies that investigate the pathogenesis of AGA are warranted so that we may develop more effective and targeted treatments. For decades we have based our treatment of AGA on observations made in other disease states (hypertension, prostate disease). It is time to explore other ways of treating AGA to help improve quality of life for this patient population.

ARTICLE INFORMATION

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