

What do we know about 5-alpha reductase inhibitors?

O que sabemos sobre os inibidores da 5 alfa redutase?

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ABSTRACT

Five-alpha reductase inhibitors – finasteride and dutasteride – are drug classes that have antiandrogenic properties. These drugs are commonly used to treat benign prostatic hyperplasia and androgenic alopecia. The U. S. Food and Drug Administration (FDA) has approved finasteride in 1991 for benign prostatic hyperplasia, and in 1997 for male androgenetic alopecia. In 2002, dutasteride was approved by the FDA only for benign prostatic hyperplasia, and is currently approved in Japan and South Korea for treating male androgenetic alopecia. The authors offer a comprehensive and up-to-date review on this drug's efficacy and safety.

Keywords: Alopecia; Androgens; Finasteride; Secondary effect; Dutasteride; Alopecia/therapy

RESUMO

Os inibidores da 5 alfa redutase, finasterida e dutasterida, são classes de drogas com propriedades antiandrogênicas. Esses fármacos são utilizados habitualmente nos tratamentos da hiperplasia prostática benigna e da alopecia androgênica. Desde 1991, a finasterida é aprovada pelo U. S. Food and Drug Administration (FDA) para hiperplasia prostática benigna e desde 1997 para alopecia androgênica masculina. Em 2002 a dutasterida foi aprovada pelo FDA apenas para hiperplasia prostática benigna, e atualmente no Japão e na Coreia do Sul essa droga tem seu uso aprovado para o tratamento de alopecia androgênica masculina. Apresenta-se uma revisão ampla e atualizada sobre a eficácia e segurança dessas drogas

Palavras-Chave: Alopecia; Efeito secundário; Finasterida; Dutasterida; Alopecia/terapia;

In addition to minoxidil, 5 Alpha-reductase (5AR) inhibitors are the most traditionally used treatments for androgenetic alopecia (AA). Finasteride is an inhibitor of 5AR type II and has a variable half-life of 6 to 8 hours, reducing the level of dihydrotestosterone (DHT) by 70% when used at a 5mg / day dose. Dihydrotestosterone levels return to normal 14 days after discontinuation of treatment with oral finasteride, and a reversal of the results is expected to take place 12 months after discontinuation of the treatment.¹ Dutasteride is an inhibitor of 5AR types I and II, with an half-life of 4 weeks, reducing DHT levels by more than 90% when used at a 0.5mg / day dose, being three times more efficient in inhibiting 5AR type I and 100 times more efficient in inhibiting 5AR type II.² Type I 5AR is predominantly found in extraprostatic tissues, such as in the skin and liver, whereas type II is found in normal or hyperplastic prostatic tissue.^{3,4}

Despite the fact that they have been used for many years, 5AR inhibitors have been the subject of much criticism and

Review Articles

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mistrust regarding their safety and effectiveness. In the face of so many doubts, the authors prepared the present review in search of what is new on this subject, using the Pubmed, Cochrane and Google academic databases.

Several studies have already been published on the efficacy of 1mg / day finasteride and 0.5mg / day dutasteride, with both drugs having been classified as Level I evidence in the treatment of male AA.⁵

The pathogenesis of AA is linked to the conversion of testosterone into DHT by the 5AR enzyme. Therefore, 5AR inhibitors are considered classical drugs in the treatment of AA. A clinical trial in 2014 compared 1mg / day finasteride with different doses of dutasteride and a placebo, concluding that dutasteride at a 0.5mg / day dose is more effective than 1mg / day finasteride, within similar safety standards.⁶

In the history of 5AR inhibitors use, there is an association with increased risk of sexual domain related side effects, however clinical practice in general indicates that these symptoms would be low in incidence and reversible.⁷ Several studies have shown that side effects of sexual nature are libido reduction, erectile dysfunction and abnormality in the volume of ejaculated sperm.⁸ Some articles suggest that these effects are more frequent in patients using dutasteride and that this fact could be justified by interference in the activation of the nitric oxide synthase enzyme.⁹

Some studies dating from the 1990's show the incidence of side effects in the sexual domain in patients using finasteride (5 and 1mg), with a variable percentage of 2% - 15.8%.¹⁰⁻¹² Later on, Tosti et al. found an incidence of sexual domain related side effects of 0.5% with the ingestion of 1mg / day finasteride.¹³

A prospective study in 2014 showed that Korean men with AA who had not responded to treatment with 1mg / day finasteride for 6 months, had a 77.4% improvement after undergoing 0.5mg / day dutasteride, however with transient erectile dysfunction in 17.1% of patients.¹⁴ A multicentric study including 120 patients demonstrated that dutasteride would be a potential drug for the treatment of male AA at doses of 0.5mg / day, with good tolerability and efficacy.¹⁵ In 2016, a meta-analysis reviewed 493 articles, including patients with a mean age of 60 years using finasteride or dutasteride, having demonstrated the presence of a relative risk of sexual dysfunction of 2.56 for patients with benign prostatic hyperplasia (BPH) and 1.21 for patients with AA; for erectile dysfunction the risk was 1.55 in patients with BPH and 0.66 in patients with AA; while the risk of decreased libido was 1.69 in patients with BPH and 1.11 in patients with AA.¹⁶

For some years, there have been reports and articles questioning persistent side effects in the group of patients who use 5R inhibitors.¹⁷ Some authors describe that sexual domain related side effects may be persistent and might lead to extreme situations of suicidal ideation.¹⁸ In 2017, a review article examining persistent erectile dysfunction (PED) included four variables: prostatic disease, duration of exposure to 5AR inhibitors, age, and concomitant use of non-steroidal anti-inflammatory drugs (NSAIs). That study demonstrated an incidence of 1.4%

of PED and 4.45% of transient erectile dysfunction. In the group of younger patients (16-42 years old), the risk of erectile dysfunction was greater when these patients were under prolonged use (> 205 days) of 5AR inhibitors associated with the use of NSAIs, with the risk being 4.9 times greater in these patients. That study also demonstrated some predictors of PED, such as prostate disease, prostate surgery and time of exposure to 5AR inhibitors.¹⁹

In addition to the side-effects in the sexual domain, the term *post finasteride syndrome* (PFS) has recently been used in studies of low scientific quality aimed at characterizing persistent side effects triggered during or after discontinuation of 5AR inhibitors. Symptoms include: decreased libido, erectile dysfunction, sexual anhedonia, decreased sperm count, gynecomastia, skin changes, cognitive impairment, fatigue, anxiety, depression, and suicidal ideation. In the literature, persistent side effects are only documented in low quality studies with strong bias in the selection of participants, which was carried out via blogs on the Internet. The only good quality study documenting a persistent sexual effect indicates that it is more frequent in the placebo group than in the group of patients using 5AR inhibitors, thus implying the fact that persistent side effects are not necessarily related to treatment with 5AR inhibitors. Secondary psychiatric side effects have only been documented in moderate to low quality studies, including those in patients with sexual domain related secondary side effects, which could have had an influence on the psychological state of the evaluated patients, in addition to the fact that most of the studies recruited patients through websites. It is not yet known whether PFS is real, and this question remains unanswered to date. Secondary side effects related to the sexual and psychiatric domains following the use of 5AR inhibitors are not documented by prospective studies in a way that would otherwise allow establishing the true incidence, frequency, and direct correlation with those drugs.²⁰

In the female population there are fewer studies evaluating the efficacy of 5AR inhibitors. Finasteride is classified as Level III of evidence for this group of patients. A retrospective, multicentric study published in 2014 demonstrated similar improvement in the subjective and objective evaluations for the groups of patients who used finasteride and dutasteride. Nevertheless, in the group of patients younger than 50 years old, there seems to be a better response to treatment with 0.15mg / day dutasteride than with 1.25mg / day finasteride.²¹ A 2016 review article found few side effects related to the sexual function in studies with finasteride and dutasteride in female AA.²² Another more recent review article published in 2017 shows that 1mg / day finasteride does not seem to yield better outcomes than the placebo.²³

Recently published European guidelines (2018) note that studies with 1 mg / day finasteride in male AA has led to a significant outcome in hair counts (evidence Level I) for the use of finasteride in men with AA. In female AA, the use of 1mg / day finasteride is not effective, however, a 5mg / day dose may possibly yield some results (evidence Level III) in pre-menopausal and normoandrogenic women. Nonetheless, no place-

bo-controlled trial was evaluated in female AA. Dutasteride in male AA has a good therapeutic response (evidence Level I) and would be indicated for off-label use in cases in which patients do not respond to treatment with 1mg / day finasteride after 12 months. The article mentions that men taking oral finasteride can not donate blood and that the level of finasteride in their sperm is very low, even in those using 5mg / day, meaning there would not be risk in sexual intercourse with pregnant women.⁵

In light of so many questions about the oral use of 5AR inhibitors, some studies are being published aiming at demonstrating alternative ways to use these drugs. The first study on topical finasteride was published 20 years ago, and included 28 men and 24 women who were randomized to use 0.005% finasteride in topical solution or placebo twice daily. Results in the 0.005% finasteride solution group appeared to be significantly better than in the placebo group, with no significant changes in plasma levels of total testosterone, free testosterone and DHT in the studied groups.²⁴ Most of the studies related to topical finasteride have been published in the last eight years.²⁵ One study compared 1% finasteride gel (twice daily) with 1mg / day oral finasteride for six months, with a similar therapeutic response and improvement in the two groups studied.²⁶ In 2014, Caserini et al. compared topical finasteride (0.25%) with 1mg / day oral finasteride in a group of 24 men with AA, having found that in the first week of treatment both topical finasteride and oral finasteride caused a decrease in serum DHT Levels – which was less evident in the first group.²⁷ Subsequently, in 2016, this same group compared 0.25% topical finasteride at different dosages, with outcomes suggesting that a single daily application appeared to be more effective than two daily applications, and 100uL (0.2275mg) and 200uL (0.455mg) doses would be the most effective treatment regimens.²⁸ One study compared the use of 3% minoxidil lotion (Group 1) with 3% minoxidil + 0.1% finasteride lotion (Group 2): Group 2 yielded better outcomes than Group 1, with no significant difference regarding the side effects in the two groups.²⁹ Another article, published in 2015 by Indian authors, found that initiating treatment with oral finasteride (1mg / day) associated with 5% minoxidil lotion (twice daily) could be useful at the time of oral finasteride withdrawal. After achieving a good response with oral finasteride, it would be suspended, and the patient would continue with the use of 5% minoxidil + 0.1% finasteride (twice a day), with reasonable maintenance of the results previously obtained with the oral medication.³⁰ In 2013, Dutch authors presented a study at the 7th World Congress of Hair Research testing the serum and serum level of DHT in patient groups using 0.25% topical finasteride once a day (Group 1), 0.25% topical finasteride twice a day (Group 2), and 1mg / day oral finasteride (Group 3). The level of DHT in the scalp was reduced by 47% in Group 1, 70% in Group 2, and 50% in Group 3. Given that it was a pilot study with 18 men bearers of AA, further prospective studies with a greater number of patients would be necessary so that a more robust analysis could be performed. For the treatment of AA, the variability in the efficacy of topical finasteride also depends on the vehicle used.³¹ To date, several topical presentations, such as

gels and solutions with different concentrations, are being tested and all appear to be effective in the treatment of AA.²⁵ There is, however, no study comparing gels and topical solutions, and it is not known which vehicle would yield better outcomes. Some investigators try to optimize the penetration of topical finasteride through nanoparticles and liposomes, as well as through the inclusion of ethanol and propylene glycol in the formulations.³²⁻³⁶ Studies on topical finasteride range from 0.005% to 1% concentrations, with diverse vehicles (solutions and gels) and one or two doses per day. Although most studies use two daily doses, a single application per day appears to be more effective in lowering DHT levels in the scalp. Further studies are needed in order to allow that an optimal vehicle, posology and concentration be defined, and a better evaluation of the side effects' profile is obtained.

Finally, capillary mesotherapy with dutasteride has been studied by several groups, and is emerging as a therapeutic option. In 2013, a study in Egypt evaluated mesotherapy in female AA, comparing 86 patients using dutasteride mesotherapy with a placebo group of 40 patients. The patients who underwent mesotherapy with dutasteride obtained improvement of 62.8%, while in the control group the improvement was of 17.5%. There seemed to be a better response when the development time of female AA was shorter, with minimal side effects and no statistical differences between the two groups.³⁷ Another study in the same year evaluated mesotherapy with 0.05% dutasteride in 90 patients with male AA for three months. The patients did not present complaints linked to the libido or erectile dysfunction during this period, nevertheless the study takes into consideration that systemic absorption with effect on spermatogenesis would be possible, especially when mesotherapy is performed unlimitedly. It is important to note that dutasteride's half-life is 4 weeks and that its effect on the sexual function is questionable; it would therefore not be recommended for patients wishing to become pregnant and with borderline sperm or ejaculatory / erectile dysfunction, with a greater number of studies being needed to ascertain these data.³⁸ A recently published study shows improvement in hair density and hair diameter in patients bearers of male AA treated with monthly 0.01% dutasteride mesotherapy, with absence of side effects or significant DHT alterations.³⁹

FINAL CONSIDERATIONS

Five alpha-reductase inhibitors have been studied for a long time, especially in male AA. In general, most studies show reversible side effects and low incidence in the sexual related domain. Despite the fact that the authors of the present paper have recently found some studies describing the existence of persistent side effects, including PFS, it is not yet known if this is a reality, calling for further well-designed prospective studies aimed at establishing the actual incidence, frequency and direct correlation with 5AR inhibitors. Some articles on alternative routes for the use of 5AR inhibitors, such as the topical route, mesotherapy and even associations, have been published in recent years. However, although experience with and knowledge

of these drugs is increasing, available studies are still precarious and do not offer conditions for the indiscriminate adoption of these approaches. It should be borne in mind that even if the medication is not taken orally, systemic absorption is possible in these new administration routes (topical, mesotherapeutic), since

the scarce current research does not present conclusive results. For the future, the authors of the present study hope that further prospective studies with high evidence level are capable of assessing persistent side effects and new paths for the use of 5AR inhibitors. ●

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