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Use of Minoxidil Sulfate versus Minoxidil Base in Androgenetic Alopecia Treatment: Friend or Foe?

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Dear Editors,

Androgenetic alopecia (AGA) represents an important cause of hair loss affecting 73% of men and 57% of women until the age of 80 years [1–3], with an age-dependent increase in frequency, and the perspective of rising incidence due to a general increase in life expectancy [2]. Due to its emotional impact with a negative effect on patient's quality of life, it is important to establish an early diagnosis and treatment plan in order to avoid progression of hair loss.

The drugs currently available for treatment of AGA with approval of the US Food and Drug Administration are: topical minoxidil (MX) and 1 mg oral finasteride for men, and topical MX for women [3].

MX was introduced into the market in the 1980s, originally as an antihypertensive medication of which the effect is related to the opening of potassium channels in the cellular membrane of vascular smooth muscle cells, promoting vasodilation. The observed side effect of hypertrichosis and improvement of baldness in men led to further investigations into its topical use for treatment of male, and later female AGA [4].

MX arrests hair loss or induces mild to moderate hair regrowth in patients with AGA [3]. The exact mechanism of action of MX in the treatment of AGA is not completely defined [4]. In order to act, the pro-drug MX needs to be converted to its activated metabolite MX sulfate (MXS), by virtue of MX sulfotransferase enzyme activity present in the liver and in the outer root sheath of the hair follicle [4, 5].

Studies in vitro with MXS proved that its efficacy is 14 times higher than MX base [4]. However, MXS has a molecular weight of 289.3 g/mol, while MX has 209.3 g/mol, a difference of nearly 40% [6]. As molecular weight is a determinant factor for the degree of transcutaneous penetration, this may present a problem for absorption of topical MXS compared to topical MX [6, 7].

MX, either as ready-for-use or custom-made formulation (i.e., in a solution of glycerine, water, and ethanol), is widely used for the treatment of AGA. All clinical trials that evaluated its efficacy for treatment of male and female AGA have been carried out with MX base, and not with MXS [3].

In Brazil, alternatively, there has been a rise in the prescription and use of MXS-based formulations due to its pharmaceutical solubility [6, 7]. However, in addition to the issue of its higher molecular weight, MXS is naturally unstable in aqueous solution, negatively affecting its bioavailability to the hair follicle and increasing its irritation potential to the scalp. Therefore, efficacy of MXS compared to MX base for the treatment of AGA may be impaired, and the same efficacy may not be expected as in the original clinical trials with MX base.

The MX sulfotransferase activity is not the same in every individual. MXS represents an alternative with advantage over MX in individuals with low MX sulfotransferase activity, since the demonstration of an association between MX response and the degree of MX sulfatation [8]. However, in order to compensate such decreased response, MXS would have to be used at higher concentrations (10–15%) due to its decreased capacity of transcutaneous absorption and packaged in small volumes, because of its high degree of degradation.

Indeed, a Swiss retrospective study of 44 patients with AGA (13 males with Hamilton-Norwood type AGA class III or above and 31 females with Ludwig type AGA I–III) unresponsive to a minimum of 6 months of 5% MX solution b.i.d. showed increase in hair growth in 97.7% using a 10% MXS solution once daily during a mean treatment period of 4.09 months. The treatment was well tolerated by patients, among whom 6.8% suffered from irritation, erythema, and folliculitis of the scalp. No major adverse effect was noted [9].

We aim to emphasize the differences between topical formulations of MX and MXS available on the Brazilian market, i.e., penetration and stability issues for MXS formulations, and the problem of low sulfotransferase activity for MX prescriptions. Our opinion is that topical MX base remains the first-line topical agent for treatment of male and female AGA, unless the patient proves to be unresponsive, then a formulation of MXS at probably higher concentrations may present an alternative with enhanced efficacy. For this purpose, a novel enzymatic assay may predict MX response [10].

Comparative clinical trials and pharmacological studies with different formulations, either ready for use or custom made, with MX base or MXS, should be conducted in order to make final recommendations for optimal use in AGA treatment.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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