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CASE AND RESEARCH LETTER

Tolerance and Safety Profile of Sublingual Minoxidil in the Treatment of Androgenic Alopecia

Tolerancia y perfil de seguridad de minoxidil sublingual en el tratamiento de la alopecia androgénica

To the Editor,

Low-dose oral minoxidil (LDOM) has revolutionized the treatment of female and male androgenetic alopecia. LDOM is effective and safe and is endorsed by numerous reports, including the latest review of more than 1400 treated patients, with a 20.6% incidence rate of adverse effects which is mainly dose-dependent,[1] and a treatment discontinuation rate of only 1.7%.[2]

However, active monitoring by questionnaire collecting data on side effects, for example those collected by Sanabria et al.,[3] has resulted in much higher incidence rates. Although these collateral symptoms could be limited to reducing the dose of minoxidil, this could in turn, reduce treatment efficacy.[4]

Recently, to clarify this, Sinclair et al. conducted a phase 1b double-blind randomized clinical trial to assess the safety and efficacy profile of sublingual minoxidil tablets as an alternative to LDOM.[5] The rationale behind this route of administration is to avoid the first hepatic step of metabolism – including hepatic sulfation – the mechanism essentially responsible for its hemodynamic action, which could reduce the side effects and improve the drug safety.[6] Sulfation would, therefore, be exerted by follicular sulfotransferase, which may raise efficacy doubts as it is like the conventional mechanism of sulfation of topical minoxidil. However, the substrate of this enzyme would be increased in the sublingual route, thus overcoming the percutaneous absorption barrier and the concentration and formulation limitations of the traditional topical form of minoxidil.[7] Specific targeted studies would be required to check any interferences with other drugs, such as acetylsalicylic acid, with this follicular sulfotransferase when administered with sublingual minoxidil.[8]

To assess the safety profile of sublingual minoxidil, we retrospectively studied all patients who received this formulation from August 2021 through March 2022 in Instituto Medico Ricart Centers (Spain). Sublingual minoxidil was prepared in one solution and two different concentrations of 0.25 mg or 0.5 mg through spray route of administration (Fig. 1). A pressure valve allows proper dosage per spray and mint flavor seemed pleasant to the patients.

Figure 1 Spray form of sublingual minoxidil with spray application dispenser (0.5 mg/per spray application) and composition.

Selecting this type of presentation was based on a faster and more constant absorption vs the erratic absorption provided by the tablet, which must first be dissolved. Dose titration is facilitated by changing the number of spray applications, without having to reformulate the compound or

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alter the number of tablets administered. Due to this sublingual presentation, we can combine the above-mentioned advantages of the sublingual route of administration with fewer adverse effects associated with its metabolic pathway and possible lower dosage, along with those of the formulation in solution, with a faster and more constant absorption at pharmacokinetic level and easy dose titration in spray.

We studied a total of 87 patients diagnosed with androgenic alopecia (73 women and 14 men), with median weights and heights of 63.5 kg (45–112 kg) and 165 cm (153–186 cm), respectively. The median dose among women was 0.5 mg/day (0.25–1 mg/day) vs 1 mg/day (0.25–1 mg/day) among men. Three months into therapy, active follow-up was conducted via phone questionnaire to assess the onset and time sequence of side effects (supplementary material, Table 1).

Table 1 (supplementary data) shows the main findings and compares data with representative LDOM studies.[1,3] The incidence of adverse effects in both men and women was lower vs those reported by Sanabria et al.[3] who used the same active follow-up method with questionnaires, and similar to those reported by Vañó-Galván et al.[1] The timing of the onset of adverse events was similar to the one previously mentioned, except for an earlier onset of hypertrichosis and a later onset of dizziness and headache in our sample. Although sublingual minoxidil doses may be lower and maintain their efficacy, as published, in our series the drug dose was not substantially down titrated among women – the majority of patients in our series – which should be taken into account when considering the rates of adverse effects. On the other hand, the data collection methodology was active survey, as in the report by Sanabria et al.,[3] which may overestimate the adverse effects reported when the patient was asked on each one of these questionnaires. In the series by Vañó-Galván et al.,[1] data were collected from the patients' health records. This information is also necessary for a proper interpretation.

The limitations of our study include its retrospective nature, short follow-up, and small number of men in our study sample. Moreover, since the doses used in men were lower than those from the LDOM studies, the efficacy data for this drug and the doses used should be evaluated.

In conclusion, low-dose sublingual minoxidil in spray could be a safe and easy alternative to LDOM. Nonetheless, comparative studies are required to evaluate differences between these 2 therapies.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ad.2023.09.031.

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