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Title page

Title: Novel Topical Booster Enhances Follicular Sulfotransferase Activity in Patients with Androgenetic Alopecia: A New Strategy to Improve Minoxidil Response

Running title: Sulfotransferase booster for AGA treatment

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Topical minoxidil has been used as a topical treatment for androgenetic alopecia (AGA) for more than 30 years. Approximately 60 to 70% of patients do not achieve hair growth.[1]

Minoxidil is a pro-drug. In order to exert biological activity, minoxidil requires conversion to minoxidil sulfate by sulfotransferase enzymes (SULT1A1).[2] We have reported extensively that SULT1A1 activity in the outer root sheath (ORS) of the hair follicle correlates directly with topical minoxidil response. We have demonstrated the clinical utility and validity of a colorimetric test to measure the follicular SULT1A1 activity in plucked hair as a method to predict minoxidil responders.[3,4] This same test also predicts clinical response to oral minoxidil.[5]

Sulfotransferases are phase II xenobiotic metabolizing enzymes expressed in the liver, platelets and hair follicle.[3,6] Additionally, sulfotransferase has been reported as a biomarker for hypoxia found in humans as a result of altitude sickness.[7]

Hypoxia is difficult to mimic in a therapy; as such, we sought other mechanisms that would affect similar regulatory pathways intersecting hypoxia and sulfotransferase activity. One such mechanism is intercellular pH (pHi). Intracellular pH is an important regulatory mechanism, which can influence cellular function and lead to cell differentiation in a range of stem cells.[8] Cell differentiation is associated with the altered expression of many proteins including xenobiotic-metabolizing enzymes. Specifically, increased sulfotransferase is a biomarker for keratinocyte differentiation.[9] As such, we set out to increase the pH of the follicular stem cells as a means of increasing

sulfotransferase activity. To address this problem, we have developed a novel topical formula.

Here we aim to evaluate a novel topical adjuvant to minoxidil (booster) developed to increase sulfotransferase activity in hair follicles of patients with AGA. The formula uses a liposomal encapsulated alkalizing agent (sodium bicarbonate) to change the pHi of the ORS. The encapsulated chemistry was needed to increase penetration of the alkalizing agent into the cells.

Twenty patients with clinical diagnosis of AGA were recruited for a fourteen day study. Twelve hairs from boarder of scalp with alopecia and normal scalp were plucked for sulfotransferase analysis at the first visit. Subsequently, the patients were provided the adjuvant therapy and instructed to apply 2 ml of the new minoxidil booster twice a daily in the same target area. After fourteen days, twelve hairs from the same location were collected again for sulfotransferase analysis. Follicular sulfotransferase activity was conducted following the method of Goren et al.[3,4]

Nineteen subjects successfully completed the study. Follicular sulfotransferase activity, as measured by the sulfotransferase assay (OD), increased for 10 of 19 patients (Table 1). More importantly, subjects predicted to be non-responders to minoxidil (OD<0.4) had a significant increase in their minoxidil response. Pre-treatment, the average OD in the non-responder group was 0.2206 (95%CI: 0.1661 to 0.2750) compared to post-treatment 0.4946 (95%CI: 0.2036 to 0.7855) ($p<0.03$). None of the subjects presented with any adverse events.

Topical minoxidil has been widely used for AGA for decades and low-dose oral minoxidil is a promising alternative being explored.[10] Unfortunately, many patients do not present significant clinical response or present only mild improvements after using minoxidil. As our previous work demonstrated, one of the main obstacles to clinical response is the low activity of SULT1A1 in the ORS.[4,5] Increasing SULT1A1 activity could be an effective way to improve clinical response to minoxidil.

This study demonstrates the ability of a topical booster to increase the activity of SULT1A1 in the ORS of the hair follicle. Increasing the activity of SULT1A1 can improve

the efficacy of topical and low dose oral minoxidil for the treatment of AGA. If proven in clinical trial, the booster could present great clinical importance to patients with AGA, converting minoxidil non-responders to responders.

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Table 1. Follicular sulfotransferase enzyme activity before and after application of the novel booster for 14 days.

Subject number	Age (years)	Sex	OD before	OD after
1	24	Female	1.290	0.686
2	24	Male	0.938	0.954
3	27	Male	0.727	0.291
4	30	Male	0.678	0.162
5	25	Female	0.639	0.584
6	25	Male	0.623	0.127
7	27	Male	0.510	0.347
8	18	Male	0.484	0.657
9	26	Female	0.483	0.685
10	29	Female	0.436	0.558
11	31	Female	0.306	0.567
12	26	Female	0.268	0.810
13	29	Female	0.265	0.106
14	30	Male	0.254	0.186
15	28	Female	0.247	1.117
16	23	Female	0.246	0.566
17	27	Male	0.179	0.090
18	32	Male	0.110	0.159
19	25	Female	0.110	0.850

OD = Follicular sulfotransferase activity, as measured by the sulfotransferase assay

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