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# **SULT1A1 (Minoxidil Sulfotransferase) Enzyme Booster Significantly Improves Response to Topical Minoxidil for Hair Regrowth**

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**Ethics statement:** The study was conducted in compliance with the protocol approved by the hospital's Ethics Committee ethics committee (LTM Medical College & Hospital Sion, Mumbai, India) and according to Good Clinical Practices.

**Data availability statement:** No additional data will be made available from this study.

**Key Words:** minoxidil, SULT1A1, sulfotransferase, alopecia

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## **SULT1A1 (Minoxidil Sulfotransferase) Enzyme Booster Significantly Improves Response to Topical Minoxidil for Hair Regrowth**

### **Abstract**

**Background:** Minoxidil is a widely used over the counter topical treatment for hair loss. The response rate for topical minoxidil is relatively low. Minoxidil is a pro-drug, converted to its active form, minoxidil sulfate, by SULT1A1 enzymes located in the scalp. Recently, a novel topical formula that increases the activity of SULT1A1 in hair follicles was reported.

**Aims:** To evaluate any benefit of applying the SULT1A1 enzyme booster prior to daily 5% minoxidil treatment.

**Methods:** Male androgenic alopecia patients were recruited to a randomized blinded placebo controlled study. Patients were randomized to receive 5% topical minoxidil plus the novel formula or minoxidil plus a sham adjuvant. Patient's hair growth was monitored using global photography over 60 days.

**Results:** Twenty-four males with androgenic alopecia (Norwood scale average 4.4, range 2-6) were randomized and completed the trial; 12 in the active arm and 12 in placebo. 75% of the subjects who used the SULT1A1 adjuvant with their daily minoxidil treatments for 60 days regrew hair verses 33% of those using the placebo adjuvant ( $p=0.023$ ).

**Conclusions:** In a small cohort of androgenetic alopecia men, adding the SULT1A1 adjuvant to their daily minoxidil treatment regimen improved hair regrowth.

## Introduction

Minoxidil is the only topical drug approved by the US FDA to regrow hair. It is approved for use in men and women and is a ubiquitous over-the-counter product. Unfortunately, minoxidil has a relatively low efficacy rate. In clinical trials, minoxidil was shown to re-grow hair in approximately 35% of subjects after 16 weeks of use.<sup>1,2</sup> Compliance with the 16-week topical regimen remains a major barrier to success, while 30-40% of subjects in physician-guided studies report success, that number is drastically reduced in subjects that self-administer minoxidil.<sup>3</sup> A Consumer Report survey of approximately 8,000 users of minoxidil found that only 4% of users were satisfied with the results of treatment.<sup>4</sup> Given the length of time required to observe efficacy, improving the number of patients that respond to minoxidil could have a dramatic effect on both compliance and clinical benefit.

Minoxidil is a pro-drug. It is converted to its active form, minoxidil sulfate, by sulfotransferase enzymes in the outer root sheath (ORS) of hair follicles.<sup>5</sup> Specifically, endogenous sulfotransferase 1A1 (SULT1A1) has been demonstrated to be the dominant isoform of sulfotransferase responsible for minoxidil conversion in the scalp.<sup>6</sup> Numerous studies have demonstrated the direct relationship between SULT1A1 activity and minoxidil response.<sup>7,8</sup> SULT1A1 activity has been used as a diagnostic to predict the likelihood of minoxidil response for individuals to help guide treatment for alopecia.<sup>9</sup> However, predicting minoxidil response has limited utility because there is currently no treatment option to remedy low SULT1A1. Accordingly, increasing SULT1A1 activity in the hair follicle has been a major goal of our research.

Intracellular pH is a key regulatory mechanism contributing to cell differentiation in a number of stem cells.<sup>10</sup> Further, sulfotransferase has been demonstrated to be a biomarker of

keratinocyte differentiation.<sup>11</sup> As such, we hypothesized that increasing intercellular pH would lead to an upregulation of SULT1A1 in the ORS. Recently, we reported the successful development of a novel topical formula that was shown to increase scalp SULT1A1 in patients via alterations to intercellular pH of the ORS.<sup>12</sup> Here we aimed to test whether applying the novel topical formula prior to topical minoxidil would increase the overall efficacy of minoxidil.

## Methods

Male subjects over the age of 18 who were suffering from hair loss were recruited from an outpatient dermatology department at a hospital (LTM Sion, Mumbai, India). Included patients had diagnosed androgenetic alopecia and had never used minoxidil. Patients were excluded if they had scalp conditions that might be irritated by topical treatments or interfere with treatment (e.g., seborrheic dermatitis). All subjects provided informed consent before enrolment in the trial. The trial was conducted with approval from the hospital ethics committee. Trial approval was granted September, 2020.

Each subject was given either a 30-day supply of the SULT1A1 adjuvant or a sham placebo solution. The SULT1A1 topical product is a proprietary cosmetic solution with patents pending. The minoxidil adjuvant and placebo solution were packaged in identical bottles. The principle investigator and the subjects were blinded to the contents of the bottles. Patients were also supplied with a 30-day supply of 5% topical minoxidil. Subjects were instructed to apply the minoxidil adjuvant therapy 5-10 minutes before the application of minoxidil. Subjects returned to the hospital at 30 days and 60 days for follow up appointments with the principal investigator. At each follow up appointment, global photography was used to track the patient's progress. At each appointment a new 30-day supply of minoxidil and adjuvant treatment were provided to the subjects. The trial was conducted over 60 days.

Global photography was used to document each patient's hair loss at baseline, 30 days, and 60 days. At the trial completion, global photographs were assessed by three independent

reviewers who were dermatologists having expertise in androgenetic alopecia. The reviewers were blinded to the arm assignment of each subject. The treatment response was rated on a 7-point scale as follows: -3 (significantly worse), -2 (moderately worse), -1 (slightly worse), 0 (no change), +1 (slightly improved), +2 (moderately improved) and +3 (significantly improved). A conglomerate score was calculated from the three independent reviews for comparisons of efficacy. The student's t-test was used to compare the average change between the two groups to determine statistical significance.

## **Results**

Twenty-four male patients were recruited to the trial. 12 were randomized to the active arm and 12 to the placebo. The baseline average Norwood scale was 4.3 (range 2-6) and 4.4 (range 3-6) for the active and placebo arms, respectively. No patient reported any adverse reaction to treatment in either arm.

The global photographs collected during the trial were reviewed by 3 independent blinded experts. The results are displayed in Table 1. Scores for efficacy were tabulated as the median score between the experts where allowed, i.e., agreement between two of three experts was required for a confirmed score. In two instances, no two scores from the experts agreed; in this case, a conservative estimate was used to best reflect the scores of the experts.

Amongst the group using minoxidil plus the SULT1A1 adjuvant treatment, 9 of 12 subjects (75%) had a positive increase in hair growth as determined by the independent blinded reviews of the global photographs at 60 days. In the minoxidil plus placebo group, 4 of 12 (33%) subjects had a positive increase in hair growth. The minoxidil response rates between the subjects using the SULT1A1 adjuvant and those using a placebo was found to be statistically significant (student's t-test,  $p=0.023$ ).

## **Discussion**

SULT1A1 activity in the scalp is required for minoxidil efficacy.<sup>9</sup> Here we demonstrate in a randomized blinded controlled study that a SULT1A1 inducing topical formula is an effective adjuvant for improving minoxidil response. After 60 days of use, subjects who used both minoxidil and the SULT1A1 adjuvant demonstrated more than twice the response to those using minoxidil and sham adjuvant.

Given the long time required to observe benefits from minoxidil treatment, compliance with the topical regime likely contributes to the low satisfaction rate amongst patients. This is a possible explanation for the lower response rates observed in over the counter use compared to monitored subjects in controlled trials.<sup>2-4</sup> We believe that improving the rate of minoxidil response would also positively benefit compliance with the treatment regimen and have a synergistic benefit on efficacy.

Minoxidil is the only drug approved for hair growth in both men and women. Increasing the number of patients that can benefit from minoxidil treatment can have important impact of patients experiencing alopecia. In our small study, we demonstrated that a novel topical formula that increases the activity of SULT1A1 in the scalp<sup>12</sup> improves the likelihood of minoxidil response. A limitation of this study was the small sample size. Additionally, the 60-day endpoint used in this trial is difficult to compare with the 90-day endpoint reported in the pivotal trials for minoxidil.<sup>1,2</sup> Currently, we are planning larger studies to further elucidate the benefits of a SULT1A1 adjuvant therapy to minoxidil users.

## **Conclusion**

In the reported study, we demonstrate the ability of a SULT1A1 inducing topical treatment to significantly increase the response rate of patients using minoxidil to treat hair loss. 75% of subjects treated with the SULT1A1 adjuvant responded to minoxidil treatment after 60 days of use versus 33% of those treated with a placebo adjuvant (p=0.023).

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**Table 1. Independent expert assessment of global photographs after 60 days of treatment with minoxidil plus SULT1A1 adjuvant versus treatment with minoxidil and placebo adjuvant.**

Subject	Arm	Investigator 1	Investigator 2	Investigator 3	Final Score
1	Active	1	1	1	1

2	Active	1	1	2	1
3	Active	1	-1	1	1
4	Active	-1	-2	-1	-1
5	Active	1	2	1	1
6	Active	0	0	1	0
7	Active	2	1	2	2
8	Active	0	0	0	0
9	Active	1	1	1	1
10	Active	1	2	1	1
11	Active	0	0	0	0
12	Active	1	0	1	1
13	Placebo	-1	0	0	0
14	Placebo	1	0	0	0
15	Placebo	0	-2	0	0
16	Placebo	-1	-2	-1	-1
17	Placebo	1	1	1	1
18	Placebo	0	-1	0	0
19	Placebo	1	1	1	1
20	Placebo	1	1	1	1
21	Placebo	1	0	0	0
22	Placebo	1	0	1	1
23	Placebo	0	-2	-1	-1
24	Placebo	1	-2	0	0