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Oral Minoxidil Bio-activation by Hair Follicle Outer Root Sheath Cell Sulfotransferase Enzymes Predicts Clinical Efficacy in Female Pattern Hair Loss

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Topical minoxidil (TM) is the only FDA-approved medication for the treatment of female pattern hair loss (FPHL). Minoxidil is a pro-drug. TM efficacy in FPHL requires bio-activation into minoxidil sulfate by sulfotransferase enzymes. Sulfotransferases are xenobiotic metabolizing enzymes expressed in many tissues with the highest expression found in the human liver. Hair follicle outer root sheath cells (ORS) also express sulfotransferase, and ORS sulfotransferase activity predicts TM therapeutic response.

The clinical response to TM is variable. Several strategies have been previously explored to overcome lack of response to 5% TM secondary to low ORS sulfotransferases activity. Use of higher concentrations of TM is effective in up to 60% of non-responders.
We also recently conducted a head to head trial comparing 1mg daily oral minoxidil (OM) once daily to 5% topical once daily in the treatment of FPHL. As OM is extensively metabolized by the liver, we sought to determine whether liver or ORS sulfotransferases are primarily responsible for OM bio-activation and efficacy in the treatment of FPHL. We also sought to develop a predictive biomarker for OM therapeutic response in FPHL.

Thirteen women with Sinclair's Stage II-IV FPHL received 1mg OM daily for 24 weeks. Hair counts were performed in a target (tattooed) area on the parietal scalp before and after treatment. Ten anagen hairs were plucked from the affected scalp, trimmed to a length of 1cm and immersed, bulb first, in 100µL of assay solution. Assay solution consisted of 50mM phosphate buffer (pH 8), 5mM potassium p-nitrophenyl sulfate, 20µM adenosine 3',5'-diphosphate, 100µM minoxidil, and 5mM MgCl₂. Hair bulbs were then incubated for 24h at room temperature before the optical absorbance of the solution at 405nm was determined with a spectrophotometer (Shimadzu UV-1700, Kyoto, Japan) using a single scan and 1cm path length. Values less than 0.4 Absorbance Units (AU) are a validated marker of low follicular ST activity.

The baseline hair count, percentile of hair increase and three cut-off parameters for OD are presented in figure 1. Women with low sulfotransferase activity had less hair re-growth (9.0+/−4.36) compared to women with a high sulfotransferase enzymatic activity (18.4+/−9.17) (p=0.06).

A Receiver Operator Characteristics analysis (ROC) of the data (Graph 1) was conducted with a dichotomous categorization variable based on clinical response as defined by <13.7% increase in hair density. Using the previously reported response rate of OM in the treatment of FPHL of 79.7%, the optimal criteria for the ROC analysis is an OD>0.254 i.e., 100% of the subjects below 0.254 OD were non-responders. While the sample size of this study is small, the ROC analysis demonstrates that a lower follicular enzymatic activity threshold is required for bio-activation of OM compared to TM.

With respect to the relative the role of liver versus ORS sulfotransferase activity on OM bio-activation, our results show that ORS bioactivation predicts clinical response in the treatment of FPHL. While the dataset reached marginal significance (p=0.06) for an enzymatic activity cut-off of 0.4 OD, the ROC analysis demonstrated that the optimal cut-off for non-responders to OM in our study was 0.254 OD. This demonstrates that a lower follicular enzymatic activity threshold is required for bio-activation of OM compared to TM. This might be due to a contribution of liver and platelets on OM conversion and/or higher follicular accumulation of minoxidil. Using the
ROC analysis from this study as a “training dataset” for future investigations, we plan to elucidate the exact mechanism of OM bio-activation.

Figure 1. Baseline hair density versus percentile of hair increase in this sample. Three cut-off points for Optical Density (OD) regarding sulfotransferase are represented.

Figure 2. Receiver Operator Characteristics analysis (ROC) of the raw data with a dichotomous categorization variable based on response <13.7% hair re-growth.

REFERENCES


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