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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).[1] Minoxidil is a pro-drug. TM efficacy in FPHL requires bio-activation into minoxidil sulfate by sulfotransferase enzymes.[2] Sulfotransferases are xenobiotic metabolizing enzymes expressed in many tissues with the highest expression found in the human liver.[3] Hair follicle outer root sheath cells (ORS) also express sulfotransferase, and ORS sulfotransferase activity predicts TM therapeutic response.[4-6]

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.[7] Use of higher concentrations of TM is effective in up to 60% of non-responders.[8]

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.[9] 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 $MgCl_2$. 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.[4]

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%,[10] 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.

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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.