DR. PAULO MÜLLER RAMOS (Orcid ID : 0000-0002-1561-414X)

Article type : Letter to Editor

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

Authors:

Ramos PM¹; Goren A²; Sinclair R³; Miot HA¹.

¹ Department of Dermatology and Radiotherapy, São Paulo State University - UNESP, Botucatu, SP, Brazil.

² Applied Biology, Inc. Irvine, California, USA

³ Sinclair Dermatology, Melbourne, VIC, Australia

Correspondence:

Paulo Müller Ramos

Av; Prof. Mário Rubens Guimarães Montenegro, sn

UNESP – Campus Botucatu

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JDV.15891](#)

This article is protected by copyright. All rights reserved

22 18618687 – Botucatu - SP

23 Email: dermatopaulo@gmail.com

24 Phone/FAX: +55 43 99912 5333

25

26 **Key words:** androgenetic alopecia, sulfotransferase, oral minoxidil, female pattern hair
27 loss, treatment

28

29

30 **Word count:** 569

31

32 **Figures/Tables:** 2

33

34 **Funding source:** none

35

36 **Conflict of interest:**

37 Ramos PM: no conflict of interest

38 Goren A: no conflict of interest

39 Sinclair R: is the inventor of US patent 10226462 detection and treatment of excessive
40 hair shedding

41 Miot HA: no conflict of interest

42 Topical minoxidil (TM) is the only FDA-approved medication for the treatment of female pattern
43 hair loss (FPHL).¹ Minoxidil is a pro-drug. TM efficacy in FPHL requires bio-activation into
44 minoxidil sulfate by sulfotransferase enzymes.² Sulfotransferases are xenobiotic metabolizing
45 enzymes expressed in many tissues with the highest expression found in the human liver.³ Hair
46 follicle outer root sheath cells (ORS) also express sulfotransferase, and ORS sulfotransferase
47 activity predicts TM therapeutic response.⁴⁻⁶

48 The clinical response to TM is variable. Several strategies have been previously explored to
49 overcome lack of response to 5% TM secondary to low ORS sulfotransferases activity.⁷ Use of
50 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 100 μ L of assay solution. Assay solution consisted of 50mM phosphate buffer (pH 8), 5mM potassium p-nitrophenyl sulfate, 20 μ M adenosine 3',5'-diphosphate, 100 μ M 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.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 $\pm$ 4.36) compared to women with a high sulfotransferase enzymatic activity (18.4 $\pm$ 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.

REFERENCES

1. Van Zuuren EJ, Fedorowicz Z. Interventions for female pattern hair loss. *JAMA Dermatol.* 2017;153:329-30.
2. Buhl AE, Waldon DJ, Baker CA, Johnson GA. Minoxidil sulfate is the active metabolite that stimulates hair follicles. *J Invest Dermatol.* 1990;95(5):553-7.
3. Falany CN, Kerl EA. Sulfation of minoxidil by human liver phenol sulfotransferase. *Biochem Pharmacol.* 1990;40(5):1027-32.
4. Goren A, Castano JA, McCoy J, Bermudez F, Lotti T. Novel enzymatic assay predicts minoxidil response in the treatment of androgenetic alopecia. *Dermatol Ther.* 2014;27(3):171-3.
5. Goren A, Shapiro J, Roberts J, McCoy J, Desai N, Zarrab Z, et al. Clinical utility and validity of minoxidil response testing in androgenetic alopecia. *Dermatol Ther.* 2015;28(1):13-6.

6. Roberts J, Desai N, McCoy J, Goren A. Sulfotransferase activity in plucked hair follicles predicts response to topical minoxidil in the treatment of female androgenetic alopecia. *Dermatol Ther.* 2014;27(4):252-4.
7. Dias PCR, Miot HA, Trueb RM, Ramos PM. Use of Minoxidil Sulfate versus Minoxidil Base in Androgenetic Alopecia Treatment: Friend or Foe? *Skin Appendage Disord.* 2018;4(4):349-350.
8. McCoy J, Goren A, Kovacevic M, Shapiro J. Minoxidil dose response study in female pattern hair loss patients determined to be non-responders to 5% topical minoxidil. *J Biol Regul Homeost Agents.* 2016;30(4):1153-5.
9. Ramos PM, Sinclair R, Kasprzak M, Miot HA. Minoxidil 1 mg orally versus minoxidil 5% solution topically for treatment of female pattern hair loss: a randomized clinical trial. Free communication presented at 11th World Congress of Hair Research; Sitges, Barcelona 24-27 April 2019.
10. Rodrigues-Barata AR S-CD, Moreno-Arrones O, Morales C, Vañó-Galvan S. Low-dose oral minoxidil for the treatment of female pattern hair loss. Poster presented at the 11th World Congress of Hair Research; Sitges, Barcelona 24-27 April 2019.

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.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ramos, PM;Goren, A;Sinclair, R;Miot, HA

Title:

Oral minoxidil bio-activation by hair follicle outer root sheath cell sulfotransferase enzymes predicts clinical efficacy in female pattern hair loss

Date:

2019-09-11

Citation:

Ramos, P. M., Goren, A., Sinclair, R. & Miot, H. A. (2019). Oral minoxidil bio-activation by hair follicle outer root sheath cell sulfotransferase enzymes predicts clinical efficacy in female pattern hair loss. JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY, 34 (1), pp.E40-+. <https://doi.org/10.1111/jdv.15891>.

Persistent Link:

<http://hdl.handle.net/11343/286405>