Male balding as a major risk factor for severe COVID-19: A possible role for targeting androgens and transmembrane protease serine 2 to protect vulnerable individuals

To the Editor: We would like to praise Lee et al[1] for extra data to support the role of androgens in the COVID-19 pandemic. Lee et al showed increased positivity for COVID-19 among individuals previously self-identified as having pattern 4 baldness. Pattern 4 (frontal plus vertex) baldness could be interpreted as very severe baldness or Hamilton-Norwood scale score of 4 to 7.[2] They further showed in multivariate logistic regression that very severe baldness had a higher odds ratio for COVID-19 positivity than hypertension, dyslipidemia, diabetes, obesity per body mass index, or age.[1] It is noteworthy that severe baldness was reported to be a better predictor of test result positivity than obesity, because there are many reports linking obesity to COVID-19 disease severity. This underscores the need for further studies and the communication of these findings beyond the dermatology community.

In the context of symptomatic presentations reported by Lee et al,[1] the baldness survey was conducted many years ago. Some patients who initially self-reported as having frontal baldness or vertex baldness (patterns 2 or 3, respectively) could have developed pattern 4 by 2020. Therefore, we believe the numbers with very severe baldness may be even greater than what was reported. The main evidence of vulnerability is the clinical outcome during the course of COVID-19, particularly intensive care unit (ICU) admission and fatality rates. Severe baldness, the Gabrin sign (Hamilton-Norwood scale score of 3 to 7), has been associated with both increased ICU admissions and increased death rates.[2]

Understanding the mechanisms leading to host susceptibility provides an opportunity for pharmacologic interventions to protect vulnerable individuals. We have proposed that androgen sensitivity is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, possibly through androgen-promoted transmembrane protease serine 2 (TMPRSS2).[3] Recently, results of a study using bromhexine hydrochloride, a common over-the-counter cough medication only available outside the United States, were reported. Bromhexine was the first drug identified to be a TMPRSS2 inhibitor. The open-label, randomized, standard protocol-controlled trial enrolled 78 patients for treatment of clinical and radiologic pneumonia suspected to be due to COVID-19.[4] The arm with bromhexine was superior to the standard protocol, with only 2 patients admitted to the ICU and 0 deaths versus 11 patients admitted to the ICU ($P = .006$) and 5 deaths in the standard protocol arm ($P = .027$).[4]

Reduced expression of TMPRSS2 is also achieved by blocking androgens with medications commonly used in dermatology.[3] Results of our recent COVID-19 prospective cohort study involving 77 hospitalized men were also particularly encouraging: only 1 out of 12 individuals was admitted to the ICU (8%) in the cohort of men using 5-alpha-reductase inhibitors or other antiandrogen drugs (dutasteride, n = 9; finasteride, n = 2; and spironolactone, n = 1) versus 38 out of 65 men (58%) not taking antiandrogens ($P = .0015$).[5] Raw data available via Mendeley at https://doi.org/10.17632/6gpc32dyy7.2.

Medications that target TMPRSS2 have shown improved COVID-19 outcomes in clinical studies and have the potential to protect vulnerable individuals during the pandemic. We hope that in the near future, more data will be available regarding interventions focused on inhibiting host factors that increase susceptibility to SARS-COV-2, such as the androgen-TMPRSS2 pathway.

Carlos Gustavo Wambier, MD, PhD,[a] John McCoy, PhD,[b] and Andy Goren, MD[b]

From the Department of Dermatology, Alpert Medical School of Brown University, Providence, Rhode Island[a]; and Applied Biology, Inc, Irvine, California.[b]

Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

Reprints not available from the authors.

Correspondence to: Carlos Gustavo Wambier, MD, PhD, Department of Dermatology, Rhode Island Hospital, 593 Eddy St, APC building, 10th Floor, Providence, RI 02903

E-mail: carlos_wambier@brown.edu

REFERENCES

1. Lee J, Yousaf A, Fang W, Kolodney M. Male balding is a major risk factor for severe COVID-19. *J Am Acad Dermatol*. 2020;83:e353-e354.
2. Wambier CG, Vaño-Galván S, McCoy J, Pai S, Dhurat R, Goren A. Androgenetic alopecia in COVID-19: compared to age-matched epidemiologic studies and hospital outcomes

with or without the Gabrin sign. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2020.07.099.

3. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *J Am Acad Dermatol*. 2020;83:308-309.
4. Ansarin K, Tolouian R, Ardalan M, et al. Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: a randomized clinical trial. *BioImpacts*. 2020;10(4):209-215.
5. Goren A, Wambier CG, Herrera S, et al. Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men. *J Eur Acad Dermatol Venereol*. Published online September 25, 2020. https://doi.org/10.1111/jdv.16953.

https://doi.org/10.1016/j.jaad.2020.09.015