Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

immunocompetence (e.g. systemic glucocorticoid treatment and/or chemotherapy) were not disclosed. Additionally, whether patients on ADT were still undergoing ADT while hospitalized for COVID-19 and the length of ADT before Sars-CoV-2 infection were also not reported, further hampering definitive analysis.

These limitations notwithstanding, the analysis by Montopoli et al. shows that androgens are at least in part to blame for COVID-19 male incidence,[1] consistent with earlier reports of high androgenetic alopecia prevalence in hospitalized COVID-19 patients and decreased activity of the ACE2 SARS-CoV-2 receptor following experimental orchidectomy.[7] Since SARS-CoV-2 *is* gender-biased, a possible mechanism for increased male infection may be in the immunosuppressive properties of androgens. A recent study showed that male mice under ADT mount a more robust immune response[8] and in humans, genes associated with poor virus response are up-regulated by androgens.[9] Finally, men presenting high serum androgen levels display the weakest influenza immune response.[9] These data suggest that androgens may yet be a determinant of SARS-CoV-2 susceptibility, just unlikely through TMPRSS2.

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DISCLOSURE

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REFERENCES

1. Montopoli M, Zumerle S, Vettoret R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study ($n = 4532$). *Ann Oncol*. 2020;31:1040-1045.
2. The Human Protein Atlas. TMPRSS2, *The Human Protein Atlas*. Available at https://www.proteinatlas.org/ENSG00000184012-TMPRSS2/tissue. Accessed February 6, 2020.
3. The Human Protein Atlas. AR, *The Human Protein Atlas*. Available at https://www.proteinatlas.org/ENSG00000169083-AR/tissue. Accessed February 6, 2020.
4. Baratchian M, McManus J, Berk K, et al. No evidence that androgen regulation of pulmonary TMPRSS2 explains sex-discordant COVID-19 outcomes. *BioRxiv*. 2020. https://doi.org/10.1101/2020.04.21.051201.
5. Mikkonena L, Pihlajamaaa P, Sahua B, et al. Androgen receptor and androgen-dependent gene expression in lung. *Mol Cell Endocrinol*. 2010;317:14-24.
6. Leach DA, Isac A-M, Bevan CL, et al. TMPRSS2, required for SARS-CoV-2 entry, is downregulated in lung cells by enzalutamide, a prostate cancer therapeutic. *Research Square*. 2020. https://doi.org/10.21203/rs.3.rs-34503/v1.
7. Goren A, McCoy J, Wambier CG, et al. What does androgenetic alopecia have to do with COVID-19? An insight into a potential new therapy. *Dermatol Ther*. 2020:e13365. https://doi.org/10.1111/dth.13365.
8. Polesso F, Hipfinger C, Sehrawat A, et al. Androgen receptor targeted therapy sensitizes tumor bearing mice to effective immunotherapy. *J Immunol*. 2020;204(Suppl 1):241.34.
9. Furman D, Hejblum BP, Simon N, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proc Natl Acad Sci U S A*. 2014;111:869-874.

Reply to the Letter to the Editor "Androgen deprivation therapy may constitute a more effective prophylactic than therapeutic strategy in COVID-19 patients" by N. Bennani and I. M. Bennani-Baiti

We read with interest the correspondence by Bennani and Bennani-Baiti[1] on our publication. The authors express concerns that our data do not support the hypothesis that androgen-deprivation therapy (ADT) is an effective therapy in patients with coronavirus disease 2019 (COVID-19) but may instead be used for prophylactic treatment.

Our observational study using data from the Veneto Cancer Registry indicates that ADT in patients with prostate cancer is associated with a reduced probability of developing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. However, as highlighted by Bennani and Bennani-Baiti,[1] the small sample size of patients with prostate cancer infected by SARS-CoV-2 under ADT in our study ($N = 4$ patients) did not allow us to evaluate whether ADT ameliorates the disease outcomes in infected patients. Thus, the results of validation analysis on larger patient cohorts, as well as of currently ongoing clinical trials investigating the contribution of androgen-suppression therapies for COVID-19 treatment, will be important to answer to this clinically relevant question.

Interestingly, a recent study from the United States involving 58 patients with prostate cancer infected by SARS-CoV-2 showed that the use of ADT was associated with lower rates of hospitalization and oxygen requirement, thus suggesting that ADT may limit severe COVID-19 complications.[2]

Concerning the mechanism of action, the androgen-dependent regulation of *TMPRSS2* expression in the lung represents one possible explanation for the increased susceptibility of men to the development of more severe SARS-CoV-2 infections. We agree with Bennani and Bennani-Baiti[1] that data supporting this link are still controversial. Several studies have previously demonstrated that *TMPRSS2* is regulated at the transcriptional and post-translational levels by androgens, mostly in the context of prostate tissue and prostate cancer. Moreover, androgen administration increases *TMPRSS2* expression in human lung epithelial cells.[3] However, in contrast to these findings, recent studies showed that the expression levels of *TMPRSS2* and *ACE2* in the human lung are lower when compared with other tissues such as the nasal cavity, the gallbladder, and the prostate.[4] Finally, one recent paper showed that ADT has no effect on *TMPRSS2* messenger RNA expression in mouse lungs.[5]

Thus, clear evidence demonstrating that androgen receptor-dependent *TMPRSS2* overexpression in the context of SARS-CoV-2 infections is still missing, and androgens might affect the severity of SARS-CoV-2 infection in men by other mechanisms, such as by modulating the immune response, as suggested in our article and further stressed by Bennani and Bennani-Baiti.[1] Sex differences have been observed, both in the innate and in the adaptive immune responses, and sex hormones have been shown to play a fundamental role.[6] For instance, androgens can increase the production of interleukin (IL)-1β, IL-10, IL-2, and transforming growth factor-β (TGF-β) by immune cells, decrease the antibody response to viral infections, and increase the number and function of circulating neutrophils.[6] In this respect, recent evidence demonstrates that neutrophils are responsible for the cytokine storm syndrome, observed in patients with severe COVID-19.[7]

Understanding the key role of androgens in the context of COVID-19 pathology may allow for the identification of high-risk patients, as well as the definition of potential treatment and/or prophylaxis strategies.

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REFERENCES

1. Bennani N, Bennani-Baiti IM. Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy. *Ann Oncol*. 2020;31(11):1585-1586.
2. Patel VG, Zhong X, Liaw B, et al. Does androgen deprivation therapy protect against severe complications from COVID-19? *Ann Oncol*. 2020;31(10):1419-1420.
3. Mikkonen L, Pihlajamaa P, Sahu B, Zhang F-P, Jänne OA. Androgen receptor and androgen-dependent gene expression in lung. *Mol Cell Endocrinol*. 2010;317(1-2):14-24.
4. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26(5):681-687.
5. Baratchian M, McManus J, Berk M, et al. No evidence that androgen regulation of pulmonary TMPRSS2 explains sex-discordant COVID-19 outcomes. *bioRxiv*. Published online April 21, 2020. https://doi.org/10.1101/2020.04.21.051201.
6. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-638.
7. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J Exp Med*. 2020;217(6):e20200652.

Reply to the letter to the editor: DPD testing in radical chemoradiation for anal squamous cell carcinoma? by R. Muirhead, H. Jones, D. Gilbert, A. Gilbert & C. Jacobs

We thank Jones et al.[1] for their comments on our article in a recent issue of the *Annals of Oncology* highlighting the adverse effects of poor compliance to chemotherapy and chemoradiation in the ACT II trial.[2] The authors advocate