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.

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DISCLOSURE

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Androgen deprivation therapy may constitute a more effective COVID-19 prophylactic than therapeutic strategy

Cellular transmembrane-serine-protease-2 (TMPRSS2), first cloned in 1997, has been intermittently the subject of intensive medical research, starting with the discovery of its role in recurrent TMPRSS2/ETS fusions and prostate cancer pathogenesis. TMPRSS2 protein was subsequently shown to proteolytically activate human respiratory tract viruses including influenza A, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). Following the emergence of SARS-CoV-2 underlying the current coronavirus disease 2019 (COVID-19) pandemic, eyes naturally turned to the androgen-regulated *TMPRSS2* gene for SARS-CoV-2 lung tropism, mortality rates, and gender bias.

A study by Montopoli et al. in the *Annals of Oncology* reported findings congruent with the prevailing notion that high SARS-CoV-2 infection rates and disease severity in men may be the result of high androgen-driven *TMPRSS2* expression in the lungs. The authors posit that since *TMPRSS2* is under positive transcriptional control by the androgen receptor (AR), reduction of *TMPRSS2* expression following androgen deprivation therapy (ADT) in prostate cancer patients would be expected to correlate with reduced SARS-CoV-2 incidence, and in case of infection, with lesser disease severity.[1] While fewer prostate cancer patients undergoing ADT contracted the virus, androgen suppression did not lessen disease severity (Table 1).

Several findings indicate that TMPRSS2 is unlikely to play a major role in SARS-CoV-2 lung pathology in men (and women): first, modulation of SARS-CoV-2 by TMPRSS2 has so far been observed only in TMPRSS2 protein overexpression experiments and no patient data to this effect are available. Moreover, while high *TMPRSS2* mRNA levels have been documented in the human lung,[2] AR and TMPRSS2 proteins do not appear to be highly expressed in the lungs.[2,3] This indicates that androgens do not control *TMPRSS2* expression in the lungs and that while TMPRSS2 protease experimentally activates SARS-CoV-2 *in vitro*, it is probably not the host cell co-factor for SARS-CoV-2 lung infection in the clinical setting. In addition, recent studies showed no differences in *TMPRSS2* mRNA lung expression in men versus women[4] or male versus female mice,[4,5] further supporting a lack of androgen control of *TMPRSS2* expression in the lung or of a role for TMPRSS2 in mediating the increased SARS-CoV-2 incidence in men. Accordingly, ADT has no effect on *TMPRSS2* mRNA expression in mouse lungs,[4,5] further challenging the notion of a putative androgen—TMPRSS2 axis mediating SARS-CoV-2 gender bias and virulence. Another study, however, showed that ADT decreased *TMPRSS2* transcripts in murine lungs, though the same study showed that *TMPRSS2* lung expression is not reduced following castration.[6] Finally, *TMPRS22* transcripts are moderately modulated *in vitro* by androgens in the human lung adenocarcinoma cell line A549, raising the possibility of *TMPRSS2* transcript modulation by androgens in patients afflicted with lung adenocarcinoma.[5]

It is not completely clear from the study by Montopoli et al. if the reduced COVID-19 incidence in the ADT cohort is solely due to ADT, or whether it might be due to additional clinical variables inherent to the ADT group. In particular, disease stage and the type of treatment that may affect AR or TMPRSS2 expression and/or patients'

Table 1. Comparison of COVID-19 outcomes between prostate cancer patients undergoing (+ADT) or not (−ADT) androgen deprivation therapy (ADT)

Outcome	+ADT	−ADT
Hospitalizations	2 out of 4 (**50%**)	76 out of 114 (**66.7%**)
Mild disease	3 out of 4 (**75%**)	83 out of 114 (**72.8%**)
Severe disease	1 out of 4 (**25%**)	31 out of 114 (**27.2%**)
Admission to ICU	1 out of 4 (**25%**)	13 out of 114 (**11.4%**)
Deaths[a]	0 out of 4 (**0%**)	18 out of 114 (**15.8%**)

The current thinking posits that under ADT, expression of TMPRSS2 (a co-factor for SARS-CoV-2 activation and virulence) would be reduced in the lungs, leading to less severe disease, hospitalizations, ICU admissions, and deaths. Data in this table from the Italian Veneto region contradict this widely accepted supposition: ADT imparts no major positive effects on hospitalization, disease severity, or ICU admissions.
ICU, intensive care unit.
[a] A definitive analysis of mortality rates is rendered difficult owing to the very small size of the cohort of SARS-CoV-2-positive prostate cancer patients undergoing ADT (4 patients only). Nevertheless, if one were to assume that the fatality rates of the control group without ADT (~16%) are similar to those of the ADT group, one would predict less than one death in the latter, a finding consistent with the lack of fatalities in this group.

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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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]