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European Association of Urology

Letter to the Editor

Re: Karin Welén, Ebba Rosendal, Magnus Gisslén, et al. A Phase 2 Trial of the Effect of Antiandrogen Therapy on COVID-19 Outcome: No Evidence of Benefit, Supported by Epidemiology and In Vitro Data. Eur Urol. 2022;81:285–293

We read with interest the paper by Welén et al [1]. In the first section, the authors report on the time to discharge from hospital for men and women older than 50 yr with a positive SARS-CoV-2 polymerase chain reaction (PCR) test randomized to an enzalutamide group or a control group (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.20–0.93). The authors found no effect of 4-d enzalutamide treatment on virus replication ($p = 0.084$) in an in vitro primary lung model of human bronchial epithelial cells (HBECs). Enzalutamide treatment did not decrease the mRNA expression of *TMPRSS2* or *ACE2*. The authors also found no preventive effect of androgen inhibition therapy, while the combination of androgen deprivation therapy (ADT) and abiraterone acetate or enzalutamide increased the risk of dying from COVID-19 (HR 2.51, 95% CI 1.52–4.16). They have provided valuable insights into the effects of androgen inhibition in COVID-19. However, some points are worthy of further discussion.

In the second part of the study, HBECs were used to investigate the effect of enzalutamide treatment on mRNA expressions of *TMPRSS2* and *ACE2*, but evidence for androgen receptor (AR) expression in human lung cells is currently lacking [2]. Therefore, the lack of a decrease in *TMPRSS2* and *ACE2* mRNA expression levels is possibly due to the absence of a target for enzalutamide in HBECs. In previous studies, effects of enzalutamide on *TMPRSS2* and *ACE2* mRNA expression levels were mostly observed in murine animal models. Enzalutamide may possibly act on ARs in prostate cells and affect various downstream cytokine activities, thereby eventually changing the microenvironment surrounding lung cells [3]. Therefore, we would recommend that the authors use a co-culture system of prostate normal (or cancer) cells and HBECs and further analyze the changes in the downstream cytokines in their blood samples to clarify their study outcomes.

We would also recommend that the authors use a positive control with another antiandrogen therapy (eg, ARN-509 or abiraterone) to validate the results presented for the second part of the study. In addition, none of the three trials specified the SARS-CoV-2 strain(s) used, which might have affected the study outcomes. We suggest that the authors should perform a subgroup analysis by SARS-CoV-2 strain. We also note that Table 2 [1] lists very different grade 3 adverse events between the enzalutamide and control groups, even though all events were labeled as not related or unlikely to be related to enzalutamide. We would recommend that the authors explain the possible underlying reasons for the differences in grade 3 adverse events observed in the two groups. Finally, we suggest that the authors should perform a multivariable analysis for Table 1 to investigate the effects of potential confounding variables, such as medications used in treatments and ventilator usage, on primary and secondary outcomes.

In conclusion, we are convinced that a co-culture system, analysis of cytokine levels in blood, and a positive control are all required to further validate the results presented for the second part of the study. Residual confounders and the differences in grade 3 adverse events also require some explanation.

Conflicts of interest: The authors have nothing to disclose.

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