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EDITORIAL

Little support for a protective effect of ADT against COVID-19

In the present issue of *Scandinavian Journal of Urology*, Gedeborg et al. [1] report a study based on Prostate Cancer Database Sweden (PCBaSe) on the risk of COVID-19 death among men with prostate cancer. In the study the authors assessed outcome during the COVID-19 pandemic for men on and not on androgen deprivation therapy (ADT). Although there was an increased risk of death from COVID-19 in men on ADT, no increased risk remained after adjustment for age, comorbidity, and cancer stage [1]. In a previous publication Gedeborg et al. compared all-cause mortality in all men in Sweden with prostate cancer during the spring of 2020 with that in previous years. They found no difference in changes in death rate between men on or not on ADT suggesting that ADT does not protect against death from COVID-19 [2]. These results are in line with a recent review of 14 other retrospective trials by Caffo et al. that included studies using various methodology and outcomes. The conclusion of the review was that there is little evidence in support of a protective effect of androgen signaling inhibition for COVID-19 outcomes [3]. Two additional studies have recently been published including retrospective data with the same conclusion [4,5]. One of these studies included, similar to the Gedeborg studies, epidemiological data from Swedish national COVID-19 register (including 1,057,174 COVID-19 cases). That analysis included 6206 prostate cancer patients without any hormonal treatment during the COVID-19 pandemic, 789 patients on ADT, 676 on bicalutamide alone, and 214 on ADT plus abiraterone/enzalutamide. Also similar to Gedeborg et al., after adjustments for comorbidity and age there was no evidence of any beneficial role of androgen signaling inhibition neither for risk of hospitalization, need of intensive care nor mortality. The only remaining significant association was an increased risk of COVID-19 related deaths in patients treated with abiraterone acetate or enzalutamide in addition to ADT, but no difference in risk between the two different drugs. The authors state that this increased risk was most likely due to the frailty in this group, not easily adjusted for by the comorbidity index used in the analysis [5].

The presumed connection between castration, prostate cancer and COVID-19 is based on the mechanism used by SARS-CoV-2 for entrance into the respiratory epithelium. The virus binds to the ACE2 receptor, but this is preceded by priming by a serine protease called TMPRSS2, which is known to be androgen receptor (AR) regulated [6]. In prostate cancer, TMRPSS2 is part of a common DNA re-arrangement that leads to fusion between TMPRSS2 and any of the oncogenes of the ERG family, resulting in AR-regulated oncogene expression. In early 2020, AR was the only known regulator of TMPRSS2 expression, and also ACE2 was shown to be regulated to some degree by AR [6]. Consequently, the hypothesis that androgen signaling inhibition therapies may decrease the virulence of SARS-CoV-2 was theoretically sound. The hypothesis that testosterone as the culprit in COVID-19 has been challenged and Auerbach et al. [7] based on the protective role of testosterone in inflammatory response and the observation that low testosterone levels in hospitalized patients increase the risk of intensive care and fatal outcome. However, it is known that severe disease can decrease testosterone levels by inhibiting the hypothalamic pituitary-testicular axis, which makes the association more likely to be a consequence of the disease rather than causing the worse outcome [7].

The only published randomized clinical trial testing the testosterone hypothesis by using an approved antiandrogen is the recently published COVIDENZA trial (NCT04475601) [5,8]. The study included 42 patients randomized 2:1 to five days enzalutamide + standard of care compared to standard of care alone. The study was stopped early due to futility, after suggestion from the data safety and monitoring board. The primary outcome was time to mechanical ventilation or discharge from hospital and secondary endpoint included viral load, laboratory parameters and mortality. The enzalutamide group stayed longer in hospital and none of the primary or secondary end point was showing any benefit for the experimental arm.

Thus, the accumulating evidence points to that androgen signaling inhibition is neither a friend or foe in COVID-19. However, there is one study by a group of researchers testing the anti-androgen proxalutamide in a randomized trial in Brazil, which showed a clear support of the initial hypothesis. The results are remarkable with 70–90% reduction of hospitalization in COVID-19 patients [9]. Proxalutamide, an antiandrogen, is a not yet approved drug but is currently used in trials on prostate and breast cancer (NCT03899467 and NCT04103853). The difference in results from the studies using the anti-androgens enzalutamide and proxalutamide is intriguing. However, soon a trial evaluating degarelix (GnRH antagonist) by Rettig et al. [10] will be presented. That study investigates medical castration by degarelix in hospitalized COVID-19 patients with a similar protocol as the COVIDENZA trial. Hopefully, the results will help in interpreting the conflicting trial results regarding the potential of targeting androgen signaling to decrease COVID-19 symptoms.

In conclusion, despite an increasing number of publications on the subject, there is little support for the hypothesis that inhibition of androgen receptor signaling is protective against COVID-19. Thus, the reasons for the increased risk of severe COVID-19 in men compared to women remains to be elucidated.

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