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.

Re: Androgen-deprivation Therapies for Prostate Cancer and Risk of Infection by SARS-CoV-2: A Population-based Study (*n* = 4532)

Montopoli M, Zumerle S, Vettor R, et al

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Experts' summary:

Montopoli et al [1] analyzed data from 9280 patients (4532 males) with laboratory-confirmed SARS-CoV-2 infection from 68 hospitals in Veneto, one of the regions in Italy mostly affected by the COVID-19 pandemic. While women were slightly more likely to be infected (56% of the study population), men developed more severe complications and had worse clinical outcomes: 60% of men versus 40% of women required hospitalization and 78% versus 22% required intensive care. More men also died (62% vs 38%). Cancer patients overall had a higher risk of infection compared to non-cancer patients; however, it also became apparent that prostate cancer (PCa) patients not receiving androgen deprivation therapy (ADT) had a significantly higher risk of SARS-CoV2 infection compared to patients treated with ADT (odds ratio [OR] 4.05, 95% confidence interval [CI] 1.55–10.59). In addition, there was a greater difference between patients with any other cancer type and PCa patients receiving ADT (OR 5.17, 95% CI 2.02–13.40).

Experts' comments:

During the COVID-19 pandemic one striking difference became apparent: men are more susceptible to severe outcomes than women. A disproportionately lower rate of adult females compared to males among severe cases (42% vs 58%) has been reported [2]. Similarly, severe cases have rarely been seen among prepubescent children (0.6%) [2]. New data are now supporting the theory that androgen levels and factors associated with androgen receptor (AR) activation may be involved in COVID-19–related pathophysiology.

The study by Montopoli et al [1] indicates that PCa patients receiving ADT had a significantly lower risk of SARS-CoV-2 infection compared to patients not treated with ADT; an even greater difference was found when compared to patients with any other cancer type. Their findings suggest that androgens may increase SARS-CoV-2 virulence and that PCa patients receiving ADT appear to be partly protected from the infection.

One hypothesis potentially explaining sex-specific effects may be attributed to low AR expression and androgen levels before puberty and explain more severe infections in men compared to women. In this regard one key pathological mechanism related to cell entry of SARS-CoV-2 is considered relevant. The first essential step required for potential infectivity of SARS-CoV-2 involves binding of the viral spike protein to ACE2 and priming of the protein by TMPRSS2 [3,4]. In addition, TMPRSS2 may cleave ACE2 for augmented viral entry. An investigation of cell types expressing ACE2 and TMPRSS2 also revealed that pneumocytes I/II in males compared to females more often express ACE and that in type II pneumocytes, TMPRSS2 expression is associated with increased AR expression [5,6]. AR activation is a requirement for TMRPSS2 gene transcription; to date, no other gene promoter has been described in humans [3]. In murine models it has been shown that TMPRSS2-deficient mice show reduced viral kinetics in the lungs, and a lack of TMPRSS2 was accompanied by less severe immunopathology [7]. Additional evidence indicates the impact of sexual dimorphism on lung disorders; it has long been recognized that newborn male infants are more susceptible to respiratory distress syndrome and that fetal pulmonary surfactant production is influenced by the AR [8]. Male vulnerability may be further enhanced by X-linked inheritance of genetic polymorphisms (AR and ACE2 are chromosome X–related), and it has been shown that ACE2 expression and activity are reduced by experimental orchiectomy [3].

The current evidence indicating male susceptibility to COVID-19 owing to male hormones might point to potential treatment targets. Inhibition of TMPRSS2 may represent an option for host factor modulation to decrease the severity of SARS-CoV-2 infections. In rabbits, dihydrotestosterone inhibited pulmonary surfactant production in males and females, while an antiandrogen, flutamide, abrogated the dimorphism in surfactant production [9]. Acknowledging the importance of androgens, the potential impact of AR antagonists, androgen synthesis inhibitors, and antigonadotropins on host vulnerability via androgen suppression will need to be further evaluated, either as monotherapy or in combination with protease inhibitors; studies are currently ongoing. Finally, the epidemiology of COVID-19 patients predisposed to either lower or higher AR expression should be evaluated; in addition, analysis of ethnic variations in AR expression may predict geographical mortality differences.

Conflicts of interest: Sabine D. Brookman-May is an employee of Janssen Research and Development Oncology.

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