BRIEF COMMUNICATION

Clinical Research

Serendipity for the intervention of COVID-19 and prostatic adenocarcinoma (PaC)

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Prostatic adenocarcinoma (PaC) shares similarities with COVID-19 that can be more challenging for patients but a gateway to new targets for co-therapy of both diseases. The cellular entry of SARS-CoV-2 depends on ACE2-R and TMPRSS2 (oncogenic gene) in the pathogenesis of PaC. The androgen axis regulates the transcription of TMPRSS2, related to susceptibility and high mortality of PaC patients to COVID-19. To date, there is no standard therapy approved for COVID-19 and redefining the use of antiandrogens and anti-TMPRSS2 seems a promising strategy for COVID-19 management. In this brief communication, the association between COVID-19 and PaC was evaluated using current scientific literature.

PaC, prevalent cancer in elderly men, metastasizes to lymph nodes, bone marrow, and blood vessels [1]. According to Johns Hopkins Coronavirus Resource Center, SARS-CoV-2 has caused more than 270 million infections and more than 5 million 300 deaths as of December 12, 2021 [2]. According to the 2021 Global Cancer Report, there have been about 14 million new cases of PaC and 3.8 million new deaths worldwide, and the global incidence ranks third after breast and lung cancer [3]. Since December 2019, when COVID-19 surfaced in Wuhan City and spread rapidly across China, a study conducted at various centers found that 58% of males out of 1099 patients after high throughput sequencing or RT-PCR assay of nasal and pharyngeal swab specimens. There were 0.9% cancer patients with 3% severe morbidity of viral infection [4].

From December 2019 to January 2020, a retrospective observational study at a single center was conducted in Wuhan, China showed that 67% of COVID-19 patients were men. Of these men, 40% had another chronic disease and 13.5% had comorbidity from cerebrovascular diseases with 100% mortality in 4 weeks. Another study estimated the presence of pathogenic COVID-19 through RT-PCR detection and reported that older men are more prone to COVID-19 infection [5]. A study with a particular focus on morbidity and mortality from COVID-19 in men and women was conducted in Wuhan, and results of that study confirmed the severity of COVID-19 disease was more pronounced in men than in women [6]. A preliminary case study was conducted at the Wuhan Union Hospital in China from January 29, to February 15, 2020. A total of 1099 COVID-19 cases were analyzed, including 37 deceased cases, 70.3% were men aged 65–81 years (interquartile range 11–18 days of symptoms). Among deceased cases, 64.9% had at least one comorbidity related to high BP, hyperglycemia, and cardiovascular and/or respiratory illness and concluded that men were associated with worse outcomes regardless of age and COVID-19 with preexisting comorbidities. This higher incidence and severity can be associated with shorter life expectancy in men vs women worldwide [7]. A review article published in *Communication Biology* reporting gender-based discrimination of COVID-19 and higher risk in PaC. It supported the gender-based disproportion, i.e., 2.8:1.7% male:female mortality rate in China and in France, Germany, Iran, Italy, South Korea, England, and America [8]. The researcher reported 58% deaths in men and 42% in women as of June 2020 and 60.3% of hospitalized patients were male and 66.5% of men were over 20 years old. It concluded that chemotherapy causes systemic immunosuppression and make patients more prone to viral infections. A cohort study was conducted from March to December 2020 and compared the severity of COVID-19 in prostate cancer, gastrointestinal cancer, breast cancer, and solid cancers. This study reported higher hospitalizations and death among PaC compared to other malignancies [9].

The interaction of angiotensin-converting enzyme 2 (ACE2) receptor, transmembrane serine proteases II (TMPRSS2), and another protein furin protease with the SARS-CoV-2 spike glycoprotein plays an important role in virus entry and are the ideal points of attack for the development of medical approaches and novel treatments. TMPRSS2 are widely recognized as a critical host cell factor involved in the pathogenesis of variety of cancer and viral infections, including influenza A viruses and SARS-CoV coronaviruses. TMPRSS2 was first identified for its role in prostate cancer pathogenesis following the discovery of its oncogenic fusion gene with ETS transcription factor such as ETS related genes (ERG). TMPRSS-ERG protein is overexpressed in local and metastatic tumors. Downregulating these proteins is one of the strategies used to treat prostate cancer. TMPRSS2, along with its oncogenic potential in PaC, also facilitates cellular entry of the respiratory syndrome viruses. SARS-CoV2 enters the cell by binding to the ACE2 receptor on alveolar epithelial cells, then TMPRSS2 cleaves S-glycoprotein of the coronavirus, resulting in viral fusion with cell membranes. Camostat mesylate and nafamostat are protease inhibitors employed to study the role

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Table 1. Clinical trials usingTMPRSS2 and antiandrogen inhibitors for management of COVID-19 (Clinicaltrials.gov).

TMPRSS2 inhibitors						
Drug	**NCT#**	**Condition**	**Clinical trial phase**	**Location**	**Participants**	**Start date**
Camostat mesilate	NCT04470544	COVID-19 hospitalized patient	2	United States, Arizona	264	July 28, 2020
	NCT04321096	COVID-19 (outpatient and hospitalized patients)	1, 2	Denmark	580	April 4, 2020
	NCT04608266	COVID-19	3	France	596	December 3, 2020
Bromhexine plus hydroxychloroquine	NCT04355026	COVID-19	4	Slovenia	90	April 10, 2020
	NCT04340349	COVID-19 prophylaxis in healthcare	1	Mexico	214	February 1, 2021
Nafamostat mesilate	NCT04352400	COVID-19	2, 3	Italy	256	June 4, 2021
Aerosolized 13 cis retinoic acid plus Inhalation administration by nebulization captopril 25 mg (indirect inhibition of TMPRSS2)	NCT04578236	COVID-19	2	Kafrelsheikh University	360	November 2020
Alpha one antitrypsin inhalation	NCT04385836	COVID-19	1	Saudi Arabia	150	June 1, 2020
Isotretinoin (13 cis retinoic acid) capsules isotretinoin (aerosolized 13 cis retinoic acid)	NCT04353180	COVID-19	3	Kafrelsheikh University	100000	August 2021
Antiandrogens						
Proxalutamide	NCT04446429	COVID-19 Androgenic alopecia Bengin prostate hyperplasia	Not defined	Brazil	268	September 15, 2020
	NCT04853134	COVID-19	3	Brazil	200	November 1, 2020
	NCT04728802	COVID-19 hospitalized patients	3	Brazil	645	February 1, 2021
	NCT04853927	COVID-19 in ICU	3	Brazil	600	February 8, 2021
EAT-DUTA AndroCoV trial dutasteride 0.5 mg plus azithromycin plus nitazoxanide	NCT04729491	COVID-19 Prostate cancer Androgenic alopecia	1, 2	Brazil	138	June 30, 2020
Enzalutamide	NCT04475601	COVID-19	2	Sweden	500	July 15, 2020
Bicalutamide	NCT04374279	COVID-19	2	United States, Maryland Johns Hopkins Hospital	0	Withdraw due to limited resources
Camostat mesilate plus bicalutamide150 mg	NCT04652765	COVID-19	1	United States, Maryland Johns Hopkins Hospital	40	February 3, 2021

of TMPRSS2 in virus entry into the cells. These protease inhibitors can block TMPRSS2 expression, thereby preventing viruses from entering the lung epithelial cells. However, severe systemic toxicities, including cerebral hemorrhage, limit the clinical use of these protease inhibitors. Redesign of TMPRSS2 inhibitors with reduced toxicity may open a new gateway for the development of novel options to prevent these viral infections. The upregulation of ACE2 in conjunction with excessive production of angiotensin II reduces tissue damage. This hypothesis was employed to treat COVID-19. Androgen receptors (AR) regulate the transcription of TMPRSS2 and ACE2. Meanwhile, overexpression of TMPRSS2 in PaC due to elevated testosterone levels also increases the susceptibility to developing SARS-CoV2 infection [10]. TMPRSS2 inhibitors and antiandrogens serve as potential drug targets for the treatment of PaC and COVID-19. Several clinical studies have been developed to evaluate the effectiveness of such inhibitors as a therapeutic option in COVID-19 (Table 1).

Developing novel strategies to combat SARS-CoV-2 is an emerging need in this era of pandemic. Evidence from preclinical studies suggested that TMPRSS2 expression can be modified by suppressing ARs to treat SARS-CoV-2 infection. Previous retrospective clinical studies examining the potential of androgen antagonists in COVID-19 and PaC have drawn controversial results due to the small sample size. Detailed observational studies are required to develop evidence of the beneficial use and safety profile of androgen antagonists prior to clinical use.

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AUTHOR CONTRIBUTIONS

FN: conceptualization and writing. TA: review and supervision. RG: drafting and writing. SA: review and proofreading.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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