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LETTER

Androgen sensitivity in COVID-19 and antiandrogens: Prospective data are still needed

Dear Editor

Men are disproportionately affected by COVID-19 and have an increased risk of ICU admittance as well as mortality. In contrast, prepubescents appear to be largely protected from COVID-19 severe symptoms.[1] The androgen receptor regulates the transcription of the transmembrane protease, serine 2 (TMPRSS2), and angiotensin converting enzyme 2 (ACE2) which are required for the COVID-19 infectivity; thus, raising the hypothesis of androgen sensitivity as a risk factor.[2,3] The recent association of androgenetic alopecia (AGA) with COVID-19 severity strengthens the androgen theory.[2] Testosterone levels are low not only in prepubescents but also in elderly men[4] and recent observations point out that disease severity may be best correlated with specific gene loci, rather than ACE2 or TMPRSS2 receptors.[5] Furthermore, serum androgens do not always correlate with tissue androgens or androgen mediated disease. For example, AGA and prostate cancer can be exacerbated by elevated tissue androgen in genetically predisposed patients.[6]

In order to elucidate the effect of androgens on COVID-19 outcomes, some epidemiological studies were conducted. Since TMPRSS2 are expressed in the lungs, the use of antiandrogens or androgen-depleting therapies (ADT), currently used for prostate cancer, represent an appealing target for prevention or treatment of COVID-19.[4] An Italian study compared infectivity and outcomes of COVID-19 in prostate cancer patients treated with or without ADT (androgen deprivation therapies). The study concluded that ADT was associated with reduced risk of infection and with reduced COVID-19 disease burden[7]; however, to-date, no large epidemiological study attempted to evaluate the potential protective role of diverse antiandrogens in COVID-19 infection.

TABLE 1 Main clinical and demographic data from 374 male confirmed COVID-19 patients, according to the severity of the disease

		Disease severity			Odds ratio (CI 95%)*		Odds ratio (CI 95%)*	
Variables	Total	Home	Hospitalization	*ICU/MV*	Home vs hospitalization	*P* value	Home vs ICU/MV	*P* value
n	374	308	37	29				
Antiandrogen therapy: *n* (%)	17 (4.5)	15 (4.9)	1 (2.7)	1 (3.4)	0.30 (0.03-3.23)	.323	0.19 (0.01-3.28)	.256
Age (years): n (%)						.926		.580
<30	56 (15.0)	51 (16.6)	3 (8.1)	2 (6.9)	1 (–)		1 (–)	
31-60	279 (74.6)	229 (74.4)	28 (75.7)	22 (75.9)	1.19 (0.33-4.34)		1.99 (0.43-9.19)	
>60	39 (10.4)	28 (9.1)	6 (16.2)	5 (17.2)	1.39 (0.27-7.19)		2.74 (0.40-18.81)	
Body composition: *n* (%)						.186		.011
Eutrophic	200 (53.5)	167 (54.2)	18 (48.6)	15 (51.7)	1 (–)		1 (–)	
Heavy	149 (39.8)	127 (41.2)	14 (37.8)	8 (27.6)	0.68 (0.30-1.52)		0.51 (0.19-1.37)	
Obese	25 (6.7)	14 (4.5)	5 (13.5)	6 (20.7)	2.23 (0.62-8.01)		4.19 (1.20-14.67)	
Smoking: *n* (%)						.544		.966
Never	273 (73.0)	228 (74.0)	25 (67.6)	20 (69.0)	1 (–)		1 (–)	
Ever smoking	101 (27.0)	80 (26.0)	12 (32.4)	9 (31.0)	1.29 (0.57-2.91)		0.98 (0.36-2.64)	
Hypertension: *n* (%)	85 (22.7)	58 (18.8)	19 (51.4)	8 (27.6)	3.14 (1.39-7.10)	.006	0.80 (0.28-2.30)	.675
Diabetes: *n* (%)	32 (8.6)	15 (4.9)	9 (24.3)	8 (27.6)	4.94 (1.74-14.03)	.003	7.10 (2.24-22.52)	.001
Heart disease: n (%)	12 (3.2)	7 (2.3)	1 (2.7)	4 (13.8)	0.44 (0.03-5.99)	.534	3.74 (0.76-15.55)	.106

Abbreviations: Hospitalization, without mechanic ventilation; ICU, Intensive Care Unit; MV, mechanic ventilation.

*Adjusted *P* value and odds ratio estimated by multivariate logistic regression.

To gather large scale data, we performed a population survey through snowball sampling. Participants were invited to complete an electronic questionnaire comprising baseline demographic, COVID-19 status (never, suspected, or confirmed), disease severity (home, hospitalization without mechanical ventilation, and intensive care unit/mechanical ventilation—ICU/MV), use of antiandrogen therapy (ADT for prostate cancer, finasteride, dutasteride, flutamide, bicalutamide, spironolactone, and cyproterone), and other factors associated with disease severity.

Forty-one thousand five hundred twenty-nine participants were enrolled (38 350 healthy, 2148 suspected, and 1031 confirmed). Among male, 554 (4.7%) healthy and 17 (4.5%) COVID-19 infected participants reported current use of any antiandrogenic therapy. The data related to outcomes and antiandrogen therapy, adjusted by comorbidities, are presented in Table 1. The use of antiandrogen therapy was not associated with the incidence or the outcomes (home vs hospitalization without mechanical ventilation and ICU/MV) of COVID-19 when adjusted by other known risk factors.

Despite the biologic plausibility of androgens promoting COVID-19 infection, several factors remain unexplained, as stated by Pozzilli et al.[4] Others arguments are that different regulators, rather than androgens, may influence the TMPRSS2 protease and androgen receptor ethnic genetic variations may pre-dispose certain populations to have different responses to antiandrogen therapy.[4] In addition, TMPRSS2 also plays a role in infectivity of influenza.[8] Disease burden due to the influenza-A virus is often higher in men, but fatality following exposure to pathogenic influenza-A is higher in women and men before puberty.[9] Moreover, the variability between outcomes in men and women could also be due to anatomical and immunological differences.[9]

Even though our survey could not establish an association between antiandrogen therapy and prophylaxis of COVID-19 infection or severity, the hypothesis remains to be confirmed. Not all antiandrogens have the same potency (eg, androgen deprivation therapy for prostate cancer compared with finasteride for androgenetic alopecia in men); thus, different medications and equivalent dosages must be carefully evaluated. The elucidation of the role of testosterone towards COVID-19 infection turns out to be an urgent need. Many candidates could be potential drugs such as androgen receptor inhibitors, steroidogenesis inhibitors, and 5-alpha reductase inhibitors.[2] To date, there are six trials with antiandrogen therapies registered in clinicaltrials.gov.

DATA AVAILABILITY STATEMENT

All data from the study are available from the corresponding author upon request.

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