Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men

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Abbreviations:
COVID-19: Coronavirus Disease 2019
ICU: Intensive care unit
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.
Dear Editor, The COVID-19 pandemic has disproportionately affected men.¹ Men infected with SARS-CoV-2 are more than twice as likely to be admitted to the intensive care unit (ICU).² This disparity in ICU admissions suggests the important role of androgens in COVID-19 severity.³ Previously, we reported that among 122 men hospitalized due to COVID-19, 79% were diagnosed with androgenetic alopecia (AGA),⁴ which is commonly treated with anti-androgens. Anti-androgens commonly used in the treatment of AGA such as finasteride, dutasteride, spironolactone, and bicalutamide could improve outcomes among men infected by SARS-CoV-2.

A prospective cohort study was conducted from the data of men hospitalized due to COVID-19 followed in an observational genetic case-control study (NCT04368897). The subjects were categorized into two cohorts: those taking anti-androgens for at least 6 months or those not taking anti-androgens prior to hospitalization. Enrollment occurred in a sequential order from late March to early May 2020. The subjects were followed for a period of 60 days from the date of hospitalization. The primary outcome was the rate of ICU admission.

77 subjects were included, mean age was 68.6 ±12.7 (Table I). 12 men (15.6%) were taking anti-androgens: dutasteride (n=9), finasteride (n=2), or spironolactone (n=1). 65 men (84.4%) were not taking anti-androgens. The average age of those taking anti-androgens was higher, 80.6 ±8.2, versus 66.4 ±12.2, p=0.0002. The proportion of subjects admitted to the ICU taking anti-androgens was significantly lower, 1/12 (8%) versus 38/65 (58%), p=0.0015, Figure. 1. Because the age of the subjects taking anti-androgens was skewed older, an age-matched subset (>65 years old) analysis was performed. There were 34 subjects in the age-matched subset with an average age of 75.9 ±8.0. The ICU admission rate in the age-matched group was 44%. The proportion of subjects admitted to the ICU taking anti-androgens was significantly lower than the proportion of subjects admitted to the ICU in the age-matched subset, p=0.018. The relative risk for ICU admission for subjects taking anti-androgens was (RR 0.14, 95% CI: 0.02-0.94). The relative risk for ICU admission for subjects taking anti-androgens compared to the age-matched group was (RR 0.19, 95%CI: 0.03-1.28). When the patient taking spironolactone was excluded from the analysis, the use of 5-alpha-reductase inhibitors maintained statistical significance for reduced ICU admissions, p=0.0028. Different from all other patients on the anti-androgen cohort, the patient taking spironolactone did not have the
diagnosis of benign prostate hyperplasia, and was taking it due to cardiovascular reasons (hypertension and congestive heart failure). The rates of diabetes mellitus, obesity, and hypertension (known risk factors for worse outcomes) were similar in all groups.

We recognize the limitations of this small study; however, these results, as well as previous data presented in a retrospective study of androgen deprivation in prostate cancer patients (with stronger anti-androgens such as bicalutamide in association with chemical castration),\textsuperscript{5} suggest that anti-androgens may represent a promising treatment modality for COVID-19. Recently, it has been demonstrated that both dutasteride and spironolactone reduce the levels of both angiotensin converting enzyme 2 (ACE2) and TMPRSS2 in embryonic cardiac stem cell model.\textsuperscript{6} Tamsulosin, which is used in combination with dutasteride for benign prostate hyperplasia also demonstrated reduction of ACE2 levels. Among the anti-androgen modalities, 5-alpha reductase inhibitors are the most well-tolerated due to specific blockade of local (intracellular) dihydrotestosterone production in target tissues, not affecting testosterone levels. Due to the long half-life of dutasteride (5 weeks), activity is still expected if stopped upon admission. Dermatologists are encouraged to advise their patients to maintain systemic AGA therapy with anti-androgens, particularly 5-alpha reductase inhibitors during the pandemic. These results should encourage larger studies of anti-androgens in COVID-19 patients. A large double-blinded interventional study with dutasteride is ongoing (NCT04446429).
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Figure Legend

Figure 1. Hospital Outcomes. Prospective cohort of 77 men hospitalized due to severe COVID-19 in Madrid, Spain. Individuals were categorized by use of anti-androgens for at least 6 months before hospital admission, and followed for 60 days. The relative risk for intensive care unit (ICU) admission for individuals taking anti-androgens was 0.14 (95% confidence interval: 0.02-0.94).

Table Legend

Table I. Characteristics of the anti-androgen group, and non-anti-androgen groups.
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|                                | Anti-Androgen Group | non-Anti-Androgen Group | Aged Matched non-Anti-Androgen Group |
|--------------------------------|---------------------|-------------------------|--------------------------------------|
| Subjects                       | n=12                | n=65                    | n=36                                 |
| Age                            | 80.6 (+/-8.2)       | 66.4 (+/-12.2)          | 75.3 (+/-8.2)                        |
| Intensive Care Unit Rate       | 1 (8.3%)            | 38 (58.5%)              | 17 (47.2%)                           |
|                                | p=0.0014            | p=0.018                 |                                      |
| Deaths                         | 1 (8.3%)            | 4 (6.2%)                | 2 (5.6%)                             |
|                                | p=0.58              | p=1.00                  |                                      |
| Comorbidities                  |                     |                         |                                      |
| Prostate Cancer                | 0 (0%)              | 1 (1.5%)                | 1 (2.8%)                             |
|                                | p=1.00              | p=1.00                  |                                      |
| Benign Prostate Hyperplasia    | 11 (91.7%)          | 10 (15.4%)              | 9 (25%)                              |
|                                | p=0.000001          | p=0.000069              |                                      |
| Hypertension                   | 8 (66.7%)           | 30 (46.2%)              | 21 (58.3%)                           |
|                                | p=0.22              | p=0.74                  |                                      |
| Immunosuppression              | 0 (0%)              | 8 (12.3%)               | 4 (11.1%)                            |
|                                | p=0.34              | p=0.559667              |                                      |
| Cardiovascular                 | 8 (66.7%)           | 18 (27.7%)              | 13 (36.1%)                           |
|                                | p=0.017             | p=0.095                 |                                      |
| Neurological                   | 3 (25%)             | 13 (20%)                | 10 (27.8%)                           |
|                                | p=0.71              | p=1.00                  |                                      |
| Endocrine (mainly Diabetes Mellitus) | 6 (50%)       | 26 (40%)                | 20 (55.6%)                           |
|                                | p=0.54              | p=0.75                  |                                      |
| Respiratory                    | 2 (16.7%)           | 11 (16.9%)              | 8 (22.2%)                            |
|                                | p=1.00              | p=1.00                  |                                      |
Renal | 2 (16.7%) | 5 (7.7%) | 4 (11.1%)
---|---|---|---
p=0.75 | p=0.63

**Bold**: Statistically significant difference between groups (p<0.05).
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