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

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Journal

Journal of the European Academy of Dermatology and Venereology, 35(1)

ISSN

0926-9959

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Publication Date

2021

DOI

10.1111/jdv.16953

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was positive in eight cases, borderline in two, and negative in three, including the COVID-19 patient.

Overall, serology for S1-specific IgA and IgG in the 30 patients shows that 16 (53.3%) were positive for IgA, whereas IgG was detectable in five (16.6%; Fig. 1f).

We have recently reported that high levels of IgG and IgA can be detected in adult patients with severe COVID-19, while IgA, and to a lower extent IgG, is increased in asymptomatic individuals.[6] As IgA is the most abundant antibody at mucosal sites, a strong local protection may prevent viral spread and damage to the respiratory tract, explaining the lack of symptoms. The ELISA used for the detection of anti-S1 IgG and IgA has been demonstrated to be specific and sensitive.[7,8] Of note, antibodies against S1 are often neutralizing[9] and may prevent severe disease and further immune responses.[6] Our findings indicate that, similar to asymptomatic adults, paediatric patients would respond to SARS-CoV-2 producing more IgA than IgG. On the other hand, a single patient had detectable IgG against SARS-CoV-2 nucleoprotein. Anti-nucleoprotein IgG is present in the great majority of hospitalized adult patients, but only in one-third of paucisymptomatic individuals, suggesting that disease severity influences the specificity of the antibodies produced.[10]

In conclusion, the detection of S1-specific IgA in paediatric patients with chilblain-like lesions strongly points to a previous, mostly asymptomatic SARS-CoV-2 infection with inflammatory sequelae.

Acknowledgements

We thank the patients and their parents for accepting to participate in this study. The patients in this manuscript have given written informed consent to publication of their case details. We thank Mr. Gabriele Bacile for iconography preparation.

Three of the authors (MEH, AD and GZ) of this publication are members of the European Reference Network ERN-SKIN and two of them (MEH, AD) are also members of vascular anomalies working group (VASCA WG) of the ERN for rare multisystemic vascular diseases (VASCERN).

Conflicts of interest

None to be reported for all authors.

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References

1 Freeman EE, McMahon DE, Lipoff JB *et al*. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. *J Am Acad Dermatol* 2020; **83**: 486–492.

2 Andina D, Noguera-Morel L, Bascuas-Arribas M *et al*. Chilblains in children in the setting of COVID-19 pandemic. *Pediatr Dermatol* 2020; **37**: 406–411.

3 Le Cleach L, Dousset L, Assier H *et al*. Most chilblains observed during the COVID-19 outbreak occur in patients who are negative for COVID-19 on PCR and serology testing. *Br J Dermatol* 2020; **183**: 866–874.

4 El Hachem M, Diociaiuti A, Concato C *et al*. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. *J Eur Acad Dermatol Venereol* 2020; **34**: 2620–2629.

5 Salgado F, Handler MZ, Schwartz RA. Shedding light on onychomadesis. *Cutis* 2017; **99**: 33–36.

6 Carsetti R, Zaffina S, Mortari EP *et al*. Spectrum of innate and adaptive immune response to SARS CoV 2 infection across asymptomatic, mild and severe cases; a longitudinal cohort study. *medRxiv* 2020. https://doi.org/10.1101/2020.06.22.20137141 [Epub ahead of print].

7 Beavis KG, Matushek SM, Abeleda APF *et al*. Evaluation of the EUROIMMUN Anti-SARS-CoV-2 ELISA assay for detection of IgA and IgG antibodies. *J Clin Virol* 2020; **129**: 104468.

8 Caturegli G, Materi J, Howard BM, Caturegli P. Clinical validity of serum antibodies to SARS-CoV-2: a case-control study. *Ann Intern Med* 2020; **173**: 614–622.

9 Seydoux E, Homad LJ, MacCamy AJ *et al*. Analysis of a SARS-CoV-2-infected individual reveals development of potent neutralizing antibodies with limited somatic mutation. *Immunity* 2020; **53**: 98–105.

10 Grzelak L, Temmam S, Planchais C *et al*. SARS-CoV-2 serological analysis of COVID-19 hospitalized patients, pauci-symptomatic individuals and blood donors. *medRxiv* 2020. https://doi.org/10.1101/2020.04.21.20068858 [Epub ahead of print].

DOI: 10.1111/jdv.16934

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

Dear Editor,

The COVID-19 pandemic has disproportionally affected men.[1] Men infected with SARS-CoV-2 are more than twice as

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Table 1 Characteristics of the anti-androgen group and non-anti-androgen groups

	Anti-androgen group	Non-anti-androgen group	Age-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%)** ***P* = 0.0014**	**17 (47.2%)** ***P* = 0.018**
Deaths	1 (8.3%)	4 (6.2%) *P* = 0.58	2 (5.6%) *P* = 1.00
Comorbidities			
Prostate cancer	0 (0%)	1 (1.5%) *P* = 1.00	1 (2.8%) *P* = 1.00
Benign prostate hyperplasia	**11 (91.7%)**	**10 (15.4%)** ***P* = 0.000001**	**9 (25%)** ***P* = 0.000069**
Hypertension	8 (66.7%)	30 (46.2%) *P* = 0.22	21 (58.3%) *P* = 0.74
Immunosuppression	0 (0%)	8 (12.3%) *P* = 0.34	4 (11.1%) *P* = 0.559667
Cardiovascular	**8 (66.7%)**	**18 (27.7%)** ***P* = 0.017**	13 (36.1%) *P* = 0.095
Neurological	3 (25%)	13 (20%) *P* = 0.71	10 (27.8%) *P* = 1.00
Endocrine (mainly diabetes mellitus)	6 (50%)	26 (40%) *P* = 0.54	20 (55.6%) *P* = 0.75
Respiratory	2 (16.7%)	11 (16.9%) *P* = 1.00	8 (22.2%) *P* = 1.00
Renal	2 (16.7%)	5 (7.7%) *P* = 0.75	4 (11.1%) *P* = 0.63

Bold: Statistically significant difference between groups ($P < 0.05$).

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. Enrolment 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.

Seventy seven subjects were included, mean age was 68.6 ± 12.7 (Table 1). 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, vs. 66.4 ± 12.2, $P = 0.0002$. The proportion of subjects admitted to the ICU taking anti-androgens was significantly lower, 1/12 (8%) vs. 38/65 (58%), $P = 0.0015$ (Fig. 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 with 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),[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.[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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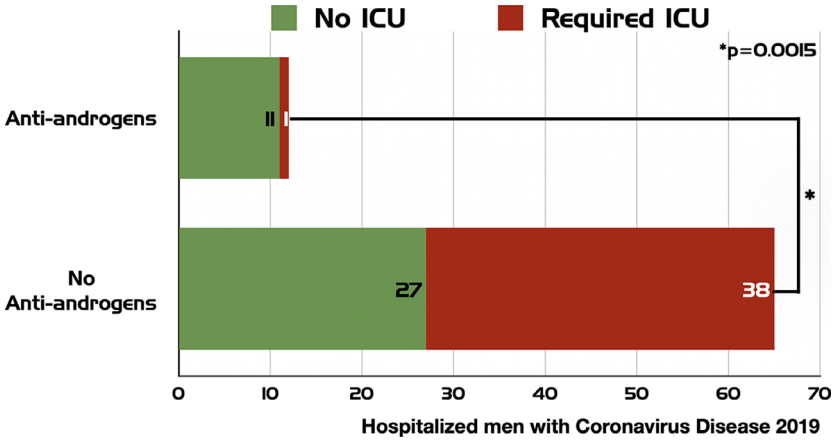

Figure 1 Hospital outcomes. Prospective cohort of 77 men hospitalized due to severe COVID-19 in Madrid, Spain. Individuals were categorized by use of anti-androgens for at least 6 months before hospital admission, and followed for 60 days. The relative risk for intensive care unit (ICU) admission for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

Conflicts of interest

None declared.

Funding sources

None.

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IRB approval status: The study was approved by the ethics committee at Ramon y Cajal Hospital.

References

1 Wadman M. Sex hormones signal why virus hits men harder. *Science* 2020; **368**: 1038–1039.
2 Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 2020; **11**: 29.
3 Wambier CG, Goren A, Vaño-Galván S *et al.* Androgen sensitivity gateway to COVID-19 disease severity. *Drug Dev Res* 2020; **81**: 771–776.
4 Wambier CG, Vaño-Galván S, McCoy J *et al.* Androgenetic alopecia present in the majority of hospitalized COVID-19 patients – the "Gabrin sign". *J Am Acad Dermatol* 2020; **83**: 680–682.
5 Montopoli M, Zumerle S, Vettor R *et al.* Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol* 2020; **31**: 1040–1045.
6 Ghazizadeh Z, Majd H, Richter M *et al.* Androgen regulates SARS-CoV-2 receptor levels and is associated with severe COVID-19 symptoms in men. *bioRxiv*. January 2020:2020.05.12.091082. https://doi.org/10.1101/2020.05.12.091082

DOI: 10.1111/jdv.16953

Androgen receptor genetic variant predicts COVID-19 disease severity: a prospective longitudinal study of hospitalized COVID-19 male patients

To the Editor,

Men infected with SARS-CoV-2 are more likely to be admitted to the intensive care unit (ICU) compared with women.[1] Previously, we have reported that among hospitalized men with COVID-19, 79% presented with androgenetic alopecia (AA) compared with 31–53% that would be expected in a similar aged match population.[2] AA is known to be mediated by variations in the androgen receptor (*AR*) gene.[3] In addition, the only known promoter of the enzyme implicated in SARS-CoV-2 infectivity, transmembrane protease, serine 2, is regulated by an androgen response element.[4] The polyglutamine repeat (CAG repeat) located in the *AR* gene is associated with androgen sensitivity and AA.[3] These observations led us to hypothesize that variations in the *AR* gene may predispose male COVID-19 patients to increased disease severity.

We conducted a prospective longitudinal study of hospitalized COVID-19 males. The subjects were categorized into two

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