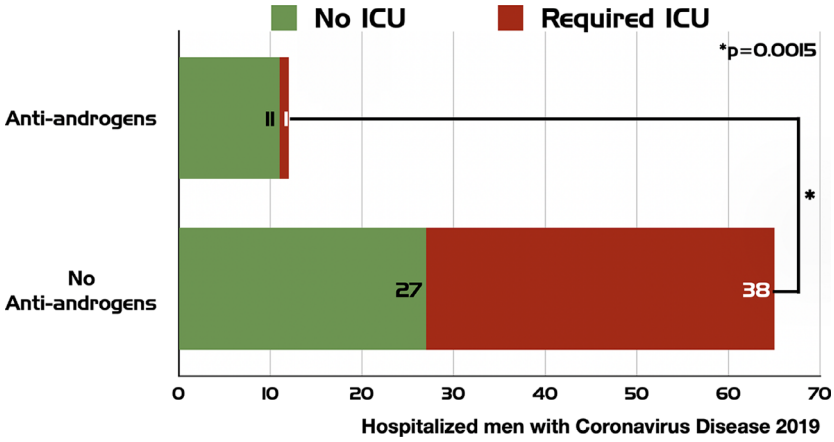

Figure 1 Hospital outcomes. Prospective cohort of 77 men hospitalized due to severe COVID-19 in Madrid, Spain. Individuals were categorized by use of anti-androgens for at least 6 months before hospital admission, and followed for 60 days. The relative risk for intensive care unit (ICU) admission for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

Conflicts of interest

None declared.

Funding sources

None.

A. Goren,[1] C.G. Wambier,[2,*] S. Herrera,[3] J. McCoy,[1] S. Vaño-Galván,[4] F. Gioia,[3] B. Comeche,[3] R. Ron,[3] S. Serrano-Villar,[3] P.M. Ramos,[5] F.A. Cadegiani,[6] M. Kovacevic,[7] A. Tosti,[8] J. Shapiro,[9] R. Sinclair[10]

[1]Applied Biology, Inc., Irvine, CA, USA, [2]Department of Dermatology, Alpert Medical School of Brown University, Providence, RI, USA, [3]Infectious Diseases Unit, Ramón y Cajal Hospital, Madrid, Spain, [4]Dermatology Department, Ramón y Cajal Hospital, Madrid, Spain, [5]Department of Dermatology, São Paulo State University, Botucatu, Brazil, [6]Department of Clinical Endocrinology, Federal University of São Paulo Medical School, Sao Paulo, Brazil, [7]Department of Dermatology and Venereology, Hospital Sestre Milosrdnice, Zagreb, Croatia, [8]Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, FL, USA, [9]Ronald O. Perelman Department of Dermatology at the New York University School of Medicine, New York, NY, USA, [10]Sinclair Dermatology, Melbourne, VIC, Australia

*Correspondence: C. G. Wambier. E-mail: carlos_wambier@brown.edu

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

© 2020 European Academy of Dermatology and Venereology

cohorts: subjects with a CAG ≥ 22 and subjects with a CAG < 22. Subjects taking androgen modifying drugs, e.g. 5-alpha reductase inhibitors, were excluded. DNA was collected using ORAcollect•Dx: (DNA Genotek, Ottawa, ON, Canada). *AR* CAG repeat region was PCR-amplified and 300 bp paired-end sequencing was performed using a MiSeq (Illumina, San Diego, CA, USA). Reads were mapped to reference *AR* sequences containing 1–50 CAG repeats, the reference with the greatest number of mapped reads was reported as the CAG repeat count. Subjects were followed for a period of 60 days from the date of hospitalization. Primary and secondary outcomes were the rate of ICU admissions and length of hospitalization, respectively.

Seventy-seven COVID-19-positive men were recruited to the study; 12 were excluded due to their use of androgen modifying drugs, leaving 65 patients enrolled in the study. 31 (48%) subjects had a CAG < 22, with average age of 67.9 (±12.3). The median duration of hospitalization among subjects with a CAG < 22 was 25 days (95% CI: 9.000–41.6512), and 14 (45.2%) were admitted to the ICU. 34 (52%) subjects had a CAG ≥ 22, their average age was 65.0 (±12.15). Among the 34 subjects with a CAG ≥ 22, the median duration of hospitalization was 47.5 days (95% CI: 22.9533–49.0935), and 24 (70.6%) were admitted to the ICU.

The proportion of subjects admitted to the ICU with CAG < 22 was significantly lower than the proportion of subjects with CAG ≥ 22 (Fisher's exact test $P = 0.046791$. Subjects with a CAG ≥ 22 had a higher risk for ICU admissions compared to subjects with a CAG < 22: OR: 2.9143(95% CI: 1.0487–8.0985) and likelihood ratio 1.705 (95% CI: 0.985–2.951). Further, estimating 40% of hospitalized COVID-19 male patients are likely admitted to the ICU,[5] the Bayes' adjusted positive predictive value of the AR CAG score in predicting ICU admissions was 53.202% (95% CI: 39.646–66.301) and the negative predictive value was 71.938% (95% CI: 60.693–80.974).

Our data suggest that longer *AR* CAG score is associated with more severe COVID-19 disease. In some androgen-mediated disease, short CAG has been associated with worse prognosis, e.g. in prostate cancer.[6] However, in skeletal muscle, a long CAG repeat length produces higher androgen-mediated activity.[7] We believe this discrepancy can be explained by the tissue dependent expression of cofactors important for activation of the androgen response element (*ARE*).[8] For example, protein arginine methyltransferase six has been shown to be highly expressed in lung and has been shown to be a specific co-activator of the androgen receptor.[9]

The results of this study suggest that the *AR* CAG repeat length could potentially be used as a biomarker to identify male COVID-19 patients at risk for ICU admissions. More importantly, identification of a biomarker associated with the androgen receptor is yet another piece of evidence supporting the important role of androgens in SARS-CoV-2 disease severity. We recognize the limitations of this small study; however, our findings, combined with previous reports implicating androgens in COVID-19 disease severity,[3–5] should encourage other groups to explore interventional studies of anti-androgens in COVID-19-infected patients. Currently, we are conducting a double-blinded interventional study with dutasteride (NCT04446429).

Conflicts of interest

None declared.

Funding sources

None.

IRB approval status

The study was approved by the ethics committee at Ramon y Cajal Hospital.

Disclosure

John McCoy, Carlos Gustavo Wambier, Sabina Herrera, Sergio Vaño-Galván, Francesca Gioia, Belen Comeche, Raquel Ron, Flávio Adsuara Cadegiani, Natasha Atanaskova Mesinkovska, Jerry Shapiro, Rodney Sinclair and Andy Goren have nothing to disclose. Sergio Serrano-Villar reports grants, personal fees and non-financial support from Gilead Sciences, grants, personal fees and non-financial support from Merck, Sharp and Dohme, personal fees and non-financial support from ViiV Healthcare, personal fees from Janssen, outside the submitted work. Rafal M Iwasiow and Michael A Tayeb reports personal fees from DNA Genotek, Inc. outside the submitted work.

J. McCoy,[1,*] C.G. Wambier,[2] S. Herrera,[3] S. Vaño-Galván,[4] F. Gioia,[3] B. Comeche,[3] R. Ron,[3] S. Serrano-Villar,[3] R.M. Iwasiow,[5] M.A. Tayeb,[5] F.A. Cadegiani,[6] N.A. Mesinkovska,[7] J. Shapiro,[8] R. Sinclair,[9] A. Goren[1]

[1]Applied Biology, Inc., Irvine, CA, USA, [2]Department of Dermatology, Alpert Medical School of Brown University, Providence, RI, USA, [3]Infectious Diseases Unit, Ramón y Cajal Hospital, Madrid, Spain, [4]Dermatology Department, Ramón y Cajal Hospital, Madrid, Spain, [5]DNA Genotek Inc., Ottawa, ON, Canada, [6]Department of Clinical Endocrinology, Federal University of São Paulo Medical School, Sao Paulo, Brazil, [7]Department of Dermatology, University of Claifornia, Irvine, CA, USA, [8]Ronald O. Perelman Department of Dermatology, New York University School of Medicine, NY, USA, [9]Sinclair Dermatology, Melbourne, VIC, Australia

*Correspondence: J. McCoy. E-mail: johnm@appliedbiology.com

References

1 Wadman M. Sex hormones signal why virus hits men harder. *Science (80)* 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.

© 2020 European Academy of Dermatology and Venereology

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. https://doi.org/10.1016/j.jaad.2020.05.079
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. https://doi.org/10.1016/j.annonc.2020.04.479
6 Tirabassi G, Cignarelli A, Perrini S *et al*. Influence of CAG repeat polymorphism on the targets of testosterone action. *Int J Endocrinol* 2015; **2015**: 298107.
7 Sheppard RL, Spangenburg EE, Chin ER, Roth SM. Androgen receptor polyglutamine repeat length affects receptor activity and C2C12 cell development. *Physiol Genomics* 2011; **43**: 1135–1143.
8 Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. *Endocr Rev* 2007; **28**: 778–808.
9 Scaramuzzino C, Casci I, Parodi S *et al*. Protein arginine methyltransferase 6 enhances polyglutamine-expanded androgen receptor function and toxicity in spinal and bulbar muscular atrophy. *Neuron* 2015; **85**: 88–100.

DOI: 10.1111/jdv.16956

Effects of lockdown on health of patients with severe atopic dermatitis treated with dupilumab

Dear Editor,

Use of dupilumab as treatment for severe adult atopic dermatitis (AD) increased over time since its introduction in September 2018, due to its established efficacy. AD is one of the most common chronic inflammatory skin disease affecting up to 14.3% of adults, with 63.3% of these cases first appearing before 18 years of age.[1] Patients' disease burden is important with high rate of discomfort, less confidence in daily life activities and psycho-social distress. The introduction of dupilumab changed the natural history of this disease, drastically improving AD manifestations and therefore quality of life.[2]

In 2020, the COVID-19 epidemics started spreading in Italy, leading the Government to establish urgent and strict restriction measures in avoid to contain the spread of the infection. Lombardy region has been the first epicentre of the health crisis starting mid-February. Shortly after, the virus spread to other regions with a relevant number of infected patients, forcing a general lockdown from March 9 to May 4. During this time span, individuals were allowed to leave the household only for grocery shopping and proven basic necessities, while only first-need shops and services were allowed to operate. In the hospital setting, only urgent visits were performed, and our ward was only available to dispense dupilumab and assess severe cases.

We describe our experience in the Dermatology Unit of our hospital in Milan, observing how lockdown period influenced clinical and psychological aspects of patient with severe AD in therapy with dupilumab.

The cohort was made up of 106 out of 252 adult patients with severe AD in treatment with dupilumab in our centre (Table 1).

Inclusion criteria were a follow up visit during or shortly after the lockdown period (March 1–June 15) and correct adherence to the therapy for at least 1 year.

After clinical evaluation, we calculated Eczema Area and Severity Index (EASI) and asked each patient to complete a survey including Numeric Rating Scale (NRS) for the evaluation of itch, NRS for evaluation of sleep quality, Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM); then we also assessed disease's psychological impact on quality of life and Hospital Anxiety and Depression Scale (HADS) for depression (HADS-D) and anxiety (HADS-A).

We decided to exclude patients under therapy for <1 year because we felt that clinical improvement and perception of better quality of life could be over-felt by the patient during this phase, inducing a bias.

We performed a retrospective analysis comparing surveys collected during the lockdown time against baseline from the same

Table 1 Data analysis

Scores	Mean predupilumab	Mean Prelockdown	Mean Postlockdown	Variation %	*P*-value
EASI	31.7	3.89	3.01	−23%	<0.005
HADS-D	7	2.92	3.60	23%	<0.005
HADS-A	7.8	3.38	3.51	3.8%	*
ITCH NRS	8.8	2.69	2.65	−0%	*
SLEEP NRS	6.9	0.63	0.62	−0%	*
DLQI	16.2	3.10	3.18	2.6%	*
POEM	21.5	6.93	6.42	−7.4%	*

Prelockdown: December 1 – February 29.
Postlockdown: March 1 – June 15.
*Other changes in variables considered were not statistically relevant.

© 2020 European Academy of Dermatology and Venereology