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.5 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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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).
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, 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. However, in skeletal muscle, a long CAG disease, short CAG has been associated with worse prognosis, more severe COVID-19 disease. In some androgen-mediated activity was 71.938% (95% CI: 60.693–80.974). 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.

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, 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**
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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 forced to leave the household 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 predupilum | 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.