EBioMedicine 68 (2021) 103426

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Letter

In response to the letter to the editor by Soha Ghanian et al. re our publication "Shorter androgen receptor polyQ alleles protect against life-threatening COVID-19 disease in European males"

Andrea M. Isidori[a], Marco Marcelli[b], Maria Grazia Castagna[c], Margherita Baldassarri[d,e], Francesca Fava[d,e,f], Alessandra Renieri[d,e,f,*]

[a] Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[b] Department of Medicine, Baylor College of Medicine, Houston TX, USA
[c] Department of Medical, Surgical and Neurological Sciences, University of Siena, Italy
[d] Medical Genetics, University of Siena, Italy
[e] Med Biotech Hub and Competence Center, Department of Medical Biotechnologies, University of Siena, Italy
[f] Genetica Medica, Azienda Ospedaliero-Universitaria Senese, Italy

ARTICLE INFO

Article History:
Received 6 May 2021
Accepted 19 May 2021
Available online 13 June 2021

DHT synthesis is reduced only in the prostate, skin, and liver of men treated with the 5αRi Dutasteride (Dut), while testosterone (T), the major male androgen and precursor of DHT, increases in the bloodstream and every target tissue, and maintains its ability to activate the androgen receptor (AR). Based on this, 5αRi-treated subjects are not androgen-deprived, and 5αRi is not a classic antiandrogen. The AndroCoV trial did not measure T and DHT levels; however, as Dut increases tissue and serum T, the reported positive effects observed in this trial in Dut-treated individuals are not due to changes in T levels or activity. Additionally, the effect of Dut among these subjects is attenuated, because 21% of controls and 18% of those on dutasteride were taking T or other drugs (SERMS or aromatase inhibitors), known to increase androgen levels [1].

Of note, viral clearance is almost complete within seven days from the infection, even among individuals with a poor outcome [2]. In contrast, in AndroCoV, most of the time-to remission outcomes were measured after 7-10 days, when virus clearance plays a minor role and the outcome depends on abnormal immune response and endothelial damage. Our paper [3] explains that at this stage, AR function correlates with a beneficial immune-modulatory effect in patients with increased T, that overcomes receptor resistance. As a consequence, we would not expect clinical effects of testosterone-induced modulation of TMPRSS2 in COVID-19 patients seven or ten days after the onset of symptoms, as shown in a study where androgen deprivation therapy did not protect against SARS-CoV-2 [4].

Regarding the other questions, McCoy investigated the AR CAG repeat length in men with androgenic alopecia and found that they are more likely to become infected with COVID-19. Poorer prognosis was reported in those with longer AR CAG repeats [5]. This observation (reference # 37 in our manuscript) agrees with our results, but the interpretation provided is opposite. Going along with the concept that AR with longer CAG repeats is less transcriptionally active, we hypothesized that longer CAG repeats are associated with a more aggressive COVID-19 phenotype. In comparison, we think that less aggressive COVID-19 infections result from more active ARs with shorter CAG repeat [3]. McCoy reached the opposite conclusion, that ARs with longer CAG repeats are more active, due to different expressions of coactivators versus corepressors in the lungs. Hence, the lung's biological environment would be responsible for increased AR transcription and the more aggressive COVID-19 phenotype present in these patients [5]. We are unaware of evidence proving that longer CAG repeats confer decreased or increased transcriptional activity depending on the local environment. For example, Kennedy's disease is caused by a germline mutation, and ARs with longer CAG repeats are present in every tissue. Despite the claim by Ghanian that "*In skeletal muscle long AR CAG confer increased transcriptional activity in response to testosterone*" Kennedy's patients have androgen insensitivity in every tissue, including the muscles, that are affected by a phenotype of generalized weakness.

Declaration of Competing Interest

The authors have no competing interests.

Contributors

AI, MM and AR drafted the letter. All authors reviewed and edited the letter.

E-mail address: alessandra.renieri@unisi.it (A. Renieri).

https://doi.org/10.1016/j.ebiom.2021.103426

References

[1] Cadegiani FA, McCoy J, Gustavo Wambier C, Goren A. Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to-remission in males with COVID-19: a randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV Trial - Biochemical). Cureus 2021;13:e13047.

[2] Farina N, Ramirez GA, De Lorenzo R, Di Filippo L, Conte C, Ciceri F, Manfredi AA, Rovere-Querini P. COVID-19: pharmacology and kinetics of viral clearance. Pharmacol Res 2020 Nov;161:105114. doi: 10.1016/j.phrs.2020.105114.

[3] Baldassarri M, et al. Shorter androgen receptor polyQ alleles protect against life-threatening COVID-19 disease in European males. EBioMedicine 2021:103246.

[4] Klein EA, Li J, Milinovich A, Schold JD, Sharifi N, Kattan MW, Jehi L. Androgen deprivation therapy in men with prostate cancer does not affect risk of infection with SARS-CoV-2. J Urol 2021 Feb;205(2):441–3 Epub 2020 Sep 8. PMID: 32897764. doi: 10.1097/JU.0000000000001338.

[5] McCoy J, et al. Androgen receptor genetic variant predicts COVID-19 disease severity: a prospective longitudinal study of hospitalized COVID-19 male patients. J Eur Acad Dermatol. Venereol. 2020;35(1):e15–7.