Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Letter to the Editor on "COVID-19 Infection in Men on Testosterone Replacement Therapy"

To the Editors,

Rambhatla et al recently investigated whether testosterone replacement therapy (TRT) is associated with worse COVID-19 clinical outcomes.[1] The authors performed a retrospective study and identified 32 men undergoing TRT and matched them with 63 other men not on TRT. They concluded that TRT is not associated with worse clinical outcomes in men diagnosed with COVID-19.[1]

We do not agree with this conclusion, and suspect that the opposite is true based on the data reported in the article. The cohort of men undergoing TRT showed an extremely high hospitalization rate (62.5%) and fatality rate (9.4%).[1] These rates are significantly higher than the hospitalization and death rates reported by the CDC for men in a similar age group in the United States.

The authors used the Greedy Nearest Neighbor method to select for matched controls based on age, race, body mass index, and ZIP code. We respectfully request to see data for the entire population of men, as well as an analysis that compares clinical outcomes for the population of men undergoing TRT to the total population of men not on TRT within the same age group. Based on recent studies that demonstrate benefits of antiandrogen therapy in men diagnosed with COVID-19, we hypothesize that androgen therapy does not have a neutral impact on COVID-19 disease severity, but rather contributes to more severe COVID-19 symptoms.[2–4]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry and subsequent infection is mediated by the transmembrane protease, serine 2 (TMPRSS2), which is promoted by the androgen receptor.[5] Further, men infected with SARS-CoV-2 are more than twice more likely to be admitted to the ICU than women infected with SARS-CoV-2.[6] As such, it is plausible to hypothesize that androgens play an important role in COVID-19 severity, while estrogen and progesterone may play a protective role.[7]

Dutasteride is a 5-alpha-reductase inhibitor (5ARi) that works by blocking the conversion of testosterone to dihydrotestosterone (DHT), a more potent androgen. A retrospective study showed a reduction of COVID-19 symptoms in males with androgenic alopecia (AGA) who were taking dutasteride at the time of COVID-19 diagnosis compared to males with AGA who were not taking a 5ARi.[2] In addition, the results from a randomized, placebo-controlled clinical trial (RCT) suggest that early therapy with dutasteride reduces viral shedding time and inflammatory markers in males infected with SARS-CoV-2 compared to males treated with a placebo.[3] Similarly, the results from a RCT utilizing proxalutamide, a very potent anti-androgen, were associated with a marked reduction of COVID-19 symptoms and hospitalization rates in men.[8] When proxalutamide was used to treat both males and females diagnosed with mild-to-moderate COVID-19 enrolled in a RCT, it displayed improvement in multiple biochemical markers for disease severity, including viral shedding time.[9] Lastly, a recent case study demonstrated that administration of proxalutamide markedly improved symptoms and laboratory markers of COVID-19 disease severity in 24 hours in an otherwise healthy 28-year-old male patient who had been taking the androgenic anabolic steroid oxandrolone.[4]

These studies suggest the potential for increased COVID-19 severity in men diagnosed with COVID-19 undergoing TRT. As such, we disagree with the conclusion presented in the article, and hypothesize that androgen therapy is likely associated with worse clinical outcomes in men diagnosed with COVID-19.

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Comment on "Role of Serum High-Sensitivity C-Reactive Protein as a Predictor of Therapeutic Response to Tadalafil in Patients With Erectile Dysfunction: A Prospective Observational Study"

Dear Editor,

I read with great interest the article by Jamaluddin et al[1] about evaluating the relationship among High-Sensitivity C-Reactive Protein (hs-CRP) level, mechanism and severity of erectile dysfunction (ED), and response to tadalafil in a recent issue of the journal. Hs-CRP level is a marker of inflammation, and has been shown to be a strong predictor of future risk for adverse cardiovascular events.[1] In their study, Jamaluddin et al[1] observed that the baseline hs-CRP level was more higher in the vasculogenic ED group. Following tadalafil treatment, a reduction in hs-CRP levels was detected in all patients, but this decrease was more significant in the nonvasculogenic ED group. Their findings showed that hs-CRP level of ≥2.35 mg/L was associated with poorer response to tadalafil (with 39.5% sensitivity and 75.4% specificity).Based on their multivariate analysis, shorter duration of ED, nonvasculogenic origin, and higher baseline erectile function scores were found to be significant predictors of the response to tadalafil. However, the significant effect of hs-CRP level on predicting improvement in ED was not shown in the multivariate analysis. As mentioned by the authors, the predictive accuracy of hs-CRP level was modest and it was not found to be an independent determinant of therapeutic responsiveness to tadalafil.[1]

Previous studies have shown that the underlying mechanism of ED is an important determinant of the response to phosphodiesterase-5 inhibitors (PDE5i) and response rates are poorer in vasculogenic ED.[2,3] In our recent study investigating this issue, only vasculogenic ED patients were included and all patients were divided into three cardiovascular risk groups according to the Framingham risk score, a nomogram predicting the 10-year risk of cardiovascular disease.[4] Clinical responses to tadalafil of patients in different cardiovascular risk groups were assessed. At admission, erectile function scores were found to be worse in the high-risk group. After 12 weeks of tadalafil treatment, the lowest complete response rate was observed in the high-risk group. This rate was found to be 4.127 times greater with lower Framingham score and 3.102 times greater with lower baseline severity of ED. Each parameter used in calculating the Framingham score was also found to be a significant predictor of the failure in complete responsiveness. These parameters were as follows: hypertension (OR = 2.217), diabetes mellitus (OR = 1.528), smoking (OR = 1.486), patient age (OR = 1.308), body mass index (OR = 1.189), HDL level (OR = 1.022), total cholesterol level (OR = 1.009).Contrary to Jamaluddin et al,[1] we observed that the duration of ED did not significantly affect response rates.

The study of Jamaluddin et al[1] is valuable in terms of being the largest study investigating a predictor marker for therapeutic response to tadalafil. However, it is not practical to use hs-CRP as a reliable marker since it does not have an independent predictive value for this purpose, and there are many factors (eg, inflammation, tumor, drugs) that increase its level. We consider that it would be beneficial to expand the clinical use of the Framingham risk score, which is very easy to calculate. In this way, individualized treatment strategies can be developed, and other treatment options may be recommended initially for patients who are unlikely to benefit from PDE5i.

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