

COVID-19 and The Prostate Cancer Connection

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the first worldwide pandemic in over 100 years. The disease caused by this newly discovered novel corona virus has been named COVID-19 (Corona Virus Disease 2019). This disease runs the spectrum from mild upper respiratory symptoms through respiratory and multiorgan failure and death. There appears to be disparities regarding COVID-19 and gender. In addition to the documented age and comorbidities risk factors for COVID-19, male gender increases risk for more severe forms of the disease with death rates of men higher than in women. These preliminary sex disparity observations almost immediately opened the possibility that androgens could worsen the disease and that estrogens could be protective.

Early published data sparking the most interest in this area was from a study in the Veneto region of Italy, one of the hardest hit regions early in the pandemic.¹ In a study of over 9,000 patients first reported on-line in May 2020, when considering ICU admissions 78% of men versus 22% of women required intensive care with more men dying than women (62% versus 38%). They also noted that cancer patients overall had an increased risk of SARS-CoV-2 infections compared with non-cancer patients. Surprisingly, prostate cancer patients receiving ADT had a significantly lower risk of SARS-CoV-2 infection compared with men who did not receive ADT. The greatest difference in infection risk was seen when comparing prostate cancer patients receiving ADT versus patients with any other type of cancer. This was one of the first clinical suggestions that prostate cancer patients on ADT were offered some level of protection from SARS-CoV-2 infections. Could men with prostate cancer on ADT experience lower COVID-19 morbidity and mortality because of lower androgen levels?

While the major focus on COVID-19 strategies is currently on vaccine development, the concept of androgen blockade-based therapies is now being tested in numerous clinical trials. A Spanish study hypothesized that men with androgenic alopecia are more likely to be hospitalized with COVID-19 related pneumonia.² A trial is now evaluating the anti-androgen dutasteride, used for alopecia and benign prostate enlargement, as a COVID-19 therapeutic intervention.³ Bicalutamide is a well-known orally administered non-steroidal anti-androgen that is being investigated in patients with COVID-19. The Veterans Administration is conducting a phase II trial using the LHRH antagonist degarelix in men with documented COVID-19 infection with support from the Prostate Cancer Foundation/VA network of centers of excellence.

While these recent observational studies have suggested a link between the use of androgen deprivation with improved outcomes, is there any basic science rationale that supports these new clinical trials? In fact, there is a basic science foundation behind these unique approaches. One clue may be how the SARS-CoV-2 virus enters the cell.

Cell entry of the SARS-CoV-2 virus depends on binding of the viral spike (S) proteins to angiotensin-converting enzyme 2 and on (S) protein priming by the transmembrane protease, serine 2 (TMPRSS2).⁴ TMPRSS2 facilitates activation of SARS-CoV-2 for cell entry and is also an androgen-regulated gene, frequently up-regulated in prostate cancer. The androgen receptor is a transcription regulator of TMPRSS2. Androgen-deprivation decreases the levels of TMPRSS2 supporting the concept that anti-androgen strategies may be effective in SARS-CoV-2 infections.

The SARS-CoV-2 virus has always been classified as a “novel” corona virus. Some of the strategies under study to treat a viral agent may also be considered novel such as high dose steroids, monoclonal antibody “cocktails”, suspending the use of angiotensin-converting enzyme (ACE) inhibitors and anti-malarial medications. To the list of novel therapeutics, we can now add strategies to block androgens in the world-wide race to end the current pandemic.

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References

1. 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(8):1040-1045.
2. Goren A, McCoy J, Wambier CG et al. What does androgenetic alopecia have to do with COVID-19? An insight into a potential new therapy. *Dermatol Ther* 2020:e13365. Online ahead of print.
3. ClinicalTrials.gov Identifier: NCT04446429.
4. Stopsack KH, Mucci LA, Antonarakis ES et al. TMPRSS2 and COVID-19: Serendipity or opportunity for intervention? *Cancer Discov* 2020;10(6):779-782.