www.medscape.com

Androgens May Explain Male Vulnerability to COVID-19

Pam Harrison

May 07, 2020

Editor's note: Find the latest COVID-19 news and guidance in Medscape's Coronavirus Resource Center.

As the COVID-19 pandemic has swept across the world, a striking difference has been seen between the sexes. But why are men so much more susceptible to severe outcomes from COVID-19 than women?

Suspicions naturally turn to the sex hormones, and there have been suggestions that estrogen may be protective against COVID-19 in females and/or that androgens worsen COVID-19 outcomes in males.

New data supporting the androgen theory come from a study in Italy.

These researchers found that patients with prostate cancer being treated with androgen deprivation therapy (ADT) were less likely to become infected with COVID-19 and die from the disease than other groups, including other patients with cancer.

The findings suggest that androgens somehow make the virus more virulent and that this exacerbates the severity of disease in men, they say. They also speculate that ADT may be protective against COVID-19.

The study was published online May 7 in *Annals of Oncology.*

The team analyzed data from 68 hospitals in the Veneto region, one of the areas in Italy most severely affected by the COVID-19 pandemic.

They found data on 9280 patients with laboratory-confirmed SARS-CoV-2 infection — of whom 4532 were males.

Women in the region were actually slightly more likely to be infected with COVID-19 than men, 56% vs 44%, the researchers point out.

However, men were more prone to develop more severe forms of the disease: 60% of men vs 40% of women required hospitalization, rising to 78% of men vs 22% of women who required intensive care. Also, more men died than women (62% vs 38%).

The team then turned their focus onto patients with cancer.

Of the entire male population of Veneto, those with cancer had an almost twofold higher risk of becoming infected with COVID-19 than men without cancer ($P < .0001$).

However, when the team looked specifically at men with prostate cancer, they found "strikingly, only four out of 5273 patients receiving ADT developed SARS-CoV-2 infection and none of these patients died."

This compared to 37,161 men with prostate cancer who were not receiving ADT, among whom 114 men developed COVID-19 and 18 died.

Among another 79,661 patients in the Veneto region with cancer other than prostate cancer, 312 developed COVID-19 and 57 died.

"This is the first paper to suggest a link between ADT and COVID-19," commented lead author Andrea Alimonti, MD, PhD, Università della Svizzera Italiana in Lugano, Switzerland.

"Patients with prostate cancer receiving ADT had a significant fourfold reduced risk of COVID-19 infections compared to patients who did not receive ADT. An even greater difference (fivefold reduction in risk) was found when we compared prostate cancer patients receiving ADT to patients with any other type of cancer," he said.

The finding raises "the hypothesis that androgen levels can facilitate coronavirus infections and increase the severity of symptoms, as has been seen in male patients," he said.

"These data are very interesting and raise a fascinating hypothesis," said Richard Martin, PhD, professor of clinical epidemiology at the University of Bristol, UK, commenting about the study. "But they do need independent validation in other large population-wide datasets...with appropriate statistical analysis including adjustment for important risk factors for SARS-CoV-2."

He noted that the Italian study results were not adjusted for potential confounders, for example, age, body mass index, and cardiometabolic comorbidities, that are strong risk factors for SARS-CoV-2. In addition, men taking ADT may have been more likely to self-isolate and so be at reduced risk of getting the infection, he suggested.

How Do Androgens Interact With the Virus?

Alimonti and colleagues offer a mechanistic explanation of how androgens interact with the virus.

Coronavirus gains entry into the human cell by binding its viral spike (S) proteins to ACE2 and on S protein priming by TMPRSS2. TMPRSS2 is a member of a family of proteins called type II transmembrane serine proteases, which are involved in a number of processes including cancer and viral infections, they explain.

"Intriguingly, TMPRSS2 is an androgen-regulated gene that is upregulated in prostate cancer where it supports tumor progression," they point out.

There is also evidence that the same androgen receptor regulates TMPRSS2 expression in nonprostatic tissues, including the lung.

"[This] may explain the increased susceptibility of men to develop SARS-CoV-2 severe infections when compared to women," the authors speculate.

Because ADT is known to decrease TMPRSS2 levels, they suggest that androgen receptor antagonists "could be used to block or decrease the severity of SARS-CoV-2 infection in male patients."

They go even further and suggest that men without prostate cancer at high risk for COVID-19 could take ADT to prevent infection.

For men who do become infected with COVID-19, ADT might also help reduce symptom severity, they add.

Given that the effects of androgen receptor antagonists are reversible, "they could be used transiently (eg, 1 month) in patients affected by SARS-CoV-2, thereby reducing the risk of side effects due to long-term administration," the authors suggest.

Another Theory: Is Estrogen Protective?

Another theory to explain the male/female difference for severe COVID-19 is that the female hormone estrogen may be protective.

"People have to stop putting estrogen in that 'female hormone box' because it's a molecule that we all use as humans, it's just not women," Sharon Nachman, MD, told *Medscape Medical News.*

"Looking at estrogen as having potentially important immune effects is part of thinking outside the box," she said.

Nachman is associate dean for research at the Renaissance School of Medicine, Stony Brook University in New York, and is working together with Antonios Gasparis, MD, professor of surgery at the same center.

They are exploring the use of a transdermal estrogen patch in patients with COVID-19 in a randomized trial with a placebo-controlled arm. They are recruiting patients who present to their emergency department with signs and symptoms of COVID-19, and enroll them into the trial if they are interested.

"We are testing everyone as well, but we are starting patients on the medication at the time of entry as opposed to waiting until we have a test result back," Nachman explained.

The primary objective of the study is to evaluate whether the transdermal patch, applied to the skin for 7 days, might reduce the need for intubation in men and women infected with COVID-19 versus standard of care.

The product is the same single-use transdermal estradiol patch (*Climara,* 25 cm^2, Bayer) prescribed for postmenopausal women and will be used at the same dose, which is known to be safe.

After the patch is removed, patients will be carefully tracked for symptoms over the next 45 days to see if the patch reduced symptom severity, and if so, in which patients.

Nachman would have preferred to enroll patients before they had overt symptoms, but this simply isn't possible in a medical center where symptomatic patients present, she told *Medscape Medical News*.

However, she does know that even at their own medical center, the odds are stacked against male COVID-19 patients — and something is needed to mitigate its severity in this patient group.

As they were developing the protocol for the current study, the team decided to see who was in their ICU during a single study day.

The answer: mostly males. Intubation and death rates in men in their ICU for that single day was approximately 80% compared with only 20% among women.

"We have a new horrific pathogen that is pandemic and we're all probably going to get it, it's just a question of when and how sick we'll be from it," Nachman said.

Alimonti and coauthors have reported no relevant financial relationships as well as Goulder and Nachman.

Ann Oncol. Published online May 7, 2020. Full text

For more from Medscape Oncology, follow us on Twitter: @MedscapeOnc.

Cite this: Androgens May Explain Male Vulnerability to COVID-19 - *Medscape* - May 07, 2020.