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Letter to the Editor

Reply to Bexultan Kazybay and Yingqiu Xie's Letter to the Editor re: Herjan J.T. Coelingh Bennink, Jean-Michel Foidart, Frans M.J. Debruyne. Treatment of Serious COVID-19 with Testosterone Suppression and High-dose Estrogen Therapy. Eur Urol 2021;80:523–5

When summarizing our androgen-deprivation and estrogen therapy (ADET) hypothesis [1], it is important to mention that both testosterone suppression by androgen deprivation therapy (ADT) and estrogen treatment have the same beneficial suppressive effect on ACE2 and TMPRSS2. Since ADT also suppresses estrogens, the favorable anti-COVID effects of estrogens are lost during ADT, which is restored by adding the estrogen treatment.

Kazybay and Xie state that ADT has not been tested in females, which is not correct. The same luteinizing hormone–releasing hormone (LHRH) agonists used for prostate cancer (PC), treatment such as goserelin and leuprolide, are also used for the treatment of advanced breast cancer (BC) [2] and gynecological diseases such as endometriosis with the intention to suppress estrogens, so there is extensive clinical experience with the use of this class of drugs in women. We understand that Kazybay and Xie raise concerns with regard to potential side effects of ADT. However, first-order toxic side effects do not occur with gonadotrophin-releasing hormone (GnRH)/LHRH analogs (agonists and antagonists).

Second-order side effects are the unwanted endocrine effects. The desired effect is suppression of testosterone (in PC) or estrogens (in BC) to inhibit tumor growth. Unwanted effects in males are the decrease in sexual function and libido. A second-order side effect of more importance is the loss of estrogens during ADT in both sexes. Since all estrogens are synthesized via aromatization of androgens, no testosterone also means no estradiol, causing serious estrogen deficiency with ADT in both sexes, which leads to a wide range of unwanted subjective and objective side effects, including hot flushes and bone health problems [3]. All these problems are prevented by adding estrogen to ADT.

Third-order side effects are the comorbidities experienced by aging persons with serious cancer [3]. However, in the acute situation of serious COVID-19 and intensive care unit (ICU) admission, these side effects of ADT and comorbidities are clinically less relevant, with the exception of the increase in the risk of venous thromboembolism with high-dose estrogens [4]. Therefore, we advise combining ADET with anticoagulant treatment.

ADET requires immediate suppression of testosterone and therefore LHRH/GnRH agonists are not suitable because of the initial testosterone flare. GnRH antagonists do not cause a testosterone rise and must therefore be used in ADET. Until recently, only degarelix was available for clinical use, but in 2021 the oral GnRH antagonist relugolix also became available on the market. Kazybay and Xie question the efficacy of degarelix for the suppression of testosterone, but their opinion is based on a small phase 2 study. Large, pooled phase 3 studies have shown that degarelix is even superior to LHRH agonists [5].

The anti-COVID antitestosterone effect of ADET may be more prominent in male patients, but in males and females the anti-COVID estrogen effect is expected to be similar. Therefore, both males and females qualify for ADET. Since the majority by far of ICU patients with SARS-COV-2 infection are aged $\geq$60 yr, we agree that in a future ADET study this should be the target patient population.

Conflicts of interest: Herjan J.T. Coelingh Bennink is CEO of Pandora Endocrine Innovation and president and shareholder of Pantarhei Oncology, an affiliate of Pantarhei Bioscience BV. He has submitted a patent application for the ADET treatment concept. Jean-Michel Foidart is cofounder of Mithra Pharmaceuticals and chairman of its scientific board. Mithra holds a patent for E4 treatment of severe viral infections. Frans M.J. Debruyne is Medical Director of Andros Men's Health Institutes and is a paid consultant for Pantarhei Oncology BV, the company developing ADET for the treatment of advanced prostate cancer.

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