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.

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Letter to the Editor

Reply to Carlos G. Wambier and Gerard J. Nau's Letter to the Editor re: Karin Welén, Ebba Rosendal, Magnus Gisslén, et al. A Phase 2 Trial of the Effect of Antiandrogen Therapy on COVID-19 Outcome: No Evidence of Benefit, Supported by Epidemiology and In Vitro Data. Eur Urol. 2022;81:285–93. Positive Effects of Enzalutamide for Hospitalized COVID-19 Patients

Still No Positive Effect of Enzalutamide for Hospitalized COVID-19 Patients

We read with interest the letter regarding our study [1] from Wambier and Nau, who recently presented data from Brazil with contrasting results on the role of antiandrogens in COVID-19 [2,3].

Wambier and Nau argue that the results of the COVIDENZA trial are wrongly interpreted, and that conclusions were affected by outliers, inadequate cortisone use, or the higher frequency of diabetic and ordinal scale 5 patients in the treatment group at baseline. Sensitivity analyses confirmed the worse outcomes for hospital stay and oxygen supplementation for patients treated with enzalutamide [4].

We strongly object to the way in which Wambier and Nau focus on single observations (one death and three cases of mechanical ventilation) and extrapolate those to estimates from national data to substantiate a possible hidden beneficial effect of enzalutamide, disregarding the statistically significant disadvantage demonstrated regarding evaluable parameters. First, the principle of analysis of clinical trials is to accept that single observations may be random, and second, the inclusion and exclusion criteria used in the trial make any comparisons or extrapolations to overall outcomes incorrect.

Wambier and Nau further argue that the 5-d treatment duration for enzalutamide contributes to the lack of beneficial effect on the basis of two cases of mechanical ventilation (days 5 and 9). The half-life of enzalutamide is 6 d, meaning that a vanished effect of enzalutamide is unlikely to be the cause of these worse outcomes.

The natural course of recovery from an infection is that virus levels decrease. The simplified recalculations performed by Wambier and Nau and based on our graph indicate that virus load decreases only in the enzalutamide group. However, although a trend was observed, there is no statistically significant difference in virus decrease between the groups, as shown in the original publication. It is also important to note that patients who recovered early were not sampled after their discharge from hospital, which is why a large proportion of the control group was not included in this analysis.

Regarding the in vitro study, the high variance in viral copy numbers from infected HBEC ALI cultures discussed by Wambier and Nau probably reflects susceptibility differences between different donor origins. Analysis of matched pairs (enzalutamide vs controls) showed no significant difference in viral load for any of the 12 donors.

We disagree that epidemiologic studies generally support the hypothesis that androgen inhibition is beneficial for COVID-19 outcomes. A recent review and two new studies show no effect of antiandrogens [5–7]. In addition, the study mentioned by Wambier and Nau [8] was expanded to 465 prostate cancer patients and no longer finds any association of androgen deprivation or androgen receptor–targeting therapy with COVID-19 outcomes [9].

In summary, after initial enthusiasm, we now disagree with Wambier and Nau regarding the value of antiandrogens in the treatment of COVID-19. Nevertheless, the results from Brazil are intriguing and we eagerly await results from the HITCH trial investigating the gonadotropin-releasing hormone antagonist degarelix in a similar setting (NCT04397718), which may provide further information regarding the value of androgen inhibition as a treatment for COVID-19.

Conflicts of interest: Andreas Josefsson has received an unconditional research grant for COVIDENZA from Astellas Pharma and honoraria from Astellas Pharma, Ipsen, Sandoz, and Janssen-Cilag. William K. Oh has received honoraria from Astellas Pharma, AstraZeneca, Bayer, Janssen, Sanofi, Sema4, and TeneoBio. Magnus Gisslén serves on a data safety monitoring board for AstraZeneca; serves on scientific advisory boards for Gilead, GSK/ViiV, and MSD; has received honoraria from Amgen, Biogen, BMS, Gilead, GSK/ViiV, Janssen-Cilag, MSD, Novocure, and Novo Nordic; and has received institutional grants or contracts from Gilead Sciences and Janssen-Cilag. The remaining authors have nothing to disclose.

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Karin Welén [a]
Ebba Rosendal [b]
Eva Freyhult [c]
William K. Oh [d]
Magnus Gisslén [e]
Clas Ahlm [b]
Anne-Marie Fors Connolly [b,f]
Anna K. Överby [b,f]
Andreas Josefsson [a,g,h,*]

[a] *Institute of Clinical Sciences, Department of Urology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[b] *Department of Clinical Microbiology, Umeå University, Umeå, Sweden*
[c] *Department of Cell and Molecular Biology, National Bioinformatics Infrastructure Sweden, Science for Life Laboratory, Uppsala University, Uppsala, Sweden*
[d] *Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA*
[e] *Institute of Biomedicine, Department of Infectious Diseases, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[f] *The Laboratory for Molecular Infection Medicine Sweden, Umeå, Sweden*
[g] *Department of Surgical and Perioperative Sciences, Urology & Andrology, Umeå University, Umeå, Sweden*
[h] *Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden*

*Corresponding author. Department of Surgical and Perioperative Sciences, Urology & Andrology, Umeå University, Umeå 90185, Sweden.
E-mail address: andreas.josefsson@umu.se (A. Josefsson).

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