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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European Association of Urology

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

We read with interest the article by Welén et al. [1] with data from the pilot phase of a trial using enzalutamide for hospitalized COVID-19 patients. Using parallel lines of evidence, the authors argue that all investigations into antiandrogen therapy in COVID-19 should be halted. There are several considerations, however, that suggest that this conclusion is premature.

The principal argument against using enzalutamide is the decision from the data safety monitoring board (DSMB) decision. The trial was stopped early, but conclusions were based on key, uneven distributions between groups. More patients with greater severity were randomized to enzalutamide (80% of those requiring high-flow oxygen). Therefore, outcomes could be skewed by outliers (Fig. 1A, B [1]). Diabetes mellitus was over-represented and corticosteroids were underutilized in the enzalutamide group, complicating the analysis along with the open label design. An alternative analysis may also have dissuaded the DSMB from stopping the study. Enzalutamide significantly reduced the viral load on day 4 (p = 0.002) and day 6 (p = 0.018), but usual care did not (day 4, p = 0.66; day 6, p = 0.69; one-sided sign test using Stata/SE v17.0).

Over-reliance on insufficient patient recruitment can lead to other interpretations. Patients in the control group progressed to mechanical ventilation at twice the rate of those in the enzalutamide group (8% vs 4%); in the control group, patients were intubated <24 h after enrollment, while the time to intubation in the enzalutamide group was 5–9 d, suggesting inadequate duration of therapy. Moreover, 100% of the patients who died were in the control group (n = 1). Mortality is the most objective outcome of interest in COVID-19. Despite low numbers followed in usual care (n = 10), 10% mortality is typical in Sweden [2]. Thus, three deaths or more would be expected for enzalutamide (n = 29) owing the higher rate at baseline of high-flow oxygen requirement. A mortality reduction among patients requiring oxygen at baseline is consistent with results from a larger randomized, double-blind, placebo-controlled study of androgen receptor blockade [3]. We are not advocating for extensive analyses, because COVIDENZA was terminated as a small, pilot study with undefined power, which makes intergroup hypothesis testing and sensitivity analysis challenging. These observations, however, illustrate how outcomes were assessed prematurely.

The authors rely on supportive evidence from in vitro and epidemiologic studies. In vitro experiments failed to show an effect of enzalutamide, although the million-fold variance in viral copy number is difficult to interpret using median values instead of matched pairs. Enzalutamide could also act in cells other than bronchial epithelial cells [4]. The epidemiologic analysis is confounded by the heterogeneity inherent to patients with cancer and results are mixed in the literature. An alternative study of 16 million Medicare beneficiaries showed that prostate cancer patients were protected from COVID-19 hospitalization (odds ratio [OR] 0.88, 95% confidence interval [CI] 0.84–0.91) and death (OR 0.82, 95% CI 0.77–0.87) [5]. A careful definition of effective androgen deprivation therapy, however, highlights the positive impact of androgen reduction [6].

Tremendous progress against SARS-CoV-2 has been made through accelerated research. Despite this progress, recurrent waves threaten global health. The long-term utility of new antiviral medications against a virus that readily generates variants is unknown. Therefore, we propose that it is too soon to abandon investigations of antiandrogens for COVID-19.

Conflicts of interest: Carlos G. Wambier has served as an advisor to Applied Biology, Allergan, Chemistry Rx, and Young Pharmaceuticals; has served as a speaker for Galderma and Cynosure; has served as an investigator for clinical trials sponsored by CoNCERT Pharmaceuticals, Eli Lilly & Co, Incyte, and Pfizer (Janus kinase inhibitors); and has been a volunteer in the conceptualization, design, and interpretation of results of clinical trials of antiandrogens for COVID-19 and a volunteer investigator in epidemiologic studies on hormonal, seasonal, and environmental factors in COVID-19. Carlos G. Wambier and Gerard J. Nau participated in conceptualization of the initial theory on androgen sensitivity in COVID-19 disease severity, are actively looking to initiate local clinical trials of antiandrogens for COVID-19 including NCT05009732 (Kintor Pharmaceuticals) and to further explore mechanisms of antiandrogen actions in inflammation and viral replication, and are co-inventors on a provisional patent application for androgen inhibition to treat sepsis and shock.

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