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EDITORIAL

Antiandrogen activity of drugs for COVID-19. The case of sabizabulin

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Coronavirus disease 2019 (COVID-19) caused over six hundred million confirmed cases and six million deaths as of September 2022. Currently, few therapeutic drugs are recommended in treatment guidelines, including dexamethasone, remdesivir, baricitinib, tocilizumab, and heparin [1]. The mortality rate in severe and critical COVID-19 is still high despite these treatments and supportive care, and further high-quality randomized controlled trials are urgently needed.

Sabizabulin is a promising drug under investigation for the treatment of COVID-19. Sabizabulin is an oral, novel microtubule disruptor that binds the alpha- and beta-tubulin subunits in order to inhibit polymerization and induce depolymerization of microtubules in cells. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires microtubules to enter host cells. In addition, microtubules play an important role in triggering cytokine storm and acute respiratory distress syndrome. Since cytokine storm is the crucial pathophysiological stage causing the exacerbation of COVID-19 infection and acute respiratory distress syndrome is the leading cause of mortality in COVID-19, microtubule disruptors may be beneficial for COVID-19 treatment.

So far, two randomized trials have assessed the effect of sabizabulin in COVID-19 patients. The first one is a phase 2, randomized, placebo-controlled trial enrolling 39 hospitalized patients with COVID-19, which reports reduced mortality in patients taking sabizabulin compared with the ones taking the placebo (5.3% (1/19) *vs.* 30% (6/20)) [2]. The second one is a phase 3 randomized controlled trial enrolling hospitalized adult patients with moderate to severe COVID-19, which was recently published in *NEJM Evidence* [3]. A pre-specified interim analysis testing the first 150 randomized patients revealed the superiority of sabizabulin compared to placebo: all-cause mortality 60 days after randomization decreased in hospitalized patients with moderate to severe COVID-19 (20% *vs.* 45%; relative risk: 0.45 (95% confidence interval: 0.27–0.74)); therefore, the trial was terminated in advance. In addition, patients assigned to the sabizabulin arm also experienced significantly shorter duration of mechanical ventilation and intensive care unit stay, as well as in-hospital stay. Of note, two-thirds of the enrolled patients were categorized as severe COVID-19 and required non-invasive ventilation, high-flow oxygen therapy, or invasive mechanical ventilation at enrollment. Although the beneficial effects of sabizabulin have been attributed by the authors to its antiviral and anti-inflammatory activities, these two mechanisms alone seem to be insufficient to explain the absolute risk reduction in mortality of up to 25% (relative risk reduction of 55%), especially when compared to drugs such as the antiviral remdesivir, which has been proven to be effective against COVID-19. Nonetheless, a recent meta-analysis of randomized controlled trials showed that the mortality reduction comparing remdesivir with control was only observed in non-ventilated patients requiring oxygen (risk ratio: 0.89 (95% confidence interval: 0.79–0.99)) and not in patients requiring mechanical ventilation (risk ratio: 1.08 (95% confidence interval: 0.88–1.31)) [4]. Moreover, one-third of the sabizabulin study patients had already received remdesivir as the standard of care, limiting the understanding of sabizabulin's additional beneficial antiviral activity. Furthermore, when analyzing sabizabulin's anti-inflammatory effects on these patients, it must be kept in mind that over 80% of the participants received dexamethasone as the standard of care. Moreover, meta-analyses comparing interleukin-6 antagonists with placebo or standard therapy concluded that the odds ratio of mortality was 0.86 (95% confidence interval: 0.79–0.95) [5]. Therefore, additional antiviral or anti-inflammatory therapy would result in limited survival effects.

On top of the antiviral or anti-inflammatory activities, the antiandrogen activity of sabizabulin might have contributed to decreasing mortality. Sabizabulin manifests antiandrogen effects by disrupting the transport of androgen receptors from

the cytoplasm to the nucleus and is under evaluation as a possible treatment for metastatic prostate cancer. There are several reasons why antiandrogen activity could benefit COVID-19 patients. Firstly, in theory, antiandrogen agents can protect host cells from the entry of SARS-CoV-2. SARS-CoV-2 enters host cells through angiotensin-converting enzyme 2 receptor on the host cell surface as well as through proteolytic activation of the viral spike protein by the host cell transmembrane protease 2 (TMPRSS2) [6]. By regulating TMPRSS2 gene expression by the androgen receptor [7], antiandrogen agents might have a protective effect on COVID-19. Of note, patients on chronic antiandrogen therapy have a lower risk of COVID-19 infection than patients not receiving them [8, 9]. Secondly, a multicenter cohort study enrolling adult patients with septic shock showed that females aged less than or equal to 55 years had lower 28-day mortality than males of the same age (29% *vs.* 40%), while females older than 55 years of age had higher 28-day mortality than males equal in age (43% *vs.* 38%) [10]. This study suggested that female hormones, in addition to organ protective effects, may have specifically a protective effect on females of childbearing potential by ameliorating the excessive host immune response, which is the common trigger of septic shock in COVID-19 patients. Thirdly, several randomized controlled trials report beneficial effects of antiandrogen agents as compared to placebo or usual care in various COVID-19 populations. A randomized trial reported that subcutaneous progesterone administration resulted in better clinical improvement in hospitalized males with COVID-19 seven days after randomization [11]. Another randomized controlled trial enrolled symptomatic COVID-19 patients aged 40 years or older who did not require oxygen supplementation or mechanical ventilation at randomization, to assess the effect of raloxifene, a selective estrogen receptor modulator [12]. Results showed that raloxifene increased the proportion of undetectable SARS-CoV-2 seven days after treatment, as compared to placebo. Dutasteride, a 5-alpha-reductase inhibitor, was reported to facilitate viral remission in males with mild COVID-19 compared to placebo in a randomized trial [13]. No safety issue was raised during these trials, and no significant serious adverse events were reported in the previously mentioned study on sabizabulin. Unfortunately, these randomized trials were not powered or rigorous enough to be definitive (small sample size and single-center design). However, these findings suggested that the antiandrogen activity of sabizabulin could benefit this population of patients.

To date, several antiandrogen drugs have been tested in various COVID-19 settings. However, more research is necessary to determine whether the reported beneficial effects may be replicated in high-quality randomized controlled trials and which population is most likely to benefit from which antiandrogen drug.

In conclusion, the interim analysis of a phase 3 randomized controlled trial [3] comparing sabizabulin with placebo among patients with moderate to severe COVID-19 provided novel evidence of the survival benefit of a drug that has antiandrogen activity among its many mechanisms of action, opening the way to future confirmatory studies on antiandrogen agents in the treatment of COVID-19.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YK, BR, MAB, and GL ideated and wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni and Yuki Kotani are serving as the Editorial Board members of this journal. We declare that Giovanni Landoni and Yuki Kotani had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

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