Sabizabulin for the Treatment of Patients Hospitalized with Moderate–Severe COVID-19 (Requiring Oxygen) Who Were at High Risk for Acute Respiratory Distress Syndrome and Death

An Expert Interview with Paula K Skarda

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Keywords

Acute respiratory distress syndrome, COVID-19, sabizabulin, hospitalized patients, clinical trials

Disclosures: Paula K Skarda, MD, has no financial or non-financial relationships or activities to declare in relation to this article.

Acknowledgements: Medical writing support was provided by Katrina Mountford of Touch Medical Media.

Review process: This is an expert interview and, as such, has not undergone the journal's standard peer-review process.

Compliance with ethics: This article is an interview and did not involve any studies with human or animal subjects performed by the author.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

Received: 16 August 2022

Accepted: 24 August 2022

Published online: 24 October 2022

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases.* 2022;7(2):Online ahead of journal publication

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Support: No funding was received in the publication of this article.

The coronavirus disease 2019 (COVID-19) pandemic is now in its third year, with more than 600 million confirmed cases and global deaths in excess of 6.4 million.[1] Despite the increasing availability of antivirals and anti-inflammatory/immunomodulatory agents, mortality and morbidity remain high. There remains a need for new effective and safe therapies to reduce the risk of death in patients who are hospitalized with COVID-19. One of the major causes of mortality in patients with COVID-19 is acute respiratory distress syndrome.[2]

Sabizabulin is an oral, novel microtubule disruptor that has dual antiviral and anti-inflammatory activities. In an expert interview, Paula Skarda discusses the mechanism of action of sabizabulin and the recently published results of a phase III study investigating its use in hospitalized adults with COVID-19.[3]

Q. What were the unmet needs in the treatment of patients hospitalized with COVID-19 at high risk for acute respiratory distress syndrome at the time of this study?

At the time of the phase II safety trial for sabizabulin, little other than supportive care was available (Randomised evaluation of COVID-19 therapy [RECOVERY]; ClinicalTrials.gov identifier: NCT04381936). Remdesivir was on the market,[4] and we used it; however, its impact was not substantial. By the beginning of the phase III study, we had started using dexamethasone,[5] but there were no other proven therapeutic options for our critically ill patients, especially in the patient population experiencing cytokine storm.

Q. Could you tell us a little about sabizabulin and the rationale for its use in the treatment of COVID-19?

Sabizabulin is a drug that was originally designed for the treatment of prostate cancer. As we know, microtubule-based transportation is a critical aspect of viral replication. Sabizabulin behaves as a microtubule depolymerizing agent that acts at the host level. One of sabizabulin's intriguing mechanisms of action is its ability to disrupt the microtubule trafficking critical for virus replication. In addition to preventing viral replication, sabizabulin's inhibition of tubulin polymerization leads to a colchicine-like effect in modulating leukocyte-mediated inflammatory activities, including inhibiting the production of inflammatory superoxides and various cytokines. The rationale for using sabizabulin is to both prevent the replication of severe acute respiratory syndrome coronavirus and inhibit the 'cytokine storm' that follows in some patients, resulting in their rapid

clinical deterioration.[6] This dual action makes sabizabulin a promising treatment option.

Q. What were the design and eligibility criteria of the VERU-111 clinical trial?

VERU-111 was a double-blind, placebo-controlled trial with 2:1 randomization to the drug or placebo (VERU-111 in the treatment of SARS-CoV-2 infection by assessing its effect on the proportion of patients who die on study; ClinicalTrials.gov identifier: NCT04842747).[3] Hospitalized patients with moderate to severe COVID-19 were randomized to receive either 9 mg of sabizabulin or placebo from the time of enrolment through day 21 or until discharge from the hospital, whichever came first. The primary endpoint was death at day 60. Secondary endpoints included days on a ventilator, days in the intensive care unit, days in the hospital and viral load. In terms of eligibility, this study used the World Health Organization (WHO) Ordinal Severity Scale. Patients with a WHO Ordinal Severity Scale of 4 (those on O_2 by mask or nasal prongs) required at least one high-risk comorbidity for the development of acute respiratory distress syndrome, such as asthma, chronic lung disease, hypertension, severe obesity (body mass index ≥40), residing in a long-term care facility, or immunosuppression. Patients with a WHO Ordinal Severity Scale of 5 or 6 were enrolled regardless of the presence of comorbidities.

Q. What were the efficacy and safety findings of the study?

The sabizabulin group showed a 55% relative reduction in deaths compared with the placebo group and statistically significant reductions in the secondary endpoints.[3] Safety findings were similar to those seen in the phase II study: the medication was well tolerated, and the main side effects of the medication were the elevation of the liver function test and diarrhoea. The drug was associated with fewer adverse events than the placebo, and no serious adverse events were attributable to the drug.[3]

Q. Where do you see sabizabulin potentially sitting in the treatment paradigm for patients hospitalized with COVID-19, and what will be its impact?

Sabizabulin's mechanism of action, both in blunting the inflammatory response and preventing viral replication at the host level, could be a really important tool in our fight against COVID-19. Using sabizabulin early in the treatment course of patients with a WHO Ordinal Severity Scale of 4 and 5 may help prevent intubation and the progression of disease in moderately to critically ill patients, filling a gap in the care of our hospitalized patients. ❑

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