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Dampening inflammation in COVID-19 response

Targeting acute respiratory distress syndrome, Tetra Bio-Pharma's novel anti-inflammatory drug, ARDS-003, may be a treatment option for patients with COVID-19 and sepsis.

Tetra Bio-Pharma is pursuing the discovery and development of drugs targeting the endocannabinoid system. The company's lead product candidate, ARDS-003, is a new molecular entity activating a receptor encoded by the *CNR2* gene. ARDS-003 dampens inflammatory responses via activation of multiple downstream pathways that reduce the systemic hyperinflammatory response which can occur in sepsis or as a complication of SARS-CoV-2 infection.

Guy Chamberland, Tetra's CEO and CRO, stated, "As a result of over a decade of experience using models of inflammation and sepsis, we were able to rapidly initiate a program investigating the potential of ARDS-003 in acute respiratory distress syndrome (ARDS) in COVID-19 patients." ARDS-003 is slated to enter a phase 1 trial this year, followed by testing in COVID-19 patients.

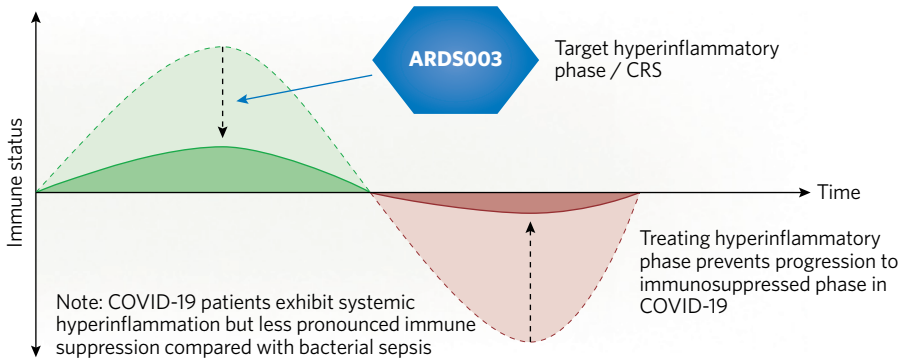

Fig. 1 | Potential impact of ARDS-003 on COVID-19 clinical course. Once infected with SARS-CoV-2, most patients enter an acute inflammatory response phase (green) where pathologic inflammation leads to organ system damage and the onset of ARDS. Treatment with ARDS-003 aims to dampen the inflammatory response and preserve some immune function to allow host viral clearance. Some patients develop immunosuppression (red) due to immune exhaustion induced by early pathologic inflammation. ARDS, acute respiratory distress syndrome; CRS; cytokine release syndrome.

Preventing ARDS with ARDS-003

ARDS-003 targets an area of unmet need, as ARDS develops in up to two-thirds of critically ill COVID-19 patients and occurs in three-quarters of ICU admissions. ARDS is the leading cause of mortality in COVID-19 patients and may develop secondary to a hyperinflammatory immune response that in some patients resembles cytokine release syndrome (CRS) (Fig. 1). Elevation of cytokines is associated with COVID-19, with interleukin 6 (IL-6) emerging as a biomarker for disease severity. Steroids may be used to combat inflammation, yet the general immunosuppression they cause may hinder a patient's ability to clear the virus and combat secondary infections.

Further, past experience with SARS and MERS has revealed that corticosteroid treatment could exacerbate lung injury in infected patients. While additional therapies are emerging, because of its unique mechanism of action, ARDS-003 is not expected to induce side-effects commonly associated with other inflammatory treatments including steroids. There currently remains a large unmet need for nonsteroidal therapies, such as ARDS-003, to prevent ARDS.

ARDS-003 was developed to address multiple inflammatory diseases using classical drug discovery methods, employing medicinal chemistry and preclinical testing to understand structure-activity relationships. Sepsis, like ARDS, is characterized by acute hyperinflammation driven by excessive production of cytokines such as IL-6 and TNF-α, as well as other proinflammatory immune modulators. Preclinical studies with the active agent in ARDS-003 demonstrated a significant anti-inflammatory effect in an animal model of acute lung injury, reducing both pro-inflammatory cytokines and lung pathology. Similarly, in a model of chemically-induced pulmonary fibrosis, a single dose of the ARDS-003 active agent lowered levels of IL-6 and decreased the severity of pulmonary fibrosis, as measured by the Ashcroft score, a histological scale that grades lung fibrosis, following repeated treatments with the drug. Additional in vitro work has provided further confirmation that the active ingredient in ARDS-003 reduces fibrosis-associated inflammatory responses when tested in human lung cells derived from patients with inflammatory pulmonary disease. Based on these preclinical results, Tetra is pursuing development of ARDS-003 for COVID-19-infected patients to prevent development of ARDS, reducing the risk of organ failure and death. As such, ARDS-003 is currently under further evaluation in a murine model of SARS-CoV-2 infection carried out by researchers at the Biocontainment Laboratory-George Mason University National Center for Biodefense and Infectious Diseases.

Phase 1 trials

Tetra's phase 1 trial will define the pharmacokinetic profile for ARDS-003 and the company plans to initiate a phase 2 study in patients with COVID-19 to evaluate efficacy readouts of CRS severity, ARDS, and survival. Tetra has funds to support both planned phases and estimates that by 2026, revenues from ARDS-003—such as royalties, milestones, and upfront payments—could exceed $500 million. The company has developed and patented a method for ARDS-003 synthesis, formulated as a sterile solution for intravenous delivery. GMP batch manufacturing, analytic quality control, and scale up are underway in preparation for clinical testing.

Tetra's pipeline is broad, including both additional indications for ARDS-003 and other products. ARDS-003 is also being developed for use in treating sepsis, another area of high unmet medical need driven by systemic inflammatory disease. According to WHO figures, nearly 49 million cases of sepsis occurred in 2017, resulting in 11 million deaths. Sepsis accounts for 8.5% of cancer deaths, and post-trauma sepsis in hospitals results in the death of 1 in 5 patients with sepsis. Sepsis is characterized by a cytokine storm, activation of pattern recognition receptors (e.g. Toll-like receptors), complement pathway, and tissue damage, in some cases leading to organ failure and death. Once the disease process begins, there are few effective therapies available.

Beyond COVID-19 and sepsis, Tetra is also pursuing novel therapies for ocular inflammation, including uveitis and proliferative vitreoretinopathy (PVR). Tetra's PPP003 received Orphan Drug Designation from the US Food and Drug Administration as a preventative treatment for PVR, an inflammatory response to surgery that accounts for up to 10% of retinal detachment surgery failures. PPP003 has exhibited robust preclinical efficacy in the prevention and treatment of experimental anterior, posterior and pan-uveitis. PPP003 is being developed both as a proprietary topical eyedrop and an injectable formulation for uveitis and PVR.

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