



Clinical Course of Two Patients with COVID-19 Respiratory Failure After Administration of the Anticancer Small Molecule, RRx-001

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Abstract: Two critically ill COVID-19 infected patients, who had exhausted all available treatment options, were treated with the small-molecule RRx-001 with subsequent improvement. RRx-001, a first-in-class small molecule with anti-inflammatory, vascular normalizing and macrophage-repolarizing properties, has been safely administered 300+ patients in clinical trials. This is the first report of RRx-001 treatment of COVID-19.

Keywords: COVID-19, SARS-CoV-2, critical care, ARDS, RRx-001, nitric oxide, viral diseases

Background

RRx-001 (N-(bromoacetyl)-3,3-dinitroazetidine) is a hypoxia-activated, small-molecule nitric oxide (NO) donating immunotherapeutic with minimal toxicity, which also mediates NLRP3 inhibition,¹ Nrf2 and p53 upregulation, NFκB inhibition and platelet deaggregation.²⁻⁴ The main impetuses to evaluate RRx-001 in COVID-19 cases and more generally in patients with cardiorespiratory disease are 1) its favorable safety profile in over 300 patients with cancer,⁵ many of whom have been and are highly comorbid due to older age and tobacco use, 2) evidence of anti-inflammatory properties mediated through NLRP3 inflammasome inhibition based on evidence that an overactivation of inflammasome signaling is a driver of severe cases of COVID-19,⁶ 3) its preclinical alleviation of some of the cardiopulmonary complications endemic to severe COVID-19 such as pulmonary artery hypertension, heart failure,⁷ vasospasm,⁸ thromboembolism, and shock,⁹ 4) evidence of antiviral properties in the form of activity against Ebola and 5) hypoxia-mediated generation of nitric oxide,¹⁰ a free radical species that induces vasodilatory, bronchodilatory and antimicrobial effects. This case report summarizes the clinical courses of 2 severe COVID-19 patients treated under compassionate use protocols with RRx-001.

Case Reports

Case 1

The first patient is a 59-year-old severely ill COVID-19 male patient comorbid for hypothyroidism, diabetes mellitus type II and hypertension with acute respiratory distress syndrome (ARDS) on VV-ECMO who received four 4 mg doses of RRx-001 given twice weekly intravenously for two weeks. Previous treatments included hydroxychloroquine, azithromycin, convalescent plasma, tocilizumab, meropenem and vancomycin. The CT result showed bilateral ground glass dense opacities (GGOs). Following his initial treatment with RRx-001, for which no adverse events or drug-drug interactions were observed, hemodynamic parameters stabilized, and interstitial GGOs decreased. He was able to wean

from VV-ECMO, although he continued to require mechanical ventilation via tracheostomy and was ultimately discharged forty-six days later to a tertiary center for lung transplant evaluation due to clinical signs of pulmonary fibrosis. There he underwent surgical intervention for a gangrenous gallbladder and was discharged to a subacute nursing facility to recuperate.

Case 2

The second patient is a 36-year-old severely ill morbidly obese male with COVID-19 pneumonia, who was transferred from an outside hospital for VV-ECMO initiation. On day 24 of hospitalization, he continued to be profoundly hypoxemic despite 100% oxygen supplementation, maximal VV-ECMO and high-pressure control ventilation. His course was also complicated by bilateral pneumothoraces. Given his grave condition, he was treated with four 4 mg doses of RRx-001 given twice weekly intravenously over two weeks. Previous treatments included plasma exchange, corticosteroids and tocilizumab. At the time of treatment with RRx-001, he was three weeks into his hospitalization and remained severely hypoxemic despite prone positioning, maximal VV-ECMO, tracheostomy and ventilatory support and had received treatment with multiple courses of antibiotics including Vancomycin, levofloxacin, ganciclovir, meropenem, piperacillin/tazobactam, linezolid and ceftazidime and therapeutic anticoagulation. Following his initial treatment with RRx-001, for which no adverse events or drug–drug interactions were observed, the patient clinically and radiographically improved to the point of VV-ECMO decannulation after 45 days on pump and was successfully discharged back to his original institution 59 days after admission. His chest tubes and tracheostomy were subsequently discontinued, and he was discharged home 109 days after his initial admission for COVID-19 on 2 liters nasal cannula oxygen.

Conclusion

In an attempt to keep pace with the rapid spread of the pandemic and the near daily revelations about the complex, protean and system-wide clinical manifestations of SARS-CoV-2, over 300 trials have been launched with repurposed antivirals like hydroxychloroquine and chloroquine, immunomodulators like tocilizumab, experimental agents like RRx-001 and vitamin C in what has been described as a “tsunami” and a “torrent”.^{11,12} Whether this inundation with 300+ trials is counterproductive, because it spreads resources (and patients) thin and actually renders clinical investigation less conclusive, or whether it is an ethical and moral imperative to evaluate as many therapies as possible, in the event that one or more of them provides evidence of benefit, is a matter of debate.

In the case of RRx-001, it was administered, in desperation, under an FDA emergency compassionate use as a “Hail Mary” due to the lack of any remaining known adequate therapies, all other potential ones having already been deployed in the ICU, failure to qualify for existing clinical trials nearby, and because the probable risk from RRx-001, as a minimally toxic anticancer agent in a Phase 3 clinical trial¹³ with anti-inflammatory properties was deemed to be much less than the risk of imminent death from COVID-19 and acute respiratory distress syndrome (ARDS).¹⁴ Compassionate use, which is also known as expanded access, refers to the use of an unapproved drug like RRx-001 for individual patients in an “n-of-1” setting outside of a clinical trial.¹⁵

Much has been written about the pros and cons of “n-of-1” treatment.¹⁶ While it is certainly true that generalizability to a broader population is impossible, especially in this case given the marked heterogeneity of COVID-19 and ARDS in terms of presentation, course, and outcomes,¹⁷ it is equally true that the more granular data on individual patients, which they provide, may identify unintended/unexpected effects that are less evident and discoverable in an entire patient population where the law of averages operate.¹⁸ The clinical improvement of these two RRx-001-treated patients that a priori were deemed likely to die from COVID-19 and ARDS potentially lends support to the hypothesis that the anti-inflammatory and NO-donating effects¹⁹ of RRx-001 increased blood flow to ischemic tissues and ameliorated inflammatory and oxidative damage through NLRP3 inhibition since RRx-001 has been found in *in vitro* and *in vivo* experiments to bind directly to and block the NLRP3 inflammasome¹ as well as Nrf2 and p53 upregulation. RRx-001 consists of a highly strained four-membered ring, an azetidine, which is substituted with two strongly electron-withdrawing nitro groups. Under conditions of severe hypoxia and acidosis, the ring fragments and liberates the vasodilatory antiviral agent, nitric oxide.^{2,20} A table, which demonstrates clinical characteristics of the two patients is shown in Table 1.

Table I Characteristics of Two Patients

	Patient 1	Patient 2
Age years	59	36
Sex	Male	Male
Comorbidities	Hypothyroidism, diabetes mellitus type II and hypertension	Morbid obesity
Previous Therapies	Hydroxychloroquine, azithromycin, convalescent plasma, tocilizumab, meropenem, vancomycin	Plasma exchange, corticosteroids, tocilizumab, VV-ECMO
Dose and number of treatments of RRx-001	4 mg x 4	4 mg x 4
ICU days	46	109
Survival	Yes	Yes

It is possible that the clinical improvement that was documented after treatment with RRx-001 was not due to RRx-001; rather these patients experienced an inflammatory lung process, which coincidentally may have peaked in severity around the time of enrollment or that a confounding effect from one or more of the other prior treatment regimens was present. Nevertheless, given the lack of any documented adverse effects or drug–drug interactions with RRx-001, further controlled trials enrolling larger sample of patients with COVID-19 and/or severe cardiopulmonary failure are warranted, especially with the current rampant infectivity of the Omicron subtype of the coronavirus, which is increasingly immune to vaccines and monoclonal antibodies.

Abbreviations

ARDS, acute respiratory distress syndrome; COVID-19, novel coronavirus disease 2019; NO, nitric oxide; NRF2, nuclear factor erythroid 2-related factor 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VV-ECMO, venovenous extracorporeal membrane oxygenation.

Ethical Approval

The study was approved by the institutional review board at the treating medical centers.

Consent to Publish

Informed consent to publish was obtained from the patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

BO, SC, TRR are employed by EpicentRx, Inc. TCH, RCL, TMJ, JG, AH, SK have no conflicts to disclose in this work.

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