Outpatient Inhaled Nitric Oxide in a Patient with Vasoreactive IPAH and COVID-19 Infection

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To the Editor:

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of respiratory illness COVID-19, is associated with significant pulmonary morbidity and acute respiratory distress syndrome (ARDS)-like illness(1). The unprecedented global COVID-19 pandemic is impacting the wellbeing of vulnerable patients, particularly the elderly and those with underlying cardiopulmonary diseases(2). As no specific anti-viral therapy is currently approved for COVID-19, treatment is supportive (at times intensive) and has severely stretched global hospital staffing and equipment capacity. Here we report on an outpatient management of a patient with concomitant idiopathic pulmonary arterial hypertension (iPAH) and COVID-19 disease using inhaled nitric oxide (iNO).

CASE

A 34-year-old female with vasoreactive iPAH [Table 1], historically stable on nifedipine (60 mg extended release daily), tadalafil, and macitentan, presented through telehealth visit with progressive dyspnea and fatigue in the setting of recent positive COVID-19 PCR test. The patient reported a recent 2-week trip to Egypt, including a Nile cruise, flying roundtrip from United States thru Germany to Egypt. Upon return, the patient initially noticed onset of anosmia followed by low-grade fever for which she sought medical care. Five days later, she was contacted by the county health authority, advised of positive test, and asked to self-quarantine. On the same day she contacted her PAH care center and was immediately evaluated.

On initial telehealth assessment, the patient was noted to be more than 350 miles away and reporting WHO III symptoms with significant fatigue and dyspnea on exertion. She was tolerating her routine PAH medications and denied any active chest pain, palpitations, lightheadedness, or lower extremity edema. Vital signs included a temperature of 98.9°F, heart rate 90 bpm, blood pressure 88/57 mmHg, and oxygen saturation (SpO₂) 97% on room air. We diagnosed her with COVID-19 respiratory infection with potential PAH exacerbation and advised on supportive therapy. The patient expressed desire to avoid hospitalization based on personal and public health (contagion risk, resource utilization) concerns. A home-based telehealth care plan was activated with a twice-daily remote check-in for evaluation of heart failure symptoms and vital signs. With the help of her non-clinician caregiver, patient carried out routine vital and SpO₂ monitoring, and BID six-minute walk tests (6MWT). She also completed a daily EmPHasis-10 (E10) report – a validated health-related quality of life (HRQoL) questionnaire(3). With the assistance of a local tertiary care academic medical center, a proactive back-up evaluation and hospitalization plan were established.

Given the patient's symptoms and underlying preserved vasoreactivity we proposed that she might benefit from iNO treatment. An emergency investigational new drug (EIND) application for off-label use of an approved therapy and delivery system was requested and accepted by the United States Food and Drug Administration (USFDA). The Stanford IRB was notified of the EIND-based protocol and the patient provided written informed consent. We used GENOSYL (nitric oxide for inhalation) (Vero Biotech, Atlanta, GA), the only tankless iNO delivery system (GENOSYL DS®) approved by the USFDA for the treatment of persistent pulmonary hypertension in the newborn (PPHN). Within 24 hours of EIND approval, the GENOSYL DS® with cassettes, an oxygen generation circuit, nasal canula tubing, a pulse oximeter with integrated noninvasive methemoglobin measurement capability (SpMet®, Masimo US, Irvine, CA), and a digital blood pressure cuff were delivered to patient's residence. Technical assistance and equipment set-up were provided via telehealth. After a monitoring regimen was well established, iNO was initiated at 20 ppm plus 2 LPM supplemental oxygen via nasal canula for 12-14 hours per day, gradually weaning in stepwise doses (10, 5, 0 ppm) each night over 2-3 hours.

Over the course of the following 11 days, the patient was monitored remotely and demonstrated a substantial response to iNO (Figure 1), as evidenced by her symptomatic relief and progressive increase in home-administered 6MWT. Nightly iNO weanings were well tolerated and methemoglobin levels remained within normal range (0-0.5%). Given her symptomatic improvement, we began iNO dose reduction from day 13-17, initially at 10 ppm then 5 ppm and eventually off. Patient did not require any urgent care, emergency department, or hospital visits.

DISCUSSION

Without well-established treatments, the COVID-19 pandemic is a threat to the health and care of PAH patients(4). This report is the first to our knowledge of outpatient telehealth management of an iPAH patient with COVID-19 disease, implementing a home-administered sub-maximal exercise test along with E10 questionnaire to follow patient's clinical progress. Under an EIND from the USFDA, we activated an outpatient therapeutic iNO protocol within 24 hours.

Inhaled nitric oxide is approved by the USFDA for the treatment of PPHN(5), and used for vasodilatory challenge during right heart catheterization(6). INO is known to provide relief of dyspnea and improve exercise tolerance in adult patients with pulmonary hypertension (PH) and other pulmonary diseases(7), and is widely used a rescue therapy for severely hypoxemic patients with and without PH(8). INO has been associated with varying results in adults with ARDS(9), but more consistent benefit in ARDS associated with a coronavirus pulmonary complication such as SARS(10). Additionally, *in vitro* work has demonstrated that coronaviruses are generally highly susceptible to NO, suggesting that treatment may inhibit viral replication in coronavirus-associated SARS and reduce lung inflammation(10).

The overall utility of iNO in managing PH is limited by interindividual variations in response, cost, and logistics. While hospitals may readily stock the large, weighty tank system required for conventional delivery of iNO, the recent FDA approval of the GENOSYL tankless system creates opportunities for out-of-hospital or home use. Given the current extraordinary demand on the global healthcare system in managing COVID-19 disease, especially in patients with pre-existing comorbidities such as PH, out-of-hospital tankless iNO therapy is appealing for managing respiratory symptoms. The additional considerations of a potential anti-viral effect and the overall safety of intermittent iNO therapy made this approach reasonable for our patient.

This patient was remotely managed by clinicians, and was more amenable (as a physician herself) to self-monitoring and self-directed therapy than the ordinary patient. This is not a typical case, while the clinical improvement she experienced may not be wholly generalizable, her care represents a first step towards support for the outpatient use of iNO to treat exacerbation of PH symptoms due to COVID-19. This approach should not replace best clinical practices when patients present with more substantial symptoms and progressive worsening. While this case may serve as a proof of concept,

it does not "prove" the utility of iNO in treating respiratory manifestations of COVID-19. Well-designed clinical trials are needed to evaluate the effectiveness of iNO in the setting of COVID-19 disease. If demonstrated to be effective, outpatient iNO may serve not only to improve clinical outcomes but also to reduce the strain on inpatient resources in the current pandemic.

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FIGURE 1: Serial 6MWD, emphasis-10 score, WHO symptom class, and iNO dose over the course of patient's COVID-19 infection. WHO = World Health Organization symptom classification, 6MWD = six minute walk distance, E10 = EmPHasis-10 score, iNO = inhaled nitric oxide, PPM = parts per million.

	Diagnosis (2011)	Last Follow-up (2019)
WHO/NYHA class	IV	I
6MWD (m)	475	702
Hemodynamics		
Baseline		
mRA (mmHg)	5	7
mPAP (mmHg)	40	45
CO (L/min)	2.97	3.47
PCWP (mmHg)	7	13
PVR (dynes.sec.cm-5)	888.9	737.8
iNO @ 20 ppm x 5 min		
mRA (mmHg)	-	-
mPAP (mmHg)	19	20
CO (L/min)	3.27	3.63
PCWP (mmHg)	10	12
PVR (dynes.sec.cm-5)	220.2	176.3

Table 1: Clinical Characteristics at Diagnosis and at Last Follow-up Appointment



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