Title

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Outpatient Inhaled Nitric Oxide in a Patient with Vasoreactive Idiopathic Pulmonary Arterial Hypertension and COVID-19 Infection

To the Editor:

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (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 well-being of vulnerable patients, particularly the elderly and those with underlying cardiopulmonary diseases (2). Because no specific antiviral 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 outpatient management of a patient with concomitant idiopathic pulmonary arterial hypertension (iPAH) and COVID-19 using inhaled nitric oxide (iNO).

Case

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

On the initial telehealth assessment, the patient was noted to be more than 350 miles away and reporting World Health Organization III symptoms, with significant fatigue and dyspnea on exertion. She was tolerating her routine PAH medications and denied having any active chest pain, palpitations, lightheadedness, or lower-extremity edema. Her vital signs included a temperature of 98.9°F, heart rate of 90 bpm, blood pressure of 88/57 mm Hg, and oxygen saturation as measured by pulse oximetry (Sp_{O_2}) of 97% on room air. We made a diagnosis of COVID-19 respiratory infection with potential PAH exacerbation and advised on supportive therapy. The patient expressed a desire to avoid hospitalization based on personal and public health concerns (e.g., risk of contagion and use of resources). 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 nonclinician caregiver, the patient performed routine monitoring of vitals and Sp_{O_2}, and twice daily 6-minute-walk tests. She also completed a daily EmPHasis-10 report, which is a validated health-related quality-of-life questionnaire (3). With the assistance of a local tertiary care academic medical center, a proactive backup evaluation and hospitalization plan was 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 submitted to the U.S. Food and Drug Administration (FDA) and approved. The Stanford Institutional Review Board was notified of the EIND-based protocol and the patient provided written informed consent. We used GENOSYL (NO for inhalation) administered via a GENOSYL DS (both from Vero Biotech), the only tankless iNO delivery system approved by the FDA for the treatment of persistent pulmonary hypertension (PH) in the newborn (PPHN). Within 24 hours of EIND approval, the GENOSYL DS with cassettes, an oxygen generation circuit, nasal cannula tubing, a pulse oximeter with integrated noninvasive methemoglobin measurement capability (SpMet; Masimo U.S.), and a digital blood pressure cuff were delivered to the patient's residence. Technical assistance and equipment setup were provided via telehealth. After a monitoring regimen was well established, iNO was initiated at 20 ppm plus 2 L/min supplemental oxygen via nasal cannula for 12–14 hours per day, with gradual weaning in stepwise doses (10, 5, and 0 ppm) each night over 2–3 hours.

Over the course of the next 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 6-minute-walk test scores. Nightly iNO weanings were well tolerated and methemoglobin levels remained within the normal range (0–0.5%). Given her symptomatic improvement, we reduced the iNO dose during Days 13–17, from 10 ppm to 5 ppm and eventually zero. The 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 patients with PAH (4). To our knowledge, this is the first report of outpatient telehealth management of a patient with iPAH and COVID-19, which included a home-administered submaximal exercise test along with an EmPHasis-10 questionnaire to follow the patient's clinical progress. Under an EIND from the FDA, we activated an outpatient therapeutic iNO protocol within 24 hours.

iNO is approved by the FDA for the treatment of PPHN (5) and is 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 PH and other pulmonary diseases (7), and is widely used as 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 has shown a more consistent benefit in ARDS associated with a

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This letter has a related editorial.

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

	Diagnosis (2011)	Last Follow-up (2019)
WHO/NYHA class	IV	I
6-minute-walk distance, m	475	702
Hemodynamics		
Baseline		
mRA, mm Hg	5	7
mPAP, mm Hg	40	45
CO, L/min	2.97	3.47
PCWP, mm Hg	7	13
PVR, dynes · s · cm^{-5}	888.9	737.8
iNO, 20 ppm × 5 min		
mRA, mm Hg	—	—
mPAP, mm Hg	19	20
CO, L/min	3.27	3.63
PCWP, mm Hg	10	12
PVR, dynes · s · cm^{-5}	220.2	176.3

Definition of abbreviations: CO = cardiac output; iNO = inhaled nitric oxide; mPAP = mean pulmonary arterial pressure; mRA = mean right atrial pressure; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization.

coronavirus pulmonary complication such as SARS (10). In addition, *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 for managing PH is limited by interindividual variations in responses, costs, and logistics. Although hospitals may readily stock the large, weighty tank system required for conventional delivery of iNO, the recent FDA approval of the GENOSYL DS tankless system has created opportunities for out-of-hospital or home use. Given the current extraordinary demands placed on global healthcare systems in managing COVID-19, especially with regard to patients with preexisting comorbidities such as PH, out-of-hospital tankless iNO therapy is an appealing option for managing respiratory symptoms. The additional considerations of a potential antiviral effect and the overall safety

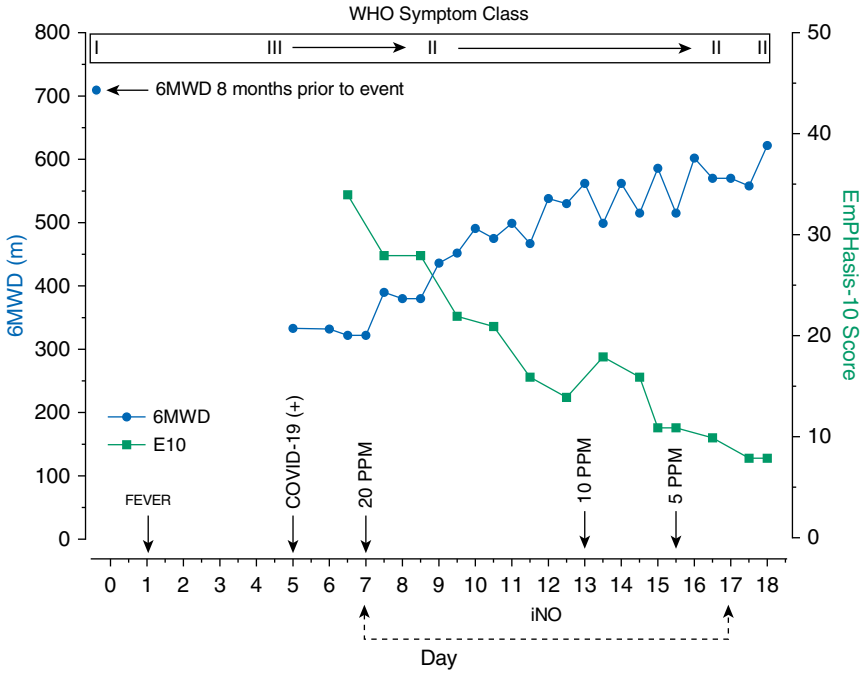

Figure 1. Serial 6-minute-walk distance (6MWD), EmPHasis-10 (E10) score, World Health Organization (WHO) symptom class, and inhaled nitric oxide (iNO) dose over the course of a patient's coronavirus disease (COVID-19) infection.

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 would be. This is not a typical case, and although the clinical improvement she experienced may not be wholly generalizable, her care represents a first step toward support for 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. Although this case may serve as a proof of concept, it does not prove the utility of iNO for treating respiratory manifestations of COVID-19. Well-designed clinical trials are needed to evaluate the effectiveness of iNO in the setting of COVID-19. If this approach is demonstrated to be effective, outpatient iNO may serve to not only improve clinical outcomes but also reduce the strain on inpatient resources in the current pandemic. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201: 1299–1300.
2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19); [accessed 2020 Apr 2]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html.
3. Yorke J, Deaton C, Campbell M, McGowen L, Sephton P, Kiely DG, *et al*. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. *BMJ Open Respir Res* 2018;5: e000263.
4. Ryan JJ, Melendres L, Zamanian RT, Oudiz RJ, Chakinala M, Rosenzweig EB, *et al*. Care of patients with pulmonary arterial hypertension during the coronavirus (COVID-19) pandemic. *Pulm Circ* 2020;10:2045894020920153.
5. Sokol GM, Konduri GG, Van Meurs KP. Inhaled nitric oxide therapy for pulmonary disorders of the term and preterm infant. *Semin Perinatol* 2016;40:356–369.
6. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, *et al*.; ACCF/AHA. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;119:2250–2294.
7. Hasuda T, Satoh T, Shimouchi A, Sakamaki F, Kyotani S, Matsumoto T, *et al*. Improvement in exercise capacity with nitric oxide inhalation in patients with precapillary pulmonary hypertension. *Circulation* 2000; 101:2066–2070.
8. Teman NR, Thomas J, Bryner BS, Haas CF, Haft JW, Park PK, *et al*. Inhaled nitric oxide to improve oxygenation for safe critical care transport of adults with severe hypoxemia. *Am J Crit Care* 2015;24: 110–117.
9. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev* 2016;2016:CD002787.
10. Chen L, Liu P, Gao H, Sun B, Chao D, Wang F, *et al*. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004;39: 1531–1535.

COVID-19–associated Pulmonary Aspergillosis

To the Editor:

Late December 2019, China reported an outbreak of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has become a global threat, with high attack rates, ICU admissions, and mortality. Initial cohort studies reported a substantial case fatality rate in patients admitted to the ICU, of whom half developed secondary infections (1). Late February, the Southern

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