

1 **Nebulized in-line endotracheal dornase alfa and albuterol administered to mechanically**
2 **ventilated COVID-19 patients: A case series**

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26 **ABSTRACT**

27 **Background**

28 Mechanically ventilated patients with coronavirus disease 2019 (COVID-19) have a mortality of
29 24–53%, in part due to distal mucopurulent secretions interfering with ventilation. Dornase alfa
30 is recombinant human DNase 1 and digests DNA in mucoid sputum. Nebulized dornase alfa is
31 FDA-approved for cystic fibrosis treatment. DNA from neutrophil extracellular traps (NETs)
32 contributes to the viscosity of mucopurulent secretions. NETs are found in the serum of patients
33 with severe COVID-19, and targeting NETs reduces mortality in animal models of acute
34 respiratory distress syndrome (ARDS). Thus, dornase alfa may be beneficial to patients with
35 severe COVID-19—acting as a mucolytic and targeting NETs. However, delivery of nebulized
36 drugs can aerosolize SARS-CoV-2, which causes COVID-19, increasing the infection risk for
37 staff. Here, we report a single center case series where dornase alfa was administered through
38 an in-line nebulizer system to minimize risk of virus aerosolization.

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40 **Methods**

41 Demographic, clinical data, and outcomes were collected from the electronic medical records of
42 five mechanically ventilated patients with COVID-19—including three requiring veno-venous
43 extracorporeal membrane oxygenation (VV-ECMO)—treated with nebulized in-line endotracheal
44 dornase alfa co-administered with albuterol (used to increase delivery to the alveoli), between
45 March 31 and April 24, 2020. Data on tolerability and responses, including longitudinal values
46 capturing respiratory function and inflammatory status, were analyzed.

47

48 **Results**

49 Following nebulized in-line administration of dornase alfa with albuterol, the fraction of inspired
50 oxygen requirements was reduced for all five patients. All patients remain alive and two patients
51 have been discharged from the intensive care unit. No drug associated toxicities were identified.

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Conclusions

The results presented in this case series suggest that dornase alfa will be well-tolerated by critically ill patients with COVID-19. Clinical trials are required to formally test the dosing, safety, and efficacy of dornase alfa in COVID-19, and two have recently been registered (*NCT04359654* and *NCT04355364*). With this case series, we hope to contribute to the development of management approaches for critically ill patients with COVID-19.

Keywords

SARS-CoV-2, COVID-19, coronavirus, mucopurulent secretions, dornase alfa, neutrophil extracellular traps, ARDS, VV-ECMO

78 **BACKGROUND**

79 Critically ill patients with coronavirus disease 2019 (COVID-19), caused by the severe acute
80 respiratory syndrome coronavirus 2 (SARS-CoV-2), progress to hypoxemic and then mixed
81 respiratory failure, secondary to acute respiratory distress syndrome (ARDS) (1, 2).

82 Approximately 79–88% of patients admitted to the intensive care unit (ICU) with COVID-19
83 require intubation and mechanical ventilation, with a mortality of 24–53% (3–6). ARDS in
84 COVID-19 is characterized by ventilation failure, in part attributable to distally located
85 mucopurulent secretions.

86
87 Dornase alfa (Pulmozyme®) is recombinant human DNase 1 and a safe mucolytic that is
88 administered in nebulized form. It is FDA-approved in combination with standard therapies for
89 patients with cystic fibrosis to improve sputum clearance and pulmonary function (7). It is also
90 used off-label as a mucolytic in other diseases, including ARDS (8, 9). A mechanism by which
91 dornase alfa might improve ventilation is by reducing the DNA-mediated viscosity of neutrophil-
92 rich secretions (10). There are multiple sources for the DNA in mucoid sputum, one of which is
93 neutrophil extracellular traps (NETs). Recently, we collaboratively reported that in the discarded
94 serum of patients with COVID-19, the levels of NETs were increased and were correlated with
95 lactate dehydrogenase (LDH), D-dimer, and C-reactive protein (CRP) levels (11). Targeting
96 NETs reduces mortality in animal models of ARDS (12). Despite recognition that mucolytic
97 treatment may be beneficial for patients with COVID-19, administration of nebulized
98 medications, such as dornase alfa, have been limited due to risk of viral aerosolization. If risk of
99 viral aerosolization can be avoided, dornase alfa may benefit patients with severe COVID-19. by
100 acting as a mucolytic and by reducing NET levels in the lungs, thereby improving oxygenation
101 and ventilation. We report the clinical course, safety, and outcomes after nebulized in-line
102 endotracheal dornase alfa treatment for five intubated and mechanically ventilated patients with
103 PCR-confirmed COVID-19.

104

105 **METHODS**

106 The Northwell Health institutional review board that focuses on COVID-19 research approved
107 this case series as minimal-risk research using de-identified data from routine clinical practice.
108 Data were collected from the enterprise health record (Sunrise Clinical Manager; Allscripts)
109 reporting database, and included patient demographics, comorbidities, inpatient medications,
110 laboratory studies, treatment, and outcomes. We further obtained longitudinal values of FiO_2
111 and of the arterial partial pressure of carbon dioxide (PaCO_2) as measures of respiratory
112 function during treatment. FiO_2 values of the circuit were reported for those patients who
113 required veno-venous extracorporeal membrane oxygenation (VV-ECMO). Ferritin, CRP, LDH,
114 and D-dimer were obtained as measures of systemic disease and inflammation. Not all patients
115 had laboratory investigations on the same days in relation to the nDA+A treatment. In the
116 following case synopses, each measurement is therefore followed by the day in relation to the
117 first day of treatment with nDA+A (e.g. d 2 for the second day of treatment with nDA+A or d -1
118 for the day before nDA+A treatment was initiated).

119

120 **RESULTS**

121 Five patients treated with dornase alfa between March 31, 2020 and April 24, 2020 were
122 identified. These patients had met the Berlin criteria for ARDS and were treated with ventilator
123 strategies guided by the ARDSNet protocol at North Shore University Hospital within Northwell
124 Health (13). They had been treated with dornase alfa because they required high levels of
125 fraction of inspired oxygen (FiO_2) and had elevated ventilation demands. All patients received
126 the same treatment doses: nebulized dornase alfa (2.5 mg) co-administered twice daily with the
127 short-acting β_2 -agonist albuterol (2.5 mg, hereafter abbreviated as nDA+A) to improve delivery
128 to the alveoli. Of note, β_2 -adrenoreceptor agonism may also inhibit NET formation by direct
129 action on neutrophils (14). The treatment was administered with an Aerogen® Solo in-line

130 nebulizer to avoid open aerosol generation, which would place staff at risk of exposure to
131 SARS-CoV-2.

132
133 The patient characteristics are summarized in **Table 1**. Patients were treated with nDA+A
134 between 3 to 25 days. The most common characteristics of the patients included obesity
135 (BMI \geq 30) and four of the patients had hypertension. Four patients received methylprednisolone
136 dosed at 1-2mg/kg/day. All patients were treated with full dose or prophylactic dose
137 anticoagulation for thrombosis. All other medications that were administered during the course
138 of hospitalization are summarized in **Table S1**. The clinical course of the five patients treated
139 with nDA+A is summarized in **Figure 1**. **Figure 2** and **3** display the longitudinal, ventilatory, and
140 inflammatory markers for each patient.

141
142 Patient 1 is a 56-year-old Hispanic woman who presented in respiratory distress. Her respiratory
143 status deteriorated over 48 hours, requiring intubation and transfer to the ICU. She was treated
144 with nDA+A for six days, starting from day 9 of intubation. The FiO₂ requirement decreased from
145 70% (d -1) to 30% (d 6), PaCO₂ from 58 (d -1) to 37 mmHg (d 7), ferritin from 1,803 (d -1) to 472
146 ng/mL (d 6), and D-dimer from 1,619 (d -1) to 563 ng/mL (d 6). Minimal changes were noted in
147 CRP and LDH. The patient underwent a tracheostomy after 23 days of endotracheal intubation
148 and remains on an FiO₂ of 30% while pending return of mental status.

149
150 Patient 2 is a 34-year-old white man who presented to the hospital in diabetic ketoacidosis
151 without prior history of diabetes mellitus. He was intubated on admission and initiated on VV-
152 ECMO. He received nDA+A for three days and was de-cannulated after 12 days. The FiO₂
153 requirement decreased from 100% (d 0) to 80% (d 3), CRP from 14.14 (d 0) to 2.41 mg/dL (d 3),
154 ferritin from 12,281 (d 0) to 5,453 ng/mL (d 3), and D-dimer from 5,210 (d 0) to 2,099 ng/mL (d
155 3). Minimal changes were noted in PaCO₂ and LDH. The patient remains intubated.

156

157 Patient 3 is a 65-year-old Asian man who was admitted directly to the ICU for respiratory
158 distress and intubated three days later. Twelve days after intubation, he was started on nine
159 days of nDA+A treatment. The FiO₂ requirement decreased from 50% (d -1) to 40% (d 7),
160 PaCO₂ from 55 (d 0) to 43 mmHg (d 6), and CRP from 22.07 (d 0) to 26.48 mg/dL (d 6). Minimal
161 changes were noted in ferritin, LDH, and D-dimer. He was extubated one day after the
162 completion of the nDA+A course. Six days later, he was re-intubated for an additional four days
163 due to mental status changes and failure to protect his airway. The patient remains extubated in
164 ICU care.

165

166 Patient 4 is a 31-year-old Hispanic man who was intubated and transferred to the ICU from the
167 Internal Medicine service two days after presenting with respiratory distress. Nine days after
168 intubation, he was initiated on VV-ECMO. Five days after cannulation, he was started on the
169 nDA+A treatment. After nine days, he was de-cannulated and remained intubated for ten days
170 while continuing the nDA+A treatment. He was then extubated and discharged to the floor. The
171 FiO₂ requirement decreased from 90% (d -1) to 21% (d 7) and LDH from 1,054 (d -1) to 451 U/L
172 (d 7). Ferritin initially decreased from 1,669 (d -1) to 387 ng/mL (d 7). On day 15 of treatment,
173 he developed methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and bacteremia.
174 Ferritin thus increased to 1,619 ng/mL (d 13) prior to decreasing to 555 ng/mL (d 19) with
175 antibiotic treatment. Minimal changes were noted in PaCO₂, CRP, and D-dimer.

176

177 Patient 5 is a 34-year-old black woman who was intubated at an outside hospital, then
178 transferred to the North Shore University Hospital ICU. Two days later, she was cannulated for
179 VV-ECMO. She required VV-ECMO for 13 days and was intubated for a total of 29 days. She
180 was treated with nDA+A for 25 days starting three days following intubation and cannulation.
181 While on VV-ECMO for the first five days, CytoSorb therapy was applied. She was de-

182 cannulated after 23 days, extubated after 4 days, and discharged to the floor. The FiO_2
183 requirement fell from 80% (d -1) to 40% (d 7), ferritin from 1,244 (d -1) to 535 ng/mL (d 7), and
184 LDH from 844 (d -1) to 693 U/L (d 7). Minimal changes were noted in PaCO_2 , CRP, and D-
185 dimer.

186

187 **DISCUSSION**

188 At the doses utilized, no nDA+A treatment-associated toxicities were identified. FiO_2
189 requirements decreased for all five patients seven days after nDA+A treatment was initiated. All
190 patients remain alive at the time of submission of this report, with two patients discharged from
191 the ICU. We recognize that these FiO_2 changes may be independent of the nDA+A treatment.
192 Clinical trials are therefore required to test the dose range, safety, and efficacy of dornase alfa
193 in patients with COVID-19 in this setting and possibly earlier in the disease course. Endpoints
194 should include measurements of the effect on respiratory function as well as on systemic
195 inflammation, coagulopathy, secondary infections, and the presence of NETs in plasma. Two
196 such trials were recently registered (*NCT04359654* and *NCT04355364*).

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198 It is not clear whether nebulized dornase alfa will have any effect on blood NET levels or
199 systemic inflammation in COVID-19, but a reduction in systemic inflammatory markers has been
200 reported after use of dornase alfa in patients with cystic fibrosis (7). We did note a reduction in
201 CRP in two patients (patients 2 and 3) and a reduction in D-dimer in two patients (patients 1 and
202 2) during nDA+A treatment. LDH was reduced for the patients on VV-ECMO during nDA+A
203 treatment, and ferritin was reduced in four out of five patients. Due to the small sample size and
204 the common occurrence of secondary infections in ventilated patients with COVID-19, we are
205 unable to comment on any potential relationship between nDA+A administration and the risk of
206 secondary infections.

207

208 **CONCLUSIONS**

209 Nebulized dornase alfa in combination with albuterol may be a safe treatment option for
210 mechanically ventilated patients with ARDS secondary to COVID-19, including for those on VV-
211 ECMO—a patient population with an urgent, unmet need for effective therapies.

212

213 **LIST OF ABBREVIATIONS**

214 ARDS, acute respiratory distress syndrome

215 BID, bis in die (twice daily)

216 COVID-19, coronavirus disease 2019

217 CRP, C-reactive protein

218 d, day

219 FiO₂, fraction of inspired oxygen

220 gtt, guttae (intravenous drip)

221 ICU, intensive care unit

222 LDH, lactate dehydrogenase

223 MRSA, methicillin-resistant *Staphylococcus aureus*

224 nDA+A, nebulized dornase alfa plus albuterol

225 NETs, neutrophil extracellular traps

226 PaCO₂, arterial partial pressure of carbon dioxide

227 SARS-CoV-19, severe acute respiratory syndrome coronavirus 2

228 VV-ECMO, veno-venous extracorporeal membrane oxygenation

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230 **DECLARATIONS**

231 **Ethics approval and consent to participate:** The Northwell Health institutional review board
232 that focuses on COVID-19 research approved this case series as minimal-risk research using
233 de-identified data from routine clinical practice. Informed consent to participate in the study was

234 obtained from the participants or their health care proxies. The study has been registered as
235 “Dornase Alfa Administered to Patients With COVID-19 (DACOVID)” at ClinicalTrials.gov with
236 ClinicalTrials.gov Identifier: NCT04387786.

237 **Consent for publication:** Not applicable.

238 **Availability of supporting data:** All data generated or analyzed during this study are included
239 within the article.

240 **Competing interests:** Mikala Egeblad is receiving lonodelestat from Santhera for preclinical
241 studies, but has no financial relationship with Santhera. The other authors declare that they
242 have no competing interests.

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249 of data; and in writing the manuscript.

250 **Authors’ contributions:** *Concept and design, analysis and interpretation of data, and drafting*
251 *of the manuscript:* A.G.W., A.S.C., M.E., B.J.B., and T.J. *Data acquisition:* A.G.W. and B.J.B.

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255 **Authors' information:** Not applicable.

256 **Disclaimer:** The initial characteristics of 5,700 patients from Northwell Health are presented
257 elsewhere (5). This case series presented in-depth results on the clinical status of five patients
258 treated with dornase alfa that were not presented in that article.

259

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308 **FIGURE LEGENDS:**

309 **Figure 1. Overview of the clinical course of five patients treated with nebulized dornase**
310 **alfa + albuterol (nDA+A).**

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312 **Figure 2. Patient-level data of respiratory function during treatment with nebulized**
313 **dornase alfa + albuterol (nDA+A).** Values were extracted from the medical records the day
314 before and up to the seven days after the initiation of treatment. Values are graphed in black for
315 patients after they ceased nDA+A treatment. Dashed lines indicate patients on VV-ECMO. Not
316 all markers were measured daily for every patient. FiO₂: fraction of inspired oxygen; PaCO₂:
317 partial pressure of carbon dioxide.

318
319 **Figure 3. Patient-level data of systemic disease during treatment with nebulized dornase**
320 **alfa + albuterol (nDA+A).** Values were extracted from the medical records the day before and
321 up to the seven days after the initiation of treatment. Values are graphed in black for patients
322 after they ceased nDA+A treatment. Dashed lines indicate patients on VV-ECMO. Not all
323 markers were measured daily for every patient. CRP: C-reactive protein; LDH: lactate
324 dehydrogenase.

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335 **Table 1. Patient data from five patients with COVID-19 who received dornase alfa**
 336 **with albuterol March–April, 2020.**

Patient	1	2	3	4	5
Clinical Characteristics					
Date of admission	29 March	4 April	16 March	16 March	26 March
Age	56	34	65	31	34
Gender	F	M	M	M	F
Ethnicity	Hispanic	White	Asian	Hispanic	Black
BMI	38	41	32	30	38
Date of ICU admission	31 March	4 April	16 March	18 March	26 March
Comorbidities					
Hypertension	Yes	Yes	Yes	Yes	
Diabetes mellitus, type 2	Yes				
Asthma	Yes		Yes		Yes
Hyperlipidemia		Yes			
Migraine					Yes
Chronic gastritis					Yes
ECMO					
Date of ECMO initiation	-	4 April	-	27 March	28 March
Date of ECMO cessation	-	16 April	-	10 April	20 April
Dornase alfa (DA) + albuterol (A) parameters					
Administration (DA: 2.5 mg, A: 2.5 mg, both twice daily using the Aerogen® Solo nebulizer)					
Date of DA + A initiation	9 April	4 April	31 March	1 April	31 March
Date of DA + A cessation	14 April	6 April	8 April	19 April	24 April
Toxicities	None	None	None	None	None
Other COVID-19 treatment					
Methylprednisolone	Yes	Yes		Yes	Yes
Anakinra		Yes		Yes	
CytoSorb					Yes
Anticoagulants *					
Enoxaparin	40 mg BID	120 mg BID	40 mg BID	100 mg BID	120 mg BID
Argatroban		Yes		Yes	Yes
Heparin gtt			Yes		Yes
Venous thromboembolism	None	None	None	Right SDVT Right CVT	None
Current State	Recovery post tracheostomy	Intubated	Recovery	ICU discharge (23 April)	ICU discharge (28 April)

337 *Patients were not on simultaneous anticoagulation therapies. BMI: body mass index; ICU: intensive care unit;
 338 ECMO: extracorporeal membrane oxygenation; BID: bis in die (twice a day); gtt: guttae (intravenous drip); SDVT:
 339 soleal deep vein thrombosis; CVT: cephalic vein thrombosis.

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346 **Supplemental Table 1. Additional medications that dornase alfa+albuterol-treated COVID-**
 347 **19 patients received while in the hospital.**

Patient	1	2	3	4	5
Hospital medications					
Amiodarone		Yes		Yes	
Ampicillin					Yes
Ascorbic acid			Yes	Yes	Yes
Azithromycin	Yes		Yes	Yes	
Bumetanide		Yes	Yes		
Caspofungin			Yes	Yes	Yes
Cefepime	Yes			Yes	Yes
Ceftriaxone				Yes	
Cisatracurium			Yes	Yes	Yes
Dexmedetomidine	Yes		Yes	Yes	Yes
Dobutamine	Yes				
Esmolol				Yes	
Fentanyl	Yes	Yes	Yes	Yes	Yes
Fluconazole	Yes		Yes		
Fosphenytoin	Yes				
Furosemide	Yes		Yes	Yes	Yes
HCQ/CQ	Yes		Yes	Yes	Yes
Hydromorphone				Yes	
Insulin	Yes	Yes	Yes	Yes	Yes
IVIG		Yes			
Ketamine	Yes	Yes	Yes	Yes	Yes
Levetiracetam	Yes				
Meropenem		Yes	Yes	Yes	Yes
Metronidazole		Yes		Yes	
Midazolam	Yes	Yes	Yes	Yes	Yes
Milrinone		Yes			
Nicardipine				Yes	
Nitroprusside				Yes	
Norepinephrine	Yes	Yes	Yes	Yes	Yes
Pantoprazole	Yes	Yes	Yes	Yes	Yes
Phenylephrine	Yes	Yes	Yes	Yes	
Propofol	Yes	Yes	Yes	Yes	Yes
Rocuronium	Yes	Yes	Yes		Yes
Sodium bicarbonate				Yes	
TPN			Yes		
Vancomycin		Yes	Yes	Yes	Yes
Vasopressin		Yes			Yes
Vecuronium				Yes	Yes
Zosyn			Yes	Yes	

348 Note: All antimicrobials were given at treatment doses. HCQ: hydroxychloroquine; CQ: chloroquine; IVIG: intravenous
 349 immunoglobulin; TPN: total parenteral nutrition

Figure 1

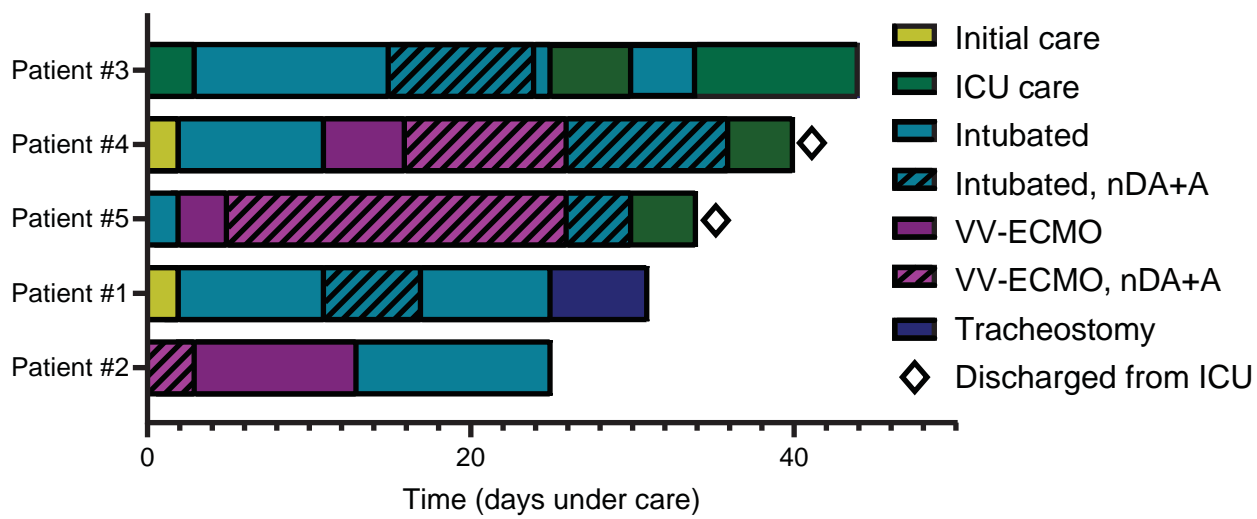


Figure 2

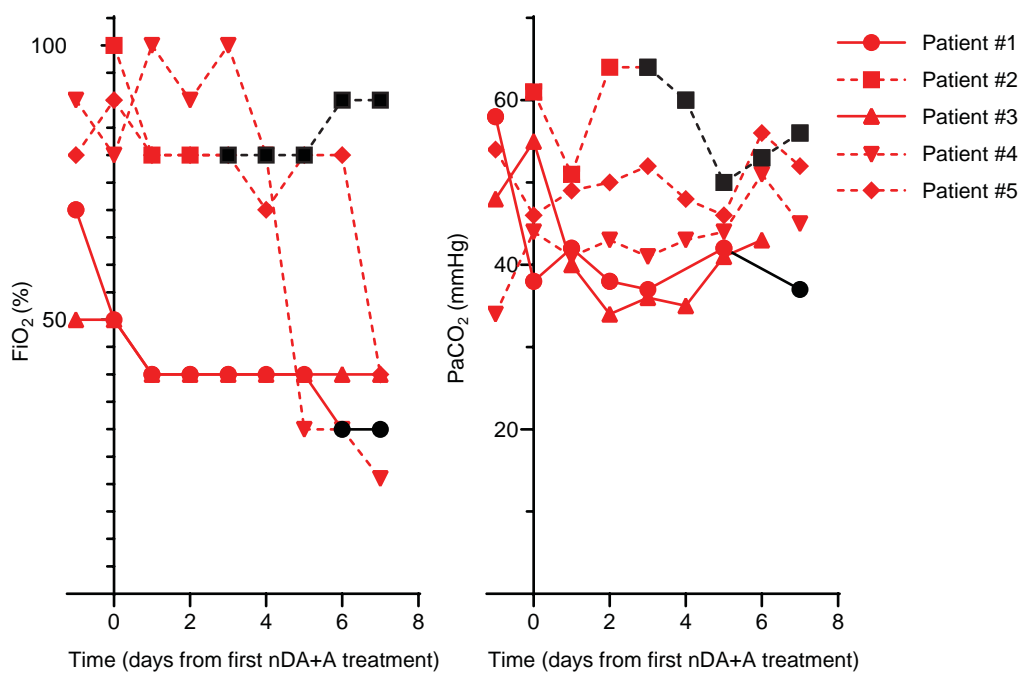


Figure 3

