

Acyclovir for SARS-CoV-2: An old drug with a new purpose



Abstract

Currently, remdesivir is the only Food and Drug Administration approved antiviral for COVID-19. Recent reports of viral mutations in the novel coronavirus are leading to a more infectious agent than at the beginning of the pandemic. Presented in this article are cases that were treated with an old drug, acyclovir. To date, 38 patients have received treatment with acyclovir. The following 4 cases highlight the benefits of acyclovir. Three of these cases had severe pulmonary disease and one had splenomegaly. One of the three pulmonary cases had worsening pulmonary involvement after hospitalization during which remdesivir in conjunction with dexamethasone was used. Acyclovir has proven to be effective, safe and inexpensive in 29 patients. Nine patients are still under treatment. No adverse effects or death have been observed with this treatment thus far. Further studies comparing acyclovir to remdesivir are needed to validate benefits from acyclovir for SARS-CoV-2 infection.

Keywords: acyclovir, antiviral, COVID-19, pneumonia, splenomegaly, remdesivir

Introduction

As of January 1, 2021, the COVID-19 pandemic has resulted in 83,000,000 cases worldwide, with almost 20,000,000 of them in the United States alone, and 1.8 million deaths worldwide, with about 350,000 of them having occurred in the United States [1]. Health officials first noted COVID-19 and its causal agent, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), in Wuhan, China. Initial patients had Novel Coronavirus-Infected Pneumonia (NCIP), which persists to this day [2]. COVID-19 patients have also seen severe symptoms like Acute Respiratory Distress Syndrome (ARDS), which causes high levels of mortality [3]. While some patients do not have such complications, the unlucky ones with physician-diagnosed pneumonia, fluid-filled lungs, and ARDS must be hospitalized, and the number of hospitalizations continues to increase, contributing to an overwhelmed health care system [4]. The National Institutes of Health recommended remdesivir as the only FDA-approved drug for COVID-19 treatment thus far. However, it has also mentioned that treatment plans, including the use of remdesivir, should not be mandated, and the choice to use it rests with the patient and provider [5]. While guidelines promote remdesivir, the drug has

come with mixed outcomes and a high cost. The drug lacks a “demonstrated survival benefit,” and so new developments must be made [6]. Most recently, Louisiana congressman-elect Luke Letlow died at 41 years of age. He was taking remdesivir and corticosteroids. While his condition seemed to improve, the virus still proved fatal [7]. Chris Long, a Ph.D. student, returned to the hospital after being discharged due to pneumonia, fluid in the lungs, and low oxygen levels, despite intensive care efforts. Mr. Long is one of possibly hundreds of thousands of rehospitalizations [8]. Patients in our care have experienced the same worsening conditions even with remdesivir. Analogues like remdesivir have made patient care expensive, while lacking substantial resolution, which necessitates another visit to the hospital.

In March 2020, acyclovir was deemed invalid [9]. Since July 2020, our clinic has used acyclovir as a primary antiviral for COVID-19 treatment. Acyclovir is a nucleoside analogue used to treat herpes virus infections, which is selective to the herpes simplex enzyme thymidine kinase. The drug inhibits viral DNA polymerase through phosphorylation of the acyclovir compound [10]. Acyclovir has been an inexpensive, safe, and well tolerated alternative to treating mild-to-severe cases of COVID-19 for our hospitalized

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and non-hospitalized patients. The following cases lend support to this statement.

Clinical Presentation: Case 1

A 76-year-old African American female with a history of diabetes, hypertension, hyperlipidemia, hypothyroidism, osteoporosis, and acid reflux, was initially presented to an urgent care center on October 23, 2020 for symptoms of fever, chills, urine frequency, and fatigue for the past 3 days. The patient underwent nasal swab to test for COVID-19, which resulted NEGATIVE, so she was treated with oral acetaminophen, intramuscular ceftriaxone, and oral trimethoprim-sulfamethoxazole for presumed urinary tract infection. The patient came to our outpatient clinic on October 27 for follow-up care from the urgent care visit. The patient repeated testing with nasal swab, which resulted in SARS-CoV-2 NAA POSITIVE, so she was started on treatment of oral glucocorticoid and oral famciclovir (for a vesicular rash). She developed hypoxemia with O₂ saturation of low 80s with physical movement and was admitted to the hospital on October 30. While an inpatient, she was treated

with supplemental oxygen, oral bronchodilators, intravenous steroids, remdesivir, and intravenous antibiotics azithromycin and ceftriaxone. She was discharged from the hospital on November 11 with home oxygen therapy and resumption of previous home medications. The patient underwent routine labs with chest x-ray on November 12 **FIGURE 1a, FIGURE 1b and FIGURE 1c**. Oral acyclovir, a low dose of oral dexamethasone, famotidine, subcutaneous enoxaparin, and oral-inhaled glucocorticoid were initiated on November 13 **TABLE 1 and TABLE 2**.

Clinical Presentation: Case 2

A 33-year-old African American male healthcare worker with a history of obstructive sleep apnea on BIPAP, diabetes and hypertension presented to outpatient clinic on July 23, 2020, due to symptoms of weakness for several days and palpitations for the past week, intermittent anterior chest tightness for the past several days, low oxygen saturation of 89 s to 90 s, dyspnea on exertion, and dysgeusia/dysosmia for the past week. He mentioned that several people were out at work. The patient declined to go to the

FIGURE 1a. Chest radiograph prior to hospital admit. Right and left lower lobe infiltrates (Case 1).

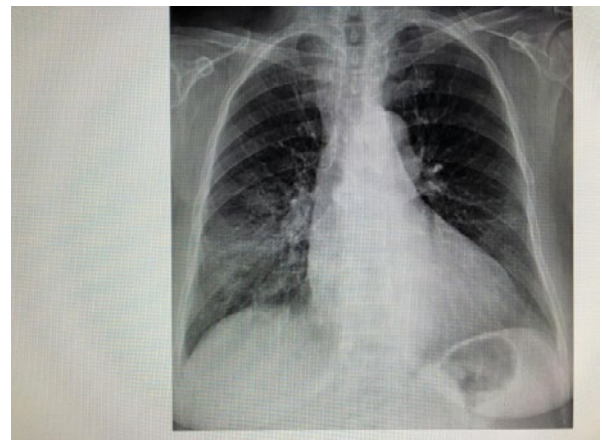


FIGURE 1b. Chest radiograph 1 day after hospital discharge and upon completing 10-day course of remdesivir and high-dose dexamethasone. Progressive infiltrative process with consolidation (Case 1).



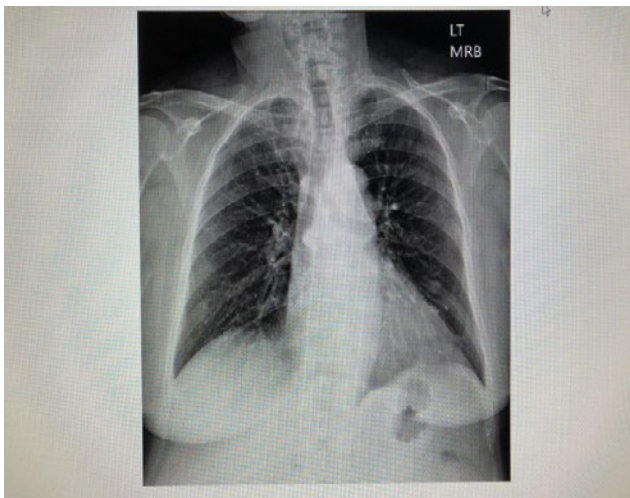


FIGURE 1c. Chest radiograph 6 weeks after treatment with acyclovir. Successful treatment of acyclovir, as noted by clearing of consolidation in bilateral lung fields (Case 1).

TABLE 1. Case 1 vital signs.

	BP	Pulse Ox	Temp	HR	RR	BMI
10/15/2020	126/70	97% at 21%	97.8	60	16	-
10/27/2020	-	92% at 21%	98.6	64	18	-
10/28/2020	-	90% at 21%	99.6	64	18	-
10/29/2020	-	90% at 21%	98.8	64	-	-
11/13/2020	-	97% at 32 %	98.4	61	18	-
11/18/2020	-	96% at 28%	97.8	76	16	-
11/25/2020	120/54	99% at 26%	98.6	56	16	-
12-09-2020	112/60	95% at 21%	97.3	68	16	28
12/30/2020	124/68	99% at 21%	97.7	58	16	-

Blood Pressure (BP) in mmHg, Pulse Oxygen (Pulse Ox) in fraction of inspired oxygen, Temperature (Temp) in Fahrenheit, Heart Rate (HR) in beats per minute, Respiration Rate (RR) in breaths per minute. Supplemental O₂ was discontinued on 12/24/2020.

TABLE 2. Case 1 lab results.

	Na	K	Cl	CO ₂	Glucose	BUN	CRT	HgbA1C
10/13/2020	143	4.1	107	24	128	19.6	0.99	6.5
10/27/2020	140	4.7	107	21	115	33.8	2	-
11/12/2020	142	3.8	105	27	164	18.3	0.71	-
11/17/2020	142	4.1	105	28	254	18.1	0.86	7.2
11/24/2020	139	4.6	104	27	172	18.9	0.89	-
12/08/2020	139	3.5	102	28	258	20.1	0.97	-
12/23/2020	140	3.5	106	25	213	16.2	0.82	-
	WBC	RBC	Hgb	Plt	CRP	ESR	D-dimer	egfr
10/13/2020	5.6	3.72	11.5	187	-	-	-	>60
10/27/2020	3.83	3.49	10.9	129	9.8	60	534	29
11/12/2020	7.61	3.18	9.9	281	1.14	98	1573	>60
11/17/2020	8.02	3.16	9.9	229	0.24	70	1800	>60
11/24/2020	5.7	3.37	10.5	210	0.1	40	934	>60
12/08/2020	6.37	3.47	11.1	200	0.11	20	592	>60
12/23/2020	6.6	3.5	11.3	200	0.18	15	457	>60

Sodium (Na) in mmol/L, Potassium (K) in mmol/L, Chloride (Cl) in mmol/L, CO₂ in mmol/L, Glucose in mg/dL, Blood Urea Nitrogen (BUN) in mg/dL, Creatinine (CRT) in mg/dL, Hemoglobin A1C (HgbA1C), White Blood Cell count (WBC) in thousand/ul, Red Blood Cell count (RBC) in million/ul, Hemoglobin (Hgb) in g/dl, Platelet count (Plt) in thousand/ul, C-Reactive Protein (CRP) in mg/dL, Erythrocyte Sedimentation Rate (ESR), Estimated Glomerular Filtration Rate (egfr)

emergency room for evaluation due to being the provider and caretaker of his young children. On physical exam, the patient was found to be lethargic and dyspneic when walking

approximately 30 feet and febrile with a temperature of 100. Patient self-reported oxygen saturation of 60's to 70's on room air. He had fair-to-poor air movement on

auscultation of the chest. The patient underwent a nasal swab, which resulted in SARS-CoV-2 not being detected **FIGURE 2a and FIGURE 2b**. This prompted an initial treatment of dexamethasone, azithromycin, and acyclovir. In a follow-up visit 5 days later, the patient reported no fever for the past 48 hours, but there was nausea development, for which famotidine was initiated. Sucralfate was added for development of oral ulcers on August 20. SARS-CoV-2 was detected in patient on August 19 *via* serologic finding of SARS-CoV-2 IgG and IgM antibodies **TABLE 3 and TABLE 4**.

Patient self-reported pulse oxygen of 60s-70s in supine position during first week of infection.

Clinical Presentation: Case 3

A 68-year-old female with a history of leiomyosarcoma of uterus, chronic arthritic pain, hypothyroidism, hyperlipidemia, diabetes, hypertension, gastric bypass, and end-stage renal failure with recent left brachiocephalic vein fistula placement on July 14, 2020 for initiation of hemodialysis presented to urgent

care on September 14, 2020 due to symptoms of fever and weakness for the past 2-3 days. Patient reported her daughters to be positive for COVID-19, and her brother had died on October 17, 2020. However, the patient and her family decided to go to local ER due to symptoms of shortness of breath. Their test results from urgent care displayed positivity of COVID-19. On admission to the hospital, the patient was found to be hypoxic with an O₂ saturation of 88%, and a chest x-ray revealed bilateral infiltrates, so the patient was started on dexamethasone, ceftriaxone, oral inhalers (Atrovent, Pulmicort), and azithromycin intravenously **FIGURE 3a and FIGURE 3b**. On day 2 at the hospital, oral acyclovir was initiated. Hemodialysis was initiated on hospital day 5, which the patient tolerated well **TABLE 5 and TABLE 6**.

Clinical Presentation: Case 4

A 68-year-old female with a history of hypertension, hyperlipidemia and herpes zoster was presented to our outpatient clinic

FIGURE 2a. Chest radiograph at initial diagnosis of COVID-19 pneumonia with bilateral infiltrates and early consolidation (Case 2).

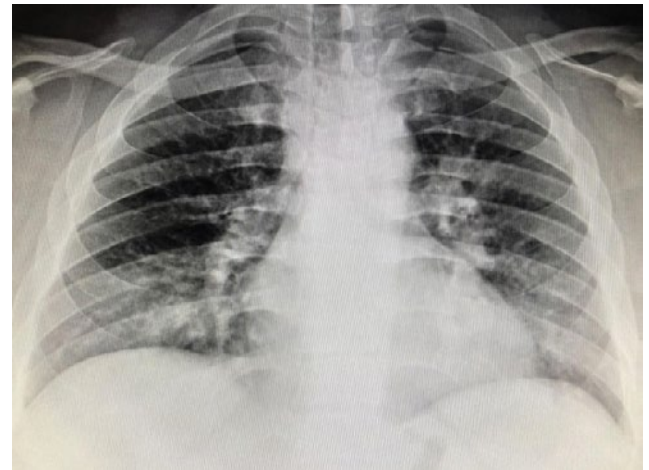


FIGURE 2b. Chest radiograph 5 weeks after treatment with acyclovir. Improvement in infiltrative and consolidation processes at bilateral lung fields (Case 2).



TABLE 3. Case 2 vital signs.

	BP	Pulse Ox	Temp	HR	RR	BMI
5/18/2020	102/60	98% at 21%	97.2	80	16	>60
7/23/2020	-	96% at 21%	100.1	85	16	-
7/28/2020	-	96% at 21%	98	65	20	-
08/04/2020	-	97% at 21%	98	76	18	-
8/19/2020	-	96% at 21%	97	84	16	-
09/02/2020	132/90	97% at 21%	98	75	16	-

Blood Pressure (BP) in mmHg, Pulse Oxygen (Pulse Ox) in fraction of inspired oxygen, Temperature (Temp) in Fahrenheit, Heart Rate (HR) in beats per minute, Respiration Rate (RR) in breaths per minute

TABLE 4. Case 2 lab results.

	Na	K	Cl	CO ₂	Glucose	BUN	CRT	HgbA1C
05/12/2020	-	-	-	-	-	-	-	6
7/23/2020	140	3.85	106	26	92	12.49	0.8	-
08/03/2020	139	4.19	102	27	230	16.45	0.84	-
8/17/2020	140	4.34	104	26	282	19.91	0.98	-
11/10/2020	141	3.7	103	28	139	11.97	0.74	7.4
	WBC	RBC	Hgb	Plt	CRP	ESR	D-dimer	egfr
7/23/2020	5.39	5.33	13.9	202	2.1	13	242	>60
08/03/2020	20.97	5.47	14	338	2.05	12	226	>60
8/17/2020	13.47	5.2	13.5	190	-	-	-	>60
11/10/2020	9.33	5	13.1	245	-	-	-	>60

Sodium (Na) in mmol/L, Potassium (K) in mmol/L, Chloride (Cl) in mmol/L, CO₂ in mmol/L, Glucose in mg/dL, Blood Urea Nitrogen (BUN) in mg/dL, Creatinine (CRT) in mg/dL, Hemoglobin A1C (HgbA1C), White Blood Cell count (WBC) in thousand/ul, Red Blood Cell count (RBC) in million/ul, Hemoglobin (Hgb) in g/dl, Platelet count (Plt) in thousand/ul, C-Reactive Protein (CRP) in mg/dL, Erythrocyte Sedimentation Rate (ESR), Estimated Glomerular Filtration Rate (egfr)



FIGURE 3a. Chest radiograph on admission to hospital. Bilateral infiltrates with consolidation (Case 3).



FIGURE 3b. Chest radiograph 1 month after treatment with acyclovir. Bilateral clearing of infiltrates and consolidation (Case 3).

TABLE 5. Case 3 vital signs.

	BP	Pulse Ox	Temp	HR	RR	BMI
8/20/2020	136/76	99% at 21%	96.9	60	16	32.9
9/17/2020	132/91	88% at 21%	99.2	87	22	-
9/17/2020	144/63	90% at 32%	99.2	83	24	-
9/18/2020	163/75	93% at 36%	98.7	83	19	-
9/22/2020	137/66	93% at 28%	98.4	84	18	-
9/24/2020	159/71	97% at 21%	98.7	66	20	-
9/26/2020	128/59	96% at 21%	99.2	60	16	-
9/27/2020	126/62	99% at 21%	99.4	78	20	-
9/30/2020	-	95% at 21%	98.2	68	16	-
10/14/2020	-	95% at 21%	98.2	68	16	-
10/21/2020	-	98% at 21%	97.9	63	16	-
12/07/2020	123/80	100% at 21%	97.6	67	16	-

Blood Pressure (BP) in mmHg, Pulse Oxygen (Pulse Ox) in fraction of inspired oxygen, Temperature (Temp) in Fahrenheit, Heart Rate (HR) in beats per minute, Respiration Rate (RR) in breaths per minute. On 9/17/2020, patient required supplemental oxygen.

TABLE 6. Case 3 lab results.

	Na	K	Cl	CO ₂	Glucose	BUN	CRT	HgbA1C
8/18/2020	139	4.42	106	21	114	62	3.46	6.6
9/17/2020	138	4.47	110	15	195	60.31	5.47	-
9/18/2020	139	5.06	111	14	183	65.49	5.98	-
9/20/2020	137	5.1	106	18	219	93.22	6.98	-
9/21/2020	137	5.13	104	16	217	193.85	7.68	-
9/24/2020	138	4.59	199	28	128	56.09	5.31	-
9/26/2020	137	4.2	101	25	96	47.16	4.84	-
10/01/2020	137	4.3	98	26	113	42	4.43	-
11/25/2020	139	3.3	101	29	95	18.68	3.02	5.6
	WBC	RBC	Hgb	Plt	CRP	ESR	D-dimer	egfr
8/18/2020	5.04	3.15	9.2	232	-	-	-	16
9/17/2020	6.61	3.66	10.9	233	-	80	-	10
9/18/2020	6.19	4.06	12.1	257	11.38	-	529	8
9/20/2020	9.71	3.64	10.7	31.5	3.93	94	442	7
9/21/2020	10.28	4.11	11.8	337	-	-	-	6
9/24/2020	-	-	-	-	1.137	67	2260	10
9/26/2020	10.61	3.18	9.3	261	0.677	50	1862	11
10/01/2020	7.1	2.93	8.7	349	-	-	-	11
11/25/2020	5.91	3.15	9.6	233	0.05	48	543	18

Sodium (Na) in mmol/L, Potassium (K) in mmol/L, Chloride (Cl) in mmol/L, CO₂ in mmol/L, Glucose in mg/dL, Blood Urea Nitrogen (BUN) in mg/dL, Creatinine (CRT) in mg/dL, Hemoglobin A1C (HgbA1C), White Blood Cell count (WBC) in thousand/ul, Red Blood Cell count (RBC) in million/ul, Hemoglobin (Hgb) in g/dl, Platelet count (Plt) in thousand/ul, C-Reactive Protein (CRP) in mg/dL, Erythrocyte Sedimentation Rate (ESR), Estimated Glomerular Filtration Rate (egfr).

on January 30, 2020 with symptoms of left upper quadrant abdominal pain with nausea for the past few days. The physical exam revealed a possible mild enlargement of the spleen and tenderness on palpation. The patient underwent a CT scan, which revealed a spleen size of 12.5 cm, which is mildly increased compared to a scan from October 3, 2016. The patient returned for a follow-up visit on June 25, 2020, and she was found to have neutropenia, so she underwent an ultrasound imaging of her spleen.

The ultrasound revealed a spleen size of 14.8 cm. An extensive workup for splenomegaly revealed SARS-COV-2 IgG detected. An initial treatment of acyclovir, dexamethasone, famotidine, and oral steroid inhaler was given on October 1, 2020. A follow-up 6 weeks later revealed a spleen size of 13.2 cm, so the medication regimen was continued. A follow-up ultrasound on January 7, 2021 revealed the spleen size to be 11.9 cm, which is the upper end of normality **TABLE 7, TABLE 8 and TABLE 9.**

TABLE 7. Case 4 vital signs.

Vitals	BP	Pulse Ox	Temp	HR	RR	BMI
12/19/2019	126/72	99% at 21%	97.4	52	16	-
1/30/2020	126/72	100% at 21%	97.6	62	16	29.8
02/11/2020	130/66	99% at 21%	97.7	62	16	-
3/24/2020	120/70	98% at 21%	96.9	75	16	-
6/25/2020	100/60	98% at 21%	97.4	57	16	-
7/28/2020	140/70	98% at 21%	97.2	59	16	-
08/06/2020	-	97% at 21%	97.6	64	16	-
08/09/2020	110/60	100% at 21%	97	58	16	-
10/01/2020	110/60	97% at 21%	97.4	57	16	-
10/26/2020	104/68	99% at 21%	97.3	52	16	-
12/03/2020	110/70	98% at 21%	96.4	66	16	-
12/14/2020	114/62	99% at 21%	96.4	64	16	-
12/23/2020	118/74	98% at 21%	98.2	81	18	-

Blood Pressure (BP) in mmHg, Pulse Oxygen (Pulse Ox) in fraction of inspired oxygen, Temperature (Temp) in Fahrenheit, Heart Rate (HR) in beats per minute, Respiration Rate (RR) in breaths per minute.

TABLE 8. Case 4 lab results.

	Na	K	Cl	CO ₂	Glucose	BUN	CRT	egfr
12/16/2019	143	4.27	109	27	103	14.83	0.78	-
3/17/2020	141	4.61	110	23	106	22.54	0.78	-
6/18/2020	141	4.17	108	25	108	16.82	0.82	-
7/14/2020	144	4.45	112	25	87	13.46	0.83	-
7/29/2020	141	4.53	109	25	118	16.38	0.8	-
9/15/2020	142	3.9	111	23	119	17.92	0.84	-
11/24/2020	141	4.1	107	26	104	15.39	0.7	-
12/23/2020	139	4.1	106	24	113	9.55	0.72	-
	WBC	RBC	Hgb	Plt	CRP	ESR	D-dimer	egfr
12/16/2019	3.8	4.83	14.5	162	-	-	-	>60
3/17/2020	3.45	4.46	13.5	158	-	-	-	>60
6/18/2020	2.3	4.52	14.2	123	-	-	-	>60
7/14/2020	4.39	4.52	13.3	178	<0.5	27	-	>60
7/29/2020	3.49	4.52	13.8	162	-	-	262	>60
9/15/2020	3.16	4.38	13.3	145	-	-	-	>60
11/24/2020	3.14	4.68	14.6	162	0.19	12	238	>60

Sodium (Na) in mmol/L, Potassium (K) in mmol/L, Chloride (Cl) in mmol/L, CO₂ in mmol/L, Glucose in mg/dL, Blood Urea Nitrogen (BUN) in mg/dL, Creatinine (CRT) in mg/dL, Hemoglobin A1C (HgbA1C), White Blood Cell count (WBC) in thousand/ul, Red Blood Cell count (RBC) in million/ul, Hemoglobin (Hgb) in g/dl, Platelet count (Plt) in thousand/ul, C-Reactive Protein (CRP) in mg/dL, Erythrocyte Sedimentation Rate (ESR), Estimated Glomerular Filtration Rate (egfr)

Discussion

COVID-19 has been a stomach-churning, catastrophic event for all involved in the care of patients since the start of this pandemic early in the year of 2020. To date, we have the use of remdesivir as the antiviral drug to treat the viral effects on the human body from a SARS-CoV-2 infection. Additional drugs utilized have been convalescent plasma and immunoglobulin products. Monoclonal antibodies have been recently added to a short list of approved therapeutics for the treatment of patients with SARS-CoV-2 who are at elevated risk for hospitalization. Corticosteroids, specifically 6 mg of dexamethasone daily for 10 days has

been recommended for mechanically ventilated patients for those requiring supplemental oxygen therapy [11]. Various intravenous and oral antibacterial compounds have become standard prophylaxis treatments for hospitalized patients.

Despite current efforts, the medical establishment has not been able to overturn the mortality and morbidity from SARS-CoV-2. As evident by chest x-ray findings in set of **FIGURES 1-3**, we conclude that acyclovir played a key role in resolving pulmonary findings in the cases 1-3. The 4 cases presented above were treated with oral acyclovir, famotidine, and dexamethasone. Cases 1 and 3 were also given enoxaparin and orally inhaled steroids. Based on these case

presentations and 34 other patients treated with acyclovir, we believe that acyclovir may have some neutralizing effect on SARS-CoV-2 infection whether given early within 5-7 days of exposure or later in the disease course of up to 3 weeks (case 1). Cases 2 and 3 were possibly halted from progression to ARDS with oral acyclovir. Case 4 reveals the possible effect of acyclovir on organs other than the lungs. Most recently, 1 hospitalized patient with a history of labile neutropenia on long-term valacyclovir tolerated intravenous acyclovir.

Conclusion

We recommend going back to basic science to assess the degree of viral neutralization of acyclovir on SARS-CoV-2. We propose further study on the use of acyclovir (oral and intravenous) in conjunction with dexamethasone, famotidine, oral inhaled corticosteroids (as needed) and enoxaparin or other heparin products (as needed) for anticoagulation in both hospitalized and non-hospitalized patients.

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