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Case Report

Rapid Recovery in COVID-19 Patients with Chronic Hepatitis B Virus Infection Treated with Tenofovir Disoproxil Fumarate

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic continues worldwide. We report here two cases of chronic hepatitis B patients with acute respiratory syndrome coronavirus 2 infection treated with tenofovir disoproxil fumarate who demonstrated a favorable outcome. This report adds some evidence that concurrent HBV infection may not worsen COVID-19 infection and tenofovir disoproxil fumarate treatment may have partial positive effect on COVID-19 rapid recovery.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues worldwide. As of on February 2, 2021, there are 102,942,987 confirmed cases and 2,232,233 deaths according to a report from the World Health Organization (WHO).

COVID-19 patients present with fever, cough, and dyspnea, with computed tomography scan displaying ground glass opacities (GGO) and bilateral lung infiltrates.[1] The critical factors associated with the severity and mortality in COVID-19 patients were considered to be advanced age and underlying diseases, such as diabetes and cardiovascular and cerebrovascular diseases.

The WHO has estimated that 257 million people had chronic hepatitis B infection by 2015, and many of them have progressed to end-stage liver disease. Data from two large cohorts showed that 0.1–2.1% of COVID-19 patients have hepatitis B virus (HBV) coinfection;[1,2] however, the clinical evidence of SARS-CoV-2 and HBV coinfection on the severity and outcome of COVID-19 is very limited. Most studies have illustrated that HBV coinfection does not aggravate the disease, while a few studies reported adverse results.[3,4] Here, we report two cases of chronic hepatitis B (CHB) patients with SARS-CoV-2 infection treated with tenofovir disoproxil fumarate (TDF) who demonstrated a favorable outcome.

Case report

Case 1

A 76 year-old male who lived in Wuhan developed a fever on February 6, 2020, with a maximum body temperature of 39.5°C, accompanied by chills, cough, chest distress and fatigue. He first presented to the fever clinic on February 11 because the symptoms had not self-resolved. Admission test results showed that his white blood cell (WBC) count was normal, while his lymphocyte count was low (decreased to 1.0×10^9/L); the chest computed tomography scan demonstrated typical viral pneumonia features. He was prescribed ceftezole, ribavirin, and lianhua qingwen capsules for 2 days. On February 13, his oropharyngeal swab test for SARS-CoV-2 RNA was positive, and he was admitted to the isolation ward. Based on his Wuhan resident history, fever symptoms, SARS-CoV-2 nucleic acid test result, and the computed tomography report, the patient was diagnosed with COVID-19.

The patient had a history of bronchiectasis and chronic obstructive pulmonary disease (COPD) for more than 30 years, type 2 diabetes for 15 years, and CHB for more than 20 years. He had undergone successive treatment with lamivudine (LAM), then LAM plus adefovir dipivoxil (ADV) for more than 10 years, and then switched to TDF within the last 2 years. Serologic tests showed that he was HBV DNA-negative, and hepatitis B surface antigen-, hepatitis B e antibody-, and hepatitis B core antibody-positive.

Keywords: COVID-19; SARS-CoV-2; Chronic hepatitis B; Tenofovir disoproxil fumarate.

Abbreviations: ADV, adefovir dipivoxil; ALT, alanine aminotransferase; ANPs, acyclic nucleoside phosphonates; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; GGO, ground glass opacities; HBV, hepatitis B virus; hsCRP, hypersensitivity CRP; IFN, interferon; IL, interleukin; ISGs, interferon-stimulated genes; LAM, lamivudine; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; Myo, myoglobin; RdRp, RNA complex RNA polymerase; SARS-CoV-2, acute respiratory syndrome coronavirus 2; TDF, tenofovir disoproxil fumarate; TNF, tumor necrosis factor; WBC, white blood cell; WHO, World Health Organization.

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On admission, the patient complained of dyspnea and chest distress after exercise. He showed a pulse of 106 beats per minute and oxygen saturation of 92% while breathing ambient air. After administration of oxygen therapy, delivered by nasal cannula at 3 L per minute, his oxygen saturation values increased up to 97%.

After admission, the patient's lymphocyte count was decreased to 0.89×10^9/L and the D-dimer level was elevated to 4.52 mg/L. Alanine aminotransferase (ALT) level was 60 U/L and aspartate aminotransferase (AST) level was 135 U/L. The levels of myocardial enzymes, including creatine kinase (CK), lactate dehydrogenase (commonly referred to as LDH), and myoglobin (referred to as Myo), were elevated (CK of >1,300 U/L, LDH of 497 U/L, and Myo of 287.7 μg/L). C-reactive protein (commonly referred to as CRP) levels were increased significantly (to 168 mg/L), as was erythrocyte sedimentation rate (commonly referred to as ESR) (to 61 mm/h); procalcitonin was normal. Cytokine test indicated that the level of interleukin (IL)-6 was elevated (to 45.84 ng/mL) (Table 1). The levels of lymphocyte subsets, immunoglobulin, and complement were normal. Computed tomography scan of the lungs and the abdomen demonstrated that scattered GGO were present in both lungs, especially in the subpleural area; dense strips were seen in the middle lobe of the right lung and the lingula of the left lung. Emphysema of bilateral lungs and atherosclerosis of coronary and aortic vessels were observed. Liver cirrhosis was suspected in this patient, due to widening of liver fissures and atrophy of the left lobe of the liver (Fig. 1A, D).

The patient had moderate fever in the first 4 days after admission, with a maximum body temperature of 38.5°C, which was controlled by physical cooling. The patient's symptom of chest distress and dyspnea lasted for 6 days, with the oxygen saturation remaining above 95% on nasal oxygen delivery at 3 L/min. The patient demonstrated intermittent cough and gradual improvement. He was re-tested for SARS-CoV-2 nucleic acid on February 20 and February 22 respectively, and the results were both negative. His chest computed tomography scans on February 22 and February 28 indicated that the lesion was gradually decreasing in size (Fig, 1B, C). Laboratory results demonstrated an improvement in lymphocyte count, ALT, AST, CK, hypersensitivity CRP (referred to as hsCRP), IL-6 (Table 1), and SARS-CoV-2-IgM; IgG test on February 29 was positive. On March 2, the patient was discharged after 18 days of hospitalization and was recommended self-isolation for at least 14 days.

In hospital, he was administered arbidol (200 mg three times daily, oral) as antiviral therapy, ceftizoxime (2 g every 8 h, intravenous) to control lung infection, vitamin C (2 g once daily, intravenous) as antioxidant, and magnesium isoglycyrrhizinate (150 mg once daily, intravenous) to improve liver function. He was also administered acarbose (50 mg three times daily, oral) and gliclazide (60 mg once daily, oral) to control blood glucose level, TDF (300 mg once daily, oral) as an anti-HBV medicine, and traditional Chinese medicine No. 2 according to the Guidelines of the Diagnosis and Treatment of COVID-19 (version 5) published by the National Health Commission of China.

Case 2

A 32 year-old male community worker in Wuhan, who had close contact with COVID-19 patients for 3 weeks due to work requirements, was required by the government to visit a fever clinic to rule out SARS-CoV-2 infection on February 13. He did not exhibit any symptoms of fever, cough, or fatigue. His computed tomography scan showed single small GGO under the pleura in the middle lobe of the right lung (Fig. 1E). Counts for WBC and lymphocytes, and tests for liver function, kidney function, and hsCRP on February 14 were normal. SARS-CoV-2 nucleic acid and IgM tests for mycoplasma pneumoniae, chlamydia pneumoniae, syncytial virus, adenovirus, and coxsackie virus were negative. The SARS-CoV-2 nucleic acid was rechecked on February 15, and the results suggested that the 2019-nCoV open reading coding frame lab (nCoVORFlab) was positive and 2019-nCoV-N gene was negative. Thus, the patient was classified with asymptomatic COVID-19 infection and was admitted to the mobile cabin hospital for isolation.

The patient had received hepatitis B e antigen-positive CHB diagnosis decades prior. He had showed elevated ALT and AST, jaundice, and HBV DNA up to 10^7 IU/mL the past June, when computed tomography of the abdomen had also suggested fatty liver. He underwent antiviral treatment with TDF (300 mg once daily, oral) last June and his HBV DNA load had dropped to less than 100 IU/mL last November. After that, he continued to take TDF daily.

After admission, the patient was administered arbidol (200 mg three times daily, oral) as antiviral therapy, moxifloxacin (400 mg once daily, oral) to prevent secondary infection, lianhua qingwen capsules (4 capsules three times daily, oral) and traditional Chinese medicine No. 2 (twice daily, oral). His SARS-CoV-2 nucleic acid tests on February 29, March 1, and March 2 were negative and lung computed tomography performed on March 2 demonstrated no obvious abnormalities (Fig. 1F). He was discharged on March 3 and recommended self-isolation for at least 14 days.

Discussion

The two cases we report herein involve CHB patients taking TDF with concurrent COVID-19 infections. Case 1 was an elderly male with multiple underlying illnesses, and the patient had an immunocompromised status. On admission, the low oxygen saturation values and significantly abnormal laboratory results classified this patient as a severe case, while the lung lesions on computed tomography were relatively less severe. After 7 days of hospitalization, his SARS-CoV-2 nucleic acid had rapidly changed to negative, with an improvement in laboratory results and lung lesions. Prior to discharge, his SARS-CoV-2-IgM and IgG statuses were confirmed to be positive as well. As an immunocompromised patient, his progression of COVID-19 was not very severe and he achieved a relatively quick recovery. Case 2 was an asymptomatic infection diagnosed by positive SARS-CoV-2 nucleic acid and single small GGO on lung computed tomography. His SARS-CoV-2 nucleic acid results changed to negative and the GGO in lung computed tomography disappeared after treatment, while laboratory results, such as those for lymphocyte count, liver and renal function, and hsCRP, were normal throughout the course of his illness. Although the patient had underlying liver disease, his condition was very mild.

TDF, a nucleotide reverse transcriptase inhibitor recommended as one of the most potent drugs to suppress HBV and a first-line anti-human immunodeficiency virus drug by the WHO, has been well-documented to have a role in regulating immunity. Studies have shown that after 12 months of TDF treatment, the frequency and function of natural killer (CD56+CD3-) cells in CHB patients were significantly increased compared with baseline,[5] suggesting that TDF might contribute to the activation of natural killer cells. In addition, studies have found that the nucleotide analogues (TDF and ADV) might have an effect on inducing interferon (IFN)-λ3 compared to nucleoside analogs (LAM and entecavir) both *in vitro* and *in vivo*.[6] IFN-λ3 can induce phosphorylation and up-regulate the expression of interferon-stimulated genes (commonly referred to as ISGs)

Table 1. Symptoms, treatments and laboratory results of case 1

Date	2.13	2.14	2.15	2.16	2.17	2.18	2.19	2.20	2.21	2.22	2.23	2.24	2.25	2.26	2.27	2.28	2.29	3.1	3.2
Symptom																			
Fever, °C	38.1	38.3	38.5	37.7															
Dyspnea	√	√	√	√	√	√													
Cough	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Treatment																			
Ceftizoxime		√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Arbidol		√	√	√	√	√	√	√	√	√	√								
Vitamin C		√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Magnesium isoglycyrrhizinate		√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Chinese herbal											√	√	√	√	√	√	√	√	√
Acarbose and gliclazide										√	√	√	√	√	√	√	√	√	√
TDF	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Oxygen therapy at 3 L/m	√	√	√	√	√	√	√	√	√	√	√	√	√	√					
Laboratory results																			
WBC count as $\times 10^9$/L	–	7.68	–	–	–	–	–	5.74	–	–	–	7.04	–	5.88	–	–	–	–	–
Neutrophil count as $\times 10^9$/L	–	6.31	–	–	–	–	–	4.31	–	–	–	5.04	–	4.14	–	–	–	–	–
Lymphocyte count as $\times 10^9$/L	–	0.89*	–	–	–	–	–	0.76*	–	–	–	1.28	–	1.11	–	–	–	–	–
Albumin	–	31.9*	–	–	–	–	–	32.7*	–	–	–	–	–	–	–	–	–	–	–
Globulin	–	30.3#	–	–	–	–	–	32.7#	–	–	–	–	–	–	–	–	–	–	–
ALT in U/L	–	60#	–	–	–	–	–	49#	–	–	–	–	–	–	–	–	–	–	–
AST in U/L	–	135#	–	–	–	–	–	37	–	–	–	–	–	–	–	–	–	–	–
CK in U/L	–	>1300#	–	–	–	–	–	107	–	–	–	–	–	–	–	–	–	–	–
LDH in U/L	–	497#	–	–	–	–	–	255#	–	–	–	–	–	–	–	–	–	–	–
Myo in μg/L	–	287.7#	–	–	–	–	–	–	–	–	–	28.3	–	–	–	–	–	–	–
CRP in mg/L	–	168#	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
hsCRP in mg/L	–	–	–	–	–	–	–	28.86#	–	–	–	0.95	–	5.95#	–	–	–	–	–
Procalcitonin in μg/L	–	<0.13	–	–	–	–	–	0.07	–	–	–	–	–	–	–	–	–	–	–
ESR in mm/h	–	–	–	–	–	–	–	61#	–	–	–	–	–	60#	–	–	–	–	–
IL-2 in mg/L	–	2.88	–	–	–	–	–	–	–	–	–	–	–	5.22#	–	–	–	–	–
IL-4 in mg/L	–	1.95	–	–	–	–	–	–	–	–	–	–	–	9.75#	–	–	–	–	–
IL-6 in mg/L	–	45.48#	–	–	–	–	–	–	–	–	–	–	–	10.4#	–	–	–	–	–
IL-10 in mg/L	–	3.98	–	–	–	–	–	–	–	–	–	–	–	6.64#	–	–	–	–	–
IFN-α in mg/L	–	2.96	–	–	–	–	–	–	–	–	–	–	–	4.79	–	–	–	–	–
IFN-γ in mg/L	–	4.9	–	–	–	–	–	–	–	–	–	–	–	5.53	–	–	–	–	–

√ represents the duration of symptoms and treatments. * represents values below limits. # represents values above limits.

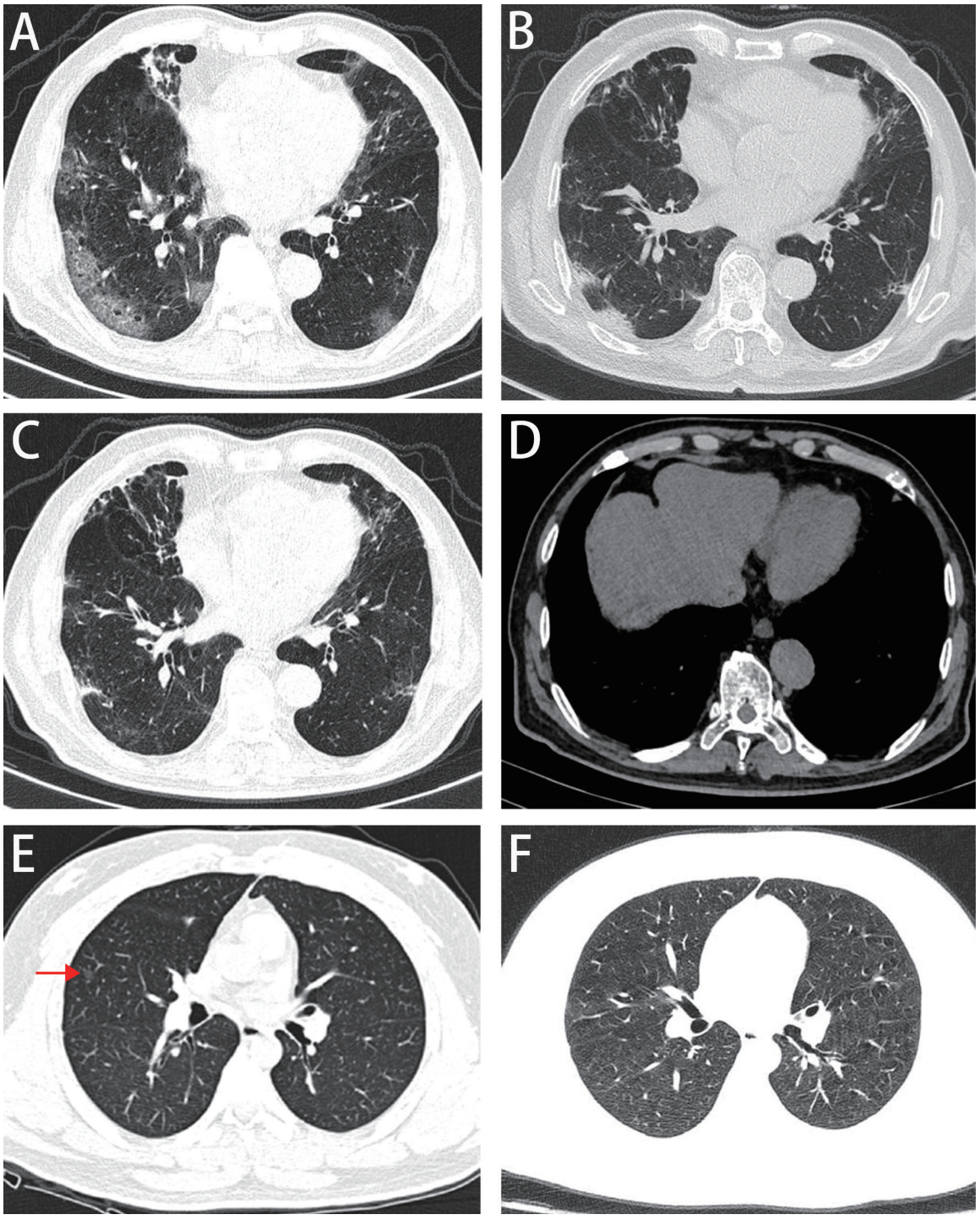

Fig. 1. Lung and abdomen CT scans of case 1 and case 2. (A–D) Case 1: Lung CT scans on February 14 (A), February 22 (B), and February 28 (C), and abdomen CT scan on February 14 (D). (E–F) Case 2: Lung CT scans on February 13 (E) and March 2 (F). CT, computed tomography.

and produce some antiviral proteins to exert antiviral effects.[7] Studies have revealed that cellular metabolites of acyclic nucleoside phosphonates (commonly referred to as ANPs, including TDF and ADV) can inhibit lipopolysaccharide (commonly referred to as LPS)-mediated production of IL-10 and, thus, induce the production of IL-12p70 and tumor necrosis factor-α (commonly known as TNF-α) in a dose-dependent manner, and plays an immunoregulatory role in HBV patients, with antiviral and antihepatocellular carcinoma properties.[8]

A recent study showed that tenofovir binds tightly to the SARS-CoV RNA complex RNA polymerase (commonly known as RdRp) and terminates the RNA synthesis catalyzed by SARS-CoV-2 RdRp,[9] providing the molecular basis

for tenofovir to be considered as a potential therapeutic for COVID-19. In addition, a large-scale cohort study conducted in Spain found that the incidence of SARS-CoV-2 infection in patients with CHB treated with tenofovir decreased (0.4%, 8/1,764), which indirectly reflects TDF's positive effect on the resistance to SARS-CoV-2.[3]

Lastly, patients with COVID-19 often exhibit immune system dysfunction, such as lymphopenia, decreased number of CD4+ T cells, and abnormal levels of cytokines (including cytokine storms), and this might be an indicator related to severity and mortality of the disease. Immunocompromised patients, such as the elderly, and patients with other comorbidities, might be more susceptible to SARS-CoV-2. We speculated that according to our SARS-CoV-2-infected patients with CHB treated with TDF; in addition to inhibiting the SARS-CoV-2 RdRp, the TDF medication might also improve the immune functions of these patients by restoring the activity levels of T cells and natural killer cells, inducing IFN-λ3 production, inhibiting IL-10 secretion, and inducing IL-12 production, thereby suppressing a cytokine storm caused by SARS-CoV-2. It might also have certain antiviral properties. Ultimately, TDF might alleviate the symptoms and shorten the course of COVID-19 in patients with CHB.

In conclusion, our observation from these two cases provided more evidence that concurrent HBV infection may not worsen COVID-19 infection and TDF treatment may partially contribute to a more rapid recovery from COVID-19. Large-cohort clinical studies are needed to subsequently explore the effects of HBV and TDF treatment on the clinical outcomes of COVID-19.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (XZ), acquisition of data (XC), analysis and interpretation of data (DY, XZ), drafting of the manuscript (XC), critical revision of the manuscript for important intellectual content (DL, XZ), administrative, technical, or material support, study supervision (XZ).

Data sharing statement

All data are available upon request.

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