Case Report

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TANAFFOS

Could Remdesivir be used in the Presence of Elevated Liver Enzymes Secondary to COVID-19 Infection in Children? A Case Report

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Abnormal liver biochemistry values are not unusual in patients with COVID-19 infection. Remdesivir is one of the drugs that is currently used for the treatment of COVID-19 infection, but one of the side effects of this drug is hepatotoxicity. According to the local guidelines of the Iranian Ministry of Health, remdesivir should be monitored serially before, during, and at the end of treatment, and withheld if liver function tests (LFTs) rise more than 5 times the upper limit of normal. Herein, we report a pediatric case of severe acute respiratory syndrome (SARS) coronavirus (CoV)-2(SARS-CoV-2) pneumonia and elevated liver enzymes who was treated with remdesivir despite the first LFTs of more than five times the upper limit of normal. The LFTs improved during treatment and reached near-normal values at the time of hospital discharge. Indications of remdesivir usage in the setting of elevated liver enzymes due to SARS-CoV-2 infection remain to be defined.

Keywords: COVID-19; Hepatitis; Liver enzyme; Pandemics; Remdesivir

INTRODUCTION

Currently, the global COVID-19 pandemic is ongoing. In 2021, Iran emerged from the fifth peak of COVID-19, mainly driven by the delta variant. Many children were affected, and despite previous peaks, the prominent presentation in this population was pneumonia. Compared with earlier peaks of the pandemic, the manifestations were more severe.

Abnormal liver biochemistry values are not unusual in patients with COVID-19 (1). While more severe cases are more probably associated with elevated liver enzymes, a safe, effective, and approved drug in this situation is not yet available in the pediatric field.

Herein, we report a 6- year- old female with pneumonia and elevated liver enzymes secondary to SARS-CoV-2 infection. She was treated with remdesivir despite elevated LFTs that were more than five times the upper limit of normal. The LFTs improved during treatment and reached near-normal values at hospital discharge. The consent form was signed by the patient's guardians for reporting the case.

CASE SUMMARIES

A previously healthy 6-year-old female with seven days of fever, cough, and fatigue was admitted to our hospital with a positive PCR test for COVID-19 infection.

Her parents and grandfather and mother were serially infected with the COVID-19 virus before she became symptomatic. She had no diarrhea but a sore throat, nausea, and abdominal pain. On admission, she was febrile and tachypneic (33/min). Blood pressure and pulse rate were 90/65 mmHg and 115/min, respectively. The oxygen saturation (SpO_2) was 86% on room air and increased to 92% with supplemental oxygen at 5 L/min administered via nasal cannula.

There were no cutaneous manifestations, jaundice, right upper quadrant tenderness, hepatomegaly, or splenomegaly. The patient did not have any history of taking medicine around her disease onset.

The first chest CT is shown in Figure 1, showing scattered subpleural and peribronchovascular mixed ground-glass and consolidated nodular opacities in both lower lobes and the left upper lobe, in addition to lobar consolidation in the right middle lobe (RML). The laboratory data are shown in Table 1. On admission, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values were 286 and 217 U/L, respectively. Abdominal sonogram was normal.

She was treated with remdesivir 5mg/kg on the first day and 2.5mg/kg from the 2nd to the fifth day of treatment.

Dexamethasone (0.15mg/kg/day) was also started simultaneously with Remdesivir. Fever subsided after 48 hours but started again on the 6th day of hospitalization. She was dependent on supplemental oxygen, and there was no reduction in oxygen demand. Meropenem was added with a probable impression of bacterial superinfection.

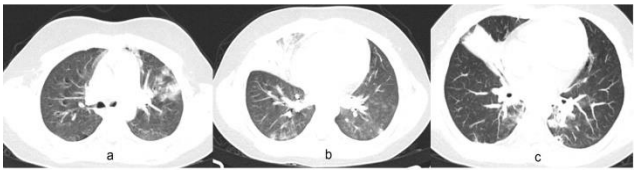

Figure 1. a. First chest CT scan: There are scattered subpleural and peribronchovascular mixed ground-glass and consolidated nodular opacities in both lower lobes and the left upper lobe. **b.** First chest CT scan: Lobar consolidation in the right middle lobe (RML) is also found. **c.** Second chest CT scan: Partial resolution of RML consolidation, decreased number and size of nodular opacities with development of vacuolar sign in some nodular opacities and parenchymal bands in basal segments of both lower lobes without parenchymal distortion.

Chest CT was repeated on the 6th day of treatment when the fever started again. The second chest CT is shown in Figure 1, displaying partial resolution of RML consolidation and decreased number and size of nodular opacities.

On day 8 of treatment, the patient's oxygen requirement decreased to 2–3 L/min of supplemental oxygen. Supplemental oxygen was discontinued on day 10 of hospitalization.

ALT and AST levels decreased during remdesivir therapy. This improvement continued throughout the patient's hospitalization, with liver enzyme levels approaching normal values at the time of discharge (Table 1).

She was discharged after 14 days of hospitalization, and one- and two-week follow-up visits revealed no complications.

Table1. Laboratory characteristics of the patient

	First day	Third day	Fifth day	Seventh day	Discharge day
D –Dimer (<200ng/ml)	<200	<200	200	200	<200
LDH (<615U/lit)	1533	-	-	637	360
CPK (20-180U/lit)	263	-	40	-	25
Ferritin (7-140ng/ml)	>800	2533	1978	1989	788
CRP (<10mg/L)	26	5.7	2.1	<1	<1
ESR (<20mm/h)	45	25	13	35	48
WBC (4000-10000/mm³)	4800	3700	10100	11600	11400
Platelet (150,000-450,000/mm³)	210,000	340,000	630,000	594,000	534,000
pro-BNP (<125pg/ml)	-	8.5	-	3.6	-
SGOT (5-40U/L)	286	102	25	27	27
SGPT (5-40U/L)	217	207	66	50	48

DISCUSSION

Iran was among the countries affected by the COVID-19 pandemic shortly after the first cases were reported in Wuhan, China, in December 2019. In 2021, Iran experienced its fifth wave of the COVID-19 pandemic, which predominantly affected children and young adults.

Unfortunately, at the time of writing this paper, there is still no proven effective drug against COVID-19 infection in pediatrics despite the fact that nearly three years have passed since the pandemic.

The U.S. Food and Drug Administration (FDA) approved the antiviral drug remdesivir under an Emergency Use Authorization (EUA) originally issued on May 1, 2020, for treatment of COVID-19 infection in adults and pediatric cases 12 years of age and older weighing ≥40 kilograms requiring hospitalization (2). According to the last update of the NIH guideline in December 2022, sufficient data and evidence either for or against the use of remdesivir in pediatrics<12 years of age are lacking (3). While there is insufficient evidence for using remdesivir in children younger than 12 years of age, we have been using it in Iran, similar to many countries, during this pandemic, secondary to the lack of any other effective and licensed drug in this age group.

One of the side effects of this drug is hepatotoxicity. It may be caused by direct toxicity, possibly due to inhibition of mitochondrial RNA polymerase (4). However, elevated LFTs seen in trials with remdesivir may be partially secondary to infection, rather than solely due to the remdesivir hepatotoxicity.

Therefore, according to the guidelines of the Iranian Ministry of Health, liver function tests (LFTs) should be monitored serially before, during, and at the end of treatment. Remdesivir should be withheld if LFT values exceed five times the upper limit of normal.

However, COVID-19 infection per se could raise liver enzymes to different degrees, similar to any other viral infection. Increased ALT and AST levels were first reported in patients infected with SARS-CoV-2 from Wuhan Jinyintan Hospital (5). However, the prevalence of abnormal LFTs on the initial presentation of COVID-19 is still undetermined (6).

The liver may also have some degree of damage in some cases infected with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) (7).

Liver involvement in patients with SARS-CoV-2 infection might be caused by direct infection of liver cells, since Angiotensin-converting enzyme 2 (ACE2) is expressed in both liver cells and bile duct cells (8), more highly expressed in cholangiocytes (59.7%) than hepatocytes (2.6%) (9). In addition, immune-mediated inflammation and hypoxia may also have some adverse effects on the function of hepatocytes, and secondarily, liver function tests (10,11).

Although there are a few reports of elevated liver enzymes even in asymptomatic cases of COVID-19 infection (12), it seems that more severe cases of COVID-19 infection may be more associated with elevated liver enzymes, and severe forms are known to increase LFTs. However, the elevation of aminotransferases is usually mild and associated with disease severity (12). Therefore, use of remdesivir may be more mandatory in situations of COVID-19 infection, which may be accompanied by hepatitis.

There is a case report by Sabers et al that showed the use of remdesivir in the case of hepatitis secondary to COVID-19, which not only did not worsen the hepatitis but also decreased the LFTs during improvement of COVID-19 infection (11).

As far as we are aware, this is the first report of elevated liver enzymes caused by COVID-19 infection, with LFTs more than five times the normal value, which was treated with remdesivir in the pediatric age group. The risks and benefits of remdesivir and the possibility of its use when LFTs are elevated at baseline remain to be defined.

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