

## Review Article

# Precautions Prior to Use of Interleukin Inhibitors for COVID-19 Infection - A Teachable Moment

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## Abstract

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has affected humans globally with cases in the US rising every day. Coronavirus Disease 2019 (COVID-19), the disease caused by SARS-CoV-2 has been reported to have multiple systemic manifestation, although primarily pulmonary but has been reported to have renal, cardiac, neurological and hepatic manifestation. Available evidence indicates that the most critical patients can develop a so-called cytokine storm, characterized by increased production of many cytokines which, in turn, sustain an aberrant systemic inflammatory response. Therapies aimed to halt hyper activation have been tried including tocilizumab and systemic steroids, which in recent studies have shown benefits. The feared complications of these drugs including hepatitis B reactivation should be kept in mind and proper screening should be done.

**Keywords:** COVID 19; SARS; Hepatitis B; IDT

## Case Presentation

A 55-year-old Vietnamese male (migrated to the US in 1983) with asymptomatic chronic hepatitis B infection presented with acute shortness of breath. Initial vitals: fever of 101 F, pulse 90/min, oxygen saturation 94% on 4 L oxygen *via*. nasal cannula. Initial physical exam: alert and awake in mild respiratory distress, chest: bibasilar crackles, rest of the physical exam was unremarkable. His SARS-CoV-2 PCR nasal swab was positive and he had elevated inflammatory markers including LDH, ferritin, CRP, fibrinogen and D-dimer. Chest X-ray showed bibasilar ground glass opacities consistent with multifocal viral pneumonia. Hospital stay was complicated by superimposed bacterial infection requiring broad-spectrum antibiotics and acute pulmonary embolism requiring systemic anticoagulation. Due to persistently elevated inflammatory markers and increased oxygen need he was started on systemic steroids, received a course of tocilizumab (IL-6 inhibitor), and convalescent plasma therapy. Fortunately, he did not require intubation and was discharged to acute rehab on oxygen via nasal cannula for functional optimization. His Liver Function Tests (LFT) continued to trend up as shown in (Table 1), and the hepatitis panel confirmed acute hepatitis B flare as shown in (Table 2). He had no prior treatment for hepatitis B infection.

## Discussion

This patient's experience illustrates a scenario which is expected to be faced more often in the coming months. With the ongoing rise in Coronavirus Disease 2019 (COVID-19) affected cases in the southern

states of the United States and a feared second wave in the northeast corridor, we will be using Immunosuppressive Drug Therapy (IDT) more often than before.

Coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2 has been reported to have multiple systemic manifestations, primarily pulmonary but has been reported to have renal, cardiac, neurological and hepatic manifestation. The most critical patients can develop a so-called cytokine storm, characterized by increased production of many cytokines which, in turn, sustain an aberrant systemic inflammatory response [1]. Therapies aimed to halt hyper activation have been tried including anti-inflammatory medications such as interleukin inhibitors (tocilizumab, sarilumab, etc.) [2] and systemic steroids [3], which in recent studies have shown benefits.

Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. Viral infections such as varicella-zoster, hepatitis B and C can reactivate and be fatal complications of immunosuppressive therapy. Hepatitis B flares can lead to acute liver failure and death if undetected and untreated [4].

Hepatitis B Virus (HBV) infection is endemic in many countries and is common in Asian and African immigrants to the United States. American Association for the Study of Liver Diseases (AASLD) recommends HBV screening for patients born in countries with a high prevalence of HBV infection (HBsAg- positive >2% of population). American Gastroenterological Association (AGA) recommends screening with HBsAg and HBcAb followed by a sensitive HBV DNA test if positive [5]. As per AGA guidance patients who are to receive immunosuppressive drugs can be stratified into high, moderate and low risk for HBV reactivation depending on HBsAg status and type of immunosuppression. AGA and AASLD recommend that all patients with HBsAg positive should be on prophylactic antiviral therapy at the onset of Immunosuppressive Drug Therapy (IDT). Tenofovir and Entecavir are favored over first or second generation agents (e.g., lamivudine, adefovir, telbivudine) and recommend at least 6 months

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**Table 1:** Comparison of Liver Function Test (LFT) before receiving IL inhibitor and 2020 (after receiving IL inhibitor).

Liver Function Test	Normal Values	2013	2017	2018	2020
Alkaline Phosphatase	<130 U/L	77	63	57	74
Aspartate Aminotransferase (AST)	<50 U/L	30	23	25	370
Alanine Transferase (ALT)	<40 U/L	23	18	19	531
Total Bilirubin	<1.2 mg/dL	0.7	0.6	0.7	0.3
Direct Bilirubin	<0.5 mg/dL	0.2	0.2	0.2	0.2

**Table 2:** Comparison of Hepatitis B panel before receiving IL inhibitor and 2020 (after receiving IL inhibitor).

	Normal values	2013	2017	2018	2020
Hepatitis B surface Antigen	Nonreactive	Reactive	Reactive	Reactive	Reactive
Hepatitis B surface Antibody	Nonreactive	Nonreactive	Nonreactive	Nonreactive	Nonreactive
Hepatitis B core antibody	Nonreactive	Reactive	Reactive	Reactive	Reactive
Hepatitis B E Antibody	Nonreactive	Reactive	Reactive	Reactive	Reactive
Hepatitis B E Antigen	Nonreactive	Nonreactive	Nonreactive	Nonreactive	Nonreactive
Hepatitis B Viral DNA Quantitative (Viral Load)	Target Not Detected IU/mL	1747	382	2946	>10,000,000

duration following completion of IDT. Ideally antiviral prophylaxis should be started 2- 4 weeks before the IDT or as soon as possible following initiation of IDT.

During the acute surge of pandemics, providers are more concerned about saving patients, and usual precautionary steps may easily be overlooked. The feared complication of these drugs including hepatitis B reactivation should be kept in mind and proper screening tests should be ordered for patients who may be considered for the therapy (Figure 1).

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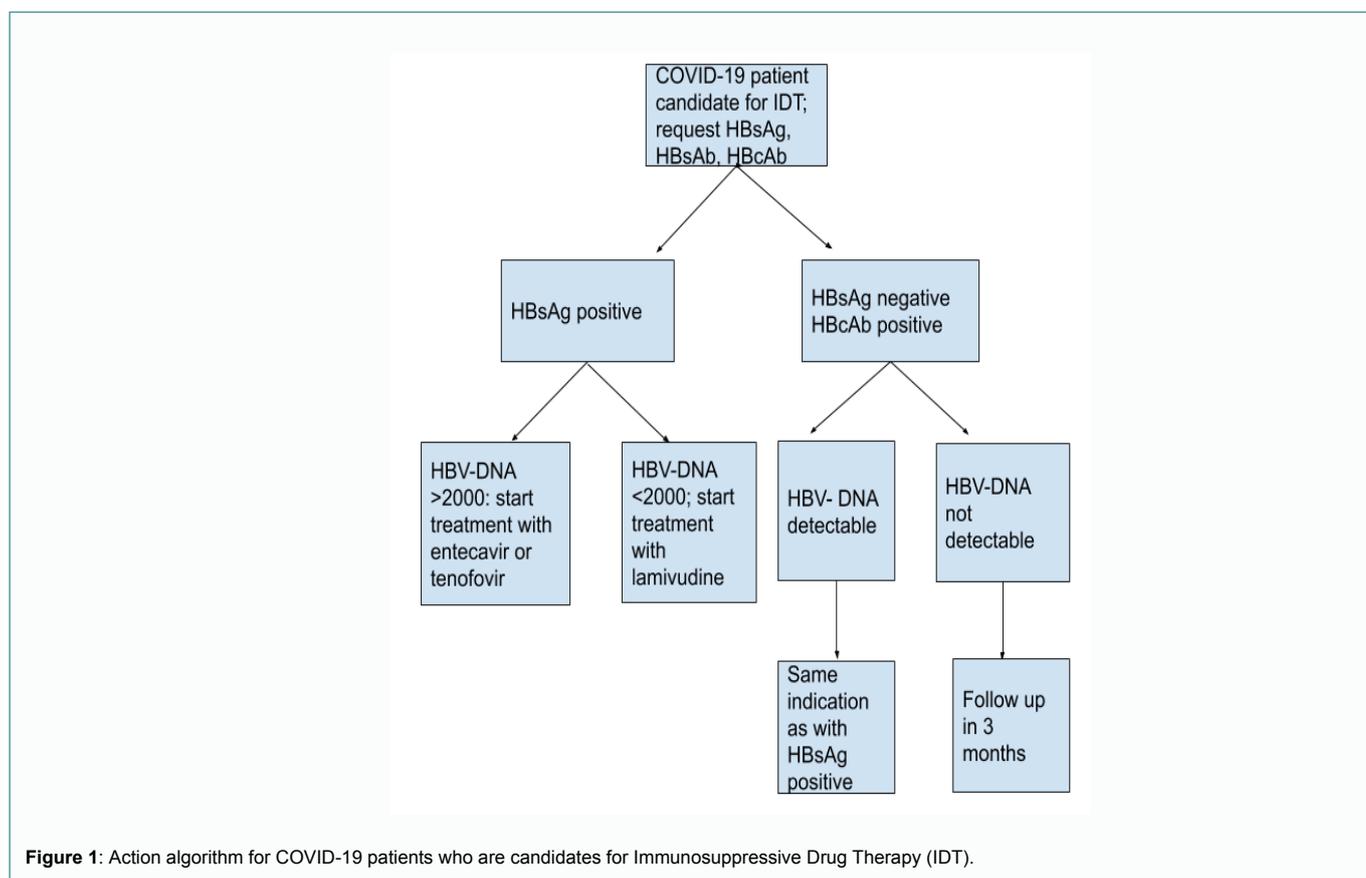
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**Figure 1:** Action algorithm for COVID-19 patients who are candidates for Immunosuppressive Drug Therapy (IDT).