1. The safety of statins for use in patients infected with COVID-19. Atorvastatin 40 mg QD is being considered for use as a therapeutic in the treatment of COVID-19.

   COVID-19 has been reported to cause increased liver biochemistries in 15-53% of patients [1,2]. The profile of the liver biochemistry abnormalities is most commonly an elevation of the aminotransferases (AST and ALT), with occasional alkaline phosphatase and total bilirubin elevations [1-3]. There has been only one reported case of severe liver injury in the context of COVID-19 infection with the ALT reaching 7590 U/L and AST 1445 U/L, but no details about concomitant diagnoses or medications were reported [4]. Liver injury appears to be more common in severe cases of COVID-19.

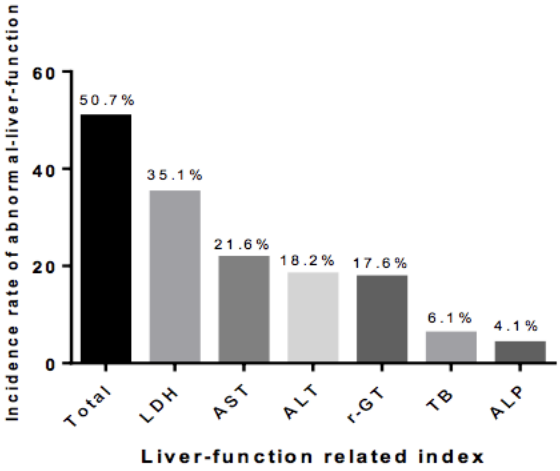

Figure from citation 2.

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)

Figure adapted from citation 3.

We know that the SARS virus from China in 2002 was found in parenchymal and vascular endothelium of the liver. That SARS virus used angiotensin-converting enzyme 2 (ACE2) as the receptor for cell entry, which is found abundantly in the liver [1]. Studies into the mechanism of COVID-19 related liver injury is limited, but may also use ACE2 receptors for cell entry [1]. Postmortem analysis of a COVID-19 patient revealed moderate microvascular steatosis and mild lobular and portal activity. Whether those changes can be attributed to COVID-19 infection or are the result of some other cause such as drug-induced liver injury remains unclear [5].

According to NIH Liver Tox and their supporting references, atorvastatin (as an example) is associated with mild and transient ALT and/or AST elevations in 1-3% of patients. Transaminase elevations above 3 times the upper limit of normal occur in 0.7% of cases, though higher (2.3%) with higher atorvastatin doses of 80 mg daily. Most elevations self-resolved without dose modification. Atorvastatin leads to severe hepatic injury in 1:3000-1:5000 cases. The presentation of atorvastatin hepatotoxicity can be cholestatic (most common), hepatocellular,

or mixed. Atorvastatin can also very rarely induce autoimmune hepatitis. The injury typically arises within 6 months of initiation or dose escalation.

The risk of statin related DILI is no higher in patients with baseline abnormal liver biochemical abnormalities than those without. A study compared 342 patients with baseline LFT abnormalities and 1437 patients without LFT abnormalities who were started on a statin. It showed no difference between the groups in the development of severe LFT elevation, which occurred in 0.6% of cases [6]. The group with abnormal LFTs was more likely to have mild-moderate elevations in LFTs with statin initiation, at a rate of 4.7%. Severe elevation was defined here as TB > 3 mg/dL or ALT or AST 10 times the upper limit of normal or the patient's baseline value. HBV and HCV patients were excluded from the abnormal LFT group.

We propose the following liver safety monitoring strategy for initiation of statin therapy for COVID-19: do not initiate statin therapy in patients with AST and ALT already 3 times the upper limit of normal (i.e. ALT > 165 U/L, AST 120 U/L) or ALP and TB 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL) unless approved by hepatology consultation. Monitor LFTs daily while on statin therapy for COVID and discontinue therapy if AST and ALT exceed 5 times the upper limit of normal (i.e. ALT > 275 U/L, AST 200 U/L) or ALP and TB exceed 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL). The statin therapy should be held until LFTs have returned to under these values.

2. Proposed hepatic monitoring for patients being initiated on Remdesivir:

   We propose the following liver safety monitoring strategy for initiation of Remdesivir for COVID-19 therapy: do not initiate Remdesivir therapy in patients with AST and ALT already 5 times the upper limit of normal (i.e. ALT > 275 U/L, AST 200 U/L) or ALP and TB 3 times the ULN (ALP > 345 U/L, or TB > 3.0 mg/dL). Monitor LFTs daily while on Remdesivir therapy for COVID and discontinue therapy if LFTs exceed the above values. Remdesivir therapy should be held until LFTs have returned to under these values and re-initiation can be considered on a case by case basis.

3. Evaluation of abnormal LFTs in a person presenting with suspected or confirmed COVID-19.

   - COVID-19 is associated with elevated LFTs in 15-53% of patients
   - LFT pattern is often mild AST and ALT elevations
   - Severe liver injury appears to be rare
   - HBV/HCV viral load (PCR) testing should be AVOIDED unless there is an identifiable risk factor or needed for a COVID-treatment protocol
   - Ultrasound should be AVOIDED unless there is concern for biliary obstruction, cholangitis, or venous thrombosis
   - Consider medications as a cause of LFT elevations
   - Monitor the LFT trend daily and consult hepatology for LFTs over 5 times the upper limit of normal or rapid rise

References:

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