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Rationale for Consideration of Statins for COVID-19 Patients

There is no clinical evidence to date that statins are benefit for patients with COVID-19. However, there are at least 4 reasons we might consider them for these patients. First one of the greatest risk factors for severe COVID-19 disease is underlying cardiovascular disease (and another is diabetes), so many of these patients likely already have a primary indication for them. Second, there have been described a number of cardiovascular complications of COVID-19 infection and statins might be beneficial in preventing these. Third, there is the theoretical role that statins may play in protecting innate immune responses to viral respiratory infections (including to SARS-CoV) through inhibiting the MYD88 pathway. And fourth, there is some epidemiological evidence that statins may lead to fewer severe viral pneumonias. Importantly statins are safe and widely prescribed and so the likelihood of harm is felt to be very low with these agents with which we have extensive experience.

A. Risk Factors for Severe COVID-19 Presentations:

Diabetes and pre-existing cardiovascular disease are two of the major risk factors for severe COVID-19 disease. This has been shown in multiple studies to date. In a series of 138 hospitalized patients cardiovascular disease was found in 25% of patients in ICU compared with 10.8% non-ICU ($p=0.04$) and diabetes in 22.2% of ICU patients and 5.9% of non-ICU patients ($p=0.009$).⁽¹⁾ In another study of 191 hospitalized patients 31% of non-survivors had diabetes compared with 14% of survivors ($p=0.0051$) and 24% of non-survivors had coronary heart disease, compared with 1% of survivors ($p<0.0001$).⁽²⁾ In a series of 1099 patients, 16.2% of severe patients had diabetes compared with 5.7% of non-severe patients and 5.8% of severe patients had coronary heart disease compared with 1.8% of non-severe patients.⁽³⁾ In a summary report of 72,314 cases of COVID-19 from China, the authors noted the overall case fatality rate



(CFR) was 2.3%. However, they noted the CFR was elevated to 10-15% for those with pre-existing cardiovascular disease and 7.3% for those with pre-existing diabetes.(4) Another analysis also reportedly markedly elevated risk of death for patients with COVID-19 with underlying cardiovascular disease.(5)

Unfortunately, there is not currently available data about the epidemiology of these patients and how many were on statins at the time of infection. Hopefully this will be published soon.

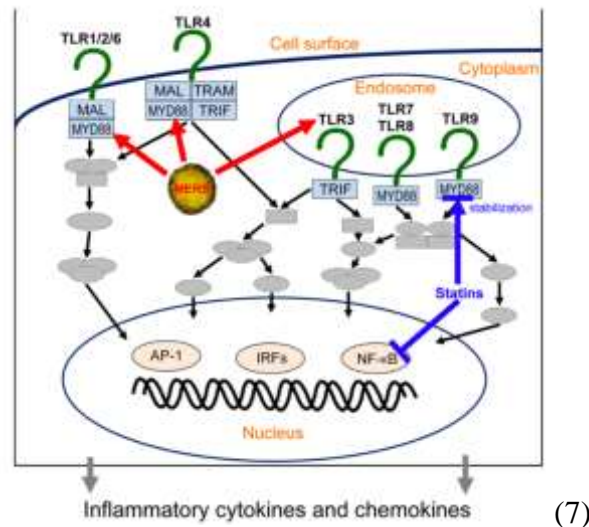
B. *Cardiovascular Complications of COVID-19:*

From many of the same studies discussed above, we know that elevated troponins and myocardial injury are more frequently seen in patients with severe presentations compared to non-severe presentations.(1, 2) Furthermore patients with pre-existing cardiovascular disease seemed more likely to have cardiac complications of COVID-19. The mechanisms for this are not yet worked out. We know that ACE2 receptors are present in the myocardium and there may be a direct viral myocarditis in some patients.(6) Furthermore some patients present to care with cardiovascular complaints including palpitations and chest tightness or pain. From follow up studies of patients who survived SARS, we know that there can be long term changes in lipid profiles.

C. *Statins and Innate Immunity:*

There is an additional theoretic role that statins might play in helping protect the innate immune response to COVID-19. It was noted that SARS-CoV infection led to the MYD88 gene being highly induced.(7) Downstream effects of this include activation of the NF-kB pathway (and a reduction in type 1 interferon) and marked inflammation, a hallmark of SARS-like infections.(8) When NF-kB inflammation is attenuated, SARS-infected transgenic mice are more likely to survive.(8) Of note MYD88^{-/-} mice are more prone to infection from SARS-like coronaviruses.(9) It seems a balance of this pathway is important to maintain.

Statins are known inhibitors of the MYD88 pathway.(7) Importantly they do not significantly alter the level of MYD88 under normal conditions but rather maintain normal levels during hypoxia and under stress (such as after treatment with hydrogen peroxide).(7) The ability of statins to maintain MYD88 levels at normal levels, may be protective for patients with COVID-19.



(7)

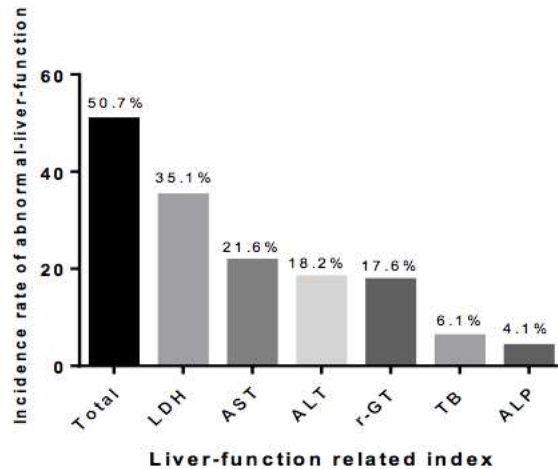
D. Statins and Viral Pneumonia:

While no clinical data yet exists for a protective role for statins for COVID-19 infection, there are some data that are suggestive that they may be associated with less severe viral pneumonia (perhaps for similar reasons described in point C). A large matched cohort study found a reduced risk of COPD death and influenza death for patients on moderate dose statins compared to not.(10) Another found a statistically significant but small protective effect against influenza mortality among statin users. Another study showed a similar protective effect of statins on influenza related mortality.(11) An analysis of hospitalized patients with pandemic H1N1 influenza did not find a statistically significant association between pre-admission statin use and severity of outcome after adjustment for age and sex but they noted “point estimates are compatible with a small but clinically significant protective effect of statin use.”(12)

E. Safety of Statins:

There is extensive clinical experience with statins, and they are accepted as quite safe medications in general. The overall safety of statins in patients with COVID-19 disease has not yet been established.

COVID-19 has been reported to cause increased liver biochemistries in 15-53% of patients.(13, 14) 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.(3, 13, 14) 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.(15) Liver injury appears to be more common in severe cases of COVID-19.



(14)

Table 2. Radiographic and Laboratory Findings.^a

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)

(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.(13) Studies into the mechanism of COVID-19 related liver injury is limited, but may also use ACE2 receptors for cell entry.(13) 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.(16)

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.(17) 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.

F. Recommendations:

- We recommend continuing previous statins in house even with new LFT abnormalities which are more likely due to other causes.
- If there is a clear pre-existing primary indication, consider starting for cardioprotection given the CV complications late in severe COVID-19.
- For patients naïve to statins, this would be best studied under a clinical trial and they should not be started specifically for COVID-19.

G. Dosing:

If not on interacting meds, then atorvastatin 40 mg daily

If on interacting meds, pravastatin 80 mg daily or pitavastatin 4 mg daily

H. Availability:

We do not expect shortages of these medications



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