In-hospital statin treatment of COVID -19

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Memel and colleagues have published an important observational study showing that inpatient statin treatment reduces COVID-19 mortality [1]. Their study confirms findings from 11 other observational studies (Table) [2, 3]. They also confirm the detrimental effects of statin withdrawal, i.e., the discontinuation of outpatient statin treatment after hospital admission [1, 2, 4]. Importantly, physicians caring for COVID-19 patients were encouraged to prescribe statins without considering cardiovascular risk factors that are the usual reasons for prescribing these drugs. The findings of Memel et al clearly suggest that inpatient treatment of COVID-19 patients with statins (and perhaps other generic drugs [5]) saves lives.

COVID-19 causes extensive endothelial dysfunction, which can be associated with immunothrombosis, multi-organ failure and death [6]. Generic drugs like statins have beneficial effects on the signaling pathways underlying these disturbances [7]. These drugs have long been advocated for treating the host response to pandemic infections, not the viruses themselves. Despite an estimated 15 million or more excess deaths due to COVID-19 worldwide [8], investigators have insisted on randomized controlled trials (RCTs) to demonstrate the efficacy of any COVID-19 treatment. With the exception of dexamethasone, which reduces COVID-19 mortality in patients who require oxygen therapy, potential sponsors of clinical studies, including the World Health Organization and international foundations, have shown no interest in undertaking studies of generic drugs [7]. Except for dexamethasone and selective serotonin reuptake inhibitors (SSRIs) [9], no RCTs of generic drug treatment of COVID-19 have been reported. None is expected before 2022.

Some observational studies of inpatient statin treatment of COVID-19 have been small and have given insufficient attention to confounding variables. One recent study suggests that in-hospital statin treatment had no effect on mortality or severe disease [10]. This study is difficult to interpret. Statin use was documented based on the (presumably inpatient) medication administration record. However, the investigators provided no information on the duration of treatment or whether statin treatment was ever discontinued. In contrast, Memel et al categorized patients into groups that either (1) continued (n=466) or (2) discontinued (n=42) outpatient statin treatment after hospital admission, (3) initiated treatment after hospital admission (n=311) or (4) never used statins (n=360) [1]. They also calculated E-values to evaluate the robustness of their findings to unmeasured confounding. In all instances, inpatient statin treatment was associated with reductions in COVID-19 mortality.

Given the results of observational studies reported by Memel et al and several others (Table) [1-3], one could ask whether a RCT demonstrating the efficacy of inpatient statin treatment for COVID-19 is necessary [10]. Both types of studies are useful. They could be especially important for people who live in low- and middle-income countries that have struggled to obtain adequate supplies of highly effective COVID-19 vaccines. These countries will also struggle to obtain (and pay for) limited

supplies of newly developed antiviral treatments. Given the ongoing need for inexpensive, widely available, and effective pandemic treatments that could save lives in resource-poor countries, clinicians in these countries should undertake studies of generic drug treatment [7, 9, 12].

Treating the host response with generic drugs could also be useful for COVID-19 patients who live in high-income countries. Despite the demonstrated effectiveness of COVID-19 vaccination (including booster vaccination), fully vaccinated individuals still get infected [13]. Some of them require hospitalization and a few of them die. Inpatient statin treatment might save some of those who develop severe illness. One potential disadvantage of generic drug treatment is that vaccine-hesitant individuals might continue to refuse vaccination, knowing that if they require hospitalization they could be treated.

No one can predict the future course of the COVID-19 pandemic. Reinfections occur in previously infected individuals and breakthrough infections in those fully vaccinated [14]. If new variants appear with enhanced transmissibility combined with the ability to escape host immunity, there will be an even greater need for "… effective treatments of COVID-19, especially those that are easy to use, show good tolerability, can be administered orally and have widespread availability at low cost to allow their use in resource-poor countries …" [9]. Inpatient statins could be one of these treatments.

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TABLE - Reduction in 28-30-day COVID-19 mortality

following in-hospital statin treatment and statin withdrawal*

First author (ref)	Methods	Adjusted HR/OR	95% CI	p value
Zhang (2)	CCS, PSM (4:1)	0.58	0.43-0.80	0.001
Rodriguez-Nava (2)	cohort, ICU	0.38	0.18-0.77	0.008
Mallow (2)	cohort	0.54	0.49-0.60	<0.001
Saeed (2)	Diabetes mellitus, multivariate adjusted PM, IPTW*	0.51 0.88	0.43-0.61 0.84-0.91	0.001 <0.001
Masana (2)	GM (1:1)	0.60	0.39-0.92	0.020
Fan (2)	cohort, PSM	0.25	0.07-0.92	0.037
Torres-Pena (2)	PSM, statins continued vs. withdrawal**	0.67	0.54-0.84	<0.001
Memel (1, 2)	marginal structural Cox model, IPTW statins continued vs. withdrawal***	0.57 0.27	0.37-0.86 0.11-0.64	0.008 0.003
Byttebier (2, 5)	CCS, PSM (1:1)	0.56	0.39-0.93	0.020
Terlecki (2)	logistic regression	0.54	0.33-0.84	0.008
Lohia (2)	cohort, PSM (1:1)	0.47	0.32-0.70	<0.001
Choi (3)	Cox model, high intensity statin	0.53	0.43-0.65	Not done
Ayeh (10)	Cox proportional regression	0.92	0.53-1.59	Not significant

*Adapted from reference

Abbreviations: CCS, case-control study; CI, confidence interval; GM, genetics-matched; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability treatment weighted; OR, odds ratio; PSM, propensity score-matched.

[a] The PS matched IPTW cohort analysis included demographic and comorbidity factors, clinical and laboratory test values, and the use of ACE inhibitors and angiotensin receptor blockers.

[b] Statin treatment continued after hospital admission versus statin withdrawal; conditional logistic regression.

[c] Statin treatment continued after hospital admission versus statin withdrawal; marginal structural Cox model.