Received: 14 April 2022 | Accepted: 1 June 2022

DOI: 10.1002/prp2.988

INVITED REVIEW

A practical treatment for COVID-19 and the next pandemic

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Keywords: ACE inhibitors, ARBs, COVID-19, generic drugs, next pandemic, statins, treatment

Scientists are concerned about the origins of SARS-CoV-2, which has caused a devastating global pandemic. In a letter recently published in *Science*, 18 investigators called for more studies of its origins.[1] In 2001 and in a different context, Malcom Gladwell wrote "it is a strange kind of public health policy that concerns itself more with the provenance of illness than with its consequences …".[2] Studies on the origins of SARS-CoV-2 are unlikely to be undertaken, primarily for political reasons. As a result, investigators can only speculate on the origins of SARS-CoV-2 and its many variants: delta and more recently omicron.[3,4]

Scientists and health officials believe we will eventually face another pandemic. Its impact on global mortality could be worse than the more than 20 million or more excess deaths we have experienced thus far.[5] Highly effective COVID-19 vaccines have been developed, but vaccine nationalism and vaccine hesitancy have meant they have been used largely in developed countries. Scientists also

Gary Grohmann, Lester Kobzik, and Masato Tashiro: Retired.

hope to develop better antiviral drugs. Pharmaceutical companies have developed two new antivirals that appear to reduce the development of serious disease when given to patients when they first test positive for SARS-CoV-2. However, these drugs will be expensive for people living in developed countries and they will not be available in developing countries anytime soon. Moreover, antiviral resistance will always be a threat. For the next pandemic, as with the current COVID-19 pandemic, it is unlikely that people in resource-poor countries (where most deaths will occur) will ever get new vaccines and antivirals in time to significantly reduce mortality.[6]

Instead of counting on vaccines and treatments that target a newly emergent pandemic virus, we could also target the host response to infection and excessive inflammation using inexpensive repurposed generic drugs. This idea was suggested more than a decade ago.[7] Generic drugs are inexpensive and most of them are familiar to practicing physicians everywhere. They would be available on the first pandemic day in any country with a basic healthcare system.[6] Several generic drugs already meet these criteria.

Severe COVID-19 is dominated by endothelial dysfunction,[8,9] which is associated with immunological dysfunction and often immunothrombosis.[10,11] For COVID-19, most of the attention on repurposed generic drugs for host response treatment has focused on statins, ACE inhibitors, and angiotensin receptor blockers (ARBs). These drugs help maintain or restore endothelial barrier integrity.[12] They are safe to use in patients with acute critical illness. Dexamethasone is another inexpensive generic drug that reduces COVID-19 mortality in patients who require oxygen treatment with or without mechanical ventilation.[13] It is not effective in those not receiving respiratory support. Early treatment with selective serotonin reuptake inhibitors (SSRIs) is also effective in reducing symptomatic COVID-19.[14] It is uncertain whether supplies of SSRIs and physician familiarity with this group of drugs will ever be sufficient to allow them to be widely used in resource-poor countries.

Most studies of statin treatment of COVID-19 are based on outpatient documentation, which does not account for statin withdrawal after hospital admission.[15,16] However, in all but one of 13 observational studies, inhospital statin treatment reduced COVID-19 mortality (Table 1).[15,17–19] Perhaps more important, inhospital treatment with a combination of a statin and either an ACE inhibitor or an ARB was associated with a threefold reduction in the risk of 28-day COVID-19 mortality.[19] This is not surprising. In an earlier study, combination statin/ACE inhibitor treatment was associated with reduced inflammatory biomarkers in patients with coronary artery bypass surgery.[20]

We (a group of 17 clinicians and investigators) believe that greater emphasis should be given to testing treatment with generic statins, ACE inhibitors, or ARBs (either by themselves or in combination) during the current COVID-19 pandemic. These studies could

TABLE 1 Observational studies of the reduction in 28–30-day COVID-19 mortality following inhospital statin treatment and statin withdrawal. Adapted from reference[15]

First author		Adjusted		
(ref)	Methods	HR/OR	95% CI	*p* value
Zhang[15]	CCS, PSM (4:1)	0.58	0.43–0.80	.001
Rodriguez-Nava[15]	cohort, ICU	0.38	0.18–0.77	.008
Mallow[15]	Cohort	0.54	0.49–0.60	<.001
Saeed[15]	Diabetes mellitus, multivariate adjusted	0.51	0.43–0.61	.001
	PM, IPTW[a]	0.88	0.84–0.91	<.001
Masana[15]	GM (1:1)	0.60	0.39–0.92	.020
Fan[15]	cohort, PSM	0.25	0.07–0.92	.037
Torres-Pena[15]	PSM, statins continued versus withdrawal[b]	0.67	0.54–0.84	<.001
Memel[15]	Marginal structural Cox model, IPTW	0.57	0.37–0.86	.008
	Statins continued versus withdrawal[c]	0.27	0.11–0.64	.003
Byttebier[15,19]	CCS, PSM (1:1)	0.56	0.39–0.93	.020
Terlecki[15]	Logistic regression	0.54	0.33–0.84	.008
Lohia[15]	Cohort, PSM (1:1)	0.47	0.32–0.70	<.001
Choi[17]	Cox model, high-intensity statin	0.53	0.43–0.65	Not done
Ayeh[18]	Cox proportional regression	0.92	0.53–1.59	Not significant
Kuno[19]	Statins continued versus withdrawal, PSM (l:1)	0.53	0.41–0.62	<.001

Abbreviations: CCS, case–control study; CI, confidence interval; GM, genetic-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.

include randomized controlled trials,[21] although they should not discount the value of observational studies.[22] Because these drugs target the host response, they could also be tested against everyday critical illness (sepsis, community-acquired pneumonia, and seasonal influenza). For COVID-19, they might even be used for patient treatment before this research is undertaken.[23]

We believe that treating patients with these repurposed generic drugs could help reduce mortality during the current and all future pandemics.[6] Undertaking studies of this idea before the next pandemic might provide convincing evidence that these drugs could reduce its mortality. A few randomized controlled trials of these drugs have been undertaken in COVID-19 patients, but their results will not be reported for some time. (When the results of statin trials become available, investigators should be able to identify hyperinflammatory subphenotypes that might show improved survival with statin treatment.[24,25]) In the meantime, thousands will continue to die of COVID-19 every day. This includes patients in high-income countries, some of whom have received three or more doses of COVID-19 vaccines.[26]

For patients who live in resource-poor countries, the social and economic consequences of the COVID-19 pandemic have been extraordinarily severe and might dwarf those of the disease itself.[27] For patients and physicians in these countries, "… there is no guarantee that treating the host response will be effective, but we urgently need to find out. If a highly virulent and easily transmissible pandemic … virus emerges, it will spread rapidly throughout the world, overwhelming healthcare systems everywhere. In the absence of pandemic vaccines and effective antiviral treatments, the only way, physicians might reduce pandemic mortality will be to treat seriously ill patients with easily administered inexpensive generic drugs that are already available and that modify the host response to infection. … (T)he challenge of the next pandemic must make this the central element of preparedness planning".[28]

In 2001, Malcolm Gladwell also wrote that many threats to health and happiness "are the result of what, through simple indifference, we do to ourselves".[2] We were unprepared for COVID-19 and are still not prepared to reduce global mortality during the next pandemic. The World Health Organization and non-governmental organizations and foundations have been disinterested in sponsoring laboratory and clinical studies of these generic drugs to treat the host response. This represents a failure of both scientific and political imagination.[6] We believe this must change.

ACKNOWLEDGMENTS

This article contains no new data. All co-authors agree with its contents. They declare no conflicts of interest related to this article.

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How to cite this article: Bhattacharya J, Booy R, Casadevall A, et al. A practical treatment for COVID-19 and the next pandemic. *Pharmacol Res Perspect*. 2022;10:e00988. doi: 10.1002/prp2.988