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Previews

Teaching Old Drugs New Tricks: Statins for COVID-19?

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The COVID-19 pandemic has driven unprecedented efforts to identify existing treatments that can be quickly and effectively repurposed to reduce morbidity and mortality. In this issue of *Cell Metabolism*, Zhang et al. (2020) report an association between statin use and improved outcomes in a large observational study of hospitalized COVID-19 patients. Given the widespread availability, low cost, and safety of statins, this promising result should be further investigated in randomized controlled trials.

The COVID-19 pandemic has led to an explosion of interest in finding medicines that reduce the morbidity and mortality of the disease. Repurposing drugs is faster and far more economical than starting development from scratch, and many drug targets are shared across diseases. Historically, there have been several notable drug repurposing successes (e.g., sirolimus for lymphangiolyomyomatosis, thalidomide for multiple myeloma), but there are also quite a few challenges, such as prioritizing drug candidates, overcoming limited intellectual property, selecting the appropriate study design and endpoints, and competing with off-label use. There has been a great deal of interest and enthusiasm for drug repurposing in COVID-19; in fact, over 100 different off-label and experimental drugs were reported to be given to COVID-19 patients in the first 3 months of the pandemic (Fajgenbaum et al., 2020). COVID-19 has revealed both the pitfalls and promise of drug repurposing. For example, hydroxychloroquine achieved unmatched exposure and off-label use before demonstrating limited benefits and potential toxicities in clinical trials, while dexamethasone was strongly recommended against by global health organizations before demonstrating a striking mortality benefit in the most ill COVID-19 patients (Horby et al., 2020) (Figure 1A).

Statins are inhibitors of a key cholesterol synthetic enzyme, HMGCoA reductase, and have been on the market since the late 1980s as highly effective agents for reducing cholesterol levels and risk of coronary heart disease. They are among the most widely used class of drugs in the world, have an outstanding record of safety, and are very cheap and widely available. Statins are known to have anti-inflammatory and immunomodulatory properties; furthermore, lipid metabolism has been implicated in the pathogenesis of the SARS-CoV-2 virus. On the other hand, statins increase the cellular expression of ACE2 (Shin et al., 2017), the primary receptor for SARS-CoV-2. Therefore, the effect of statins on COVID-19 outcomes warrants investigation. Drug repurposing efforts often include non-randomized observational studies to gain insights into the potential effects of drugs on clinical outcomes (Figure 1B). In *Cell Metabolism*, Xiao-Jing Zhang and colleagues report the first large observational study of statin use in COVID-19 (Zhang et al., 2020). They performed a retrospective cohort study examining the association between statin use and outcomes in 13,981 patients hospitalized with COVID-19 in Hubei Province, China, among which 1,219 received statins. As expected, there were considerable differences in clinical characteristics between patients on statins and those not on statins. Based on a Cox model with time-varying exposure and a mixed-effect Cox model after propensity score-matching, the authors found that the risk for 28-day all-cause mortality was 5.2% in the matched statin group and 9.4% in the matched non-statin group (hazard ratio, 0.58; 95% CI, 0.43–0.80; $p = 0.001$). There are important limitations and caveats of this study, such as the retrospective nature of the study preventing causal inferences, the lack of data on pre-hospital statin use, limitations of matching techniques to eliminate all confounders, and the lack of data on other concomitant medications such as corticosteroids that could have confounded the results. The generalizability of the result to other racial and ethnic groups is also uncertain. Nevertheless, this surprising finding establishes statins as a class of medication that urgently merits additional observational (replication), mechanistic, proof-of-concept, and randomized studies for its potential to help fight COVID-19.

There are several plausible mechanisms through which statins may exert a beneficial effect in this disease. In COVID-19, the host's immune system must mount an effective response to control the virus but avoid responding too aggressively and inducing a "cytokine storm," which likely poses the greatest risk of death. This has led to great interest in medicines that could potentially limit immune hyperactivation. *In vitro* and *in vivo* experiments have shown that statins can suppress TLR4/MyD88/NF-κB signaling and modulate the NLRP3 inflammasome (Henriksbo et al., 2014; Yuan et al., 2014). Statins have also been shown to modulate proinflammatory cytokine release such as interleukin-6 (Rezaie-Majd et al., 2002), which

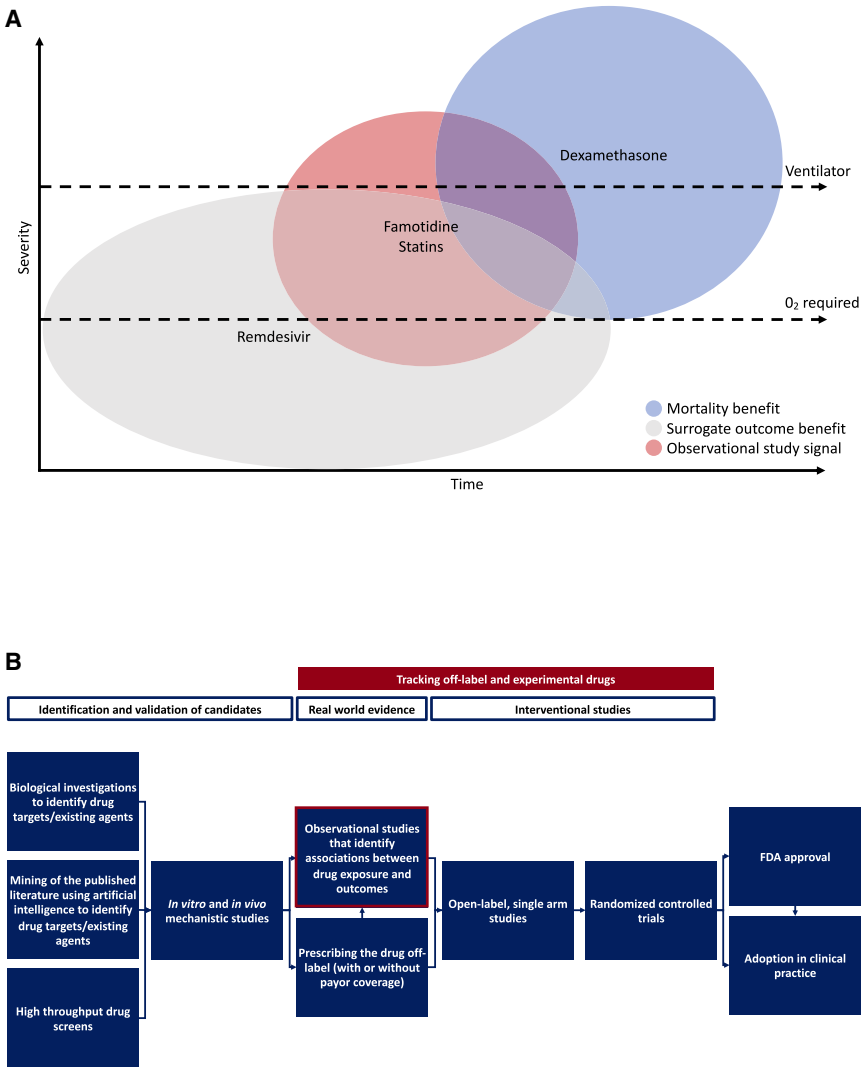

Figure 1. Drug Repurposing for COVID-19 and Beyond

(A) Promising repurposed drugs for COVID-19 presented on a theoretical time versus severity graph. Blue represents the COVID-19 cases in which a mortality benefit has been demonstrated for dexamethasone (hospitalized patients on supplemental oxygen therapy or ventilation). Gray represents the COVID-19 cases in which a surrogate outcome benefit has been demonstrated for remdesivir (greater benefit if given earlier in disease course). Red represents the COVID-19 cases in which observational studies have suggested a potential mortality benefit for statins and famotidine (hospitalized patients). Like statins, a well-matched retrospective cohort study of famotidine suggested improved outcomes in hospitalized COVID-19 patients (Freedberg et al., 2020).

(B) A conceptual framework for drug repurposing. Drug repurposing candidates are preliminarily identified through laboratory investigation of drug targets, mining of published literature, and high-throughput drug screens. While the success rate of high-throughput drug screens has been low historically, the basic understanding of SARS-CoV-2 biology, as well as the large number of efforts, likely increases the potential for success. These candidates can be validated and refined through orthogonal *in vitro* and *in vivo* studies. Observational studies of widely used drugs are often performed to search for associations between drug exposure and outcomes. In this case, the observational study by Zhang et al. provided the first indication that statins may be effective in COVID-19 (red border highlights this aspect of the framework). Open-label, single-arm, or preferably, randomized controlled trials are then performed to investigate efficacy (and safety) and determine if the drug should be adopted in clinical practice and/or given regulatory approval for the new indication. In parallel, it is important to track all drugs being used off-label and experimentally to identify promising candidates for further investigation. The CORONA Project tracks off-label and experimental drugs used in COVID-19 (red box). There is very high interest in drug repurposing for COVID-19 from multiple sectors, including the US Food & Drug Administration (FDA), which will likely speed up the time from candidate identification to approval.

is considered to be a potential driver of the COVID-19 cytokine storm, as well as immune cell functioning in patients with other viral and bacterial pneumonias (Pertzov et al., 2019). Another potential mechanism of action of statins in COVID-19 could be through inhibiting SARS-CoV-2 entry into cells by binding the main protease (Reiner et al., 2020). However, as noted above, concerns about statins' ability to increase expression of ACE2 have caused some concern about their safety in COVID-19. In this context, the study by Zhang et al. suggests that statins are not harmful in hospitalized COVID-19 patients and could even possibly be beneficial.

Promising signals from observational studies like this must be replicated, as well as rigorously tested in high-quality randomized controlled trials (RCTs) (Figure 1B). The importance of randomized studies can be seen from previous experience with statins in sepsis: observational studies and meta-analyses suggested reduced mortality with statins in patients with sepsis-associated ARDS, but RCTs found no mortality benefit (Truwit et al., 2014). In light of the study by Zhang et al., it is essential that well-powered RCTs of statins in COVID-19 be implemented, with careful consideration given to the design. Given the ubiquity of statin use (over 25% of adults in the US are prescribed statins; Salami et al., 2017) and the fact that more serious COVID-19 disease occurs in older patients and those with cardiometabolic disease who are even more likely to be on statin therapy, many patients presenting with COVID-19 are already on a statin. The usual multi-week washout period prior to randomization will not be possible for patients acutely ill with COVID-19. Patients that are statin-naive may need to be studied separately from those that have previously received chronic statin therapy. As with other RCTs of repurposed drugs for COVID-19, the inclusion criteria will need to be carefully considered, in particular the severity of disease for entry into the study. Based on Zhang et al., a case might be made for positioning statins in the disease course somewhere between remdesivir and dexamethasone (Figure 1A). We believe that randomized investigation of the benefit of statins would be a good fit for a master protocol trial following a randomized adaptive trial design like the UK RECOVERY

(Randomized Evaluation of COVID-19 Therapy) trial, the WHO's SOLIDARITY trial, or the international REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) study. Although the study of Zhang et al. was focused on hospitalized patients, the fact that statins are safe, cheap, and easily accessible also leads to the consideration of studying their benefit early in disease, for example at time of a positive diagnosis of symptomatic SARS-CoV-2 infection, with the goal of preventing progression to more serious illness. Importantly, given the accessibility of statins, we have a concern that in light of this report, statins may be utilized off-label for the prevention and treatment of COVID-19 before the appropriate studies are performed. While we recognize that risk-benefit assessments may be different during a pandemic, we feel it is critical to capture these data before there is widespread use.

To improve the process of drug repurposing in the urgency of the current pandemic, we mapped out the steps involved in drug repurposing (Figure 1B) and launched the COVID-19 Registry of Off-Label and New Agents (CORONA) project to track drug repurposing efforts (https://cdcn.org/CORONA/), documenting that well over 200 drugs have been explored for treating COVID-19 to date (Fajgenbaum et al., 2020). In light of the study by Zhang et al., statins must now be added to this growing list. As we noted above, unlike the majority of drugs being considered for this purpose, statins have the advantage of being inexpensive, widely accessible, and very safe. It is therefore of great public health importance that appropriately designed and powered RCTs of statins be performed to formally address the question of whether they will help reduce morbidity and mortality in COVID-19.

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