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Introduction

In the last week, two major pharmaceutical companies announced the preliminary results of their vaccine trials, promising a potential end to the pandemic. At the same time, we are entering the worst phase of the pandemic, with infections spiking across the nation, hospitalizations at an all-time high,[1] and deaths climbing. Until vaccines become widely available, therapeutic treatments for COVID-19 will continue to play an important role in reducing deaths among those who are infected. Researchers are continuing to gather evidence on the use, safety, and efficacy of different treatments in clinical trials, including several testing outpatient treatments. The early evidence from some of these trials is promising, while other treatments have now been discredited through robust Randomized Controlled Trials (RCTs). I will outline four major categories of outpatient therapies and the evidence for their effectiveness before discussing the importance of adhering to established scientific approaches in evaluating these treatments, and other coronavirus countermeasures.

Early Outpatient Treatments

A key goal for therapeutics for SARS-CoV2 has been early outpatient therapy. Early intervention, ideally with a treatment that prevents severe complications of the disease, can prevent hospitalizations, disability, and death. By treating people at home or in their physicians' offices, we can avoid maxing out hospital capacity at a time when our medical resources are stretched to the limit.

Four classes of COVID-19 therapies have been investigated for use in the treatment of early disease in the outpatient setting: 1) antivirals; 2) monoclonal antibodies; 3) convalescent plasma; and 4) hydroxychloroquine.

Dexamethasone (a steroid) has been shown to be highly effective in clinical trials, but only in people with advanced disease (those with low oxygen levels or hypoxemia); giving this drug early in the disease course appears to increase mortality, not lower it. Therefore, it is likely not suitable for outpatient therapy except in very rare circumstances where hospital services may not be available.

I.   Antivirals

Remdesivir has had a mixed track record, with some clinical trials finding benefit and others none. A Randomized Controlled Trial in the New England Journal of Medicine found treating patients with remdesivir shortened hospitalization times and improved patient outcomes. However, the WHO Solidarity Trials, in their interim report, found no effects of remdesivir on improving mortality or recovery.[2, 3] Clinical trials in early outpatient settings are ongoing, and inconclusive. Gilead is running a Phase III trial of around 1200 outpatients, to estimate the effectiveness of remdesivir.[4] They have also begun Phase I/II trials for inhaled remdesivir as opposed to intravenous doses.[5] Last month, Atrium Health initiated three outpatient trials to test remdesivir.[6]

New antivirals are also being developed for mild outpatient cases, including MK-4482 from Merck and Synairgen's SNG001. These have been facilitated by Operation Warp Speed and the NIH's

ACTIV-2 (Adaptive Platforms Treatment Trial for Outpatients with COVID-19) trials.[7] Although we are in the first stages of these clinical trials, the preliminary data seems promising.

Merck's MK-4482 antiviral is still in Phase IIb trials, with interim results due early next year.[8] But more evidence has been released for SNG001 - an antiviral originally developed to treat chronic obstructive pulmonary disease. The Lancet recently published results from a Randomized Controlled Trial (RCT) focusing on hospitalized patients who were not receiving intensive care or ventilation.[9] The researchers found a strong improvement in clinical status for those who received the treatment, an effect that became more pronounced later in the disease course. Another trial is underway for both hospitalized and non-hospitalized high-risk patients, but we do not yet have enough evidence in outpatient settings to claim efficacy.[10]

Camostat Mesylate, a protease inhibitor, has been shown to reduce levels of TMPRSS2, a serine protease highly associated with the spread of infectious diseases.[11] Camostat has proved effective in combating the original SARS virus, SARS-CoV, but has not yet been tested in patients with SARS-CoV-2.[12] Clinical trials are ongoing, but some reports suggest Camostat Mesylate, and its cousin Nafamostat Mesylate, may be effective in inhibiting the spread of COVID-19 in human lungs.[13]

II.   Monoclonal Antibodies

Alongside antivirals, pharmaceutical companies have been working to develop effective monoclonal antibodies, which work to target the virus and inhibit its spread. The first data from Regeneron's REGN-2 antibody in late September covered 275 patients.[14] The next round of data

was released in late October and included an additional 524 patients from Phase II/III.[15] Patients were randomized to receive either a high dosage, low dosage, or placebo. Only non-hospitalized, healthy individuals were eligible for the trials. The preliminary results suggest viral loads, medical visits, and time to alleviate symptoms were all reduced compared to the placebo. On average, treated patients had a more than 10-fold reduction in viral loads.[15] The largest benefits were reported in patients who had not yet mounted their own immune response, and those classified as highest risk. Regeneron has submitted their data to the FDA for Emergency Use Authorization (EUA) consideration and have committed to continuing their trials. The UK Recovery project has also added REGN-2 as a treatment option for participants, though preliminary data is still being gathered.[16]

Eli Lilly's antibody has also shown positive results in the same patient population. An interim analysis of the ongoing Phase II clinical trial (BLAZE-1) found patients who received the Ly-CoV555 antibody had slightly lower severity of symptoms, and lower hospitalization rates compared with the placebo.[17] The medium dosage resulted in a significant reduction in viral load, and patients did not report adverse effects. Given the positive results demonstrated through this randomized-controlled trial, the FDA recently issued an EUA for Ly-CoV555 for treatment of mild to moderate COVID-19 cases in patients who are at high risk of progressing to severe illness or hospitalization.[18]

III.   Convalescent Plasma

Naturally occurring antibodies are also found in convalescent plasma, which has already been used as a therapy for COVID-19. Unfortunately, the results from convalescent plasma trials have not been nearly as encouraging.

Convalescent plasma, a treatment in which blood from recovered COVID-19 patients is transfused into actively infected individuals, was first approved through an EUA on August 23, 2020. The observational data backing the EUA for convalescent plasma showed that patients who received the therapy earlier in the disease course demonstrated a lower 7-day mortality than those receiving the therapy later in the disease course.[19] However, in the absence of an RCT, it is impossible to disentangle whether these results indicate a benefit of treatment with the drug early or a harm of the drug later on. In the first RCT of convalescent plasma, the therapy did not significantly reduce the time to clinical improvement within 28 days.[20] Furthermore, an RCT conducted in the Netherlands demonstrated no difference in mortality, length of hospital stay, or disease severity at Day 15 between those who received convalescent plasma therapy and those receiving standard of care.[21] Both of these trials were terminated early and therefore, their results must be interpreted with caution. But a more recent RCT examining convalescent plasma therapy failed to demonstrate a statistically significant reduction in disease progression or mortality.[22] The study found that 15% of patients who completed the therapy died, compared with 14% of those who received usual care. The trial did demonstrate some benefits, such as relief from shortness of breath and an increased likelihood of testing negative after 7 days, but these benefits must be interpreted with caution, given the non-blinded nature of the study. Further, the administration of convalescent plasma treatment does not come without risks. A commentary in the British Medical Journal noted the risk of convalescent plasma included blood clots, among other common complications.[23] In fact,

convalescent plasma poses a number of other potential risks to patients, such as transfusion-related risks (to both those receiving convalescent plasma treatments and comparators receiving regular plasma during clinical trials) and allergy or anaphylaxis.[24] While this therapy has not yet been testing in the outpatient setting, a number of clinical trials of convalescent plasma for outpatients are currently underway.[25]

IV.   Hydroxychloroquine

Hydroxychloroquine was the first therapy that received an EUA for COVID-19. The evidence cited by President Trump and the FDA centered around a small trial of 26 COVID-positive patients run by French scientist Didier Raoult. After receiving six daily doses of hydroxychloroquine, 70% of treated patients returned a negative test. However, following the publication of the results, many European scientists questioned the trial procedures, including the small sample and biases in patient selection. Raoult's findings were soon discredited.[26]

Today, the consensus in the scientific community, based on overwhelming evidence, is that hydroxychloroquine provides no benefits in treating COVID-19, and may produce significant harms. Results from an RCT published in the New England Journal of Medicine found hydroxychloroquine had no effect on the chances of becoming infected after exposure.[27] The UK Recovery Trials, which prescribed hydroxychloroquine to hospitalized individuals, reported *higher* mortality for COVID patients for those in the treatment arm.[28] Interim results from the WHO Solidarity Trials also reported no significant difference in the mortality for those assigned to hydroxychloroquine as opposed to a placebo.[3] The TEACH clinical trials found similar effects, concluding diagnosed COVID patients who were assigned hydroxychloroquine as opposed to a

placebo did not perform better across clinical outcomes, and had longer hospital stays.[29] Another systematic review of 29 papers found hydroxychloroquine alone did not reduce mortality, and in combination with another commonly used therapeutic, azithromycin, actually increased deaths.[30] Yet another study analyzed a WHO database of over 21 million records across 130 countries and found strong evidence of a disproportionate share of reported adverse reactions in patients taking hydroxychloroquine, either alone or in combination with azithromycin.[31] The Veterans Administration ran a retrospective analysis of veterans' electronic health records, and concluded that hydroxychloroquine, alone or with azithromycin, did not reduce ventilations or overall mortality, but were instead linked to longer hospital stays.[32] The best evidence suggests that hydroxychloroquine is ineffective in improving COVID-19 outcomes. Similar to initial observations suggesting hydroxychloroquine would be effective against COVID-19 throughout the course of illness, some now suggest that there is a benefit to using the drug very early on, in the first 5-10 days after symptom onset.[33] However, there is no evidence to support this contention and better data are clearly needed.

Not only has hydroxychloroquine demonstrated minimal to no benefit in treating COVID-19, but it also poses substantial risks to patients. Hydroxychloroquine, an aminoquinoline derivative, has a very narrow therapeutic range. Only a small range of doses can be tolerated without leading to toxicity.[34] While hydroxychloroquine toxicity is not very common, its use for COVID-19 requires a higher dosage than normally employed, and therefore, raises concern of greater side-effects and toxicity. In April of 2020, we saw a 93% increase in hydroxychloroquine and chloroquine exposures reported to the U.S. Poison Control Centers, compared with April of 2019, presumably due to the large number of people taking hydroxychloroquine for COVID-19.

The EUA Approval Process

The central question in evaluating new therapies is whether FDA should approve Emergency Use Authorizations (EUAs) to fast track the deployment of these drugs. EUAs permit the usage of unapproved medical products to diagnose, treat, or prevent deadly diseases or conditions. They are reserved for patients with life-threatening conditions and chronic illnesses. In order to approve EUAs, the FDA asks a series of linked questions. Do the potential benefits outweigh the risk? Will the product actually be effective? Are we confident we can follow up with patients and track their long-term health outcomes? And do we have sufficient data to make a decision?[35, 36] Because of the immense impact of an EUA, the decision process must take into account evidence from each phase of clinical trials.

Many of the preliminary findings from early outpatient therapeutics are promising, especially for antivirals and monoclonal antibodies. And the data on monoclonal antibodies, especially from Lilly, appears to be enough to issue an EUA. But we must remain vigilant about not giving in to the temptation to issue EUAs without clear evidence. Our lapse in judgement during the first stage of this pandemic has provided us with a valuable lesson: we need to let science do its job. We must not authorize a treatment for widespread use before its efficacy and safety are clear. We cannot set arbitrary timelines for the scientific process to deliver us results. And we absolutely cannot politicize this process.

Both hydroxychloroquine and convalescent plasma were lauded as "miracle cures" but have recently been proven ineffective, and potentially dangerous. In both cases, the politicization of the

scientific process pressured the FDA into prematurely issuing EUAs, despite lack of adequate evidence on efficacy or safety. Hydroxychloroquine is still embraced by many to this day. As an unpatented drug, it is relatively affordable and was widely available, making it a popular option for treatment. Many patients took hydroxychloroquine in the early months of the pandemic. After all, nothing else was on hand, and it was effective against other diseases. The first double-blind clinical trials of the drug were approved with a rapid turnaround. Yet before they could even begin, a series of preprints asserting the efficacy of hydroxychloroquine in treating COVID-19 led to a social media storm. Despite warnings from public health officials on the lack of evidence linking hydroxychloroquine to stronger patient outcomes, the FDA approved an EUA less than two weeks later, on March 27th.[37]

A very similar approach was taken to justify the use of convalescent plasma to treat COVID patients. The FDA processed an EUA in late August, during a televised announcement by the Trump administration. The Commissioner of the FDA, Dr. Stephen Hahn, and President Trump both exaggerated the benefits of plasma despite a lack of evidence on its ability to temper infections or reduce mortality. Just nine days later, the NIH countered the FDA, stating there was not enough evidence for an EUA to have been approved.[38]

The willingness to approve these drugs, despite clear concerns from the scientific community, seemed to stem from political considerations and the election timeline, in keeping with Dr. Stephen Hahn's tweets and President Trump's promises of a vaccine before the election. These comments suggested that the President's reelection campaign was more important than patient safety, with

the result that 72% of Republicans, and 82% of Democrats were concerned that politics would influence vaccine approvals.[39]

The risks of prematurely issuing an EUA for a therapy extend beyond direct patient harm. Such approvals present additional barriers to conducting randomized-controlled trials and generating rigorous scientific evidence. Once a drug has been advertised as effective through an EUA, patients become increasingly unwilling to receive a placebo treatment and physicians increasingly hesitant to prescribe one, making it more challenging to enroll participants in RCTs.[40]

Fueled by misinformation and the politicization of public health, many Americans have come to see these unproven therapeutics as cures. Politicization breeds misinformation, and misinformation fuels politicization. Disagreements between our country's leading health agencies on safety and efficacy of previously approved drugs undermines trust in public health measures across the board.

The Harms of Uninformed Policy Decisions

Deploying novel therapeutics and treatments without robust and rigorous scientific evidence can threaten the health and safety of Americans, and ultimately hinder our nation's ability to bring this pandemic under control. This risk is well established; historically, we have witnessed the harms of prematurely electing an unproven therapy. During the 2003 SARS coronavirus outbreak, for example, physicians began to treat patients with a combination of steroids and high-dose ribavirin, despite thin evidence for the drug's use with coronavirus and many serious side effects. These same mistakes were repeated during the 2014-16 Ebola outbreak, when physicians utilized novel

therapies such as ZMapp, a triple monoclonal antibody cocktail, which was ultimately deemed ineffective through RCTs.[41]

Premature approval of EUAs for experimental treatments has likewise harmed patient health and safety during the COVID-19 pandemic. The approval of convalescent plasma relied on retrospective, indirect evaluations rather than randomized-controlled trials, the gold standard needed to demonstrate safety and efficacy. Hydroxychloroquine demonstrated even less scientific promise than convalescent plasma but was highly promoted by the President. Despite a lack of evidence, an EUA was issued in late March. The results from later clinical trials were clear: hydroxychloroquine did not work. The FDA was forced to revoke its EUA, and clinical trials were paused. In many ways, our approach to hydroxychloroquine and convalescent plasma have been prime examples of what *not* to do in a public health crisis.

In April, about one month after President Trump praised hydroxychloroquine and falsely advertised its benefits, the price of the drug skyrocketed, with a 100-gram container of hydroxychloroquine sulfate increasing in price by about 350%.[42] Following President Trump's statements touting the drug, U.S. pharmacies saw a 46-fold spike in prescriptions for hydroxychloroquine, resulting in shortages across the nation and patients unable to obtain their usual prescriptions for other chronic conditions.[41, 43] This same price increase followed the President's use of dexamethasone, which demonstrated a price increase of 137% in recent months.[44] Hydroxychloroquine can be an effective therapy for individuals with lupus and rheumatoid arthritis while dexamethasone is critical in treating various autoimmune diseases.

Ultimately, overstating the benefits of these drugs in treating COVID-19 made this medication less accessible for individuals living with diseases for which the benefits are well established.

While the unprecedented circumstances of this global pandemic justifies urgency, and a willingness to try out new treatments that demonstrate potential, these tradeoffs must be evaluated carefully. Some have justified the rapid approval of these experimental treatments with the Right to Try Act, a law that enables patients with life-threatening conditions to access certain unapproved or experimental treatments. And while there is a time and a place for this type of legislation, the COVID-19 pandemic is certainly not that. The Right to Try is generally employed in desperate situations, for conditions that offer no tried-and-true alternative. But we do have other options when it comes to COVID-19, including treatments and therapeutics that have demonstrated some success in randomized-controlled trials and are shown to help the most critically ill patients, such as remdesivir and dexamethasone.

It is of the utmost importance that our federal agencies, the gold standard for our nation and the world at large, are respected and left to do their work in peace. And more importantly, the process of review must be transparent, unbiased, and rigorous, restoring our nation's faith in the scientific method before vaccines become widely available in 2021. Leaders of federal agencies also need to be well versed in their own work, so that they don't need to retract erroneous statements and issue apologies for inaccuracies later.

Conclusion

We have a range of potential therapies for COVID-19, including many that appear promising from the preliminary data. But for the good of our patients, we must avoid the temptation to short-circuit the scientific process of gathering and analyzing data, even in the midst of this pandemic. Short-circuiting the scientific process risks a number of serious harms to patients, in both inpatient and outpatient settings.

First, therapeutics that are not adequately vetted and studied can cause direct medical harm to some patients, as seems to be the case with hydroxychloroquine, which can precipitate cardiac arrhythmia, or even poisoning. Second, encouraging the off-label or unauthorized use of inadequately vetted therapeutics through EUAs or other public communications, can radically distort the market, raising prices and causing shortages that affect patients who need drugs to treat labelled conditions. Third, encouraging use of treatments prematurely can gravely impair efforts to gather precisely the data we require to understand if and when to use candidate therapies. Widespread, unregulated use of hydroxychloroquine significantly delayed our ability to assess its efficacy in clinical trials. Likewise, the unstructured and unregulated deployment of convalescent plasma muddied the evidence as to the efficacy of the treatment, including whether it is effective early or late in the course of disease, by limiting the number of patients who could be recruited to study trials and limiting the availability of the treatment itself. Closely related, studying a candidate treatment carries a significant opportunity cost. The effort to expand treatments like convalescent plasma is extremely demanding, requiring the identification of recruitment of volunteers, plasma collection and purification, even before it is administered to patients. We have limited resources, and no time to spare. Investing heavily in such treatments in the absence of robust evidence of efficacy impedes efforts to identify and test other potential treatments.

As a physician, I need to know six key facts about any treatment before I take responsibility for administering it to my patients:

1. In which patients is the treatment effective?

2. How effective is the treatment?

3. What are comparable alternative treatments?

4. At what point in the disease course is it effective?

5. When should treatment be discontinued?

6. What are the major side effects of the treatment?

At present, we simply don't have enough evidence to answer many of these questions for hydroxychloroquine or convalescent plasma. The answers can only come from well-designed RCTs. The scientific community has made a superhuman effort to identify and test novel therapeutics, working at unprecedented speed. If we short-circuit these processes, we risk undermining all of our work, to the detriment of patients. Clinical trials can be done quickly with resources and effort and history has shown us that they are the only way to have confidence in our treatment options. Going forward, the federal government must handle the EUA process in an apolitical, transparent, and scientifically-grounded manner.

We must protect the health and safety of patients by relying on science and moving things quickly by investing more, not cutting corners. Only by following established standards of evidence can we ensure that experimental treatments are not harmful to patients, either directly through side effects or indirectly through the exclusion of individuals with other chronic conditions.

The death toll of this pandemic is unprecedented, and it comes as no surprise that many of us - physicians, patients, and policymakers - are desperate for solutions, and are tempted to resort to desperate measures. But it is precisely during a pandemic that we need science most - when the risk of sacrificing that scientific rigor is greatest. Recent announcements suggest that we will be able to deploy highly effective vaccines in a few months, thanks to scrupulous adherence to scientific principles by those responsible for running and evaluating vaccine candidates. To protect those who will be infected before a vaccine is widely available, we must use the same rigor in evaluating COVID-19 treatments.

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