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COVID-19: The therapeutic landscape

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Therapeutics for hospitalized COVID-19 patients were identified through a robust research response with several lessons learned: clinical trial data should guide therapeutic use, results should not be extrapolated between disease stages, and robust studies should be designed to give clinically relevant data. These lessons should be applied to the outpatient research response.

In late 2019, patients with coronavirus disease 2019 (COVID-19) were first recognized and in early January 2020, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the etiologic agent of this new disease. In certain sub-populations of patients, COVID-19 was associated with high morbidity and a relatively high case fatality rate ranging from <1% to 9%.¹ Confronted by a unique group of patients who developed rapid, and in some cases fatal, progression of respiratory symptoms, clinicians were faced with a challenging dilemma: addressing a novel virus with no proven treatment strategies amid an overwhelming need to “offer something” to growing numbers of critically ill patients. Over the course of the past year, several key lessons have been learned that should be applied to the COVID-19 therapeutics research strategy moving forward.

COVID-19 pathogenesis and natural history inform therapies

Early in the COVID-19 pandemic, the medical community understood which patients were most likely to develop severe COVID-19, identifying risk factors such as age ≥ 65 years and medical comorbidities including diabetes, obesity, and heart disease.² The reason that certain individuals develop severe disease, however, was more difficult to discern, although astute clinicians made two crucial hypothesis-generating observations. First, they noted that the vast majority of patients, approximately 80%,³ were asymptomatic or mildly ill and never required hospital care. Second, patients who did develop severe illness often were hospitalized in the second week after infection with a clinical course that resembled cytokine release syndrome. This led to the hypothesis that COVID-19 is a biphasic illness with early disease/mild symptoms driven by viral

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replication and later disease/more severe symptoms perpetuated by a dysregulated inflammatory and immune response.

Subsequently, much has been learned about the viral biology of SARS-CoV-2 and the host responses seen in severe COVID-19. In this regard, SARS-CoV-2 enters the body primarily through the upper respiratory tract and binds airway and alveolar epithelial cells, vascular endothelial cells, and alveolar macrophages through interactions between the receptor binding domain of the viral spike (S) protein and the host receptor, angiotensin-converting enzyme 2 (ACE2). After binding to upper airway epithelial cells, SARS-CoV-2 replicates and moves further down the respiratory tract into the lungs, the main site of tissue tropism. In most cases, viral replication triggers rapid and robust innate immune responses followed by adaptive responses that lead to viral clearance. In a subset of patients, however, the immune response is dysregulated leading to a suboptimal innate immune response in which unabated viral replication occurs and initiation of the adaptive immune response is delayed. It has been postulated that this dysregulation is driven at least in part by an innate immune response with an inappropriately suppressed interferon pathway and an increased nuclear factor κB (NF-κB)-driven pro-inflammatory cytokine response — perhaps the body’s attempt to compensate for unchecked viral replication. Thus far, immune profiling of hospitalized patients has revealed several distinct immunologic phenotypes associated with severe COVID-19, which suggest that further research is needed to fully delineate the host and/or viral factors that drive these heterogeneous inflammatory and immunologic imbalances. It seems clear, however, that the biphasic illness first described early in the COVID-19 pandemic represents a virus-host inter-

action different than that seen with other respiratory viruses and that effective treatments may vary based on where the patients are in the course of their disease.

**Early months: Off-label and compassionate-use therapies**

Despite the reasonable hypotheses to explain severe COVID-19 (e.g., immune dysregulation), there was a paucity of data, early in the pandemic, regarding appropriate treatment strategies. The scientific literature consisted of reports of agents with in vitro antiviral activity against SARS-CoV-2 and anecdotal case reports or small cohorts detailing treatment successes with agents targeting either the virus itself or the aberrant inflammatory response triggered by the virus. Randomized controlled trials coupled with supportive care were endorsed by the global research community and several large clinical trial networks were rapidly mobilized to initiate studies evaluating COVID-19 treatments. Unfortunately, most hospitals did not have access to clinical trials or, those that did, had limits on the numbers of patients they could enroll. Impediments to the conduct of scientifically sound clinical research were because of a number of factors including a lack of research infrastructure, health systems and staff that were overwhelmed by critically ill patients, shortages of personal protective equipment, and stringent infection control requirements. In addition, patients and their families often deferred enrollment in clinical trials in favor of off-label or compassionate-use therapeutics touted by the media, politicians, or medical personnel with whom they had a relationship. Thus, many clinicians defaulted to using “something,” making the sometimes-incorrect assumption that the potential benefit of this approach would outweigh any potential risk of harm to the patient. Randomized, controlled trials eventually proved a lack of efficacy and in some cases revealed severe adverse events or worsened COVID-19 outcomes for many off-label or compassionate-use therapeutics. One notable example was hydroxychloroquine/chloroquine, which has in vitro antiviral activity against SARS-CoV-2, as well as potentially beneficial immunomodulatory effects on various cytokines. This biologically plausible potential benefit was coupled with an endorsement for use by prominent political officials. In March 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for hydroxychloroquine/chloroquine in COVID-19 patients. Ultimately, numerous randomized controlled clinical trials showed a lack of efficacy for hydroxychloroquine/chloroquine and a concern for safety. In June 2020, the FDA revoked the EUA for hydroxychloroquine/chloroquine and the global research community now recommends against the use of these agents in COVID-19 patients. The story of hydroxychloroquine/chloroquine clearly illustrates the problems with administering off-label or compassionate use therapeutics without supportive clinical trial data.

**Hospitalized patients: Data-driven approaches emerge**

Based on the aforementioned hypothesis regarding pathogenic mechanisms of disease, COVID-19 treatment trials in hospitalized patients were developed — recognizing the need for a multidimensional therapeutic approach that targets the virus itself, the dysregulated host immune response, and complications arising from extensive tissue damage, hypercoagulability, and vascular leak. Even though there were substantial challenges associated with performing these studies while also contending with a pandemic, these data ultimately moved the science forward and led to improved clinical care of hospitalized COVID-19 patients.
The first agent to show clear benefit in treating hospitalized COVID-19 patients was remdesivir, a viral RNA-dependent, RNA polymerase inhibitor that targets the replication of SARS-CoV-2. Prior to being studied in COVID-19, it had known in vitro activity against other coronaviruses, efficacy against coronaviruses in animal models, and a well-established safety profile from prior clinical trials conducted in Ebola patients. The Adaptive Covid-19 Treatment Trial (ACTT) evaluated remdesivir in a large phase 3, double-blind, placebo-controlled clinical trial of hospitalized patients with COVID-19. The ACTT showed that remdesivir reduced the time to recovery by five days in hospitalized patients with COVID-19 pneumonia (median 10 days treatment group versus 15 days control group, rate ratio for recovery, 1.29; 95% confidence interval [CI], 1.12–1.49; p < 0.001) with a non-statistically significant trend toward decreased mortality in the treatment group (11.4% treatment group and 15.2% placebo group at day 29, hazard ratio 0.73; 95% CI, 0.52–1.03). The timing of initiation of remdesivir treatment and the baseline clinical status of the patient impacted the response, with the clearest benefit seen in patients requiring low-flow oxygen. The identification of remdesivir as a modestly effective antiviral represented an important first step in the treatment of COVID-19 and thus far it is the only antiviral shown to have a measurable impact on clinical outcomes in hospitalized patients with COVID-19. It is likely that the earlier an antiviral is administered, the greater the chance of a beneficial effect because, theoretically, they will have their greatest impact when viral replication is the key driver of pathogenesis. This point is well illustrated by randomized controlled trials of anti-SARS-CoV-2 monoclonal antibodies, which have been ineffective in hospitalized patients but are beneficial when administered to outpatients early in infection.

Several agents targeting the dysregulated host immune response have shown benefit in subgroups of hospitalized COVID-19 patients. The first such agent was dexamethasone, which showed benefit in the RECOVERY trial, a large, randomized, open-label COVID-19 treatment trial conducted in the United Kingdom. The RECOVERY trial found a 2.8% reduction in the incidence of death in the dexamethasone group compared with a group receiving standard of care (22.9% treatment group versus 25.7% standard-of-care group). The largest mortality benefit was seen in those requiring invasive mechanical ventilation (29.3% treatment group versus 41.4% standard-of-care group; rate ratio, 0.64; 95% CI, 0.51–0.81) with a lesser impact in non-intubated patients on supplemental oxygen (23.3% treatment group versus 26.2% standard-of-care group; rate ratio, 0.82; 95% CI, 0.72–0.94) and no impact/potential harm in patients on room air (17.8% treatment group versus 14.0% standard-of-care group; rate ratio, 1.19; 95% CI, 0.92–1.55). Based on these data, dexamethasone is now standard of care for patients who require mechanical ventilation or high or rapidly increasing levels of supplemental oxygen. In this trial, no substantial benefit on mortality was seen in patients that received remdesivir, and thus the WHO does not recommend its routine use. In contrast, the NIH and IDSA guidelines committees recommend remdesivir use, acknowledging that while the ACTT was not powered to show an impact on mortality, it did show a trend toward improved mortality and a decreased duration of hospital stay is nonetheless valuable, particularly in a pandemic when healthcare systems are overwhelmed. Additionally, the intervention of the Solidarity primary endpoint, mortality, may be impacted by biases implicit in an open-label trial design as well as an inability to control for variations in standard of care and healthcare capability between trial sites. Also, important variables, such as duration of symptoms and baseline severity of illness, which impacted the interpretation of the Solidarity primary endpoint, mortality, may be impacted by biases implicit in an open-label trial design as well as an inability to control for variations in standard of care and healthcare capability between trial sites. Also, important variables, such as duration of symptoms and baseline severity of illness, which impacted the...
utility of remdesivir within the ACTT cohort, were not reported in the Solidarity dataset. The use of other immunomodulators and the ability to target these agents based on patient characteristics is even less clear. Because of its impact on time to recovery in the ACTT, baricitinib has been proposed as an alternative to dexamethasone in certain situations; however, results of a direct comparison between dexamethasone and baricitinib (currently underway in the ACTT) is needed to truly understand the differences between the two agents. Trials of interleukin-6 inhibitors, such as tocilizumab, have been fraught with limitations in study design leading to conditional recommendations for certain groups of patients and variable use by clinicians.

**Outpatients: Applying lessons learned from the inpatient research response**

To end the COVID-19 pandemic, outpatient treatments for COVID-19 will be needed as an adjunct to vaccination and other prevention measures. Effective treatments could be utilized to achieve several critical goals: preventing infection in high-risk groups before or after an exposure; decreasing viral shedding and reducing transmission among infected individuals; mitigating severity of symptoms; and favorably impacting COVID-19 complications such as long-term sequelae, hospitalizations, and deaths. The lessons learned in treating hospitalized patients must be applied to the management of outpatients, with a focus on using randomized controlled clinical trial data to define standard of care. We have seen outpatient providers utilize many off-label treatments for COVID-19, such as ivermectin, inhaled corticosteroids, fluvoxamine, colchicine, and vitamin and mineral combinations prior to the availability of convincing safety and efficacy data. This approach is in some ways akin to the early usage of hydroxychloroquine/chloroquine and should be curtailed as much as feasible in favor of supportive care and enrollment in clinical trials. Additionally, immunomodulators, such as dexamethasone, that have shown success in the inpatient setting are now being prescribed to outpatients. This is concerning, as pathogenesis in early disease is most likely driven by viral replication that theoretically may be increased by adding an immunosuppressive agent. This idea is supported by data that suggest that corticosteroids are associated with harm in outpatients with early COVID-19 disease and in hospitalized COVID-19 patients who do not require oxygen. It is important that data from one phase of illness not be extrapolated to another as the biphasic pathogenesis of disease almost certainly makes the timing of therapeutic intervention critical to success.

Outpatient COVID-19 treatment trials are arguably more difficult than studies performed in the inpatient setting. This is due to the large numbers of patients needed to support critical but relatively uncommon endpoints such as hospitalization and death, stringent infection prevention protocols that make in-person evaluation of COVID-19 outpatients challenging, shortages of personal protective equipment and SARS-CoV-2 testing supplies, and a lack of research infrastructure associated with the majority of outpatient clinic sites. Creative trial design and ongoing development of research infrastructure will be needed to facilitate generation of data in the outpatient setting. In this regard, the NIH in collaboration with other United States government agencies and the private sector has established the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to facilitate multiple COVID-19 therapeutics studies. This effort includes trials designed to move promising therapeutic agents forward in the outpatient setting.

**Outpatients: Data-driven approaches**

Currently, few therapeutic options are available for the outpatient population, and care remains mostly supportive. In outpatients at high-risk of severe COVID-19, anti-SARS-CoV-2 monoclonal antibodies, are recommended. This guidance is based on clinical trial data suggesting decreased progression to hospitalization and death if given early after infection. As these agents are given via an intravenous infusion that can be performed only in certain locations, the overall impact of monoclonal antibodies has been limited by availability and delays in administration. Improving access to these agents or developing SARS-CoV-2 monoclonal antibodies that can be administered through alternative
routes, e.g., subcutaneously, intramuscularly, or via inhalation, will have a critical impact on outpatient COVID-19 care. In addition, SARS-CoV-2 variants may render current anti-SARS-CoV-2 monoclonal antibodies less effective or ineffective, thus requiring the development of monoclonal antibodies targeting either new epitopes on the mutated viruses or conserved regions of the virus that are less likely to change.

Targeted design of direct-acting, orally available antiviral drugs remains a very high priority in the COVID-19 therapeutics research response. The spectacular successes of this approach in the development of combinations of antiretroviral drugs for HIV and the development of curative therapies for hepatitis C serve as a model. In this regard, promising agents under evaluation in clinical trials include molnupiravir (Merk Co.), which is a viral ribonucleoside inhibitor, as well as PF-07321332, (Pfizer) an oral viral protease inhibitor.

Conclusions

Over the past year, major advances have been made in the discovery of therapeutics for a novel pathogen, SARS-CoV-2. Valuable lessons have been learned through this initial research response including the concepts that: (1) it is critical to base treatment approaches on safety and efficacy from randomized controlled clinical trials, (2) data cannot be extrapolated from one stage of COVID-19 disease to another, and (3) trials must be designed to provide the most robust and clinically relevant data possible. Despite the recent implementation of several highly efficacious vaccines, COVID-19 almost certainly will remain with us and our armamentarium of therapeutics will serve as a stopgap for breakthroughs in prevention measures. Substantial resources and a commitment to ongoing therapeutics research is crucial to ending the COVID-19 pandemic. Lessons learned thus far must guide us to further the COVID-19 therapeutics research response and must shape the path forward when considering strategies during future pandemics.

DECLARATION OF INTERESTS

Dr. Fauci declares no competing interests. Dr. Paules is the site principal investigator at Penn State Health for The Adaptive Covid-19 Treatment Trial (ACTT), which receives funding from the National Institutes of Health.

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