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CURRENT OPINION

Novel Strategies for the Treatment of COVID-19

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Abstract
On 4 September, 2020, the US National Institutes of Health launched a new clinical trial, "A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19." This open-label, placebo-controlled, multicenter, adaptive platform study was designed to evaluate therapeutic options for patients hospitalized with mild, moderate, or severe COVID-19. A variety of drugs and drug classes were selected, including heparin, the monoclonal antibody crizanlizumab, sodium-glucose cotransporter-2 inhibitors, and purinergic signaling receptor Y_{12} inhibitors. These medications have been widely used in the treatment of other conditions, from sick cell disease to type 2 diabetes mellitus and some forms of cardiovascular disease, but their inclusion in a study of COVID-19 was somewhat unexpected. This article examines the rationale behind the use of these disparate agents in the treatment and prevention of adverse outcomes in patients with COVID-19 and explores how these strategies may be utilized in the future to address the severe acute respiratory syndrome coronavirus 2 pandemic.

Key Points

Randomized controlled trials are urgently needed to accelerate the development of effective therapeutics for the treatment of COVID-19.

The monoclonal antibody crizanlizumab has shown therapeutic promise in small studies of patients with COVID-19.

Sodium-glucose cotransporter-2 inhibitors prevent reabsorption of glucose in the kidney, lower blood glucose, and may provide benefit for patients infected with severe acute respiratory syndrome coronavirus 2.

1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has exposed the need for high-quality clinical trials to optimize the treatment of coronavirus disease 2019 (COVID-19) [1]. Although hundreds of therapeutic agents have been studied, very few have been evaluated within the confines of randomized controlled trials [2–4]. These studies are labor intensive, however, and more efficient randomized controlled trial designs are urgently needed to accelerate development, minimize costs, and make trials more appealing to patients [5]. One potential pathway involves adaptive platform trials in which multiple experimental treatment groups are concurrently compared with a single control group [6, 7]. This approach allows experimental groups to enter and exit the trial at different times and may be modified as the standard of care evolves [8].

On 17 April, 2020, the National Institutes of Health announced the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to facilitate the development of the most promising treatments and vaccines [9]. Within the ACTIV platform, the Therapeutics Clinical Working Group was charged with evaluating a variety of therapeutic candidates for COVID-19 with near-term potential. These therapeutic agents could be broadly grouped into immunomodulators, which have been studied in ACTIV-1, monoclonal antibody therapies, direct-acting antiviral therapies, and host targeted therapies, which have been studied in ACTIV-2, ACTIV-3, and ACTIV-5, and antithrombotic therapies, which have been evaluated in ACTIV-4, and repurposed drugs for outpatients

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with COVID-19, which have been evaluated in ACTIV-6 [3, 10–12]. Other targeted host therapies, such as TRV027, TXA127, and fostamatinib, have also been selected for clinical trials involving patients with COVID-19. Some of these studies have completed enrollment while others are ongoing [12–14].

ACTIV-4a is an open-label, placebo-controlled, multicenter, adaptive platform study currently evaluating therapeutic options for patients hospitalized with mild, moderate, or severe COVID-19. A variety of drugs and drug classes were selected based on findings from smaller studies, including the monoclonal antibody crizanlizumab, which has been used to treat sickle cell disease; sodium-glucose cotransporter-2 inhibitors, which are used to treat type 2 diabetes and some cardiovascular diseases; and purinergic signaling receptor Y_{12} (P2Y12) inhibitors, which are used to treat some forms of heart disease. This article examines the rationale for including these medications in a trial evaluating the treatment of COVID-19.

2 Crizanlizumab

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin and prevents its interaction with P-selectin glycoprotein ligand 1 [15]. P-selectin is present on the surface of endothelial cells as well as activated platelets and has been associated with sickle cell pain crises [16, 17]. A double-blind, randomized, placebo-controlled, phase II trial of 198 patients with sickle cell disease found that crizanlizumab therapy resulted in a significantly lower rate of sickle cell-related pain crises than placebo and was associated with a low incidence of adverse events [18]. Further analyses of secondary endpoints demonstrated that crizanlizumab significantly increased time-to-first pain crisis compared with placebo [19]. In November 2019, crizanlizumab received approval by the US Food and Drug Administration, where it is indicated to reduce the frequency of vaso-occlusive crisis in adults and pediatric patients aged 16 years and older with sickle cell disease [20, 21].

Given the widespread and complex mechanism of action, crizanlizumab may have applications beyond the realm of sickle cell disease [22–24]. COVID-19 is characterized by vascular inflammation and thrombosis, including elevations in P-selectin. Leucker and colleagues tested the effect of P-selectin inhibition on biomarkers of thrombosis and inflammation in patients with COVID-19 [25]. In a double-blinded study, hospitalized patients with moderate COVID-19 were randomly assigned to receive either crizanlizumab or placebo. The authors found that crizanlizumab reduced P-selectin levels by 89%, increased D-dimer levels by 77%, and decreased the prothrombin fragment, suggesting that crizanlizumab may induce thrombolysis in the setting of COVID-19 [22].

Osburn and colleagues showed that increased levels of P-selectin are linked to the severity of pulmonary disease in COVID-19 and correlate with biomarkers of inflammation and vascular inflammation, further supporting the hypothesis that COVID-19 is a vascular disease that involves endothelial injury that may be amenable to treatment with crizanlizumab [22].

However, data from a robust randomized trial are lacking. ACTIV-4a is now evaluating crizanlizumab in the treatment of hospitalized patients with mild or moderate COVID-19. This arm of the study aims to enroll approximately 1000 patients. Patients are randomly assigned to one dose of crizanlizumab plus standard of care or standard of care alone and results are expected in 2023.

3 Sodium-Glucose Cotransporter-2 Inhibitors

Phlorizin is a glucose molecule attached to two aromatic rings that was first isolated from the root bark of an apple tree in 1835 and was initially used in the treatment of malaria [26]. In 1886, phlorizin was found to lower plasma glucose through glucosuria, although the mechanism was unknown [27, 28]. It was later learned that glucose is filtered in the glomerulus and is almost fully reabsorbed by the proximal renal tubules through active co-transport of glucose and sodium [29, 30]. When transport is inhibited by phlorizin, both glucose and sodium are excreted in the urine [31–33].

Although potent, phlorizin is poorly absorbed from the gastrointestinal tract [34, 35]. Phlorizin analogs, which became the first chemically engineered sodium-glucose cotransporter-2 inhibitors, have improved systemic absorption and are well tolerated [36–39]. Sodium-glucose cotransporter-2 inhibitors (henceforth referred to as gliflozins) are now used widely in clinical medicine to prevent the reabsorption of glucose in the kidney and have been shown to lower blood glucose and glycated hemoglobin in patients with type 2 diabetes without causing hypoglycemia [40, 41]. Gliflozins also improve systolic and diastolic blood pressure, improve cardiac function in patients who have heart failure, improve renal function, and contribute to weight loss, with few adverse effects [42–46]. Until recently, however, gliflozins have had a limited role in the treatment of infectious diseases.

The role of gliflozins during the SARS-CoV-2 pandemic has been controversial [47, 48]. This drug class exerts systemic anti-inflammatory effects by reducing adipose tissue inflammation beyond that commonly observed with weight loss [49, 50]. Gliflozins also have been shown to increase hematocrit, reduce hypoxia, and provide cellular protection

due to reductions in cytoplasmic Na^+ and Ca^{++} concentrations, all of which may be therapeutically useful in the setting of SARS-CoV-2 infection [49, 51–53]. However, in both randomized controlled trials and observational studies, gliflozins have been associated with a two-fold higher risk of diabetic ketoacidosis compared with placebo or other active glucose-lowering agents [51, 52]. Sainsbury and colleagues did not observe an increased risk of COVID-19 in primary care amongst those prescribed gliflozins, suggesting these drugs could be safely used during the pandemic and may, in fact, be beneficial [54].

For example, dapagliflozin has shown significant cardiorenal benefits in patients with type 2 diabetes, heart failure, and chronic kidney disease, and may provide similar organ protection in high-risk patients with COVID-19 [55–58]. The Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial showed that in 1250 patients hospitalized with COVID-19, treatment with dapagliflozin versus placebo reduced organ failure or death, although these differences were not statistically significant [59]. Importantly, the drug was well tolerated and there were no concerns about an increased risk of diabetic ketoacidosis, volume depletion, or acute kidney injury in trial participants [60].

The findings from DARE-19 suggest a need for future clinical trials to determine whether gliflozins might provide organ protection in hospitalized patients who are at an increased risk for progressing to severe disease, with a focus on randomized controlled studies to evaluate prevention of organ failure and death. ACTIV-4a is now evaluating gliflozins in the treatment of patients hospitalized with mild or moderate COVID-19. The trial aims to close enrollment in late 2022 with topline results in 2023.

4 P2Y12 Inhibitors

Platelet adhesion, activation, and aggregation play a pivotal role in thrombosis, which is a hallmark of severe COVID-19 [14, 22, 61]. An essential component in the platelet activation process is the interaction of adenosine diphosphate with the platelet P2Y12 receptor [13, 62, 63]. The P2Y12 receptor is a G-inhibitory-protein receptor in the platelet membrane that belongs to a family of P2Y receptors whose ligands are purine and pyrimidine nucleotides [64–66].

Serum biomarkers reflecting platelet activity, including soluble CD40 ligand, P-selectin, and thromboxane B_2, have been found to be independently associated with the risk of severe disease, thrombosis, and death in patients with COVID-19, suggesting activated platelets may represent a therapeutic target to improve outcomes in patients with COVID-19 [67].

Despite the therapeutic promise of platelet inhibition, early data have been disappointing. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial found that the use of aspirin, another platelet antagonist, was not associated with improved survival or reduced risk of progression to invasive mechanical ventilation or death [68]. The authors speculate that the absence of meaningful benefit from aspirin could be due to a variety of factors, from the timing of intervention to other non-platelet pathways leading to thrombosis and alveolar damage.

Berger and colleagues performed a Bayesian, adaptive randomized clinical trial of 562 non-critically ill patients with COVID-19 in which patients received a therapeutic dose of heparin plus a P2Y12 inhibitor, compared with a therapeutic dose of heparin only [13]. They found that the addition of a P2Y12 inhibitor did not improve survival or increase the number of days free of cardiovascular or respiratory organ support. A portion of the ACTIV-4A P2Y12 inhibitor study has read out and shown no benefit in moderately ill patients. However, there is still potential that this drug, in combination with heparin, will be beneficial above heparin alone in critically ill patients.

In light of these therapeutic setbacks, important questions remain. The use of P2Y12 inhibitor as a sole antithrombotic agent may improve outcomes in patients with COVID-19; moreover, the potential for benefit with a longer treatment duration or at an earlier stage of illness may also be beneficial.

5 Future Directions

SARS-CoV-2 leads to severe disease through a variety of mechanisms and the optimal treatment of COVID-19 is in flux [69–71]. The virus damages a wide range of tissues and may induce aberrant signaling of the immune system [72–74]. Abnormalities of the clotting cascade, including low platelets and elevated D-dimer levels, are common in patients with severe COVID-19 and are associated with increased mortality [75]. This cascade serves as a potential therapeutic target.

ACTIV-4a is an open-label randomized multicenter trial studying a variety of targets involved to varying degrees in the clotting cascade and vascular homeostasis in patients with COVID-19. Heparin has shown benefit in some patients at risk for thrombotic disease. Crizanlizumab and P2Y12 inhibitors interfere with P-selectin through different mechanisms, which in turn impairs the clotting cascade (22, 76, 77). Gliflozins have been shown to increase hematocrit and reduce hypoxia in certain patients, which may be therapeutically useful in the setting of SARS-CoV-2 infection.

ACTIV-4a continues to enroll patients. The primary endpoint is 21-day organ support-free days, which is defined as

the number of days that a patient is free of organ support through the first 21 days after trial entry. Organ support is defined as the receipt of non-invasive mechanical ventilation, high-flow nasal canula oxygen, mechanical ventilation, or vasopressor therapy, or death. This adaptive study enables the study of multiple therapeutics simultaneously and allows the standard of care to change in conjunction with local, national, and international guidelines.

As our understanding of COVID-19 evolves, so too must our therapeutic approach. Severe acute respiratory syndrome coronavirus 2 induces a wide range of abnormalities in humans, which opens up the potential therapeutic arsenal to classes of drugs not traditionally associated with infectious diseases as well as targeted host therapies. ACTIV-4a serves as an important testing ground for several classes of drugs. Overall results from this study are expect in 2023, and will inform clinical management for years to come.

Declarations

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Conflicts of Interest/Competing Interests Matthew W. McCarthy has no conflicts of interest that are directly relevant to the content of this article.

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