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 Y12 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.
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, multi-center, 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 Y12 (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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**References**

1. Grobler JA, Anderson AS, Fernandes P, Diamond MS, Colvis CM, Menetski JP, et al. Accelerated preclinical paths to support rapid development of COVID-19 therapeutics. Cell Host Microbe. 2020;28(5):638–45.

2. Guharoy R, Krenzelok EP. US Food and Drug Administration (FDA) emergency use authorization: glass half full or glass half empty? Clin Infect Dis. 2021;73(3):549–52.

3. Hewitt JA, Lutz C, Florence WC, Pitt MLM, Rao S, Rappaport J, et al. ACTIVating resources for the COVID-19 pandemic: in vivo models for vaccines and therapeutics. Cell Host Microbe. 2020;28(5):646–59.

4. Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. Nat Rev Drug Discov. 2021;20(4):254–5.

5. Freidlin B, Korn EL, Gray R, Martin A. Multi-arm clinical trials of new agents: some design considerations. Clin Cancer Res. 2008;14(14):4368–71.

6. Dodd LE, Freidlin B, Korn EL. Platform trials: beware the non-comparable control group. N Engl J Med. 2021;384(16):1572–3.

7. Collignon O, Burman CF, Posch M, Schiel A. Collaborative platform trials to fight COVID-19: methodological and regulatory considerations for a better societal outcome. Clin Pharmacol Ther. 2021;110(2):311–20.

8. Selukar S, May S, Law D, Othus M. Stratified randomization for platform trials with differing experimental arm eligibility. Clin Trials. 2021;18(5):562–9.

9. Collins FS, Stoffels P. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): an unprecedented partnership for unprecedented times. JAMA. 2020;323(24):2455–7.

10. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRIV-196 plus BRIV-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 2022;22(5):622–35.

11. Buchman TG, Draghia-Akli R, Adam SJ, Aggarwal NR, Fessel JP, Higgins ES, et al. Accelerating coronavirus disease 2019 therapeutic interventions and vaccines: selecting compounds for clinical evaluation in coronavirus disease 2019 clinical trials. Crit Care Med. 2021;49(11):1963–73.

12. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med. 2021;385(9):790–802.

13. Berger JS, Kornblith LZ, Gong MN, Reynolds HR, Cushman M, Cheng Y, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. JAMA. 2022;327(3):227–36.

14. Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021;385(9):777–89.

15. Sims JW, Mager DJ, Davis SCAT, Biemond BJ, Fijnvandraat K. Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review. Blood Adv. 2017;1(19):1598–616.

16. Darbari DS, Sheehan VA, Ballas SK. The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management. Eur J Haematol. 2020;105(3):237–46.

17. Gardner RV. Crizanlizumab in vaso-occlusive crisis caused by sickle cell disease. Drugs Today (Barc). 2020;56(11):705–14.

18. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrish J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017;376(5):429–39.

19. Kutlar A, Kanter J, Liles DK, Alvarez OA, Cançado RD, Friedrish JR, et al. Effect of crizanlizumab on pain crises in subgroups of patients with sickle cell disease: a SUSTAIN study analysis. Am J Hematol. 2019;94(1):55–61.

20. Ali MA, Ahmad A, Chaudry H, Aiman W, Aamir S, Anwar MY, et al. Efficacy and safety of recently approved drugs for sickle cell
pilocarpine affects neurodegeneration process in hippocampus. Epilepsy Behav. 2016;61:258–68.
40. Bonadonna RC, Borghi C, Consoli A, Volpe M. Novel antidiabetic drugs and cardiovascular risk: primum non nocere. Nutr Metab Cardiovasc Dis. 2016;26(9):759–66.
41. Bonner C, Kerr-Conte J, Gmvr V, Queniat G, Moerman E, Thévenet J, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med. 2015;21(5):512–7.
42. Braunwald E. Gliflozins in the management of cardiovascular disease. N Engl J Med. 2022;386(21):2024–34.
43. Borges-Júnior FA, Silva Dos Santos D, Benetti A, Poldoroz JD, Wisnivesky ACT, Crajoianas RO, et al. Empagliflozin inhibits proximal tubule NHE3 activity, preserves GFR, and restores euvolemia in nondiabetic rats with induced heart failure. J Am Soc Nephrol. 2021;32(7):1616–29.
44. Dumann E, Menne J. SGLT2 inhibitors: what is new? Nephrol. 2021;16(4):241–55.
45. Faillie JL. Pharmacological aspects of the safety of gliflozins. Pharmaco Res. 2017;118:71–81.
46. Fonseca-Correa JJ, Correa-Rotter R. Sodium-glucose cotransporter 2 inhibitors mechanisms of action: a review. Front Med (Lausanne). 2021;8:777861.
47. Milder TY, Stocker SL, Day RO, Greenfield JR. Potential safety issues with use of sodium glucose cotransporter 2 inhibitors, particularly in people with type 2 diabetes and chronic kidney disease. Drug Saf. 2020;43(12):1211–21.
48. Mirabelli M, Chieffari E, Puccio L, Foti DP, Brunetti A. Potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis. Int J Environ Res Public Health. 2020;17(10):3664.
49. Soni S, Dyck JRB. The Multiple effects of SGLT2 inhibitors suggest potential benefit in COVID-19 patients. Can J Cardiol. 2020;36(10):1691.e3.
50. Sun B, Huang S, Zhou J. Perspectives of antidiabetic drugs in diabetes with coronavirus infections. Front Pharmacol. 2020;11:592439.
51. Scheen AJ. SGLT2 inhibition during the COVID-19 epidemic: friend or foe? Diabetes Metab. 2020;46(5):343–4.
52. Schnell O, Battelino T, Bergenstal R, Böhmer M, Broiuss F, et al. Report from the CVOT Summit 2021: new cardiovascular, renal, and glycemic outcomes. Cardiovasc Diabetol. 2022;21(1):50.
53. Spertus JA, Birmingham MC, Nassif M, Damaraju CV, Abbate A, Butler J, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nat Med. 2022;28(4):809–13.
54. Sainsbury C, Wang J, Gokhale K, Acosta-Mena D, Dhalla S, Byne N, et al. Sodium-glucose co-transporter-2 inhibitors and susceptibility to COVID-19: a population-based retrospective cohort study. Diabetes Obes Metab. 2021;23(1):263–9.
55. Aberle J, Menzen M, Schmid SM, Terkamp C, Jaeckel E, Rohwedder K, et al. Dapagliflozin effects on haematocrit, red blood cell count and reticulocytes in insulin-treated patients with type 2 diabetes. Diabetologia. 2020;63(2):22396.
56. Adamson C, Juand PS, Docherty KF, Bélohlavék J, Chiang CE, Diez M, et al. Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. Eur J Heart Fail. 2021;23(10):1662–72.
57. Alatrach M, Agyin C, Solis-Herrera C, Lavryneko O, Adams J, Gastaldelli A, et al. Dapagliflozin impairs the suppression of endogenous glucose production in type 2 diabetes following oral glucose. Diabetes Care. 2022;45(6):1372–80.
59. Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparian SB, Koch GG, et al. Dapagliflozin in patients with cardio-metabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;9(9):586–94.

60. Heerspink HJL, Furtado RHM, Berwanger O, Koch GG, Martinez F, Mukhtar O, et al. Dapagliflozin and kidney outcomes in hospitalized patients with COVID-19 infection: an analysis of the DARE-19 randomized controlled trial. Clin J Am Soc Nephrol. 2022;17(5):643–54.

61. Freda CT, Yin W, Ghebrehiwet B, Rubenstein DA. SARS-CoV-2 structural proteins exposure alter thrombotic and inflammatory responses in human endothelial cells. Cell Mol Bioeng. 2021;15(1):43–53.

62. Jain V, Al Rifai M, Mahtta D, Liu J, Hussain A, Virani SS. Highlights from studies presented at the virtual American College of Cardiology Scientific Sessions 2021: staying updated with the latest advancements in prevention. Curr Atheroscler Rep. 2021;23(9):50.

63. Szarpak L, Michalski TA, Smereka J, Gasecka A, Pruc M, Jaguszewski MJ. Efficacy and safety of ticagrelor use in pre-hospital setting. Am J Emerg Med. 2022;52:265–6.

64. Zhang K, Wang Y, Liu T, Niu X. Comparison of aspirin and P2Y12 inhibitors for secondary prevention of ischaemic stroke: a systematic review and meta-analysis. Curr Rev Clin Exp Pharmacol. 2022.

65. Zhang J, Chang H, Rockman C, Patel VI, Veeraswamy R, Berland T, et al. Hypogastric artery flow interruption is associated with increased mortality after open aortic repair. Ann Vasc Surg. 2022.

66. Zou L, Liu S, Li L, Yang R, Xu X, Li G, et al. Implication of P2Y. Eur J Pharmacol. 2022;927:175049.

67. Barrett TJ, Lee AH, Xia Y, Lin LH, Black M, Cotzia P, et al. Platelet and vascular biomarkers associate with thrombosis and death in coronavirus disease. Circ Res. 2020;127(7):945–7.

68. Group RC. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399(10320):143–51.

69. Cubeddu LX, de la Rosa D, Ameruoso M. Antiviral and anti-inflammatory drugs to combat COVID-19: effects on cardiac ion channels and risk of ventricular arrhythmias. Bioimpacts. 2022;12(1):9–20.

70. Hammarström L, Marrotte H, Piralla A, Baldanti F, Pan-Hammarström Q. Antibody therapy for COVID-19. Curr Opin Allergy Clin Immunol. 2021;21(6):553–8.

71. Després JP. Severe COVID-19 outcomes: the role of physical activity. Nat Rev Endocrinol. 2021;17(8):451–2.

72. Díaz-García E, García-Tovar S, Altaro E, Zamarrón E, Mangas A, Galera R, et al. Role of CD39 in COVID-19 severity: dysregulation of purinergic signaling and thromboinflammation. Front Immunol. 2022;13:847894.

73. Geng J, Chen L, Yuan Y, Wang K, Wang Y, Qin C, et al. CD147 antibody specifically and effectively inhibits infection and cytokine storm of SARS-CoV-2 and its variants delta, alpha, beta, and gamma. Signal Transduct Target Ther. 2021;6(1):347.

74. Rommazi F, Nasiri MJ, Mirsaedi M. Immunomodulatory agents for COVID-19 treatment: possible mechanism of action and immunopathology features. Mol Cell Biochem. 2022;477(3):711–26.

75. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.

76. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:2040620720955000.

77. Yu Z, Blankenship L, Jaiyesimi I. Crizanlizumab in sickle cell disease. N Engl J Med. 2017;376(18):1795–6.