DOI: 10.4274/csmedj.galenos.2022.2022-12-1

Cam and Sakura Med J 2023;3(3):91-100

CSMJ

Treatment of COVID-19: Antivirals, Antibody Products, Immunomodulators, Antithrombotic Therapy, and Supplements

Asuman İnan[1], Sibel Bolukçu[2]

[1]University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

[2]Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

With the advent of the pandemic, the landscape of treatment options has undergone rapid transformations in response to evolving viral variants. Current guidelines advocate tailoring treatments based on disease severity and the distinction between outpatient and inpatient settings. Remdesivir is endorsed for hospitalized cases, whereas molnupiravir is recommended for managing mild to moderate coronavirus disease-2019 (COVID-19) in individuals at high risk of progressing to severe disease. Baricitinib holds Food and Drug Administration (FDA) approval in the United States for use in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Furthermore, dexamethasone is indicated for severely ill COVID-19 patients who require supplemental oxygen or ventilator support. Notably, tocilizumab has demonstrated limited efficacy in reducing the risk of disease progression. The FDA has granted Emergency Use Authorization for bebtelovimab, specifically for the treatment of mild to moderate COVID-19. Tixagevimab and cilgavimab have received FDA authorization for emergency use as pre-exposure prophylaxis against COVID-19. Although there is a recommendation against the use of an intermediate dose of low-molecular-weight heparin in critically ill COVID-19 patients, supported by moderate-level evidence, this recommendation does not extend to outpatient settings. However, there is insufficient evidence to endorse or discourage the use of supplements for treating COVID-19, both in non-hospitalized and hospitalized patients.

Keywords: COVID-19, treatment, pandemic

Introduction

Coronavirus disease-2019 (COVID-19) has evolved into a pandemic characterized by a rapidly escalating incidence of infections and fatalities. Several pharmacologic interventions are currently under consideration for treatment. Acknowledging the swiftly expanding body of literature, organizations such as the Infectious Diseases Society of America (IDSA) recognize the imperative to develop dynamic, regularly updated evidence-based guidelines. These guidelines aim to provide comprehensive support to patients, clinicians, and other healthcare professionals in their strategic decision-making processes regarding the treatment and management of individuals afflicted by COVID-19.

Outlined below are the recommendations, accompanied by pertinent commentary, as delineated in the clinical practice guidelines of both the IDSA and the National Institutes of Health (NIH) for the treatment of COVID-19.

Address for Correspondence: Assoc. Prof. Asuman İnan, University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

Phone: +90 216 542 32 32 **E-mail:** asumaninan@hotmail.com **ORCID ID:** orcid.org/0000-0002-6182-1262

Received: 08.12.2023 **Accepted:** 19.12.2023

Antiviral Treatment

Remdesivir

Remdesivir is a novel nucleotide analog that is metabolized to its active metabolite, remdesivir triphosphate. Remdesivir triphosphate is a structural analog of adenosine triphosphate and competes with the natural substrate for incorporation by RNA polymerase into nascent viral RNA, which results in delayed chain termination during replication and consequently inhibits viral replication (1,2). The Food and Drug Administration (FDA) has approved remdesivir for hospitalized children aged 12 and above and adults with COVID-19, regardless of disease severity (3). One of the most recent and largest studies describing the effectiveness of remdesivir in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection reported that despite its conditional recommendation, remdesivir may still be effective in achieving early clinical improvement. It reduces early-stage mortality and the need for high-flow oxygen supplementation and invasive mechanical ventilation among hospitalized COVID-19 patients (4). Despite the World Health Organization (WHO) reviewing its recommendation on remdesivir for hospitalized patients, guidelines from the NIH and IDSA recommend remdesivir (5,6,7).

Paxlovid (Nirmatrelvir-Ritonavir)

Nirmatrelvir inhibits the activity of the SARS-CoV-2-3CL protease, an enzyme crucial for viral replication, and co-administration with ritonavir extends the duration and increases the concentration of nirmatrelvir activity in the body (8). The FDA issued an Emergency Use Authorization (EUA) for paxlovid in December 2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age). Paxlovid is available by prescription only and should be promptly initiated after the diagnosis of COVID-19 and within five days of symptom onset (9).

Several large observational studies have linked paxlovid to clinical benefits in vaccinated individuals with underlying risk factors for severe disease (10,11,12,13,14,15). For instance, a study involving 1,130 vaccinated adults who received paxlovid within five days of COVID-19 diagnosis and 1,130 controls matched for age, gender, race, and comorbidities found that paxlovid was associated with a lower rate of emergency department visits, hospitalization, and death [odds ratio (OR): 0.5, CI 0.39-0.67] (12). Notably, all 10 deaths occurred in the untreated group. These observational studies were conducted in 2022, during the predominance of Omicron subvariants, suggesting that paxlovid retains efficacy against these variants.

Molnupiravir

Molnupiravir is a pro-drug of the nucleotide analog N4-hydroxycytidine and exhibits broad-spectrum antiviral activity against RNA viruses, including influenza, Ebola, coronaviruses, and respiratory syncytial virus (14).

In a recent study involving 202 participants, a significantly lower percentage of individuals receiving an 800 mg dose of molnupiravir (1.9%) had isolatable virus on day 3 compared with the placebo group (16.7%) ($p=0.02$). By day 5, virus isolation was not possible from any participant receiving 400 or 800 mg of molnupiravir, whereas it was still evident in 11.1% of those in the placebo group ($p=0.03$). Molnupiravir was generally well tolerated, with similar adverse events observed across all groups (2).

In an international randomized controlled trial (RCT) involving 1,433 non-hospitalized, unvaccinated adults with mild to moderate COVID-19 symptoms onset within five days and at least one risk factor for severe disease, molnupiravir demonstrated an approximately 33% reduction in the risk of hospitalization or death. The combined outcome occurred in 6.8% versus 9.7% of patients compared with the placebo group, although this difference was not statistically significant (16). Among the 10 deaths reported among trial participants, one occurred in the molnupiravir group and nine occurred in the placebo group.

The FDA has approved molnupiravir for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization or death, when alternative FDA-authorized COVID-19 treatment options are either inaccessible or clinically inappropriate (17).

Favipiravir

Favipiravir is a selective and potent inhibitor of RNA-dependent RNA polymerase, which inhibits viral genome replication. It boasts a broad antiviral spectrum, allowing its use in various infections such as influenza and Ebola. Originally synthesized in 2005, it was first approved for the treatment of influenza in Japan and later received approval in Russia for the treatment of COVID-19 (14,18).

Clinical studies on the efficacy of favipiravir for COVID-19 treatment have yielded conflicting results. In a meta-analysis, the pooled analysis of five studies indicated that favipiravir was associated with a higher clinical improvement rate than the control group, although the difference did not reach statistical significance [OR: 1.54; 95% confidence interval (CI): 0.78-3.04]. Additionally, the viral clearance rate at days 4-5, 7-8, and 10-12 did not differ between favipiravir and the comparator, and the risk of adverse events was similar between the groups

(18). However, in another recent meta-analysis of nine studies comparing the efficacy of favipiravir with that of other control groups, a significant clinical improvement was observed in the favipiravir group versus the control group during the seven days following hospitalization (RR: 1.24, 95% CI: 1.09-1.41; p=0.001). Although viral clearance was higher 14 days after hospitalization in the favipiravir group, this finding did not reach statistical significance (RR: 1.11, 95% CI: 0.98-1.25; p=0.094). The mortality rate was observed to be 30% lower in the favipiravir group, but this finding did not achieve statistical significance (19).

Lopinavir/Ritonavir

Lopinavir and ritonavir were among the first drugs investigated in clinical trials for the treatment of COVID-19. Despite showing inhibitory effects against SARS-CoV-2, three RCTs conducted among hospitalized patients with COVID-19 indicated that treatment with lopinavir/ritonavir failed to demonstrate any significant benefits in terms of mortality, the need for invasive mechanical ventilation, or 28-day hospital discharge rates (20,21,22,23). Current guidelines discourage the use of the lopinavir/ritonavir combination in hospitalized patients with COVID-19 (5,6,7,14).

Adjuvants/Supportive Treatment

Dexamethasone

Dexamethasone is a synthetic glucocorticoid, a fluorinated derivative of prednisone, known for its potent and prolonged anti-inflammatory and immunosuppressive effects. Glucocorticoids, including dexamethasone, have been investigated for their potential to modulate inflammation-mediated lung injury, thereby reducing the progression to respiratory failure and death in COVID-19 patients (15).

The primary efficacy data on glucocorticoids in COVID-19 comes from a substantial open-label trial conducted in the United Kingdom. In this study, 2104 patients with confirmed or suspected COVID-19 were randomly assigned to receive dexamethasone (administered at 6 mg orally or intravenously (IV) daily for up to 10 days), whereas 4,321 patients received usual care (24). The primary endpoint was mortality at 28 days. The results showed that 22.9% of patients in the dexamethasone group and 25.7% in the standard care group died within 28 days after randomization (age-adjusted OR: 0.83, 95% CI: 0.75-0.93; p<0.001).

Furthermore, the study demonstrated that the dexamethasone group had a lower death rate than the standard care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; RR: 0.64, 95% CI: 0.51-0.81) and those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; RR: 0.82, 95% CI: 0.72-0.94). However, no significant difference was observed among patients who did not receive respiratory support at the time of randomization (17.8% vs. 14.0%; RR: 1.19, 95% CI: 0.92-1.55).

In conclusion, the study indicated that dexamethasone treatment resulted in lower 28-day mortality in patients hospitalized for COVID-19 who were undergoing mechanical ventilation or oxygen therapy. However, it did not show a significant benefit for patients who did not receive respiratory support at the time of randomization. Consequently, dexamethasone is recommended for severely ill COVID-19 patients requiring supplemental oxygen or ventilator support.

Tocilizumab

Tocilizumab is a recombinant humanized IgG1 monoclonal antibody (mAbs) that specifically binds to both soluble and membrane-bound receptors for IL-6, thereby inhibiting this signaling pathway and reducing its pro-inflammatory effects of interleukin (IL)-6 (25).

Cumulative evidence suggests a mortality benefit associated with tocilizumab (26,27). In a meta-analysis encompassing 27 randomized trials involving over 10,000 patients hospitalized with COVID-19, all-cause mortality was lower among those receiving tocilizumab than among those receiving placebo or standard of care (OR: 0.83, 95% CI: 0.74-0.92) (26,27). The two largest trials within this analysis, conducted in patients with severe and critical COVID-19, provide support for the use of tocilizumab. However, several other trials failed to demonstrate a mortality benefit or other clear clinical advantages with these agents (28,29,30). As an example, a double-blind, randomized trial involving 243 patients with severe COVID-19, who were not intubated but showed evidence of a proinflammatory state (elevations in C-reactive protein, ferritin, D-dimer, or lactate dehydrogenase), did not reveal a significant difference in the rate of intubation or death with a single dose of tocilizumab compared with placebo (10.6% versus 12.5%, hazard ratio: 0.83, 95% CI: 0.38-1.81) (31). Tocilizumab also did not reduce the risk of disease progression.

Baricitinib

Baricitinib, a selective inhibitor of Janus activated kinase 1 (JAK1) and Janus activated kinase 2 (JAK2), serves as a modulator of signaling pathways for cytokines and growth factors that are pivotal in hematopoiesis, inflammation, and immune response (32). Beyond its immunomodulatory

effects, it is conjectured that baricitinib may exhibit antiviral properties by disrupting viral entry.

Emerging data posit a mortality advantage associated with baricitinib for patients with severe disease, even when concurrently administered with dexamethasone (33). In an expansive open-label randomized trial encompassing over 8,000 hospitalized COVID-19 patients, baricitinib demonstrated a reduction in 28-day mortality compared with standard care alone (12% vs. 14%; relative risk: 0.87, 95% CI: 0.77-0.99) (34). Noteworthy is the fact that nearly all participants (95%) were concurrently receiving glucocorticoids, with 20% on remdesivir and 23% having received tocilizumab. While these outcomes align with those of prior baricitinib trials, it is noteworthy that the relative reduction in mortality was marginally lower in this particular trial (35,36,37). In the United States, the FDA has granted approval for the use of baricitinib in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (38). Tofacitinib, another JAK inhibitor, is a potential alternative in situations where baricitinib is not readily available.

Anakinra

Anakinra inhibits the biological activity of IL-1, a proinflammatory cytokine associated with severe COVID-19. It counteracts the production of nitric oxide, prostaglandin E2, and collagenase in the synovium, fibroblasts, and chondrocytes (14,15).

A systematic review and patient-level meta-analysis conducted by Kyriazopoulou et al. (39) examined pooled data from 1,185 patients across nine studies, including individual patient data from 895 patients in six of the analyzed studies. Mortality was significantly lower in patients treated with anakinra (11%) than in those receiving standard care with or without a placebo [25%; adjusted OR: 0.32 (95% CI: 0.20-0.51)]. The use of anakinra, compared with standard care, was not associated with a significantly increased risk of secondary infections [OR: 1.35 (95% CI: 0.59-4.0)].

However, several trials of IL-1 inhibitors, including anakinra in hospitalized patients with non-severe COVID-19 and canakinumab in patients with severe COVID-19, have not demonstrated a reduction in ventilator-free or overall survival (40,41,42). Consequently, it remains uncertain whether anakinra offers advantages over other immunomodulatory agents that have demonstrated efficacy, such as IL-6 or JAK inhibitors.

Agents Supporting the Host Natural Immunity

Interferons

All viruses trigger an antiviral response that relies on the immediate production of interferon (IFN)-β in the host. The binding of IFN-β to its receptor then triggers the production of IFN-α. If the production of IFN-α/β occurs immediately and is intense enough, the infection can be stopped (14,15).

IFNs play a role in the pathogenesis of SARS-CoV-2. Low levels of IFN-I and IFN-III have been found among patients infected with SARS-CoV-2, and impaired IFN production has been associated with low viral clearance (14). Inborn errors of TLR3- and IRF7-dependent type I IFN immunity have been found to be related to life-threatening COVID-19 pneumonia (43).

In situations of an inefficient IFN response, the virus replicates, triggering a second inflammatory/immune response, which may become explosive and potentially result in a cytokine storm and acute respiratory distress syndrome.

In a meta-analysis of five RCTs regarding the effectiveness of IFN-β for the treatment of COVID-19, the average mortality rate was reported as 6.1% and 18.0% in the intervention and control groups, respectively. Likewise, the median days of hospitalization were lower in the intervention group (9 days) than in the control group (12.25 days), and IFN-β was found to increase the overall discharge rate (RR: 3.05; 95% CI: 1.09-5.01) (44).

However, in the SOLIDARITY clinical trial, death occurred in 243 of 2,050 patients receiving IFN and in 216 of 2,050 receiving the control (rate ratio: 1.16; 95% CI: 0.96 to 1.39; p=0.11), and IFN did not reduce mortality, overall or in any subgroup, or reduce initiation of ventilation or hospitalization duration (23).

Consequently, IFN-β could have a role for treating COVID-19, especially if started earlier during the disease, but further RCTs, including a larger number of patients, are needed.

Anti-SARS-CoV-2 Monoclonal Antibodies

mAbs represent a focal point in ongoing investigations for the therapeutic management of COVID-19. These antibodies are typically synthesized through the identification of pathogen-specific B-cells sourced from individuals convalescing from recent infections or via the immunization of genetically modified mice possessing a humanized immune system (45).

After the identification of B-cells, the genes encoding immunoglobulin heavy and light chains are extracted, and their expression yields mAbs characterized by a specific affinity toward a predetermined target. This manufacturing methodology distinguishes itself from convalescent plasma, which comprises polyclonal antibodies obtained from individuals in the recovery phase of infection (46).

A preponderance of mAb products designed to combat SARS-CoV-2 predominantly targets the viral spike protein, which is pivotal for the virus's cellular entry mechanism, thereby obstructing viral attachment and subsequent entry into human cells. FDA-authorized formulations encompass bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovima (47,48,49,50,51).

The Omicron variant has emerged as the dominant SARS-CoV-2 variant in the United States. This variant, along with its subvariants, exhibits notable reductions in *in vitro* susceptibility to several anti-SARS-CoV-2 mAbs, particularly bamlanivimab plus etesevimab and casirivimab plus imdevimab. While sotrovimab maintains efficacy against the Omicron BA.1 and BA.1.1 subvariants, its *in vitro* neutralization activity substantially diminishes against the Omicron BA.2, BA.4, and BA.5 subvariants. Conversely, bebtelovimab retains *in vitro* neutralization activity against circulating Omicron subvariants (47,53,54).

Given the ascendancy of the Omicron variant in the United States, bebtelovimab is currently the solitary mAb recommended for the treatment of COVID-19.

At present, no specific product is designated for post-exposure prophylaxis. Nevertheless, the IDSA guideline panel suggests the post-exposure employment of casirivimab/imdevimab only under conditions where predominant regional variants exhibit susceptibility, accompanied by a conditional recommendation and low certainty of evidence. Recommendations also extend to the use of tixagevimab plus cilgavimab for pre-exposure prophylaxis (PrEP) (55). Tixagevimab/cilgavimab has received emergency authorization as PrEP against COVID-19 for immunocompromised individuals or those unable to be vaccinated or mount an effective post-vaccination immune response.

Administration of anti-SARS-CoV-2 mAbs necessitates a setting equipped to manage severe hypersensitivity reactions, including anaphylaxis. Post-injection, patients should undergo monitoring for a minimum duration of 1 hour.

Bebtelovimab

In February 2022, the FDA issued an EUA for bebtelovimab to address mild to moderate cases of COVID-19 in adults and specific pediatric patients aged 12 or above, particularly when alternative treatment options are either inaccessible or deemed clinically inappropriate (56). Bebtelovimab, classified as a neutralizing IgG1 mAbs, specifically targets the spike protein of SARS-CoV-2. Significantly, it retains binding and neutralizing efficacy against all currently identified and reported variants of concern, including Omicron and BA.2 (57).

For non-hospitalized adults aged 18 years and older presenting with mild to moderate COVID-19 and at an elevated risk of progressing to severe disease, the Panel recommends the administration of bebtelovimab as a single 175 mg IV dose at the earliest opportunity post-diagnosis and within seven days of symptom onset. Moreover, bebtelovimab is a therapeutic choice for hospitalized adults aged 18 years and older with mild to moderate COVID-19, unrelated to their hospitalization cause, provided they satisfy the FDA EUA criteria for outpatient treatment (55).

Tixagevimab Plus Cilgavimab

Tixagevimab and cilgavimab received EUA from the FDA for PrEP against COVID-19 in specific adults and pediatric patients in December 2021, with a dosing revision in February 2022. According to the IDSA guidelines, PrEP with tixagevimab/cilgavimab is recommended over tixagevimab/cilgavimab for moderately or severely immunocompromised individuals at an elevated risk of an inadequate immune response to the COVID-19 vaccine or for whom the vaccine is not recommended because of a documented serious adverse reaction, with a conditional recommendation and low certainty of evidence (58,59).

The STORM CHASER study, which focused on post-exposure prophylaxis, showed a non-significant reduction in the overall study population's risk of symptomatic COVID-19. Nevertheless, tixagevimab/cilgavimab is not authorized for post-exposure prophylaxis in individuals exposed to SARS-CoV-2 (60,61). Notably, the FDA's EUA was amended in February 2022 to increase the initial dosing of tixagevimab/cilgavimab for PrEP because of potential decreased activity (12 to 424-fold) against Omicron subvariants BA.1 and BA.1.1, while maintaining presumed neutralization efficacy against the BA.2 subvariant.

Similarly, the recommendations from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) include conditional recommendations for the use of tixagevimab-cilgavimab in high-risk, unvaccinated outpatients with mild-to-moderate COVID-19, contingent upon its activity against the infecting variant or the predominant variants based

on epidemiological data, with a moderate recommendation. There are also conditional recommendations for the use of tixagevimab-cilgavimab in high-risk outpatients at risk of vaccine failure with mild-to-moderate COVID-19, but with a very low recommendation. However, there are insufficient data to provide a recommendation for fully vaccinated patients with no risk factors for vaccine failure (62). In addition, the panel decided not to evaluate drugs currently unavailable outside the United States, such as bebtelovimab.

Sotrovimab

Data regarding sotrovimab for the treatment of COVID-19 have predominantly emanated from two clinical trials-one involving outpatients and the other focusing on hospitalized patients (53,63). In alignment with the recommendations of the ESCMID, conditional suggestions have been proposed for the application of sotrovimab in high-risk, unvaccinated outpatients exhibiting mild-to-moderate COVID-19. The stipulation for this recommendation is the confirmed activity of sotrovimab against the infecting variant, determined through individual testing, or its efficacy against the predominant variants based on epidemiological data. The quality of evidence substantiating this recommendation is moderate.

In addition, conditional suggestions are in place for the use of sotrovimab in high-risk outpatients susceptible to vaccine failure with mild-to-moderate COVID-19. Analogous to the prior scenario, confirmation of sotrovimab activity against the infecting variant through individual testing or its effectiveness against predominant variants based on epidemiological data is required. However, the quality of evidence supporting this recommendation is considered very low. Regrettably, the available data do not provide adequate information to describe a recommendation for fully vaccinated patients devoid of identified risk factors for vaccine failure.

COVID-19 Convalescent Plasma

Plasma obtained from individuals who have recovered from COVID-19 may contain antibodies against SARS-CoV-2, potentially aiding in the suppression of viral replication (64). In April 2020, the FDA established an Expanded Access Program (EAP) and an Emergency Investigational New Drug pathway, allowing individuals to access convalescent plasma. The EAP served as a primary means of obtaining convalescent plasma in the United States (65), and detailed information about both programs was made available on the FDA website.

In August 2020, the FDA issued an EUA for COVID-19 convalescent plasma (CCP) for treating hospitalized COVID-19 patients. High-titer convalescent plasma has demonstrated efficacy in reducing the risk of COVID-19-associated hospitalization. However, challenges exist in the collection, screening, and quantification of convalescent plasma antibody levels. The EUA, revised in February 2021, restricted the authorization for high-titer CCP to treat hospitalized patients with COVID-19 early in their disease course or those with impaired humoral immunity. Subsequent revisions in December 2021 limited the use of CCP to outpatients or inpatients with COVID-19 having an immunosuppressive disease or receiving immunosuppressive treatment, excluding its authorization for use in immunocompetent patients (66,67).

Given the dominance of the Omicron variant in the United States, the COVID-19 Treatment Guidelines Panel strongly advises against using CCP collected before the emergence of the Omicron variant for COVID-19 treatment. Furthermore, the Panel recommends against CCP use for treating COVID-19 in hospitalized, immunocompetent patients based on strong recommendations and evidence from one or more randomized trials without major limitations. Regarding the use of high-titer CCP collected after the emergence of Omicron for treating immunocompromised patients and non-hospitalized, immunocompetent patients with COVID-19, there is insufficient evidence for a definitive recommendation. *In vitro* data suggest neutralizing activity against the Omicron variant but do not provide conclusive evidence of clinical efficacy in the current context (68,69,70,71).

The IDSA guidelines align with these recommendations, strongly advising against the use of CCP for hospitalized patients with COVID-19 based on moderate certainty of evidence. The FDA recommends administering 1 unit of convalescent plasma (approximately 200 mL), with an additional unit being considered based on clinical judgment. High-titer CCP is preferred, especially when administered early in the disease course (preferably within 3 days of diagnosis). However, predicting the antibody titer in plasma is challenging, and measurement before use is recommended when feasible. The FDA defines “high-titer” convalescent plasma on the basis of neutralizing antibody titers in specific assays (72).

The safety and efficacy of CCP during pregnancy and in pediatric patients have not been systematically evaluated in clinical trials. Published data are limited to case reports and case series, suggesting that the use of CCP in these populations should be considered on a case-by-case basis, adhering to EUA criteria. Adverse effects associated with CCP administration include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile non-hemolytic reactions, transfusion-related acute

lung injury, transfusion-associated circulatory overload, hemolytic reactions, hypothermia, metabolic complications, and post-transfusion purpura.

Anticoagulant and Antiplatelet Therapy

It is recommended that patients with COVID-19 who are undergoing anticoagulant or antiplatelet therapies for underlying conditions should continue these medications, unless significant bleeding develops or other contraindications are present (73). For hospitalized patients with COVID-19 experiencing rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, it is recommended to evaluate the patients for thromboembolic disease (70). In hospitalized patients, low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over oral anticoagulants because of their shorter half-lives, quick reversibility, ability for IV or subcutaneous administration, and fewer drug-drug interactions. When heparin is used, LMWH is preferred over UFH.

In non-hospitalized patients with COVID-19, the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis is not recommended, except in a clinical trial. This recommendation does not apply to patients with other indications for antithrombotic therapy.

The COVID-19 treatment guidelines of the NIH recommend against routinely continuing venous thromboembolism prophylaxis after hospital discharge for patients with COVID-19, unless they have another indication or are participating in a clinical trial. For patients discharged after COVID-19-related hospitalization who are at high risk of venous thromboembolism and at low risk of bleeding, there is insufficient evidence for the Panel to recommend either for or against continuing anticoagulation unless another indication for VTE prophylaxis exists (70). The ESCMID guidelines recommend against the use of an intermediate dose of LMWH in critically ill patients with COVID-19 at a moderate evidence level. However, the use of intermediate or therapeutic doses of LMWH in non-critically ill patients with COVID-19 is recommended only in the context of a clinical trial at the moderate evidence level (62).

Supplements

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin that has been investigated for potential therapeutic effects in individuals with varying degrees of illness severity. Functioning as an antioxidant and free radical scavenger, it exhibits anti-inflammatory properties, influences cellular immunity and vascular integrity, serves as a cofactor in endogenous catecholamine generation, and has been scrutinized in numerous disease states, including COVID-19 (74,75). However, most studies on COVID-19 suffer from significant limitations, such as small sample sizes, a lack of randomization or blinding, divergent doses or formulations of vitamin C, disparate outcome measures, and heterogeneous study populations comprising patients with varying concomitant medications and COVID-19 disease severity.

To offer more definitive guidance on the role of vitamin C in the prevention and treatment of COVID-19, it is imperative to conduct adequately powered, well-designed, and meticulously executed clinical trials. At present, there is insufficient evidence to either recommend or discourage the use of vitamin C for treating COVID-19 in both non-hospitalized and hospitalized patients (70).

Vitamin D

Vitamin D plays a crucial role in bone and mineral metabolism. The expression of the vitamin D receptor in immune cells, including B-cells, T-cells, and antigen-presenting cells, coupled with the ability of these cells to synthesize the active vitamin D metabolite, suggests that vitamin D can modulate both innate and adaptive immune responses (76). This immunomodulatory capacity raises the possibility that vitamin D could offer protection against SARS-CoV-2 infection or mitigate the severity of COVID-19. Notably, vitamin D deficiency is more prevalent among older individuals and those with obesity and hypertension, conditions that have been correlated with poorer outcomes in COVID-19 patients (77). Consequently, there is currently insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19 (70). Further research is needed to establish clearer guidelines regarding the role of vitamin D in COVID-19.

Zinc

Elevated intracellular concentrations of zinc have demonstrated effective inhibition of the replication processes of various RNA viruses (78). The correlation between zinc and COVID-19, exploring the impact of zinc deficiency on the severity of COVID-19 and the potential improvement of clinical outcomes through zinc supplementation, is currently a subject of investigation. Accurately measuring zinc levels proves challenging because of its distribution as a component of diverse proteins and nucleic acids (79). To provide

comprehensive guidance on the role of zinc in preventing and treating COVID-19, there is an urgent need for adequately powered, well-designed, and rigorously conducted clinical trials.

The present lack of sufficient evidence has led the NIH Panel to refrain from making a definitive recommendation either for or against the use of zinc in treating COVID-19. The panel advises against employing zinc supplementation beyond the recommended dietary allowance (i.e., 11 mg of zinc daily for men, 8 mg for non-pregnant women) for preventing COVID-19, except within the context of a clinical trial. This stance is based on a moderate recommendation and expert opinion (70).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.İ., S.B., Concept: A.İ., S.B., Design: A.İ., S.B., Data Collection or Processing: A.İ., S.B., Analysis or Interpretation: A.İ., S.B., Literature Search: A.İ., S.B., Writing: A.İ., S.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies. Diabetes Metab Syndr 2020;14:641-648.
2. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. medRxiv [Preprint].
3. Veklury. US FDA approved product information; Foster City, CA: Bristol Gilead Sciences, Inc; October 2020. Accessed November 22, 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf
4. Angamo MT, Mohammed MA, Peterson GM. Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis. Infection 2022;50:27-41.
5. Agarwal A, Hunt B, Stegemann M, et al. A living WHO guideline on drugs for COVID-19. BMJ 2020;370:m3379. Update in: BMJ. 2020;371:m4475. Update in: BMJ 2021;372:n860. Update in: BMJ 2021;374:n1703. Update in: BMJ 2021;374:n2219. Erratum in: BMJ 2022;377:o1045.
6. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Accessed September 08, 2022. Available from: https://covid19treatmentguidelines.nih.gov/
7. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Accessed September 30, 2021. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
8. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe Covid-19 outcomes during the omicron surge. N Engl J Med 2022;387:790-798.
9. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. Accessed November 08, 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
10. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. Clin Infect Dis 2023;76:e342-e349. Erratum in: Clin Infect Dis 2023;76:1158-1159.
11. Epic Research. Paxlovid significantly reduces COVID-19 hospitalizations and deaths. Accessed September 29, 2022. Available from: https://www.epicresearch.org/articles/paxlovid-significantly-reduces-covid-19-hospitalizations-and-deaths
12. Ganatra S, Dani SS, Ahmad J, et al. Oral nirmatrelvir and ritonavir in nonhospitalized vaccinated patients with coronavirus disease 2019. Clin Infect Dis 2023;76:563-572.
13. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. Lancet 2022;400:1213-1222.
14. Şimşek-Yavuz S, Komsuoğlu Çelikyurt FI. An update of anti-viral treatment of COVID-19. Turk J Med Sci 2021;51:3372-3390.
15. Drożdżal S, Rosik J, Lechowicz K, et al. An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. Drug Resist Updat 2021;59:100794.
16. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509-520.
17. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. Accessed September 29, 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
18. Chen PJ, Chao CM, Lai CC. Clinical efficacy and safety of favipiravir in the treatment of COVID-19 patients. J Infect 2021;82:186-230.
19. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. Sci Rep 2021;11:11022. Erratum in: Sci Rep 2022;12:1996.
20. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res 2020;178:104786.

21. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-1799.
22. Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020;396:1345-1352.
23. WHO Solidarity Trial Consortium; Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med 2021;384:497-511.
24. RECOVERY Collaborative Group; Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
25. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. Am J Health Syst Pharm 2008;65:1413-1418.
26. Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;3:CD013881.
27. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA 2021;326:499-518.
28. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. Accessed August 04, 2020. Available from: https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00
29. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med 2021;384:1503-1516.
30. Reuters. Roche rheumatoid arthritis drug fails to help COVID-19 patients in Italian study. Accessed August 04, 2020. Available from: https://www.reuters.com/article/us-health-coronavirus-roche-hldg/roche-rheumatoid-arthritis-drug-fails-to-help-covid-19-patients-in-italian-study-idUSKBN23O3GG
31. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:2333-2344.
32. Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. echanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med 2020;12:e12697.
33. Kramer A, Prinz C, Fichtner F, et al. Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev 2022;6:CD015209.
34. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. Lancet 2022;400:359-368. Erratum in: Lancet 2022;400:1102.
35. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407-1418.
36. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021;384:795-807.
37. Stebbing J, Sánchez Nievas G, Falcone M, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. Sci Adv 2021;7:eabe4724.
38. US Food and Drug Administration. Accessed November 18, 2022). Available from: https://www.fda.gov/media/143822/download
39. Kyriazopoulou E, Huet T, Cavalli G, et al. Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. Lancet Rheumatol 2021;3:e690-e697.
40. CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med 2021;9:295-304.
41. Davidson M, Menon S, Chaimani A, et al. Interleukin-1 blocking agents for treating COVID-19. Cochrane Database Syst Rev 2022;1:CD015308.
42. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA 2021;326:230-239.
43. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with lifethreatening COVID-19. Science 2020;370:eabd4570.
44. Nakhlband A, Fakhari A, Azizi H. Interferon-beta offers promising avenues to COVID-19 treatment: a systematic review and meta-analysis of clinical trial studies. Naunyn Schmiedebergs Arch Pharmacol 2021;394:829-838.
45. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 2020;324:131-132.
46. Marston HD, Paules CI, Fauci AS. Monoclonal antibodies for emerging infectious diseases - borrowing from history. N Engl J Med 2018;378:1469-1472.
47. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885-1898.
48. US Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. Accessed May 20, 2021. Available from: https://www.fda.gov/media/145802/download
49. US Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab with imdevimab). Accessed May 20, 2021. Available from: https://www.fda.gov/media/145611/download
50. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325:632-644.
51. Huang DT, McCreary EK, Bariola JR, et al. Effectiveness of casirivimab-imdevimab and sotrovimab during a SARS-CoV-2 delta variant surge: a cohort study and randomized comparative effectiveness trial. JAMA Netw Open 2022;5:e2220957.

52. Fact Sheet For Healthcare Providers: Emergency Use Authorization For Bebtelovimab Avaliable from: https://www.fda.gov/media/156152/download
53. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2022;327:1236-1246.
54. Yu J, Collier AY, Rowe M, et al. Comparable neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. medRxiv [Preprint]. 2022.
55. Infectious Diseases Society of America guideline. Avaliable from: https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/
56. Coronavirus (COVID-19) Update: FDA Authorizes New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant. Avaliable from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains
57. Westendorf K, Žentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. bioRxiv. 2022. [Preprint].
58. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Avaliable from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-14
59. T-cells C. AZD7442 PROVENT Phase III prophylaxis trial met primary endpoint in preventing COVID-19.
60. Mode D, Stockholm LC. AstraZeneca: AZD7442 reduced risk of developing severe COVID-19 or death in TACKLE Phase III outpatient treatment trial.
61. CHASER S. Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19 (Form 6-K). Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html#
62. Bartoletti M, Azap O, Barac A, et al. European society of clinical microbiology and infectious diseases guidelines for coronavirus disease 2019: an update on treatment of patients with mild/moderate disease. Clin Microbiol Infect 2022;28:1578-1590.
63. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022;22:622-635.
64. Writing Committee for the REMAP-CAP Investigators; Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically Ill patients with COVID-19: a randomized clinical trial. JAMA 2021;326:1690-1702.
65. Convalescent plasma therapy. Available from: https://www.mayoclinic.org/tests-procedures/convalescent-plasma-therapy/about/pac-20486440
66. US Food and Drug Administration. Convalescent plasma: EUA letter of authorization. Accessed June 27, 2022. Available from: https://www.fda.gov/media/141477/download
67. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med 2021;27:2012-24.
68. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049-2059.
69. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 2021;384:610-618.
70. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/
71. Emergency Use Authorızatıon (EUA) of Covid-19 Convalescent Plasma for Treatment of Coronavırus Disease 2019 (COVID-19). Available from: https://www.fda.gov/media/141478/download
72. Clinical Memorandum. Available from: https://www.fda.gov/media/141480/download
73. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021;5:872-888.
74. Wei XB, Wang ZH, Liao XL, et al. Efficacy of vitamin C in patients with sepsis: an updated meta-analysis. Eur J Pharmacol 2020;868:172889.
75. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. Crit Care Med 2011;39:1454-1460. Erratum in: Crit Care Med 2011;39:2022.
76. Aranow C. Vitamin D and the immune system. J Investig Med 2011;59:881-886.
77. People with Certain Medical Conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
78. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176.
79. Hambridge K. The management of lipohypertrophy in diabetes care. Br J Nurs 2007;16:520-524.