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Potential COVID-19 Therapeutic Agents and Vaccines: An Evidence-Based Review

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Elnaz Khani, PharmD[1], Sajad Khiali, PharmD[1], and Taher Entezari-Maleki, PharmD, PhD[1,2]

Abstract

Since the early days of 2020, the severe acute respiratory syndrome coronavirus 2 pandemic has become a global health concern. Currently, some therapies and vaccines have received US Food and Drug Administration approval or emergency use authorization for the management of coronavirus disease 2019. According to the pathophysiology of the disease, several medications have been evaluated in different clinical conditions of the disease. Evidence-based reviewing and categorizing these medications can guide the clinicians to select the proper medications according to each patient's condition. Therefore, we performed this review to categorize the coronavirus disease 2019 potential therapeutics and vaccines.

Keywords

baricitinib, colchicine, convalescent plasma, COVID-19, dexamethasone, IFN-β-1a, methylprednisolone, remdesivir, SARS-CoV-2, tocilizumab

Since the end of 2019, a novel coronavirus emerging from Wuhan, China, has infected about 100 million cases across the globe, with nearly 2.2 million deaths as of early 2021. The International Committee on Taxonomy of Viruses called this novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the diseases caused by the virus named coronavirus disease 2019 (COVID-19) based on a World Health Organization (WHO) statement.[1–3]

Based on the epidemiologic data, SARS-CoV-2 has a lower rate of mortality with a higher rate of infectivity than the previous outbreaks of SARS-CoV in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.[4,5]

According to the Centers for Disease Control and Prevention, most of the infected cases experience similar symptoms, including fever; cough; sore throat; shortness of breath or difficulty breathing; fatigue; muscle, joint, or body pain; headache; nausea or vomiting; congestion or runny nose; the recent loss of taste or smell; and diarrhea. Of note, it mainly affects the lower respiratory tract. It can cause acute respiratory distress syndrome (ARDS) in severe conditions that lead to respiratory failure, multiple organ failure, and even death.[6–8] Currently, there are several potential therapeutic agents used for the management of patients with COVID-19 with different levels of evidence. In this review, we aimed to categorize the potential medications and vaccines reported in the literature for the management of COVID-19 on the basis of evidence-based medicine (EBM) to guide clinicians for better management of the disease.

Virology and Viral Phase

Coronaviruses infect both humans and several animal types. They are related to the Orthocoronaviridae subfamily and Coronaviridae family. They are classified into alpha, beta, gamma, and delta genera.[9] All coronaviruses' common feature is their single-stranded RNA genome, which is the largest genome among all identified RNA viruses.

These pathogens have halo-like features under the electron microscope due to their structural proteins that are protruding from the membrane of the virus, including spike (S) glycoprotein, the matrix, and the envelope proteins. The nucleocapsid protein is the other structural protein that surrounds the RNA.[10]

The S protein is the most known surface protein of the coronavirus, which can bind to the host cell receptors, including angiotensin-converting enzyme 2 (ACE2) and CD147. ACE2 presents in the lower respiratory tract of humans and accelerates both the cross-species and human-to-human transmissions. Also, CD147 (Basigin/Emmprin) relates to the

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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Corresponding Author:
Taher Entezari-Maleki, PharmD, PhD, Associate Professor of Clinical Pharmacy, Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
Email: tentezari@gmail.com

immunoglobulin superfamily and is expressed in several tissues and cells, including neuronal and epithelial cells.[11–14] Besides the structural proteins, several nonstructural proteins, like RNA-dependent RNA polymerase (RdRp), are responsible for duplicating genetic information and making the virus with high mutation ability.[15] These properties cause a high diversity of coronaviruses, which can infect different hosts. The infections of a wide variety of animal species with coronaviruses supported the idea that these types of viruses are zoonotic and are transmitted to humans from animals, particularly bats. This idea supports the hypothesis that these pathogens are bat viruses that infect intermediate animals and, finally, humans. In the 1960s, the first human coronavirus was detected with mild upper and lower respiratory tract diseases. It was estimated that approximately one-third of the common colds of humans were related to coronaviruses. However, this condition entirely changed with the SARS-CoV outbreak in 2003 and MERS-CoV in 2012 due to their high hospitalization and mortality rate. Recently, in December 2019, a novel coronavirus, SARS-CoV-2, was detected in China. This novel coronavirus genome has high similarity with previous coronaviruses in bats and shares 79.5% identity to SARS-CoV. Thus, it can be concluded that SARS-CoV-2 originally came from bats and then infected humans. Like former coronaviruses, SARS-CoV-2 also binds to ACE2 as a cellular receptor for infecting humans.[9,16]

Immunologic Phase

After virus cell entry, the immune system is activated by antibodies, cytotoxic cells, and interferons (IFNs). In the advanced stages of COVID-19, hyperinflammation causes ARDS, cytokine release syndrome (CRS), and multiple organ failure. In this stage, alveolar infiltration of T cells, activated macrophages, and neutrophils results in cytokine secretion such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α. These cytokines trigger further inflammatory pathways through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway and T-helper cell activation. The virus envelope protein was also contributing to the IL-1β secretion, which leads to lung injury. Moreover, IL-6 also plays a pivotal role in the recruitment of macrophages, progression of inflammation, CRS, and ARDS. This excessive inflammatory response enhances vascular permeability and lung epithelial and endothelial cell apoptosis, which leads to ARDS and ventilation requirement.[17] Furthermore, this hyperinflammatory situation associates with coagulopathy, disseminated intravascular coagulation, and thromboembolisms in a small fraction of patients with critical COVID-19. Among the mechanistic pathways of SARS-CoV-2–induced coagulopathy, overexpression of tissue factor (TF) has a key role in coagulation cascade activation. It is hypothesized that downregulation of ACE2 receptors on monocytes and macrophages after viral binding leads to angiotensin II accumulation, IL-6 elevation, and TF production. Unlike normal conditions, in hyperinflammatory states TF contacts with coagulation factor VII, which leads to activation of the extrinsic coagulation pathway. The activation of toll-like receptors, which are expressed in the various innate immune cells, was also indicated to be responsible in COVID-19–induced coagulopathy. It is noteworthy that increased levels of inflammatory factors, including IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin, along with the procoagulant biomarkers such as fibrinogen and d-dimers, are interrelated with a higher mortality rate.[18–20]

Class of Recommendation and Level of Evidence

For better management of patients with COVID-19, in this review, we classify studies based on their class of recommendation and level of evidence, which was adapted from the American College of Cardiology/American Heart Association Clinical Practice Guidelines Recommendation Classification System (Table 1).[21] This guideline classifies medications based on the strength of recommendation (strong = I, IIa = moderate, IIb = weak, and III = moderately no benefit or strongly harmful) and quality of evidence (A = high quality randomized clinical trials, B-R = moderate quality randomized clinical trial, B-NR = moderate quality non-randomized clinical trial, C-LD = limited data, and C-EO = expert opinion). The categorization of medications with at least 1 randomized clinical trial have been summarized in Table 2.

Remdesivir (I B-R, US Food and Drug Administration Approved)

Remdesivir is an adenosine analog with a broad-spectrum antiviral activity, which first was used to treat Ebola virus infection. It exerts antiviral activity through premature termination of nascent RNA and results in decreased replication and RNA synthesis of the virus. Of note, it can improve pulmonary function and reduce the load of the virus, unlike lopinavir-ritonavir and IFN-β in MERS-CoV infection.[22,23] Previously, its benefits in the management of SARS-CoV and MERS-CoV were evaluated in in vitro and animal models, making it a potential agent for the treatment of COVID-19.[24,25]

In a randomized, double-blind, placebo-controlled, multicenter clinical trial in China, 237 patients with

Table 1. Class of Recommendation and Level of Evidence Adapted From ACC/AHA Clinical Practice Guideline Recommendation Classification System

Class (Strength) of Recommendation Class I (Strong) Benefit >>> Risk

Suggested phrases for writing recommendations:
• Is recommended
• Is indicated useful/effective/beneficial
• Should be performed/administered/other
• Comparative-effectiveness phrases:
  • Treatment/strategy A is recommended/indicated in preference to treatment B
  • Treatment A should be chosen over treatment B

Class IIa (Moderate) Benefit >> Risk

Suggested phrases for writing recommendations:
• Is reasonable
• Can be useful/effective/beneficial
• Comparative-effectiveness phrases:
  • Treatment/strategy A is probably recommended/indicated in preference to treatment B
  • It is reasonable to choose treatment A over treatment B

Class IIb (Weak) Benefit ≥ Risk
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well established
Class III: No Benefit (Moderate) Benefit = Risk
(Generally, LOE A or B Use Only) Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
Class III: Harm (Strong) Risk > Benefit
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality Should not be performed/administered/other
Level (Quality) of Evidence
Level A
• High-quality evidence from >1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Level B-R (Randomized)
• Moderate-quality evidence from ≥1 RCT • Meta-analyses of moderate-quality RCTs
Level B-NR (Nonrandomized)
• Moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
Level C-LD (Limited Data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Level C-EO (Expert Opinion)
Consensus of expert opinion based on clinical experience

LOE, level of evidence; RCT, randomized clinical trial.

confirmed SARS-CoV-2 infection were randomized to 2 groups in a 2:1 ratio. After randomization, 233 patients were analyzed; 155 were assigned to the remdesivir group and 78 to the placebo group. Remdesivir was given 200 mg intravenously on day 1 and 100 mg on days 2 through 10 subsequently. According to reverse transcription polymerase chain reaction (RT-PCR), patients aged 18 years or older who were diagnosed with COVID-19 pneumonia based on imaging, oxygen saturation (SaO_2) of ≤94%, or partial pressure of oxygen in arterial blood (PaO_2):fraction of inspired oxygen (FiO_2) ratio of ≤300 mm Hg within 12 days of symptom onset underwent randomization. Exclusion criteria of the study were severe renal failure (estimated glomerular filtration rate [GFR] of <30 mL/min/1.73 m^2), hepatic disease (cirrhosis and alanine aminotransferase [ALT] or aspartate aminotransferase [AST] above 5 times the upper limit of normal [ULN]), pregnancy, and breastfeeding. The primary end point of the study was the time to clinical improvement up to day 28 including the time from randomization to decline of 2 points on a 6-point ordinal scale of clinical grade or leaving the hospital alive. In comparison with the placebo group, this study did not support the beneficial effects of intravenous remdesivir on clinical improvement, virus clearance, and mortality in patients with severe COVID-19.[26]

In another clinical trial by Antinori et al,[27] a total of 35 patients (18 in the intensive care unit [ICU] and 17 in the infectious disease ward) received a 200-mg intravenous loading dose of remdesivir on the first day and continued with the intravenous 100-mg daily dose from day 2 to day 10. In addition to remdesivir, patients also received standard treatment except for lopinavir/ritonavir. Patients were enrolled in the study if they were aged >18 years, had confirmed SARS-CoV-2 infection based on RT-PCR and pneumonia found on chest radiograph or computed tomography

Table 2. Categorization of Medications With at Least 1 RCT in Different Clinical Status

Medication	Author/Country	Sample Size	Design	Clinical Status	Dose/Duration	Outcomes	Class of Recommendation and Level of Evidence
Remdesivir	Wang et al[26]/China	233	RCT	Severe	200 mg IV day 1; 100 mg IV days 2-10	No beneficial effects on clinical improvement, virus clearance, and mortality	I B-R
	Antinori et al[28]/Italy	35	Non-RCT	Severe	200 mg IV day 1; 100 mg IV days 2–10	Clinical improvement on day 10 and 28 was observed among: 22.2% and 38.9% of ICU patients and 35.3% and 88.2% of patients in IDW, respectively	
	Grein et al[29]/ Multiple countries	53	Non-RCT (cohort)	Severe	200 mg IV day 1; 100 mg IV days 2-10	Clinical improvement on day 18 was 68%; cumulative incidence of clinical improvement on day 28 was 84%	
	WHO Solidarity trial[32]/Multiple countries	5451	Multicenter RCT	Hospitalized patients	200 mg IV on day 1; 100 mg IV days 2-10	Similar death rate ratios, initiation of ventilation, and hospitalization duration	
	Beigel et al[33]/ Multiple countries	1062	RCT	Severe (85%)	200 mg IV on day 1; 100 mg IV days 2-10	Improvements in time to recovery during 28 days and clinical status on day 15, decreased mortality	
Baricitinib/Remdesivir	The ACTT-2 trial[36]/ Multiple countries	1033	Multicenter RCT	Hospitalized patients	4 mg PO baricitinib up to 14 days/ 200 mg IV remdesivir on day 1; 100 mg IV days 2-10	Improvements in time to recovery during 28 days particularly in patients on high-flow oxygen or noninvasive ventilation, similar mortality rate, and lower serious adverse events	IIa B-R
Casirivimab and Imdevimab	Weinreich et al[38]/ United States	275	Multicenter RCT	Mild or moderate nonhospitalized patients	2.4 or 8 g IV in a 250-mL normal saline	Decreased viral load and medical visits particularly in patients without initiation of endogenous immune response	IIa B-R
Bamlanivimab	Chen et al[40]/USA	452	Multicenter RCT	Mild or moderate non-hospitalized patients	700, 2800, or 7000 mg single IV infusion	Decreased viral load by 2800 mg on day 11 and overall rate of hospitalization at 28 days particularly in high-risk patients with BMI of $\geq$35 or age $\geq$65 years	IIa B-R
Dexamethasone	The RECOVERY Collaborative Group [42]/United Kingdom	6425	Multicenter RCT	Receiving either IMV or oxygen alone	6 mg PO or IV once daily up to 10 days	Decreased 28-day mortality	IIa B-R
Methylprednisolone	Jeronimo et al[44]/ Brazil	393	RCT	Hospitalized patients with SaO_2 94% or less while breathing room air or patients supported by oxygen, or IMV	5 mg/kg IV twice a day up to 5 days	Similar mortality on day 7,14, and 28; similar proportion of patients need IMV, significant reduction in 28-day mortality among patients aged >60 years in methylprednisolone group	III B-R

(*Continued*)

Table 2. (Continued)

Medication	Author/Country	Sample Size	Design	Clinical Status	Dose/Duration	Outcomes	Class of Recommendation and Level of Evidence
Tocilizumab	Xu et al[47]/China	21	Retrospective single-center case series	Severe or critical	400 mg IV; 1 or 2 doses	100% resolution in fever, 91% improvements in imaging, 75% reduction of oxygen support, and 53% normalization in lymphocyte count	IIb B-R
	Sciascia et al[48]/Italy	63	Prospective multicenter case series	Severe	8 mg/kg IV or 324 mg SC; 1 or 2 doses (12-h interval)	Improvements in CRP, ferritin, d-dimer, lymphocyte count, and PaO_2:FiO_2 and decreased mortality	
	Toniati et al[49]/Italy	100	Prospective single-center case series	Severe	8 mg/kg IV; 2 or 3 doses	Clinical improvement in 77% of patients and improvements in CRP, fibrinogen, and ferritin levels	
	Lan et al[50]	592	Systematic review and meta-analysis	Severe	400 mg or 8 mg/kg; 1 or 2 doses (12-h interval)	No conclusive evidence	
	Guaraldi et al[51]/Italy	544	Retrospective cohort	Severe	8 mg/kg IV or 324 mg SC; 2 doses	Decreased risk of IMV or death	
	Narain et al[54]/USA	5776	Retrospective multicenter				
	Salvarani et al[55]/Italy	126	Multicenter RCT	Hospitalized patients with PaO_2:FIO_2 ratio between 200 and 300 mm Hg and inflammatory response	8 mg/kg IV (maximum of 800 mg); 2 doses (12-h interval)	Similar clinical deterioration during 14 days, similar overall mortality within 14 to 30 days	
	Hermine et al[56]/ France	130	Multicenter RCT	Moderate to severe	8 mg/kg IV on first and third day	Similar clinical improvements, reduced the risk of noninvasive ventilation, mechanical ventilation, or death by day 14, similar 28-day mortality	
	Stone et al[57]/USA	243	Multicenter RCT	Moderately ill hospitalized patients	8 mg/kg IV (maximum of 800 mg); 1 dose	Similar prevention of intubation, death, and clinical deterioration during 28 days	
IFN-β-1a	Dastan et al[64]/Iran	20	Non-RCT	Severe	44 μg SC every other day for 10 days	100% resolution in fever, negative RT-PCR in 18 patients after 14 days, significant improvements in radiological imaging	IIb B-R
	Davoudi-Monfared et al[65]/Iran	81	RCT	Severe	44 μg/mL (12 million IU/mL) SC 3 times per week for 2 weeks	Similar time to the clinical response between the 2 groups, improved the mortality rate through early use of IFN-β-1a	

(*Continued*)

Table 2. (Continued)

Medication	Author/Country	Sample Size	Design	Clinical Status	Dose/Duration	Outcomes	Class of Recommendation and Level of Evidence
	WHO Solidarity trial[32]/Multiple countries	4100	Multicenter RCT	Hospitalized patients	44 μg/mL SC 3 doses in 6 days	Similar death rate ratios, initiation of ventilation, and hospitalization duration	
Colchicine	Deftereos et al[72]/Greece	105	RCT	Mostly with median clinical score of 4	1.5 mg orally followed by 0.5 mg after 1 h, then 0.5 mg orally for 3 weeks	Time to clinical deterioration was significantly improved in colchicine group, no significant differences in biochemical phase	IIb B-R
Ruxolitinib	Cao et al[74]/China	41	Multicenter RCT	Severe	5 mg orally twice a day	Similar time to clinical improvement, significant improvement of chest CT scan on day 14 in ruxolitinib group	IIb B-R
Convalescent plasma	Li et al[77]/China	103	Multicenter RCT	Severe or life-threatening		Similar 28-day mortality and time to clinical improvement within 28 days, higher negative RT-PCR at 24, 48, and 72 h	IIb B-R
	Liu et al[78]/United States	195	Retrospective case control	Severe or life-threatening		Improved survival and lower rate of clinical status worsening	
	Agarwal et al[79]/India	464	Multicenter RCT	Moderate	200 mL: 2 doses (24-h interval)	Similar rate of progression to severe disease or all-cause mortality at 28 days	
Sofosbuvir/Daclatasvir/Ribavirin	Abbaspour Kasgari et al[86]/Iran	48	RCT	Moderate	400 mg sofosbuvir/60 mg daclatasvir once a day and 600 mg ribavirin twice a day	Similar duration of hospitalization and time to recovery	IIb B-R
Sofosbuvir/Daclatasvir	Sadeghi et al[87]/Iran	66	Multicenter RCT	Moderate to severe	400 mg sofosbuvir/60 mg daclatasvir once a day for 14 days	Reduced duration of hospitalization and increased chance of hospital discharge in the sofosbuvir/daclatasvir group, similar clinical improvement and all-cause mortality between the 2 groups	IIb B-R
Sofosbuvir/Daclatasvir versus Ribavirin	Eslami et al[88]/Iran	62	RCT	Severe	400 mg sofosbuvir/60 mg daclatasvir once a day versus 600 mg ribavirin twice a day for 14 days	Sofosbuvir/Daclatasvir was significantly more effective than ribavirin regarding improvement of clinical symptoms, reduction of duration of hospitalization and mortality	IIb B-R
Favipiravir	Lou et al[91]/China	29	RCT	Hospitalized patients	1600 or 2200 mg initial dose, then 600 mg 3 times a day, up to 14 days	Similar proportion of patients with viral negative and time to clinical improvement	IIb B-R
Baloxavir marboxil	Lou et al[91]/China	29	RCT	Hospitalized patients	80 mg on day 1 and day 4	Similar proportion of patients with viral negative and time to clinical improvement	IIb B-R

(*Continued*)

Table 2. (Continued)

Medication	Author/Country	Sample Size	Design	Clinical Status	Dose/Duration	Outcomes	Class of Recommendation and Level of Evidence
Ivermectin	Ahmed et al[99]/ Bangladesh	72	RCT	Hospitalized patients with fever (≥37.5°C), cough, and/or sore throat	12 mg orally daily for 5 days	Decreased mean time to viral clearance, similar duration of hospitalization	IIb B-R
	Chachar et al[100]/ Pakistan	50	RCT	Mild	12 mg orally twice a day	Similar number of asymptomatic patients on day 7	
Hydroxychloroquine	Geleris et al[131]/ United States	1376	Cohort	Moderate to severe	600 mg twice a day on day 1, 400 mg daily for days 2-5	No significant change in intubation or death	III B-R
	Tang et al[132]/China	150	Multicenter RCT	Mild to moderate	1200 mg for 3 days followed by 800 mg daily for 2 weeks	Similar viral elimination between the 2 groups, higher adverse events in hydroxychloroquine group	
	Gautret et al[133]/ France	36	Non-RCT	Mostly with upper respiratory tract infection (61.1%), 22.2% with lower respiratory tract infection, and 16.7% asymptomatic	600 mg daily for 10 days	Higher viral elimination in the hydroxychloroquine group	
	WHO Solidarity trial[32] /Multiple countries	1706	Multicenter RCT	Hospitalized patients	800 mg at the beginning, and at 6 h, and 400 mg on 12th h for 10 days	Similar death rate ratios, initiation of ventilation, and hospitalization duration	
	The RECOVERY Collaborative Group[134]/United Kingdom	4716	Multicenter RCT	Hospitalized patients	800 mg at the beginning and at 6 h; then 12 h after the first dose 400 mg was given every 12 h on days 2-10	Similar 28-day mortality, longer duration of hospitalization, and lower chance of discharge alive from hospital in the hydroxychloroquine group	
Lopinavir/Ritonavir	Cao et al[138]/ China	199	RCT	Severe	400 mg lopinavir/100 mg ritonavir twice a day for 2 weeks	Similar time to clinical improvement and mortality between the 2 groups	III B-R
	WHO SOLIDARITY trial[32]/Multiple countries	2771	Multicenter RCT	Hospitalized patients	400 mg lopinavir/100 mg ritonavir for 2 weeks	Similar death rate ratios, initiation of ventilation, and hospitalization duration.	
	The RECOVERY Collaborative Group[139]/United Kingdom	5040	Multicenter RCT	Hospitalized patients	400 mg lopinavir/100 mg ritonavir for 10 days	Similar 28-day mortality, time to discharge alive from hospital, and duration of hospitalization	

ACTT-2, Adaptive COVID-19 Treatment Trial-2; BMI, body mass index; CRP, C-reactive protein; CT, computerized tomography; ICU, intensive care unit; IDW, infectious disease ward; IFN-β-1a, interferon-β-1a; IL-6, interleukin-6; IMV, invasive mechanical ventilation; IV, intravenous; PaO_2:FiO_2, ratio of the partial pressure of oxygen to the fraction of inspired oxygen; RCT, randomized clinical trial; RT-PCR, real-time polymerase chain reaction; SaO_2, oxygen saturation; SC, subcutaneous; WHO, World Health Organization.

(CT) scan, were mechanically ventilated or had an SaO_2 <94% on room air, or a National Early Warning Score 2 (NEWS2) of ≥4.[28] Also, patients with GFR <30 mL/min, and ALT or AST >5 times the ULN level were not enrolled in the study. Most of the analyzed patients were men (74.3%), with a median age of 63.0 years. As the primary end point, this study evaluated the improvement of patients' clinical status on the 10th and 28th days of the intervention using a 7-category ordinal scale. Assessment of the adverse events was the secondary end point of the study. The results showed that 22.2% and 38.9% of ICU patients achieved improvement in hospitalization status on days 10 and 28 of follow-up, respectively. The clinical improvement on days 10 and 28 of the intervention was 35.3% and 88.2%, respectively, among patients in the infectious disease ward. As a secondary outcome, 42.8% of patients experienced hepatotoxicity. The second most common adverse event was acute kidney injury (22.8%), which led to remdesivir discontinuation. Consequently, this study showed that non-ICU patients can benefit more from remdesivir than ICU patients.[27] However, larger-scale studies are required to confirm findings.

In a cohort of patients with severe COVID-19 (confirmed by RT-PCR or SaO_2 <94% or 94% while breathing ambient air or requiring oxygen support), the use of remdesivir was investigated. All patients in this study had a GFR >30 mL/min and ALT and AST <5 times the ULN. Also, they agreed not to use other potential treatments of COVID-19 for investigation. A total of 53 patients were treated with intravenous remdesivir with a loading dose of 200 mg for the first day and 100 mg per day for days 2 through 10. The clinical improvement of patients was evaluated on the basis of a reduction of 2 points on the ordinal scale category according to the WHO Research and Development Blueprint Group or discharge live from the hospital. In this regard, 36 of 53 patients (68%) were improved, and the clinical status of 8 patients (15%) deteriorated. Also, on day 28 of the follow-up period, the cumulative incidence of clinical improvement was 84%.[29] However, for interpretation of these data, placebo-controlled randomized trials are needed.

The differences between 5- and 10-day administration of remdesivir were evaluated in a randomized trial by Goldman et al.[30] Patients with RT-PCR–confirmed severe COVID-19 who had an SaO_2 of ≤94% while the patient was breathing ambient air or receiving oxygen support and pneumonia-related radiologic signs were included in the study. The study exclusion criteria were age <12 years, ALT and/or AST more than 5 times the ULN, GFR <50 mL/min, multiple organ failure, and receiving mechanical ventilation or extracorporeal membrane oxygenation at the screening. All patients (n = 397) received 200 mg of intravenous remdesivir on day 1, and 100 mg of remdesivir daily for the remaining 4 days (n = 200) or 9 days (n = 197). The patients' demographic properties at baseline were similar, whereas the patients with severe clinical conditions were mostly assigned to the 10-day course of remdesivir. After adjustment for baseline clinical features, the clinical improvements were evaluated after 14 days by a ≥2-point reduction on the 7-category ordinal scale. The results showed improvement in 64% of patients on the 5-day course and 54% on the 10-day course. Also, assessment of adverse events after 30 days of intervention showed a similarity between the 2 groups (70% in the 5-day course vs 74% in the 10-day course). However, in this study, the efficacy of remdesivir cannot be evaluated due to the lack of a placebo-controlled group.

Recently, a meta-analysis of 4 randomized controlled trials analyzed a total of 2290 patients with COVID-19 in 3 groups: 400 patients received remdesivir for 5 days, 1090 received remdesivir for 10 days, and 800 were treated with only standard care. The comparison of the remdesivir groups with the standard-care group showed a significantly higher rate of improvements in clinical status (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.40-2.56; $P < .001$; and OR, 1.38; 95%CI, 1.15-1.66; $P < .001$, for 5-day and 10-day remdesivir groups, respectively). Also, patients who received remdesivir for 5 days showed a better clinical improvement than the 10-day remdesivir group (OR, 1.37; 95%CI, 1.01-1.85; $P = .041$).[31] However, this study could not consider further outcomes such as mortality and safety concerns. Conversely, the results of the WHO Solidarity trial could not support the beneficial effects of remdesivir on COVID-19. From 30 countries of the WHO regions, 2750 patients were assigned to the remdesivir group and treated with standard care and 200 mg of intravenous remdesivir on the first day and 100 mg for 9 days. A total of 2725 patients were also assigned to the control group and received only standard care. The results of in-hospital mortality as a primary outcome showed no significant differences between the 2 groups. The ratios for death (number of patients dead to the randomized patients) were 301 of 2743 for remdesivir and 303 of 2708 for the control group (risk ratio [RR], 0.95; 95%CI, 0.81-1.11; $P = 0.50$). As secondary end points, the duration of hospitalization and initiation of ventilation showed similarities between the groups.[32] However, it should be noted that the contrary results of this trial may be a result of significant heterogeneity in the study population and the quality of patients' care, lack of placebo use, and sample size calculation.

In a double-blinded, randomized, placebo-controlled trial by Beigel et al,[33] the time to recovery was assessed as a primary end point in 1062 patients with COVID-19. Of these, 541 were treated with a

200-mg loading dose of remdesivir on the first day, then 100 mg per day for the remaining 9 days. The control group included 521 patients who received placebo for 10 days. All patients received standard-care medications. Included patients were mostly men with a mean age of 58.9 years. The majority of patients had severe disease (85%), which was defined by a need for supplemental oxygen, SaO_2 of ≤94% on ambient air, or a respiratory rate of 24 per minute or more. The results of comparison of primary end point during the 28 days showed a significant improvement in the remdesivir group (10 days vs 15 days; rate ratio for recovery, 1.29; 95%CI, 1.12-1.49; $P < .001$). After adjustment for severity of the disease, the clinical improvement of the remdesivir group was better than the placebo group on day 15 (OR, 1.5; 95%CI, 1.2-1.9). The results of mortality comparison were 6.7% vs 11.9% on day 15 and 11.4% vs 15.2% on day 29 after enrollment for the remdesivir and placebo groups, respectively (hazard ratio [HR], 0.73; 95%CI, 0.52-1.03). Also, serious adverse events were observed in 24.6% of patients in the remdesivir group and 31.6% in the placebo group. Given the strength points of the trial design, including large sample size, placebo use, and blinded protocol, it can be considered as a study with high evidence. Recently, the US Food and Drug Administration (FDA) approved remdesivir for hospitalized patients with COVID-19 for patients aged >12 years weighing ≥40 kg. However, the time for initiation of the treatment is important and should be started sooner to be effective.[34]

Baricitinib (IIa B-R, Emergency Use Authorization From the FDA)

Baricitinib is an FDA-approved medication for the management of moderate to severe rheumatoid arthritis. It exerts anti-inflammatory properties through JAK inhibition. Consequently, it can prevent the activation of STAT. The JAK/STAT pathway involves in the signaling of several cytokines. Thus, blocking this pathway may be a rational way to mitigate the SARS-CoV-2–induced immunopathology. Moreover, several medications with this mechanism showed an antiviral effect by interfering with virus cell entry.[35]

In the Adaptive COVID-19 Treatment Trial-2, a randomized, double-blind placebo-controlled study, the effectiveness of the baricitinib plus remdesivir combination has been evaluated in hospitalized patients with COVID-19. Of the 1033 patients who underwent randomization, 515 were received 4 mg of oral baricitinib for up to 14 days, and 518 received placebo. Besides the standard supportive care, all patients were treated with intravenous remdesivir with a loading dose of 200 mg on the first day and 100 mg for the remaining 9 days. As a primary end point, the time to recovery within the 28 days was significantly improved in the baricitinib plus remdesivir group compared to the control group (7 days vs 8 days; rate ratio, 1.16; 95%CI, 1.01–1.32; $P = .03$). This difference was largest among patients who were supported with high-flow oxygen or noninvasive ventilation (10 days vs 18 days; rate ratio, 1.51; 95%CI, 1.10-2.08). However, due to the fact that the estimation of the time to recovery during the 28 days was difficult in this subgroup, the results should be considered carefully. The comparison of mortality between the 2 groups showed a similar result over the 28 days of follow-up (OR, 0.65; 95%CI, 0.39-1.09). Also, fewer serious adverse events were observed in patients assigned to the baricitinib group (95%CI, −9.8 to −0.3; $P = .03$).[36]

Casirivimab and Imdevimab (REGN-COV2) (IIa B-R, Emergency Use Authorization From the FDA)

Neutralizing antibodies have promising effects against SARS-CoV-2 infection. Recently, it was announced that an antibody cocktail named REGN-COV-2 by Regeneron Pharmaceuticals has beneficial effects in outpatients with COVID-19. The combination of casirivimab and imdevimab inhibits the binding of the receptor-binding domain of the virus to the host cells. According to the phase 1 to 3, placebo-controlled, double-blinded, randomized clinical trial, combined doses of REGN-COV2 improved the viral clearance between days 1 and 7 (95%CI, −1.02 to −0.11). It also reported that medical visits were reduced by using combined doses of REGN-COV-2 (3% vs 6%; 95%CI, −16 to 9). In the patients with negative serum antibody at baseline, better results were achieved by using combined REGN-COV-2 doses considering both viral load reduction (95%CI, −0.71 to −0.10) and medical visits (6% vs 15%; 95%CI, −29 to 11). The inclusion criteria of this study were outpatients with aged ≥18 years. Also, the time from positive COVID-19 test result and symptom onset to the randomization should be <72 hours and 7 days, respectively. Of the 275 patients who underwent randomization in this trial, 182 patients were assigned to receive 2.4 or 8 g of REGN-COV-2, and 93 patients were assigned to the placebo group. The median age of patients was 44.0 years, and 51% were female. The median time from symptom onset to the randomization was 3 days. It should be noted that beneficial effects of REGN-COV-2 were seen particularly in the patients whose immune response was not yet initiated. Also, it is unknown whether other groups of patients with COVID-19, including pregnant and younger patients, could benefit from this medication.[37,38]

Bamlanivimab (LY-CoV555) (IIa B-R, Emergency Use Authorization From the FDA)

In various animal studies, neutralizing antibodies have shown beneficial effects on SARS-CoV-2 infection by reducing the load of virus in the respiratory tract.[39] LY-CoV555, a monoclonal antibody developed by Eli Lilly, has a potent binding affinity to the receptor-binding domain of SARS-CoV-2 and shows a strong activity against spike protein. It has been derived from convalescent plasma of patients recovered from COVID-19. In a multicenter, placebo-controlled, double-blinded randomized clinical trial, the role of LY-CoV555 has been assessed on nonhospitalized patients with COVID-19 with mild or moderate disease. The outpatients with at least 1 mild or moderate sign of COVID-19 who were aged ≥18 years could be entered in the study.

Of the 452 randomized patients, 309 patients were assigned to the intervention group and received a single intravenous infusion of LY-CoV555 with doses of 700 mg (n = 101), 2800 mg (n = 107), or 7000 mg (n = 101). Also, 143 patients were assigned to the placebo group. The median age of patients was 45 and 46 years in the intervention and control groups, respectively. More than half of the patients (55%) were women in the both groups. Approximately 70% of the patients had at least 1 risk factor, including age ≥65 years, a body mass index (BMI) ≥35, or concomitant disease. The median time between symptom onset and intervention was 4 days for both groups. On day 11, LY-CoV555 at a dose of 2800 mg had significantly improved the reduction of viral load compared to the placebo group, with a mean difference of −0.53 (95%CI, −0.98 to −0.08; $P = .02$). However, this difference between the intervention and placebo groups was not significant for 700 mg and 7000 mg of LY-CoV555, with a mean change of −0.20 and 0.09, respectively. Also, the overall hospitalization percentage at 29 days was lower among patients who received LY-CoV555 (1.6% vs 6.3%). Of note, this difference was more noticeable among high-risk patients with a BMI of ≥35 or age ≥65 years (4.2% vs 14.6%). The proportion of patients who experienced serious adverse events was 22.3% and 24.5% in the LY-CoV555 and the placebo groups, respectively.[40] However, due to exclusion criteria of this study, including pregnant women and patients aged <18 years, further studies are needed to exactly determine the potential benefits of LY-CoV555 in these patients. Also, the primary outcome of this study was based on the RT-PCR–confirmed viral load reduction, which is not a precise way to assess viral neutralization. It should be noted that viral RNA can be detected even in the replication-deficit virus for a considerable period. It is unclear whether RT-PCR is an accurate measure of viral neutralization, since viral RNA may persist for some time even in the absence of replication-competent virus.

Dexamethasone (IIa B-R)

The excessive immunologic response during SARS-CoV-2 infection results in severe pneumonia that can lead to mortality. Blocking the inflammation pathways involved in the severe forms of COVID-19 can be considered a way to improve outcomes in patients with SARS-CoV-2 infection.[41] Glucocorticoids may reduce the inflammation-induced lung damage and, as a result, inhibit the progression to respiratory failure and death. In this regard, the effects of dexamethasone on COVID-19 have been evaluated in hospitalized patients by The RECOVERY Collaborative Group. In this controlled, open-label trial patients were randomized into the groups of 6-mg once-daily dexamethasone for 10 days plus standard care (n = 2104) and standard care (n = 4321). The standard care of this trial consisted of hydroxychloroquine, lopinavir/ritonavir, or azithromycin. The primary end point was mortality within 28 days after randomization. The mean ± standard deviation (SD) of the patients' age was 66.1 ± 15.7 years, and 36% of the patients were women. Mortality at 28 days was significantly lower in the dexamethasone group compared to the standard-care group, with deaths reported in 482 of 2104 patients (22.9%) and 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95%CI, 0.75-0.93; $P < .001$). This study's critical point was inclusion of patients receiving either invasive mechanical ventilation or oxygen alone. Thus, the results cannot be generalized to patients with no or other levels of respiratory support. Moreover, remdesivir was not used as a part of the standard care within the study time. Another limitation of this study was the small number of pregnant and pediatric patients, which limits the interpretation of findings in this population. Adverse effects of dexamethasone, particularly hyperglycemia and infection risk, may limit its use in all patients with COVID-19. Possible drug interactions should also be monitored due to the moderate induction of cytochrome P450 3A4 by dexamethasone.[42]

The other multicenter, randomized trial has assessed the effects of dexamethasone in moderate to severe COVID-19 ARDS (PaO_2: FiO_2 of ≤200 mm Hg and FiO_2 of ≥0.5 at 24 hours after ARDS onset). Patients were randomly assigned to dexamethasone (n = 139) and control (n = 138) groups. The dose of dexamethasone was 20 mg per day from days 1 to 5, followed by 10 mg per day from day 6 to day 10. Both groups were supported by mechanical ventilation and continued standard care. The mean ages of patients were 56 and 58 years in the dexamethasone and control

groups, respectively. Also, 69% of patients were men in both groups. Regarding the clinical status, the number of patients with the moderate form of the disease (PaO_2:FiO_2, 100-200 mm Hg) was higher than the patients with severe type (PaO_2:FiO_2, $\leq$100 mm Hg). Also, the mean respiratory rate of the included patients was 23 breaths per minute for both groups.

The number of days alive and without mechanical ventilation was analyzed at 28 days as a primary end point, which was significantly higher in the dexamethasone group, with a mean difference of 4.8 days ($P < \cdot 0001$). All-cause mortality after 60 days was the secondary end point, which was 21% and 36% in the dexamethasone and control groups, respectively ($P = 0{\cdot}0047$). No significant differences were observed regarding adverse events in both groups. According to these results, it can be concluded that the early use of dexamethasone in moderate to severe ARDS might improve the need for a ventilator and decrease mortality. However, its efficacy and safety in other patients with different clinical status are unclear.[43]

Methylprednisolone (III B-R)

As another glucocorticoid, the effectiveness of methylprednisolone on COVID-19 has been assessed in a placebo-controlled, double-blinded, randomized clinical trial. The diagnosis of COVID-19 was based on clinical symptoms and/or imaging findings. Hospitalized patients with SaO_2 of $\leq$94% while breathing room air or patients supported by oxygen or invasive mechanical ventilation were included in the study. Of the 393 patients who underwent randomization, 194 patients received intravenous methylprednisolone at a dose of 0.5 mg/kg twice a day for 5 days, whereas 199 patients received saline solution as placebo. All patients were treated with ceftriaxone and azithromycin according to the hospital standard care. The median time from symptom onset to randomization was 13 days for both groups. The majority of the patients were men with a mean age of 55 years. As a primary end point of the study, the results for 28-day mortality were 37.1% and 38.2% in the methylprednisolone and placebo groups, respectively ($P = .629$). Likewise, the comparison of mortality on days 7 and 14, and need for invasive mechanical ventilation at day 7 showed no significant differences between the study groups. Similar results were achieved in subgroup analysis. However, the administration of methylprednisolone was associated with a significant reduction in 28-day mortality in patients aged >60 years (46.6% vs 61.9%; HR, 0.634; 95%CI, 0.411-0.978; $P = .03$). Also, insulin therapy requirement at day 28 was significantly higher among patients in the methylprednisolone group (59.5% vs 49.4%; $P = .05$). It is important to mention that the diagnosis of COVID-19 was according to clinical symptoms and/or imaging findings. Notably, 81.3% of patients had RT-PCR–confirmed COVID-19.[44]

Tocilizumab (IIa B-R)

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor that is approved as an antirheumatic medication. It antagonizes the IL-6 receptors and has potential activity in the management of CRS.[45]

Previous literature showed that the abnormal and excessive immune responses were associated with fibrosis and lung damage, affecting the mortality of seriously ill patients. Of note, CRS is considered one of the key mechanisms that result in deterioration of the situation in COVID-19 by causing ARDS and multiple organ failure.[46]

Thus, it makes the tocilizumab a potential candidate in critically ill patients with lung injury and high levels of IL-6.

In a retrospective, single-center case series, effects of tocilizumab were evaluated in 21 patients with critical (needing mechanical ventilation or organ support in the ICU) or severe (tachypnea and/or respiratory failure) COVID-19. The mean $\pm$ SD of the age of patients was 56.8 $\pm$ 16.5. In addition to standard care, 18 patients received 1 dose of 400-mg intravenous tocilizumab, and 3 received 2 doses 12 hours apart. It was indicated that tocilizumab administration is associated with resolution in fever, improvements in radiologic ground-glass opacities, reduction of oxygen support, and normalization of lymphocyte count in 100%, 91%, 75%, and 53% of participants, respectively. In addition, 5 days after the treatment, the mean CRP level dropped from 75.1 $\pm$ 66.8 mg/mL to 2.72 $\pm$ 3.6 mg/mL.[47]

A prospective, multicenter case series was done in 63 patients with severe COVID-19 with SaO_2 <300 mm Hg, and $\geq$3 of the following criteria: CRP >10 times normal values, LDH> 2 times the ULN, ferritin >1000 mg/L, and d-dimer >10 times normal values.

The patients' mean age was 62.0 $\pm$ 12.5 years (mean $\pm$ SD), with a male majority of 88.8%. Twenty-nine patients received subcutaneous tocilizumab (8 mg/kg), and 34 received intravenous tocilizumab (324 mg). Within 24 hours of the first administration, 62 patients received an additional dose. The mortality rate was 11%, with no statistically significant difference between intravenous and subcutaneous administrations. No moderate to severe adverse events related to tocilizumab were reported. Additionally, the levels of CRP, ferritin, d-dimer, and lymphocyte count improved significantly. Also, PaO_2:FiO_2 increased from 152 $\pm$ 53 mm Hg to 283.73 $\pm$ 115.9 mm Hg and 302.2 $\pm$ 126 mm Hg on days

7 and 14, respectively. Analysis of results revealed that the administration of tocilizumab reduced mortality chance (HR, 2.2; 95%CI, 1.3-6.7; $P < .05$).[48]

Another prospective case series was done in 100 patients with severe COVID-19. The median age of patients was 62 years, and 82% were men. The Brescia COVID-19 Respiratory Severity Scale was used for assessing respiratory disease severity. The Brescia COVID-19 Respiratory Severity Scale classifies the severity of patients on the basis of oxygen supplementation as well as the need for ventilator support and provides a step-up therapeutic approach for the administration of antiviral and anti-inflammatory agents. All participants received the standard pharmacologic protocol, including dexamethasone, hydroxychloroquine, antiviral agents, and antibiotic prophylaxis. In addition, 87% received 2 administrations of intravenous tocilizumab (8 mg/kg) 12 hours apart, and 13% received 3 doses. Among 100 patients, 77% experienced improvement or stabilizing of clinical condition, and 23% worsened (20% died). In addition, serum levels of CRP, fibrinogen, and ferritin were improved.[49]

A systemic review and meta-analysis of 7 retrospective studies, including 592 patients (352 in the control group and 240 in the tocilizumab group), was carried out to evaluate the effects of tocilizumab for the treatment of patients with severe COVID-19. The most common tocilizumab dose was a fixed dose of 400 mg or 8 mg/kg, administered once or twice. ICU admission risk (35.1% vs 15.8%; RR, 1.51; 95%CI, 0.33-6.78; $I^2 = 86\%$) and the mechanical ventilation requirement (32.4% vs 28.6%; RR, 0.82, 95%CI, 0.14-4.94; $I^2 = 91\%$) were not statistically different between the tocilizumab and control groups. All-cause mortality was lower in the tocilizumab group compared with the control group. However, the difference was not statistically significant (16.3% vs 24.1%; RR, 0.62; 95%CI, 0.31-1.22; $I^2 = 68\%$).[50]

A retrospective, observational cohort study was done on 544 adult patients with severe COVID-19 pneumonia defined as ≥1 of the following criteria: lung infiltrates of >50% within 1 to 2 days, tachypnea (respiratory rate ≥30 breaths per minute), PaO_2:FiO_2 ratio <300 mm Hg on room air, peripheral SaO_2 <93% on room air. All of the patients received the standard of care, including low-molecular-weight heparin, antiretroviral, supplemental oxygen, hydroxychloroquine, and azithromycin. Among them, 179 patients also received either intravenous (8 mg/kg, up to 800 mg, twice, with a 12-hour interval) or subcutaneous (162 mg twice, simultaneously). The eligible criteria for tocilizumab treatment were SaO_2 <93% and PaO_2:FiO_2 ratio <300 mm Hg on room air or a >30% decrease in PaO_2:FiO_2 ratio 24 hours after hospitalization. Notably, patients in the tocilizumab group had higher levels of LDH, CRP, and IL-6 than the non-tocilizumab group. Data analysis revealed that treatment with tocilizumab decreased the risk of invasive mechanical ventilation or death (adjusted HR, 0·61; 95%CI, 0.40-0.92; $P = .020$). In addition, 4% and 13% of patients were diagnosed with a new infection in the no-tocilizumab and tocilizumab groups, respectively ($P < .0001$).[51]

Considering the limited as well as controversial data regarding efficacy and safety of tocilizumab in patients with COVID-19, evaluation of the patients considering clinical and paraclinical characteristics of hyperinflammation, and the pharmacokinetic aspects of tocilizumab would be beneficial in the determining of the indications as well as the exact dose, duration, and route of administration of the medication in the patients with COVID-19.[52,53]

A retrospective analysis of electronic health records through the Northwell Health System was conducted to evaluate immunomodulatory therapy effects on survival in COVID-19–related cytokine storm (ferritin >700 ng/mL, CRP >30 mg/dL, or LDH >300 U/L). Patients were subdivided into 6 groups: no immunomodulatory treatment (standard of care) and 5 groups who received either corticosteroids, anti–IL-6 antibody (tocilizumab), or anti–IL-1 therapy (anakinra) alone or in combination with corticosteroids. The primary outcome was hospital mortality. Data analysis of 5776 patients revealed that administration of a corticosteroid and tocilizumab combination led to lower mortality compared with standard-of-care treatment (HR, 0.44; 95%CI, 0.35-0.55; $P < .0001$) and with corticosteroids alone (HR, 0.66; 95%CI, 0.53-0.83; $P = .004$) or in combination with an IL-1 antagonist (anakinra) (HR, 0.64; 95%CI, 0.50-0.81; $P = .003$). In addition, corticosteroid use either alone (HR, 0.66; 95%CI, 0.57-0.76; $P < .0001$) or in combination with tocilizumab (HR, 0.43; 95%CI, 0.35-0.55; $P < .0001$) or anakinra (HR, 0.68; 95%CI, 0.57-0.81; $P < .0001$) reduced hospital mortality compared with patients receiving standard-of-care treatment.[54]

In Salvarani and colleagues'[55] randomized clinical trial of 126 patients with COVID-19 with a PaO_2:Fio_2 ratio between 200 and 300 mm Hg, and an inflammatory phenotype defined by fever and/or elevated CRP, 2 administrations of intravenous tocilizumab (8 mg/kg up to a maximum of 800 mg) with a 12-hour interval did not decrease the worsening clinical risk. Of note, the median time from symptom initiation to admission was 8 days. In this multicenter, open-label, randomized clinical trial, within 14 days since randomization, clinical deterioration was observed in 28.3% of the intervention group patients and 27.0% of the standard-care group patients (rate ratio, 1.05; 95%CI, 0.59-1.86; $P = .87$), which was not significantly different. Also, overall mortality of patients during 14 days (1.7% and 1.6% in

the tocilizumab and standard-care groups, respectively; rate ratio, 1.05; 95%CI, 0.07-16.4) and 30 days (3.3% and 1.6% in the tocilizumab and standard-care groups, respectively; rate ratio, 2.10; 95%CI, 0.20-22.6) between the 2 groups showed similarity. Given the fact that this study was not blinded and the sample was small, the potential risk of bias limits the interpretation of results. Furthermore, 14 patients in the standard-care group received tocilizumab after deterioration of their clinical status, which might affect the overall mortality results.

Hermine et al[56] reported a multicenter randomized clinical trial of 130 hospitalized patients with moderate to severe COVID-19 pneumonia, in which 1 dose of intravenous tocilizumab (8 mg/kg on first and third day) did not decrease the WHO 10-point Clinical Progression Scale scores to <5 at day 4. Still, it might have reduced the risk of noninvasive ventilation, mechanical ventilation, or death by day 14. No difference on day 28 mortality was observed. Notably, 47% of patients received an additional fixed intravenous dose of tocilizumab 400 mg on day 3.

A randomized, double-blind, placebo-controlled trial was carried out on 243 patients with COVID-19 with hyperinflammatory states and ≥2 of the following criteria: the need for supplemental oxygen to maintain oxygen saturation >92%, pulmonary infiltrates, or fever. Data analysis within 28 days showed similarity regarding the prevention of intubation or death in moderately ill hospitalized patients with COVID-19 (HR, 0.83; 95%CI, 0.38-1.81; $P = .64$). The clinical status deterioration of patients in the tocilizumab and control groups was also similar (HR, 1.11; 95%CI, 0.59-2.10; $P = .73$).[57]

Interferons

IFN-β-1a (IIb B-R) and IFN-α-2b (IIb C-LD)

There are 2 types of IFNs: type I and type II. IFN-α belongs to type I and exerts a fast response against the virus as a part of the innate immune system. IFN-α combat coronaviruses by blocking the replication of the virus.[58] As well, IFN-β could block the SARS-CoV replication based on the in vitro studies.[59] Conversely, the investigation of INF-γ on SARS-CoV did not show beneficial effects.[60] Haagmans et al[61] also indicated that pretreatment with PEGylated recombinant IFN-α-2b, an approved medication for chronic hepatitis C, attenuates lung damage in SARS-CoV infection by decreasing the replication of the virus and protecting pneumocytes. The beneficial effects of IFN- α were also demonstrated in a clinical trial on patients with SARS.[62] Moreover, IFNs have also been found to be potent inhibitors of MERS-CoV replication.[63] In a noncontrolled trial by Dastan et al,[64] 20 patients with confirmed severe COVID-19 were treated with IFN-β-1a, hydroxychloroquine (200 mg twice daily) and lopinavir/ritonavir (200/50 mg, 2 tablets 4 times daily). This study's definition of severe disease was SaO_2 of ≤90% or PaO_2:FiO_2 of ≤300 mm Hg or respiratory rate of 30 breaths per minute or more. The dose of IFN-β-1a was 44 μg, which was given every other day subcutaneously for 10 days. The mean ± SD of patients' age was 58.55 ± 13.4, and 80% of them were men. The evaluation of symptoms during the follow-up period showed that after 8 days, fever was improved among all patients. Also, after 14 days except for 2 patients, the results of RT-PCR samples of all patients became negative, and imaging studies were improved significantly. The results should be interpreted with caution due to the small sample size, lack of control groups, and confounding factors.

Recently, the effectiveness and safety of IFN-β-1a on 81 patients with severe COVID-19 have been assessed in a randomized clinical trial. The severe clinical condition was defined by at least 1 of the following situations: hypoxemia (achieving SaO_2 of >90% by noninvasive or invasive oxygen support), hypotension (systolic blood pressure <90 mm Hg or needing vasopressor), COVID-19–induced renal failure, COVID-19–induced neurologic impairment (reduction of at least 2 scores on the Glasgow Coma Scale), COVID-19–induced thrombocytopenia (platelet count <150,000/mm^3), and severe gastrointestinal adverse events caused by COVID-19.

In addition to the standard care, 42 patients received subcutaneous IFN-β-1a at a dose of 44 μg/mL (12 million IU/mL) 3 times per week for 2 weeks. In contrast, 39 patients in the control group received only standard care. The majority of the analyzed patients were men (54.3%), and the mean ± SD of their ages were 56.0 ± 16 and 59.5 ± 14 years in the IFN-β-1a and control groups, respectively. Time to clinical improvement was analyzed as a primary end point and defined by the number of days needed for a ≥2-point reduction in the patient's ordinary scale. The comparison of primary end point between the groups showed similarity (9.7 ± 5.8 days for IFN-β-1a vs 8.3 ± 4.9 days for the control group; $P = .95$). The 28-day mortality was significantly lower in the IFN-β-1a group compared to the control group (19% vs 43.6%; $P = .015$). Of note, early use of IFN-β-1a significantly improved the mortality rate (OR, 13.5; 95%CI, 1.5 -118). Also, no significant differences were observed regarding adverse events, mostly including gastrointestinal symptoms. Of 42 patients in the IFN-β-1a group, 8 patients (19%) experienced INF-induced injection reactions. Some details should be taken into account during the interpretation of the results. Not all of the patients in this study had confirmed COVID-19

by RT-PCR. Imaging results, signs, and symptoms were also used for the diagnosis. Also, at the end of the study, further PCR tests or imaging should be conducted for better judgment.[65]

In the WHO Solidarity trial, 4100 patients were randomly assigned 1:1 into 2 groups of IFN-β-1a and control groups. In the intervention group, patients received subcutaneous IFN-β-1a at a dose of 44 μg 3 times over 6 days. Furthermore, intravenous IFN, in conditions like high-flow oxygen ventilators or extracorporeal membrane oxygenation use was given at a dose of 10 μg once per day for 6 days. Death rate ratios were 243 of 2050 and 216 of 2050 for the IFN and control groups, respectively (RR, 1.16; 95%CI, 0.96-1.39; $P = .11$). The duration of hospitalization and initiation of ventilation as secondary end points showed no significant differences between the 2 groups.[32]

A retrospective cohort study was carried out on 446 patients to evaluate the use and time of administration of IFN-α-2b. The median age of patients was 50 years, and most were men. Of these, 216 patients received early administration ($\leq$5 days after admission) of IFN-α-2b alone or in combination with lopinavir/ritonavir or umifenovir. Also, 26 patients received late administration of IFN-α-2b. Of the 204 remaining patients, 122 received only lopinavir/ritonavir, and 82 received only umifenovir. According to the results, the mortality rate was significantly different between the early (0.9%), late (15.4%), and no-IFN (4.9%) groups. Compared to the group with no IFN administration, the early administration of IFN-α-2b led to a lower mortality (OR, 0.1; $P = .02$), and the late administration resulted in a higher mortality rate (OR, 3.53; $P = .046$). The improvements in CT scan or hospital discharge were not observed in early IFN-α-2b administration. However, the late use of IFN-α-2b resulted in delayed recovery. Regarding a better combination therapy choice in this study, the combination of early IFN-α2b and umifenovir or each of these alone led to decreased mortality and improved recovery compared with lopinavir/ritonavir therapy alone.[66] It should be considered that the retrospective design and selection bias could affect the results. Also, presence of some other supportive therapies that may affect the mortality rate was not controlled in this study.

The other noncontrolled trial was conducted in China and evaluated the effects of IFN-α-2b against confirmed SARS-CoV-2 infection based on RT-PCR. The patients were given nebulized IFN-α-2b (7 patients) or arbidol (24 patients) or a combination of nebulized IFN-α-2b and arbidol (46 patients). The outcome analysis revealed that viral clearance was significantly faster with IFN-α-2b ($P = .002$), either alone (21.1 days) or combined with arbidol (20.3 days) compared to the arbidol alone group (27.9 days). Furthermore, the significant reduction of inflammatory cytokines and markers, including IL-6 and CRP, was achieved among patients who received IFN-α-2b. Due to the small sample size, lack of control group, and unbalanced baseline characteristics including comorbidities between the treatment groups, further studies are needed for justification of beneficial effects of IFN-α-2b.[67]

Colchicine (IIb B-R)

Colchicine is a cheap medication with a good safety profile that has been approved for the management of gout and familial Mediterranean fever. The beneficial effects of colchicine have been indicated in several inflammatory conditions, including pericarditis, Behcet disease, and osteoarthritis. The well-known mechanism of colchicine is blocking the polymerization of β-tubulin into microtubules, leading to tubulin and cytoskeletal disruption. This mechanism results in the prevention of various inflammatory pathways, including inhibition of neutrophil chemotaxis and cytokine release. In addition, colchicine exerts its anti-inflammatory effects by interfering with inflammasome signaling, leading to a reduction in active IL-1β production.[68] In another study on patients with acute coronary syndrome, it has been indicated that colchicine can significantly reduce the local cardiac output of IL-1β, IL-18, and IL-6 cytokines.[69]

It has been revealed that the intense inflammatory response leads to overproduction of inflammatory cytokines and CRS, which has a direct relation with lung injury and ARDS in patients with COVID-19.[70] Thus, considering this pathophysiologic pathway, colchicine may have potential benefits due to its anti-inflammatory activity with fewer adverse effects than steroids and nonsteroidal anti-inflammatory drugs.[71] Recently, a randomized clinical trial by Deftereos et al[72] evaluated the effects of colchicine on hospitalized patients with COVID-19. Patients with RT-PCR–confirmed SARS-CoV-2 infection, fever, and at least 2 of the following criteria: PaO_2 <95 mm Hg, sustained sore throat, sustained cough, and loss of sense of smell and/or taste were included in the study. A total of 105 patients with a median age of 64 years (range, 54-76 years) and male majority (58.1%) were randomly assigned to the intervention (n = 55) and control (n = 50) groups. Along with standard treatment protocols, the intervention group was also treated with a 1.5-mg loading dose of colchicine followed by 0.5 mg after 1 hour and maintenance doses of 0.5 mg 2 times per day for 3 weeks. Chloroquine and hydroxychloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, and anticoagulants were used as standard-care medications. The clinical status score for the most of the patients in both groups ($\geq$60%) was 5. Also, PaO_2 <95 mm Hg

was observed in 66% and 74.5% of the patients in the control and colchicine groups, respectively. The clinical end point of the study was the time from baseline to the elevation of 2 grades on an ordinal clinical scale according to the WHO Research and Development Blueprint Ordinal Clinical Scale within 3 weeks after randomization or until hospital discharge. The biochemical end points were the evaluation of the differences between groups regarding the levels of maximal high-sensitivity cardiac troponin and the time for the elevation of CRP levels up to 3 times the ULN. The clinical end point rate was 14.0% and 1.8% in the control and colchicine groups, respectively ($P = .02$). This result showed that the time to clinical deterioration was significantly improved in the colchicine group. In contrast, there were no significant differences between the 2 groups considering the end points in the biochemical phase. The comparison of adverse events also showed similarities in the 2 groups. It should be noted that most of the medications used as standard care in this trial are not recommended against COVID-19. Thus, by using new standard-care treatments including remdesivir, the finding might be different. Furthermore, the open-label design and lack of placebo use are the other limitations for this study. Also, the reason for using colchicine was its anti-inflammatory effects, while the levels of inflammatory markers were not assessed.

Ruxolitinib (IIb B-R)

Ruxolitinib has FDA and European Medicines Agency approval for the treatment of polycythemia vera and myelofibrosis due to the potent inhibition of JAK1 and JAK2, selectively. Also, its effectiveness on reduction of abnormal host inflammatory response makes it a potential medication against steroid-refractory acute graft-vs-host disease after allogeneic hematopoietic stem cell transplantation or secondary hemophagocytic lymphohistiocytosis.[73] As previously indicated, COVID-19–induced CRS is associated with mortality. High amounts of released inflammatory cytokines in this process can result in extensive tissue injury, deterioration of ARDS, and finally death.[41] Thus, it can be assumed that as a potent anti-inflammatory medication, ruxolitinib might have beneficial effects on decreasing cytokine levels during SARS-CoV-2 infection.

In a multicenter, randomized, single-blind, placebo-controlled trial, the effects of ruxolitinib on severe COVID-19 have been evaluated by Cao et al.[74] The definition of severe clinical state in this study was based on Chinese management guideline for COVID-19 (version 5.0). Of the 41 analyzed patients, 20 patients assigned to the treatment group (received 5 mg ruxolitinib twice daily plus standard care) and 21 patients assigned to the control group (received 100 mg vitamin C as a placebo twice daily plus standard care). Study patients were mostly men (58.5%), and the median age was 63 years. The median time from disease onset to randomization was 20 days. The clinical status evaluation of patients by NEWS2 score showed a median score of 5, and 87.8% required supplemental oxygen.

The comparison of time to clinical improvement showed no significant difference between the 2 groups (HR, 1.669; 95%CI, 0.836-3.335; $P = .147$). On day 14 after randomization, significant improvement was observed in the chest CT scans of patients in the ruxolitinib group compared to the control group (90% vs 61.9%; $P = .04$). Of note, patients on invasive mechanical ventilation were excluded from this study, and the findings cannot be generalized to these patients. Also, the small sample size of this trial should be considered during the evaluation of the results.

Convalescent Plasma (IIb B-R)

Neutralizing antibodies have a crucial role in the clearance of the virus and can be considered as a protection against viral disease. The beneficial effects of convalescent plasma against SARS-CoV, influenza, and Ebola have been indicated in previous studies. Thus, neutralizing antibodies in the plasma of patients who have recovered from COVID-19 can be a rational way to combat SARS-CoV-2 infection through mitigation of the inflammatory response. These antibodies were detected even in patients in the early stages of the disease.[75,76]

A multicenter randomized clinical trial by Li et al[77] evaluated the treatment results with convalescent plasma in patients with severe or life-threatening COVID-19 in China. The definition of severe condition was respiratory rate of $\geq$30 breaths per minute, SaO_2 of $\leq$93%, or PaO_2:FIO_2 of $\leq$300. Also, life-threatening condition was clarified by needing mechanical ventilation, patients in the ICU with organ failure, or shock. A total of 103 patients were randomly assigned, with 52 patients assigned to the intervention group (receiving convalescent plasma plus standard treatment) and 51 assigned to the control group (receiving only standard treatment). Time to clinical improvement within 28 days (discharging live from the medical center or improvement of 2 points in 6-point disease severity scale) was considered the study's primary end point.

The age range of patients was 62 to 78, with a median of 70 years. The comparison of the sex of patients in both groups showed that the number of men was greater in the control group (65% vs 52%). The analysis of the primary end point showed no significant difference between the 2 groups (HR, 1.40; 95%CI, 0.79-2.49; $P = .26$). Also, 28-day mortality was similar between the intervention and the control groups, at 16% and 24%, respectively (OR, 0.65; 95%CI, 0.29-1.46; $P = .30$). In addition, the percentage of negative RT-PCR at

24, 48, and 72 hours was significantly higher in patients receiving convalescent plasma with *P* values of .003, .001, and <.001, respectively. Although these results could not support the use of convalescent plasma in patients with COVID-19, due to the small population and short time of the mentioned study, further blinded studies are needed for better interpretation.

Another retrospective and case-control study evaluated the efficacy of convalescent plasma in 39 patients with COVID-19 with severe or life-threatening clinical status. The severe condition was defined as respiratory rate of ≥30 breaths per minute, SaO_2 of ≤93%, PaO_2:FIO_2 <300, and/or deterioration of lung infiltration >50% within 44 to 48 hours. Life-threatening clinical status was defined by multiple organ failure, respiratory failure, or septic shock.

A total of 156 patients were selected from the hospital's database as the control group, retrospectively. The mean ± SD of the age of patients receiving convalescent plasma was 55 ± 13, and 64% were men. On the transfusion day, most of the patients (87%) were on noninvasive supplemental oxygen, and 4 patients (10%) were supported with mechanical ventilation. After 14 days, a worsening of clinical status was observed in 17.9% of the convalescent plasma group and 28.2% of the control groups (adjusted OR, 0.86; 95%CI, 0.75-0.98; $P = .025$). Furthermore, the convalescent plasma group's survival improved significantly (adjusted HR, 0.34; 95% CI, 0.13-0.89; $P = .027$). Of note, the interpretation of the results is limited due to a lack of randomization and potential bias in the selection of patients.[78]

An open-label, parallel-arm, phase 2, multicenter, randomized clinical trial was carried out on 464 patients to evaluate the role of convalescent plasma therapy in moderate COVID-19. Besides the standard treatment, the intervention group was administered 2 doses of 200 mL of convalescent plasma, 24 hours apart (n = 235), whereas the control group received only the standard treatment (n = 229). Moderate disease was defined as PaO_2:FiO_2 ratio between 200 mm Hg and 300 mm Hg or respiratory rate >24 per minute with SaO_2 of ≤93% while breathing room air. Data analysis revealed that progression to severe disease or all-cause mortality at 28 days after enrollment were observed in 19% and 18% of patients in the intervention and control groups, respectively (risk difference, 0.008; 95%CI, −0.062 to 0.078; risk ratio, 1.04; 95%CI, 0.71-1.54). Thus, this study could not support the beneficial effect of convalescent plasma on reduction of progression to severe COVID-19 or all-cause mortality.[79] However, the exact role of convalescent plasma cannot be elucidated without the prior measurement of neutralizing antibody titers in donors who have recovered from COVID-19.

Anti–Hepatitis C Virus Nucleotide Analogs Including Sofosbuvir/Daclatasvir and Ribavirin (IIb B-R)

Like coronaviruses, the hepatitis C virus (HCV) is a single-stranded RNA virus that replicates by RdRp. As known, the SARS-CoV-2 RdRp can be considered a key protein for drug targeting. This polymerase active site and catalytic mechanisms remain similar among several positive-sense RNA viruses, such as coronaviruses and HCV.[80] As in other viruses, the coronavirus RdRp is susceptible to errors, making it able to accept adjusted nucleotide analogs as substrates.[81] Among antiviral medications, nucleotide analogs play a central role in the treatment of HCV as polymerase inhibitors.[82] The anti-HCV agents, including sofosbuvir, daclatasvir, ribavirin, and galidesivir, were evaluated in previous literature using molecular docking and polymerase extension experiments predicting that these agents have an inhibitory effect on SARS-CoV-2 RdRp.[83–85] However, clinical trials need to be conducted for further evaluation.

The effectiveness of sofosbuvir combined with daclatasvir on moderate COVID-19 was evaluated in a randomized clinical trial. SaO_2 of ≥94%, respiratory rate of ≤24 breaths per minute, initiation of symptoms <8 days before admission, and compatible results in the chest CT scan were classified as moderate disease. A total of 48 patients were randomized to the intervention (n = 24) and the control groups (n = 24). The intervention group was treated with 400 mg of sofosbuvir plus 60 mg of daclatasvir once a day and 600 mg of ribavirin twice a day. The control group received 400 mg of hydroxychloroquine once daily and 400 mg of lopinavir plus 100 mg of ritonavir twice a day with or without 600 mg of ribavirin twice a day. The median time from the initiation of the symptoms and admission was 5 days for both groups. As a primary end point, the duration of hospital stay for both groups was the same, with a median of 6 days. The median time to recovery, which was defined as live discharge from hospital, was 6 days for both groups, with a significant difference between the 2 groups ($P = .033$) but after adjustment for the baseline features of patients the difference was not significant.[86] The limitations of this study, including small sample size, imbalanced baseline features, and excluding elderly patients aged >80 years, make it difficult to interpret results accurately.

Another multicenter randomized clinical trial by Sadeghi et al[87] compared the efficacy of sofosbuvir/daclatasvir and standard treatment protocol on severe to moderate COVID-19.

Of the 66 patients who underwent randomization, 33 patients were assigned to receive sofosbuvir/daclatasvir (400 mg and 60 mg once daily) plus standard care for 14 days, and 33 patients were assigned to standard care including 200 mg of hydroxychloroquine twice a day

with or without 200 mg of lopinavir/50mg of ritonavir twice a day. Patients with a temperature of ≥37.8°C; compatible findings on chest CT scan; and at least 1 of SaO_2 >94%, PaO_2:FiO_2 ratio <300 mm Hg, or respiratory rate >24 breaths per minute entered the study. Of note, the time between initiation of symptoms and admission must be ≤8 days. Among the included patients, 52% were men, with a median age of 58 years. The clinical improvement during 14 days was analyzed as a primary outcome and was experienced by 88% and 67% of the patients in the intervention and the control groups, respectively ($P = .076$); however, after adjustment for baseline features, this effect was significant.

Also, treatment with sofosbuvir/daclatasvir significantly reduced the duration of hospitalization (6 vs 8 days; $P = .02$) and increased the chance for hospital discharge ($P = .04$). No difference was observed regarding the all-cause mortality, with 3 deaths in the intervention group and 5 deaths in the control group ($P = .70$). This study suffers from several limitations. First, it was not blinded and placebo controlled. Second, more patients in the control group received lopinavir/ritonavir, which may affect the results. Third, the sample size was limited. Thus, the potential risk of bias should be taken into consideration when interpreting the findings.

Eslami et al[88] compared the effects of sofosbuvir/daclatasvir versus ribavirin against severe COVID-19 in a randomized clinical trial. Of the 62 patients, 35 were assigned to the sofosbuvir/daclatasvir group (400/60 mg once daily) and 27 patients to the ribavirin group (600 mg twice a day with a 12-hour interval) for 14 days. All patients received standard care including a single dose of 400-mg hydroxychloroquine and lopinavir/ritonavir (200/50 mg twice a day for 5 days). The median time for hospitalization was significantly lower in the sofosbuvir/daclatasvir group (5 versus 9 days; $P < .01$). Also, the mortality was 6% in the sofosbuvir/daclatasvir group and 33% in the ribavirin group with a death relative risk of 0.17 (95%CI, 0.04–0.73, $P = .02$) and 3.6 (95%CI, 2.1-12.1; $P < .01$), respectively. However, lack of blinding, the third group receiving only placebo, and small sample size cannot rule out ribavirin over sofosbuvir/daclatasvir.

Favipiravir (IIb B-R)

Favipiravir is an analog of nucleic purine acid that exerts antiviral activity through inhibition of RdRp. It was developed in Japan and was approved to manage the influenza-A virus infection in 2014. It is also effective against Ebola and norovirus.[89] In a nonrandomized clinical study by Cai et al,[90] the efficacy of favipiravir against COVID-19 was compared to lopinavir/ritonavir when added to 60 μg of IFN-α-1b. Thirty-five patients were assigned to the intervention group and received 1600 mg of favipiravir twice daily on the first day, followed by 600 mg twice daily on days 2 through 14. Forty-five patients were assigned to receive lopinavir/ritonavir (400/100 mg twice daily on days 1 through 14) in the control group. Inclusion criteria were patients aged 16 to 75 years and without severe clinical status (respiratory rate >30 breaths per minute, SaO_2 <93%, oxygenation index <300 mm Hg, respiratory failure, shock, and/or ICU patients), with <7 days between disease onset and enrollment. The median age was 47 years, and BMI was 22.9, with a majority of women (56.2%).

The effectiveness of medications was evaluated on the basis of the time of the viral clearance and the rate of improvement in CT scans. The comparison of chest imaging showed better improvement in the favipiravir arm (91.4% vs 62.2%). Also, the clearance of the virus was faster (2 days in the favipiravir group and 11 days in the lopinavir/ritonavir group).

The favipiravir arm also showed a better safety profile in comparison with the control group (11.4% vs 55.6% adverse events). These results can be an opening for additional clinical trials for better evaluation.

A randomized clinical trial by Lou et al[91] evaluated the effectiveness of baloxavir marboxil and favipiravir on 29 hospitalized patients with confirmed COVID-19. This study had 3 groups: 10 patients assigned to the baloxavir group (received the standard antiviral treatment plus 80 mg of oral baloxavir once daily on the first and fourth days and on the seventh day only for patients with positive virus test), 9 patients assigned to the favipiravir group (received the standard antiviral treatment plus oral favipiravir with an initial dose of 1600 mg or 2200 mg, then 600 mg 3 times a day, up to 14 days), and 10 patients assigned to the control group and received only the standard antiviral treatment (400 mg of lopinavir/100 mg of ritonavir twice daily or 800 mg of darunavir/150 mg of cobicistat once daily and 200 mg of arbidol 3 times daily, and inhalation of 100 000 units of interferon-α 3 or 4 times a day). The mean ± SD of patients' age was 52.5 ± 12.5, and 72.4% were men. The degree of disease severity was calculated by NEWS2 and showed a median score of 4 for all 3 groups.

The in vitro evaluation showed that baloxavir acid had a superior antiviral effect compared to the favipiravir. A negative viral test occurred in 70% of patients in the baloxavir marboxil group, 77% of patients in the favipiravir group, and 100% of the control group. The median time for clinical improvement was 14, 14, and 15 days for the baloxavir, favipiravir, and control groups, respectively. The mean days from initiation of symptoms to randomization were 12.7 in the baloxavir marboxil group, 8.5 in the favipiravir

group, and 13.6 in the control group; however, this difference was not considered in this study. Also, this study considered only the plasma concentrations for in vitro analysis of antiviral effects, whereas the intracellular concentration of favipiravir is also important. For these reasons, the finding should be discussed with caution.

Baloxavir (IIb B-R)

In the past years, baloxavir marboxil was approved for the treatment of influenza. It affects the endonuclease function that results in the inhibition of messenger RNA (mRNA) transcription and virus replication. Its novel antiviral mechanism makes it possible to treat COVID-19 infection, and the idea can be used for further studies.[92,93] As previously discussed in favipiravir, Lou and colleagues'[91] randomized clinical trial could not support the beneficial effects of baloxavir marboxil to the standard antiviral therapy.

Ivermectin (IIb B-R)

Ivermectin is an FDA-approved antiparasitic medication, and its antiviral activity has been investigated in several in vitro studies. Particularly, its efficacy on RNA viruses, including influenza, West Nile virus, and Venezuelan equine encephalitis virus, has been revealed in former literature.[94–96] It has been shown that it can combat HIV-1 through inhibition of virus integrase protein interaction with the importin-α/β1 and virus replication.[97] Previously, the role of importin-α/β1 was revealed during the SARS-CoV infection. Thus, the inhibitory effect of ivermectin against nuclear transport and its good safety profile makes it a potential candidate for COVID-19. Caly et al[98] investigated the in vitro activity of ivermectin against SARS-CoV-2 infection. In this study, investigators used Vero/hSLAM cells infected by SARS-CoV-2. The results showed that adding 5 μM of ivermectin as a single dose resulted in an ≈5000-fold decline in viral RNA at 48 hours. Thus, ivermectin can be investigated in humans for possible benefits.

A double-blinded, randomized, placebo-controlled study by Ahmed et al[99] assessed the safety and efficacy of ivermectin on hospitalized patients with RT-PCR–confirmed COVID-19. Patients entered the study if they were aged 18 to 65 years, temperature of ≥37.5°C, and/or sore throat. Included patients (n = 72) were assigned to receive ivermectin (12 mg per day for 5 days), ivermectin (12-mg single dose) plus doxycycline (200 mg on the first day, then 100 mg every 12 hours on days 2 through 5), or placebo. The mean age of patients was 42 years, and 54% were women. The mean days between disease duration and assessment was 3.8. As the primary outcome, the mean time to viral clearance was significantly lower in the ivermectin group compared to the placebo group (9.7 vs 12.7 days; 95%CI, 7.8-11.8 days; $P = .02$). However, this difference was not significant between the ivermectin plus doxycycline and placebo groups (11.5 vs 12.7 days; 95%CI, 9.8-13.2 days; $P = .27$). No significant differences were observed regarding duration of hospitalization and adverse events between the groups. Although this study supported the beneficial effects of ivermectin against COVID-19, it should be noted that patients with chronic disease such as chronic kidney or liver disease and pregnant women were not included in this study. Thus, the results in these groups of patients should be interpreted rigorously. Other important limitations of this study were the small sample size and lack of categorization of patients based on their clinical status.

Another open-label, randomized clinical trial evaluated the efficacy of ivermectin in mild RT-PCR–confirmed COVID-19. Of the 50 included patients, half of them received ivermectin at a dose of 12 mg followed by 12 mg after 12 and 24 hours. The mean age of patients was 40.60, and most of them were men. The comparison of asymptomatic patients on day 7 showed similarity between the groups ($P = .5$).[100] The small sample size, lack of placebo group, and open-label design of this study should be considered during the interpretation of the results.

Recently, a meta-analysis of 4 observational studies was conducted to evaluate ivermectin efficacy on COVID-19. Of the 629 included patients with mild or moderate to severe COVID-19, 397 received ivermectin plus standard care. Except for 1 study that administered 2 doses of ivermectin, the remaining studies assessed the 150 to 200 μg/kg of ivermectin as a single dose.

As a primary end point, all-cause mortality showed a significant reduction among the ivermectin group (OR, 0.53; 95%CI, 0.29-0.96; $P = .04$). The requirement for respiratory support was significantly improved in the ivermectin group (OR, 1.98; 95%CI, 1.11-3.53; $P = .02$). However, the time required for hospital discharge and viral clearance was similar between the 2 groups.[101] It should be taken into account that the included studies have low quality and level of evidence due to the high risk of bias resulting from the small sample size, various confounding factors, and observational design.

Sarilumab (IIb C-LD)

Benucci and colleagues'[102] clinical series of 8 hospitalized patients with RT-PCR–confirmed COVID-19 assessed sarilumab administration. In addition to standard treatment, these patients received 3 intravenous doses of sarilumab at doses of 400, 200, and 200 mg at 24, 48, and 96 hours after hospital admission, respectively. The mean age of patients was 62 years, and 6 of the patients were men. Standard treatment in this study consisted of 400 mg of hydroxychloroquine, 500 mg of

azithromycin, 800 mg of darunavir, 150 mg of cobicistat, and enoxaparin 100 U/Kg. Among the patients, 7 were discharged within 14 days of hospitalization. One patient had no clinical improvement and died 13 days after hospitalization. However, the interpretation of these results cannot be confirmed without standard randomized clinical trials.

Based on an observational clinical cohort study of Gremese et al,[103] a total of 53 patients with severe COVID-19 pneumonia received intravenous sarilumab (400 mg). Among enrolled patients, 88.7% were male, with a median age of 66 years (range, 40-95 years). According to the patients' clinical situations, 1 or 2 doses of sarilumab, antivirals, antibiotics, hydroxychloroquine, glucocorticosteroids, and heparin were considered. Among 53 patients, 73.6% and 26.4% were treated in medical wards and ICU, respectively. Within the medical wards, 89.7% of patients significantly improved, 70.6% were discharged from the hospital, and 85.7% no longer needed oxygen therapy. Within patients in ICU, 64.2% were discharged from the ICU to the ward, and 35.8% were still alive at the last follow-up. Finally, the overall mortality rate was 5.7%.

In an open-label observational study, 56 patients with severe COVID-19 pneumonia with elevated inflammatory markers and serum IL-6 levels were included. All patients received standard of care, and 28 patients received intravenous sarilumab (400 mg). Of note, all patients were supported with high-flow oxygen, and most of them were also supported with noninvasive ventilation due to moderate ARDS (PaO_2:FiO_2, 100-200 mm Hg with a positive end-expiratory pressure $\geq$5 cm H_2O; 39%) or severe ARDS (PaO_2:FiO_2 <100 mm Hg with a positive end-expiratory pressure $\geq$5 cm H_2O). Data analysis showed that there were no statistically significant differences between the sarilumab-treated group and the comparison group regarding fever resolution (100% vs 100%; $P = .99$), CRP normalization (86% vs 61%; $P = .06$), clinical improvement (60% vs 64%; $P = .99$), death (7% vs 18%; $P = .42$), live discharge (60% vs 60%; $P = .99$) on 28-day follow-up; however, time to fever resolution (1 day vs 4 days; $P < .0001$), time to CRP normalization (6 days vs 12 days; $P < .0001$), and time to death (19 days vs 4 days; $P = .006$) were significantly higher in the comparison group compared with the sarilumab-treated group.[104]

A retrospective case series was carried out on 15 patients with COVID-19 with SaO_2 <93% or oxygen therapy or mechanical ventilation requirements. Among them, 12 patients received a single subcutaneous injection of sarilumab (400 mg), and 3 received 2 doses with a 24-hour interval. Furthermore, considering clinical situations, patients were treated with standard care (hydroxychloroquine, lopinavir/ritonavir, and heparin/methylprednisolone). The median time from symptom onset to treatment was 11 days (range, 6-21). The median PaO_2:FiO_2 at baseline for all patients was 122 (range, 83-240), and 8 of 15 (53.3%) were intubated at the time of sarilumab administration. After sarilumab administration, 67% of patients experienced improvements in respiratory parameters, and 34% died.[105] However, it should be considered that given the design of observational studies and their potential high risk of bias, further well-designed randomized controlled trials are needed for better interpretation.

According to preliminary data of a phase 2/3 clinical trial on 457 hospitalized patients with COVID-19 with severe disease, critical disease, or multisystem organ dysfunction, in patients with the critically ill disease, the percentage of on ventilator cases or dead was lower in the sarilumab 400-mg group than the sarilumab 200-mg, and the placebo groups. In addition, negative trends for most outcomes in patients with severe disease were observed.[106]

Anakinra (IIb C-LD)

Some of the patients with COVID-19 develop a hyperinflammatory situation that resembles CRS. IL-1 is one of the cytokines that attributes to this condition. Blocking the excessive release of cytokines might be the rational way for preventing the complications induced by CRS, including lung damage and ARDS. Anakinra is an IL-1 receptor antagonist used in several inflammatory disorders, including familial Mediterranean fever and systemic-onset juvenile idiopathic arthritis. Thus, considering the CRS attributed to COVID-19, the idea of using the cytokine-blocking agent anakinra can be investigated in SARS-CoV-2 infection. Recently, a meta-analysis by Putman et al[107] assessed the use of antirheumatic agents in COVID-19. In this review, 1 case series and 2 cohort studies were included to evaluate anakinra use in patients with COVID-19. In a cohort study by Huet et al,[108] the effects of anakinra on severe COVID-19 were evaluated. It included a prospective cohort of patients in the intervention group (n = 52) and a retrospective cohort of the control group (n = 44). Both groups' inclusion criteria were severe laboratory- or imaging-confirmed COVID-19, SaO_2 $\leq$93% while breathing ambient air, and age of $\geq$18 years. The intervention group received subcutaneous anakinra (100 mg twice daily for 72 hours and then 100 mg per day for 7 days) and the standard treatments. In contrast, the control group was only managed with standard care including hydroxychloroquine 600 mg daily for 10 days, azithromycin 250 mg daily for 5 days, and β-lactam antibiotics (intravenous ceftriaxone 1 g daily or intravenous amoxicillin 3 g daily) for 7 days. The mean age of patients was 71 years in both groups, and most were men. It is concluded that the use of anakinra was associated with a decreased rate

of death or requirement for mechanical ventilation (25% vs 73%; HR, 0.22; 95% CI, 0.11-0.41; $P < .0001$) in severe COVID-19 with no severe adverse events. It is noteworthy that imbalanced baseline characteristics between the groups, particularly the higher rate of obesity in the control group, could affect the findings. Also, due to the observational design of this study, the results should be interpreted with caution.

In the other cohort study, patients with moderate to severe ARDS and hyperinflammatory state and aged ≥18 years were included. The diagnosis of COVID-19 in this study was based on either RT-PCR or imaging results. Hyperinflammation was defined by CRP ≥100 mg/L or ferritin ≥900 ng/mL. The definition of moderate to severe ARDS was explained by respiratory failure PaO_2:FiO_2 ≤200 mm Hg and positive end-expiratory pressure >5 cm H_2O without cardiogenic edema. In addition to the standard care, 29 patients were treated with high-dose anakinra (5 mg/kg twice a day intravenously), and 7 patients received low-dose anakinra (100 mg twice a day subcutaneously). Also, 16 patients were managed with only standard care. All patients were managed with noninvasive ventilation outside of the ICU. The outcomes were analyzed after 21 days, and results showed that 72% of patients on high-dose anakinra safely experience improvements in clinical status compared with 50% in the control group. Also, the survival of patients was significantly higher in patients receiving a high dose of anakinra (90% vs 56%; $P = .009$).[109]

Statins (IIb C-LD)

Statins are known as 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors that are used to reduce serum cholesterol by inhibiting its synthesis in the hepatic cells. In addition to its common lipid-lowering activity, statins have antioxidant, antithrombotic, anti-inflammatory, and immunomodulatory properties.

Patients with COVID-19 have a greater risk of cardiovascular problems and thrombotic events. Thus, statins may be considered an adjunctive treatment for reducing endothelial dysfunction and imbalanced inflammation in patients infected with SARS-CoV-2. According to the previous literature, other possible favorable effects of statins in patients with COVID-19 were interfering with virus entry and affecting the SARS-CoV-2 receptors, including ACE2 and CD147. Moreover, statins could exert protective effects by regulating virus replication or degradation through inducing autophagy activation. The anti-inflammatory properties of statins, including blocking several molecular mechanisms such as nuclear factor kappa-light-chain enhancer of activated B cells, NLRP3 inflammasome, and myeloid differentiation primary response 88, could prevent the cytokine storm in patients with severe COVID-19 and lead to decreased mortality.[110,111]

In a retrospective study on 13 981 patients admitted to the hospital, the effects of statin therapy on COVID-19 mortality was evaluated. Among them, 1219 patients were on statins. The analysis of risk for all-cause mortality after 28 days revealed 5.2% in the statin group and 9.4% in the patients without statin treatment (adjusted HR, 0.58). Thus, it showed the possible beneficial effects of statin therapy on patients with COVID-19.[112]

In the other retrospective study, a total of 2626 patients with RT-PCR–confirmed COVID-19 were analyzed. Among them, 951 patients were previous statin users. The demographic and clinical data of 648 statin users were matched with 648 patients not using statins. The propensity-matched analysis results showed that inpatient mortality during the 30 days of the follow-up period was significantly lower in statin users (OR, 0.48; 95%CI, 0.36-0.64; $P < .001$).[113] However, the results of these studies should be confirmed by randomized clinical trials due to the limitations in the design of retrospective studies including high risk of bias and effect of cofounding factors.

Camostat Mesylate (IIb C-EO)

COVID-19 enters the host cell through binding of its S proteins to the cell receptors. ACE2 acts as a SARS-CoV receptor and is known as a key factor for COVID-19 transmissibility. The cellular protease TMPRSS2 is needed for the priming of S protein. Thus, the protease inhibitors such as camostat mesylate can be candidates for the treatment of COVID-19 infection. Recently, Hoffmann et al[114] showed that camostat mesylate blocks the cell entry of SARS-CoV-2 by the mentioned mechanism.

Niclosamide (IIb C-EO)

Niclosamide is the FDA-approved anthelmintic agent that has the potential to exert antiviral activity through several mechanisms.[115] It can act as a proton carrier and blocks the human rhinovirus entry by preventing the endolysosomal parts' acidification.[116] Chikungunya virus is also inhibited by niclosamide through interfering with both virus entry and transmission.[117] Furthermore, the transportation of human adenovirus from the endosome to the nuclear envelope can be inhibited by niclosamide.[118] It also exerts antiviral activity against the Epstein-Barr virus and HCV through interfering with virus replication.[119,120]

Wu et al[121] revealed that niclosamide could combat SARS-CoV by inhibiting virus replication and synthesis of the virus antigen. In addition, a study by Gassen et al[122] showed beneficial effects of niclosamide against MERS-CoV by the same mechanism. Considering the similarity between the sequences of viruses that belongs

to the *Betacoronavirus* genus and antiviral features of niclosamide, it can be considered a potential choice for COVID-19 treatment.

Chloroquine and Hydroxychloroquine (III B-R)

Chloroquine is an antimalarial agent that has immunomodulatory effects.[123] Several studies have been shown that chloroquine can combat coronavirus by several pathways. First, it interferes with the fusion of the virus to the cell membrane by increasing endosomal pH. Second, it inhibits ACE2, which is one of the binding sites for the S protein of COVID-19. Third, it affects the replication of nucleic acid, glycosylation of receptors, and transportation of new virus particles.[124–126] Hydroxychloroquine, an analog of chloroquine, is more tolerable and has fewer interactions in comparison with chloroquine. Chloroquine and hydroxychloroquine also exert vigorous anti-inflammatory activity, which makes them effective for rheumatoid arthritis and systemic lupus erythematosus.[127–129]

One study revealed that in comparison with chloroquine, hydroxychloroquine has better in vitro antiviral activity against COVID-19, which makes it a better candidate for prevention and treatment of SARS-CoV-2 infection.[130]

The association between hydroxychloroquine use and intubation or death was evaluated in an observational study in hospitalized patients with COVID-19. Of the total of 1446 consecutive patients admitted to the hospital, 1376 patients were included in the study. Seventy patients were excluded from analysis since they were already intubated or dead. They were discharged after inpatient admission or were directly admitted to alternative facilities within 24 hours after presentation to the emergency department. Of the 1376 patients, 811 patients received 600 mg of hydroxychloroquine twice daily on the first day, followed by 400 mg per day for a median of 5 days. The study baseline to intubation or death showed no significant relationship between administration of hydroxychloroquine and intubation or death (HR, 1.04; 95%CI, 0.82-1.32). Of note, patients who received hydroxychloroquine had more severe clinical status with a lower PaO_2:FiO_2 at baseline than the non-hydroxychloroquine group (median of 233 vs 360 mm Hg). Furthermore, given the observational design of the study, ignored confounding factors, and possible risk of bias, the results need precise evaluation.[131]

In a multicenter randomized clinical trial by Tang et al,[132] 150 patients (148 patients with mild to moderate and 2 patients with severe COVID-19) were entered. Mild disease was defined by mild symptoms without pneumonia signs on imaging. Moderate disease was defined by respiratory symptoms such as cough, sputum production, fever, and pneumonia signs on imaging without severe pneumonia manifestations including SaO_2:SpO_2 <94% while breathing room air or a PaO_2:FiO_2 ratio of ≤300 mm Hg.

Besides the suggested standard treatment, 75 patients in the intervention group received a 1200-mg loading dose of hydroxychloroquine for 3 days, followed by a maintenance dose of 800 mg daily. The duration of intervention was 2 weeks for mild to moderate state and 3 weeks for the severe condition. Generally, the possibility of negative conversion of RT-PCR samples over 28 days was 85.4% (95%CI, 73.8%-93.8%) for the hydroxychloroquine group and 81.3% (95%CI, 71.2%-89.6%) for the standard-care group. The results of this trial did not support the beneficial effects of adding hydroxychloroquine on virus elimination in comparison with standard care. Furthermore, gastrointestinal adverse events were significantly higher in the intervention group. This study suffers from some limitations. First, the study's open-label design with no placebo can lead to a potential risk of bias. Second, since this trial mostly included patients with mild to moderate disease, the role of hydroxychloroquine on the progression of disease was not applicable.

Another nonrandomized clinical trial included 36 patients with RT-PCR–confirmed COVID-19 (hydroxychloroquine group = 20 and control group = 16). The dose of hydroxychloroquine was 600 mg daily for 10 days. Patients were categorized into 3 groups regarding the clinical status: asymptomatic, upper respiratory tract infection, and lower respiratory tract infections with the overall proportion of 16.7%, 61.1%, and 22.2%, respectively. For the prevention of bacterial infection, 6 patients in the hydroxychloroquine group were also administered azithromycin at a dose of 500 mg on the first day, then 250 mg daily for the following 4 days. On day 6, after inclusion, the proportion of negative nasopharyngeal PCR tests was significantly higher in the hydroxychloroquine group compared to the control group (70% vs 12.5%, P = .001). In addition, the nasopharyngeal PCR test turned negative for 100% of patients who received hydroxychloroquine combined with azithromycin, 57.1% of patients in the hydroxychloroquine group, and 12.5% in the control group (P < .001). However, the high risk of bias, limited sample size, lack of randomization, and short follow-up period should be accounted for during the interpretation of the findings. Also, this study did not compare the 2 groups regarding the adverse events.[133]

The WHO Solidarity trial analyzed 947 patients for hydroxychloroquine sulfate administered at a dose of 800 mg at the beginning, 800 mg at the sixth hour, and 400 mg at the 12th hour for 10 days. Also, 906 patients were analyzed as the control group. The comparison of data rate ratios between groups did not show

significant differences (RR, 1.19; 95%CI, 0.89-1.59; $P = .23$; 104/947 for hydroxychloroquine vs 84/906 for the control group). Also, similar results were achieved regarding the duration of hospitalization and initiation of ventilation.[32]

Similarly, a randomized controlled trial by the RECOVERY Collaborative Group did not support the beneficial effects of hydroxychloroquine on patients with confirmed COVID-19. In this trial, 4716 patients underwent randomization. Of these, 3155 patients received hydroxychloroquine sulfate at a loading dose of 800 mg at the beginning and at 6 hours. Then 12 hours after the first dose, 400 mg was given every 12 hours for days 2 through 10. All of the patients were managed with the standard care treatment. Included patients were mostly men (62%), and the mean ± SD of age was 65.4 ± 15.3 years. As a primary outcome of the study, 28-day mortality did not differ between the 2 groups, with 27% and 25% in the hydroxychloroquine group and in the standard-care group, respectively (rate ratio, 1.09; 95%CI, 0.97-1.23; $P = .15$). Also, the duration of hospitalization was longer among patients who received hydroxychloroquine with median 16 and 13 days and the chance for leaving hospital alive during 28 days was lower in the hydroxychloroquine group (59.6% vs 62.9%; rate ratio, 0.90; 95%CI, 0.83-0.98).[134] Although the appropriate sample size was not calculated in this trial and the placebo was not used, these results can be a strong recommendation against the use of hydroxychloroquine in hospitalized patients with COVID-19 due to a large sample size and randomization.

Lopinavir-Ritonavir (III B-R)

Lopinavir and ritonavir are generally coadministered as an enhanced protease inhibitor for the management of HIV infection. The half-life of lopinavir is increased by adding ritonavir to the regimen through inhibition of cytochrome P450.[135] In previous in vitro studies, this combination has antiretroviral effects on SARS-CoV and MERS-CoV.[136,137] However, its efficacy on COVID-19 is not approved due to the lacking data. Recently, in a randomized clinical trial by Cao et al, 199 patients were randomized into 2 groups: 99 were assigned to the intervention group and 100 to the standard care group. The study's inclusion criteria were patients with positive RT-PCR test, pneumonia based on chest imaging, and SaO_2 of 94% or PaO_2:FiO_2 ≤300 mm Hg. Patients with hypersensitivity to lopinavir-ritonavir, severe liver disorder, or diagnosed HIV infection; pregnant and breastfeeding women; patients who were using medications that are contraindicated with lopinavir-ritonavir; and patients who were unable to swallow lopinavir-ritonavir were excluded from the study. The majority of patients were men (60.3%), and the median age of patients was 58 years. The intervention group received 400 mg of lopinavir and 100 mg of ritonavir twice a day for 2 weeks besides the standard care. In comparison, the second group received only standard care. The time to clinical improvement after randomization was considered as a primary end point of the study. The comparison of baseline demographic and clinical data of patients showed no significant differences between the 2 groups. In conclusion, the time to clinical improvement was similar between the 2 groups (HR, 1.24; 95%CI, 0.90-1.72). Also, the mortality of critically ill patients at 28 days did not significantly change with lopinavir and ritonavir combination therapy (19.2% in the lopinavir/ritonavir group and 25% in the standard-care group).[138]

Recently, the data of 1399 patients were compared to 1372 patients in the control group in a WHO Solidarity trial. During the 14 days of the study period, patients were treated with 400 mg of lopinavir plus 100 mg of ritonavir. The results of ratios for the death rate in the lopinavir/ritonavir group (148/1399) did not differ with the control group (146/1372) significantly (RR, 1.0; 95%CI, 0.79-1.25; $P = .97$).[32]

Also, the RECOVERY Collaborative Group recommended against the beneficial effects of lopinavir (400 mg) combined with ritonavir (100 mg) for 10 days. A total of 1616 patients were assigned to receive lopinavir/ritonavir for 10 days along with the standard treatment protocol, and 3424 patients received only the standard care. The mean ± SD of age of the patients was 66.2 ± 15.9 years. The mortality during the 28 days was 23% in the lopinavir/ritonavir group and 22% in the control group (rate ratio, 1.03; 95%CI, 0.91-1.17; $P = .60$). The time to discharge alive from hospital with median of 11 days and duration of hospitalization were also similar between the 2 groups.[139] These results bring a strong recommendation against the use of lopinavir/ritonavir in hospitalized patients with COVID-19.

Concomitant Medications

Antithrombotic Agents

Infection with SARS-CoV-2 is complicated with inflammation and coagulopathy, which can lead to the deterioration of the clinical condition and high rates of mortality. In comparison with healthy individuals, the levels of fibrinogen, d-dimer, and fibrin/fibrinogen degradation products were considerably higher in patients with COVID-19.[140,141]

In a prospective cohort study of 150 ICU patients, it has been shown that the incidence of pulmonary embolism was substantially higher in patients with COVID-19–related ARDS than in patients without COVID-19 ARDS.[142] In another study on 184 ICU patients with confirmed SARS-CoV-2 infection, the

incidence of thrombotic complications was reported to be 31%, which is substantially high.[143] Thus, it can be reasonable to use antithrombotic agents as adjunctive therapy for COVID-19. Of note, the prophylaxis and treatment of venous thromboembolism was better achieved with low-molecular-weight heparin (LMWH) or unfractionated heparin than direct oral anticoagulants. They have less drug-drug interaction with the COVID-19 investigational drugs due to their non–cytochrome P450-mediated metabolism. Furthermore, heparin (both LMWH and unfractionated) exerts anti-inflammatory effects, which makes it a medication with potential benefits during SARS-CoV-2 infection.[144,145]

In a study by Tang et al, 499 patients with confirmed severe COVID-19 were evaluated retrospectively. Among these, 94 patients were treated with LMWH (40-60 mg of enoxaparin daily), and 5 patients were treated with unfractionated heparin (10 000-15 000 units daily) for at least 7 days. All patients received standard supportive care after admission. Severe COVID-19 was defined as a respiratory rate of $\geq$30 breaths per minute, SaO_2 $\leq$93%, or PaO_2:FiO_2 $\leq$300 mm Hg. Most of the enrolled patients were men, and the mean $\pm$ SD of the age of patients was 65.1 $\pm$ 12.0 years. The comparison of 28-day mortality showed no significant difference between heparin users and nonusers, at 30.3% and 29.7%, respectively ($P = .910$). However, a significant reduction in 28-day mortality was observed among heparin users compared to nonusers in patients with a sepsis-induced coagulopathy score $\geq$4 (40.0% compared with 64.2%; $P = .029$) or d-dimer >6-fold of the ULN (32.8% compared with 52.4%; $P = .017$). The limitations of this study, including potential bias in selecting patients, ignoring the effects of other therapies, and changing the management guidelines during the study period, limit the interpretation. Also, the selection between LMWH and unfractionated heparin and the doses were not explained in the study; thus, the choice should be judged by a clinician.[146]

Lately, a retrospective cohort study evaluated the role of LMWH in cytokine storm in patients with severe COVID-19. Among enrolled patients (n = 42), half of them received LMWH. The results showed a significant reduction in IL-6 levels among heparin users compared with nonusers (15.76 $\pm$ 25.71 and 78.24 $\pm$ 142.41, respectively; $P = .00039$), which can indicate the anti-inflammatory effect of LMWH.[147]

Other multicenter retrospective cohort study showed a reduced mortality in patients with COVID-19 who received heparin, even when the model was adjusted for age and sex (OR, 0.55; 95%CI, 0.37-0.82; $P = .003$), SaO_2 <90%, and temperature >37°C (OR, 0.54; 95%CI, 0.36-0.82; $P = .003$), and consumption of concomitant therapies (OR, 0.42; 95%CI, 0.26-0.66; $P < .001$).[148]

A retrospective single-center study by Paranjpe et al[149] evaluated the role of anticoagulation on the survival of hospitalized patients with COVID-19. Of 2773 patients with COVID-19, 786 (28%) were treated with systemic therapeutic-dose anticoagulants during their hospitalization for a median duration of 3 days. Generally, the comparison of in-hospital mortality between anticoagulant users and nonusers showed no significant difference, at 22.5% and 22.8%, respectively. The need for invasive mechanical ventilation was higher among anticoagulant users compared to nonusers (29.8% vs 8.1%; $P < .001$). Also, in patients who were mechanically ventilated, in-hospital mortality decreased significantly by using anticoagulants 29% in the anticoagulant group vs 63% in no anticoagulant group; $P < .01$). Similarly, this study has some limitations. First, confounding variables were not taken into account. Second, particular anticoagulant medication and their indication were not indicated for the evaluation. Third, it is no indicated whether nonusers of anticoagulants managed with a prophylactic dose of anticoagulants.

Recently, the use of aspirin in patients with COVID-19 has been evaluated in an observational retrospective cohort study. Of the 412 included patients in this study, 98 patients (23.7%) used aspirin 7 days before enrollment or within 24 hours of admission. The comparison of 2 groups showed that the use of aspirin reduced the mechanical ventilation rate (35.7% vs 48.4%; $P = .03$), admission to the ICU (38.8% vs 51.0%; $P = .04$) significantly. However, no significant difference was observed regarding in-hospital mortality with 26.5% for aspirin use and 23.2% without aspirin use ($P = .51$). Also, the risk of mechanical ventilation (adjusted HR, 0.56; 95%CI, 0.37-0.85; $P = .007$), admission to the ICU (adjusted HR, 0.57; 95%CI, 0.38-0.85; $P = .005$), and in-hospital mortality (adjusted HR, 0.53; 95%CI, 0.31-0.90; $P = .02$) was reduced significantly by aspirin use after adjustment for confounding factors. Similar results were achieved between the 2 groups regarding the bleeding or thrombosis.[150] It should be considered that these findings are extracted from the observational study with an insufficient sample size. Also, patients with aspirin use might be supported by various medical care that can increase the bias risk. Furthermore, other unrecorded effective medications on coagulation might be used that can affect findings.

Thus, these findings cannot elucidate the beneficial effects of aspirin until the conduction of randomized clinical trials.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

As previously discussed in the virology section, ACE2 is the cell surface receptor for SARS-CoV-2 that has a crucial role in the pathogenesis of COVID-19. It

has been assumed that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) could inhibit or increase the replication of SARS-CoV-2 by altering ACE2.[151] In this regard, a retrospective cohort study analyzed 4480 patients with COVID-19. Of them, 895 patients were ACEI/ARB users, and 3585 were nonusers. The comparison of mortality revealed that there was no significant difference between the 2 groups (adjusted HR, 0.83; 95%CI, 0.67-1.03). Also, in a case-control study, a comparison of ACEIs/ARBs with other antihypertensive agents was conducted among 494 170 hypertensive patients. The results showed that prior use of ACEIs/ARBs did not increase the incidence of COVID-19 (adjusted HR, 1.05; 95%CI, 0.80-1.36). Of note, this study was an observational study with potential bias in selecting patients, and not all patients were confirmed COVID-19 cases.[152] In a retrospective single-center study by Lam et al,[153] 614 patients with prior hypertension history and COVID-19 were evaluated. Among them, 279 patients did not use ACEIs/ARBs. Of 335 ACEI/ARB users, 171 patients discontinued ACEIs/ARBs in the hospital, and the rest continued their medications. The comparison between ACEI/ARB users and nonusers showed similarity in both mortality and admission to the ICU. Among ACEI/ARB users patients who continued their medication showed decreased rate of mortality rate (6% compared to 28%; OR, 0.215; 95%CI, 0.101-0.455; $P = .001$) and admission to ICU (12% compared to 26%; OR, 0.347; 95%CI, 0.187-0.643; $P = .001$). However, the retrospective design, small sample size, and unidentified time of discontinuation of medications should be considered in the interpretation of results.

Vaccines

BNTv162b2 (Emergency Use Authorization From the FDA)

The Pfizer-BioNTech pharmaceutical company's vaccine, named BNT162b2a, is an mRNA-based vaccine that triggers the cells to make the SARS-CoV-2 full-length S glycoprotein. Consequently, similar to real SARS-CoV-2 infection, the host's immune system makes neutralizing antibodies. Thus, in cases of future infections, the immune system of vaccinated persons learns to combat SARS-CoV-2. According to the results from investigations on healthy individuals, 30 μg of BNT162b2 produced powerful antibodies and antigen-specific T cells against SARS-CoV-2. Furthermore, based on an observer-blinded, placebo-controlled trial on 43 548 individuals aged >16 years from 152 countries, administration of 2 doses of BNT162b2 (30 μg per dose, given 21 days apart) is associated with 95% efficacy. In this trial, 37 706 participants received the first dose of vaccine (n = 18 860) or placebo (n = 18 846). Afterward, 18 556 and 18 530 received the second doses of vaccine and placebo 21 days later, respectively. Among 36 523 participants without current or previous SARS-CoV-2 infection, 8 vaccinated participants and 162 placebo receivers experienced COVID-19 at least 7 days after the second dose. This difference means 95.0% vaccine effectiveness after the 2 doses, while this rate was 52% after the first dose. The efficacy of the vaccine was not changed after adjusting the results for confounding factors.

The vast majority of individuals complained of mild to moderate pain at the injection site during the first week of an injection, which was lasted for 1 to 2 days. The patients aged >55 years experienced a lower rate of pain compared to the younger participants (71% vs 83% at the first dose; 66% vs 78% at the second dose). Less than 1% of patients experienced severe pain. Regarding the systemic reactions, most of the participants experienced fatigue and headache. These reactions were more frequent in the participants aged <55 years compared with the older patients (fatigue after the second dose: 59% versus 51%; headache after the second dose: 52% vs 39%). The rate of most serious systemic reactions was <2% with the first or second dose, excepting fatigue (3.8%) and headache (2%) after the second dose.[154]

The nature of mRNA technology has the benefit of rapid manufacturing against emerging pathogens. This trial strongly approved the safety and efficacy of the vaccine for individuals aged >16 years. Future studies should evaluate whether the vaccine is effective and safe in immunocompromised patients, pregnant women, and individuals aged <16 years. Furthermore, the long-term efficacy and safety of the vaccine are unknown. Also, the instability of the mRNA-based vaccines is the other concern. Consequently, the need for freezing temperatures is a challenging issue in the shipping and storage of the vaccine, especially for the poor-income countries.

mRNA-1273 (Emergency Use Authorization From the FDA)

The Vaccine Research Center at the National Institute of Allergy and Infectious Diseases and Moderna developed another mRNA-based lipid-nanoparticle vaccine called mRNA-1273. This vaccine encodes the virus S glycoprotein stabilized in its prefusion conformation and triggers the immune system to make antibodies. Following the promising effects demonstrated by earlier studies, a multicenter phase 3 trial in the United States also showed that the administration of 2 injections of the vaccine at a dose of 100 μg 28 days apart is associated with 94.1% efficacy in the prevention of the symptomatic COVID-19 in individuals aged ≥18 years.

In this trial, a total of 30 420 participants received either 2 doses of mRNA-1273 (n = 15 210) or placebo (n = 15 210). The mean age of the members was 51.4 years, and 52.7% were men.

In the follow-up period, 11 and 185 individuals in the vaccine and placebo groups were infected with the virus, respectively, which indicated 94.1% of prevention (95%CI, 89.3%-96.8%; $P < .001$).

Regarding the local adverse events, low-grade injection-site pain was the most frequent complaint of the participants, which was resolved in 2.6 to 3.2 days. Headache and fatigue were the most common systemic adverse event among the vaccinated participants. These systemic reactions were observed more frequently in the vaccine compared with the placebo group, after either the first dose (54.9% vs 42.2%) or the second dose (79.4% vs 36.5%). The rate of both local and systemic reactions was higher in patients with ages ranging from 18 to 65 years.[155] Of note, pregnant women and children were not included in this trial. Another limitation of this trial was that the prevention rate was assessed only against symptomatic SARS-CoV-2 infection, while information for the evaluation of asymptomatic cases was not sufficient. One of the most important strength points of this vaccine to the BNTv162b2 is the stability at temperatures of 2 to 8°C (35.6-46.4°F). Also, it could be stabilized in a syringe for >8 hours at room temperature before injection.

AZD1222

According to the promising effects of ChAdOx1 MERS, a chimpanzee adenovirus-vectored vaccine that encodes the S protein of MERS-CoV, Oxford University and AstraZeneca developed and manufactured the ChAdOx1 nCoV-19 vaccine (AZD1222) that consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the gene of S glycoprotein. According to the interim analysis of 4 randomized controlled trials in the United Kingdom, Brazil, and South Africa, the vaccine has an acceptable safety and efficacy against symptomatic COVID-19. In the primary efficacy analysis, individuals with symptomatic COVID-19 in seronegative with a nucleic acid amplification test–positive swab at least 14 days after a second dose of vaccine were included. In the safety analysis, randomized participants who received at least 1 administration in all trials are included.

A total of 11 636 individuals aged ≥18 years were randomly assigned to the vaccine (n = 5807) or placebo (n = 5829) groups. Among the intervention group participants, 4440 received 2 standard doses (containing 5 × 1010 viral particles) of the vaccine, while 1367 received a low dose followed by a standard dose. The timing of priming and booster vaccine administration varied from within 6 weeks to at least 12 weeks.

In individuals who received 2 standard doses, the efficacy of the vaccine was 62.1% (0.6% vs 1.6%; 95%CI, 41.0-75.7), in individuals who received low dose as priming vaccine administration, efficacy was 90.0% (0.2% vs 2.2%; 95%CI, 67.4-97.0), and overall vaccine efficacy was 70.4% (0.5% vs 1.7%; 95.8%CI, 54.8-80.6). Finally, 84 and 91 severe adverse events per 74 341 person-months of safety follow-up were observed in the vaccine and placebo groups, respectively. Among these events, 3 were classified as possibly related to a vaccine admonition.[156]

Other Vaccines

Other vaccine candidates such as CoronaVac (Sinovac) and Sinopharm vaccines (Beijing, China), use an inactivated version of SARS-CoV-2 to trigger the immune system. Based on the phase 2 randomized clinical trial of the Sinovac vaccine, immune response was achieved with seroconversion rates >90% in both the 3-μg and 6-μg groups. This study included healthy participants aged 18 to 59 years. In late December 2020, the Turkey trial informed that CoronaVac was 91.25% effective at preventing symptomatic disease in 1322 participants. The latest data from late-stage trials in Brazil indicated that this vaccine was 50.4% effective at preventing severe and mild COVID-19; however, these results cannot be interpreted before data are published. The WHO team in China is studying manufacturing performance for the Sinovac vaccine to determine whether to give emergency use authorization (EUA). The results of a phase 2 clinical trial of the Sinopharm vaccine in patients aged 18 to 59 years showed the incidence of adverse reactions was 19.0% within 28 days after 2 doses, and the seroconversion rates of the neutralizing antibody 97.6% at 21 days apart.[157]

Recently, the phase 1/2 trial of the Ad26.COV2.S vaccine developed by Johnson & Johnson revealed satisfactory safety and efficacy after a single vaccination with either the low or high dose on participants aged 18 to 55 years and those ≥65 years. After the first and second dose administration, patients mostly experienced headache, fatigue, and injection-site pain. Also, fever was the most frequent systemic reaction, which had a lower rate in the low-dose group and patients aged >65 years. Antibody titers were detected in >90% of individuals 29 days after receiving the first dose. Also after 14 days, CD4+ T-cell responses were detected in 76% to 83% of the participants in volunteers aged 18 to 55 years and in 60% to 67% of volunteers aged ≥65 years. Ad26.COV2.S is a recombinant, replication-deficient adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 S protein. However, for better interpretation, the results of phase 3 studies should be released.[158]

Table 3. Vaccine Candidates for Protection Against COVID-19

Vaccine	Developer	Type	Trial Phase/Included Participants	Efficacy	Distribution	EUA
BNTv162b2[154]	Pfizer-BioNTech	mRNA	Completed/ 43 548 participants aged ≥16 y	52% after the first dose, 95% after the second dose	Freezing temperatures	Yes
mRNA-1273[155]	Moderna	mRNA	Completed/ 30 420 participants aged ≥18 y	94.1% after the second dose	2-8°C for >30 days	Yes
AZD1222[156]	AstraZeneka and Oxford university	Replication-deficient viral vector	Phase 3/ 11 636 participants aged ≥18 y	70.4% after the second dose	2-8°C	Expected
CoronaVac[157]	Sinovac	Inactivated virus	Phase 1/2 participants aged 18-59 years	Unknown	2-8°C	Not yet applied
Sinopharm[157]	Sinopharm	Inactivated virus	Phase 1/2 participants aged 18-59 years	Unknown	2-8°C	Not yet applied
Ad26.COV2.S[158]	Johnson & Johnson	Replication-deficient viral vector	Phase 1/2 participants aged 18-55 or ≥65 y	Unknown	2-8°C	Not yet applied
rAd26 and rAd5[159]	Sputnik V	Recombinant viral vectors	Phase 1/2 participants aged 18-60 y	Unknown	2-8°C for lyophilized form	Not yet applied
NVX-CoV2373[160]	Novavax	Protein subunit	Phase 1/2 participants aged 18-59 y	Unknown	2-8°C	Not yet applied

EUA, emergency use authorization; mRNA, messenger ribonucleic acid.

Another phase 1/2 trial from Russia analyzed the safety and efficacy of vaccine on participants aged 18 to 60 years. This vaccine was designed with 2 various adenovirus vectors named recombinant Ad26 (rAd26) and recombinant Ad5 (rAd5). These vectors transport the full-length S glycoprotein gene of the SARS-CoV-2. Measures of anti-SARS-CoV-2 antibodies, T-cell responses, INF-γ concentration, and safety showed acceptable results. Therefore, the ongoing phase 3 trial will show the exact efficacy and safety rates.[159]

Another vaccine candidate named NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine that consists of trimeric full-length SARS-CoV-2 S glycoproteins and Matrix-M1 adjuvant, which was developed by Novavax company. The results of phase 1/2 of this vaccine on volunteers aged 18 to 59 years showed that 2 doses of vaccine at 21 days apart had good safety and efficacy. However, we should wait for phase 3 results for better interpretation. Recently, a phase 3 trial enrolled individuals aged 18 to 64 years and those aged ≥65, with an aim of recruiting >25% of all volunteers who are ≥65 years.[160,161] All discussed vaccines are summarized in Table 3.

Discussion

In this review, we categorized the potential medications against COVID-19 based on the evidence of the studies. Generally, these medications combat the viral or immunologic phases of the disease, or have immune-based mechanisms. Herein, we discussed the main drugs with high evidence compared with other recommendations. Also, we summarized the vaccine candidates for prevention of COVID-19.

Medications With Antiviral Properties

In this category, remdesivir was the medication with the highest evidence. According to the 1 randomized clinical trial with 1062 patients and 2 nonrandomized cohorts, remdesivir was beneficial against severe COVID-19. According to the promising effects of remdesivir in clinical trials, on October 22, 2020, the FDA[34] approved the first agent in hospitalized patients aged ≥12 and weighing ≥40 kg. Notably, the Wang et al trial[26] with no overall significant promising results was not considered in the remdesivir FDA approval process. Furthermore, the WHO Solidarity trial recommended against the use of remdesivir with the same doses and duration. It should be taken into account that patients in this trial were not categorized based on the severity of the disease. Second, this trial was carried out in 500 hospitals in over 30 countries with variable health care quality and treatment guidelines, which could affect the results. Third, the lack of a placebo increased the risk of bias.[32] Considering the above, we put remdesivir as a medication with strongest recommendation and highest evidence. Similarly, the National Institutes of Health (NIH)[162] recommended remdesivir in patients on supplemental oxygen, whereas in patients on mechanical ventilation, the beneficial effects of remdesivir are still unknown.

In parallel with NIH and WHO guidelines, we strongly recommended against the use of lopinavir plus ritonavir in patients with COVID-19. This rationale can be due to results of randomized clinical trials, especially the RECOVERY collaborative group's trial. Moreover, the evaluation of the pharmacokinetics of lopinavir/ritonavir in patients with COVID-19 showed that the usual doses of lopinavir plus ritonavir cannot affect the SARS-CoV-2 replication due to low concentrations.[163] Similarly, unlike the in vitro studies, the clinical trials did not support the beneficial effects of hydroxychloroquine in patients with COVID-19. In addition, several observational studies assessed the effectiveness of chloroquine or hydroxychloroquine. However, these studies might have high risk of bias due to confounding factors and unbalanced study groups. In addition, the adverse effects and drug interactions of chloroquine and hydroxychloroquine raise the concerns about safety issues. Particularly, it has been reported that hydroxychloroquine might reduce the antiviral effect of remdesivir. Thus, regarding the safety and efficacy concerns, we put chloroquine and hydroxychloroquine in class III of recommendation. Both the WHO and NIH panels were also strongly opposed to the use of chloroquine and hydroxychloroquine.[32,162] Some clinical trials supported the use of ivermectin in patients with COVID-19; however, these studies have major limitations. We categorized ivermectin in as IIb B-R medication. Based on the NIH statement, currently there are not sufficient data to recommend either for or against the administration of ivermectin in patients with COVID-19.

Medications With Immunomodulatory Properties and Immune-Based Agents

In the category of immunomodulatory agents, dexamethasone and baricitinib were medications with the highest class of recommendation and level of evidence considering the results of RECOVERY and Adaptive COVID-19 Treatment Trial-2 trials.[36,42,162] According to the NIH[162] recommendation, dexamethasone could improve survival in hospitalized patients with COVID-19 who need supplemental oxygen, especially among individuals who require mechanical ventilation. On November 19, 2020, the combination of baricitinib with remdesivir got an EUA from the FDA for COVID-19 patients aged ≥2 years who were supported with oxygen, extracorporeal membrane oxygenation, or invasive mechanical ventilation.[164] According to the NIH recommendations, the combination of baricitinib plus remdesivir is a rational treatment option in conditions in which corticosteroids cannot be administered and in nonintubated patients with oxygen supplementation.

Casirivimab plus imdevimab and bamlanivimab were also received EUA for outpatients with mild to moderate COVID-19 aged ≥12 years, weight of ≥40 kg, and high risk for progressing to severe COVID-19 or hospitalization.[165,166] However, due to the inadequate studies, the NIH panel[162] did not mention whether these monoclonal antibodies useful. In our review, both casirivimab plus imdevimab and bamlanivimab were in the IIa B-R categorization based on the previously mentioned studies.

Although most observational studies supported the beneficial effects of tocilizumab and sarilumab in patients with severe COVID-19, we could not certainly conclude about their efficacy and safety due to the mixed results. Consequently, we put tocilizumab as IIb B-R medication. , we categorized the IL-6 inhibitor sarilumab as IIb C-LD due to lack of clinical trials. Of note, the NIH panel[162] recommends against the administration of IL-6 inhibitors including tocilizumab, sarilumab, and siltuximab.

Vaccines

The FDA issued an EUA for 2 vaccines including BNTv162b2 (Pfizer-BioNTech) in participants aged ≥16 years and mRNA-1273 (Moderna) in participants aged ≥18 years to prevent COVID-19.[167,168] Both of these vaccines are based on mRNA technology and are given in 2 doses. However, the temperature required for the distribution of the Pfizer-BioNTech vaccine is freezing temperatures, while the Moderna vaccine can be stay stable for >30 days in 2 to 8°C. The AstraZeneka, Sinovac, and Sinopharm vaccines are other promising vaccine candidates, but the results of the phase 3 trial should be completed before an exact interpretation is made. Also, the recruitment of phase 3 trials are ongoing for several vaccines including the Johnson & Johnson, Sputnik V, and Novavax vaccines.

Limitations

This review may have some limitations. First, because of mounting data in the field of COVID-19, we could not include all evidence; however, we focused on the crucial and clinically relevant studies. Second, because of newly published evidence, the potential role of some medications in the treatment of COVID-19 may be changed. The EUA of current medications or vaccines may be changed to an FDA approval status or may be revoked. What is currently clear about COVID-19 is that still more data are needed to confirm current investigational therapies in the management of COVID-19.

Conclusion

Reviewing the available data showed that remdesivir has a high class of recommendation and level of evidence against severe COVID-19. Among patients receiving either invasive mechanical ventilation or oxygen alone,

dexamethasone can be useful. Based on the mentioned studies, hydroxychloroquine and lopinavir-ritonavir have no benefit and are even harmful, and their use is not recommended. In patients on high-flow oxygen or noninvasive ventilation baricitinib can be beneficial in combination with remdesivir. Also, outpatients with mild to moderate COVID-19 can benefit from the casirivimab plus imdevimab and bamlanivimab in circumstances in which the patient's condition progresses to severe. The usefulness of tocilizumab, IFN-β-1a, colchicine, ruxolitinib, convalescent plasma, ivermectin, and anti-HCV medications including sofosbuvir/daclatasvir and ribavirin is unclear according to the clinical trials and needs more studies. Because of the limited clinical trials regarding the use of anakinra, favipiravir, IFN-α-2b, and methylprednisolone, their effectiveness on COVID-19 should be evaluated by further studies. Several vaccines with different mechanisms have been investigated and used for COVID-19 prevention. Among them, currently 2 vaccines including Pfizer-BioNTech and Moderna have received the EUA from the FDA.

Conflicts of Interest

The authors declare no conflicts of interest.

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