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Review Article
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Review of COVID-19 Therapeutics by Mechanism: From Discovery to Approval

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ABSTRACT

The global research and pharmaceutical community rapidly mobilized to develop treatments for coronavirus disease 2019 (COVID-19). Existing treatments have been repurposed and new drugs have emerged. Here we summarize mechanisms and clinical trials of COVID-19 therapeutics approved or in development. Two reviewers, working independently, reviewed published data for approved COVID-19 vaccines and drugs, as well as developmental pipelines, using databases from the following organizations: United States Food and Drug Administration (US-FDA), European Medicines Agency (EMA), Japanese Pharmaceutical and Medical Devices Agency (PMDA), and ClinicalTrials.gov. In all, 387 drugs were found for initial review. After removing unrelated trials and drugs, 66 drugs were selected, including 17 approved drugs and 49 drugs under development. These drugs were classified into six categories: 1) drugs targeting the viral life cycle 2) Anti-severe acute respiratory syndrome coronavirus 2 Monoclonal Antibodies, 3) immunomodulators, 4) anti-coagulants, 5) COVID-19-induced neuropathy drugs, and 6) other therapeutics. Among the 49 drugs under development are the following: 6 drugs targeting the viral life cycle, 12 immunosuppression drugs, 2 immunostimulants, 2 HIF-PHD targeting drugs, 3 GM-CSF targeting drugs, 5 anti-coagulants, 2 COVID-19-induced neuropathy drugs, and 17 others. This review provides insight into mechanisms of action, properties, and indications for COVID-19 medications.

Keywords: COVID-19; SARS-CoV-2; Clinical Trials; Review

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China in December 2019 and rapidly spread around the world.[1] As of December 24, 2023, a total of 773,119,173 people were confirmed to have been infected with COVID-19 worldwide. Of these, 6,990,067 patients died, with a mortality rate of 1%.[2]

Because the COVID-19 pandemic was an unanticipated and unprecedented worldwide crisis, there were no established treatments or vaccine. The National Institutes of Health (NIH)

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Disclosure

The authors have no conflicts of interest to disclose.

Data Availability Statement

Raw data are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Cho SK. Data curation: Choi HS, Choi AY. Supervision: Cho SK, Kopp JB, Winkler CA. Writing - original draft: Cho SK, Choi HS, Choi AY. Writing - review & editing: Cho SK, Kopp JB, Winkler CA.

announced the accelerating COVID-19 therapeutic interventions and vaccines (ACTIV) public-private partnership to develop a coordinated research strategy for prioritizing and speeding the development of the most promising treatments and vaccines on April 17, 2020.[3] Developing a strategy for COVID-19 treatment took a multi-disciplinary approach that emphasized preventing virus replication and relieving symptoms and complications. Following this initiative, most major research organizations around the world have launched studies and clinical trials for repurposing known drugs and for discovering new ones.

Currently, there are several approved drugs for COVID-19. As of May 2023, World Health Organization (WHO) declares end to COVID-19 as a global health emergency thanks to improved clinical management and wide-spread acquired immunity by natural infection or vaccines or both; however, certain populations, which include the very young, the elderly and those who are immunocompromised, are still experiencing severe covid and death. There are many on-going clinical trials to develop drugs effective against new variants, to prepare for the next new strain of SARS-CoV2, to shorten the dosing period, or to reduce drug-drug interactions and side effects.

Herein, we summarize mechanisms and clinical trials of COVID-19 therapeutics that have been approved or are under development to illustrate the road we have taken and what the world is preparing for in the next phase.

METHODS

Two independent reviewers reviewed data on approved COVID-19 drugs and developmental pipelines using the following databases: US-FDA, European Medicines Agency (EMA), Japanese Pharmaceutical and Medical Devices Agency (PMDA), and ClinicalTrials.gov. Mechanisms of action and clinical trials of treatments were searched via PubMed, medRxiv, public institution websites, pharmaceutical companies' sites, and ClinicalTrials.gov. Ambiguous points in data collection and summarization were resolved through discussion among reviewers. We investigated updated information on treatments through March 2023. **Fig. 1** illustrates the selection process for the reviews. Most trials used a primary endpoint assessed by an 8-point National Institute of Allergy and Infectious Disease (NIAID) ordinal scale of COVID-19 severity[4] or a 0 to 10-point WHO clinical progression scale.[5]

We identified COVID-19 treatments in databases using keywords such as 'COVID-19,' 'SARS-CoV-2,' and 'Coronavirus.' A total of 387 drugs were identified, of which 248 were less relevant to COVID-19 treatment. After removing these, the remaining 139 drugs were classified based on whether they were approved or are under development. **Table 1** summarizes European Use Authorization (EUA), US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved for drugs approved within specific countries.

The key elements of treatment for COVID consist of antiviral therapy, immunomodulation, prevention of blood-coagulation, and hypoxic damage control. We classified drugs into six categories, which included 1) Anti-SARS-CoV-2 monoclonal antibodies (**Table 2**), 2) viral life cycle inhibitors (**Table 3**), 3) immunomodulators (**Tables 4-6**), 4), anti-coagulants (**Table 7**), 5) drugs for treating COVID-19 induced neuropathy (**Table 8**), and 6) drugs targeting other mechanisms (**Tables 9** and **10**). During the review process, we also identified and classified drugs in a list of withdrawn COVID-19 medications: 1) the pipeline was discontinued for

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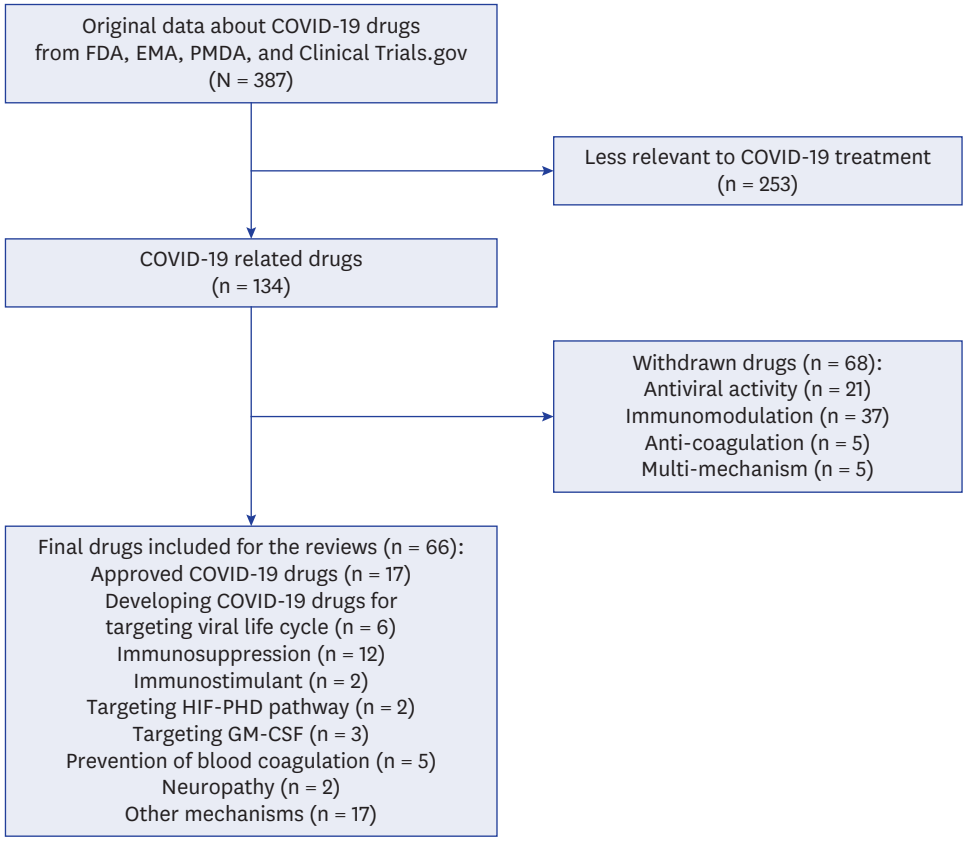

Fig. 1. Flow chart showing the review process for selection of publications to be reviewed.
COVID-19 = coronavirus disease 2019, FDA = US Food and Drug Administration, EMA = European Medicines Agency, PMDA = Japanese Pharmaceutical and Medical Devices Agency, HIF-PHD = hypoxia-inducible factor prolyl hydroxylase, GM-CSF = granulocyte-macrophage colony-stimulating factor.

further development, 2) clinical trials failed to meet the primary end-point, 3) clinical trials were not active for more than a year, 4) drug was no longer listed in the company's pipeline, 5) the most recent clinical trial was terminated, and 6) exploratory clinical trials without further development (**Supplementary Table 1**).

RESULTS

The NIH ACTIV public-private partnership classifies treatments based on severity of illness.[6] We classified treatments based on the mechanism of action. This review included all drugs from ACTIV trials. We further investigated developing pipelines, worldwide. Each drug was reviewed for status of approval, indication for treatment, dose information, route of administration, and reported side effects.

Part 1. Approved COVID-19 Therapeutics
Part 2. Anti-SARS-CoV-2 Monoclonal Antibodies
Part 3. Developing COVID 19 drugs targeting the viral life cycle
Part 4. Developing COVID 19 immunomodulators
Part 5. Developing anti-coagulants in COVID-19
Part 6. Developing drugs for COVID-19-induced neuropathy
Part 7. Other mechanism drug for COVID-19 therapeutics under development

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Table 1. Approved medications for COVID-19 (N = 18)

Name of drug	Generic name	Company	Country of development	Dosage information (adults)	MOA	Approval	References
Paxlovid	Nirmatrelvir/ ritonavir	BioNTech & Pfizer	USA	Nirmatrelvir 300 mg and ritonavir 100 mg taken together orally every 12 hours for 5 days.	Inhibitor of the SARS-CoV-2 main protease (Mpro).	EUA/EMA	7-9
Lagevrio	Molnupiravir	Ridgeback Biotherapeutics & Merck	USA	Molnupiravir 800 mg taken orally every 12 hours for 5 days.	Cytidine nucleoside analogue to inhibition of viral replication.	EUA	13-15
Azvudine	2′-deoxy-2′-β-fluoro-4′-azidocytidine	Genuine Biotech	China	Azvudine 5 mg per day orally.	Nucleoside analogue	NMPA	16,17
Veklury	Remdesivir	Gilead Sciences	USA	Remdesivir 200 mg via intravenous infusion on day 1. Remdesivir 100 mg via intravenous infusion on day 2 and onwards.	Analog of adenosine triphosphate (ATP) and competitive inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RDRP).	FDA/EMA	18,19
Mindvy (VV116)	-	Shanghai Junshi Biosciences	China	Under development.	Oral version of remdesivir that inhibits RdRP	NMPA	25,26,186
2-DG	2-deoxy-D-glucose	Dr. Reddy's Laboratories	India	Under development.	Glucose analogue.	DCGI	27,28,187
Kineret	Anakinra	Swedish Orphan Biovitrum	Sweden	Anakinra 100 mg via subcutaneous injection once daily for 10 days.	Interleukin-1 type I receptor (IL-1RI) inhibitor for immunomodulation.	EUA/EMA	29,31,32
Artlegia	Olokizumab	R-Pharm	Russian Federation	Single subcutaneous injection of olokizumab 64 mg once every 4 weeks.	IL-6 inhibitor	Minzdrav	24,33
Actemra	Tocilizumab	Roche	Switzerland	Single intravenous infusion of tocilizumab 8 mg/kg in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.	Interleukin-6 receptor that blocks inflammation signals.	EUA/EMA	34,36,37
Ilsira	Levilimab	Biocad	Russian Federation	Under development.	IL-6 receptor monoclonal antibody that inhibits inhibit cytokine storm	Minzdrav	38-40
Alzumab	Itolizumab	Biocon	India	Itolizumab 1.6 mg/kg for the first dose of the treatment via intravenous infusion. 0.8 mg/kg for additional dose after 1 week.	CD6 monoclonal antibody that inhibits proinflammation.	DCGI	41,42,188
Olumiant	Baricitinib	Eli lilly	USA	Baricitinib 4 mg once daily for 14 days.	Janus kinase (JAK) inhibitor that blocks inflammation signals.	FDA	43,45,46

MOA = mechanism of action, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, EUA = Emergency Use Authorization, EMA = European Medicine Administration, NMPA = National Medical Products Administration, FDA = US Food and Drug Administration, DCGI = Drugs Controller General of India, Minzdrav = Ministry of Health of the Russian Federation.

PART 1. APPROVED COVID-19 THERAPEUTICS

Approved anti-viral agents

Paxlovid (nirmatrelvir/ritonavir)

Paxlovid consists of two molecules. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. A peptidomimetic is a molecule whose structure mimics that of a natural peptide. Inhibition of SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors, thus preventing viral replication. In contrast, ritonavir is a protease inhibitor that boosts the activity of nirmatrelvir by inhibiting cytochrome P450 3A (CYP3A), the enzyme required for metabolizing nirmatrelvir. When administered together with nirmatrelvir, ritonavir increases plasma concentrations of nirmatrelvir. Paxlovid received an EUA from the FDA on December 22, 2021 for treating adults and pediatric patients with mild-to-moderate COVID-19 who are at high risk for progressing to severe COVID-19.[7] Paxlovid received final approval from the FDA for treating mild to moderate COVID-19 on March 17, 2023. EU approval was received on January 28, 2022. It is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19, nor is it authorized for use as pre-exposure or as post-exposure prophylaxis.

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Table 2. Anti-SARS-CoV-2 monoclonal antibodies

Name of drug	Generic name	Company	Country of development	Dosage information (adults)	MOA	Approval	References
Evusheld	Tixagevimab/ cilgavimab	AstraZeneca	UK	Tixagevimab 150 mg and cilgavimab 150 mg via separate sequential intramuscular injections for pre-exposure prophylaxis. Tixagevimab 300 mg and cilgavimab 300 mg via separate sequential intramuscular injections for treatment.	Monoclonal antibodies bind to non-overlapping regions of the spike protein RBD of SARS-CoV-2 and block virus cellular entry.	EMA	49-52
Regkirona	Regdanvimab	Celltrion	Korea	Regdanvimab 40 mg/kg via intravenous infusion.	Monoclonal antibody binds to the RBD of the spike(s) protein and blocks virus cellular entry.	EMA	53
Ronapreve	Casirivimab/ imdevimab	Roche	Switzerland	Casirivimab 600 mg and imdevimab 600 mg via intravenous infusion.	Monoclonal antibodies bind to non-overlapping regions of the spike protein RBD of SARS-CoV-2 and block virus cellular entry.	EMA	55
Xevudy	Sotrovimab	Vir Biotechnology	USA	Sotrovimab 500 mg via intravenous infusion.	Monoclonal Antibody binds to the spike proteins and blocks virus cellular entry.	EMA	56-58
BRII-196/ BRII-198	Amubarvimab/ romlusevimab	Brii Biosciences	China	Separate sequential intravenous infusions of amubarvimab 1,000 mg and romlusevimab 1,000 mg immediately.	Monoclonal antibodies bind to non-overlapping regions of the spike protein and block virus cellular entry.	NMPA	59

MOA = mechanism of action, RBD = receptor binding domain, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, EMA = European Medicine Administration, NMPA = National Medical Products Administration.

Table 3. COVID-19 drugs under development targeting viral life cycle (N = 6)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Meplazumab	Jiangsu Pacific Meinuoke	China	CD147 inhibitor	2, 3	NCT04586153 (Recruiting)	June 6, 2022	http://www.pacificmeinuoke.com/	60,61
Plitidepsin	PharmaMar	Spain	eEF1A inhibitor	2	NCT05705167 (Recruiting)	June 18, 2023	https://pharmamar.com/en/	62
Ebselen (SPI-1005)	Sound Pharmaceuticals	USA	Main protease (Mpro) inhibitor	2	NCT04483973 (Enrolling by invitation)	November 8, 2022	https://soundpharma.com/	66,67
Obeldesivir (GS-5245)	Gilead Sciences	USA	Nucleoside analogue	3	NCT05603143 (Recruiting)	June 23, 2023	https://www.gilead.com/	68
Sabizabulin	Veru	USA	Microtubule disruptor	3	NCT04842747 (Completed)	April 18, 2023	https://verupharma.com/	69
Ampligen (rintatolimod)	AIM ImmunoTech	USA	Toll-like receptor 3 agonist	2	NCT05592418 (Not yet recruiting)	June 29, 2023	https://aimimmuno.com/	71

MOA = mechanism of action, eEF1A = eukaryotic translation elongation factor 1α.

The recommended Paxlovid dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19. It should be also be administered within 5 days of symptom onset.[8] It cannot be used for over 5 days.[9] Paxlovid is not recommended for those with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2).[8] In Korean clinical studies, Paxlovid demonstrated safety and a reduction in viral load against the omicron variant.[10] Moreover, it lowered the requirement for supplemental oxygen.[11]

Lagevrio (molnupiravir)

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to a cytidine nucleoside analog, forming a pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation into SARS-CoV-2 RNA by viral RNA polymerase (nsp12) introduces copying errors during viral RNA replication. This mechanism of action is known as 'viral error catastrophe' and the drug was originally developed at Emory University[12] to treat influenza.

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Table 4. Immunosuppressive drugs under development for COVID-19 treatment (N = 12)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Jaktinib	Suzhou Zelgen Biopharmaceuticals	China	JAK inhibitor	2	NCT05686629 (Not yet recruiting)	March 24, 2023	https://www.zelgen.com/en/	73,74
Reparixin	Dompe	Italy	Inhibitor of IL-8 receptors, CXCR1, CXCR2	3	NCT05254990 (Recruiting)	June 1, 2023	https://www.dompe.com/en	78-80
Taltz (ixekizumab)	Eli Lilly and Company	USA	IL-17A antagonist	3	NCT04724629 (Completed)	July 28, 2022	https://www.lilly.com/	81,82
Remicade (infliximab)	Janssen Biotech	USA	TNFα inhibitor	3	NCT04593940 (Completed)	April 21, 2023	https://www.janssen.com/	83,84
Orencia (Abatacept)	Bristol-Myers Squibb	USA	CTLA4 Ig (Competitor of CD28)	3	NCT04593940 (Completed)	April 21, 2023	https://www.bms.com/	85,86
Vascepa (icosapent ethyl)	Amarin	Ireland	Ethyl ester of eicosapentaenoic acid (EPA) that decreases hsCRP levels	3	NCT04460651 (Completed)	September 17, 2021	https://amarincorp.com/	87,88
NuSepin	Shaperon	South Korea	FGF19 analogue (Cytokine storm inhibitor)	2,3	NCT05352347 (Recruiting)	March 21, 2023	http://shaperon.com/eng/main/	89
Ruconest (conestat alfa)	Pharming Group	Netherlands	C1 esterase inhibitor	2	NCT04530136 (Completed)	June 3, 2022	https://www.pharming.com/	90,91
MN-166 (ibudilast)	Kyorin	Japan	Inhibition of macrophage migration inhibitory factor	2	NCT04429555 (Active, not recruiting)	May 30, 2023	https://www.kyorin-pharm.co.jp/en/	92-94
CAP-1002	Capricor Therapeutics	USA	Cardiosphere-derived cells for immunomodulation	2	NCT04623671 (Completed)	February 13, 2023	https://capricor.com/	95,96
GB-0139	Galecto	USA	Galectin-3 inhibitor	1, 2	NCT04473053 (Recruiting)	November 2, 2022	https://galecto.com/	97,98
Remestemcel-L	Mesoblast	Australia	Mesenchymal stromal cells	-	NCT04456439 (Available)	May 6, 2023	https://www.mesoblast.com/	99,100

MOA = mechanism of action, JAK = Janus kinase, CXCR = C-X-C motif chemokine receptor, TNF = tumor necrosis factor, CTLA4 = Cytotoxic T Lymphocyte Antigen-4, hsCRP = high-sensitivity C-reactive protein, FGF19 = fibroblast growth factor 19.

Table 5. Immunostimulants under development for COVID-19 legend (N = 2)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
IMM-101	Immodulon Therapeutics	UK	Heat killed *Mycobacterium obuense*	3	NCT04442048 (Active, not recruiting)	January 31, 2023	https://www.immodulon.com/	102,103
Sarconeos (BIO101)	Biophytis	France	Activates the Mas receptor to protect RAS	2, 3	NCT04472728 (Terminated)	May 15, 2023	https://www.biophytis.com/fr/	104-106

MOA = mechanism of action, RAS = renin–angiotensin system.

Table 6. Drugs under development targeting GM-CSF (N = 3)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Leukine (sargramostim)	Partner Therapeutics	USA	GM-CSF for immunostimulation	4	NCT04326920 (Completed)	November 16, 2022	https://www.partnertx.com/	110,111
Plonmarlimab	I-Mab Biopharma	China	GM-CSF monoclonal antibody	2,3	NCT04341116 (Completed)	May 6, 2023	https://www.i-mabbiopharma.com/	112,113
Lenzilumab	Humanigen	USA	GM-CSF monoclonal antibody	2	NCT04583969 (Completed)	June 5, 2023	https://www.humanigen.com/	114,115

MOA = mechanism of action, GM-CSF = Granulocyte-macrophage colony-stimulating factor.

Molnupiravir received an EUA from the FDA on December 23, 2021 to treat mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.[13] However, EMA did not approve the drug for treating COVID-19 in adults until February 23, 2023, with the main reason being that the clinical benefit of molnupiravir was limited for those with COVID-19 who were not receiving supplemental oxygen.[14]

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Table 7. Drugs under development for preventing blood coagulation in COVID-19 (N = 5)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Heparin	Multiple companies	-	Factors Xa and thrombin inhibitor	4	NCT04505774 (Active, not recruiting)	April 25, 2023	https://valeopharma.com/	116-120
Xarelto (rivaroxaban)	Bayer	Germany	Factor Xa inhibitor	3	NCT04324463 (Active, not recruiting)	May 26, 2023	https://www.bayer.com/en/	123,189
rNAPc2	ARCA Biopharma	USA	Factor Xa and tissue factor-factor VIIa (TF/FVIIa) inhibitor	2, 3	NCT04655586 (Completed)	February 21, 2023	https://arcabio.com/	124
Tavalisse (fostamatinib disodium hexahydrate)	Rigel	USA	Spleen tyrosine kinase (SYK) inhibitor	2, 3	NCT04924660 (Recruiting)	June 5, 2023	https://www.rigel.com/	128-130,190
Defitelio (defibrotide sodium)	Jazz Pharmaceuticals	Ireland	Plasmin agonist	2	NCT04652115 (Recruiting)	January 5, 2023	https://www.jazzpharma.com/	131,132

MOA = mechanism of action.

Table 8. Drugs under developing for treating COVID-19-induced neuropathy (N = 2)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Cerebrolysin (FPF-1070)	Ever Neuro Pharma	Austria	Brain-specific pleiotropic agent	4	NCT04830943 (Completed)	January 3, 2023	https://www.everpharma.com/	133
NA-831 (traneurocin)	Biomed Industries	USA	Main protease (Mpro) inhibitor	2,3	NCT04452565 (Recruiting)	February 16, 2022	https://www.biomedind.com/	134-136

MOA = mechanism of action.

Table 9. Drugs under development targeting the HIF-PHD pathway (N = 2)

Name of drug	Company	Country of development	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Avastin (bevacizumab)	Roche	Switzerland	VEGF inhibitor	3	NCT04305106 (Recruiting)	June 27, 2023	https://www.roche.com/	140-142
Vadadustat (AKB-6548)	Akebia Therapeutics	USA	HIF-PHD inhibitor	2	NCT04478071 (Completed)	February 17, 2023	https://akebia.com/	143,144

MOA = mechanism of action, VEGF = vascular endothelial growth factor, HIF-PHD = hypoxia-inducible factor prolyl hydroxylase.

The dose for adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. The dug is not authorized for use for longer than five consecutive days. It is not authorized for use in patients who are less than 18 years of age, nor for initiation of treatment in patients who are hospitalized due to COVID-19. Molnupiravir is also not authorized for pre-exposure or post-exposure prophylaxis.[15]

Azvudine

Azvudine is a thymus-homing nucleoside analogue drug that inhibits viral RNA-dependent RNA polymerase (RdRp).[16] It was approved by the National Medical Products Administration (NMPA) of China (the equivalent of the US Food and Drug Administration) on July 25, 2022 for COVID-19 treatment.[17] Although there are no specified dosage guidelines for COVID-19, the usual clinical dose of azvudine is 5 mg orally once daily.[16]

Veklury (remdesivir)

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form a pharmacologically-active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by SARS-CoV-2 RNA-dependent RNA polymerase. Remdesivir triphosphate also inhibits viral RNA synthesis through incorporation of the complementary natural nucleotide.

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Table 10. Other medications for COVID-19 (N = 19)

Name of drug	Company	Country of development	Class	MOA	Phase	Highest phase NCT and status	NCT last update	Website	References
Trimodulin (BT588)	Biotest AG	Germany	Antiviral activity	Polyvalent antibodies (IgG, IgA, IgM)	3	NCT05531149 (Recruiting)	May 18, 2023	https://www.biotest.com/de/de/index.cfm	145,146
Octagam	Octapharma	Switzerland	Antiviral activity	IgG antibody	2	NCT04480424 (Completed)	October 7, 2022	https://www.octapharma.com/	147,148
Opaganib	RedHill Biopharma	Israel	Antiviral activity & Anti-inflammation	Sphingosine kinases 2 (SK2), dihydroceramide desaturase (DES1), and glucosylceramide (GCS) inhibitor	2,3	NCT04467840 (Completed)	July 20, 2021	https://redhillbio.com/home/default.aspx	150
Arakoda (tafenoquine)	60 Degrees Pharmaceuticals	USA	Antiviral activity	TMPRSS2 inhibitor & viral protease inhibitor (Mpro)	2	NCT04533347 (Completed)	January 17, 2023	https://www.gsk.com/en-gb/	152
Niclosamide (ANA001)	NeuroBo Pharmaceuticals	USA	Antiviral activity & Anti-inflammation	Endosomal pH neutralization & inhibition of pro-inflammatory cytokine	4	NCT05087381 (Completed)	November 4, 2022	https://www.neurobopharma.com/	162-164
Luvox (fluvoxamine)	Abbott	USA	Antiviral activity & Anti-inflammation	Blocking reuptake of serotonin	3	NCT04885530 (Recruiting)	May 6, 2023	https://www.abbott.com/	153,154
Pyramax (artesunate/pyronaridine)	Shin Poong Pharmaceutical	South Korea	Antiviral activity & Anti-inflammation	ACE2 inhibitor & viral protease inhibitor (PLpro)	3	NCT05084911 (Completed)	June 18, 2023	https://shinpoong.co.kr/en/main/main.php	155,157,158
Apabetalone	Resverlogix	Canada	Antiviral activity & Anti-inflammation	Bromodomain and extraterminal domain (BET) protein inhibitor	2, 3	NCT04894266 (Unknown)	January 21, 2022	https://www.resverlogix.com/	159-161
KIN001 (pamapimod/pioglitazone)	Kinarus Therapeutics	Switzerland	Antiviral activity & Anti-inflammation	p38 MAPK inhibitor & PPARγ agonist	2	NCT05659459 (Recruiting)	December 21, 2022	https://www.kinarus.com/about-us/company-overview.htm	165,166
Xpovio (selinexor)	Karyopharm Therapeutics	USA	Antiviral activity & Anti-inflammation	p53 inhibitor & inhibition of pro-inflammatory cytokine & activating Nrf2, PPAR-γ	2	NCT04349098 (Completed)	January 20, 2023	https://www.karyopharm.com/	167,168
Alinia (nitazoxanide)	Romark Laboratories	USA	Antiviral activity & Stimulation of host antiviral immune responses	Upregulates the innate antiviral mechanisms	3	NCT04423861 (Recruiting)	October 31, 2022	https://www.romark.com/	169,170
VirX / enovid (nitric oxide nasal spray)	Sanotize	Canada	Antiviral activity & Systemic vasodilator	NO stimulant (treatment of ARDS)	3	NCT05109611 (Active, not recruiting)	May 6, 2023	https://sanotize.com/	171-173
Hesperco (hesperidin)	Valeo Pharma	Canada	Antiviral activity & Antioxidant properties	Antioxidant agent	2	NCT04715932 (Completed)	April 8, 2022	https://ingenewpharma.com/	174,175
Lipitor (Atorvastatin calcium)	Viatris	USA	Anti-inflammation & Anti-coagulation	HMG-CoA reductase inhibitor	3	NCT04904536 (Recruiting)	April 12, 2023	https://www.pfizer.com/	176,177
Zilucoplan	UCB	Belgium	Anti-inflammation & Anti-coagulation	Complement protein C5 inhibitor	3	NCT04590586 (Completed)	June 29, 2022	https://www.ucb.com/	178-180
Vilobelimab	InflaRx	Germany	Anti-inflammation & Anti-coagulation	Complement protein C5a inhibitor	2,3	NCT04333420 (Completed)	June 5, 2023	https://www.inflarx.de/	181-183
Lyfaquin (centhaquine)	Pharmazz	India	Improve tissue perfusion & oxygenation	Improved tissue perfusion by stimulating α2B, α2A adrenergic receptors (ARDS treatment)	2	NCT05241067 (Not yet recruiting)	June 22, 2023	https://www.pharmazz.com/index.php	184,185

MOA = mechanism of action, Ig = immunoglobulin, ACE2 = angiotensin converting enzyme-2, MAPK = mitogen activated protein kinase, PPARγ = peroxisome proliferator- activated receptor-γ, Nrf2 = nuclear factor erythroid-2-related factor 2, NO = nitric oxide, HMG-CoA = β-hydroxy = β-methylglutary.

Remdesivir received FDA approval for adult and pediatric patients with COVID-19 requiring hospitalization[18] on October 22, 2020 as the first approved treatment for COVID-19. FDA expanded its use for treating outpatients with mild-to-moderate COVID-19 on January 21, 2022. Remdesivir received EMA approval on July 3, 2020. According to the EMA, it is indicated for patients with pneumonia requiring supplemental oxygen.

The recommended dose is a 200 mg intravenous infusion on the first day and 100 mg intravenous infusion on the following day. Treatment duration is at least 5 days but not more than 10 days. Treatment duration is 3 days for patients who do not require supplemental oxygen. It must not be given as an intramuscular injection. The recommended dose and treatment duration vary for pediatric patients. Increased liver enzymes (transaminases) and a coagulation tendency are its common adverse effects, affecting more than 1 in 10 patients.[19] In the treatment guidelines for mild to moderate COVID-19 patients in South Korea, Remdesivir is widely utilized.[20] Additionally, hepatic injury and anemia have been identified as the most common side effects.[21]

It was reported that remdesivir is superior to placebo in shortening the time to recovery in adults who were hospitalized with SARS-CoV-2 infection and had no effect on all-cause mortality at up to day 28 in hospitalized adults with SARS-CoV-2 infection.[22,23]

Mindvy (VV116)

Mindvy is an oral analogue of remdesivir. Mindvy is a nucleoside triphosphate analog drug that binds to the active site of RdRp and inhibits viral replication by creating an error-ridden and therefore defective genome.[24-26] It was conditionally approved by NMPA for treating adult patients with COVID-19.[25] It is also approved in Uzbekistan. A dose of 200 mg twice daily is recommended for COVID-19 treatment.[26]

2-DG (2-deoxy-D-glucose)

2-DG (2-deoxy-D-glucose) is a glucose analogue that competes with it and inhibits metabolism within host cells. It inhibits synthesis of viral molecules and energy production.[27] 2-DG received approval from the Drugs Controller General of India (DCGI) on May 1, 2021, for adjunctive treatment of moderate-to-severe COVID-19 illness. A clinically tolerable dose is 63 mg/kg. Further studies are underway to determine the optimal dose.[28]

Approved COVID-19 immunomodulators

Kineret (anakinra)

Anakinra is an immunmodulating, interleukin (IL)-1 type I receptor inhibitor that blocks both IL-1α and IL-1β.[29] Anakinra has received FDA approved for treatment of three diseases: rheumatoid arthritis (RA), cryopyrin-associated periodic syndromes, and deficiency of IL-1 receptor antagonist.[30] Anakinra received an EUA from the FDA on November 8, 2022 to treat hospitalized COVID-19 pneumonia adult patients requiring supplemental oxygen who are at high risk for progressing to severe respiratory failure and likely to have an elevated soluble urokinase plasminogen activator receptor (suPAR).[31] EU approval was obtained on December 17, 2021.[32] The recommended dose is 100 mg subcutaneous injection once daily for 10 days. Common side effects (occurring more than 10% of patients) are pain and redness at the injection site and increased total cholesterol levels.[29]

Artlegia (olokizumab)

Olokizumab is a monoclonal antibody targeting IL-6.[24] It received approval from the

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Ministry of Health of the Russian Federation (Minzdrav) for COVID-19 pneumonia.[33] The recommended dose is a single subcutaneous injection of 64 mg, administered in the thigh or anterior abdominal wall once every four weeks. It is not recommended for patients aged below 18 years of age.[24]

Actemra (tocilizumab)

Tocilizumab is an IL-6 receptor (IL-6R) inhibitor that binds membrane-bound IL-6 receptors.[34] It has FDA approval for RA, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis, cytokine release syndrome (CRS), and COVID-19.[35]

Tocilizumab received an EUA from the FDA on June 24, 2021 for hospitalized COVID-19 patients aged 2 years and older with systemic glucocorticoids who require supplemental oxygen or mechanical ventilation. On December 21, 2022, tocilizumab received Biologics License Application (BLA) 125276 for the same patients.[36] EU approval of tocilizumab was obtained on December 7, 2021.[37]

The recommended dose of tocilizumab is a single 60-minute intravenous infusion at 8 mg/kg (maximum 800 mg). If any clinical improvements are found, one additional infusion can be administered after an interval of at least 8 hours. Patients with abnormal levels of liver enzymes, absolute neutrophil count (ANC), and platelet count are not recommended to receive tocilizumab.[34]

Ilsira (levilimab)

Levilimab is a monoclonal antibody targeting the IL-6 receptor. Levilimab was developed to prevent cytokine storm caused by COVID-19.[38,39] It received approval from the Ministry of Health of the Russian Federation (Minzdrav) on June 5, 2020 for COVID-19 treatment.[38] Subcutaneous injection of Levilimab at 324 mg is generally recommended.[40] It apparently has not been approved in the USA.

Alzumab (itolizumab)

Itolizumab is a monoclonal antibody against CD6, a costimulatory molecule that stimulates T cell proliferation. The drug was developed to prevent CRS or acute respiratory distress syndrome (ARDS) due to COVID-19. It was approved for chronic plaque psoriasis in 2013 in India. Itolizumab also received restricted emergency use approval from the Drugs Controller General of India (DCGI) in July 2020 for treating COVID-19-related CRS or ARDS.[41]

The recommended dose of itolizumab is 1.6 mg/kg for the first dose, administered as an intravenous infusion. One week later, a second dose 0.8 mg/kg is given.[42] Patients with hepatic or renal disease, those with infectious diseases, and pregnant or lactating women are not recommended to receive itolizumab.[41]

Olumiant (baricitinib)

Olumiant, also known as baricitinib, is a Janus kinase (JAK) inhibitor.[43] Baricitinib received FDA approval for RA, alopecia areata, and COVID-19.[44] It received an EUA from the FDA on November 19, 2020 for use in combination with remdesivir for COVID-19 patients requiring supplemental oxygen. On May 10, 2022, the FDA approved baricitinib for hospitalized COVID-19 adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[44] On October 27, 2022, FDA

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expanded the EUA for use of baricitinib in hospitalized adults and pediatric patients aged 2 to 18 years requiring supplemental oxygen.[45] However, the EMA did not approve baricitinib for treating hospitalized COVID-19 patients until December 7, 2022.[46]

The recommended dose of baricitinib for pediatric patients 9 years and older and for adult patients is 4 mg. For pediatric patients aged 2 to 9 years, the recommended dose of baricitinib is 2 mg orally once daily. The recommended treatment duration is 14 days or until hospital discharge.[43-45] In Korea, various immunomodulators, including baricitinib, were administered to patients requiring supplemental oxygen.[47] Dosage modifications are recommended for patients with renal or hepatic impairment.[43] Olumiant is not recommended for patients with an absolute lymphocyte count less than 200 cells/μL or an ANC less than 500 cells/μL.[44] Known adverse events are serious venous thromboses including pulmonary embolism.[43]

According to the NIH COVID-19 treatment guidelines, non-hospitalized patients at risk of progressing to severe COVID-19 symptoms may be offered Paxlovid, remdesivir, or molnupiravir. For hospitalized patients, those not requiring supplemental oxygen may receive remdesivir, while those requiring supplemental oxygen may receive dexamethasone and remdesivir, and in more severe cases, baricitinib or tocilizumab may be considered.

PART 2. ANTI-SARS-COV-2 MONOCLONAL ANTIBODIES

Monoclonal antibodies blocking SARS-CoV-2 cell attachment are no longer recommended in treating COVID-19 due to an immune evasion mechanism.[48] Approved therapeutic monoclonal antibodies have failed to neutralize either omicron subvariants such as BQ.1.1 or XBB. The FDA has updated drug labels to address the limitation of monoclonal antibodies blocking SARS-CoV-2 cell attachment. New therapeutic monoclonal antibodies are needed for future COVID pandemics. After WHO declares an end to COVID-19 as a global health emergency, it is likely there will be no new monoclonal antibodies at advanced stages of research.

Anti-SARS-CoV-2 monoclonal antibodies

Evusheld (tixagevimab/ cilgavimab)

Evusheld (previously known as AZD8895 and AZD1061) contains tixagevimab and cilgavimab. Tixagevimab and cilgavimab were designed to attach to the spike protein of SARS-CoV-2 (the virus that causes COVID-19) at two different sites. Evusheld hinders viral entry by attaching to the viral spike protein.[49]

On December 8, 2021, Evusheld receive Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals, and treatment of those with mild to moderate COVID-19 who are at high risk for developing severe disease. However, due to new SARS-CoV-2 variants, EUA of Evusheld is no loonger valid in the U.S..[50,51] Currently, Evusheld approval remains valid throughout the EU.

For pre-exposure prophylaxis of COVID-19, 150 mg of tixagevimab and 150 mg of cilgavimab, administered as two separate sequential intramuscular injections, are recommended. For treatment, 300 mg of tixagevimab and 300 mg of cilgavimab within 7 days of showing symptoms of COVID-19 administered as two separate sequential intramuscular injections

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are recommended. Tixagevimab and cilgavimab must be given as separate sequential intramuscular injections at different injection sites in two different muscles, preferably in gluteal muscles. These therapies are indicated for treating adults and adolescents aged 12 years or older not requiring supplemental oxygen who are at an increased risk of progressing to severe COVID-19. Systemic hypersensitivity (allergic) reactions and local reactions at the site of injection are the most common side effects.[52]

Regkirona (regdanvimab)

Regkirona, also known as CT-P59 is a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2, consequently blocking cellular entry and SARS-CoV-2 infection. Regkirona received approval first from the MFDS (Minister of Food and Drug Safety), of Korea on December 29, 2020. Regkirona received approval from EU on November 12, 2021. It is indicated for treating confirmed COVID-19 in adult patients who do not require supplemental oxygen but are at a high risk of progressing to severe COVID-19.

The recommended dosage of Regkirona is 40 mg/kg via a single dose by intravenous infusion. The maximum dosage is 8000 mg. Adverse allergic responses, including fever, dyspnea, tachycardia, bradycardia, and itching due to Regkirona use are uncommon, occurring in about 1 person per 100.[53] With the emergence of the delta variant, Regkirona is no longer recommended.[54]

Ronapreve (casirivimab/imdevimab)

Ronapreve consists of two recombinant human monoclonal antibodies, casirivimab (IgG1κ) and imdevimab (IgG1λ), that target non-overlapping epitopes of the spike protein RBD of SARS-CoV-2. The drug prevents RBD binding to the human ACE2 receptor and thereby blocks viral entry into cells. Ronapreve received approval throughout the EU on November 12, 2021.

Ronapreve can be used for treating and preventing COVID-19. The recommended dosage for treatment is 600 mg for casirivimab and 600 mg for imdevimab, administered as a single intravenous infusion or subcutaneous injection. They should be given within seven days of the onset of COVID-19 symptoms. The recommended dosage for pre-exposure prophylaxis is 600 mg for casirivimab and 600 mg for imdevimab as an initial dose, administered as a single intravenous infusion or subcutaneous injection. Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab can be administered as a single intravenous infusion or as subcutaneous injections every four weeks, until prophylaxis is no longer required. There are no data on repeat dosing beyond 24 weeks (6 doses). The recommended dosage for post-exposure prophylaxis is 600 mg for casirivimab and 600 mg for imdevimab, administered as a single intravenous infusion or subcutaneous injection. Casirivimab combined with imdevimab should be given as soon as possible after exposure to persons with COVID-19.[55] Ronapreve is not currently authorized for use in any U.S. after emergence of omicron variants.

Xevudy (sotrovimab)

Xevudy, also known as VIR-7831 and GSK4182136, is a human IgG1 monoclonal antibody that binds to a highly conserved epitope on the spike protein RBD of SARS-CoV-2. Xevudy received an EUA from the FDA on May 26, 2021 for treating mild-to-moderate COVID-19 in adults and in children (12 years of age and older weighing at least 40 kg) (+) and those who are at high risk for progression to severe COVID-19, including hospitalization and death.

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The EUA of Xevudy is not valid for the omicron variant.[56,57] Xevudy received approval throughout the EU on December 17, 2021.

The recommended dose is a single 500 mg intravenous infusion. Allergic reactions to Xevudy are common, affecting up to 1 in 10 people.[58] Xevudy is no longer authorized to treat COVID-19 in any U.S. caused by the Omicron BA.2 sub-variants.

BRII-196/BRII-198 (amubarvimab/romlusevimab)

BRII-196/BRII-198 contains two monoclonal antibodies, amubarvimab (BRII-196) and romlusevimab (BRII-198). Each binds non-overlapping epitopes of the spike protein of SARS-CoV-2 and prevents viral entry into cells. BRII-196/BRII-198 received approval from NMPA of China in December 2021 for treating adult patients (18 years aged and older) with mild COVID-19. The recommended dose is 1,000 mg for amubarvimab and 1,000 mg for romlusevimab, administered as separate sequential intravenous infusions.[59] BRII-196/BRII-198 is no longer recommended to use after the emergence of omicron variants.

PART 3. DEVELOPING COVID 19 DRUGS TARGETING THE VIRAL LIFE CYCLE

Fig. 2 illustrates approved drugs and drugs under development that target the COVID-19 viral life cycle.

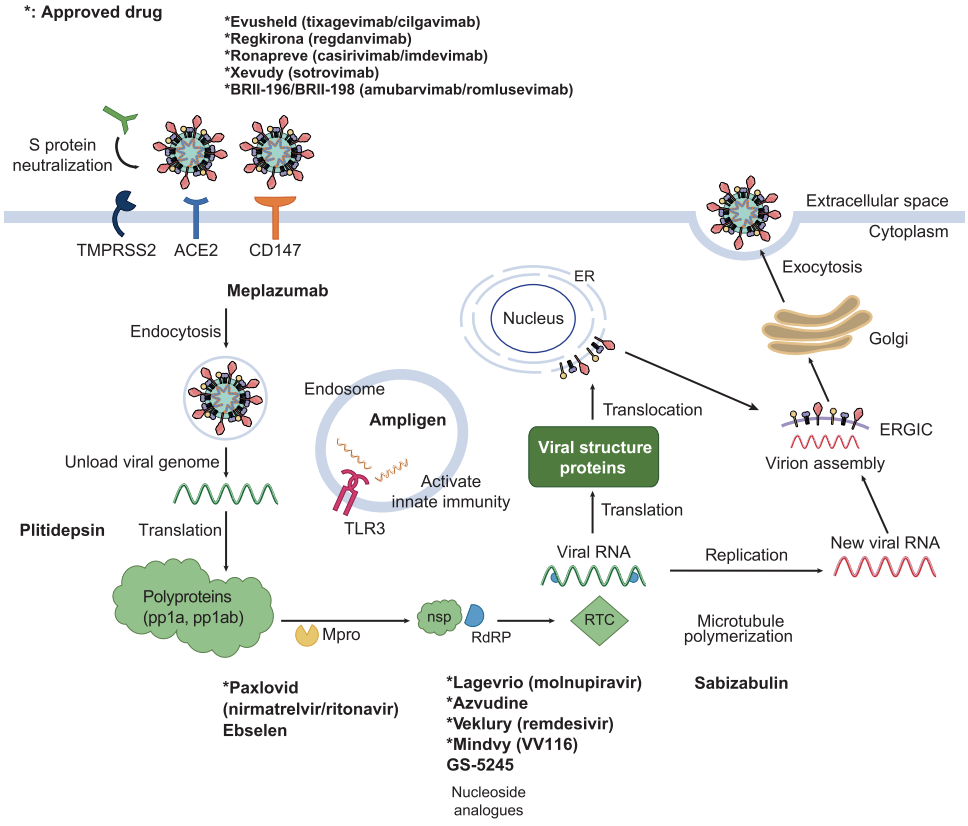

Fig. 2. SARS-CoV-2 life cycle. Medications in black font are approved. Medications in blue font are under development.
ER = endoplasmic reticulum.

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Nucala (meplazumab)

Nucala (meplazumab) is an IgG2 monoclonal antibody targeting CD147, a member of the immunoglobulin super-family with diverse functions related to cell differentiation, function, and migration. It is being studied for treating severe malaria and COVID-19 pneumonia by Jiangsu Pacific Meinuoke Pharmaceuticals in China.[60] CD147 (basigin) is a receptor for SARS-CoV-2 entry into cells, and can facilitate viral entry even when host cells lack ACE2 receptors.[61]

Meplazumab is under development to treat hospitalized COVID-19 patients by targeting CD147. A phase 2/3 study is recruiting participants in China (NCT04586153) to evaluate the safety and efficacy of meplazumab in addition to the standard of care for treating hospitalized adults with COVID-19. A total of 276 subjects will be randomized and allocated 1:1 (138:138) to receive 0.2 mg/kg meplazumab or control. The primary outcome will be reduced mortality and improved pulmonary function, as assessed by comparing the proportion of subjects who are alive and discharged without needing supplemental oxygen from day 1 to day 29 after treatment.

Aplidin (Plitidepsin)

Plitidepsin is an inhibitor of eukaryotic-translation-elongation-factor-1-alpha (eEF1A). eEF1a blocks the translation of *SARS-CoV*-1open reading frames 1A and 1B (ORF1A and ORF1B). Plitidepsin was developed for treating multiple myeloma, leukemia, lymphoma, and melanoma by PharmaMar in Spain due to its anti-tumor properties.[62,63] PharmaMar is recruiting participants for a phase 2 study (NCT05705167) to evaluate the safety and efficacy of plitidepsin in immunosuppressed COVID-19 patients. Subjects will be randomized to receive 2.5 mg plitidepsin via intravenous infusion together with supportive care, or will receive supportive care only. The primary outcome will be mortality rate from day 1 to day 30.

Ebselen (SPI-1005)

Ebselen (SPI-1005) (Sound Pharmaceuticals, Seattle WA, USA is an oral Mpro inhibitor. It is being studied for treating Meniere disease, noise-induced hearing loss (NIHL), and COVID-19.[64] It protects cells from oxidative damage.[65] The main mechanism of action of this drug in treating COVID-19 ins Mpro inhibition.[66,67] A phase 2 study to evaluate the safety and efficacy of ebselen in COVID-19 patients is enrolling subjects now (NCT04483973). Subjects will receive of 400 or 800 mg ebselen orally, or placebo, twice daily for 14 days. The primary outcome measure is the number of subjects who manifest adverse events within 30 days.

Obeldesivir (GS-5245)

Obeldesivir is an oral version of remdesivir. Obeldesivir is a nucleoside analogue that inhibits RdRp. The compound was developed by Gilead Sciences, Foster City, California.[68] Gilead Sciences is recruiting participants in the USA (NCT05603143) for a phase 3 study to evaluate the efficacy and safety of GS-5245 in patients with COVID-19 who have a high risk of developing severe illness. Participants will be randomized into GS-5245 or placebo groups. Participants in the GS-5245 group will be administered 350 mg GS-5245 orally twice daily without food, for 5 days. Participants in the placebo group will receive a placebo orally twice daily without food for 5 days. The primary outcome measure will be the proportion of COVID-19-related hospitalizations or all-cause death from the date of the first dose to day 29.

Sabizabulin

Sabizabulin is a microtubule disruptor that induces depolymerization of microtubules.[69] Sabizabulin has been studied for treating COVID-19 and cancer by Veru (Miami, FL, USA). Veru applied for an EUA for sabizabulin, however, it was rejected on March 2, 2023.[70]

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A phase 3 study to evaluate the efficacy and safety of sabizabulin in COVID-19 patients has been completed (NCT04842747); data are pending. The sabizabulin group received 9 mg of daily sabizabulin orally, together with the standard of care, until released from the hospital or for up to 21 days. The placebo group received a placebo capsule with the standard of care until released from the hospital or for up to 21 days. The primary outcome measure was the proportion of patients in the study who died within 60 days.

Ampligen (rintatolimod)

Ampligen (rintatolimod) is a Toll-like receptor 3 agonist. The compound consists of double-stranded RNA (dsRNA) developed by AIM ImmunoTech, Philadelphia, PA, USA. It has received FDA approval for treating severe chronic fatigue syndrome and pancreatic cancer. The route of administration is intravenous infusion. Rintatolimod binds Toll-like receptor 3 and thereby activates the ribonuclease L (RNase L), which degrades viral RNA. Furthermore, rintatolimod activates both innate and adaptive immune systems by stimulating production of various cytokines.[71] It is currently being studied as post-COVID treatment.[72]

A phase 2 study of rintatolimod in patients with post-COVID patients with fatigue has been conducted (NCT05592418). Subjects were randomized into two groups. The treatment group received 100 to 400 mg rintatolimod twice weekly via intravenous infusion for 12 weeks. The control group received normal saline 40 to 160 mL twice weekly via intravenous infusion for 12 weeks. The primary outcome measure was PROMIS Fatigue Score change from baseline to week 13. Anticipated study completion was November 2023.

PART 4. DEVELOPING COVID 19 IMMUNOMODULATORS

Fig. 3 illustrates approved and under development immune modulators used in COVID-19 treatment.

Developing drugs for immunosuppression in COVID-19

Jaktinib

Jaktinib is a JAK inhibitor that has been used to prevent and treat cytokine storms in COVID-19 patients. Jaktinib inhibits JAK1, JAK2, JAK3, and TYK2 by blocking the JAK-STAT signaling pathway (suppressing the release of IL-2, IL-4, IL-6, IL-7, and IL-10).[73]

Jaktinib was developed by Suzhou Zelgen Biopharmaceuticals, Shanghai, China. The drug is being studied for treating myelofibrosis, severe alopecia areata, atopic dermatitis, acute graft versus host disease (GvHD), and COVID-19.[74]

A phase 2 study to evaluate the safety and efficacy of jaktinib in severe COVID-19 pneumonia patients is planned (NCT05686629) but is not recruiting subjects yet. The treatment group will receive two 50 mg jaktinib doses or placebo tablets twice daily. The primary outcome measures will be the proportion of subjects who show clinical improvement (a score of more than 2) in the NIAID Ordinal Scale (NIAID-OS) for COVID-19, a change in the value of NIAID-OS, the time for subjects to reach 1-3 points, and the time to discharge.

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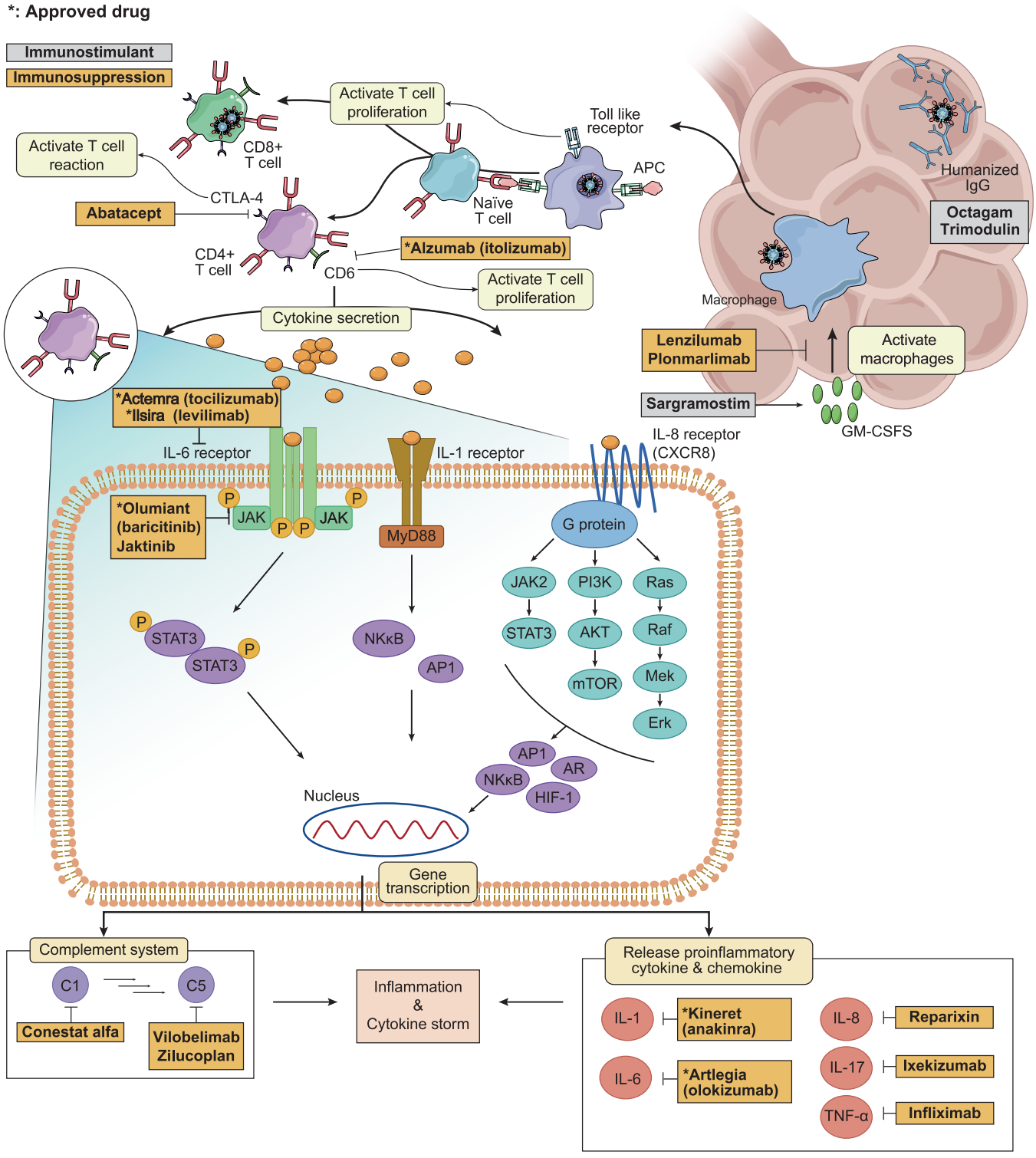

Fig. 3. Immune modulators used in COVID-19 treatment. Medications written in black are approved and medications written in blue are under development. Gray boxes denote medications that are immunostimulants. Yellow boxes denote medications that are immunosuppressants.
JAK = Janus kinase, IL = interleukin.

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Ilaris (canakinumab)

Ilaris is an IL-1β blocker developed by Novartis, Basel, Switzerland.[75] The drug is in development for autoinflammatory periodic fever syndromes and active Still disease. It is now being repurposed to alleviate clinical manifestations in patients with COVID-19.[76,77]

Katia and colleagues reported on a single center, single arm study conducted in 20209 in 20 patients with COVID-related severe acute respiratory syndrome. Treatment with canakinumab was associated with reduced requirement for supplemental oxygen.

A phase 3 study to compare the efficacy and safety of canakinumab with standard of care in COVID-19-induced pneumonia and CRS patients has been completed (NCT04362813). The canakinumab group received a single intravenous dose of canakinumab, dosed according to body weight (450 mg for 40 to 60 kg, 600 mg for 60 to 80 kg, and 750 mg for more than 80 kg) in 250 mL of 5% dextrose on day 1. The control group received a single dose of 250 mL of 5% dextrose via intravenous infusion on day 1. All subjects received standard of care. The primary outcome measure was the number of surviving participants who did not need invasive mechanical ventilation from Day 3 to Day 29. Trial results are pending.

Reparixin

Reparixin is a non-competitive allosteric inhibitor of CXCR1 (keratinocyte-derived chemokine receptor) and CXCR2 (macrophage inflammatory protein 2 receptor). Reparaxin was developed by Dompe' Pharmaceutical, Milan, Italy. By inhibiting CXCR1/2, it suppresses CXCL8 (IL-8)-induced neutrophil activation and reduces lung edema and neutrophil recruitment into the lung.[78]

Clinical studies evaluating the efficacy and safety of reparixin efficacy and safety in patients with breast cancer or with pancreatic transplantation have been completed.[79]

Due to its anti-inflammatory properties, reparixin might be a treatment option to prevent or attenuate CRS.[80] Clinical trials to test the efficacy of reparixin for treating COVID-19 are currently underway. A phase 3 study is currently recruiting participants to evaluate the efficacy of reparixin in patients with community-acquired pneumonia, including COVID-19 (NCT05254990). Subjects will receive standard of care and two 600 mg reparixin or placebo tablets three times daily with 8 hours intervals (6 tablets daily) for up to 21 days. The primary outcome will be the proportion of subjects who die or need mechanical ventilation or extracorporeal membrane oxygenation within a 28 day period.

Taltz (ixekizumab)

Ixekizumab is a humanized IL-17A antagonist developed by Eli Lilly and Company (Indianapolis, IN, USA).[81] In COVID-19 patients, overactivation of T lymphocytes, which is manifested by an increase in Th17 cell numbers, can lead to increased production of IL-17 and IL-22 cytokines. The use of an IL-17 blocking agent could be effective in treating patients with severe COVID-19.[82] Ixekizumab was approved by the FDA for treating plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.[81]

A phase 3 study aimed at finding an immune modulator of cytokines for subjects with severe COVID-19 was recently completed (NCT04724629). The trial name was Survival RTrial Using CytoKines in COVID-9 (STRUCK). The study drugs included an IL-17 inhibitor (ixekizumab), an IL-2 inhibitor (aldesleukin), and an IL-6 inhibitor (colchicine). The ixekizumab treatment group

received 80 mg by subcutaneous injection weekly for four weeks or until hospital discharge. The control group received standard of care including mechanical ventilation or dexamethasone. The primary outcome measure was the proportion of subjects who showed clinical improvement of two points on a seven-category ordinal scale on day 21. Study results are pending.

Remicade (infliximab)

Infliximab blocks tumor necrosis factor (TNF) [formerly named TNF-α) that was developed by Janssen Biotech (Horsham, PA, USA).[83] Infliximab received FDA approval for treating Crohn disease, colitis, and RA in 1998.[84] Infliximab is now being repurposed to treat COVID-19 patients.

A phase 3 study (ACTIV-1 trial) sponsored by the National Center for Advancing Translational Sciences (NCATS), NIH sought to find an effective immune modulator for patients with COVID-19 and has been completed (NCT04593940). The study consisted of three arms (infliximab, abatacept, and cenicriviroc). Participants in each arm received either drug or placebo, together with standard of care. Participants in the infliximab arm received a single 5 mg/kg dose of infliximab on day 1. The primary outcome measure was the time to recover from COVID-19 up to 29 days. Results are pending.

Orencia (abatacept)

Orencia is a selective T cell co-stimulation modulator that competes with CD28 for binding CD80 and CD86 receptors, thus decreasing T cell proliferation and inhibiting the production of cytokines such as TNF, interferon-γ, and IL-2.[85] Neutralizing inflammatory factors in CRS using abatacept could be an effective way to avoid severe inflammation in COVID-19.[86]

Abatacept was developed by Bristol-Myers Squibb (New York, NY, USA) and was approved by the FDA in 2005 for treating RA, PJIA, and psoriatic arthritis.[85] There has been interest in repurposing abatacept to treat patients with COVID-19.

A phase 3 study, the ACTIV-1 IM Trial Immunomodulators for Treating COVID-19 (NCT04593940) was sponsored by National Center for Advancing Translational Sciences (NCATS), NIH and has been complete. This study consisted of three arms. Each arm was provided with a standard of care including remdesivir. The infliximab group received a single 5 mg/kg dose of infliximab via intravenous infusion on day 1. The abatacept arm received a single 10 mg/kg dose of abatacept up to 1,000 mg via intravenous infusion on day 1. The control group received cenicriviroc, a chemokine 2 and 5 receptor antagonist (450 mg on day 1 and 300 mg on days 2 to 29) or a matching placebo. The primary outcome measure was the time to recover from COVID-19 up to day 29. None of the three therapies significantly improved outcomes compared to placebo.

Vascepa (icosapent ethyl)

Vascepa is an ethyl ester of eicosapentaenoic acid (EPA) that reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and enhances triglyceride clearance from circulating VLDL particles. The drug was developed by Amarin, Dublin, Ireland.[87] Isopent ethyl (Vascepa) received FDA approval as an adjunct to maximally tolerated statin therapy and diet to reduce triglyceride levels.

EPA improves endothelial function, limits vascular inflammation and reactive oxygen species production, and reduces vascular thrombosis. Through these mechanisms, Vascepa might reduce inflammation and improve symptoms of patients with COVID-19.[88]

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A phase 3 study of Vascepa for COVID-19 has been completed (NCT04460651). This study consisted of a prevention group (enrolling subjects at high risk of infection from COVID-19) and a treatment group (COVID-19-positive subjects). Subjects in the prevention group received 8 g oral Vascepa or placebo every 12 hours on days 1 to 3 and 4 g oral Vascepa or placebo every 12 hours for days 4 to 60. Subjects in the treatment group received 8 g oral Vascepa or placebo every 12 hours on days 1 to 3 and 4 g oral Vascepa or placebo every 12 hours for days 4 to 28. Primary outcome measures were COVID-19-positive subjects in the prevention group within 60 days and hospitalized or deceased subjects in the treatment group due to COVID-19 within 28 days. Results are pending.

NuSepin (HY209)

Nusepin is a fibroblast growth factor 19 (FGF-19) analog developed by Shaperon in South Korea. It targets cytokine storm in COVID-19 by suppressing pro-inflammatory cytokine production.[89]

A phase 2, 3 study to evaluate the safety and efficacy in COVID-19 pneumonia patients is recruiting participants (NCT05352347). Subjects in the treatment group will receive 0.2 mg/kg or 0.4 mg/kg NuSepin, twice daily by intravenous injection. Subjects in the control group will receive 100 mL normal saline twice daily. Primary outcome measures will be the time to improve more than 2 categories of the WHO 8-point ordinal scale and the time to discharge from the first dosing to day 29.

Ruconest (conestat alfa)

Ruconest (conestat alfa) is a C1 esterase inhibitor (C1INH) that promotes activation of complement. Conestat alfa was developed by Pharming Group, Leiden, Netherlands.[90] Conestat alfa targets several proteases of the contact and complement systems. Target proteases of conestat alfa are involved in the activation of complement protein C1, kallikrein, factor XIIa, and factor XIa.[90]

Activation of the complement system plays a central role in the pathogenesis of acute lung injury. The kallikrein-kinin system is also involved in thrombo-inflammation. Targeting multiple inflammatory cascades with conestat alfa could lead to clinical improvement in patients with severe COVID-19.[91] Conestat alfa received FDA approval for treating hereditary angioedema in 2014 and is under development for treating COVID-19.

A phase 2 study to evaluate the ability of conestat alfa to prevent severe disease progression in hospitalized COVID-19 patients has been completed (NCT04530136); results are pending. Participants in the conestat alfa to group received an intravenous injection of a dose of 50 U/kg (maximum dose of 4,200 U) every 12 hours for 4 days, for a total 8 injections. The control group received a standard of care. The primary outcome measure was the score of the WHO Ordinal Scale of disease severity on day 7.

MN-166 (ibudilast)

Ibudilast is an allosteric inhibitor developed by Kyorin Pharmaceutical, Tokyo, Japan.[92] Ibudilast is a selective inhibitor of phosphodiesterases acts to macrophage function. PDE 3, 4, and 10.[93] The use of PDE4 inhibitors has the potential to prevent cytokine storm in COVID-19.[94] Additionally, the inhibitor can inhibit production of proinflammatory cytokines such as IL-1β, TNF, and IL-6, while increasing the production of anti-inflammatory cytokines (IL-10, IL-4).[93]

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Ibudilast was approved by Japan in 1989 for treating bronchial asthma and improving dizziness secondary to chronic cerebral circulation impairment associated with sequelae of cerebral infarction.

Currently, ibudilast is being repurposed for use in the treatment of COVID-19. A phase 2 study to evaluate the efficacy and safety of ibudilast in COVID-19 patients is underway (NCT04429555). Participants receive MN-166 or placebo capsules twice daily for 7 days. Primary outcome measures are the proportion of subjects free from respiratory failure, the mean change from baseline in clinical status using the NIAID 8-point ordinal scale, the percentage of patients showing improvement in clinical status, and changes in cytokine levels at day 7.

CAP-1002

CAP-1002 refers to cardiosphere-derived cells (CDCs), which are stromal progenitor cells, derived from heart tissues by Capricor Therapeutics (Beverly Hills, CA, USA).[95] Cardiospheres are cell clusters that form invitro when cardiac progenitor cells are cultured. CDCs modulate activity of macrophages and effector T cells, and affect expression pro-inflammatory cytokines, potential o contributing to the pathogenesis of COVID-19. Additionally, CDCs can decrease production of proinflammatory cytokines (IFNγ, TNF, IL-1β, IL-6) and increase plasma levels of IL-10.[96]

CAP-1002 has been granted orphan drug designation by the FDA for treating Duchenne muscular dystrophy. CAP-1002 is being repurposed to treat COVID-19. A phase 2 study to evaluate the safety and efficacy of CAP-1002 in COVID-19 patients has been completed (NCT04623671). The treatment group received CAP-1002 therapy by infusion of 150 million CDCs in 5% human serum albumin. The control group received a placebo infusion. The primary outcome measure was the number of deaths within 90 days. Results are pending.

GB-0139 (Nafomostat)

GB-0139 is an inhibitor of galectin-3 (Gal-3) developed by Galecto Biotech (Boston, MA, USA). Gal-3 activates signaling pathways, including in particular those involving three molecules: extra-cellular signal regulated kinase (ERK), protein kinase B (Akt), and JAK/signal transducer and activator of transcription (STAT1). Activation of pathways leads to the release of pro-inflammatory cytokines, including IL-6, IL-8, and TNF.

Nafomostat is a synthetic serine protease inhibitor that reduces plasma levels several pro-fibrotic mediators.[97] GB-0139 being developed as treatment for idiopathic pulmonary fibrosis and for COVID-19.[98] GB-0139 might reduce viral-induced lung injury in patients with COVID-19

A phase 1/2 study to evaluate nafomostat as a therapy for COVID-19 to mitigate lung damage in patients with COVID-19 is currently recruiting participants (NCT04473053). Subjects are randomized into a nafamostat group, a GB-0139 group, and a control group. The nafamostat group will receive nafamostat via continuous intravenous infusion at 0.2 mg/kg/hr for 7 days. The GB-0139 group will receive 10 mg inhaled GB-0139 twice daily for 2 days and then 10 mg once daily for the remaining 12 days. The control group will receive standard of care. Primary outcomes will be changes of vital signs (blood pressure, heart rate, temperature and respiratory rate) up to 16 days following GB-0139 administration.

Remestemcel-L

Remestemcel-L refers to mesenchymal stromal cells (MSCs) derived from the bone marrow

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of healthy donors. Cells are prepared by Mesoblast (Melbourne, Australia). MSCs prevent T lymphocytes from entering the cell cycle, thus inhibiting clonal expansion. Additionally, MSCs promote the secretion of IL-4, impeding the secretion of IFN-γ and enhancing the development of regulatory T lymphocytes.[99] Remestemcel-L is currently under development as a drug for treating acute (GVHD), inflammatory bowel disease, and ARDS caused by COVID-19 infection.[100]

A pilot study showed that remestemcel-L improved clinical outcomes of COVID-19-associated multisystem inflammatory syndrome in children (MIS-C).[101] The primary aim is to achieve 43% reduction in mortality at 30 days in patients with moderate-to-severe acute respiratory distress (ARDS). An expanded access study to evaluate the safety and efficacy of remestemcel-L cells for MIS-C is currently enrolling subjects (NCT04456439), including children and adolescents from 2 months to 17 years of age. Subjects will receive a total of 2×10^6 remestemcel-L over 5 days. Participants will receive an intravenous infusion of diphenhydramine 0.5–1 mg/kg (up to 50 mg) prior to infusion of remestemcel-L. Subjects who are not receiving glucocorticoids for other indications will receive an intravenous infusion of 0.5–1 mg/kg hydrocortisone (up to 50 mg) prior to infusion of remestemcel-L.

Developing immunostimulants in COVID-19

IMM-101

IMM-101 is an immunotherapeutic agent containing heat-killed *Mycobacterium obuense* that was developed by Immodulon Therapeutics in Uxbridge, UK. IMM-101 is very effective at inducing cytokines expressed by innate immune cells. Recognition of IMM-101 by dendritic cells can enhance antigen processing and presentation capacity, increase expression of co-stimulatory molecules, and promote secretion of anti-viral interferon-γ, perforin, and granzyme B.[102] IMM-101 is currently being developed as a drug for treating pancreatic cancer, colorectal cancer and advanced melanoma, and colorectal cancer.[103] Additionally, clinical trials are underway to investigate potential use in the treatment of COVID-19. A phase 3 study to evaluate the safety and efficacy of IMM-101 in cancer patients with severe respiratory and COVID-19 infections is enrolling subjects (NCT04442048). The treatment group will receive 1.0 mg IMM-101 on day 0 and 0.5 mg on day 14 and day 45. Subjects in the control group will not receive any active treatment. The primary endpoint is the rate of flu-like illness or confirmed viral/bacterial respiratory infection after treatment.

Sarconeos (BIO101)

The small molecule sarconeos (Ruvembri, BIO101) activates the Mas receptor and triggers the P13K/AKT/mTOR pathway and the AMPK/ACC pathway.[104] The drug was developed by Biophytis (Paris, France). It is being developed as a drug for treating sarcopenia.[104]

Stimulating the Mas receptor may have beneficial effects on respiratory function, arterial oxygenation, and lung tissues in patients with severe COVID-19.[105] Investigation is underway to explore the potential use of sarconeos in the treatment of COVID-19. A phase 2, 3 study to evaluate the efficacy and safety of sarconeos for preventing respiratory deterioration in hospitalized COVID-19 patients was terminated due to the lack of eligible patients (NCT04472728). However, Biophytis continues developing sarconeos for COVID-19.[106]

Developing drugs targeting granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF belongs to the CSF superfamily. It is mainly produced by lymphocytes and innate

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lymphoid cells.[107] GM-CSF can stimulate mature neutrophils to exhibit chemotaxis, enhance oxidative metabolism, enhance antibody-dependent phagocytosis and killing of microorganisms, and produce various regulatory proteins. GM-CSF deficiency can lead to alveolar proteinosis, caused by failure to clear surfactant and due to a shortage of pulmonary macrophages induced by GM-CSF.[108]

GM-CSF basal circulating levels are low under homeostatic conditions. Levels quickly increase during infection or inflammation. GM-CSF is produced by a variety of cells, including fibroblasts, macrophages, endothelial cells, T cells, neutrophils, and eosinophils, among others. Expression of GM-CSF can be induced by proinflammatory cytokines, including IL-1α, IL-1β, TNF, and IL-12, whereas expression is suppressed by IL-4, interferon-γ, and IL-10.[109] During inflammation, elevated levels of systemic GM-CSF can dramatically increase monocyte and neutrophil production from bone marrow.[107]

Leukine (sargramostim)

Sargramostim is a GM-CSF manufactured by Partner Therapeutics (Lynnwood, WA, USA).[110] It stimulates the division and differentiation of partially committed progenitor cells in granulocyte-macrophage pathways.[110] Sargramostim is thought to offer benefits in the early phase of SARS-CoV-2 infection by preserving the function of alveolar macrophages.[111]

Sargramostim was approved by the FDA for treating acute myeloid leukemia and delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation. Investigations are being conducted to repurpose sargramostim for treating COVID-19.

A phase 4 study to evaluate the safety and efficacy of sargramostim in patients with COVID-19 and acute hypoxic respiratory failure has been completed (NCT04326920). The treatment group received 125 mcg inhaled sargramostim twice daily for 5 days in addition to the standard of care. If subjects in the treatment group require mechanical ventilation within 5 days, inhaled Leukine could be replaced by intravenous infusion of 125 mcg/m^2 until day 5. After day 6, clinicians could choose to administer Leukine intravenously for an additional 5 days. The control group received standard of care for 5 days. If subjects in the control group required mechanical ventilation, the clinician could decide to administer an intravenous infusion of sargramostim 125 mcg/m^2 once daily for 5 days from day 6 onwards. The primary outcome measure was mean improvement in oxygenation on day 6 or hospital discharge. Results are pending.

Plonmarlimab (TJ003234)

Plonmarlimab directly binds GM-CSF, blocking intracellular signaling. Downstream signaling from the GM-CSF receptor involves JAK2/signal transducer and activator of transcription 5 (STAT5), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), ERK, and the phosphoinositide 3-kinase (PI3K)-Akt (protein kinase B) pathway. Therefore, inhibiting GM-CSF might represent a viable treatment option for preventing the CRS.[112]

Plonmarlimab is under development for treating CRS and COVID-19. It is manufactured by I-Mab Biopharma based in China.[113]

Phase 2 and 3 studies to evaluate the safety and efficacy of plonmarlimab (also known as TJ003234) in severe COVID-19 patients have been completed (NCT04341116). In those studies, subjects were randomized to receive an infusions of placebo or plonmarlimab at low,

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medium or high dose. The primary outcome measure was the proportion of subjects who were alive and free from mechanical ventilation among subjects who were free of mechanical ventilation at baseline for 30 days. Plonmarlimab reduced mortality in the phase 2/3 trial.

Lenzilumab

Lenzilumab is a GM-CSF monoclonal antibody developed by Humanigen based in Burlingame, CA, USA. By binding to GM-CSF, lenzilumab prevent binding to the GM-CSF receptor, thereby alleviating CRS. This GM-CSF neutralization can reduce IL-6, MCP-1, macrophage inflammatory protein 1 alpha (MIP-1α), IP-10, VEGF, and TNFα levels. Consequently, lenzilumab exhibits potential immunomodulatory activity.[114] It is indicated for treating refractory chronic myelomonocytic leukemia, acute GvHD, COVID-19, among other indications.[115]

A phase 2 study, which is the ACTIV-5 Big Effect Trial (BET), sponsored by NIAID, NIH for COVID-19 patients, has been completed (NCT04583969). The experimental group received 200-mg intravenous remdesivir on Day 1, followed by a 100-mg once-daily intravenous maintenance dose up to a 10-day course while hospitalized; this group also received 600-mg intravenous lenzilumab infusion every 8 hours starting on Day 1, for a total of 3 doses. The control group received 200 mg of intravenous remdesivir on Day 1, followed by a 100 mg once-daily intravenous maintenance dose and 600-mg intravenous placebo infusion every 8 hours starting on Day 1. The primary outcome measures were the number of surviving participants and ventilation-free subjects at 29 days.

PART 5. DEVELOPING ANTI-COAGULANTS IN COVID-19

Fig. 4 illustrates drugs under development that can prevent blood coagulation.

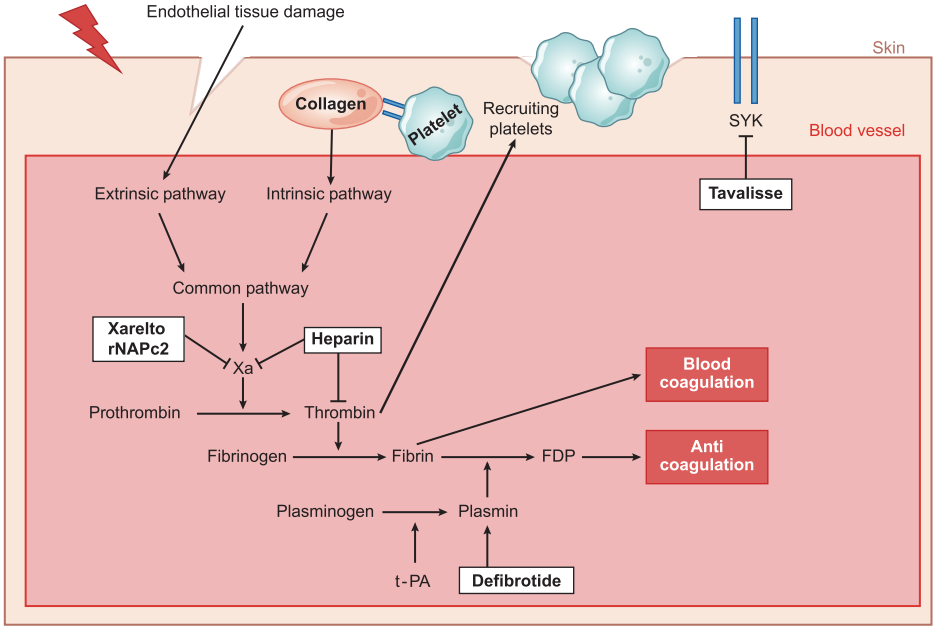

Fig. 4. Blood coagulation and anticoagulation pathways and related drugs.
Therapies are shown in white boxes.
SYK = spleen tyrosine kinase.

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Heparin

Heparin is a factor Xa and thrombin inhibitor. Heparin is isolated from porcine tissues and is available in several forms. These include Lovenox (enoxaparin sodium), by Sanofi Aventis, France,[116] Fragmin (dalteparin sodium) by Pfizer, USA,[117] and Innohep (tinzaparin sodium) by Leo Pharmaceutical, Denmark.[118] Routes of administration are subcutaneous and intravenous injections. Heparin acts by inhibiting factor Xa and thrombin, which promotes blood coagulation.[119] Many COVID-19 patients manifest coagulopathies, venous thromboembolism (VTE).[120]

The ACTIV-4A clinical trial comparing anticoagulation treatment strategies has been completed (NCT04505774). This trial tested four approaches: therapeutic and prophylactic doses of heparin, therapeutic or prophylactic doses of heparin combined with a P2Y12 inhibitor, and the standard of care with crizanlizumab (used for veno-occlusive disease). The primary outcome measure was the number of days that a patient was alive and free of organ support through the first 21 days after trial entry. Results are pending.

Xarelto (rivaroxaban)

Rivaroxaban is a factor Xa inhibitor developed by Bayer, Leverkeusen, Germany.[121] It received FDA approval for treating deep vein thrombosis (DVT), pulmonary embolism (PE), and VTE. Its mechanism of action is by inhibiting factor Xa to suppress thrombin formation and the coagulation pathway.[122] Xarelto is expected to reduce thrombotic disease progression in severe COVID-19 patients.[123]

A phase 3 study of rivaroxaban to reduce clinical progression of COVID-19 is currently active, in a not recruiting status (NCT04324463). In that study, the treatment group will be receive 2.5 mg oral tablets of Rivaroxaban twice daily for 28 days and the control group will receive the standard of care. The primary outcome measure is the time to the first occurrence of specified outcomes within the first 45 days after randomization; these outcomes include 1) requirement for high flow oxygen or mechanical ventilation and 2) major thrombosis or death.

Anpocogin (rNAPc2 [recombinant Nematode Anticoagulant Protein c2])

rNAPc2 is a factor Xa inhibitor developed by ARCA Biopharma, Westminster, CO. It is administered by subcutaneous injection.[124] Anpocogin binds factor Xa to form the FXa-rNAPc2 complex. This complex inhibits tissue factor-factor VIIa (TF/FVIIa), which is necessary for blood coagulation.[125] Therefore, rNAPc2 drug inhibits the extrinsic pathway. It may be effective in the treatment of COVID-19-induced blood coagulopathy.

A phase 2, 3 study of rNAPc2 compared to heparin, for treating hospitalized COVID-19 patients with high D-dimer levels has been completed (NCT04655586). The higher dose, group was given 7.5 μg/kg rNAPc2 via subcutaneous injection on Day 1 and 5 μg/kg via subcutaneous administration on Days 3 and 5. The lower dose group was given 5 ug/kg rNAPc2 via subcutaneous injection on Day 1 and 3 ug/kg via subcutaneous administration on Days 3 and 5. The control group was given standard-of-care heparin following local institutional guidelines (therapeutic or prophylactic regimen). Primary outcome measures were proportional change in D-dimer level from baseline up to Day 8 (phase 2), the number of major or non-major clinically relevant bleeding events within 8 days compared to heparin (phase 2, 3), and the time to recovery within 30 days (phase 3). Treatment with rNAPc2 was well tolerated without excess bleeding or serious adverse events. There was no significant reduction in the primary efficacy end point, D-dimer levels, from baseline to day 8 with rNAPc2 compared with heparin.[126]

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Tavalisse (fostamatinib disodium hexahydrate)

Tavalisse is a tyrosine kinase inhibitor that blocks enzymatic activity of spleen tyrosine kinase (SYK). The drug was developed by Rigel Pharmaceuticals, South San Francisco.[127] Fostamatinib received FDA approval for chronic immune thrombocytopenia in 2018. The route of administration is oral supplementation.[127] The major metabolite of fostamatinib is R406.

Fostamatinib inhibits signal transduction of B-cell receptor and Fc-activating receptors which bind to antibodies; the drug activates kinases,including SYK.[127,128] Activated SYK stimulates the the inflammatory pathway that promotes the release of neutrophil extracellular traps (NETs). High levels of NETs induce immunothrombosis in COVID-19 patients.[129] Fostamatinib also suppresses the activation of platelets induced by COVID-19 plasma. Therefore, fostamatinib might be effective prophylaxis for COVID-19 patients at high thrombotic risk.[130]

A phase 2, 3 (ACTIV-4) trial (NCT04924660 is randomizing subjects to either of two angiotensin antagonists, TXA127 or TRV027, fostamatinib, or placebo. The fostamatinib arm will receive 100-150 mg oral fostamatinib twice daily for 14 days (28 doses). The primary outcome measure is the number of oxygen-free days up to 28 days following randomization.

Defitelio (defibrotide sodium)

Defitelio enhances enzymatic activity of plasmin to hydrolyze fibrin clots. It was developed by Jazz Pharmaceuticals, Ireland. It received FDA approval for treating hepatic veno-occlusive disease on 2016. The route of administration is intravenous infusion.[131] Its mechanism of action is to suppress synthesis of proinflammatory cytokines such as IL-6, inhibiting generation of reactive oxygen species, and to restore nitric oxide generation. Defibrotide sodium has other mechanisms which involve anti-inflammatory and antioxidant pathways. Therefore, defibrotide sodium could be beneficial for treating COVID-19 patients with stimulated platelet aggregation and endothelial cell damage by increasing the expression of pro-coagulant factors.[132]

A phase 2 study to evaluate the efficacy and safety of defibrotide in COVID-19-related pneumonia is recruiting participants (NCT04652115). Cohort 1 consists of hospitalized patients with COVID-19 pneumonia needing supplemental oxygen or mechanical ventilation without use of anticoagulants who require no more than one vasopressor. Cohort 2 consists of hospitalized COVID-19 pneumonia patients in an intensive care unit (ICU) who are at elevated risk of hemorrhage and/or hypotension. The former is defined as a requirement for therapeutic dose anticoagulation for active thrombosis, ECMO, or continuous renal replacement therapy and the latter is defined as a requirement for two vasopressive agents to maintain hemodynamic stability). Each subject will receive an FDA-approved dose of 6.25 mg/kg defibrotide via intravenous infusion every 6 hours for 21 days.

For the cohort 2 study, a 6+6 dose de-escalation design will be applied. If 2 of 6 dose-limiting toxicities (DLTs) (grade 3/4 hemorrhage and significant new hypotension) are experienced in the first 6 subjects, subjects will receive a reduced dose of defibrotide at 10 mg/kg/d CIVI. If there are 0 or 1 DLTs in the first six subjects at the FDA-approved dose, another six subjects will be enrolled at the same dose. The primary outcome measure is the rate of a special adverse event such as bleeding or hypotension within 21 days. Results are pending.

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PART 6. DEVELOPING DRUGS FOR COVID-19-INDUCED NEUROPATHY

Cerebrolysin (FPF-1070)

Cerebrolysin is a peptide-based analog of brain-derived neurotrophic factors and developed by EVER Neuro Pharma (Unterach, Austria). It is approved for treatment of stroke and dementia in 44 countries, including Austria, China, Germany, Russia, and South Korea. Cerebrolysin increases the growth of new neurons, supports existing neurons, and protects neurons against amyloid beta toxicity.[133] Due to its neurotrophic and neuroprotective properties, cerebrolysin might be useful to treat post-COVID patients with anosmia or ageusia (NCT04830943).

A phase 4 pilot study of cerebrolysin for COVID-19-induced anosmia and ageusia has been completed (NCT04830943). The cerebrolysin group received 5 mL cerebrolysin (215.2 mg/mL cerebrolysin) via intramuscular injection once daily, five times per week. The treatment lasted at least 8 weeks (total of 40 injections) and a maximum of 24 weeks. The control group received olfactory training twice daily for 8 weeks. Primary outcome measures were a smell and taste questionnaire and odor, taste, and flavor identification testing. Results are pending.

NA-831 (traneurocin)

Transneurocin is an oral neuroprotective drug developed by Biomed Industries (San Jose, CA). It was originally studied for Alzheimer disease. Now it is being developed for treating COVID-19-induced neuropathy. Transneurocin is currently known to enhance neurogenesis. More detailed mechanisms are being investigated. This drug is being studied for use with other antiviral and anti-inflammatory drugs for COVID-19 patients.[134-136]

A phase 2, 3 study to evaluate four Traneurocin combinations for COVID-19 infection hospitalized participants is recruiting participants (NCT04452565). Arm 1 will receive 30 mg oral Traneurocin twice on day 1 and then will receive drug once a day from day 2 to day 5. Arm 2 will have oral administration of 60 mg Traneurocin and 400 mg atazanavir, twice on day 1 and then 30 mg and 200 mg respectively, once a day from day 2 to day 5. Arm 3 will be orally administered Traneurocin and dexamethasone (60 mg and 8 mg respectively) twice on day 1 and then 30 mg and 4 mg, once a day from day 2 to day 5. Arm 4 subjects receive oral Atazanavir and dexamethasone (400 mg and 8 mg respectively) twice on day 1 and 200 mg and 4 mg once a day from day 2 to day 5. The primary outcome measure will be the time to neurologic recovery, assessed up to 36 days after treatment initiation.

PART 7. OTHER MECHANISM DRUG FOR COVID-19 THERAPEUTICS UNDER DEVELOPMENT

Drugs targeting the hypoxia-inducible factor (HIF)-prolyl hydroxylase (PHD) (HIF-PHD) pathway

Tissue hypoxia is a common feature at sites of immunity and inflammation, resulting in elevated expression and activity of HIF. In response to hypoxia, specific cells increase their production of erythropoietin through activation of HIF signaling. This process counteracts a systemic decrease in pO_2 and increases the oxygen-carrying capacity of the blood through amplified erythrocyte production.[137] HIF is the most well-characterized substrate of HIF prolyl hydroxylase (HIF-PHD). HIF has two subunits: an α-subunit that quickly degrades

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in normoxia and a stable β-subunit. The HIF α-subunit is regulated by post-transcriptional modifications such as phosphorylation, acetylation, and hydroxylation. Hydroxylation (the main regulator of HIFα) is controlled by HIF-PHD belonging to the family of α-ketoglutarate-dependent non-heme iron dioxygenases.[138]

Under normoxic conditions, HIF α-subunits are hydroxylated on proline residues by three distinct enzymes (PHD1, PHD2 and PHD3), leading to HIFα ubiquitination and subsequent degradation. Hydroxylation of HIF inhibits binding of a transcriptional co-activator to prevent formation of a functional transcriptional complex.[137] Under hypoxic conditions, PHD enzymatic activity is reduced and consequently, HIF-α is degraded at lower rate. HIF-α can then be translocated to the nucleus, where it heterodimerizes with HIF-β and activates gene transcription. As a result, HIF facilitates oxygen delivery and cellular adaptation to hypoxia by regulating cellular processes such as angiogenesis, mitochondrial biogenesis, anaerobic glucose metabolism, and others.[139] **Fig. 5** illustrates drugs that are currently under development modulating the HIF-PHD pathway.

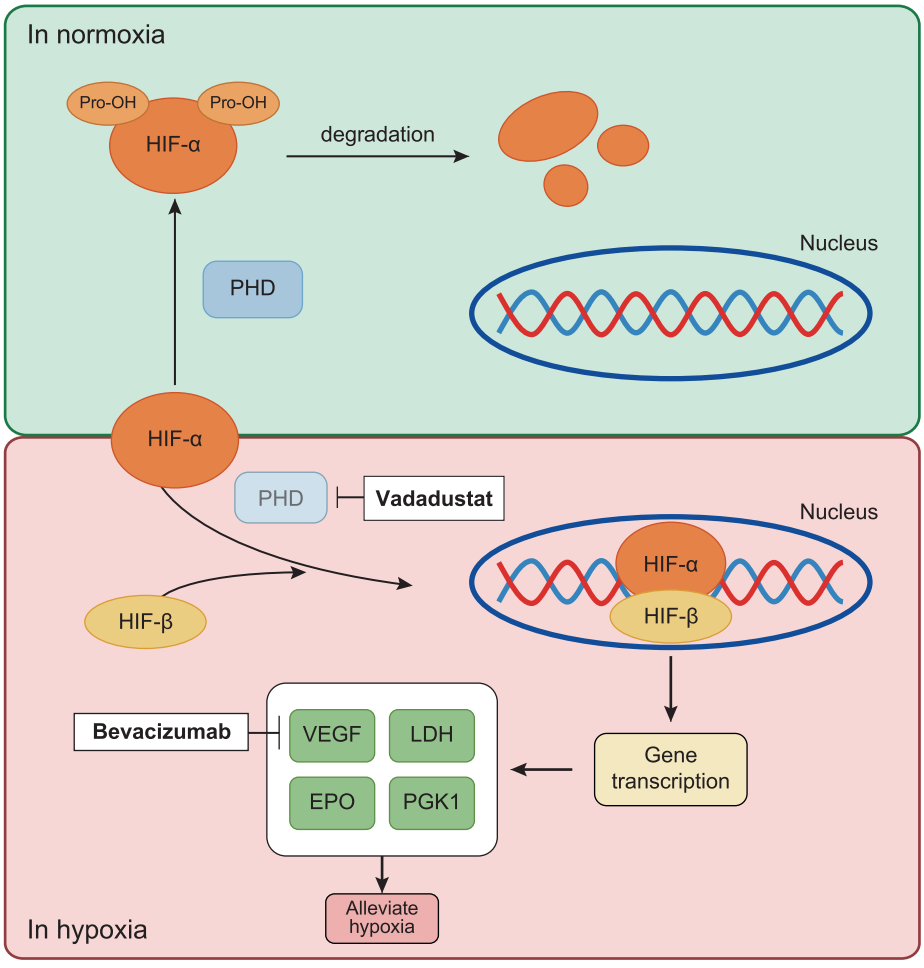

Fig. 5. Hypoxia-inducible factor-prolyl hydroxylase (HIF-PHD) pathway and its related drugs.
HIF = hypoxia-inducible factor, PHD = prolyl hydroxylase, VEGF = vascular endothelial growth factor.

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Avastin (bevacizumab)

Bevacizumab was developed by Roche in Basel, Switzerland.[140] This monoclonal antibody recognizes vascular endothelial growth factor-A (VEGF-A) and prevents the interaction of VEGF-A with the VEGF receptor. Consequentially, bevacizumab inhibits the activation of the VEGF signaling pathways and represses angiogenesis.[141] In patients with COVID-19, ARDS induces tissue hypoxia, which leads to increased VEGF expression through activation of the HIF PHD-1 pathway. In these patients, VEGF contributes to plasma extravasation and pulmonary edema, further exacerbating tissue hypoxia and lung inflammation. Therefore, blocking VEGF with Avastin (bevacizumab) can improve oxygen perfusion and elicit anti-inflammatory response in patients with COVID-19.[142]

Avastin (bevacizumab) received FDA approval in 2004 for treating metastatic colorectal cancer. Currently, it is being repurposed for treating COVID-19. A phase 3 study to evaluate the efficacy and safety of bevacizumab for patients with COVID-19 is recruiting participants (NCT04305106). The bevacizumab group will receive a single 7.5 mg/kg dose of bevacizumab via intravenous infusion with a standard of care if necessary. The control group will receive a single dose of placebo (inactive excipient) at 7.5 mg/kg via intravenous infusion, together with a standard of care. The primary outcome measures are the time to achieve a clinical improvement of two points on a seven-category ordinal scale and discharge from the hospital within 28 days.

Vadadustat (AKB-6548)

Vadadustat is a structural analog of α-ketoglutarate, a Krebs cycle intermediate that inhibits HIF-PHD. Vladadustat was developed by Akebia Therapeutics (Cambridge, MA, USA).[143] The drug inhibits PHD catalysis and stabilizes HIF-2α to a greater extent than does HIF-1α. Vadadustat increases hemoglobin levels, increases total iron binding capacity, and lowers plasma ferritin and hepcidin levels. Vadadustat was developed for treating anemia due to chronic kidney disease.[143] Currently, it is being studied for its potential application in the treatment of COVID-19-associated hypoxemia.[139]

A phase 2 study of vadadustat for preventing ARDS in COVID-19 patients is currently active but recruitment has not begun (NCT04478071). Subjects will be randomized to receive 900 mg vadadustat or placebo, taken orally once daily for 14 days. The primary outcome measure will be the number of subjects who are classified as 8 (deceased), 7 (hospitalized, on invasive mechanical ventilation or ECMO), or 6 (hospitalized, on non-invasive ventilation or high flow oxygen devices) by the NIAID ordinal scale on day 14.[144]

Trimodulin (BT588)

Trimodulin is an immunoglobulin concentrate containing IgG (~56%), IgA (~21%), and IgM (~23%). It was developed by Biotest, Germany. Initially, trimodulin was developed to treat patients with severe community-acquired pneumonia (sCAP). Trimodulint is currently under clinical development for treating patients with either sCAP or severe COVID-19.[145]

As immunoglobulin preparations have long been used as therapy for inflammatory diseases, the anti-inflammatory effects of trimodulin might be beneficial for patients with severe COVID-19.[146]

A phase 3 study to evaluate the efficacy and safety of trimodulin as an adjunctive treatment together with standard of care for patients with COVID-19 is recruiting participants

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(NCT05531149). Subjects will receive trimodulin or human albumin 1% (placebo) via intravenous infusion for five consecutive days. Primary outcome measures will be percentage of clinical deterioration rate and the percentage of mortality rate between days 6 to 29.

Octagam

Octagam is an intravenous human immune globulin preparation that supplies both opsonic and neutralizing IgG antibodies. It was developed by Octapharma in Lachen, Switzerland. The name derives from the company's expertise in developing factor 8 preparations to treat hemophilia).[147] Intravenous immunoglobulin (IVIG) enhances pro-inflammatory cell activation and suppresses T cell and B cell proliferation. As severe cytokine storm is associated with high death rates in severe COVID-19, use of IVIG might be effective.[148] Octagam received FDA approval for treating primary humoral immunodeficiency in 2004.[147] It is currently being repurposed for use in the treatment of COVID-19.

A phase 2 study to evaluate the safety and efficacy of Octagam to reduce all-cause mortality in COVID-19 has been completed (NCT04480424). The treatment groups received intravenous infusions of Octagam (500 mg/kg for 4 days or 400 mg/kg for 5 days), together with standard of care. The control group received a standard of care. The primary outcome measure was all-cause mortality rate up to 29 days. Octagam treatment was associated with improved functional status,

Opaganib

Opaganib is an oral sphingosine kinase 2 (SK2) inhibitor developed by RedHill Biopharma (Tel Aviv, Israel). Opaganib inhibits host SK2 but not viral SK2. Thus, it is less affected by viral mutations.[149] This drug is being studied for treating cancer and infectious diseases including COVID-19. Its mechanism of action is through inhibiting production of sphingosine 1-phosphate (S1P). S1P promotes TNF signaling, which promotes cytokine production. Opaganib also inhibits dihydroceramide desaturase (DES1) and glucosylceramide (GCS). DES1 inhibition promotes autophagy to inhibit viral replication, while GCS inhibition can also reduce the viral entry into cells. Hence, opaganib might be effective for treating COVID-19 through multiple mechanisms.[150]

A phase 2/3 study to evaluate the efficacy and safety of opaganib in hospitalized patients with severe COVID-19 has been completed (NCT04467840). The opaganib group received 500 mg opaganib orally every 12 hours with the standard of care. The medication can be administered as a liquid suspension via nasogastric tube. The control group received a placebo orally every 12 hours, together with standard of care. All participants received drug or placebo for 14 days. The primary outcome measure was comparing the proportion of patients no longer requiring supplemental oxygen for at least 24 hours in a time frame of 14 days. In a phase 2/3 study of 475 patients, treatment with opaganib was associated with a 62% decrease mortality in patients with moderate to severe COVID-19.

ARADKOA (Tafenoquine)

Tafenoquine is a potential TMPRSS2 and Mpro inhibitor developed by 60 Degrees Pharmaceuticals (Washington, D.C., USA). It received FDA approval for prophylaxis of malaria. It inhibits hematin polymerization and induce parasite death.[151] It has potential to inhibit TMPRSS2 and Mpro. Inhibiting TMPRSS2 can reduce virus entry. Mpro is involved in the correct cleavage of viral polyproteins translated from the viral genome. Inhibiting Mpro can reduce viral replication.[152] Therefore, tafenoquine may be effective in the treatment of COVID-19.

A phase 2 study of tafenoquine treatment in patients with mild to moderate COVID-19 been completed (NCT04533347). Subjects took two 100 mg tafenoquine tablets or two placebo tablets orally for 10 days. The primary outcome measure was the proportion of patients with clinical recovery of COVID-19 symptoms on Day 14. Results are pending.

Luvox (fluvoxamine)

Fluvoxamine is an inhalant selective serotonin reuptake inhibitor developed by Solvay in Houston, TX. It received FDA approval for treating obsessive-compulsive disorders in 1994.[153] Its mechanisms of action are diverse and include reducing histamine release from mast cells, showing lysosomotrophic effects (i.e., increasing lysosomal pH) by interfering with viral trafficking, interfering with lysosomal membrane binding of acid sphingomyelinase, affecting inositol-requiring enzyme 1α-mediated inflammation, and increasing melatonin levels.[154] Due to these anti-inflammatory and antiviral properties, *Fluvoxamine* might be effective for treating COVID-19.

A phase 3, ACTIV-6 trial to evaluate the effectiveness of repurposed medications in COVID-19 patients is recruiting participants (NCT04885530). This study consists of six subgroups (fluvoxamine and ivermectin will each have two subgroups with different doses, together with two placebo group. Each subgroup participant will receive either a study drug (fluvoxamine, ivermectin, fluticasone, montelukast) or placebo. Fluvoxamine subgroups are 'arm B' and 'arm E'. Arm B participants will self-administer 50 mg fluvoxamine or placebo orally twice a day for 10 days. Arm E participants will orally self-administer 50 mg fluvoxamine or placebo twice on day 1, and 100 mg fluvoxamine or placebo twice a day for 12 days. Primary outcome measures are number of hospitalizations, deaths and symptoms reported by subjects, all within a time frame of up to 28 days.

Pyramax (artesunate/pyronaridine)

Pyramax is an oral antimalarial drug repurposed for COVID-19 by Shin Poong Pharmaceutical, Seoul, South Korea. Pyronaridine inhibits hematin formation to protect the heme group that is toxic to malaria. Artesunate produces free radicals with antimalarial activity.[155,156] In treating COVID-19, artesunate can act as a viral infection inhibitor at the cellular post-entry level.[157] Pyronaridine modulates appropriate levels of antiviral interferons, including interferon-1β. Moreover, pyronaridine can lower high levels of CXCL1 and CCL3 involved in inflammation responses.[158] Therefore, Pyramax has potential as an effective COVID-19 treatment. A phase 3 study to evaluate the efficacy and safety of Pyramax in COVID-19 patients is currently recruiting participants (NCT05084911). The Pyramax group will receive a pyronaridine-artesunate (180/60 mg) tablet for three days and the control group will receive a placebo. The primary outcome measure will be the proportion of patients who require hospitalization or have died due to COVID-19 infection up to 29 days.

RVX-208 (Apabetalone)

Apabetalone is an inhibitor of bromodomain and extra-terminal (BET) proteins. It specifically targets bromodomain 2 (BD2). It was shown by Resverlogix (Calgary, Aberta, Canada)[159] to be a potential treatment for cardiovascular disease, pulmonary arterial hypertension, chronic kidney disease, and COVID-19. It was developed with a cardiovascular indication and was granted a Breakthrough Therapy Designation by the FDA.[160]

The mechanism of action is to prevent interactions between acetylated lysine on histone tails and transcription factors. In particular, apabetalone can suppress gene expression of vascular

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inflammation mediators whose genes are dependent for transcription on BET domain and extra terminal domain protein (BET) proteins. Apabetalone prevents BRD4 associations with key transcriptional enhancers and promoters.[159]

In addition, ACE2 expression is regulated by BET proteins. Inhibitors of BET proteins downregulate ACE2 expression and limit SARS-CoV-2 replication in vitro.[160] Due to its antiviral and anti-inflammatory effects, apabetalone is a promising candidate for treating COVID-19.[161]

A phase 2, 3 study to evaluate the safety and efficacy of apabetalone in COVID-19 patients is recruiting participants (NCT04894266). The treatment group will receive 100 mg apabetalone orally twice daily together with standard of care, and the control group will receive standard of care only. The primary outcome measure is the WHO Ordinal Scale for Clinical Improvement change on day 14.

ANA001 (Niclosamide)

Niclosamide is an inhaled preparation of salicylanilide, a derivative of salicylic acid belonging to a large group of lipophilic compounds. Niclosamide was developed by NeuroBo Pharmaceuticals, Cambridge, MA, USA.[162,163] Plausible mechanisms of action of niclosamide against COVID-19 involve four cellular processes: 1) endosomal pH neutralization to prevent viral replication, 2) promotion of autophagy through inhibition of S-phase kinase-associated protein 2 (SKP2), 3) decreased mucus plugging through inhibition of TMEM16A (calcium activated chloride channel, CaCC), and 4) prevention of syncytia formation by ion channel inhibition.[163]

Additionally, niclosamide has anti-inflammatory effects by inhibiting pro-inflammatory cytokines, mainly TNF. Furthermore, it can inhibit the progression of inflammatory airway diseases by suppressing the release of IL-8 and intracellular Ca^{+2} signaling.[164] Due to these anti-inflammatory and antiviral effects, it may be effective for treating patients with COVID-19.

A phase 4 study of niclosamide to treat patients with COVID-19 has been completed (NCT05087381) in Thailand. One treatment group received 500 mg niclosamide orally by tablet twice daily for 14 days. A second treatment group received the same dose for 14 days but in combination with one 8 mg tablet of bromhexine twice daily for 10 days. The control group received supportive care. Primary outcome measures were hospital admission or mortality related to COVID-19 within 28 days, the time taken to self-report recovery until the final day of participation, and the progression to severe COVID-19 disease until the final study day. Study results are not available.

(pamapimod/pioglitazone)

KIN001 is a combination of pamapimod, a selective inhibitor of p38 mitogen-activated protein kinase alpha (p38 MAPKα), and pioglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) agonist. The drug was developed by Kinarus Therapeutics in Switzerland for treating wet age-related macular degeneration (Wet-AMD) and idiopathic pulmonary fibrosis. The route of administration is oral inhalation.[165]

The p38 MAPK pathway plays a crucial role in viral infection. Viral p38 MAPK activation can promote endocytosis of viral receptors, including ACE2. Downstream effectors of this pathway include transcription factors and RNA binding proteins that regulate cytokine production, cell proliferation, cell differentiation, and apoptosis, as well as development. PPARs are transcription factors involved in insulin responses. Studies have suggested that

pioglitazone, a glucose-lowering medication, can improve manifestations of COVID-19 patients with type 2 diabetes. Therefore, KIN001, the combination of a p38 MAPK inhibitor with pioglitazone, might have synergistic antiviral activity against SARS-CoV-2 with anti-inflammatory effects.[166]

A phase 2 study to evaluate the efficacy and safety of KIN001 (pamapimod/pioglitazone) in non-hospitalized COVID-19 patients is recruiting participants (NCT05659459). The treatment group will receive 75 mg pamapimod and 5 mg pioglitazone orally twice daily for 14 days. The control group will receive matching tablets of KIN001 orally twice daily for 14 days. The primary outcome measure is the evaluation of COVID-19 symptoms within 28 days.

Xpovio (selinexor)

Selinexor is an oral exportin 1 (XPO1) blocker developed by Karyopharm Therapeutics, Newton, MA. In 2019, selinexor received FDA approval for treating multiple myeloma and diffuse large B-cell lymphoma.[167] In COVID-19, XPO1 inhibitors can transiently inhibit expression of ACE2 and its interaction with SARS-CoV-2. Selinexor also inhibits transport of the tumor suppressor protein p53. This results in nuclear accumulation of p53, and induction of apoptosis and cell-cycle arrest. Therefore, inhibition of the p53 pathway might induce apoptosis of SARS-CoV-2. Moreover, selinexor prevents release of pro-inflammatory cytokines and reduce oxidative and inflammatory disorders by activating nuclear factor erythroid 2-related factor-2 (Nrf2) and peroxisome proliferator-activated receptor (PPAR)-γ.[168]

A phase 2 study to evaluate the efficacy and safety of selinexor (KPT-330) in patients with severe COVID-19 has been completed (NCT04349098). In that study, subjects received standard of care together with 20 mg of oral selinexor or a matching placebo on Days 1, 3, and 5 of each week for up to two weeks. If subjects could tolerate the therapy and experienced clinical benefit, dosing could continue for an additional 2 weeks (28 days). The primary outcome measure was the proportion of subjects showing clinical improvement of at least two points on the 8-point ordinal scale within 14 days. Selinexor did not reduce mortality, reduce ICU admission rate or recovery time, compared to placebo.

Alinia (Nitazoxanide)

Nitazoxanide is an oral medication consisting of a nitrothiazole moiety and salicylamide moiety. It was developed by Romark Laboratories (Tampa, FL, USA).[169] Upon administration, the drug is rapidly deacetylated to tizoxanide (TIZ), its active metabolite.[170] Alinia received FDA approval in 2002 for treating diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum* as an anti-parasitic drug with potent antiviral activity.

Nitazoxanide's mechanism of action is to inhibit viral entry and viral replication, and to suppress pro-inflammatory responses. Nitazoxanide inhibits ACE2 receptor/TMPRSS2 interactions by inhibiting protein disulfide isomerase. It also inhibits SARS-CoV-2 fusion and entry by suppressing intracellular signaling, including via MAPK/ERK, PI3K/Akt/mTOR, and Wnt/β-catenin.

Further, nitazoxanide inhibits viral replication by inhibiting enzymatic activity of the 3-chymotrypsin-like protease (3cLpro) and (papain-like proteae (pLpro). Nitazoxanide also stimulates immune responses of host cells by activating Type-I interferon secretion and curbing proinflammatory responses. Due to these mechanisms, nitazoxanide offers potential for repurposing as therapy for COVID-19.[170]

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A phase 3 study to evaluate the efficacy and safety of nitazoxanide in patients with non-critical COVID-19 illness is recruiting participants (NCT04423861). The treatment group will receive a 600 mg tablet of nitazoxanide twice daily for 7 days and the control group will receive placebo twice daily for 7 days. The primary outcome measure will be the need for mechanical ventilation by evaluation of change in acute respiratory syndrome up to 14 days.

VirX/enovid (Nitric oxide nasal spray)

Nitric oxide nasal spray of SaNOtize is approved as a medical device in Thailand, Singapore, Hong Kong, Nepal, South Africa, Germany (branded as VirX), Israel, Indonesia and Bahrain (branded as Enovid). The drug releases nitric oxide.[171] Tandon et al.[172] have reported that NO has immediate virucidal action against SARS-CoV-2 and other respiratory pathogens. Mechanistically, NO can quickly alter structural integrity of viral proteins, including spike protein and viral protease, through reduced palmitoylation and reduced nitrosylation. In addition, NO is a systemic vasodilator endogenously produced in the endothelium. Inhaled NO induces bronchodilation, thereby improving oxygen delivery to the alveoli. Studies have indicated that NO as a therapeutic agent improves ventilation perfusion in patients with severe ARDS associated with COVID-19.[172,173]

A phase 3 study to evaluate the efficacy and safety of nitric oxide nasal spray (NONS) for preventing COVID-19 infection is ongoing (NCT05109611). The treatment group will receive a nasal spray with nitric oxide-releasing solution up to 3 times daily for 28 days. The control group will receive a nasal spray with isotonic saline up to 3 times daily for 28 days. The primary outcome measure is assessing whether subjects were infected with SARS-CoV-2 through a COVID-19 test within 28 days.

Hesperco (hesperidin)

Hesperidin is a bioflavonoid formulation with antioxidant properties that was developed by Valeo Pharma in Kirkland, Quebec, Canada.[174] The drug received a Natural Product License approval from Health Canada, authorizing its sale in Canada. Hesperidin is a potential medicine against COVID-19. Some studies have suggested that hesperidin may disrupt the interaction of ACE2 with the viral RBD. Hesperidin also has potent antioxidant properties that make it serve as an effective agent against superoxide and hydroxyl radicals. It also inhibits nitric oxide production. Therefore, Hesperidin might contribute to strategies for the prevention of COVID-19.[175]

A phase 2 study to evaluate the efficacy and safety of hesperidin in COVID-19 patients has been completed. Subjects were randomized to receive 1,000 mg hesperidin or matching placebo capsules once daily for 14 days. The primary outcome measure was the number of subjects with COVID-19 symptoms (fever, cough, shortness of breath, or anosmia) on days 3, 7, 10, and 14. Results are pending.

Lipitor (atorvastatin calcium)

Atorvostatin is an oral, selective, competitor inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase developed by Viatris in Canonsburg, PA. It received FDA approval as an adjunct to reduce low-density lipoprotein.[176] HMG-CoA reductase inhibitors (statins) and have anti-inflammatory and antithrombotic effects. Statins reduce inflammation by inhibiting the NF-kB pathway and reduce the risk of thrombotic events through its profibrinolytic activities. Therefore, statin treatment might alleviate inflammation and improve respiratory status in patients with COVID-19.[177]

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A phase 3 study to evaluate the effects of atorvastatin in Long COVID-19 neurological symptoms patients is recruiting participants (NCT04904536). The treatment group will receive six months of daily oral atorvastatin (40 mg), together with standard of care for 18 months. The control group will receive standard of care for 18 months. The primary outcome measure will be subject speed on the oral Symbol Digit Modalities Test after 18 months.

RA 101495 (Zilucoplan)

Zilucoplan is a macrocyclic peptide that binds complement factor C5 and allosterically inhibits cleavage of C5 into C5a and C5b. It was developed by Union Chemique Belgium (UCB)[178] for treating generalized myasthenia gravis and paroxysmal nocturnal hemoglobinurias.[179] Its mechanism of action is by suppressing inflammation and coagulation. The anaphylatoxin C5a attracts inflammatory cells into tissues. C5b can induce further drive the complement cascade reaction by promoting assembly of the membrane attack complex, which kills damaged cells and opsonized pathogens. C5b can also trigger the formation of microthrombi on endothelial cells.

De Leeuw et al.[180] have shown that increased complement system activation is related to a worse clinical outcomes in COVID-19 patients. As a result, complement blockade has emerged as a potential therapy for COVID-19. Zilucoplan may benefit COVID-19 patients with respiratory failure and signs of systemic inflammation.[180]

A phase 3 study to evaluate the efficacy and safety of three candidate COVID-19 drugs (Apremilast, Lanadelumab, Zilucoplan) in COVID-19 patients has been completed (NCT04590586). In that study, subjects were randomized between candidate drug or placebo with standard of care. The zilucoplan treatment group received standard of care and a subcutaneous injection of 32.4 mg zilucoplan once daily until discharge or up to 14 days. The zilucoplan control group received standard of care and a subcutaneous injection of zilucoplan matching placebo once daily until discharge or up to 14 days. The primary outcome measure was the time to discharge without re-hospitalization before day 29. This study was terminated without statistical analysis.

Vilobelimab

Vilobelimab is a chimeric monoclonal IgG4 antibody that binds human complement split product, factor C5a. The drug was developed by InflaRx in Jena Germany[181] for treating pyoderma gangrenosum, cutaneous squamous cell carcinoma, and critical COVID-19.[182] The antibody acts by suppressing inflammation and coagulation. The potent anaphylatoxin C5a recruits monocytes and neutrophils to infection sites and activates these cells, causing tissue damage by enzyme release and free radical formation. C5a also induces the release of tissue factor from endothelial cells and neutrophils, which can activate the coagulation system. Therefore, C5a inhibition can inhibit organ damage induced by neutrophils and improve microangiopathy and microthrombosis.[181]

A phase 2, 3 study of vilobelimab (IFX-1) to treat severe COVID-19 pneumonia has been completed (NCT04333420). Subjects received 800 mg vilobelimab or placebo via intravenous infusion for a maximum of six doses (days 1, 2, 4, 8, 15, and 22) with standard of care.[183] The primary outcome measure was mortality within 28 days. Results are pending.

Lyfaquin (centhaquine)

Centhaquine is an α-2B adrenergic receptor agonist developed by Pharmazz (Willobroodk, IL,

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USA). Additionally, centhaquine enhances tissue blood perfusion by stimulating central α-2A adrenergic receptors.[184] As a result, centhaquine improves tissue perfusion and oxygenation in patients with ARDS.[185]

The drug is approved in India and indicated as a resuscitative agent for treating patients with hypovolemic shock.[184] Currently, research is being conducted to repurpose centhaquine as a treatment for COVID-19 patients.

A phase 2 study to evaluate the safety and efficacy of centhaquine in COVID-19 patients with ARDS is on-going (NCT05241067). In that study, subjects are randomized to a treatment group and a control group. The treatment group will receive an intravenous infusion of 0.01 mg/kg centhaquine with standard of care. An additional dose of centhaquine is administered if oxygenation is required or SBP remains or falls below or becomes equal to, 90 mmHg; but not until 24 hours after the previous dose. The control group receives an intravenous infusion of normal saline with standard of care. The primary outcome measure is clinical improvement of moderate to severe ARDS in subjects within 28 days. Phase 3 trials have been approved by the FDA and are in the planning stage.

CONCLUSION

COVID-19 has had a devastating impact on human society globally. It has caused an estimated three million deaths and has overwhelmed health care systems in many countries. Thanks to rapid vaccine development and drug development, the COVID-19 pandemic appears to be abating. However, long COVID remains a puzzling and distressing problem. The NIH is currently preparing clinical trials aimed at investigating how best to treat this entity. Several studies are planned to investigate whether nirmatrelvir (Paxlovid) is effective in long COVID patients and how to address neuronal problems associated with long COVID. It is impossible to predict the next pandemic, with a coronavirus or other pathogen. However, the cumulative knowledge of treatment strategies gained in this pandemic, are essential as we prepare to face the next pandemic threat.

Treatment of COVID-19 has evolved rapidly since the start of the pandemic. Antiviral agents are currently available for patients with mild-to-moderate risk of disease progression. Immunomodulators are available for hospitalized patients. However. currently approved monoclonal antibodies may lose efficacy as new viral variants emerge, requiring the development of new antibodies. Immunomodulators are approved to prevent cytokine storms. Combining antiviral treatment with immunomodulation is crucial for treating patients with severe COVID-19. With antiviral and anti-inflammatory properties, JAK inhibitors showed a potential treatment for severe ARDS. Anti-coagulation is important for reducing the risk of thrombosis.

In summary, here we reviewed approved drugs and drugs in development for COVID-19 and discussed their mechanisms of action. This background is intended to help clinicians and researchers. It must be borne in mind that the virus evolves rapidly, and the field must and will do so as well.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1
Withdrawn drug list

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