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International Journal of Infectious Diseases 104 (2021) 441–451

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Pharmacological strategies to prevent SARS-CoV-2 infection and treat the early phases of COVID-19

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ARTICLE INFO

Article history:
Received 4 June 2020
Received in revised form 12 January 2021
Accepted 13 January 2021

Keywords:
SARS-CoV-2
COVID-19
Clinical trials
Prevention
Vaccines
Antivirals
Immunomodulators

ABSTRACT

A novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is the cause of coronavirus disease 2019 (COVID-19). It emerged in China in 2019 and has since spread worldwide. COVID-19 has a wide spectrum of clinical scenarios, ranging from totally asymptomatic to death. Prevention remains the best approach against SARS-CoV-2 infection and a number of strategies have been adopted, including social and medical interventions. Some vaccines have been proposed and several pharmacological approaches, mainly based on repurposing drugs, are currently under investigation and require validation. This review summarizes the ongoing clinical trials using pharmacological strategies, including vaccines, as prophylaxis to avoid SARS-CoV-2 infection or limit its transmission, and as early treatment of COVID-19 to prevent severe clinical outcomes.

Introduction

On 11 March 2020, the World Health Organization (WHO) announced a pandemic situation due to the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel positive-sense, single-stranded RNA betacoronavirus identified in humans in December 2019 in China that is the cause of coronavirus disease 2019 (COVID-19) (Wang et al., 2020a; Zhou et al., 2020c). In recent years, six other outbreaks caused by coronaviruses have been identified in humans; of these, severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) were the most pathogenic (Kuiken et al., 2003; Zhong et al., 2003; Zaki et al., 2012). SARS-CoV-2 uses the same cellular receptor as SARS-CoV-1, namely human angiotensin-converting enzyme 2 (hACE2) (Tai et al., 2020).

The severity of COVID-19 covers the full clinical spectrum from asymptomatic to death (https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/). The most common symptoms at the onset of illness are fever, cough, myalgia or fatigue. Headache, diarrhoea and dyspnoea are less common (Huang et al., 2020). Sepsis is the most common complication, followed by respiratory failure, acute respiratory distress syndrome, heart failure and septic shock (Zhou et al., 2020b).

Prevention of an infectious disease comprises primary, secondary and tertiary elements (van Seventer and Hochberg, 2017). Primary prevention aims to reduce the number of new cases by interrupting transmission of the microbiological agent to humans or increasing their resistance to infection. Secondary prevention involves the identification of new cases at the earliest stage, and intervention to halt the progression of an infection during its early, often asymptomatic phases. Finally, tertiary prevention is based on treatments that aim to prevent the worst outcomes of a disease in an individual (van Seventer and Hochberg, 2017). The efforts of international health authorities have focused on rapid diagnosis and patient isolation, as well as on the search for therapies able to tackle the most severe effects of the disease. By 7 January 2021, two vaccines–the BNT162b2-BioNTech/Pfizer vaccine and the mRNA-1273-Moderna vaccine–had been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), and administration of the first SARS-CoV-2 vaccines to the population commenced in December 2020, increasing the chance of prevention. Several other pharmacological strategies to prevent COVID-19 are currently under investigation, and most still need to be validated for clinical utility (Sanders et al., 2020). From a clinical point of view, most of the data available early in the pandemic were from retrospective studies, case reports and series (Sanders et al., 2020); a few preliminary results from randomized clinical trials are now accessible (Cao et al., 2020; Chen et al., 2020a; Hung et al., 2020; Wang et al., 2020b). No drugs have been

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https://doi.org/10.1016/j.ijid.2021.01.035

shown to have a clear relevant clinical benefit as a pharmacological strategy against COVID-19 in primary and secondary prevention. An exception is remdesivir, which is currently the only drug approved by FDA for the treatment of moderate-to-severe COVID-19. In the early phases of infection, anti-SARS-CoV-2 antibodies are most likely to have an effect. Remdesivir with or without dexamethasone is recommended for hospitalized patients who require supplementary oxygen (Information on COVID-19 Treatment, Prevention and Research, n.d.).

The aim of this review is to summarize and critically analyse the ongoing clinical trials for pharmacological primary prevention of COVID-19 or intervention in the early phase of infection (secondary prevention).

Methodological approach for the state-of-art review

All COVID-19 registered clinical trials from the WHO International Clinical Trials Registry Platform, updated on 4 December 2020, were analysed (https://www.who.int/ictrp/en/). Of 7108 available studies, those that were actively recruiting, of interventional or preventive type, and had a pharmacological strategy alone were included in this review. Studies examining patients with severe/critical COVID-19, and studies evaluating non-pharmacological substances such as medicinal herbs or gases (i.e. oxygen, ozone supplement) were excluded from this review. In total, 232 studies were included in this review. Two populations were considered: (i) SARS-CoV-2-negative or putative negative individuals, including healthcare workers or those working in other well-characterized high-risk environments, healthy volunteers, frail patients with comorbidities, and people already treated with drugs under investigation for COVID-19; and (ii) asymptomatic individuals with a positive result for SARS-CoV-2 or individuals with a positive result for SARS-CoV-2 experiencing mild-to-moderate symptoms. For these two categories, the aim of pharmacological interventions was considered as 'primary prevention' for the first population, and 'secondary prevention' for the other.

Clinical trials of pharmacological interventions for COVID-19 with ongoing recruitment

Pharmacological primary prevention

Ninety-eight of 232 (42%) clinical trials were selected which were considered to investigate pharmacological prevention. The drugs used in these ongoing trials were divided into four classes: vaccines, antiviral drugs, immune-based drugs and others (Table 1).

Vaccines

More than 100 vaccines have been proposed (Zhang et al., 2020). Several vaccines have started clinical development, and some have reached the III/IV phases. As of 2 January 2021, 23 vaccines are in phase I, 32 are in phase II, 18 are in phase III and six have been approved by at least one country: two mRNA-based vaccines (BNT162b2-BioNTech/Pfizer and mRNA-1273-Moderna), three non-replicating viral vector vaccines (Sputnik V-Gamaleya, AZD1222-Oxford/AstraZeneca and Covishield-Serum Institute of India) and one inactivated vaccine (BBIBP-CorV-Sinopharm), (https://covid19.trackvaccines.org/vaccines/). To date, only mRNA-based vaccines have been approved by FDA and EMA.

Nucleic-acid-based vaccines. DNA-based vaccines represent an innovative approach by direct injection of plasmid DNA molecules encoding antigens inducing a wide range of immune responses. INO-4800, developed by Inovio Pharmaceuticals, induces T-cell activation through the expression of SARS-CoV-2 spike (S) protein, and its safety and immunological profile were evaluated in 40 healthy volunteers in an open-label, phase I trial (NCT04336410) (Tebas et al., 2020) and in 45 healthy volunteers in a phase I trial (ChiCTR2000038152). Moreover, a randomized, placebo-controlled, double-blinded, phase II/III trial (NCT04642638) is still recruiting 6578 high-risk people in the USA.

mRNA-based vaccines act similarly to DNA-based vaccines, except that the nuclear translocation of the DNA construct and mRNA transcription are bypassed. They contain mRNAs encoding antigens translated at the host cellular machinery without genome integration. The approved BNT162b2 vaccine developed by BioNTech/Pfizer is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion-stabilized, membrane-anchored full-length S protein of SARS-CoV-2. The first registered trials, no longer recruiting, were phase I/II trials (NCT04588480 and NCT04380701) with 160 and 456 people enrolled, and a phase II (NCT04649021) trial in China with 960 people enrolled. The randomized, placebo-controlled, double-blinded, phase II/III trial (NCT04368728) is the most advanced registered trial testing the BNT162b2 vaccine, with 43,998 high-risk people enrolled (Mulligan et al., 2020; Polack et al., 2020; Walsh et al., 2020). Moreover, the BNM162b3 vaccine is under investigation in a non-randomized, open-label, phase I/II trial (NCT04537949) with 120 healthy people.

The approved mRNA-1273 vaccine, developed by Moderna, is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion-stabilized, full-length S protein of SARS-CoV-2. It was evaluated in a phase I, non-randomized, open-label trial of 120 healthy adults (NCT04283461) (Anderson et al., 2020; Jackson et al., 2020); in a phase II trial (NCT04405076) and a phase II/III trial (NCT04649151) in 600 adults and 3000 children (12–17 years old), respectively; and in the COVE phase III trial (NCT04470427) with total enrolment of 30,000 adults (Baden et al., 2020).

Another mRNA vaccine, the CVnCoV vaccine, was developed by CureVac. A randomized, double-blinded, phase II trial (NCT04515147) of 691 healthy people and an open-label, phase I trial (NCT04449276) of 284 healthy people are ongoing. Moreover, LNP-nCoVsaRNA developed by Imperial College London is under investigation in a randomized, open-label, phase I trial (ISRCTN17072692) of 320 healthy people.

Viral vector vaccines. Non-replicating viral vector vaccines consist of a viral vector (mainly adenoviral-based vectors) in which genes have been cloned using the recombinant DNA technique to produce the vaccine antigen(s) without the formation and dissemination of new viral particles.

The Gam-COVID-Vac (Sputnik V) vaccine is a human recombinant type 5 and 26 adenoviral-based vector, inactivated, that encodes the SARS-COV-2 S protein, developed by Gamaleya and approved in Russia and Belarus. Only the randomized, placebo-COntrolled, double-blinded, phase III trial (NCT04530396) in 40,000 healthy people in Russia is still ongoing. The other related phase I–III trials (NCT04437875, NCT04436471, NCT04587219, NCT04640233, NCT04564716, NCT04642339 and NCT04656613) have already concluded (Logunov et al., 2020).

The ChAdOx1 nCoV-19 vaccine, developed by University of Oxford/AstraZeneca and approved in the UK, and the GRAd-COV2 vaccine are vectors based on inactivated/attenuated adenovirus of chimpanzee and gorilla, respectively, encoding the SARS-COV-2 S protein. The ChAdOx1 nCoV-19 vaccine is being evaluated in a randomized, open-label, phase III trial for high-risk people (ISRCTN89951424) after the results obtained in the phase I/II trials (NCT04324606, NCT04568031, NCT0444674 and PACTR202005681895696) (Folegatti et al., 2020; Voysey et al., 2020).

The Ad5-nCoV vaccine is a human recombinant type 5 adenoviral-based vector encoding the SARS-CoV-2 S protein

Table 1
Recruiting clinical trials of pharmacological primary prevention for coronavirus disease 2019 (COVID-19) (updated 4 December 2020).

Drug class	Drug subclass	Trial drugs	Main sponsor/design	Phase	Population	Countries	Trial ID
Vaccines							
	mRNA vaccine	BNT162b1/ BNT162b2	BioNTech/Pfizer	II/III	High-risk	USA, Argentina, Brazil, Germany, South Africa, Turkey	NCT04368728
		BNT162b3	BioNTech/Pfizer	I/II	Healthy	Germany	NCT04537949
		mRNA.1273	Moderna	I	Healthy	USA	NCT04283461
				II/III	Healthy	USA	NCT04470427, NCT04405076, NCT04649151
		CVnCoV	CureVac	I/II	Healthy	Panama, Peru, Belgium, Germany	NCT04515147, NCT04449276
		LNP-nCoVsaRNA	Imperial College London	I	Healthy	UK	ISRCTN17072692
	DNA vaccine	INO-4800	Inovio Pharmaceuticals	I	Healthy	China	ChiCTR2000038152
				II/III	High-risk	USA	NCT04642638
	Non-replicating viral vector	Ad26.COV2.S	Janssen & Janssen	III	Healthy	USA and other countries	NCT04505722
		Ad5-nCoV	CanSino Biologics	III	High-risk	America, Pakistan	NCT04526990
				I/II	Healthy	China, Russian	NCT04552366, NCT04566770
		ChAdOx1 nCoV-19	Oxford/AstraZeneca	III	High-risk	Brazil	ISRCTN89951424
				I	Healthy	Kenya	PACTR202005681895696
		Gam-COVID-Vac	Gamaleya	III	Healthy	Russia	NCT04530396
		GRAd-COV2	ReiThera	I	Healthy	Italy	NCT04528641
		hAd5-S-Fusion+N-ETSD	ImmunityBio	I	Healthy	USA	NCT04591717
		MVA-SARS-2-S	Universitatsklinikum Hamburg	I	Healthy	Germany	NCT04569383
	Replicating viral vector	COH04S1	City of Hope Medical Center	I	Healthy	USA	NCT04639466
		TMV-083	Institut Pasteur	I	Healthy	Belgium, France	NCT04497298
		IIBR-100	Israel Institute for Biological Research	I/II	Healthy	Israel	NCT04608305
		V590	Merck Sharp & Dohme	I	Healthy	USA	NCT04569786
		V591	Merck Sharp & Dohme	I/II	Healthy	USA, Austria, Belgium	NCT04498247
	Antigen-presenting cells	COVID-19/aAPC	Shenzhen Geno-Immune Medical Institute	I	Healthy	China	NCT04299724
		bacTRL-Spike	Symvivo Corporation	I	Healthy	Australia, Canada, USA	NCT04334980
	Protein subunit	VA-MENGOC-BC	Finlay Vaccine Institute (IFV)	N/A	Healthy	Cuba	RPCEC00000314
		FINLAY-FR-1	Finlay Vaccine Institute (IFV)	I/II	Healthy	Cuba	RPCEC00000332
		NVX-CoV2373 (matrix-M1 adjuvanted)	Novavax	II	Healthy	South Africa	NCT04533399
		Sf9 cells	Jiangsu Province Centres for Disease Control and Prevention	II	Healthy	China	NCT04640402
		COVAX-19	Vaxine	I	Healthy	Australia	NCT04453852
		Sclamp (MF59 adjuvanted)	The University of Queensland	I	Healthy	Australia	NCT04495933
		MVC-COV1901	Medigen Vaccine Biologics Corp.	I	Healthy	Taiwan	NCT04487210
		CoVac-1 (or P-pVAC)	University Hospital Tuebingen	I	Healthy	Germany	NCT04546841
		RBD-Dimer (CHO cell)	Anhui Zhifei Longcom, Jiangsu Province Centres for Disease Control and Prevention	I	Healthy	China	NCT04636333
		SCB-2019	Clover Biopharmaceuticals	I	Healthy	Australia	NCT04405908
		UB-612	United Biomedical	I	Healthy	Taiwan	NCT04545749
	Virus-like particles	RBD SARS-CoV-2 HbsAg	Accelagen	I/II	Healthy	Australia	ACTRN12620000817943
	Inactivated	BBIBP-CorV (Vero cell)	China National Biotec	III	Healthy	Peru, Bahrain, Jordan, United Arab Emirates, Morocco, UAE	NCT04612972, NCT04510207, ChiCTR2000039000, ChiCTR2000034780
		BBV152 - Covaxin	Bharat Biotech International Limited	III	Healthy	India	NCT04641481
		Coronavac	PT Bio Farma, Butantan Institute, Sinovac Research and Development	I	Healthy	China	NCT04551547
				III	High-risk, Healthy	Brazil, Chile, China, Indonesia	NCT04456595, NCT04651790, NCT04617483, NCT04508075
		Inactivated SARS-CoV-2 vaccine	Chinese Academy of Medical Sciences	I/II	Healthy	China	NCT04470609, NCT04412538
		Flucelvax, fluvirin, fluzone		II	Healthy	USA	NCT04025580

Table 1 (*Continued*)

Drug class	Drug subclass	Trial drugs	Main sponsor/design	Phase	Population	Countries	Trial ID
			National Institute of Allergy and Infectious Diseases				
	Live-attenuated vector vaccine	BCG vaccine	Bandim Health Project and others	III/IV	Healthy, High-risk	India, Denmark, Netherlands, Netherlands, Australia, South Africa, Iran, Denmark, Cape Verde, Guinea-Bissau, Mozambique	NCT04475302, NCT04542330, NCT04537663, NCT04379336, NCT04327206, IRCT20200411047019N1, NCT04373291, NCT04641858
				N/A	Healthy	Netherlands	NL8547
		BCG-10 vaccine	Hanna Czajka	III	High-risk	Poland	NCT04648800
		MMR vaccine	Kasr El Aini Hospital	III	Healthy, High-risk	Egypt, USA, Canada, Ghana, Ireland, Netherlands, South Africa, Uganda, UK, Zambia, Zimbabwe, Australia	NCT04357028, NCT04333732
			Washington University School of Medicine				
		OPV	NeuroActiva	III	High-risk	USA, New Zealand, Guinea-Bissau	NCT04540185,
			Bandim Health Project	IV	Healthy		NCT04445428
		CIGB 2020	Center for Genetic Engineering and Biotechnology	I/II	High-risk	Cuba	RPCEC00000306
Antiviral drugs							
	Entry inhibitors	Chloroquine/ hydroxychloroquine	Interventional	I/II	High-risk, Healthy	USA, Iran, France, Pakistan, Italy, UK, Denmark, USA	NCT04349371, NCT04341207, IRCT20200405046958N1, NCT04359537, NCT04363827, NCT04478019, NCT04364802, NCT04632706, NCT04576312, NCT04480333
				III	High-risk	USA, Canada, Mexico, Iran	NCT04318015, NCT04341441, ISRCTN14326006, IRCT20130917014693N10, IRCT20130306012728N8, NCT04318015, NCT04352933, NCT04363450
				N/A	High-risk	Iran, Indonesia, Italy, Pakistan, Thailand, UK	IRCT20120826010664N6, NCT04303507
		Iodine-based	Interventional	I/II	High-risk	USA	NCT04478019, NCT04364802
		Niclosamide	Interventional	I	Healthy	Denmark	NCT04576312
	Protease inhibitors	Ivermectin		I	Healthy	UK	NCT04632706
	Polymerase inhibitors	Remdesivir	Interventional	I	Healthy	USA	NCT04480333
Immune-based drugs							
	Anti-SARS-CoV-2 mAb	SCTA01	Interventional	I	Healthy	China	NCT04483375
		Anti-SARS-CoV-2 IgY	Interventional	I	Healthy	Australia	NCT04567810
		BGB DXP593	Interventional	I	Healthy	Australia	NCT04532294
	Plasma-derived Ig	SAB-185	Interventional	I	Healthy	USA	NCT04468958
	Immunomodulators	Thymosin alpha 1/ interferons	Interventional	III	High-risk	China	NCT04320238
				N/A	High-risk	China	ChiCTR2000031023
		AK119 (anti-CD73 mAb)	Interventional	I	Healthy	New Zealand	NCT04516564
		PUL-042 (anti-TLR peptide)	Interventional	II	High-risk	USA	NCT04313023
		Acalabrutinib (BTKi)	Interventional	I	Healthy	Germany	NCT04564040
		Nitazoxanide	Interventional	III	High-risk	USA	NCT04359680
		HB-adMSCs	Interventional	II	High-risk	USA	NCT04348435
Other drugs							
		NA-831	Interventional	I	Healthy	USA	NCT04480333
		Melatonin	Interventional	II/III	High-risk	Spain	NCT04353128
		Nicotine	Interventional	III	High-risk	France	NCT04583410
		Vitamin D	Interventional	III	Healthy	Iran	IRCT20200401046909N2
		Vitamin super B-complex	Interventional	III	High-risk	USA	NCT04359680

Healthy, people without COVID-19 or any other disease; high risk, healthcare workers, frail patients, and people already treated with drugs under investigation for COVID-19 (i.e. antihypertensive drugs); BCG, bacille Calmette-Guérin; TLR, Toll-like receptor; HB-adMSCs, allogeneic adipose-derived mesenchymal stem cells; Ig, immunoglobulin; N/A, not available.

that has been investigated in two randomized, placebo-controlled, double-blinded, phase II and III trials for healthy (NCT04566770) and high-risk (NCT04526990) people.The hAd5-S-Fusion + N-ETSD vaccine is characterized by the expression of both SARS-CoV-2 S and nucleocapsid proteins though a human recombinant type 5 adenoviral-based vector, and is under investigation in a phase I trial (NCT04591717).

The Ad26-COV2.S vaccine is a human recombinant type 26 adenoviral-based vector, inactivated, encoding the SARS-COV-2 S protein that has been evaluated in healthy people in a randomized, placebo-COntrolled, double-blinded, phase III trial (NCT04505722).

Finally, a non-randomized, open-label, phase I trial (NCT04569383) has evaluated the effects of MVA-SARS-2-S vaccine, an inactivated Vaccinia Ankara-based vector, in healthy people.

Replicating viral vector vaccines are characterized by a viral vector, often attenuated to reduce their pathogenicity, modified to encode viral antigen(s) using recombinant DNA techniques, but still capable of replicating. The COHO4S1 vaccine is a synthetic Vaccinia Ankara virus-based vector integrated with antigenic SARS-CoV-2 DNA evaluated in a randomized, placebo-controlled, double-blinded, phase I trial (NCT04639466) in healthy people. Two other replicating viral vectors are used in trials that are still recruiting: an attenuated measles-based vector vaccine encoding a SARS-CoV-2 modified glycoprotein (TMV-083 vaccine) or the SARS-CoV-2 S protein (V591 vaccine) evaluated in phase I (NCT04497298) and phase I/II (NCT04498247) trials; and recombinant vesicular stomatitis viral vectors encoding the SARS-CoV-2 S protein (V590 vaccine and IIBR-100 vaccine) that were administered to healthy people in randomized, placebo-controlled, double-blinded, phase I (NCT04569786) and phase I/II trials (NCT04608305), respectively.

Cell-based vaccines. Antigen-presenting cell (APC) vaccines use immortalized cells that are transduced with lentiviruses to mimic endogenous APCs. The COVID-19/aAPC vaccine uses artificial APCs modified with an inactivated lentiviral vector (NHP/TYF) expressing synthetic minigene based on domains of selected viral proteins that could activate T cells against SARS-CoV-2. A phase I, open-label trial is investigating its safety and immunoreactivity on 100 healthy and COVID-19-positive volunteers (NCT04299724).

The bacTRL-Spike vaccine, based on the use of epithelial colon cells transfected with *Bifidobacterium longum* modified with a DNA plasmid with SARS-CoV-2 S protein DNA and injected into healthy people, is being tested in an open label, phase I trial (NCT04334980).

Protein-based vaccines. Protein subunit vaccines consist of a protein purified from the virus or a recombinant protein, generally requiring the addition of an adjuvant to induce a strong immune response. The two recombinant protein vaccines in the latest stages of development are the NVX-COV2373 and Sf9 cell vaccines. Both vaccines are currently under evaluation in healthy volunteers in phase II trials (NCT04533399 and NCT04640402). The NVX-COV2373 vaccine is administered with matrix-M1 as adjuvant. The FINLAY-FR-1 vaccine is based on a recombinant protein and is being tested in healthy people in a randomized, double-blinded, phase I/II trial (RPCEC00000332). Other protein vaccines, mainly differing in terms of the presence and type of adjuvant used, are in development in phase I studies in healthy volunteers, including the COVAX-19 (NCT04453852), Sclamp (NCT04495933), MVC-COV1901 (NCT04487210), CoVac-1 (NCT04546841), RBD-Dimer (NCT04636333), SCB-2019 (NCT04405908) and UB-612 (NCT04545749) vaccines.

Virus-like particle vaccines are composed of the structural viral protein necessary to form virus particles without viral genome and non-structural proteins. To date, the RBD SARS-CoV-2 HBsAg VLP vaccine is the only virus-like particle vaccine to have been developed, with a recruiting, randomized, placebo-controlled, open-label, phase I/II clinical trial for 280 healthy volunteers (ACTRN12620000817943).

Virus-based vaccines. Inactivated vaccines are traditional vaccines where the virus is no longer infectious. The BBIBP-CorV vaccine, developed by Sinopharm in Vero cells, has been approved in the United Arab Emirates, China and Bahrain. Approval is based on the results of phase I/II (ChiCTR2000032459) and phase III trials (NCT04560881, NCT04510207, NCT04612972 and ChiCTR2000034780) with a total of 69,640 subjects. The only trials that are still recruiting are NCT04510207 (45,000 subjects), NCT04612972 (6000 subjects), ChiCTR2000034780 (15,000 subjects) and ChiCTR2000039000 (600 healthy people in Morocco).

The BBV152–Covaxin vaccine is being investigated in 25,800 healthy people in a randomized, placebo-controlled, double-blinded, phase III trial (NCT04641481) in India.

The Coronavac vaccine is being tested in several phase III trials–NCT04456595 in 8870 high-risk people in Brazil (Palacios et al., 2020), NCT04651790 in 2300 high-risk people in Chile, NCT04508075 in 1620 healthy people in Indonesia, and NCT04617483 in 1040 healthy people in China–and in a phase I/II trial (NCT04551547) in 552 healthy people in China.

The Inactivated SARS-CoV-2 vaccine is under investigation in 471 and 942 healthy people in a phase I trial (NCT04470609) and a phase I/II trial (NCT04412538), respectively (Che et al., 2020).

Live-attenuated vaccines are generated by passaging in cell culture until they lose their pathogenic properties and become capable of causing only mild infection upon administration. Bacille Calmette-Guérin (BCG) is a live-attenuated vaccine against tuberculosis, and its protective non-specific effects against respiratory tract infection have been evaluated in several countries, mainly in phase III/IV studies such as the BRACE trial with 4170 healthcare workers (NCT04327206). All the other BCG vaccine recruiting studies are reported in Table 1. In addition, the measles-mumps-rubella vaccine is under investigation for its effects against SARS-CoV-2 infection in phase III studies in healthy people (NCT04357028) and high-risk people (NCT04333732). Moreover, the oral polio vaccine with or without NA-831 is being tested in a phase IV trial for healthy volunteers (NCT04445428) and a phase III trial for high-risk people (NCT04540185).

The CIGB 2020 vaccine was proposed in combination with conventional treatment in a randomized, phase I/II trial with 80 subjects (RPCEC00000306).

Antiviral drugs

Chloroquine has been found to exert antiviral effects during pre- and post-coronavirus infections by interfering with glycosylation of hACE2, and blocking the fusion of these viruses to the host cell (Zhou et al., 2020a). Hydroxychloroquine is more soluble, and has the same mechanism of action but a better safety profile than chloroquine. Hydroxychloroquine/chloroquine clinical trials against COVID-19 are reported in Table 1. Several trials are investigating chemoprophylaxis in healthcare workers [NCT04352933, NCT04363827 (Group 1), NCT04363450, NCT04318015, NCT04359537 and NCT04303507]. The results from a phase III trial (NCT04308668) in high-risk people showed that hydroxychloroquine did not prevent COVID-19 or SARS-CoV-2 infection when used as prophylaxis or early treatment (Boulware et al., 2020; Lofgren et al., 2020; Skipper et al., 2020). The NCT04341207 phase II trial is evaluating the effects of hydroxychloroquine and azithromycin in adults with any type of locally advanced and metastatic cancer.

A few phase I trials are investigating other antivirals/antimicrobials in healthy volunteers, including a nanoparticle formulation of remdesivir alone or in combination with neurosivir (NCT04480333), niclosamide inhalation (NCT04576312) and ivermectin (NCT04632706). Moreover naso-oropharyngeal antiseptics, such as povidone-iodine, are being tested in phase I and II trials as prophylaxis in healthcare workers, hospital patients and

members of the community (NCT04478019 and NCT04364802). Some interesting preliminary observations derived from ivermectin trials showed a reduction in symptom development within 14 days in high-risk contacts (NCT04422561).

Immune-based drugs

Anti-SARS-CoV-2 specific antibodies are being investigated in several trials, mainly conducted in healthy subjects. These include neutralizing antibody BGB-DXP593 (NCT04532294); anti-SARS-CoV-2 chicken egg antibody IgY (NCT04567810); SCTA01, a recombinant humanized anti-SARS-CoV-2 monoclonal antibody (NCT04483375); and SAB-185, a plasma-derived human immunoglobulin G designed to bind specifically to SARS-CoV-2 (NCT04468958).

Immunomodulators such as recombinant human interferon alpha-1b or thymosin alpha-1 are being evaluated to avoid new-onset COVID-19 in a phase III, non-randomized study with 2944 asymptomatic Chinese healthcare workers (NCT04320238), and in frail patients affected by metastatic cancer (ChiCTR2000031023). Among the immunomodulators, the anti-Toll-like receptor antibody PUL-042 is under investigation in 200 high-risk subjects (NCT04313023). Acalabrutinib (a BTK inhibitor) and AK119 (an anti-CD73 antibody) are being tested in healthy subjects (NCT04564040 and NCT04516564, respectively). Finally, mesenchymal stem cells (MSCs) have been implemented as another strategy to prevent COVID-19. A randomized, phase II study is considering the efficacy and safety of autologous adipose-derived MSC therapy in high-risk workers (NCT04348435).

Other drugs

A number of other compounds are under investigation in phase II and III trials as prophylaxis, such as melatonin among healthcare workers (NCT04353128), nicotine in caregivers (NCT04583410), nitazoxanide in healthcare workers (NCT04359680), and dietary supplementation with vitamin D (IRCT20200401046909N2).

Pharmacological secondary prevention in post-exposure and/or exclusively early/non-severe COVID-19

One hundred and thirty-five of 232 (58%) trials were considered as pharmacological interventions in secondary prevention. Drugs in ongoing trials were divided into three classes: antiviral drugs, immune-based drugs and other drugs (Table 2).

Antiviral drugs

Entry inhibitors. Several drugs are currently being investigated as a post-infection strategy to limit the spread of virus in the human body. Approximately one-quarter of studies used chloroquine and hydroxychloroquine (ChiCTR2000029899, ChiCTR2000031454, NCT04322396, NCT04329923, NCT04332094, NCT04344457, NCT04351620, NCT04350684, NCT04363827, NCT04351620, NCT04355052, NCT04329923, NCT04370782, NCT04410562, NCT04344457, NCT04349592, NCT04573153, NCT04466540, NCT04411433, NCT04387760 and NCT04403100). Studies are equally distributed in phase I/II and phase III/IV trials, with chloroquine/hydroxychloroquine mainly used as monotherapy. In the ChiCTR2000031454 trial, chloroquine has been combined with rabeprazole, a substituted benzimidazole proton-pump inhibitor, for prevention and treatment of digestive tract lesions caused by SARS-COV-2 infection. The results of a multi-centre, randomized trial involving 667 hospitalized patients with mild-to-moderate COVID-19 showed that the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical outcome compared with standard care (Cavalcanti et al., 2020).

Pyronaridine-artesunate, another antimalarial drug, was investigated in a randomized, phase II trial (NCT04475107) of 76 patients with mild-to-moderate COVID-19.

DAS181, an antiviral recombinant fusion protein that adheres to the epithelium and cleaves sialic acid on host cell-surface receptors, preventing the binding of influenza and other viruses, is also being considered in a phase III trial (NCT03808922).

Niclosamide, an anthelmintic drug, is under investigation in a novel suspension formulation in a phase III trial (NCT04558021) of 200 patients with mild-to-moderate COVID-19 with a hypothesized role of inhibiting the entry of SARS-CoV-2 by altering endosomal pH and inhibiting autophagy (Pindiprolu and Pindiprolu, 2020).

Camostat, an inhibitor of serine proteases including TMPRSS2 that are highly expressed in respiratory epithelium cells, can prevent SARS-CoV infection by inhibiting the fusion of the S protein to the host cell membrane. Four phase II trials are testing the efficacy of Camostat to reduce the viral load and disease burden in a total of 924 patients with early COVID-19 (NCT04625114, NCT04353284, NCT04583592 and NCT04530617). Moreover, bromhexine hydrochloride and nafamostat, two other serine protease inhibitors, are being evaluated in phase III trials for patients with mild-to-moderate COVID-19 (IRCT20200317046797N4 and NCT04390594). Apilimod dimesylate is being investigated in a phase II trial (NCT04446377) of 142 confirmed SARS-CoV-2-positive outpatients, and iodine complex is being investigated in a phase II trial (NCT04473261) of 30 patients with mild-to-moderate COVID-19.

Protease inhibitors. A number of ongoing trials are investigating protease inhibitors in patients with COVID-19, including asymptomatic patients and those with mild disease. For most of these studies, the primary endpoint is the incidence of composite adverse outcomes, such as deterioration of oxygen saturation, arterial partial pressure of oxygen/fraction of inspired oxygen, and respiratory rate within 14 days of admission. In this context, randomized studies are evaluating the efficacy and safety of lopinavir and ritonavir alone (ChiCTR2000029539 and NCT04372628) or in association with favipiravir (NCT04499677). Lopinavir and ritonavir prevent viral gene replication by binding to enzymes responsible for proteolytic cleavage of the viral polyproteins, and this pharmacological combination is available for treatment of human immunodeficiency virus infection. ASC09/ritonavir is being investigated for its efficacy in patients with COVID-19 in an ongoing multi-centre randomized trial to compare the safety and efficacy of both ASC09/ritonavir and lopinavir/ritonavir (ChiCTR2000029603). Danoprevir, a hepatitis C virus NS3/4A protease inhibitor, in combination with ritonavir is being evaluated in four different randomized trials (ChiCTR2000030259, ChiCTR2000030472 and ChiCTR2000031734). Lopinavir/ritonavir, telmisartan (antihypertensive) and atorvastatin (lowers blood cholesterol) are being investigated in patients with mild-to-moderate disease (NCT04466241). Moreover, a controlled trial is investigating the combination of traditional Chinese medicine with lopinavir/ritonavir (ChiCTR2000029400), with remission rate as the primary endpoint. Finally, three trials (NCT04403100, NCT04350684 and ChiCTR2000031454) are considering an arm with lopinavir/ritonavir alone or in combination with hydroxychloroquine in a phase III trial of patients with mild-to-moderate COVID-19, an arm with lopinavir/ritonavir in a phase IV trial of patients with mild disease, and an arm with lopinavir in combination with rabeprazole. Ivermectin was also considered as an antiviral against SARS-CoV-2 due to the results obtained in in-vitro studies (Caly et al., 2020). Several trials, mainly phase II, evaluating ivermectin are ongoing, as reported in Table 1 (NCT04392713, NCT04399746, NCT04425707, NCT04429711, NCT04472585, NCT04447235, NCT04529525 and NCT04438850).

Table 2
Recruiting clinical trials of pharmacological secondary prevention in post-exposure and/or exclusively early/non-severe cases of coronavirus disease 2019 (COVID-19) (updated 4 December 2020).

Drug class	Drug subclass	Trial drugs	Trial design	Phase	Population	Countries	Trial ID
Antiviral drugs							
	Entry inhibitors	Chloroquine/ hydroxychloroquine	Interventional	I/II	Asymptomatic/ mild	USA, Spain, Denmark, Italy, Bahrain	NCT04322396, NCT04332094, NCT04329923, NCT04344457, NCT04351620, NCT04363827, NCT04351620, NCT04329923, NCT04344457, NCT04387760
				II/III	Mild/moderate	Turkey	NCT04573153
				III/IV	Asymptomatic/ mild/ moderate	China, Israel, USA, Spain, Brazil, Iran, Turkey	ChiCTR2000029899, NCT04355052, NCT04370782, NCT04410562, NCT04466540, NCT04350684, NCT04411433, NCT04403100
				N/A	Asymptomatic/ mild	Qatar, China	NCT04349592, ChiCTR2000031454
		Pyronaridine-artesunate	Interventional	II	Mild/moderate	Korea	NCT04475107
		Niclosamide	Interventional	III	Mild/moderate	Turkey	NCT04558021
		Camostat (anti-TMPRSS2)	Interventional	II	Asymptomatic/ mild/ moderate	Belgium, USA, Mexico	NCT04625114, NCT04353284, NCT04583592, NCT04530617
		Bromhexine hydrochloride	Interventional	III	Mild/moderate	Iran	IRCT20200317046797N4
		Nafamostat	Interventional	III	Mild/moderate	Senegal	NCT04390594
		Apilimod dimesylate	Interventional	II	Mild	USA	NCT04446377
		Umifenovir	Interventional	IV	Mild	Iran	NCT04350684
				N/A	Mild	China	ChiCTR2000030922
		DAS118	Interventional	III	Mild/moderate	USA, Australia, China, Denmark, France, Korea, Republic of Taiwan	NCT03808922
	Protease inhibitors	Lopinavir+ritonavir	Interventional	II	Mild	Korea	NCT04307693, NCT04499677
				II/III	Mild/moderate	Ivory Coast	NCT04466241
				III/IV	Mild/moderate	Iran, Brazil	NCT04350684, NCT04403100
				N/A	Asymptomatic/ mild	China	ChiCTR2000029603, ChiCTR2000029400, ChiCTR2000029539
		ASC09+ritonavir	Interventional	N/A	Mild	China	ChiCTR2000029603
		Danoprevir +ritonavir	Interventional	IV	Mild	China	NCT04345276
				N/A	Mild	China	ChiCTR2000030259, ChiCTR2000030472, ChiCTR2000031734
		Lopinavir +rabeprazole	Interventional	N/A	Mild	China	ChiCTR2000031454
		Ivermectin	Interventional	I/II	Asymptomatic/ mild/ moderate	Pakistan, Brazil, Italy, Spain, USA	NCT04472585, NCT04447235, NCT04438850, NCT04372628
				II/III	Mild	Argentina	NCT04529525
				N/A	Asymptomatic/ mild/ moderate	Pakistan, Mexico, Egypt, Israel	NCT04392713, NCT04399746, NCT04425707, NCT04429711
	Polymerase inhibitors	Favipiravir	Interventional	II	Asymptomatic/ mild/ moderate	Bahrain, USA, UK	NCT04387760, NCT04346628, NCT04499677
				II/III	Mild/moderate	Bangladesh, Saudi Arabia	NCT04402203, NCT04464408,
				III	Mild/moderate	Turkey, Indonesia	NCT04411433, NCT04613271
		Remdesivir	Interventional	I/II	Mild	USA	NCT04539262
		Molnupiravir	Interventional	II/III	Mild/moderate	USA, Brazil, Chile, Colombia, France, Israel, Poland, Russian Federation, Spain, Ukraine, UK	NCT04575584, NCT04575597
		Triazavir	Interventional	II/III	Mild/moderate	South Africa	NCT04581915
		Ribavirin in association	Interventional	N/A	Mild	China	ChiCTR2000030922
Immune-based drugs							
	Anti-SARS-CoV-2 mAb	Bamlanivimab, etesevimab	Interventional	II	Mild/moderate	USA, Puerto Rico	NCT04634409, NCT04427501
	Plasma-derived Ig	Convalescent plasma	Interventional	I/II	Asymptomatic/ mild/ moderate	USA, Singapore, France	NCT04456413, NCT04457726, NCT04390503, NCT04345991, NCT04438057
				II/III	Mild/moderate	Philippines, USA	NCT04567173, NCT04355767
				N/A	Mild/moderate	North Macedonia	NCT04397523
		GC5131	Interventional	II	Mild/moderate	Korea, Republic of	NCT04555148
		Kamada	Interventional	I/II	Mild/moderate	Israel	NCT04550325
		SAB-185	Interventional	I	Mild	USA	NCT04469179

Table 2 (*Continued*)

Drug class	Drug subclass	Trial drugs	Trial design	Phase	Population	Countries	Trial ID
	Immunomodulators/ anti-inflammatory drugs	PUL-042 (anti-TLRs)	Interventional	II	Mild	USA	NCT04312997
		Interferons	Interventional	II	Mild/moderate	Israel	NCT04534673
				IV	Mild	Iran	NCT04350684
				N/A	Mild	China	ChiCTR2000030922
		JAKi (ruxolitinib, tofacitinib)	Interventional	I/II	Mild/moderate	Spain, UK, Brazil	NCT04348695, NCT04581954, NCT04469114
		TKi (fostamatinib, TL-896)	Interventional	I/II	Mild/moderate	UK, USA	NCT04581954, NCT04419623
		CPI-006 (anti-CD73 mAb)	Interventional	I	Mild/moderate	USA	NCT04464395
		Tocilizumab (anti-IL6R mAb)	Interventional	II	Mild	Spain	NCT04332094, NCT04435717
		Bempegaldesleukin (anti-IL2R)	Interventional	I	Mild	USA	NCT04646044
		NT-I7 (anti-IL7R)	Interventional	I	Mild	USA	NCT04501796
		MAPKi (losmapimod)	Interventional	III	Mild/moderate	USA, Brazil, Mexico	NCT04511819
		Cenicriviroc (anti-CCR2/5)	Interventional	II	Mild/moderate	Germany	NCT04500418
		Maraviroc (anti-CCR5)	Interventional	II	Mild/moderate	Spain	NCT04441385
		Dexamethasone	Interventional	IV	Mild/moderate	Egypt	NCT04528329, NCT04530409
		Ciclosonide	Interventional	II	Mild/moderate	Sweden, Korea	NCT04381364, NCT04330586
				II/III	Mild/moderate	Canada	NCT04435795
		Antroquinonol	Interventional	II	Mild/moderate	USA	NCT04523181
		Dornase alfa	Interventional	II	Mild	UK	NCT04359654
		Icosapent ethyl	Interventional	II	Mild	Canada	NCT04412018
		Leflunomide	Interventional	I	Mild	USA	NCT04361214
		Bucillamine	Interventional	III	Mild	USA	NCT04504734
		Ensifentrine (anti-PDE3/4)	Interventional	II	Mild/moderate	USA	NCT04527471
		Colchicine	Interventional	III	Asymptomatic/ mild	USA, Brazil, Canada, South Africa, Spain	NCT04322682, NCT04416334
		ABX464		II/III	Mild	Belgium, Brazil, France, Germany, Italy, Mexico, Spain, UK	NCT04393038
		Nitazoxanide		II/III	Mild/moderate	South Africa, Argentina, USA	NCT04523090, NCT04463264, NCT04486313
		MSCs	Interventional	I/II	Mild/moderate	China, USA	NCT04339660, NCT04445220
				II/III	Mild/moderate	Iran	NCT04366063
		BACTEK-R (MV130)		III	Mild	Dominican Republic	NCT04363814
		Estradiol patch		II	Mild/moderate	USA	NCT04359329
		IMU-838		II/III	Mild/moderate	Bulgaria, Germany	NCT04379271
		Methotrexate-LDE		I/II	Mild/moderate	Brazil	NCT04610567
		Prazosil		II	Mild	USA	NCT04365257
Other drugs							
		Anticoagulants/ anti-aggregants	Interventional	II	Mild/moderate	Spain, USA	NCT04420299, NCT04504032
				II/III	Mild/moderate	Ivory Coast	NCT04466241
				III	Mild/moderate	USA, Switzerland, Spain	NCT04410328, NCT04400799, NCT04604327
		Tranexamic acid	Interventional	II	Mild	USA	NCT04338074
		ACEi and ARBs	Interventional	II/III	Mild/moderate	USA, Belgium, Brazil, France, Puerto Rico	NCT04360551, NCT04472728, NCT04493359
		Nitric oxide	Interventional	II/III	Mild/moderate	UK, USA	NCT04460183, NCT04305457
		Dapagliflozin	Interventional	III	Mild/moderate	USA, Brazil	NCT04350593
		Azithromycin	Interventional	III	Mild/moderate	UK, Indonesia	NCT04381962, NCT04613271
		Vitamins	Interventional	II	Mild/moderate	India, Israel, USA, Iran, Mexico	NCT04382040, NCT04495816, NCT04551911, NCT04400890, IRCT20081019001369N3, NCT04530617
				III/IV	Mild/moderate	USA, Argentina	NCT04486313, NCT04411446
				N/A	Asymptomatic	USA	NCT04342728
		Minocycline	Interventional	II	Mild	Iran	IRCT20081019001369N4
		Xylitol nasal spray		III	Mild/moderate	USA	NCT04610801

MSCs, mesenchymal stem cells; TLRs, Toll-like receptors; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; Ig, immunoglobulin; N/A, not available.

Regarding ivermectin-based combinations with doxycycline, ivermectin showed early clinical improvement with only 14 of 183 (7.7%) patients with mild-to-moderate COVID-19 still SARS-CoV-2-positive after 14 days (NCT04523831). Ivermectin alone or in combination with aspirin/dexamethasone/enoxaparin, based on the severity of disease, resulted in improvement or non-worsening of patient condition at 7 days in all 147 patients with mild-to-moderate disease (NCT04425863).

Polymerase inhibitors. Remdesivir, a nucleotide prodrug of adenosine analogue that binds to the viral RNA-dependent RNA polymerase inhibiting viral replication through premature termination of RNA transcription, was developed for the treatment of Ebola, MERS and SARS in animal models (Sheahan et al., 2017). Although some results are available for remdesivir in patients with moderate-to-severe COVID-19 (Goldman et al., 2020; Spinner et al., 2020), a phase I/II study is still recruiting patients to evaluate its efficacy in 282 patients with mild disease at an early stage (NCT04539262). Other nucleoside analogues are being evaluated in phase II/III trials (NCT04411433, NCT04387760, NCT04402203, NCT04464408, NCT04346628, NCT04499677, NCT04613271, NCT04575584 and NCT04575597) in asymptomatic patients and those with mild-to-moderate disease. They include favipiravir, a purine-base analogue prodrug (Joshi et al., 2021), and molnupiravir, a prodrug of nucleoside derivative N4-hydroxycytidine, that introduce copying errors during SARS-CoV-2 RNA replication (Cox et al., 2021). Ribavirin plus long-acting interferon α-2a and triazavirin, two guanosine analogues, are currently being studied in patients with mild COVID-19 (ChiCTR2000030922) and hospitalized patients with mild-to-moderate disease (NCT04581915).

Immuno-based

Anti-SARS-CoV-2 monoclonal antibodies, such as bamlanivimab (LY3819253) and etesevimab (LY3832479), are currently being evaluated in phase II trials in patients with mild-to-moderate COVID-19 or outpatients at high risk for disease progression (NCT04634409 and NCT04427501). An interim analysis of the BLAZE-1 study (NCT04427501) indicates that one of three doses of neutralizing antibody LY3819253 appeared to accelerate the natural decline in viral load (Chen et al., 2020b). Moreover, hyperimmunoglobulins derived from convalescent plasma are under investigation, mainly in randomized, phase II trials in patients with mild disease (NCT04397523, NCT04456413, NCT04457726 (Group 2), NCT04390503, NCT04345991, NCT04438057, NCT04567173 and NCT04355767). Immunoglobulins manufactured from convalescent plasma of patients who have recovered from COVID-19, SAB-185, are being considered in a phase I study (NCT04469179). Dose response, efficacy and safety of other hyperimmunoglobulins, namely GC5131 and Kamada, are being evaluated in patients with mild-to-moderate COVID-19 in a randomized, phase IIa study (NCT04555148) and a phase I/II study (NCT04550325).

Immunomodulators. In the very first phases of infection, the innate immune response has a fundamental role in recognizing and promptly counteracting the viral invasion and spread. Inflammatory cytokines act locally, recruiting several immune cells such as monocytes, macrophages and natural killer cells that can quickly recognize and eliminate the infected cells, thus delaying viral outbreak into the tissues and blood. PUL-042, a combination of two synthetic molecules targeting the Toll-like receptors, is currently being evaluated in a phase II trial to reduce the severity of disease in patients with mild COVID-19 (NCT04312997). Interferons have antiviral and immunomodulatory effects (Mesev et al., 2019) and are being tested (ChiCTR2000030922, NCT04350684 and NCT04534673). Interferons binding to their receptors activate a number of pathways, including the JAK/STAT pathway. Trials evaluating JAK inhibitors such as ruxolitinib, alone or in combination with simvastatin (NCT04581954 and NCT04348695) or tofacitinib (NCT04469114), are currently underway. Moreover, the tyrosine kinase inhibitors fostamatinib and TL-896 are being evaluated in patients with mild-to-moderate COVID-19 (NCT04581954 and NCT04419623).

Interleukin 6 (IL-6) is a pleiotropic, pro-inflammatory cytokine (Tanaka et al., 2014). Tocilizumab, targeting the IL-6 receptor, is approved for use in patients with rheumatological disorders and cytokine release syndromes induced by chimeric antigen T-cell therapy, and has been proposed for the early treatment of patients with mild-to-moderate COVID-19 (NCT04332094 and NCT04435717). CPI-006, a humanized monoclonal antibody anti-CD73, was evaluated as immunotherapy for hospitalized patients with mild COVID-19 (NCT04464395).

Hempegaldesleukin, a PEGylated IL-2, was evaluated in patients with mild COVID-19 (NCT04646044). NT-I7, a long-acting immunoglobulin composed of recombinant endogenous human IL-7 and fused to a hybrid Fc region of a human antibody, with haematopoietic and immunopotentiating activities, is currently being evaluated in a phase I trial (NCT04501796). The interleukin signal can be transducted via several signalling pathways, including the MAPK/ERK pathway. For this reason, losmapimod, a p38 MAPK inhibitor, was also investigated in a randomized, phase III trial of patients with mild-to moderate COVID-19 (NCT04511819). Two chemokine receptor antagonists, Cenicriviroc (a CCR2 and CCR5 inhibitor) and Maraviroc (UK-427857; a CCR5 inhibitor), are in phase II trials of patients with mild-to-moderate COVID-19 (NCT04500418 and NCT04441385).

Anti-inflammatory drugs are currently being investigated in several trials. Dexamethasone, a corticosteroid, is strongly recommended in hospitalized patients who require supplementary oxygen, especially those requiring mechanical ventilation. Two phase IV trials are evaluating the early effects of dexamethasone in patients with mild-to-moderate disease (NCT04528329 and NCT04530409), while others are considering another corticosteroid, ciclosonide (NCT04381364, NCT04330586 and NCT04435795). Moreover, antroquinonol, dornase alfa (a recombinant human DNase enzyme), icosapent ethyl (lowers circulating pro-inflammatory biomarkers), leflunomide and bucillamine (prevent oxidative acute lung injury), ensifentrine (anti-PDE3/4 drug) and colchicine (antimitotic drug with anti-inflammatory effect blocking the NLRP3 inflammasome) are being investigated in patients with mild-to-moderate COVID-19 (NCT04523181, NCT04359654, NCT04412018, NCT04361214, NCT04504734, NCT04527471, NCT04322682 and NCT04416334). ABX464 (downregulates multiple chemokines and cytokines, including TNFalpha, IL-1beta, G-CSF, IL-6, MCP-1 and IL-17) and nitazoxanide (broad-spectrum antiviral that inhibits macrophage IL-6 production and interferes with SARS-CoV-2 glycosylation) are being investigated in phase II/III trials in patients with mild COVID-19 (NCT04393038, NCT04523090, NCT04463264 and NCT04486313).

Mesenchymal stem cells (MSCs) exhibit the capacity of homing to sites of injury and inflammation, and exert anti-inflammatory and immunomodulatory effects (Rogers et al., 2020). The use of MSCs is being investigated for COVID-19 in a randomized, phase I/II trial evaluating blood oxygen saturation (NCT04339660), and in a randomized, phase II/III trial of patients with mild-to-moderate disease considering adverse effects as the primary outcome (NCT04366063). Moreover, a phase II/III study evaluating SBI-101, a biologic/device combination product designed to regulate inflammation and promote repair of injured tissue using allogeneic MSCs, is also ongoing (NCT04445220). Preliminary results of a pilot study in seven patients with moderate-to-severe COVID-19 are available, although this is not the object of a prevention strategy (Leng et al., 2020). Another cell-based strategy, BACTEK-R (MV130), a bacterial preparation that contains a mixture of Gram inactivated bacteria, is currently being investigated in patients with mild disease (NCT04363814).

Other drugs with immunomodulatory activity, such as estradiol patch, IMU-838, methotrexate-LDE (methotrexate associated with LDL-like nanoparticles), and prazosin (an alpha-1 adrenergic receptor antagonist), are also being tested (NCT04359329, NCT04379271, NCT04610567 and NCT04365257).

Other drugs

Drugs traditionally used as anticoagulants/anti-aggregants have been proposed in some phase II/III trials to reduce the risk of developing clotting problems in patients with mild-to-moderate COVID-19: bemiparin (NCT04420299 and NCT04604327), aggrenox (NCT04410328), enoxaparin (NCT04400799), rivaroxaban (NCT04508023 and NCT04504032), rivaroxaban (NCT04504032) and atorvastatin (NCT04466241).

Tranexamic acid, which inhibits the conversion of plasminogen to plasmin and alters the endogenous protease plasmin, was also proposed to act as a SARS-CoV-2 entry inhibitor by cleaving a newly inserted furin site in the S protein, resulting in increased infectivity and virulence (NCT04338074) (Barker and Wagener, 2020; Ogawa and Asakura, 2020).

Six amino acids belonging to the receptor binding domain in the S protein of SARS-CoV-2 have been shown to be critical for viral entry through binding to hACE2 receptors (Lu et al., 2020). Phase II/III trials are being conducted to better establish the role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (NCT04493359, NCT04360551 with telmisartan, and NCT04472728 with BIO101).

Other trials are considering: nitric oxide in patients with mild-to-moderate COVID-19 (NCT04305457 and NCT04460183); minocycline in a phase II trial of patients with mild disease (IRCT20081019001369N4); dapagliflozin, an SGLT2 inhibitor, in a phase III trial of patients with mild-to-moderate disease (NCT04350593 and NCT04350593); and azithromycin in two phase III studies in outpatients or inpatients with mild-to-moderate disease (NCT04381962 and NCT04613271).

Finally, vitamins C, A and D and other dietary supplements are currently being evaluated (NCT04342728, IRCT20081019001369N3, NCT04411446, NCT04551911, NCT04400890, NCT04382040, NCT04495816 and NCT04610801).

Discussion and conclusions

The SARS-CoV-2 pandemic has highlighted the need to develop safe and effective pharmacological drugs and vaccines for the prevention of infection. This review analysed ongoing clinical trials of pharmacological prevention strategies for COVID-19 in SARS-CoV-2-negative and -positive, asymptomatic and mild-to-moderate cases, focusing on the early phases of infection.

Methodological warnings should be considered for the trials analysed. In fact, for most of the studies, the therapeutic setting (prevention, early treatment, treatment of moderate-to-severe cases) of the investigating drug was not always clearly defined. Furthermore, the primary outcome and the eligible population were often heterogeneous. Moreover, the size of the enrolled population, especially in some registered trials, was restricted, thus reducing the statistical robustness of the results. However, a clearer picture of the real clinical benefit of pharmacological prevention and early treatment is now available compared with the beginning of the pandemic as some results of randomized trials have been published.

Vaccines represent the best strategy for primary prevention. The traditional approaches adopted to develop vaccines show some limitations for their employment in the context of a pandemic. This is mainly due to the estimated time and specific instrument and laboratory structures that are needed. To overcome these limits, next-generation vaccine platforms have been used for SARS-CoV-2 vaccines. At present, two RNA-based vaccines (BNT162b2-Pfizer/BioNTech and mRNA-1273-Moderna) have been approved by FDA and EMA. This is the first time that RNA-based vaccines produced with next-generation platforms have been approved for humans. The approvals were based on the positive results obtained in two randomized, observer-blinded, placebo-controlled trials evaluating safety after a median follow-up of 2 months, and efficacy 7 days and 14 days after the second dose of BNT162b2 and mRNA-1273 vaccines in 18,556 and 14,134 subjects in the per-protocol analysis, respectively (Baden et al., 2020; Polack et al., 2020). These vaccines conferred 95% and 94.1% efficacy at preventing COVID-19, respectively. The introduction of new technologies in vaccine development and manufacturing during the COVID-19 pandemic could have permanently changed the global capability to rapidly counteract other novel emerging viruses.

A plethora of antiviral drugs, immune-based drugs (anti-SARS-CoV-2 monoclonal antibodies, plasma-derived immunoglobulins, immunomodulators) and other drugs have been used in the prevention and early treatment of COVID-19, but no final conclusions can be derived from these studies.

At present, remdesivir remains the only drug approved for the treatment of COVID-19, but its clinical benefit is narrow. The use of corticosteroids in severe COVID-19 resulted in less requirement for organ support (Writing Committee for the REMAP-CAP Investigators et al., 2020), but no final conclusions are available for prevention and early treatment.

Trials evaluating hydroxychloroquine/chloroquine, the most promising drugs in the early months of the pandemic, have produced results showing that hydroxychloroquine did not prevent new cases of COVID-19 or SARS-CoV-2 infection when used as prophylaxis in high-risk people (Abella et al., 2020; Boulware et al., 2020), and did not reduce the severity of symptoms when given at an early stage to outpatients with mild disease (Skipper et al., 2020) or patients with mild-to-moderate disease (Cavalcanti et al., 2020).

With regard to anti-SARS-CoV-2 antibodies, the interim analysis of the BLAZE-1 trial demonstrated that administration of 2800 mg bamlanivimab (LY-CoV555) accelerated the natural decline in viral load after 11 days in patients with mild-to-moderate COVID-19 and reduced the rate of hospitalization (Chen et al., 2020b). A systematic review conducted on several studies investigating convalescent plasma showed that this treatment could be safe and clinically effective, potentially reducing mortality in patients with COVID-19 (Rajendran et al., 2020).

In conclusion, this review represents an extensive report of ongoing trials of vaccines, antiviral drugs and immune-based strategies. Results from these studies could soon help to identify specific subgroups of individuals that could benefit from pharmacological prevention or early treatment of COVID-19.

Conflict of interest

None declared.

Funding source

None.

Ethical approval

None required.

Acknowledgements

The authors wish to thank Sara Colò, translator at the Experimental and Clinical Pharmacology Unit of CRO in Aviano, for editing the manuscript.

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