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BRIEF REVIEW

An Overview of Current Clinical Trials of Agents for the Treatment and Prevention of COVID-19 in the United States

Kenneth Schot Hannan[1], MD; W. Paul McKinney[2],MD*

[1]Infectious Diseases Fellow, Department of Internal Medicine, University of Louisville School of Medicine, Louisville, KY, USA
[2]Professor and Associate Dean for Research, University of Louisville School of Public Health and Information Sciences, Louisville, KY, USA

*schothannan@gmail.com

Abstract

Introduction: Given the rapid worldwide spread of SARS-CoV-2 and the attendant risks for severe complications and mortality, numerous clinical trials for its treatment and prevention have been generated in a short period. This report focuses on the categories of the wide spectrum of agents being studied in the United States and the intensity of effort involved with each so that clinicians may consider whether suggesting enrollment may be appropriate for their patients.

Methods: A search was completed of the ClinicalTrials.gov database on May 28, 2020 for all such trials underway as of that date in the US. A total 190 trials were identified; of these, 151 trials that included 83 distinct agents met the specified delimiting criteria. The salient features of each, including medication class, the total number of trials involving either treatment or ongoing prevention strategies, and the total patient enrollment, were captured in a summary table. Comprehensive descriptors of all 190 trials are made available in an appendix.

Results: The antimalarial agent hydroxychloroquine was the most frequently studied single agent by both number of trials and number of subjects involved. Antivirals were the next largest group, followed by immunomodulators, antibacterials, vaccines, renin-angiotensin-aldosterone system (RAAS) antagonists, and convalescent plasma. Of note, repurposed antineoplastic agents, stem cell therapies, steroids, and a diverse range of miscellaneous agents were also included in the list.

Conclusions: The agents currently under study for the prevention or treatment of COVID-19 include several highly publicized pharmaceuticals as well as a wide array of other experimental medications and novel applications of established drugs. In the absence of an approved vaccine at this time, it is essential that clinicians be aware of the range of trials from which important new therapeutic and prophylactic advances may rapidly emerge.

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Introduction

Since its origination in Wuhan, China in December 2019, the pandemic of coronavirus disease (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has resulted in more than 8.3 million cases and over 450,000 deaths worldwide as of June 18, 2020. [1] In light of the rapid worldwide spread of the virus and its potential for causing severe complications including multi-organ failure and death, numerous clinical trials involving novel investigative agents and drugs currently approved for the treatment of other conditions have appeared in a short period of time. This brief report provides an overview of those trials registered at the website www.ClinicalTrials.gov occurring within the United States.

This review is not intended as a detailed analysis on the pharmacology of the medications involved, since a discussion of the wide variety of their actions is beyond the scope of this report and since previous articles have chosen to focus on this topic. [2,3] Rather, the primary intent is to acquaint practitioners with the categories of drugs being studied, the wide variety of agents being assessed, and the relative intensity of effort being directed at studies of different groups of medications as reflected by the number of trials and the number of subjects targeted for enrollment in each study. While many clinical trials

are currently ongoing throughout the world, this review focuses only on those underway in the United States for two main reasons. First, clinicians here need to be familiar with domestic trials in order to enroll their patients in the most suitable one. Second, some of the agents employed abroad are not in use or available here and are therefore unlikely to be familiar or directly relevant to domestic practitioners.

Methods

On May 28, 2020, the search terms "COVID-19," "SARS-CoV-2," "severe acute respiratory syndrome coronavirus 2," "2019-nCoV," "2019 novel coronavirus," and "Wuhan coronavirus" were entered into the ClinicalTrials.gov database, delimited by interventional for study type, United States for location, and recruiting; enrolling by invitation; active, not recruiting; and completed for trial status. A total 190 trials were identified using this approach. Thirty-nine of these trials were eliminated because they lacked a radiologic or pharmaceutical intervention for the treatment or prevention of COVID-19 or its immediate physiologic consequences. Examples of those removed include the safety and feasibility of plasma donation; the effect of mindfulness sessions on levels of stress and anxiety; the utility of software messaging in the assessment of pain intensity scores among osteoarthritis patients whose surgeries had been delayed by the pandemic; and the use of alternative physical connectors in ventilators. The remaining 151 trials were categorized based on pharmacologic class, primary purpose (prevention or treatment), and targeted patient enrollment, as shown in **Table 1**.

The additional data below is available in **Appendix 1** for all 190 of the trials initially identified, for those 151 studies remaining after exclusions were applied, and for the 151 trials sorted by drug class. For cases in which multiple drugs were being studied, the trials are listed in each pertinent category.

1. National Clinical Trial (NCT) identification number;
2. official study title;
3. outcome measures assessed;
4. trial sponsor;
5. gender and age of the trial subjects;
6. trial phase;
7. trial funding source;
8. study design;
9. start date;
10. primary and final completion dates;
11. dates on which the trial was first posted and last updated; and
12. locations where subjects are being enrolled.

Results

The largest number of both total trials and total patients targeted for enrollment was in the category of antiprotozoal agents, which included hydroxychloroquine, chloroquine, primaquine, and atovaquone. The vast majority of trials and subjects in this group were those involving hydroxychloroquine.

Antiviral agents comprised the second largest group based on patient enrollment and the sixth largest based on the number of trials. Half of these trials and more than two-thirds of the total patient enrollment in this category involved remdesivir.

A diverse group of immunomodulatory agents constituted the third largest group by enrollment and the second largest by number of trials. This group consisted of twenty-one agents studied in twenty-eight trials; seventeen of these involved monoclonal antibodies. The agent in this group being studied in the largest number of patients (6,220) was colchicine. Of note, a single trial in this group involved the live attenuated Bacille Calmette-Guerin (BCG) vaccine, historically used as an immunotherapeutic agent against cancer, targeting an enrollment of 1,800 subjects.

The fourth largest group included three antibacterial agents (azithromycin, doxycycline, and clindamycin) as part of sixteen trials with a goal of 10,850 subjects to be studied. Group 5 comprised four vaccine trials seeking over 8,000 subjects. Over 90% of these subjects were included in one of the mRNA vaccine trials. The next largest group by enrollment was composed of renin-angiotensin-aldosterone system (RAAS)-related agents. Losartan was being studied in six of the seven RAAS-related trials, accounting for 97% of the total planned enrollment. Group 7 consisted of twenty convalescent plasma studies with the intention to include 3,355 subjects.

The eighth group included a diverse array of repurposed antineoplastic agents with eleven trials involving 2,834 patients. The Janus kinase (JAK) inhibitors baricitinib and ruxolitinib accounted for over 2,000 of the total targeted

Table 1. Pharmacologic interventions currently under investigation for the treatment and prevention of COVID-19 in the US.

Drug Class (Subclass)	Drug Name	Total Trials	Therapeutic Trials	Prophylactic Trials	Total Patient Enrollment
Antiprotozoals		**42[§‡]**	**33[§]**	**11**	**49,331[§]**
(4-aminoquinoline)	Hydroxychloroquine	40[§‡]	32[§]	10	48,956[§]
(4-aminoquinoline)	Chloroquine	2[§]	1[§]	1	850[§]
(8-aminoquinoline)	Primaquine	1[§]	1[§]	0	500[§]
(Hydroxynaphthoquinone)	Atovaquone	1	1	0	25
Antivirals		**10**	**10**	**0**	**14,697**
(Nucleotide Analog)	Remdesivir	5	5	0	9,932
(Protease Inhibitor)	Lopinavir/Ritonavir	1	1	0	4,000
(Viral Entry Inhibitor)	Leronlimab	2	2	0	465
(Recombinant Sialidase Fusion Protein)	DAS181	1	1	0	250
(RdRP Inhibitor)	Favipiravir	1	1	0	50
Immunomodulators		**28*[ǂ]**	**27*[ǂ]**	**1**	**12,215*[ǂ]**
(Microtubule Polymerization Inhibitor)	Colchicine	3	3	0	6,220
(Live Attenuated Vaccine)	BCG	1	0	1	1,800
(IL-6 Receptor Inhibitor)	Tocilizumab	5*	5*	0	1,100*
(Immunostimulant)	Interferon-alpha-2b	1*	1*	0	500*
(IL-1β Inhibitor)	Canakinumab	2	2	0	495
(IL-6 Receptor Inhibitor)	Sarilumab	1	1	0	400
(ST2 (IL-33 Receptor) Inhibitor)	MSTT1041A	1[ǂ]	1[ǂ]	0	300[ǂ]
(IL-22Fc)	UTTR1147A	1[ǂ]	1[ǂ]	0	300[ǂ]
(GM-CSF Inhibitor)	Gimsilumab	1	1	0	270
(IL-6 Inhibitor)	Sirukumab	1	1	0	270
(GM-CSF Inhibitor)	Lenzilumab	1	1	0	238
(Recombinant Fusion Protein)	CD24Fc	1	1	0	230
(GM-CSF Inhibitor)	TJ003234	1	1	0	144
(IL-8 Inhibitor)	BMS-986253	1	1	0	138
(Immunostimulant)	Peginterferon Lambda-1a	1	1	0	120
(Calpain Inhibitor)	BLD-2660	1	1	0	120
(IL-6 Inhibitor)	Clazakizumab	2	2	0	120
(TLR 2/6 Agonist & TLR 9 Agonist)	PUL-042	1	1	0	100
(mTOR Inhibitor)	Sirolimus	2	2	0	70
(GM-CSF Receptor Inhibitor)	Mavrilimumab	1	1	0	60
(DHODH Inhibitor)	Leflunomide	1	1	0	20
Antibacterials		**16[♭]**	**16[♭]**	**0**	**10,850[♭]**
(Macrolide)	Azithromycin	16[♭]	16[♭]	0	10,850[♭]
(Tetracycline)	Doxycycline	2[♭]	2[♭]	0	1,250[♭]
(Lincosamide)	Clindamycin	1[♭]	1[♭]	0	500[♭]
Vaccines		**4**	**0**	**4**	**8,345**
(mRNA)	BNT162b1/b2/b3	1	0	1	7,600
(mRNA)	mRNA-1273	2	0	2	705
(DNA Plasmid)	INO-4800	1	0	1	40
RAAS Antagonists		**7**	**7**	**0**	**5,682**
(ARB)	Losartan	6	6	0	5,530
(ACEI/ARB)	Unspecified ACEI or ARB	1	1	0	152
Blood Products		**20**	**20**	**0**	**3,355**
(Blood Product)	Convalescent Plasma	20	20	0	3,355
Antineoplastics		**11**	**10**	**1**	**2,834**
(JAK Inhibitor)	Baricitinib	2	2	0	1,176
(JAK Inhibitor)	Ruxolitinib	2	2	0	902
(Exportin 1 Inhibitor)	Selinexor	1	1	0	230
(Angiopoietin 2 Inhibitor)	LY3127804	1	1	0	200
(Other Antineoplastic)	Radiation Therapy	2	1	1	142
(Sumoylation Inhibitor)	TAK-981	1	1	0	80
(Topoisomerase II Inhibitor)	Etoposide	1	1	0	64
(Microtubule Polymerization Inhibitor)	Veru-111	1	1	0	40

Table 1. Cont.

Drug Class (Subclass)	Drug Name	Total Trials	Therapeutic Trials	Prophylactic Trials	Total Patient Enrollment
Antithrombotics		**5♯**	**5♯**	**0**	**1,548♯**
(LMWH)	Enoxaparin	3♯	3♯	0	1,408♯
(UFH)	Heparin	1♯	1♯	0	100♯
(Platelet Aggregation Inhibitor)	Dipyridamole	1	1	0	80
(Recombinant tPA)	Alteplase	1	1	0	60
Cell Therapies		**8**	**6**	**2**	**988**
(Multipotent Adult Progenitor Stem Cell Therapy)	MultiStem	1	1	0	400
(Bone Marrow-Derived Mesenchymal Stem Cell Therapy)	Remestemcel-L	1	1	0	300
(Adipose-Derived Mesenchymal Stem Cell Therapy)	HB-adMSCs	2	0	2	156
(Human Placenta-Derived Natural Killer Cell Therapy)	CYNK-001	1	1	0	86
(Mesenchymal Stem Cell Therapy)	UC-MSCs	1	1	0	24
(Induced Pluripotent Stem Cell Therapy)	FT516	1	1	0	12
Tissue Stromal Vascular Fraction Cell Therapy	tSVF	1	1	0	10
Inhalant Vasodilators		**4**	**4**	**0**	**742**
(Guanylate Cyclase Agonist)	Nitric Oxide	4	4	0	742
Steroids		**4**	**4**	**0**	**740**
(Glucocorticoid)	Methylprednisolone	2	2	0	590
(Steroid Sex Hormone)	Estrogen	1	1	0	110
(Steroid Sex Hormone)	Progesterone	1	1	0	40
Miscellaneous					
(Selective Serotonin Receptor Inhibitor)	Fluoxetine	1	1	0	2,000
(Mineral)	Zinc (Sulfate or Gluconate)	2	2	0	1,270
(H2-Receptor Antagonist)	Famotidine	1	1	0	1,170
(SGLT2 Inhibitor)	Dapagliflozin	1	1	0	900
(Water-Soluble Vitamin)	Vitamin C or Ascorbic Acid	2	2	1	540
(Aldose Reductase Inhibitor)	AT-001	1	1	0	500
(Opioid Antagonist)	Naltrexone	1	1	0	500
(NMDA Receptor Antagonist)	Ketamine	1	1	0	500
(Substance P Inhibitor)	Tradipitant	1	1	0	300
(Topical Antiseptic)	Povidone/Iodine	2	1	1	298
(Antinematodal)	Ivermectin	1	1	0	240
(Serine Protease Inhibitor)	Camostat Mesilate	1	1	0	240
(Alpha Adrenoreceptor Antagonist)	Prazosin	1	1	0	220
(Selective Serotonin Receptor Inhibitor)	Fluvoxamine	1	1	0	152
(VIP Analog)	Aviptadil	1	1	0	144
(Topical Antiseptic)	Multiple Agents	2	2	0	138
(CGRP Receptor Antagonist)	Vazegepant	1	1	0	120
(CRAC Channel Inhibitor)	CM4620	1	1	0	120
(Mucolytic)	N-Acetylcysteine	1	1	0	86
(NSAID)	Indomethacin	1	1	0	80
(Antiseptic)	Chlorhexidine	1	1	0	48

‡ Two RCTs of hydroxychloroquine studied its use as both therapy and prophylaxis; each of these two studies was included in the columns for both therapeutic trials and prophylactic trials but was counted once in the column for total trials.
§ One RCT of antiprotozoals with 500 patients is studying hydroxychloroquine and chloroquine, and another with 500 patients is studying hydroxychloroquine and primaquine; each of these was counted once in terms of total trials, therapeutic trials, and total patient enrollment.
* One RCT with 500 patients includes one arm for tocilizumab and another for interferon-α-2b; this group was counted once in terms of total trials, therapeutic trials, and total patient enrollment.
♮ One RCT with 300 patients includes one arm for MSTT1041A and another for UTTR1147A; this group was counted once in terms of total trials, therapeutic trials, and total patient enrollment.
♭ One RCT of antibacterials with 750 patients is studying azithromycin and doxycycline, and another with 500 patients is studying azithromycin, doxycycline, and clindamycin; each of these was counted once in terms of total trials, therapeutic trials, and total patient enrollment.
♯ One RCT of enoxaparin with 100 patients notes the need to use heparin for patients with an estimated glomerular filtration rate <30 mL/min; this group with was counted once in terms of total trials, therapeutic trials, and total patient enrollment.

enrollment for this group. Group 9 followed with five trials of antithrombotic agents involving over 1,500 subjects. The vast majority of these subjects were participating in three trials of enoxaparin, one of which included the use of unfractionated heparin only for those patients with stage 4 or stage 5 chronic kidney disease. Smaller trials of dipyridamole and alteplase made up the remainder of this category.

Eight trials of various cellular therapies involving almost 1,000 total subjects made up the tenth largest group. Stem cell therapies comprised the great majority of the total planned enrollment for this category. The next largest group included four studies underway involving nitric oxide. This is the only agent being studied as an inhaled medication. The twelfth group included four trials of steroid agents, including two of methylprednisolone and one each of estrogen and of progesterone, with 740 the total goal for participation.

An extremely wide spectrum of agents makes up the final group categorized as miscellaneous. Of these, the selective serotonin reuptake inhibitor (SSRI) fluoxetine was the largest contributor with 2,000 planned subjects.

Discussion

While the early sequencing of the SARS-CoV-2 viral genome in January 2020 has allowed for the diagnosis and tracking of COVID-19, effective therapeutic interventions have lagged behind diagnostics. Early interest and publicity surrounded the antiprotozoal agents; however, the FDA has revoked the emergency use authorization (EUA) it had previously granted for chloroquine and hydroxychloroquine, stating that these drugs were "unlikely to be effective" and that the attendant risks outweighed potential benefits. [4] It is unclear whether the withdrawal of the EUA will affect the completion of the clinical trials of these agents currently underway.

There are only two agents that have shown therapeutic efficacy based on clinical trials to date: remdesivir and dexamethasone. The nucleoside analog remdesivir was the first to achieve this status, based on a trial sponsored by the National Institutes of Health. [5] The studies supporting the benefit of dexamethasone were led by researchers in the United Kingdom [6] and are unpublished as of yet. Dexamethasone is not included in any of the studies being conducted in this country, although the related corticosteroid methylprednisolone is being studied in two US trials targeting 590 patients. If the benefit of dexamethasone stems from its suppression of cytokine storm [7], it may be expected that another promising agent may be discovered among the large number of immunomodulating agents currently under study.

In total, eighty-three distinct agents are currently being studied in the 151 US-based clinical trials assessed in this review. While the list includes several previously well-known or recently publicized medications, many utilize experimental or novel approaches of which most clinicians are likely unaware, such as nitric oxide inhalation, low-dose radiation therapy, administration of colchicine, or infusion of cell therapies. Also worthy of special mention are the antithrombotic agents, which rose to some prominence in the wake of reports of large-vessel thrombosis, including stroke, in COVID-19 patients, especially younger persons. [8] Although treatment guidelines at this time do not advocate for the routine use of antithrombotic agents in patients with this infection [9], the clinical trials listed here may be helpful in guiding future therapy.

The projected trial completion dates listed in the appendix should prove useful in tracking the approximate dates when information from these trials may be expected. In this regard, it is important to recognize that for the agents perhaps most anticipated of all, the vaccines against SARS-CoV-2, the projected primary completion dates range from March to September 2021. Consequently, given concerns about further resurgence of viral incidence in the near term [10], it is essential for clinicians to be aware of the range of trials from which their patients may benefit as they await results regarding the safety and efficacy of the interventions now under study.

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Abbreviations

RdRP	ribonucleic acid-dependent RNA polymerase	JAK	Janus-associated kinase
IL	interleukin	LMWH	low-molecular-weight heparin
ST2	suppressor of tumorigenicity 2	UFH	unfractionated heparin
Fc	fragment crystallizable region	tPA	tissue plasminogen activator
GM-CSF	granulocyte-macrophage colony stimulating factor	HB-adMSCs	Hope Biosciences adipose-derived mesenchymal stem cells
TLR	toll-like receptor	UC-MSCs	umbilical cord mesenchymal stem cells
mTOR	mammalian target of rapamycin	tSVF	tissue stromal vascular fraction
DHODH	dihydroorotate dehydrogenase	H2	histamine 2
RNA	ribonucleic acid	SGLT2	sodium-glucose cotransporter-2
mRNA	messenger ribonucleic acid	NMDA	N-methyl-D-aspartate
DNA	deoxyribonucleic acid	VIP	vasoactive intestinal peptide
RAAS	renin-angiotensin-aldosterone system	CGRP	calcitonin gene-related peptide
ARB	angiotensin receptor blocker	CRAC	calcium-release-activated calcium
ACEI	angiotensin-converting-enzyme inhibitor	NSAID	non-steroidal anti-inflammatory drug