

Major ongoing clinical trials for COVID-19 treatment and studies currently being conducted or scheduled in Japan

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Abstract: The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to global public health and economies. Currently, hundreds of clinical trials on a wide variety of treatments against COVID-19 are being conducted around the world. Here, we conducted a search for ongoing clinical trials for the treatment of COVID-19 at the clinicaltrials.gov database on April 2, 2020. In total, 48 clinical trials were identified, and of these, 41 trials adopted drug intervention and the other 7 trials utilized biological intervention. The number of trials stratified by a chief country conducting the investigation were 18 in China, 5 in the United States, 4 in Canada, 3 in Italy, 2 in France and Brazil, and 4 trials are being performed multinationally. The drugs utilized in more than one trials were remdesivir (6 trials), lopinavir/ritonavir (6 trials), hydroxychloroquine (6 trials), interferon (5 trials), methylprednisolone (3 trials), nitric oxide gas (3 trials), oseltamivir (2 trials), arbidol (2 trials), and vitamin C (2 trials). We also described the Japanese trials which are now being conducted or scheduled, utilizing lopinavir/ritonavir, remdesivir, favipiravir, ciclesonide and nafamostat.

Keywords: COVID-19, SARS-CoV-2, coronavirus disease 2019, clinical trial, Japan

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to global public health and economies (1). The SARS-CoV-2 belongs to Betacoronavirus which also contains severe acute respiratory syndrome coronavirus (SARS-CoV-1) spread in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) spread in 2012 (2). As of April 5, 2020, over 2,845 cases have been confirmed in Japan, including 69 deaths as well as over 1,169,217 confirmed cases including 63,437 deaths all over the world. Such huge numbers of infected and dead people call for an urgent demand of effective, available, and affordable treatments to control and diminish the pandemic SARS-CoV-2 infection. Currently, hundreds of clinical trials on a wide variety of treatments against COVID-19 are being conducted around the world. Here, we summarize major ongoing clinical trials registered to ClinicalTrials.gov database as of April 2, 2020, and describe the trials which are now being conducted or scheduled in Japan.

Methods

A search for ongoing clinical trials for the treatment of COVID-19 was conducted at the clinicaltrials.gov

database on April 2, 2020. The search words were "COVID-19", "SARS-CoV-2", "2019-nCoV" and "2019 novel coronavirus", and they were entered to the simple search field "conditions or disease", with "Status" being "All studies" and without any restrictions in other search windows. The subsequent filter conditions for identifying the eligible studies were as follows: recruitment is "Recruiting", "Active, not recruiting", "Enrolling by invitation", or "Completed"; study type is "Interventional"; study phase is "Phase I-IV"; and primary purpose is "treatment". The other conditions including sex, age, study results, funder type, and study documents were not restricted.

The severity of COVID-19 infection was defined according to the previous report as follows (3).

Mild: asymptomatic or symptomatic (*i.e.*, with fever, cough, or myalgia), but might not require hospitalization for treatment.

Severe: tachypnoea (≥ 30 breaths per min) or oxygen saturation 93% or higher at rest, PaO₂/FiO₂ ratio less than 300 mm Hg, and requiring hospitalization for treatment.

Critical: requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care.

Results And Discussion

Summary of the identified trials

We identified 48 clinical trials in total. Of these, 41 trials adopted drug intervention (Table 1) and the other 7 trials utilized biological intervention (Table 2).

The number of trials stratified by a chief country conducting the investigation were 18 in China, 5 in the United States, 4 in Canada, 3 in Italy, 2 in France and Brazil, and 4 trials performed multinationally. The drugs utilized in more than one trial were remdesivir (6 trials), lopinavir/ritonavir (6 trials), hydroxychloroquine (6 trials), interferon (5 trials), methylprednisolone (3 trials), nitric oxide gas (3 trials), oseltamivir (2 trials), arbidol (2 trials), and vitamin C (2 trials). The other pharmaceutical interventions included danoprevir, darunavir, ritonavir, ribavirin, cobicistat, chloroquine, bevacizumab, sarilumab, meplazumab, baricitinib, tocilizumab, anakinra, sargramostim, fingolimod, corchicine, sildenafil citrate, tetrandrine, DAS181, ASC09F, and traditional Chinese medicines.

As for the 7 clinical trials utilizing biological intervention, almost all the trials were conducted in China except one in Jordan. The biological interventions included MSCs, NK cells, aAPC vaccine and synthetic minigene vaccine. All the trials are clinical phase I or II with a relatively small target number of patients.

Clinical trials conducted or scheduled in Japan

The clinical trials which are now being conducted or scheduled in Japan for the treatment of COVID-19 are as follows, and the details of the drugs utilized in the trials are briefly summarized.

Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, and ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. Because lopinavir/ritonavir has been reported to have a benefit treating both SARS-CoV-1 (4) and MERS-CoV infection (5), similar effectiveness for COVID-19 is expected and several clinical studies using lopinavir/ritonavir are currently being conducted for COVID-19 around the world as mentioned above. However, a latest report published from China on March 18, 2020 reported no benefit of lopinavir/ritonavir treatment beyond standard care in hospitalized adult patients with severe COVID-19 (6). In Japan, lopinavir/ritonavir was administered to patients with COVID-19 from February 21, 2020 as part of an observational study. To confirm or exclude the treatment benefit of lopinavir/ritonavir, the results of the ongoing studies should be carefully observed in the future.

Remdesivir

Remdesivir is a broad-spectrum antiviral agent and was

developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection (7). The antiviral mechanism of remdesivir is a delayed chain cessation of nascent viral RNA by obscuring viral RNA polymerase and evading proofreading by viral exonuclease (7). Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses including SARS-CoV-1 and MERS-CoV infection in cultured cells, mice and non-human primate models (8-10). Based on the broad-spectrum anti-corona virus activity of remdesivir that were demonstrated in pre-clinical studies, several multinational, randomized, placebo controlled, double-blind clinical trials are currently being conducted. Of these, Japan is participating in Adaptive COVID-19 Treatment Trial, in which remdesivir (200 mg on day 1, then 100 mg/day up to 10 days) or placebo was administered to patients with severe or critical COVID-19 infection. Remdesivir is one of the most expectant and frequently investigated treatment for COVID-19 around the world, and accumulation of cases and analysis of results are awaited.

Favipiravir

Favipiravir is an antiviral compound that selectively and potently inhibits the RNA-dependent RNA polymerase of influenza and many other RNA viruses (11). Wan *et al.* revealed the antiviral effect of favipiravir to COVID-19 *in vitro* although a high concentration was required to reduce the viral infection (12). A randomized clinical trial from Wuhan, although the report has not been evaluated critically, reported that favipiravir has a higher 7 day's clinical recovery rate and more effectively reduced incidence of fever and cough compared with arbidol in ordinary COVID-19 patients untreated with antiviral previously (13). Although another clinical study comparing favipiravir with lopinavir/ritonavir for COVID-19 was published from Shenzhen on *Engineering*, it was thereafter withdrawn for some unknown reason. In Japan, Fujita Health University launched a multi-institutional, open-label, phase II study using favipiravir for asymptomatic or mild COVID-19 patients on March 2, 2020. The patients are assigned into immediate and delayed favipiravir arm, and favipiravir is administered orally for 10 days. The administration of favipiravir is scheduled as follows: immediate favipiravir arm, 1,800 mg twice a day on Day 1 followed by 800 mg twice a day from Day 2; delayed favipiravir arm, 1,800 mg twice a day on Day 6 followed by 800 mg twice a day from Day 7 to Day 15. Primary outcome is a proportion of subjects with clearance of COVID-19 virus in nasopharyngeal swab on Day 6. The collection of cases is going to be initiated in the near future.

Ciclesonide

Ciclesonide is an inhaled corticosteroid originally used in

Table 1. Clinical trials identified at Clinicaltrials.gov related to drug intervention for COVID-19 treatment

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II)	28-Mar-20	hydroxychloroquine +/- azithromycin	Severe/Critical	440	III	Recruiting	Brazil
Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial - CORIMUNO-19 - SARI	27-Mar-20	sarilumab vs. control	Severe/Critical	240	II/III	Recruiting	France
Sargramostim in Patients With Acute Hypoxic Respiratory Failure Due to COVID-19 (SARPAC)	24-Mar-20	sargramostim vs. control	Severe	80	IV	Recruiting	Belgium, Italy
Chloroquine Diphosphate for the Treatment of Severe Acute Respiratory Syndrome Secondary to SARS-CoV2	23-Mar-20	chloroquine diphosphate (high dose vs. low dose)	Severe/Critical	440	II	Recruiting	Brazil
Efficacy of Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome	23-Mar-20	methylprednisolone	Severe/Critical	104	II/III	Recruiting	Italy
Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	23-Mar-20	colchicine vs. control	Mild	6,000	III	Recruiting	Canada
Trial of Treatments for COVID-19 in Hospitalized Adults	22-Mar-20	remdesivir vs. lopinavir/ritonavir +/- interferon beta-1A vs. hydroxychloroquine vs. control	Severe/Critical	3,100	III	Recruiting	France
Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19	21-Mar-20	nitric oxide gas vs. control	Mild	240	II	Recruiting	United States
Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	21-Mar-20	nitric oxide gas vs. control	Severe/Critical	200	II	Recruiting	United States
Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)	19-Mar-20	tocilizumab	Critical	330	II	Recruiting	Italy
Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	18-Mar-20	lopinavir/ritonavir vs. control	Severe/Critical	440	II	Active not recruiting	Canada
Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	17-Mar-20	hydroxychloroquine vs. control	Mild	3,000	III	Recruiting	United States
Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	16-Mar-20	sarilumab vs. control	Severe/Critical	400	II/III	Recruiting	United States
Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study.	16-Mar-20	baricitinib vs. control	Mild	60	III	Recruiting	Italy
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	15-Mar-20	remdesivir vs. control	Mild	600	III	Recruiting	Multinational*
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	11-Mar-20	lopinavir/ritonavir vs. hydroxychloroquine sulfate vs. control	Mild	150	II	Recruiting	Korea
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	6-Mar-20	remdesivir vs. control	Severe	400	III	Recruiting	Multinational†
Tetrandrine Tablets Used in the Treatment of COVID-19	5-Mar-20	tetrandrine vs. control	Mild/Severe	60	IV	Enrolling by invitation	China
Yinhu Qingwen Decoction for the Treatment of Mild / Common CoVID-19	27-Feb-20	YinHu QingWen Decoction vs. Chinese medicine treatment vs. standard western medicine treatment	Mild	300	II/III	Active not recruiting	China
Fingolimod in COVID-19	22-Feb-20	fingolimod vs. control	Mild/Severe	30	II	Recruiting	China
Adaptive COVID-19 Treatment Trial (ACTT)	21-Feb-20	remdesivir vs. control	Severe/Critical	440	III	Recruiting	Multinational*

*United States, China, Germany, Hong Kong, Italy, Korea, Singapore, Spain, Switzerland, Taiwan, United Kingdom, †United States, Japan, Korea, Singapore.

Table 1. Clinical trials identified at Clinicaltrials.gov related to drug intervention for COVID-19 treatment (continued)

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Evaluation of Ganovo (Danoprevir) Combined With Ritonavir in the Treatment of Novel Coronavirus Infection	17-Feb-20	danoprevir + ritonavir +/- interferon nebulization	Mild	11	IV	Completed	China
Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu	15-Feb-20	N-acetylcysteine +/- Fuzheng Huayu Tablet	Mild/Severe	136	II	Recruiting	China
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	14-Feb-20	vitamine C vs. control	Severe/Critical	140	II	Recruiting	China
Mild/Moderate 2019-nCoV Remdesivir RCT	12-Feb-20	remdesivir vs. control	Mild	308	III	Recruiting	China
Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	10-Feb-20	lopinavir/ritonavir + ribavirin + Interferon β-1B vs. control	Mild/Severe/ Critical	70	II	Recruiting	Hong Kong
A Pilot Study of Sildenafil in COVID-19	9-Feb-20	sildenafil citrate	Mild/Severe	10	III	Recruiting	China
Severe 2019-nCoV Remdesivir RCT	6-Feb-20	remdesivir vs. control	Severe	453	III	Recruiting	China
Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	6-Feb-20	hydroxychloroquine vs. control	Mild/Severe/ Critical	30	III	Completed	China
Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia	3-Feb-20	meplazumab	Mild/Severe	20	I/II	Recruiting	China
Bevacizumab in Severe or Critical Patients With COVID-19 Pneumonia	Feb-20	bevacizumab	Severe/Critical	20	II/III	Recruiting	China
A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia	1-Feb-20	ASC09F + oseltamivir vs. ritonavir + oseltamivir vs. oseltamivir	Mild	60	III	Recruiting	China
A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	1-Feb-20	arbidol hydrochloride vs. oseltamivir vs. lopinavir/ritonavir vs. control	Mild/Severe/ Critical	400	IV	Recruiting	China
A Prospective/Retrospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia	1-Feb-20	arbidol hydrochloride +/- Interferon atomization	Mild/Severe/ Critical	100	IV	Recruiting	China
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia	1-Feb-20	methylprednisolone (< 40 mg/day vs. 40-80 mg/day)	Severe	100	IV	Recruiting	China
Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	30-Jan-20	darunavir + cobicistat vs. control	Mild/Severe/ Critical	30	III	Recruiting	China
Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure	26-Jan-20	methylprednisolone vs. control	Severe/Critical	80	II/III	Recruiting	China
STOP PIV - Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects	23-May-19	DAS181	Severe	250	III	Recruiting	United States
Lessening Organ Dysfunction With Vitamin C	8-Nov-18	vitamin C vs. control	Critical	800	III	Recruiting	Canada
Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections	24-Oct-17	nitric oxide gas	Mild	20	II	Active not recruiting	Canada
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia	11-Apr-16	lopinavir/ritonavir +/- hydroxychloroquine vs. Interferon β-1A vs. Anakinra vs. control	Severe/Critical	6,800	IV	Recruiting	Multinational [§]

[§]Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom

Table 2. Clinical trials identified at Clinicaltrials.gov related to biological intervention for COVID-19 treatment

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Immunity and Safety of Covid-19 Synthetic Mimigene Vaccine	24-Mar-20	LV-SMENP-DC vaccine + antigen-specific CTLs	Mild/Severe	100	I/II	Recruiting	China
A Phase I/II Study of Universal Off-the-shelf NKG2D-ACE2 CAR-NK Cells for Therapy of COVID-19	21-Mar-20	NK cells vs. IL15-NK cells vs. NKG2D CAR-NK cells vs. ACE2 CAR-NK cells vs. NKG2D-ACE2 CAR-NK cells	Mild/Severe	90	I/II	Recruiting	China
Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	16-Mar-20	WJ-MSCs	Mild/Severe/ Critical	5	I	Recruiting	Jordan
Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	5-Mar-20	MSCs vs. control	Severe	90	II/II	Recruiting	China
NK Cells Treatment for Novel Coronavirus Pneumonia	20-Feb-20	NK Cells vs. control	Mild/Severe/ Critical	30	I	Recruiting	China
Safety and Immunity of Covid-19 aAPC Vaccine	15-Feb-20	Pathogen-specific aAPC	Mild/Severe	100	I	Recruiting	China
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	27-Jan-20	MSCs vs. control	Mild/Severe/ Critical	20	I	Recruiting	China

the continuous treatment of mild-to-severe asthma (14). A recent report from National Institute of Infectious Diseases (Tokyo, Japan) revealed that ciclesonide blocks coronavirus RNA replication by targeting viral NSP15, and therefore, has an antiviral effect on COVID-19 (15). Thereafter, the efficacy of ciclesonide on three cases with early to middle-stage COVID-19 pneumonia has been reported from Kanagawa Prefectural Ashigarakami Hospital (Kanagawa, Japan). Based on these findings, a clinical trial to investigate the efficacy of ciclesonide for patients with COVID-19 pneumonia commenced on March 2, 2020 in National Center for Global Health and Medicine (Tokyo, Japan) and Fujita Health University (Aichi, Japan). After arrangement of the details, collection of the cases is going to be initiated in the near future.

Nafamostat

Nafamostat mesylate is a low molecular weight (539.6 kD) protease inhibitor that has been shown to inhibit serine proteases, such as trypsin, kallikrein, C1r and C1s, thrombin, and plasmin (16). Based on this inhibitory profile, nafamostat mesylate has been widely used in Asia to treat acute pancreatitis, disseminated intravascular coagulation, and extracorporeal circulation (17). In 2016, Yamamoto *et al.* revealed that nafamostat mesylate also blocked MERS-CoV infection *in vitro* by inhibiting the activity of TMPRSS2 and subsequent membrane fusion to the attached cell (18). In addition, Hoffmann *et al.* recently reported a similar effect on COVID-19 by camostat mesylate, an analogous drug to nafamostat mesylate (19). According to these reports, the effectiveness of nafamostat mesylate on COVID-19 was evaluated in Institute of Medical Science, The University of Tokyo (Tokyo, Japan), and they reported successful inhibition of COVID-19 infection in cultured human airway epithelial cells (Calu-3) at a lower concentration, which was around 10% compared with camostat (not published). Based on the results, a clinical trial for COVID-19 using nafamostat mesylate is scheduled in Institute of Medical Science, The University of Tokyo (Tokyo, Japan), The University of Tokyo Hospital (Tokyo, Japan) and National Center for Global Health and Medicine (Tokyo, Japan).

In conclusion, we summarized 48 major ongoing clinical trials registered to ClinicalTrials.gov database as of April 2, 2020, and presented the trials which are now being conducted or scheduled in Japan. Special attention must be paid to the results of these clinical trials to prevent further disease spread and fatal outcomes of COVID-19.

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