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Cardiovascular disease due to novel coronavirus and the search for investigational therapies

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ABSTRACT

Objective: The primary purpose of the study was to investigate and to summarize the registered trials that listed COVID-19 as the primary condition.

Methods: We performed a search on ClinicalTrials.gov using the independent search terms COVID-19, SARS, and SARS-CoV-2 and then downloaded the data file on March 23, 2020. All trials were downloaded to a csv file and searched for appropriateness.

Results: Of 124 registered trials, 56 (45.2%) were listed as recruiting. The majority (85 [68.5%]) were classified as interventional, 37 (29.8%) as observational, and one (0.8%) each as either expanded access: individual patients|treatment investigational new drug/protocol or expanded access: intermediate-size population|treatment investigational new drug/protocol. There were 67 (54.0%) trials that listed drug as the type of study. Immunologic and antiviral trials were the most common, representing approximately 30% and 21%, respectively. When immunologic and antiviral drugs were used alone or in combination, they represented 41.9% and 34.4%, respectively. Antimalarial agents are represented in 7.5% of trials. Approximately 14% of trials involved traditional Chinese medicine. The study agents used solely or in combination represented approximately 80% of therapeutic approaches to COVID-19.

Conclusions: There was a large and quick response on ClinicalTrials.gov to the COVID-19 outbreak. Many of the registered trials are currently recruiting new patients, whereas some will begin in the near future. Specific potential experimental therapies, including dosing and monitoring, might be found by reviewing content. Within ClinicalTrials.gov, patients, family members, health care professionals, and researchers can search and find ongoing and future trials for COVID-19. (J Vasc Surg 2021;73:13-7.)

Keywords: Coronavirus; COVID-19; SARS-CoV-2; Clinical trials; Therapy

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It spread rapidly, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization referred to the disease as COVID-19 (ie, coronavirus disease 2019). The virus that causes COVID-19 is structurally related to the virus that causes severe acute respiratory syndrome (SARS) and has been

referred to as (SARS-CoV-2); once previously, it was referred to as 2019-nCoV.¹⁻⁶

In our limited experience with COVID-19, approximately one of four patients require hospitalization. Early reports indicate that patients with underlying comorbidity are at high risk for development of complications and death after COVID-19. There are also some concerns that the virus may affect the heart; for example, a Chinese study of 138 hospitalized patients with COVID-19 with a median age of 56 years and coexisting medical conditions included hypertension (43 [31.2%]), diabetes (14 [10.1%]), cardiovascular disease (20 [14.5%]), and malignant disease (10 [7.2%]). The results suggested that among hospitalized patients, 16.7% of patients developed arrhythmias, 7.2% developed cardiac injury, and 8.7% developed shock. Acute respiratory distress syndrome (ARDS) appears in about 20% of patients. The first reported cardiac death was a 61-year-old smoker who succumbed to ARDS, heart failure, and cardiac arrest. Anecdotal reports suggest that some patients may have developed myocarditis similar to what has been seen with other viruses. Cardiac issues were reported to surpass pneumonia as the leading cause of death in the 1918 influenza pandemic.⁷⁻¹⁵

It is well established that many virus infections can affect the heart, and experts suspect that coronavirus

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may be no different. Viruses are known to induce inflammation of the myocardium. In a healthy patient, this may not lead to an adverse outcome; but in patients with ARDS, coronary artery disease, or heart failure, the outcomes may be poor. Because many of the patients affected by coronavirus are elderly with comorbidity, they may be at risk for adverse cardiac events. Other comorbidities like smoking, diabetes, hypertension, renal failure, and chronic obstructive pulmonary disease may also increase the risk of cardiac death in COVID-19. During the SARS and Middle East respiratory syndrome outbreak, there was also concern about adverse cardiac events like acute myocarditis, acute myocardial infarction, and rapid-onset congestive heart failure. In approximately 60% of Middle East respiratory syndrome cases, presence of one or more pre-existing comorbidities resulted in a worse outcome. Some patients were also found to have subclinical diastolic left ventricular impairment.

The COVID-19 pandemic has gained much attention; many researchers and scientists have tried to investigate all aspects of the virus, treatment, spread, and complications of the disease. With so much mainstream media attention given to COVID-19, where can researchers, scientists, health care providers, and patients look for a better understanding of available treatments and research options? One good search engine for finding published medical literature from medical journals is more commonly referred to as PubMed.¹⁶ If one (ie, researchers, scientists, health care providers, or patients) is more interested in the future or what is currently being studied, then ClinicalTrials.gov¹⁷ is a good option. ClinicalTrials.gov is an Internet-based registry that provides easy access to a whole host of publicly and privately funded clinical studies. Patients, family members, health care professionals, researchers, or anyone else can search and find ongoing and completed trials on almost any illness or condition. It is maintained by the National Library of Medicine at the National Institutes of Health. Studies are registered before they begin and list an approximate start date with the status of the study (eg, not yet recruiting, recruiting) throughout the course of the study. The primary purpose of this study was to investigate and to summarize the registered trials that listed COVID-19 as the primary condition while highlighting the importance of the registry to clinicians and patients as a source of therapeutic options.

METHODS

We performed a search on ClinicalTrials.gov using the independent search terms COVID-19, SARS, and SARS-CoV-2 and then downloaded the data file on March 23, 2020. All trials were downloaded to a csv file and searched for appropriateness. There were 125 listed trials and one trial for hypertension was placed on hold because COVID 19 was excluded. Thus, this left 124 trials

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of prospectively collected registry data
- **Key Findings:** Of the 124 eligible registered trials, 56 (45.2%) were recruiting, 51 (41.1%) were not yet recruiting, 5 (4%) were withdrawn, and 5 (4%) were completed.
- **Take Home Message:** COVID-19-related research trials can be found on ClinicalTrials.gov.

for analysis. The file was imported into SPSS version 19, and basic descriptive statistics were performed. Trial characteristics such as trial status, intervention, trial phase, and classification were summarized and placed into tables for easy comparison. In addition, the anticipated start date for the trials was used to create a summary graph of the number of studies expected to start within each month and plotted over time. This study was designed and conducted in such a manner as to apply to known Good Clinical Practice guidelines.

RESULTS

Of the 124 eligible registered trials, 56 (45.2%) were recruiting, 51 (41.1%) were not yet recruiting, 5 (4%) were withdrawn, and 5 (4%) were completed. The completed ones had not posted any results to the site. Three (2.4%) were listed as enrolling by invitation, 2 (1.6%) were listed as available, and 2 (1.6%) were listed as active, not recruiting (Table I). A larger percentage did not list the phase of the trial ($n = 39$ [31.5%]), whereas 20 (16.1%) reported the phase as not applicable. There were 23 (18.5%) listed as phase 2 trials and 13 (10.5%) listed as phase 3. There were 8 (6.5%) that listed phase 1, 8 (6.5%) that listed a combination of phase 2|phase 3, and 8 (6.5%) that listed phase 4. Three (2.4%) were listed as a combination of phase 1|phase 2 and two (1.6%) were listed as early phase 1 (Table II).

There were 67 (54.0%) trials that listed drug as the type of study, whereas 17 (13.7%) left this information blank. Sixteen (12.9%) trials listed other as intervention type, and 15 (12.1%) listed biologic. Four (3.2%) listed diagnostic test, 2 (1.6%) listed device, 1 (0.8%) listed behavioral, and 1 (0.8%) listed procedure (Table III). The majority (85 [68.5%]) were classified as interventional, 37 (29.8%) as observational, and 1 (0.8%) each as either expanded access: individual patients|treatment investigational new drug/protocol or expanded access: intermediate-size population|treatment investigational new drug/protocol (Table IV).

Immunologic and antiviral trials were the most common among the therapeutic trials (30% and 21%, respectively). Immunologic and antiviral drugs, alone or in combination, represented 41.9% and 34.4%, respectively.

Table I. Status of trials listed on clinical trials registry (www.clinicaltrials.gov)

Status	Frequency	%
Active, not recruiting	2	1.6
Available	2	1.6
Completed	5	4.0
Enrolling by invitation	3	2.4
Not yet recruiting	51	41.1
Recruiting	56	45.2
Withdrawn	5	4.0
Total	124	

Table II. Phase of trials listed on clinical trials registry (www.clinicaltrials.gov)

Phase	Frequency	%
Left blank	39	31.5
Early phase 1	2	1.6
Not applicable	20	16.1
Phase 1	8	6.5
Phase 1 phase 2	3	2.4
Phase 2	23	18.5
Phase 2 phase 3	8	6.5
Phase 3	13	10.5
Phase 4	8	6.5
Total	124	

Table III. Type of study listed on clinical trials registry (www.clinicaltrials.gov)

Type	Frequency	%
Left blank	17	13.7
Behavioral	1	0.8
Biologic	15	12.1
Combination product	1	0.8
Device	2	1.6
Diagnostic test	4	3.2
Drug	67	54.0
Other	16	12.9
Procedure	1	0.8
Total	124	

Antimalarial agents are represented in 7.5% of trials. Approximately 14% of trials involved traditional Chinese medicine. The study agents used solely or in combination represented approximately 80% of therapeutic approaches to COVID-19 (Table V).

Last, a variable was created for the month of anticipated start of enrollment, with one being October 2019

Table IV. Classification of trials listed on clinical trials registry (www.clinicaltrials.gov)

Classification	Frequency	%
Expanded access: individual patients treatment investigational new drug/protocol	1	0.8
Expanded access: intermediate-size population treatment investigational new drug/protocol	1	0.8
Interventional	85	68.5
Observational	37	29.8
Total	124	

Table V. Type of drug listed on clinical trials registry (www.clinicaltrials.gov)

Drug	Frequency	%
AM	5	7.5
AV	14	20.9
AV/AM	1	1.5
AV/I	4	6.0
AV/I/TCM	1	1.5
AV/TCM	1	1.5
I	20	29.9
I/AV/TCM	2	3.0
AM/TCM	1	1.5
Other	6	9.0
TCM	4	6.0
V	8	11.9
Total	67	

AM, Antimalarial; AV, antiviral; I, immunologic; TCM, traditional Chinese medicine; V, vasodilatory.

and one added for each subsequent month up to May 2020. The number of trials expected to start within each month was plotted over time. The majority of the trials were expecting to start in either February or March 2020 (Fig).

DISCUSSION

We found that the largest percentage (45.2%) of registered trials were currently enrolling patients; another large percentage (41.1%) are in the pipeline but not yet recruiting. It is easy to see the recent surge in activity with the highest number of anticipated start dates in February and March 2020. Knowing that the outbreak of COVID-19 started in December 2019, the research response has been large and quick. Indeed, a review of ClinicalTrials.gov on April 2, 2020, revealed an additional 157 trials, effectively doubling the number. There would be a lag in time to account for all of the work that goes into developing an idea and registering the trial. More

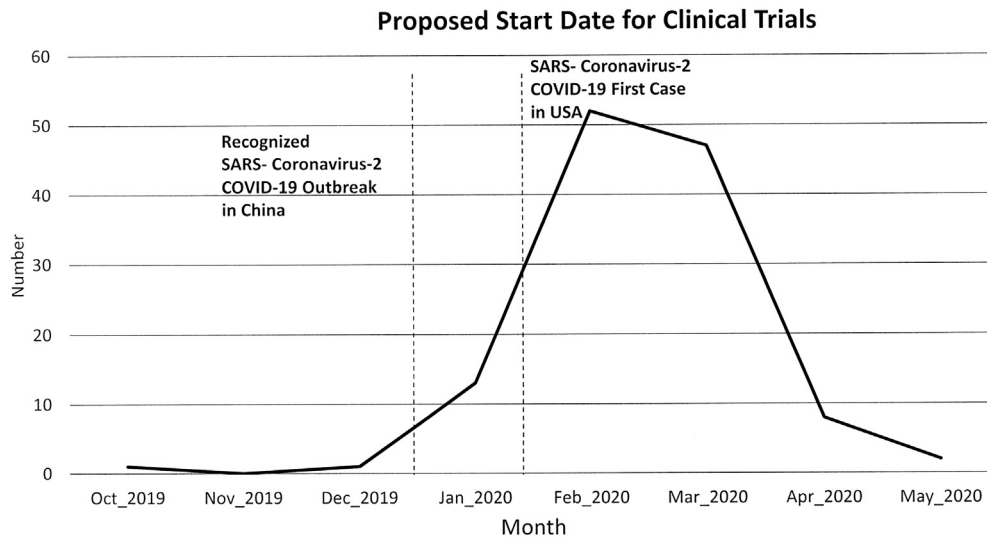


Fig. Proposed start date for clinical trials.

than half of the trials (54.0%) were drug trials, and more than half (68.5%) were classified as interventional. This serves as some evidence that the researchers associated with these trials are seeking to understand and to treat COVID-19.

As has been highlighted in the lay media, immunologic and antiviral approaches to COVID-19 are the bulk of clinical trial investigations (approximately 75% of listed trials). Several existing and experimental monoclonal antibodies and antivirals were among the listed trials. Indeed, the approved but off-label use of these agents has been inserted into local treatment algorithms.

Despite the highly publicized use of antimalarials for COVID-19, we found only 7.5% of trials including one of these agents. We would propose that the practice of using an antimalarial for the treatment of COVID-19 is happening off-label, probably as a “first-line” treatment. Therefore, we would not expect to see a large number of these trials listed. However, this is somewhat unfortunate, recognizing that more substantive efficacy and safety data are needed regarding the relative efficacy of this class of agents.

With the general acceptance of the origination of the virus in Wuhan, China, it was not surprising that 14% of the trials involved traditional Chinese medicine. Whereas agents such as the traditional Chinese medicine formula Fuzheng Huayu are not approved for medical use in the United States by the Food and Drug Administration, they may provide alternative treatment of COVID-19, especially in the context of a research trial. Presently, Fuzheng Huayu has shown promise in the treatment of viral hepatitis,¹⁸ whereas Huaier has demonstrated immunomodulatory effects.¹⁹

Although ClinicalTrials.gov was inherently useful to our caring for patients with COVID-19, there are many

additional complications that may surface for a vascular surgeon. As a result of the pathogenesis of the disease,²⁰ there is the likely increase in thromboembolic conditions, such as acute limb ischemia, acute deep venous thrombosis, and pulmonary embolism. Anticoagulation must be considered. Furthermore, vascular interventions will be performed to standard, but with extra precautions (personal protective equipment, negative pressure rooms). If it is indicated, lysis for pulmonary embolism may be done in the prone position secondary to severe respiratory compromise. Acute kidney injury will require acute placement of dialysis access in the popliteal vein if the patient is in the prone position. Unfortunately, with these and many more evolving scenarios, surgeons will have to proceed without level 1 evidence from ongoing clinical trials.

As COVID-19 was emerging as a pandemic, ClinicalTrials.gov proved to be a useful tool not only to identify clinical trial opportunities for patients but also as a stimulus for reviewing off-label options for affected patients. Of the U.S.-based clinical trials listed, our medical center is assessing four of the trials as potential options for our patient base. Listed trials provide appropriate contact information, and we encourage readers to access this resource as a contemporaneous avenue for their patients.

CONCLUSIONS

There was a large and quick response on ClinicalTrials.gov to the COVID-19 outbreak. Many of the registered trials are currently recruiting new patients, whereas some will begin in the near future. Specific potential experimental therapies, including dosing and monitoring, might be found by reviewing content. Within ClinicalTrials.gov, patients, family members, health care professionals, and researchers can search and find ongoing and future trials for COVID-19.

AUTHOR CONTRIBUTIONS

Conception and design: AM, MB, BL
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Data collection: AM, MB, BL
Writing the article: AM, MB, BL
Critical revision of the article: AM, MB, BL
Final approval of the article: AM, MB, BL
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