Review Article

Pharmacological and Nonpharmacological Studies on Coronavirus Disease 2019: A Mini-review of the Recent Evidence

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ABSTRACT

Coronavirus 19 (COVID-19) is an extremely transmittable microbial infection that has emerged in Wuhan (China) in late 2019, leading to severe acute respiratory syndrome coronavirus 2 syndrome, and caused a pandemic all over the globe. This study is a systematic review of all 927 clinical trial studies performed worldwide from the beginning of the COVID-19 mysterious pandemic in China. These researches have registered in different databases. According to the best of our knowledge, China (74.82%), the United States (4.49%), and France (2.72%) have the most significant number of clinical trials, respectively. Clinical trials can be randomized or nonrandomized. Due to our results, 32.58% of studies were randomized, and 7.12% were not randomized. Most of the studies were open-labeled studies (22.44%), and double-blinded (4.42%) and quadruple blinded (2.48%) studies stand in second and third place regarding the number of trials, respectively. The direction and quantity of clinical trials attempted to identify a possible cure for COVID-19 demonstrates the depth of this crisis. As we are writing this article, a significant international endeavor will find a cure or vaccine for containing this devastating and mysterious disease.

KEYWORDS: *2019-novel coronavirus, clinical trials, outcome, review, severe acute respiratory syndrome-coronavirus 2*

INTRODUCTION

In December 2019, the World Health Organization (WHO) got a red alert with a cluster of pneumonia cases of unknown causes observed in Wuhan, Hubei Province, People's Republic of China.[1] Based on the results of the analysis of respiratory samples, the China Center for Disease Control experts affirmed that this outbreak is related to a novel coronavirus (nCoV).[2] On February 11, 2020, the International Committee on Virus Taxonomy identified the new virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).[3] The WHO officially named the disease coronavirus 19 (COVID-19).[1] During the past two decades, several deadly epidemics affected human populations. Ghastly, two of those epidemics triggered by novel HCoV, in 2002 SARS

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known as (SARS-CoV) and in 2012, Middle East respiratory syndrome (MERS-CoV) have contributed to global outbreaks.[4] The third and most recent one is COVID-19, which has a potent transmission rate.[2]

Conferring to the latest reports released by the WHO in September 2020, over 27 million confirmed cases of COVID-19 and total death of roughly a million people worldwide. WHO quantified the global level of risk assessment as very high up to now, there are no approved specific therapies for the treatment or prevention of COVID-19. Treatment protocols are just symptomatic and using anti-viral agents like Remdesivir (on the May 1 approved by the Food and Drug Administration [FDA]) to curtail the disease period in those who are seriously ill. As the projected number of cases predicted to rise significantly, the demand for the treatment also arises. Among potential therapeutic approaches, convalescent plasma, interferon-based therapies, anti-interleukin 6 (IL6) monoclonal antibodies (mAbs), cell-based therapies, and small molecules can be mentioned.[5] However, a standard drug therapy development takes too long to be a treatment of choice in the current global emergency.[6] Repurposing existing drugs could reduce the cost and time to find a promising cure compared to INDs applications.

Moreover, this therapeutic approach is much accessible and safe.[7] Several research groups are working on a variety of preventative and therapeutic interventions globally.[6] Several strategies for containing or combating the emergence of 2019-nCoV infections can be proposed, but the development of new treatments will presumably take months or even years.

Convalescent plasma

Patients recovering from the infections have long-lasting antibodies produced by their immune system. The plasma is collected, appropriately examined, and washed to extract specific immunoglobulin G (IgGs) that could be used as a potential drug. Deployment of extracted IgGs as treatment provides "passive immune" until the patient's immune system could produce enough antibodies. This "plasma-derived treatment" is also known as convalescent plasma. Convalescent plasma or IgG immunoglobulins is an old method used in infectious disease guidelines, another possible alternative treatment for COVID. In both SARS and MERS, salvage therapy protocols were reported for convalescent plasma. Several reports with different successfulness rates have been done, and currently, recent journal articles also assess several human mAbs to block the SARS-COV-2 with a specific epitope.[8-10]

Hydroxychloroquine

The prevention and management of malaria and chronic inflammatory illness, including systemic lupus erythematosus and rheumatoid arthritis have a long-standing history of chloroquine usage. Chloroquine and much more hydroxychloroquine often prevent viral entry into cells *in vitro* by reversing the effect of enzymes used for glycosylation of host receptors. The effects of such agents are immunomodulatory by inhibiting the concentration of cytokines in the blood.[11,12]

Corticosteroids

The use of corticosteroids in COVID-19 are promoted based on reducing the host's chronic inflammation due to IL-6 secretion in the lung, which may progress to acute lung damage and acute respiratory distress syndrome. Nevertheless, adverse effects, including the disrupted viral clearance and a higher likelihood of bacterial infection, can outweigh this benefit.[13,14] The observatory experiments in SARS patients and MERS demonstrate no connection between steroids use and enhanced survival (however, they have shown a link with slow viral clearance from the respiratory system and elevated risk of severe side effects of corticosteroids like avascular necrosis).[15,16]

Monoclonal antibodies

Another potential class of adjunctive treatment options for COVID-19 is mAbs against inflammatory cytokines or other aspects of the host immune system crisis. The explanation for their application could be that the underlying pathophysiology of severe organ injuries in the lungs and other bodies are sparked by a ramped-up immune response and cytokine release, or "cytokine storm."[17] IL-6 seems to be a primary cause of this dysfunctional inflammation based on an early randomized trial in China. Tocilizumab, siltuximab, and sarilumab are utilized in clinical studies, and they displayed varied results.[18]

Antivirals

Remdesivir is a monophosphate prodrug, previously known as GS-5734. In a screening process for R.N.A. inhibitor antimicrobials, the agent was found to be active. It was designed by Gilead pharmaceutical company during the recent Ebola outbreak in Africa. In some countries, like the united states of America, it is an approved medication for the treatment of COVID-19 patients and was clinically illustrated to reduce the hospitalization period in patients who suffer from a severe form of the disease.[19,20]

Lopinavir/ritonavir

Lopinavir/ritonavir, inhibiting 3-chymotrypsin-like proteases, is an oral combination drug approved for the treatment of H.I.V. by the United States FDA, which has proven *in vitro* value in the treatment of other novel viral pathogens. Lopinavir/ritonavir

provides no successful reported trials until today. Clinical trials of this combination in some other viral diseases like MERS, SARS, and dengue fever were linked to lower deaths and intubation rates, but the study's observational nature stopped conclusions.[21] Reports of lopinavir/ritonavir usage for the treatment of COVID-19 are nonrandomized cohort studies. They include few case reports and small retrospective studies, making it difficult to ascertain the direct therapeutic effect of lopinavir/ritonavir. The latest randomized controlled trials have found about 50% of patients taking lopinavir/ritonavir suffer from side effects, whereas roughly 20% of those suffering from gastrointestinal adverse effects, and upon patient request, researchers have terminated their treatment. Another common side effect of this combination in COVID-19 experimental trials is the elevations of liver enzymes due to the observed hepatotoxicity of this combination.[22-24]

Nitazoxanide

Nitazoxanide has notable anthelminthic and anti-viral activity and a favorable overall safety profile. However, it functions against MERS and SARS-CoV-2; more data are needed to confirm its effectiveness.[25]

Guanine analogs

Guanine analogs, such as ribavirin, inhibits RNA-dependant RNA-polymerase. Its interactions with other nCoVs genes have made it a candidate for therapy of COVID-19 patients, but higher doses are needed, and this may result in more side effects.[26]

Umifenovir

Umifenovir is by far better repurposed anti-viral agent targeting the S-protein/angiotensin -converting enzyme 2 interaction and inhibiting membrane fusion of the viral envelope. Some reports from China showed that the mentioned drug reduced the mortality rate. The problem with reported studies is that they were investigated on small groups of patients.

Oseltamivir

Oseltamivir, which has been approved for influenza therapy, is repurposed in clinical trials again. The first COVID-19 outbreak in China occurred in the peak influenza season, meaning that most patients received observational Oseltamivir medication before the discovery of SARS-CoV-2. According to our knowledge, some of the clinical trials currently underway include Oseltamivir, but none of them were successful until this day. If any of them were successful, the clinical trial was performed on a tiny population, and the published papers have low quality.

Favipiravir

Favipiravir is a purine nucleotide medication previously known as T-705, which was first approved in Japan. Favipiravir was found by the Toyama Chemical Co., Ltd., chemical library screening for anti-flu viral activity. The active form of favipiravir ribofuranosyl-5'-triphosphate (RTP), which is recognized by RdRp as a substrate material, is favipiravir RTP, which inhibits R. N. A. polymerase activity.[27-29]

Interferons

Interferon-α and-β were tested against nCoVs as in 2012. Some trials on interferon-β against MERS declared the efficacy of the drug. Delayed therapy will impair the effectiveness of such agents as potential treatment. According to clinical trials until today, interferons' use to treat SARS-CoV-2 cannot be recommended at this stage.

Chinese traditional medicines

Several traditional Chinese medicine (TCM) descriptions were used in 2003 to manage and treat SARS. China provided the TCM program for the management of H1N1 infections in 2009. Many clinical trials are progressing for the treatment of COVID-19 based on previous studies and also used as an empirical treatment during the COVID-19 pandemic. Among which, some performed very well clinically. However, utilizing Chinese herbal medicine against COVID-19's is based on reducing patients' severe symptoms. Used herbs are categorized based on the severity of symptoms in patients. For instance, a mixture known as Sangju yin (a mixture of mulberry and mint) has been used for mild symptoms. On the other hand, Baihegujin Tang (a mixture of Shudihuang, Xuanshen, and Beimu) has been utilized for managing severe symptoms.[30-32]

Methods

In the status quo of the COVID-19 pandemic, an analysis of outcomes reporting from roughly a thousand globally registered clinical trials of COVID-19 has been conducted in this article. These trials were registered online on ClinicalTrials.gov, Chinese Clinical Trial Register, E.U. Clinical Trial Register, Iranian Registry of Clinical Trial, German Clinical Trials Register, Japan Primary Registries Network, Thai Clinical Trials Registry, ISRCTN, Netherlands Trial Register and ANZCTR. In the following review, we try to recapitulate the protocols and guidelines considered in clinical trials databases.

Results

This article found 927 different protocols as clinical trial studies in 33 countries [Table 1], and multiple countries carried out some guidelines.

Table 1: Frequency of eligible published clinical trials from different countries

Countries	Number of studies	Percentage
Australia	8	0.95
Belgium	4	0.47
Brazil	4	0.47
Canada	9	1.06
China	633	74.82
Denmark	6	0.71
France	23	2.72
Germany	6	0.71
Iran	10	1.18
Italy	17	2.01
Japan	4	0.47
Mexico	4	0.47
multi countries	20	2.36
Norway	4	0.47
Spain	7	0.83
The Netherlands	11	1.30
Turkey	3	0.35
United Kingdom	13	1.54
United States	38	4.49
Switzerland, Sweden, Korea, Israel, Greece, Egypt, Colombia,	2	1.68
Vietnam, French Guiana, Hong Kong, Ireland, Jordan, Pakistan, Romania, Singapore	1	1.08
Grand total	846 of 927	100.00

These researches have registered in different databases. The factors that were evaluated in these studies were: target size, population age, and recruitment status are other factors that were studied in this article. We also focus on the other elements, such as multiple types of randomization and blinding. Furthermore, different study types plus designs and clinical trial phases are included in our research. Most drugs or chemicals used in these studies were such as convalescent plasma, hydroxychloroquine, corticosteroids, mAbs, anti-virals, lopinavir/ritonavir, nitazoxanide, guanine analogs, umifenovir, oseltamivir, favipiravir, and interferons.

The most common similarities between different trials are repurposing of older medications, particularly in countries like China, that traditional medicine is focused on. Potential pharmacological guidelines of COVID-19 infection are drugs commonly used in handling SARS and MERS. Up to now, there is no significant benefit in any of the regimens that has been used for SARS and MERS therapy studies.[5,25,33,34]

Discussion

COVID-19 is, in general, a new mysterious challenge for humankind. Up until now, there is no cure or vaccine, and the mortality rate is high. Hence, it seems vitally important to conduct more research on prevention or treatment options. Information shortage and workload on clinicians are some of the obstacles to further and higher quality research. Controversy in results is reasonable according to the different races, genetics, situations, and government policies. So systematic reviews of such studies are vulnerable to summarize the last attempts and help the next studies for a better design. It can also mark the scientific spaces for researchers. The COVID-19 pandemic represents this generation's most substantive global issue, possibly, since the 1918 flu outbreak. The considerable number of clinical trials attempted to identify a possible cure for COVID-19 shows the fundamental need for international collaboration more than ever before. To date, no treatments have been demonstrated to be effective even though some medications were successful as symptomatic therapy.

This study is a systematic review of all 927 clinical trial studies performed worldwide from the beginning of the COVID-19 mysterious pandemic in China. According to our results, most studies (74.82%) are presented in China, which seems logical due to starting the China outbreak. According to the best of our knowledge, China (74.82%), the United States (4.49%), France (2.72%) have the most significant number of clinical trials, respectively. Clinical trials can be Randomized or nonrandomized. Due to our results, 32.58% 0f studies were randomized, and 7.12% were not randomized. According to our result, the number of randomized trials is superior to nonrandomized trials [Table 2].

This study is the first review that focuses on the percentage of blinding property of studies. According to our investigation, most of the studies were open-labeled studies (22.44%), and double-blinded (4.42%) and quadruple blinded (2.48%) studies stand in second and third place regarding the number of trials, respectively [Table 3]. However, Lythgoe and Middleton in their review, mentioned the blinding status of each study without statistical analysis.

This study is the first review that summarizes and calculate the type of research. According to our inquiry, 57.71% of studies were interventional studies. Observational studies with 34.73% contribution were in second place.

Most of the studies were in phase 0 (22.43%), Phase 4 (10.57%), 2 (7.55%), 3 (6.69%), 1 (4.74%) studies, respectively were in the next places. No other reviews evaluate this property.

According to our analysis of data, most studies have focused on hydroxychloroquine, an anti-malaria drug.

Table 2:Frequency of eligible published clinical trials on the basis of randomization

	Number of studies	Percentage
Nonrandomized	66	7.12
Randomized	302	32.58
Grand total	368 of 927	100

Table 3: Frequency of eligible published clinical trials on the basis of blindness

	Number of studies	Percentage
Blinded	3	0.32
Double-blinded	41	4.42
Open-labeled	208	22.44
Quadruple-blinded	23	2.48
Single-blinded	21	2.27
Triple-blinded	11	1.19
Grand total	307 of 927	100

This result aligns with the results of Lythgoe and Middleton.[6] TCM and Routine treatment of Western Medicine stand in second place.

Conclusion

Since late 2019, COVID-19 has been recognized as the biggest challenge of the present century. Numerous clinical studies have been performed on the structure and function of the virus to date, but unfortunately, no specific treatment has been introduced yet. Scientists around the world are simultaneously conducting several clinical and exploratory studies. According to the latest reports, this novel virus infected 27 million people around the world and has been responsible for the death of at least hardly a million lives. Convalescent plasma, hydroxychloroquine, corticosteroids, mAbs, and anti-viral drugs are investigated in the hope of finding a cure. Randomized and open-labeled trials have the most significant share of the trials and research up to date. According to scholars, there is no guarantee to find a cure or vaccine anytime soon. Our team decided to categorize the ongoing clinical trials according to the clinical trial types, and country-wise, we provided a statistic on the clinical trials per country.

There is a range of limitations to this review. Firstly, the massive quantity and elevated rate of submitted COVID-19 articles mean that this study's findings and guidelines are changing rapidly. Second, the articles were generally limited to papers or transcripts in English or a few translated international trials in other languages, and most of the clinical trials published in other languages are not included in this review.

Authors' Contribution

All the authors contributed to the study, and individual involvement of authors was as follow:

All authors have participated in concepts and data acquisition. Amir Hossein Alizadeh Bahmani, Mehdi hoorang, Sheida Hosseini, Mehrnoosh Eskandari, Kiana Shayestehfard were designed, collected and analyzed data, and prepared and edited the manuscript. Nazafarin Hatami-Mazinani and Saba Afifi were contributed to literature searching and data collection. Ali Mohammad Sabzghabaee reviewed and approved the manuscript. Payam Peymani, as the corresponding author of this study, participated in all sections of the study and approved this manuscript for publication.

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Conflicts of interest

There are no conflicts of interest.

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