Review Article

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Safety and Efficacy of Different Therapeutic Interventions on Prevention and Treatment of COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes coronavirus disease 2019 (COVID-19), a respiratory illness. COVID-19 has now become a global public health crisis causing alarming numbers of morbidity and mortality. Ever since the COVID-19 pandemic started scientists, researchers, universities, companies, and institutions all around the world have been endeavoring to discover a potential treatment for COVID-19. Numerous studies and clinical trials on vaccines and drugs for the prevention and treatment of COVID-19 are underway across the world. However, the uncertainty around the efficacy and safety of various treatment regimens have become one of the biggest challenges in the battle against the SARS-CoV-2. This paper is a narrative review of articles regarding the various treatments and vaccines being tested for the SARS-CoV-2, available in the PubMed database along with Google Scholar. There are ongoing clinical trials on potential drugs such as remdesivir, favipiravir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, corticosteroids tocilizumab, azithromycin, anakinra, etc. and other therapeutic modalities like convalescent plasma therapy. Likewise, vaccines against SARS-CoV-2 are being developed and tested, including mRNA, non-replicating viral vector, DNA, protein subunit candidate vaccines, etc. Although some early-stage clinical trials and studies on these drugs and vaccines have shown positive results, definitive and conclusive results are yet to be obtained.

Keywords: COVID-19; antiviral drugs; COVID-19 treatment; COVID-19 vaccine; SARS-CoV-2

INTRODUCTION

The COVID-19 pandemic continues to grow at an unprecedented rate around the world.[1,2] According to the World Health Organization (WHO), there are more than 500,000 deaths and more than 10,000,000 people have been infected as of June 11, 2020.[3]

Currently, no specific treatment or vaccine has been proven to be an effective cure for COVID-19. Available evidence suggests that SARS-CoV-2 primarily targets the pulmonary epithelial cells. A cytokine storm is the reason behind acute lung injury, and hyperactivity of the complement system through the alternate pathway has been hypothesized as the possible mechanism.[4-6]

Scientists and researchers have been working on vaccine and drug development and studies are being conducted on the use of treatment options (for COVID-19) that had been used in other coronaviruses such as SARS and MERS.[7] A review on best available evidence regarding antiviral agents is required for optimal decision making in clinical practice. Hence, this review article aims to briefly summarize the different literature available on the efficacy of various COVID-19 related drugs, vaccines, and other treatment options that are being studied and developed against it.

METHODS

We searched for clinical studies providing data on the safety and efficacy of different therapeutic interventions for the prevention and treatment of COVID-19 restricting the search to English articles. We included all clinical study trials, review papers as well as organizational reports. The electronic database PubMed along with Google Scholar search engine was used for the literature search. Endnote X7 was used for searching and retrieving the literature from the PubMed database. The keywords used for searching the literature broadly belonged to COVID-19, SARS-CoV-2, COVID-19 vaccines, COVID-19 drugs, COVID-19 treatment.

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CLINICAL TRIALS ON POTENTIAL DRUGS

Numerous drugs, for example, antivirals like remdesivir, favipiravir, lopinavir/ritonavir, oseltamivir, antimalarials like chloroquine and hydroxychloroquine, and supporting drug agents like barcitinib, tocilizumab, azithromycin, anakinra, corticosteroids, ruxolitinib, etc. are undergoing clinical research to test their efficacy in combating the COVID-19.

WHO's solidarity trial: The WHO and partners launched an international clinical trial that aims to compare four treatment options (Remdesivir, Lopinavir with Ritonavir, Lopinavir with Ritonavir plus Interferon beta-1a) against standard of care, to evaluate their relative efficacy against COVID-19.[8] This is an open-label, randomized, multinational clinical trial comparing safety and efficacy of the experimental drugs plus standard of care with standard of care alone in COVID-19 adults patients (age ≥18 years) who are recently admitted in hospital, or already hospitalized. The end points of this clinical trial include in-hospital mortality in COVID hospitals, duration of hospital stay, receipt of ventilation or intensive care, and adverse events.[8] Since the treatment landscape of COVID-19 is rapidly evolving, the Solidarity trial has been designed as an adaptive clinical trial which allows the treatment arms to be modified based on interim analyses and Data Safety Monitoring Board's decision.[8] Nepal has also already decided to join this trial and preparatory work is on progress.

On May 23, 2020, the organization temporarily suspended randomizing patients into the chloroquine/hydroxychloroquine arm of the trial due to safety concerns as one published multinational registry study reported them to have negative health effect i.e. higher mortality rate.[9] The organization restarted its hydroxychloroquine arm of the trial after the retraction of a multinational registry study reporting its negative health effects but again made an announcement on June 17, 2020, to discontinue this arm of the trial. This decision was taken on the basis of evidence provided from the Solidarity trial and UK's Recovery trial that hydroxychloroquine did not show any positive results when compared with standard care.[8,10,11]

RECOVERY trial: It stands for Randomized Evaluation of COVID-19 Therapy and is considered to be one of the biggest randomized clinical trials for COVID 19 with the participation of more than 11,000 patients at 175 sites in the United Kingdom.[12] In this, trial possible treatments such as lopinavir-ritonavir, low dose dexamethasone, azithromycin, tocilizumab, and convalescent plasma are being studied.[13] In addition to the usual standard of care, all eligible patients are allocated randomly between various treatment arms and compared with standard of care alone. Simultaneously, all eligible patients are allocated to no additional treatment vs convalescent plasma in a factorial design. For patients with progressive COVID-19 (evidence of hyper-inflammatory state) the study allows a subsequent randomization for patients: no additional treatment vs tocilizumab. Randomization will be between fewer arms for patients for whom not all the trial arms are appropriate or at locations where not all are available.[14] Mortality, discharge, ventilation need, and renal replacement therapy need will be the major results of the study. Follow-up will be done at 28 days after randomization for main analyses.[14]

Although the study results have not been published, the preliminary results released in the form of media release by RECOVERY trial investigators have shown the benefit of low dose dexamethasone therapy in patients with severe COVID-19.[15] On the other hand, chief investigators of this trial announced that there was no difference in outcome between standard of care (SOC) alone compared to hydroxychloroquine plus SOC.[11,12]

Remdesivir: A drug initially created for Ebola virus treatment has picked up considerably since the beginning of the COVID-19 pandemic as certain clinical studies indicated positive fundamental results with respect to the utilization of remdesivir. Research with the Ebola virus indicated that remdesivir had very low efficacy against the virus because it causes mutations in the Rhesus Monkey hepatitis virus RNA replicase which causes partial resistance to the virus. These mutations make the viruses less effective in nature, and the researchers believe they will likely not persist where the drug is not being used.[16]

This drug had also priorly showed encouraging results in animal trials for treating MERS and SARS, caused by coronaviruses.[17,18] Studies have demonstrated that remdesivir inhibits viral replication of SARS-COV-2 within the host cells by targeting divergent RNA-dependent RNA polymerase.[19] A preliminary report of a clinical trial of remdesivir conducted by National Institute of Allergy and Infectious Diseases (NIAID) in 1,063 hospitalized COVID-19 patients showed a positive effect by decreasing the time to recovery from 15 days to 11 days (rate ratio for recovery: 1.32, 95% CI, 1.12-1.55, $P < 0.001$) in patients receiving oxygen.[20] However, this drug alone did not have a statistically significant impact on mortality in COVID-19 patients. Also, a trial report published in The New England Journal of Medicine suggested positive results when this drug was used as a compassionate treatment in COVID-19 patients. In this

study, COVID-19 patients with severe symptoms were treated with remdesivir and 36 of 53 patients showed clinical progress, however, because this study did not include a control group it is difficult to draw definite conclusions from it.[21] Other studies and reviews have indicated encouraging results from this anti-viral drug, but indicated the need for strong, high-quality data to prove its safety in humans.[22-25] Contrary to this, a multicenter trial study carried out at ten Hubei hospitals in China failed to show the benefit of remdesivir in the treatment of COVID-19, but this trial was underpowered as it did not achieve its enrollment goal.[26] Most recently, a comparison between 5 days and 10 days of remdesivir showed equivalent outcomes in hospitalized patients with COVID-19.[27]

Favipiravir: Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses.[28] This anti-viral drug was initially developed by Fujifilm Holdings and was used for influenza treatment in Japan.[29]

As per the results of the first stage of a clinical trial carried out by ChemRar group in Russia among 60 patients, the study revealed that this drug showed a higher antiviral activity. It showed that favipiravir completely eliminated the SARS-CoV-2 virus in four days while it took nine days for patients in the control group receiving standard care.[30] A preprint paper on an open-label multicenter study of 240 COVID-19 patients with pneumonia, conducted in three hospitals in Wuhan, China, reported that favipiravir was useful in improving latency for cough and pyrexia compared to umifenovir, but favipiravir did not significantly improve the rate of clinical recovery at day 7. They also reported the side effects of favipiravir as mild and manageable.[31] Also, an open-label non-randomized control study conducted in Shenzen, China involving 80 patients reported that favipiravir had positive disease progression and viral clearance outcomes and could thus be a promising choice for treating the infection.[32]

Lopinavir- ritonavir: Lopinavir/ritonavir, a US Food and Drug Administration (FDA)–approved oral combination agent for treating HIV, demonstrated in vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease.[33] A clinical trial conducted in China among 47 patients revealed that the combination treatment with lopinavir-ritonavir and pneumonia-associated adjuvant drugs had a therapeutic effect in reducing the body temperature (experimental arm: 4.8±1.94 days vs. control arm: 7.3±1.53 days, p=0.0364) and bringing back the normal physiological mechanism with no apparent toxic effects.[34] Likewise, a phase 2 trial carried out in hospitals of Hong Kong among 127 patients showed that treatment of patients having mild to moderate COVID symptoms with early therapy of lopinavir-ritonavir and interferon beta-1b to be safe in easing symptoms and reducing the duration of hospital stay.[35] However, an open-label, randomized control trial performed in Wuhan, China involving 199 patients revealed that in hospitalized extreme COVID patients, lopinavir-ritonavir had no advantage (hazard ratio for clinical improvement: 1.31, 95% CI, 0.95-1.80) that surpassed the standard treatment.[36]

Chloroquine and hydroxychloroquine: Chloroquine and hydroxychloroquine have been previously used for malaria and rheumatoid arthritis. Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification.[37] These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[37] Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC50) in the low micromolar range.[38]

Although some studies have reported its positive preliminary outcomes, many other studies/clinical trials are underway around the world and hence definite conclusions cannot be made yet.[22] The widescale use of this drug has been discouraged until the generation of high-quality evidence on its safety and effect. In vitro studies have suggested that chloroquine and hydroxychloroquine have shown anti coronaviruses effects.[22,39] Likewise, a systematic review study also suggested chloroquine to be effective against the SARS CoV2 by limiting the virus's replication in vitro.[40] Similarly, a systematic review and meta-analysis showed that hydroxychloroquine was a safe and effective drug but suggested the requirement of more studies to confirm its efficacy.[41]

On the contrary, clinical studies have found that hydroxychloroquine receivers reported greater side effects than non-receivers.[42] A multinational registry study on hydroxychloroquine or chloroquine with or without macrolide performed on 96,000 COVID patients worldwide showed higher death rates with a higher likelihood of heart-related condition, and cautioned that it should not be used for treatment for COVID-19. However, this multinational registry study paper published in the

Lancet was recently retracted due to problems related to auditing of the study data.[43] Similarly, a retrospective cohort study conducted in 25 hospitals of New York State among 1438 hospitalized COVID-19 patients found out that treatment with hydroxychloroquine, azithromycin, or both did not aid in decreasing the COVID-19 related in-hospital deaths.[44] While the early trials showed promising results of chloroquine and hydroxychloroquine but there are not enough convincing evidences to prove that these drugs are safe alternatives for the treatment of COVID-19. The chloroquine/hydroxychloroquine arm of the Solidarity trial and RECOVERY trial have also been stopped due to the inadequate evidence on its benefits over the standard care.[8, 11]

SUPPORTING AGENTS

Adjuvant agents such as azithromycin, ascorbic acid, tocilizumab, anakinra, corticosteroids, sarilumab, are also being used for supportive care for SARS-CoV-2 infected patients.[45] Azithromycin is an antibiotic and is used to treat secondary bacterial infections in patients with a viral infection. A lot of research is being conducted around the world to assess the efficacy of these adjuvants.

A retrospective study carried out in France on the use of azithromycin along with hydroxychloroquine showed positive results but since this study has been withdrawn it raises a question about its efficacy. However, in a study conducted by Molina et al, the usage of hydroxychloroquine along with azithromycin showed no positive clinical results.[46] Therefore, future researches are essential to understand the benefits and risks of azithromycin as one of the safe treatment options.

High- dose vitamin C has been suggested to be one of the potential and beneficial alternative for treating respiratory symptoms caused by a coronavirus, with minimal side effects.[47,48] Obviously clinical trials are essential in exploring the benefits and risks of high-dose vitamin C in treating infections caused by SARS-CoV-2. In Wuhan, China, the first randomized controlled trial on ascorbic acid (vitamin C) has been initiated and this study will be checking the effects of IV vitamin C in 140 COVID-19 patients.[49]

CLINICAL TRIALS OF CONVALESCENT PLASMA THERAPY/TREATMENT

This therapy was also used during the Spanish flu epidemic, Ebola virus outbreak, H1N1 pandemic and has been used as a last resort to treat SARS. In the present context, there has been a lot of positivity about the usefulness of this treatment all over the world.[50] Multiple trials and studies are underway in various regions around the world. This treatment has been recommended by WHO, the US Food and Drug Administration (FDA), and the European Commission to be used as an investigational agent only. Likewise, it has been recommended that convalescent plasma use should be limited only for patients with severe or life-threatening illnesses secondary to COVID-19. The convalescent plasma should be obtained following standard blood bank protocols from selected donors who have completely recovered for at least 14 days prior to donation.[51-53]

In the United States, a nationwide project has been launched involving more than 1500 hospitals. This therapy is basically about harnessing the healthy antibodies through the blood of recovered COVID 19 infected patient to a healthy person and no proven adverse effects have been recorded yet. A matched control study done in 39 COVID-19 hospitalized patients in Mount Sinai Hospital in the United States revealed that their preliminary study findings indicated the possibility of convalescent treatment to be an effective intervention against the SARS-CoV-2 virus. The preprint paper reported that this treatment procedure showed probable benefits in relation to mortality due to the virus as the plasma recipients demonstrated improved survival.[54] Likewise, a pilot study conducted among 10 severe COVID-19 patients in Wuhan Jinyitan Hospital in China showed a positive clinical outcome where convalescent plasma treatment served as a potential option for treating COVID-19 infected patients. According to the report, this treatment led to a decrease in lesions in the lungs and to the elimination of the virus from the bloodstream caused by the virus within 7 days.[55] Similarly, another study carried out among 6 infected patients in China showed a similar positive clinical outcomes of convalescent plasma therapy and reported it to be effective against SARS-CoV-2.[56] A study conducted in two cases of COVID-19 with extreme pneumonia along with acute respiratory distress syndrome in Korea also reported positive results about the use of convalescent plasma therapy as a beneficial option of treatment. However, this study suggested that more clinical trials are required to provide credible evidence.[57] Most recently, Ling Li et al published results of an open-labeled, multicentered, randomized clinical trial from China, that demonstrated viral clearance in 87% of patients who received convalescent plasma transfusion compared to those who did not.[58] Nepal has also started clinical trial on convalescent plasma therapy.

CLINICAL TRIALS OF VACCINES

More than 120 vaccines against SARS CoV-2 are being

developed around the world. According to the World Health Organization's vaccine candidates list for COVID-19, 10 candidate vaccines are in the clinical evaluation phase whereas 114 candidate vaccines are in the preclinical evaluation phase.[59] It has been estimated that it may take 12 to 18 months to create a vaccine against the virus, according to WHO.[60] Various approaches have been adopted to develop the vaccines for SARS-CoV-2. Different vaccine candidates include DNA vaccines, live attenuated vaccines, mRNA vaccines, protein-based vaccines, inactivated vaccines, vaccines involving adenovirus and other viruses, etc.

According to the data demonstrated by Moderna Inc on May 18, 2020, the interim phase clinical trial revealed that the experimental SARS CoV-2 vaccine (mRNA-1273) produced protective antibodies in eight of the study subjects indicating the vaccine's possible immunogenicity. This vaccine was found to avert the replication of SARS-CoV-2 virus in the lungs of the vaccine recipients. The phase 3 experiment of this mRNA vaccine is expected to take place in July.[61] Likewise, a clinical trial, first human trial, carried out by CanSino Biological Inc in China reported that the Ad5 vector vaccine indicated its ability to trigger an immune response against the SARS-CoV-2 virus. This study was carried out in 108 healthy people and these vaccinated people's blood samples showed a rapid immune response, which is an indicator of potential effectiveness. Seventy-five percent of the vaccinated persons were reported to have antibodies in their bodies neutralizing against the virus.[62] However, the researchers suggested that human beings have pre-existing immunity to the cold virus, and can, therefore, be immune to the Ad5 virus delaying the vaccine's progression. Therefore, this finding does not actually stipulate the vaccine's efficacy in shielding people from the virus, but it definitely serves as valuable and convincing evidence for further study. A study on 25 rhesus macaques receiving six candidate DNA vaccines carried out at Beth Israel Deaconess Medical Center (BIDMC) showed that neutralizing antibodies were induced against the SARS-CoV-2 virus. According to the study, vaccinated rhesus macaques showed a lower level of virus upon being exposed to the virus after three weeks of getting a boost vaccination. Thus, this study's results may serve as valuable evidence for further investigation. ChAdOx1 nCoV-19 vaccine is being developed by the Oxford University and trials for humans started in late April 2020. The adenovirus used in this vaccine is a weakened common cold virus. This vaccine is said to produce a strong immune reaction to the contagious SARS-CoV-2 virus. The preprint paper reported that the trial performed on animal models prior to the human trial found the vaccine to be effective by averting pneumonia on vaccinated rhesus monkeys.[63] Although the initial results were encouraging, the detailed report on animal trial revealed that the monkeys who were vaccinated contracted the virus. Phase 2 and Phase 3 trials are about to begin and is expected to include over 10,000 individuals.[64]

A preclinical study conducted on a DNA vaccine candidate (INO-4800) by INOVIO pharmaceuticals in mice and guinea pigs reported producing strong neutralizing antibodies along with immune reactions against the COVID-19 virus indicating reassuring results. The phase 1 trial on this vaccine is said to begin for further investigation from June, 2020.[65] Likewise, a US biotech company Novavax carried out a preclinical trial on the protein subunit vaccine in an animal model and the reported results of this study have shown positive outcomes. This vaccine was found to be highly immunogenic and is expected to provide protection against the SARS-CoV-2 virus in humans as well. The first phase of the clinical trial of this vaccine has already been initiated in Australia.[66] The other vaccine candidates racing against the COVID-19 are from companies and institutions such as Sinopharm, Sinovac, BioNTech/Fosun Pharma/Pfizer, etc.[59]

CONCLUSIONS

The uncertainty around the successful development of safe and efficacious treatment/ preventive regimens is surely one of the biggest challenges in dealing with the SARS-CoV-2. Likewise, there also exists a challenge after the invention of successful treatment or vaccine, which will be to produce and distribute the drug or vaccine around the world at a larger scale in a rapid and equitable manner.

From our review, it can be concluded that antimicrobial agents (especially antivirals), in combination with an adjuvant therapy, may be effective in the treatment of the disease. However, concrete evidence about which agent will be most safe and efficacious is yet to be obtained. In order to determine the efficacy and safety of these therapeutic interventions for COVID-19, more adequately powered randomized clinical trials are required.

Researchers and scientists all over the world are continuously working to find out a safe and effective treatment for and vaccines against the SARS-CoV-2. Although early-stage studies and ongoing clinical trials have shown some reassuring results, doubts on the efficacy of the different treatment regimens will remain until the studies provide evidence-based, definite, and conclusive results. In addition, researchers are facing various logistic and ethical obstacles as well as time

constraints in developing drugs and vaccines against SARS COV-2. It has been projected that a possible treatment or vaccine may take up to 18 months to be developed. However, the progress (as evidenced by the study results across the globe) is highly reassuring. Despite the fact that it may take time to find the confirmed safe and effective treatment against the virus, existing and ongoing studies reassure that the treatment for COVID-19 may just be around the corner.

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