Advances in Drug and Vaccine Development for SARS-CoV-2: A Review of RCT data

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Abstract

SARS-CoV-2 is a novel coronavirus that has been causing global pandemic since December 2019. It targets the respiratory tract. As the time of writing this review, there is no specific treatment for COVID-19. A number of studies have proposed the utilization of some drugs as part of the repurpose strategy. This review was undertaken to evaluate the efficiency of drugs and vaccines being developed against SARS-CoV-2. It was based on synthesis of clinical research data whose results have been published. Three antiviral agents were identified as being effective and safe: Remdesivir, Lopinavir-ritonavir in combination with ribavirin. For the vaccine candidate, only one candidate was included in the review. This is mRNA vaccine (mRNA-1273) which was developed by Moderna, a US based company. In addition, new data although not synthesised but worth mentioning is the effect of dexamethasone, an anti-inflammatory drug. This review therefore recommended that glucocorticoids such as dexamethasone should be combined with remdesivir. In addition, the effect of combining remdesivir with lopinavir-ritonavir plus ribavirin should be elucidated both in short and long term.

Key words: Covid-19, drug, vaccine, development, epidemiology


Introduction

Novel coronaviruses targeting the respiratory system have shown an increasing impact over the last two decades. The novel coronavirus, SARS-CoV-2, causing the current pandemic is a major pathogen having an historical impact on the present generation. This virus is related to the virus that caused the severe acute respiratory syndrome (SARS) outbreak from 2002-2004 and the coronavirus group that caused Middle East respiratory syndrome (MERS) in 2012 which triggered great public health challenges. Known cases of COVID-19 in humans were first reported by the Wuhan government in December 2019, after several dozen patients were admitted to hospitals with an initial diagnosis of pneumonia of unknown cause. Initial cases were traced to the Huanan Seafood Market, a seafood and wet animal wholesale market, in Wuhan, Hubei Province, China (1, 2). Following the ruling out of other known causes such as MERS, SARS, avian flu, and adenovirus, on 11 February 2020, the World Health Organization (WHO) named the virus COVID-19 (3) and identified it as the cause as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the family of *Coronaviridae*.

The history for the emergence of this pandemic is as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2019</td>
<td>Initial cases of infection were reported</td>
</tr>
<tr>
<td>18 December to 29 December 2019</td>
<td>It was reported that 5 patients were admitted to the hospital with acute respiratory distress syndrome(5).</td>
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<tr>
<td>2 January 2020</td>
<td>41 patients admitted to the hospital were confirmed to have COVID-19 with half of them having some underlying conditions such as diabetes, hypertension and cardiovascular disease (6). It was assumed at this time that COVID-19 was not transmitted by a patient to many other individuals (super-bacterial). This was the first mistake by the global bodies.</td>
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<tr>
<td>22 January 2020</td>
<td>Approximately 571 cases of COVID-19 were reported across 25 provinces in China with an associated 56 deaths (7).</td>
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<td>30 January 2020</td>
<td>7734 cases had been confirmed in China and cases were reported around the globe, including in Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, UAE, US, Philippines, India, Australia, Canada, Finland, France and Germany.</td>
</tr>
<tr>
<td>1 May 2020</td>
<td>3,251,925 confirmed cases with the top countries being the USA (1,068,696), Spain (213,435), Italy (205,463), United Kingdom (172,478), and France (167,299)</td>
</tr>
<tr>
<td></td>
<td>Total deaths reported were 233,014</td>
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Figure 1: Timeline of COVID-19 pandemic

At the time of writing this manuscript, no definitive treatment for COVID-19 has been identified. However a variety of potential treatment protocols focusing on both antivirals and antibiotics have been proposed. Early research from China suggested that early and effective antiviral treatment is necessary to reduce the risk of bacterial co-infection and improved overall outcomes (8). The research
team recommended a treatment protocol for the management of COVID-19 patients, which included empirical treatment with moxifloxacin or levofloxacin and arbidol. Of note arbidol (Umifenovir) is only approved for use in China and Russia, but not currently approved by the United States Food and Drug Administration (USFDA). While this strategy was implemented in the clinical setting in Wuhan, China, based on real-time, on-the ground situational analysis the therapeutic strategy has not undergone clinical trials and its efficacy has not been verified. In the United States, the FDA approved the use of two quinoline antibiotics, hydroxychloroquine, and a related drug, chloroquine, for emergency use against COVID-19. However, emerging evidence from a non-peer reviewed study conducted within the Veteran Affairs system in the United States has shown that hydroxychloroquine does not reduce risk of deaths (9). The FDA has since discontinued the emergency use of Hydroxychloroquine and chloroquine. With little quality evidence and the emergent need for treatment options, a number of theories on treatment have emerged. These include the use of other antiviral drugs (repurpose strategy) such as Remdesivir, which has been shown to inhibit other coronaviruses like SARS and MERS in the laboratory. Based on the study in China and a Gilead-sponsored open-label trial, the US FDA issued Emergency Use Authorization on 1 May 2020 for the emergency use of remdesivir in hospitalized patients with COVID-19 (10, 11).

In United Kingdom, a randomized clinical trial showed a promising result in the use of Dexamethasone, an inexpensive steroid to cut deaths by up to one-third among those who were on ventilators due to COVID-19.

This systematic review will evaluate the safety and efficacy of novel drugs which are being tried for the treatment of COVID-19. In addition, as the vaccine strategy is ramped up, it will evaluate the effectiveness, safety, and immune responses elicited by novel vaccines for COVID-19.

**Method**

The main objective was to evaluate the efficacy and safety of novel antiviral drugs and vaccine formulae for the treatment and prevention of COVID-19 infections. The following protocol was followed:

**Study Design**

This systematic review was performed in two sections. In the first section, a critical analysis of novel antiviral drugs used in the management of COVID-19 was made. In the second part, an analysis of the novel vaccine candidates available for COVID-19 was made.

**Selection Criteria**
In both sections of this study, randomized controlled trials (RCTs) that evaluated the efficacy and safety of antiviral drugs and vaccine candidates were included. Only trials with completed status and published articles are included. Exclusion criteria include studies that did not follow RCTs. Also all studies that involved hydroxychloroquine were excluded.

Search Strategy

A search of PubMed, Cochrane library, and clinical trials registration databases was conducted. The key words used for this study were “COVID-19”, “antiviral therapy”, and “vaccine candidates”. The search included studies from January 2020 to April 2020. No meta-analysis was made.

Data Collection

Titles and abstracts of identified studies were reviewed. Next, the full texts of these articles were reviewed carefully. Finally, related articles based on inclusion and exclusion criteria were included in this systematic review. Finally, the articles and collected data were summarized based on the following parameters: name of the corresponding author, publication month, type of study, sample size, age and sex distribution of the subjects, the drug used, dose and duration of administration, route of administration and the treatment outcome. With the vaccine candidate, immune response was also evaluated.

Result & Discussion

Antiviral Agents

We identified 1365 articles from our electronic search of the databases. Review of the reference lists of relevant papers did not provide us with relevant articles suitable for our review. We obtained the full text of 100 articles and 3 articles were included after full-text review (12, 13, 14, 15).

Lopinavir-Ritonavirin combination with ribavirin: Hung et al. assessed the efficacy and safety of combined IFN beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients with COVID-19. The study was a multicenter, prospective, open-label, randomised, phase 2 trial which involved adults with COVID-19 who were admitted to 6 hospitals across Hong Kong. The subjects were randomly assigned to a combination group who were given lopinavir 400 mg and ritonavir 100 mg every 12 hours, ribavirin 400 mg every 12 hours and 3 doses of 8m IV of IFN-beta 1b on alternative days, and a control group who were given lopinavir 400 mg and ritonavir 100 mg every 12 hours. The time frame was 14 days in both arms. The primary endpoint was time to provision of nasopharyngeal swab which was negative for SARS-CoV-2, and the other virological endpoint was achieving a negative SARS-CoV-2 RT-PCR in all clinical samples. The study was performed in the intention-to-treat population. 127 subjects took part in the study with 86 randomly assigned to the combination group.
while 41 were assigned to the control group. In the combination group, significant reduction in media
time was reported from start of study treatment to negative nasopharyngeal swab than in the control
group. Some adverse events such as self-limited nausea and diarrhoea were reported in both groups.
One patient in the control group stopped lopinavir-ritonavir because of biochemical hepatitis. There
was no mortality reported during the study. The authors therefore concluded that early triple antiviral
therapy was superior to lopinavir-ritonavir alone in reducing the symptoms and the duration of viral
shedding as well as hospital stay in patients with mild to moderate COVID-19. However, on the basis
of the study, more studies are needed to evaluate the effect of double antiviral therapy in which IFN
beta-1b is used as a backbone. Cao et al. on the other hand evaluated the effect of lopinavir-ritonavir
among 199 patients with laboratory confirmed SARS-CoV-2 infection. 99 were assigned to the
treatment arm while 100 were assigned to the control arm (standard care). The study did not observe
any benefit of lopinavir-ritonavir treatment beyond the standard care.

Lopinavir and ritonavir are used as protease inhibitors commonly used in HIV therapy. The same
protease is used by both HIV and coronaviruses. On the other hand, ribavirin is a guanosine analogue
that has broad antiviral activities against several RNA and DNA viruses. Because there is no effective
antiviral agent purposely for COVID-19, these two drugs were utilized as a repurpose drug in the fight
against COVID-19. Some studies had earlier utilized a similar strategy in fighting viral outbreaks. In
2004, Chu et al. evaluated the effect of lopinavir-ritonavir and ribavirin for in vitro antiviral efficacy
for severe acute respiratory syndrome (SARS) by running them against a number of antiviral agents.
They found that there was favourable clinical response with lopinavir-ritonavir and ribavirin in
patients with SARS with an in vitro susceptibility analysis showing cytopathic impact of SARS
coronavirus been inhibited by lopinavir at 4µg/ml while ribavirin was given at 50µg/ml after 48 hours
of incubation. However, the inhibitory effect was observed to have worn out after 96 hours (16). A
study observed that patients with SARS when treated with lopinavir/ritonavir appeared to exhibit
milder disease course with regards to diarrhoea, the recurrence of fever, and worsening findings on
chest radiography (17). However, the course of the disease is dependent on the concentration of the
drugs used. The study by Hung et al. found that when the combination of oral lopinavir-ritonavir,
ribavirin, and injectableIFN was given within 7 days of the onset of the symptoms it led to effective
inhibition of SARS-CoV-2 shedding. This inhibition was found in both the nasopharyngeal swab and
the clinical specimens. In addition, there was significant reduction in the period of RT-PCR positivity
and viral load which was linked to clinical improvements. Most of the patients in the combination
group were found to be RT-PCR negative in all specimens by 8 days with milder and self-limiting
adverse events reported.

Remdesivir: Lu et al. (14) performed a randomised, double-blind, placebo-controlled, multicentre
trial in 10 hospitals in Hubei, China to assess the effectiveness of remdesivir on SARS-CoV-2. The
study involved 237 patients who were enrolled between 6 February 2020 and 12 March 2020 with laboratory confirmed SARS-CoV-2 infection. Patients had an interval from onset of symptoms to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractioned inspired oxygen of 300 mg Hg or less plus radiological confirmation of pneumonia. The treatment group were randomly given a 2:1 ratio to intravenous remdesivir of 200 mg on day 1 followed by 100 mg on days 2-10 in single daily infusions and a control group given same volume of placebo infusions for 10 days. Patients were allowed to concommitantly use lopinavir-ritonavir, IFN, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28 which was defined as the time in days from randomisation to the point of reduction of two levels on a six-point ordinal scale of clinical status or discharged from the hospital. They reported that remdesivir use was not associated with a difference in time to clinical improvement. However, although it was not significant, it was found that patients who were given remdesivir had a faster time to clinical improvement in comparison to the placebo group. Adverse events were reported among 102 of 155 treatment group vs. 50 of 78 in the control group. Remdesivir was stopped early due to adverse events in 18 vs. 4 patients who stopped placebo early. A preliminary data from a clinical trial from the US National Institute of Health’s National Institute of Allergy and Infectious Diseases (NIAID) (15) showed that remdesivir led to faster recovery in COVID-19 patients. The study termed ACTT involved 1063 patients who were hospitalised with advanced COVID-19 and lung involvement and compared remdesivir to placebo. An interim analysis showed that there was 31% faster time to recovery in patients who were treated with remdesivir when compared to placebo, with the median time to recovery being 11 days vs. 15 days respectively. The survival benefit was found to be 8% for the remdesivir group vs. 11% in the placebo group.

Remdesivir (also referred to as GS-5734) is a monophosphate prodrug of an adenosine analogue that has been found to possess broad antiviral spectrum against a number of viruses such as filoviruses, paramyxovirus, pneumovirus, and coronavirus (18, 19). An in vitro study showed that remdesivir inhibited all human and animal coronaviruses tested, including SARS-CoV-2 (20, 21). Earlier studies showed that there were antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV infections (20, 21, 24). When analysed in lethal murine model of MERS, remdesivir was reported to be superior in comparison to IFN beta and lopinavir-ritonavir (23). Furthermore, SARS-CoV-2 replication was shown to be inhibited by remdesivir in human nasal and bronchial airway epithelial cells (25). Finally, remdesivir was initially studied as a treatment option for Ebola virus disease where it was reported to be well tolerated but less effective in comparison to a wide variety of monoclonal antibodies therapeutics (26).

Many drugs have been shown through in vitro studies to possess antiviral activities against betacoronovirus, including lopinavir-ritonavir, ribavirin, remdesivir, IFNs, favipiravir, chloroquine,
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hydroxychloroquine, and convalescent plasma consisting of neutralising antibodies (20, 21, 22, 23, 26, 27, 28). The advantage of this strategy known as repurposing utilizes the already known characteristics including the pharmacokinetics and pharmacodynamics properties, the side–effects and the dose of these drugs. From the data of the selected trials, lopinavir-ritonavir combination with ribavirin, remdesivir, and IFN- beta have some therapeutic effect on COVID-19 especially when given early during the infection as the viral load of SAR-CoV-2 is highest around the onset of symptom. This is different when compared to SARS and MERS where the viral load can be suppressed by the antiviral treatment before it peaks around 7-10 days after the onset of symptom. However, the viral load profile of SARS-CoV-2 has been found to be similar to influenza virus because it has a high viral load at the initiation of anti-influenza therapy. One of problem of using single anti-influenza treatment is the emergence of resistant viral quasispecies in severe influenza or disease caused by H5N1, H7N9, or in immunosuppressed individuals (24, 29, 30). Therefore the use of combination therapy is used to improve clinical outcome of severe influenza infection. Although yet to be elucidated, one potential problem of using single antiviral drug in SARS-CoV-2 infection would be the emergence of resistant strains. (31, 32)

Taking lessons from HIV/AIDS, a repurposed regimen for SARS-CoV-2 infection would combine the following antiviral agents: lopinavir-ritonavir, ribavirin and remdesivir. More clinical studies would be needed to evaluate this combination in detail. Furthermore, it has been shown that SARS-CoV-2 infection does not significantly elicit type I, II, or III IFN in ex-vivo infected human lung tissue in comparison to 2003 SARS-CoV (33). Therefore the use of IFN beta-1b can be used to improve antiviral response in patients. In addition, IFN beta-1b was reported to decrease virus-associated lung fibrosis in a mouse model. This means it can be using in improving the clinical outcome of patients infected with SARS-CoV-2 with complicated acute respiratory distress (34).

Our review has some limitations. Studies that were not completed and no data posted were not included in our synthesis. In addition, we excluded studies on hydroxychloroquine and chloroquine. We also focused on only articles in English language. These biases may have impacted the outcome of our studies.

Vaccine Candidates

Search of the databases for ‘SARS-CoV-2’, ‘vaccine’, and ‘clinical trials’ resulted in 16,246 articles. After thorough analysis, only one study was considered fit to be included. The study was led by NIAID of NIH for a vaccine candidate being developed by Moderna, a US based clinical stage biotechnology company (35). The study was a phase I clinical trial with the aim of evaluating the safety of mRNA vaccine (mRNA-1273) against SARS-CoV-2 (NCT04283461). Two dose cohorts were used: 25µg and 100µg. The immunogenicity data (interim) was reported for the dose cohort.
(ages 18-55) after 2 doses (day 43) and at 250µg level (ages 18-55) after one dose (day 29). Dose dependent increase in immunogenicity was reported across the three doses levels and between prime and boost with 25µg and 100µg dose levels. All participants aged 18-55 (n=15 per cohort) across all three doses levels seroconverted by day 15 after a single dose. At day 43, two weeks after the 2nd dose, at 25µg dose level (n=15), levels of binding antibodies were similar to the level observed in convalescent tested in the same assay. At day 43, at 100µg dose level (n=10), levels of binding antibodies significantly exceeded the levels observed in convalescent sera. At the time of this synthesis, samples were not yet available for the remaining participants. Furthermore, neutralizing antibodies (nAbs) data were not available for the first four participants in each of the 25µg and 100µg dose level cohorts. mRNA-1273 vaccination was found to elicit nAbs as observed in all eight of the participants. The level of nAbs at day 43 were at or above the level generally observed in convalescent sera. mRNA-1273 was concluded to be safe and well tolerated. A single adverse event (AE) was reported in the 100µg dose cohort who experienced grade 3 erythema around the injection site. The most prominent AEs were observed at the 250µg dose level, consisting of three participants with grade 3 systemic symptoms, only after the second dose. All AEs were transient and self-resolving. No grade 4 AEs or serious AEs were reported. Based on these interim results, a phase 2 study is being planned with the 2 dose levels: 25µg and 100µg with the objective of selecting a dose for pivotal studies. A phase 3 study between 25µg and 100µg is expected to be started in July 2020 base on finalization of the clinical trial protocol.

mRNA1273 is an mRNA vaccine being developed against SARS-CoV-2 which encodes a stabilized form of the Spike (S) protein. This is the only vaccine candidate that we found to be in clinical trials with an interim report available. Because SARS-CoV-2 is novel virus, there is no available vaccine. However, a number of vaccine strategies have been described. These include INO-4800 which was created by Inovio Pharmaceuticals, chAdOX1 cCoV-19 created by University of Oxford consisting of non-replicating adenovirus vector and the genetic sequence of S protein of SARS-CoV-2. It has entered phase I/II clinical trials (NCT04324606), stabilized subunit vaccine, and nanoparticle-based vaccine. Developing vaccine(s) against SARS-CoV-2 should be a long-term strategy for preventing COVID-19 outbreaks in the future. This view is supported by the argument that COVID-19 might be a seasonal pandemic just like the flu-outbreaks. The sequencing of SARS-CoV-2 genome has given us the weapon to potentially identify multiple nucleic-acid vaccine candidates.

Conclusion

Highly specific antiviral agents are needed urgently during any novel emerging infectious diseases. However, due to the length of time to development and approval new antivirals, usually years, the strategy of repurposing an existing antiviral agent with broad-spectrum antiviral activities can be used
as a quick solution to treat other viral infections. This is an ideal approach during any pandemic where time is of utmost importance. The synthesised data from this review showed that lopinavir-ritonavir plus ribavirin, and remdesivir possess antiviral effect on COVID-19 as patients stay in the hospitals were reduced. Therefore the best combination base on the current evidence is prescribing a glucosteroid drug such as dexamethasone with remdesevir. It is essential that the effect of the combination of remdesivir with lopinavir-ritonavir plus ribavirin is critically analysed both on short and long term basis.

There is no doubt that COVID-19 has changed the way we undertake research for antiviral agents and vaccines. The WHO re-started clinical trials using hydroxychloroquine after some report showed that initial results which led to it been suspended might have some flaws however it was later halted again as the WHO decided to halt the hydroxychloroquine arm of multi arm Solidarity trial as results showed that the drug did not reduce mortality in COVID-19 patients when compared to standard care. Base on the available data, one fact is emerging: COVID-19 might become an annual pandemic just like the seasonal flu. There is still a lot to learn about this virus and when the infection level goes down, the world must not relax. We have to continue exploring the genomic content of the virus so that we are able to identify more novel targets for developing better antiviral agents and vaccine candidates. Almost all viruses are known to mutate. Some studies have shown that this novel virus also mutates. We have to understand the effect of mutation on antiviral therapy and vaccine efficiency. In addition, the latest clinical evidence shows that mortality risk is associated with coagulation in the lungs. Understanding this and developing treatment protocols would go a long way to manage this infection in future.

References


