Systematic review on current antiviral therapy in COVID-19 pandemic

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ABSTRACT

Introduction: Currently, there are several attempts to find an effective antiviral drugs against the COVID-19. Although majority of the COVID-19 patients have mild to moderate clinical events, up to 5-10% may have severe, life threatening events that urgently require effective drugs. The purpose of this systematic review is to evaluate the effectiveness of antiviral therapies in the treatment of COVID-19.

Methods: An extensive search was performed in PubMed, EMBASE, Cochrane Library for randomised controlled trials (RCTs), prospective case series studies that evaluated therapies COVID-19. The outcomes searched for were mortality, recovery rate, length of hospital stay and clinical improvement from January to May 15, 2020. Independent reviewers searched, identified, screened, and related studies were included.

Results: Total of five RCTs on 439 patients and seventeen case series involving 1656 patients were found in the specified review period that reported the use of Lopinavir, Ritonavir, Remdesivir. Oseltamivir, Ribavirin in patients with COVID-19; but none of which showed efficacy of antiviral therapy. Such current findings impede researchers from recommending an appropriate and effective antiviral therapy against COVID-19, making it a serious concern for the global community.

Discussion: In the present pandemic and any future epidemics, all the related authorities should pursue many more RCTs, cohort and case series for a prospective outcome in the management and treatment guidelines.

KEYWORDS:
COVID-19, antiviral, osaltavir, remdesivir, arbidol, lopinavir, ritonavir

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel type viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which belongs to the Corona viridae family. This family of virus was responsible for two other outbreaks in the twentieth century. The first was in 2003 caused by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). The second viral outbreaks occurred in 2012 and 2015 due to Middle East respiratory syndrome coronavirus (MERS-CoV) which is another virus from the same family. Around 8,422 cases with 11% case fatality rate (CFR) occurred during the SARS-CoV[1] and over 2500 cases with CFR 35% were reported during MERS-CoV epidemics.[2]

From late 2019 to May 15, 2020, when COVID-19 emerged from Wuhan, China a total 470 000 COVID-19 cases and approximately 314 000 deaths from the virus were reported from around the world.[3] This large number of infected patients in only five months since the first reported case of COVID-19 demonstrates that the disease is extremely contagious. The World Health Organization (WHO) announced a COVID19 pandemic in March 2020. Upon the emerging COVID-19, there was no known approved, specific, effective antiviral treatment to treat this fatal disease. A few case reports or observational studies documented some antiviral drugs that were used in the treatment of COVID-19 patients.

Structural properties: SARS-COV-2 is a positive-sense, single stranded enveloped RNA virus having a diameter of 60-140 nm, belongs to Beta coronavirus Lineage β, Sarbecovirus and emerge as the seventh member of corona family which infects humans. The genomic sequence of SARS-COV-2 shows 5' untranslated region (UTR), coding region that codes replicating enzymes consists of open reading frame (ORF) 1a and ORF1b, spike protein gene or S gene, E gene, M gene, N gene and 3' UTR along with multiple non-structural ORFs.[4]

The S gene of SARS-COV-2 is responsible for the synthesis of S protein or spike protein which is the receptor binding site and present on the viral surface. M gene encodes the membrane protein that helps to maintain the shape of the virion and promotes curvature. N gene is the coding gene for necleuocapsid protein which helps to bind virus genome and promote stability. The E gene is responsible for the synthesis of the virus envelope which plays significant role in virus release and pathogenesis. SARS-COV-2 binds with the cells that contain ACE2 receptors and present mainly in respiratory tract, gastrointestinal tract and kidneys and enter into host cell where the binding is triggered by a protease named TMPRSS2.[4]

Pathogenesis of COVID-19: Clinical symptoms of COVID-19 includes fever, myalgia, non-productive cough, fatigue, dyspnoea, diarrhoea etc. Radiological investigations show

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pneumonia like consolidation in X-ray chest and ground glass appearance in CT-scan of chest and.[5]

SARS-COV-2 has a similar approach of entry into cells in comparison with SARS. Fusion of spike protein and the ACE2 receptors of cell surface facilitates the entry of virus; after entering into the cells, the virus exposes their RNA; translation of RNA replicase occurs and a complex named RNA replicase-transcriptase is formed. After transcription and replication, negative strand RNA is produced which results in the production of structural proteins of the viruses. New viral particles are formed resulting from the assembly of structural proteins and RNA in the host cell cytoplasm. In the next step of pathogenesis these newly formed viral particles are released from the host cells through exocytosis and infect nearby cells. Thousands of copies of novel virus particles can be produced from a single infected cell and can cause target organ infections resulting in pneumonia, gastroenteritis, acute kidney injury, carditis etc.[6]

It is also a matter of great concern that how, other than end target organ damage, indirect immune response in COVID-19 infection can increase morbidity and mortality. Patients with COVID-19 infection shows high levels of proinflammatory mediators like IL-1β, IP-10, MCP– 1. Cytokine storm is thought to be linked with severity of the disease and disease outcome.[7]

As the COVID-19 belongs to the same family as SARS and MERS and patients present with same pneumonia like symptoms, variety of antiviral agents have been tried according to the clinical experience from SARS and MERS. The broad-spectrum antiviral agent like ribavirin, protease inhibitor lopinavir and ritonavir, oseltamivir and immune up-regulator interferon were most commonly used against SARS and MERS. Same antiviral agents are also being tried purposefully against SARS CoV-2.[8-16] Remdesivir, Favipiravir and arbidol are also used against SARS-CoV-2 infections in the current pendemic.[10,17,18] all the mechanism are shown in figure 2.

Common side effects of antivirals: common side effects of the antivirals used against SARS CoV-2 are diarrhoea, fatal pancreatitis, hepatitis, hepatic decompensation and increased P-R intervals by Lopinavir-ritonavir, nausea, vomiting, gastroparesis, rectal bleeding, liver dysfunction, hypotension in case of remdesivir, nausea, vomiting, diarrhoea, dizziness, headache, nosebleed, eye redness or discomfort, insomnia, cough due to osaltamavir, hemolytic anemia, hypocalcemia, and hypomagnesemia in case of ribavirin, allergic reaction and hypersensitivity due to arbidol and fever, myalgias, headaches, leukopenia, lymphopenia, autoimmune hepatitis and thyroid disease occurs in case of interferon.[8-18]

However, the efficacy and safety of these antiviral agents for COVID-19 remains unclear. Therefore, this is the crucial time to look for potential antiviral therapies for SARS-CoV-2 infected patients. Some clinical trials are currently underway to evaluate the efficacy of different antiviral agents for the treatment of COVID-19 patients, but their results have not been published as yet. On the other hand, the quality of these studies is also questionable. The objective of the current systematic review is to evaluate the evidence underlying the efficacy and safety of antiviral therapies in treatment of COVID-19 in the current pandemic.

METHODOLOGY

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All types of performed clinical studies, aiming to evaluate the efficacy and safety of antiviral drugs were included in this systematic review as shown in Figure-1. Exclusion criteria comprised *in vitro* studies, guidelines, animal studies and review studies.

An extensive search was performed on Medline (via PubMed), Scopus, Embase, CENTRAL, and Web of Science databases. The keywords were selected using Mesh, Entrée and related article titles. Treatment were reported in a small number of published articles and the use of antiviral treatments were not stated in the abstracts of the articles. The keywords were chosen with the one common keywords associated with COVID-19.

Keywords related to "antiviral therapy" were not included in the search. Also, the search date was chosen to be from late 2019 until May 15, 2020, since the first case of COVID-19 was reported in late 2019. In addition to the systematic search, an extensive search was also performed on google scholar search engines, google and in the article bibliographies.

Search queries in Medline database are like Coronavirus or COVID19 or 2019-nCoV COVID19 virus or COVID-19virus or 2019-nCoV disease or 2019 novel coronavirus disease or 2019-nCoV infection or 2019-nCoV or SARS2 or SARS-CoV-2 or 2019 novel coronavirus or 2019 novel coronavirus infection or Coronavirus disease 2019 virus or coronavirus disease-19 or coronavirus disease 2019 or Wuhan seafood market pneumonia virus or new coronavirus or Wuhan coronavirus or "COVID-19" or "severe acute respiratory syndrome coronavirus 2".

Two independent researchers reviewed the titles and abstracts of the articles obtained from the databases and selected the antiviral therapy related articles. Next, the full texts of these articles were searched and reviewed carefully. Finally, those antiviral therapy related articles which met the inclusion and exclusion criteria were included in the present systematic review (Fig 1). Data extraction was independently conducted by two researchers using a standardised data collection form, which included study characteristics (author, year of publication, region), population characteristics (age, indication), intervention characteristics (anti-viral agents, dosage, duration), and outcomes (mortality, recovery rate, clinical outcomes). Besides the pharmacological review, multiple reviewers were involved in order to avoid biasness and extreme screening for the authentic articles on antivirals to treat COVID-19.

RESULTS

The initial search yielded 354 articles. After eliminating duplication, incomplete or ongoing studies, in vitro studies, and excluding reviews, guidelines 22 studies were included .

Table I: Randomized control trials on antiviral therapy against SARS-COV-2.

First author, year, country	Sample size	Anti-V treated	Status of patients	Age (year)	Anti-viral agents	Dosage	Duration	Outcome/findings
Cao et al; 2020; China[9]	199	99	Severe COVID-19 patients	58 (50-68)	Lopinavir/ Ritonavir (LPV/r)	400mg/100mg twice daily	14	Clinical improvement and mortality rate are similar in LPV/r treated and standard care COVID- 19 groups.
Li et al; 2020; China[10]	86	69	Mild to moderate COVID patients	NR	LPV/ror arbidol	200mg/50mg twice daily, 200mg thrice daily	21	8 patients in the LPV/r group, 3 in the arbidol group and 2 in the control group are detoriorated,. 12 (35.3%) patients in the LPV/r group and 5 (14.3%) in the arbidol group experienced adverse events.
Ye et al; 2020; China[11]	47	42	COVID-19 patients	5-68	LPV/r	400mg/100mg twice daily	NR	The combination treatment of LPV/r and routine adjuvant medicine against pneumonia could produce better efficacy on COVID-19 patients compared to treatment with adjuvant medicine alone.
Grein et al; 2020; UK[17]	61	61	Severe COVID-19 patients	64 (48-71)	Remdesivir	200mg in day 1, 100mg daily for next 9 days	10	68% patients had a clinical improvement 47% were discharged, and mortality was 13%.
Wang et al; 2020; China[18]	237	158	Severe COVID-19 patients	66 (57-73)	Remdesivir	200mg in day 1, 100mg daily for next 9 days	10	65% patients show clinical improvement, 61% were discharged, and mortality was 14%. Adverse effect was reported in 66% cases.
Total	630	439						

Table II: Case-series with anti-viral therapy against SARS-COV-2

First author, year, country	Sample size	Anti-V treated	Status of patients	Age (year)	Anti-viral agents	Dosage	Duration	Outcome/findings
Chen N et al 2020 China[14]	99	75	COVID-19 patients	21-82	Oseltamivir	75 mg twice a day	3-14 days	Recover rate: 31%; Mortality rate: 11%.
ChenQ et al 2020; China[19]	9	9	Symptomatic COVID-19 patients	14-56	LPV/r	800mg/200 mg daily	4-11 days	No mortality. Time from onset of treatment to negative result of COVID was 4-11 days. Length of hospital stay was 9 to 20 days.
Guan W et al 2020; China[20]	1099	393	Non-severe and severe COVID-19 patients	47 (35-58)	Oseltamivir	NR	NR	Administration of oseltamivir did not decrease ICU admission and need for ventilator or death.
Hu Z et al 2020; Chaina[21]	24	21	Asymptomatic COVID-19 infection	5-85	Not specified	NR	NR	No mortality, no ICU admission, no severe complication.
Huang C et al 2020; China[22]	41	38	Symptomatic COVID-19	49 (41-58)	Oseltamivir	NR	NR	6 patients died 28 patients were discharged.
Liu K et al 2020; China[23]	137	105	Severe COVID-19	20-83	Not specified	NR	NR	Duration of hospital stay was 9-13 days. 1 patient died.
Liu L et al 2020; China[24]	51	51,7,2	Discharged COVID-19 patients	16-68	LPV/r Oseltamivir Arbidol	NR	NR	Duration of hospital stay was 9-13 days. 1 patient died.
QinX et al 2020; China[25]	89	84,5	ICU & Non ICU admitted COVID-19	23-86	LPV/r, interferon	NR	NR	26 patients transferred from ICU, 16 patients were discharged, and 1 patient died and 2 patients deteriorated.
Shang J et al 2020; Chaina[26]	416	380	Survived & dead COVID-19	49 (36-61)	Not specified	NR	NR	Anti-viral administration did not affect mortality rate (5.6% in non-treated vs. 12.9 treated; p=0.288).
Wang D et al 2020, China[8]	138	124	ICU & Non ICU admitted COVID-19	22-92	oseltamivir	NR	NR	6 patients died and 36 patients were admitted to ICU.
Wu J et al 2020; China[27]	80	80	Severe COVID-19 patients	46	Ribavirin	NR	2-12 days	21 patients were discharged, and 59 patients remained in hospital.
Xu X et al 2020; China[28]	62	55	Symptomatic COVID-19 patients	41 (32-52)	LPV/r Arbidol,, Interferon α	400mg twice daily. 100 mg twice daily, 50μg twice daily	NR	1 patient was discharged. Other patients remained in hospital
Yang et al 2020; China[29]	149	140	All COVID-19 patients admitted in a center	45	Not specified	NR	NR	No mortality. 73 patients were discharged and 76 remained in hospital. and 76 remained in hospital.
Young et al 2020; Singapore[30]	18	05	Symptomatic COVID-19 patients	31-73	LPV/r	NR	NR	2 patients recovered and the condition of 2 other patients deteriorated. 4 patients experienced side effects of antiviral therapy.
Zhang et al 2020; China[31]	221	196	Non severe and severe COVID-19	20-96	Not specified	NR	NR	12 patients died, Chest CT improved after administration of ECMO and IMV.
Zhou et al 2020; China[32]	10	10	confirmed COVID-19 patients	29-68	LPV/rArbidol, interferon	NR	NR	1 patient died,5 patients remained hospitalized and 4 patients were discharged.
Total	2643	1636						

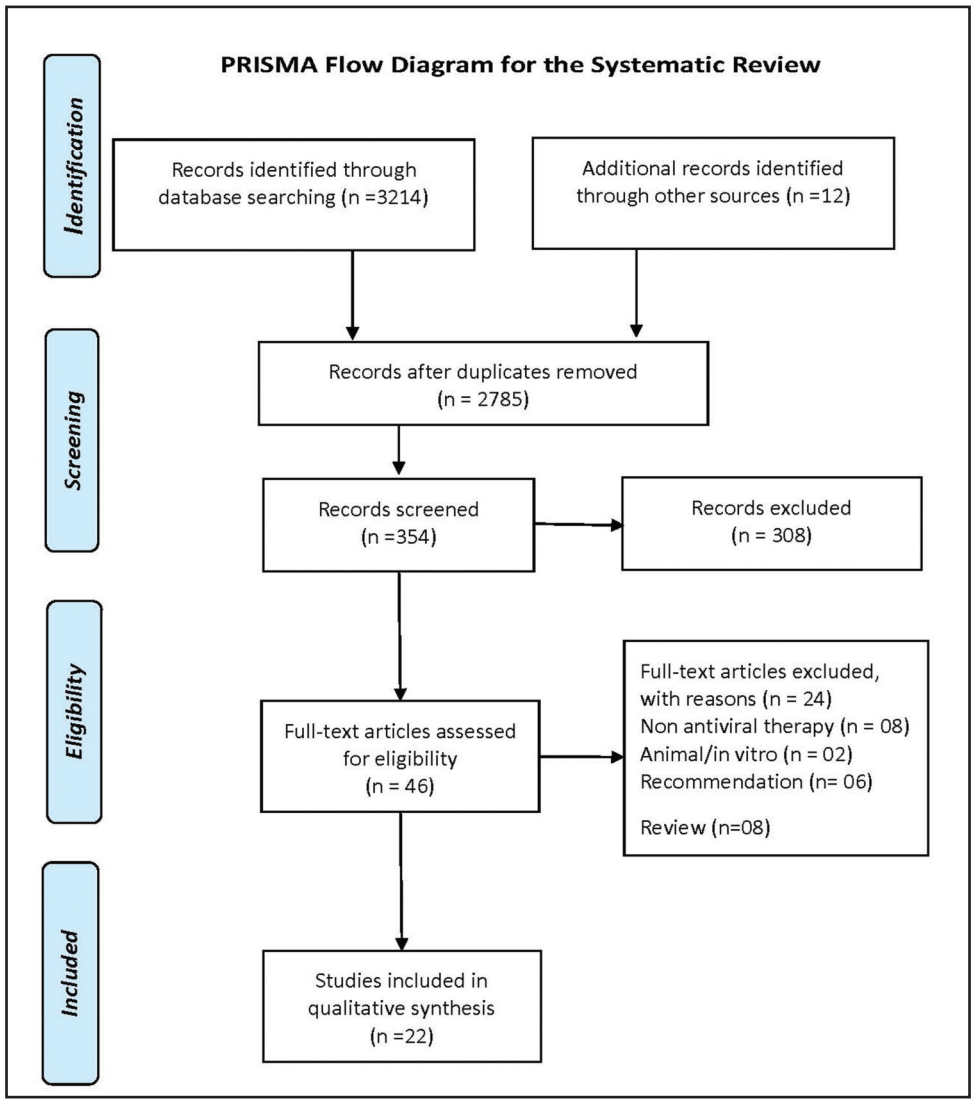

Fig. 1: PRISMA flow chart of the systematic review on antivirals against SARS-CoV-2.

Of these 20 articles were conducted in China, one in UK and one study was performed in Singapore. Five clinical trial (RCTs) and seventeen case-series were included after screening and filtering as shown in Table I. These articles studied 3294 COVID-19 patients, 2095 (63.6%) of who were all treated with antiviral agents. The most frequently used antivirals were lopinavir / ritonavir, remdisivir, oseltamivir, ribavirin, arbidol, interferon, respectively. Route and duration of administration were not reported in most of the studies. The duration of administration varied from 2 to 14 days. Concomitant drugs used in these studies are antibiotics, immunoglobin, glucocorticoids, antiparasitic and antifungal drugs.

In the randomized clinical trials, patients were divided in to two groups: antiviral (439 patients) group and standard treatment group. Antibiotics, invasive or non-invasive ventilation and extracorporeal membrane oxygenation (ECMO) and vasopressor were used as standard treatment. The findings of these studies showed that patients receiving antiviral had clinical improvement.

Most of the published case-series did not provide an analysis regarding the efficacy of antiviral therapy in the treatment course of COVID-19 patients as shown in Table II. There were also some studies available that, having an acceptable sample size, but did not report the clear findings of a large portion of their patients. However, most of the patients reviewed were still admitted in hospitals, with unclear final outcomes, during the time of publication of their articles.

DISCUSSION

The findings of the present study indicated that only five clinical trial and 22 case series were completed on the efficacy and safety of antiviral agents in management of COVID-19 patients, none of which could be taken into account when assessing the clinical usefulness of antiviral treatments against COVID-19. In general, no study has examined the efficacy of antiviral therapies alone in treatment of COVID-19 and antibiotics, immunoglobulin, interferon, glucocorticoids, antifungal and antiparasitic drugs used as concomitant drug in their studies. Hence, the reports presented cannot be attributed solely to antiviral drugs.

Lopinavir-ritonavir(LPV/r): Lopinavir (LPV) is an aspartic acid protease inhibitor, which is co-formulated with ritonavir (LPV/r) to boost the pharmacokinetic activity. Highest number of studies found with these two drugs combination, among them three are RCT,[9-11] six are case-series.[15,24,25,28,30,32] Lopinavir-ritonavir cause clinical improvement in most of the cases.[9,11,15,25,30] But some studies also deterioration[10,25,30] and adverse events.[10,30]

Remdesivir: Remdesivir is a viral RNA synthesis inhibitor, given intra-venously. Two RCT shows clinical improvements in more than 60% cases. Both trials deals with severe COVID patients, some of them needed ICU support. Adverse events and death of the patents were reported in both studies.[17,18] Though Remdesivir has recently come into extensive evaluation by limited trials and systematic reviews for re-purposeful use in COVID-19.[33]

Oseltamivir: Oseltamivir inhibits the neuraminidase enzyme, which is expressed on the viral surface. This drug used alone in four studies and with the combination with other antiviral drugs in one study.[24] No clinical trial was found. Only one study reported 31% recovery rate.[14] These case series reported the need of ICU support[8,20] and death of the patients.[8,14,20,22]

Ribavirin: Ribavirin is a purine nucleoside analog that elicits its antiviral affect through inhibition of viral RNA synthesis. Only one case series used ribavirin in severe COVID patients. Among them 21 patients were discharged and 51 remained admitted in the hospital.[27]

Arbidol (umifenovir): The drug is claimed to inhibit viral entry into target cells and stimulate the immune response. One RCT was used alone in their one group of patients. Among the 35 patents 3 deteriorated and 5 patients experienced adverse events[10]. Besides that, arbidol was used as the second line of therapy.[24,28,32]

Interferon: Interferons are endogenous signaling proteins released by host cells during response to infections or inflammation. Upregulation of IFNs stimulates the immune system to blunt viral replication and eradicate offending pathogens. Interferon was also used in combination with other antiviral drugs in COVID patients.[25,28,32] Two clinical trials on interferon are ongoing and expected to be ended by 30th May, 2020.

Therefore, the existing literature regarding the efficacy of antiviral therapy in management of COVID-19 patients has the following serious limitations. Only five clinical trial has been conducted on published time of this article. In all the existing case-series antiviral agents were used in combination with other medications. So, the observed findings cannot be solely attributed to the antiviral therapy administered. The absence of placebo group in the case-series we cannot determine if the outcomes are due to antiviral therapy or the nature of healing process or both. Follow-up was incomplete in some studies, and a great proportion of the patients have unclear outcomes. And finally the sample size was small in most of the studies.

CONCLUSION

Since COVID-19 disease has been declared pandemic by the WHO, many anti-virals have been tried for its treatment. Some of those were previously used against SARS, MERS, EBOLA, HIV and re-purposefully used against COVID-19 yet not approved by Food and Drug Administration (FDA) due to lack of significant evidence. The safety and efficacy of these antivirals require high-quality evidence from well-designed and adequately-powered clinical trials with proper sample size for recommendation and inclusion in guideline against SARS-CoV-2 pandemic.

CONFLICTS OF INTEREST

None of the authors or co-authors has any conflict of interest regarding any financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work. We also hereby state that none of the authors has any conflict including employment, consultancies, stock ownership, honorees, paid expert testimony, grants or other funding for this systematic review.

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