

Original Article

Comparison of the Efficacy of Sofosbuvir and Kaletra on the Outcome of COVID-19. Is Sofosbuvir A Potential Treatment For COVID-19?

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Abstract

Background: The COVID-19 is a family of large enveloped non-segmented positive-sense RNA viruses which was first reported in December 2019 in Wuhan, China with a cluster of unexplained pneumonia. Although various medications have been tried to manage the COVID-19 pandemic, there is no exclusive medication or vaccine so far. In this study, we aimed to focus on the effectiveness of Hydroxychloroquine + Kaletra (lopinavir/ritonavir) versus Hydroxychloroquine + Sofosbuvir in patients hospitalized with COVID-19 to given the urgent need for an effective drug against SARS-CoV-2 in the current pandemic context.

Materials and Methods: Fifty-four eligible patients with moderate to severe COVID-19 symptoms, according to the WHO criteria entered the study. Patients were randomized into two treatment groups. Thirty-two patients received Hydroxychloroquine (400 mg stat) and Kaletra (400/100 mg q 12 h) as a control group (group A) and the trial group of 22 patients, received Hydroxychloroquine (200 mg q 12 h) plus Sofosbuvir (400 mg daily) (group B) for a period of 7 to 14 days. Eventually, collected data included demographic characteristics, underlying diseases, clinical symptoms, laboratory data, and mortality were analyzed.

Results: There was no significant difference in age, sex, and underlying diseases between the two groups. There was no significant statistical difference between the two groups on the seventh day of treatment in terms of cough relief, leukocyte count, and improvement of lymphopenia however in terms of the time of defervescence of fever, there was a significant difference between the two groups.

Conclusion: Therefore, it can be said that our study is one of the first studies in the world to evaluate the effectiveness of sofosbuvir in the treatment of patients with COVID-19. According to our results, although Kaletra was assumed as an effective therapy, its superiority over Sofosbuvir was confined to the earlier effervescence of the 7-day fever and sofosbuvir can be used as an effective treatment, especially in patients with underlying heart disease who are at risk for arrhythmias with Kaletra.

Keywords: COVID-19, Sofosbuvir, Lopinavir/ritonavir, Treatment

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Introduction

After the emergence and spread of the newly discovered corona virus infection in China in December 2019, other countries, including Iran, were also faced with the prevalence of this virus. Until July 6, 2020, 240438 cases had been confirmed in Iran and 11327790 had been documented globally.

Corona virus disease 2019 (COVID-19) has reached pandemic status and an unknown animal may be responsible for spreading this new human pathogen coronavirus. The clinical manifestations of the disease consist of malaise, dry cough, shortness of breath and respiratory distress. Thus, six various strains of Human coronaviruses (HCoVs) have been reported, including the newly emerged COVID19¹.

Specific drugs may be effective in treatment, depending on the biophysical information and the genome of individual coronaviruses, such as inhibitors of specific viral enzymes, siRNA molecules involved in the viral replication cycle, and inhibitors of host cell proteases².

Sofosbuvir and Ribavirin are conventionally used against RNA dependent RNA polymerase (RdRp) of the hepatitis C virus (HCV). These drugs are nucleotides derivatives that compete with physiological nucleotides for the RdRp active site³.

Many antiviral drugs have been tested for safety in preventing SARS-CoV-2 replication in cell cultures. Hydroxychloroquine (HCQ) is one of the disease-modifying antirheumatic drugs (DMARDs). The DMARDs are widely used for curing many rheumatic diseases and show strong immunomodulatory capacity, which prevents inflammation flare-ups and organ damage⁴.

Even though many of these drugs show anti coronavirus activity in vivo and/or in vitro, their pharmacodynamic and pharmacokinetic properties, in addition to their side effect profile, but more careful clinical trials are required to validate these new specific drugs.

In general, there are no specific antiviral drugs or vaccines for 2019-nCoV. All of the drug options come from experience treating SARS, MERS or some other recent influenza virus. Active

symptomatic support remains key to treatment. The aforementioned drugs could be helpful, but further confirmation of their efficacy is required².

The newly emerged corona virus is a health concern for people all around the world. The present study aimed to investigate the efficacy and adverse effects of two groups of drugs A: (Hydroxychloroquine +kaletra) and B: (Hydroxychloroquine+sofosbuvir) in the treatment of SARA-COV2: an open label phase III among patients who had positive PCR tests or who had CT scans compatible with this infection. The medications were administered to each group of patients for at least 7 days.

Methods

This clinical trial was conducted at a referral hospital for Covid-19 patients in Tehran, Iran, between March and April 2020. The inclusion criteria in our study were as follows Age above 18, hospitalized patients with fever (Oral temperature ≥ 38 °C) and at least one of the following: a respiratory rate more than 24/min or an O₂ Saturation level less than 93% or the PaO₂/FiO₂ ratio lower than 300. Patients had to have a confirmed PCR for the nucleic acid of SARS-COV-2 in a nasopharyngeal swab specimen or a chest lung CT scan compatible with COVID-19 patterns. The exclusion criteria were dissatisfaction with being included in or continuing the study, having a known allergic reaction to interventional drugs, pregnancy or breastfeeding, any prior experimental treatments for COVID-19, a heart rate less than 60/min, taking amiodarone, evidence of multiorgan failure, requiring mechanical ventilation at the screening or an eGFR of less than 50 ml/min. Fifty-four eligible patients with moderate to severe COVID-19 symptoms, according to the WHO criteria, were enrolled in the study.

Patients were randomized into two treatment groups. Thirty-two patients made up the control group (group A) who received Hydroxychloroquine (400 mg stat) and Kaletra (400/100 mg q 12 h) and the trial group (group B) consisted of 22 patients, who were administered Hydroxychloroquine (200 mg q 12 h) plus Sofosbuvir (400 mg daily).

Collected data included demographic characteristics and underlying diseases, clinical symptoms such as fever, cough, myalgia at the time of admission and on

the seventh day of hospitalization, as well as laboratory data such as PCR test results, the number of leukocytes and lymphocytes on the day of admission and on the seventh day of hospitalization. Mortality was also compared between the two groups. Data were analyzed with IBM SPSS software version 23. Based on our pilot study criteria for the improvement of clinical symptoms and a statistical power of 80% with a type one error of 5%, a sample size of 22 patients for each group was calculated. The Independent t-test was used to compare means and Chi-two was utilized to assess frequencies. These data are presented in tables 1 to 3. This study has been approved by the ethics committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran (IR.SBMU.RETECH.REC.1399.557).

Results

A total of 32 patients with moderate to severe symptoms of COVID-19 in the control group received Hydroxichloroquine and Kaletra (group A) (15 male and 17 female). In comparison, 22 patients (14 male and 8 female) were treated with Hydroxichloroquine and Sofosbuvir (group B). There were no significant differences in terms of age and sex between the two groups. Thirty-one percent of patients in group A and thirty-six percent of patients in group B were diabetics, which was not statistically significant. Fifty-nine percent of patients in group A and fifty percent of patients in group B suffered from other underlying diseases (Table-1).

The patients in group A and half of those in group B had a positive nasopharyngeal swab test (which was statistically significant). The spiral chest CT scan of all patients who were enrolled in our study were compatible with COVID-19 patterns. Sixty-five percent of patients in group A and fifty-nine percent of patients in group B had a fever at the time of admission. (not statistically significant). Other clinical manifestations of patients in both groups at the time of admission are shown in Table 2. The numbers of leukocytes and lymphocytes at the time of admission were also compared between the two groups, the results of which were not statistically significant (Table-2).

In the follow-up of patients, sixty-eight percent of group A and seventy-two percent of group B had

lymphopenia on the seventh day. Therefore, there was no statistically significant difference between the two groups in terms of the improvement of lymphopenia on the seventh day post-treatment. All the patients in group A and eighty-six percent of those in group B had no fever on day seven of treatment. Therefore, in terms of the time of defervescence of fever, there was a significant difference between the two groups. There were no significant statistical differences between the two groups on the seventh day of treatment in terms of cough relief and leukocyte count (Table-3). The number of patients from groups A and B who withdrew from the study were 3 and 2, respectively (Table-3). The most common side effect in both groups was a headache and the difference was not statistically significant between the two groups (Table-3).

Discussion

The COVID-19 is a family of large enveloped non-segmented positive-sense RNA viruses first reported in December 2019 in Wuhan, China, presenting with a cluster of cases of unexplained pneumonia. It soon turned into a global health concern and, as of June 30, 2020, COVID-19 has resulted in 7553182 confirmed cases and 423349 confirmed deaths⁵. The typical clinical picture varies from mild acute respiratory symptoms to severe pneumonia with respiratory failure and septic shock; the severity of symptoms depends on the level of each individual's immunity and comorbidities^{6,7}.

Although various medications have been tried to manage the COVID-19 pandemic, according to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), no medication or vaccine has been sufficiently effective in its treatment⁸⁻¹⁰.

Considering the urgent need for an effective drug against SARS-CoV-2 in the current pandemic, we aimed to focus on the effectiveness of Hydroxychloroquine+Kaletra (lopinavir/ritonavir) versus Hydroxychloroquine+Sofosbuvir in hospitalized patients with COVID-19. We evaluated 32 patients administered Hydroxychloroquine+Kaletra (lopinavir/ritonavir) and 22 patients treated with Hydroxychloroquine+Sofosbuvir. Regarding age, sex

Table 1: Demographic characteristics and underlying diseases in the two groups treated for Covid-19.

	Group A (n=32)	Group B (n=22)	p value
Age (year)	60 ± 13	53 ± 15	0.09
Gender (M/F)	15/17	14/8	0.2
Diabetic	31 %	36 %	0.7
Other underlying diseases	59 %	50 %	0.6

Table 2: Clinical presentations and laboratory data of patients in the two groups at the time of admission.

	Group A (n=32)	Group B (n=22)	p value
Fever	65 %	59 %	0.7
Weakness	53 %	54 %	1
Cough	84 %	72 %	0.3
Malaise	59 %	68 %	0.6
PCR positive	100 %	50 %	P<0.001
WBC	8260 ± 4800	7400 ± 3200	0.5
Lymphocyte	1842 ± 2232	1912 ± 1432	0.7

Table 3: Mortality, side effects and day-7 clinical findings in the two groups after treatment.

	Group A (n=32)	Group B (n=22)	p value
Mortality (patients)	3	2	1
Lymphocytopenia	68%	72%	1
Anemia	0	9 %	0.1
Leukocytopenia	34%	31%	1
Headache side-effect	25%	36%	0.4
Day-7 fever	0	14%	0.03
Day-7 cough	12%	4%	0.3

and underlying commodities, no significant differences were observed. Our results revealed that Hydroxychloroquine+Kaletra was considerably more effective when it came to decreasing 7-day fever compared to Hydroxychloroquine+Sofosbuvir (P=0.03). However, we did not find statistically significant differences in terms of day-7 cough, improvement in lymphopenia and leukocytopenia, mortality, or adverse effects, such as headache, between the two study groups.

It is noteworthy that, early in the COVID-19 pandemic, Hydroxychloroquine (HCQ) had earned a reputation as a potentially promising inhibitor of SARS-CoV-2 replication in cell cultures. HCQ increases the intracellular pH and inhibits the lysosomal activity in antigen-presenting cells (APCs) like plasmacytoid dendritic cells (pDCs) and B cells, leading to the prevention of antigen processing and major histocompatibility complex (MHC) class II-mediated autoantigen presentation to T cells, which eventually leads to the reduction of T cell activation, differentiation, and expression of costimulatory proteins and cytokines produced by B and T cells. Additionally, it suppresses the toll-like receptors

(TLR7 and TLR9) signaling and interferes with the interaction between cytosolic DNA and the nucleic acid sensor cyclic GMP-AMP (cham) synthase (CGAS), both of which attenuate the inflammatory cytokine cascade^{4,11-16}.

Later, a huge number of attempts were made to develop other antiviral drugs. Favilavir was first approved by the national medical products administration of China on February 18, 2020, followed by other antivirals including Sofosbuvir, IDX184, Ribavirin, Remdisivir, Guanosine triphosphate (GTP), Uracil triphosphate (UTP), Cinnamaldehyde, Thymoquinone, and Lopinavir/ritonavir¹⁷. Lopinavir is a member of the family of protease inhibitors and ritonavir, which is commonly used against the human immunodeficiency virus (HIV), acts as a booster. There is evidence suggesting the anti-COVID-19 activity of Lopinavir/ritonavir¹⁸.

Chu et al. evaluated the three-week clinical prognosis and virological outcomes of forty-one patients treated with a combination of lopinavir/ritonavir and ribavirin in comparison to 111 patients administered ribavirin alone. Their results revealed that patients treated with

lopinavir/ritonavir and ribavirin had a lower risk of adverse clinical outcomes such as acute respiratory distress syndrome (ARDS) or death. Furthermore, the prevalence of steroid usage and nosocomial infections was less evident in patients initially treated with lopinavir/ritonavir, and these patients had a decreasing viral load and rising peripheral lymphocyte count¹⁹. Similarly, Chan et al. conducted a retrospective matched cohort study to investigate the effectiveness of Kaletra. They evaluated 75 patients with severe acute respiratory syndrome treated with lopinavir/ritonavir as either initial treatment or rescue treatment in addition to standard treatment compared with matched cohorts of 634 and 343 patients, respectively. Their results revealed that the initial therapy of lopinavir/ritonavir was associated with better clinical outcomes leading to a reduction in the overall death rate, intubation rate and methylprednisolone dosage²⁰. There are also other reports confirming the promising role of Kaletra, including a study by Elise Klement-Frutos et al. which demonstrated the effectiveness of Kaletra in decreasing the SARS-CoV-2 load and preventing the secondary immune-related severe evolution in early presenting non-severe patients²¹ or another study which revealed the superiority of triple therapy with lopinavir/ritonavir [400 mg/100 mg q12h], ribavirin [400 mg q12h], interferon beta1b [8 million IU x 3 doses q48h] (n= 86) compared to lopinavir/ritonavir alone (n=41) in shortening the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19²².

However, there are reports with disappointing results. In one randomized, controlled, open-label trial of hospitalized adults, the patients were randomized into lopinavir/ritonavir 400 mg/100 mg PO BID for 14 days added to standard care (n=99) or standard care alone (n=100). The results did not confirm the superiority of lopinavir/ritonavir in terms of time to clinical improvement or the mortality rate²³. In another study, the effectiveness of lopinavir/ritonavir or umifenovir monotherapy was compared to standard care in patients with mild-to-moderate COVID-19. Their results did not show a statistical difference between the two treatment groups²⁴.

On the other hand, Sofosbuvir was approved as an

antiviral agent against the hepatitis C virus (HCV) nonstructural protein 5 (NS5B) RdRp in 2013 with a confirmed potential against other viruses, such as the Zika virus. It is also hypothesized that the SARS-CoV-2 infection could also be susceptible to Sofosbuvir^{25,26}. Limited studies are focusing on the efficacy of Sofosbuvir, for instance, an investigation by Abdo et al, who made a model for COVID-19 RdRp by sequence analysis, modeling and docking. Consequently, the HCoV RdRp model was targeted by anti-polymerase drugs, including Sofosbuvir and Ribavirin. Their results indicated that Sofosbuvir, IDX-184, Ribavirin and Remdisvir could be deemed effective drugs against COVID-19³.

Additionally, there are ongoing clinical trials evaluating Sofosbuvir efficacy, such as one study comparing Sofosbuvir 400 mg in combination with Vepastavir 100 mg as an add-on treatment in addition to standard treatment²⁶. Moreover, there is an open-label non-randomized parallel clinical that is being conducted in Iran to compare the effectiveness of the combination of Daclatasvir+Sofosbuvir with Ribavirin in COVID-19 patients with severe symptoms. This clinical trial is currently in process²⁷.

Therefore, it can be stated that our study is one of the first studies in the world to evaluate the effectiveness of sofosbuvir in the treatment of patients with COVID-19. In our study, we compared the effectiveness of (Hydroxychloroquine+Kaletra) compared to (Hydroxychloroquine+Sofosbuvir). According to our results, although Kaletra had been considered an effective treatment, its superiority over Sofosbuvir was confined to the earlier effervescence of the 7-day fever.

Of note, the main limitation of our study was the lack of a control group which might have confound the appropriate interpretation. To determine the efficacy and safety of anti-viral drugs, more adequately powered randomized clinical trials need to be conducted.

Conclusion

There is insufficient evidence to recommend a specific drug for COVID-19 outside of research studies. All of the therapeutic options have originated from previous experiences with SARS, MERS and recent variants of the influenza virus. However, the way to recognize

therapeutic options is, and ancillary studies with greater sample size are needed to confirm the efficacy of the current drugs.

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References

- Hui IE, Azhar TA, Madani F, Ntoumi R, Kock O. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China, *International Journal of Infectious Diseases*. 2020;91:264-6.
- Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends*. 2020.
- Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci [Internet]*. 2020 May;248:117477.
- Zhou D, Dai S-M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother [Internet]*. 2020;75(7):1667–70.
- Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JI-P, et al. Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review. *J Clin Med [Internet]*. 2020;9(3):623.
- Phan LT, Nguyen T V, Luong QC, Nguyen T V, Nguyen HT, Le HQ. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *N Engl J Med*. 2020;382(9):872–4.
- Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. *J Travel Med*. 2020;27(2).
- Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. Geneva PP - Geneva: World Health Organization; 2020.
- CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). 2020.
- FDA. FDA site [Internet]. 2020. Available from: <https://www.fda.gov/emergency-preparedness-and-response/mcmissues/coronavirusdisease-2019-covid-19>
- Lotteau V, Teyton L, Peleraux A, Nilsson T, Karlsson L, Schmid SL, et al. Intracellular transport of class II MHC molecules directed by invariant chain. *Nature [Internet]*. 1990;348(6302):600–5.
- Wu S-F, Chang C-B, Hsu J-M, Lu M-C, Lai N-S, Li C, et al. Hydroxychloroquine inhibits CD154 expression in CD4+ T lymphocytes of systemic lupus erythematosus through NFAT, but not STAT5, signaling. *Arthritis Res Ther*. 2017;19(1):183.
- van den Borne BE, Dijkman BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *J Rheumatol*. 1997;24(1):55–60.
- Kužnik A, Benčina M, Švajger U, Jeras M, Rozman B, Jerala R. Mechanism of Endosomal TLR Inhibition by Antimalarial Drugs and Imidazoquinolines. *J Immunol [Internet]*. 2011;186(8):4794–804.
- Vollmer J, Tluk S, Schmitz C, Hamm S, Jurk M, Forsbach A, et al. Immune stimulation mediated by autoantigen binding sites within small nuclear RNAs involves Toll-like receptors 7 and 8. *J Exp Med [Internet]*. 2005;202(11):1575–85.
- An J, Woodward JJ, Sasaki T, Minie M, Elkon KB. Cutting edge: Antimalarial drugs inhibit IFN-β production through blockade of cyclic GMP-AMP synthase-DNA interaction. *J Immunol*. 2015;194(9):4089–93.
- Zhong H, Wang Y, Zhang Z-L, Liu Y-X, Le K-J, Cui M, et al. Efficacy and safety of current therapeutic options for COVID-19 - lessons to be learnt from SARS and MERS epidemic: A systematic review and meta-analysis. *Pharmacol Res [Internet]*. 2020;157:104872.
- Dorward J, Gbinigie K. Lopinavir/ritonavir: A rapid review of effectiveness in COVID-19 [Internet]. 2020.
- Chu CM. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax [Internet]*. 2004;59(3):252–6.
- Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MML, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J = Xianggang yi xue za zhi [Internet]*. 2003;9(6):399–406.
- Klement-Frutos E, Burrell S, Peytavin G, Marot S, Lê MP, Godefroy N, et al. Early administration of ritonavir-boosted lopinavir could prevent severe COVID-19. *J Infect [Internet]*. 2020; Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0163445320303182>
- Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet [Internet]*. 2020;395(10238):1695–704.
- Ballou A. Mayo Clinic Preparing to Commence Phase II FDA Clinical Trial for the Treatment of COVID-19 with Vicromax™ [Internet]. BioSig Technologies, Inc. 2020. Available from: <https://www.biosig.com/news-media/press-releases/detail/188/mayo-clinic-preparing-to-commence-phase-ii-fda-clinical>
- FirstWave Bio. FirstWave Bio to Initiate Phase 2a/2b Study of FW-1022, a Proprietary Form of Niclosamide, to Treat COVID-19 [Internet]. 2020. Available from: <https://pipelinereview.com/index.php/2020041074293/Small-Molecules/FirstWave-Bio-to-Initiate-Phase-2a/2b-Study-of-FW-1022-a-Proprietary-Form-of-Niclosamide-to-Treat-COVID-19.html>
- Elfiky AA. Novel guanosine derivatives against Zika virus polymerase in silico. *J Med Virol [Internet]*. 2020;92(1):11–6.
- Sayad B, Sobhani M, Khodarahmi R. Sofosbuvir as Repurposed Antiviral Drug Against COVID-19: Why Were We Convinced to

Evaluate the Drug in a Registered/Approved Clinical Trial? Arch Med Res [Internet]. 2020; Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0188440920305518>
27. Mobarak S. Comparison of the effect of two drugs Daclatasvir

+ Sofosbuvir and Ribavirin in COVID-19 patients with severe symptoms [Internet]. 2020. Available from: <https://www.irct.ir/trial/46713>
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