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Preventive Role of Hepatitis B & C Antiviral Drugs in Covid-19 Infection

Malhotra P*, Malhotra V, Gupta U, Gill PS, Pushkar and Sanwariya Y

Department of Medical Gastroenterology and Microbiology, Gynecology & Obstetrics, PGIMS, Rohtak & Director, Health Services, Haryana, India

***Corresponding author:**

Parveen Malhotra,
Department of Medical Gastroenterology and Microbiology, Gynecology & Obstetrics, PGIMS, Rohtak & Director, Health Services, Haryana, India,
E-mail- drparveenmalhotra@yahoo.com

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1. Abstract

1.1. Introduction: Covid-19 is a global pandemic around the world and has caused havoc both with human lives as well as economy. Many drugs regimen has been tried for treating it but till date no treatment has been proven to be totally successful in curing this viral infection.

1.2. Aims and objectives: To determine the prevalence of Covid 19 infection in patients taking oral antiviral drugs for Hepatitis C (Sofosbuvir 400 mg, Daclastavir 60 mg, Velpatasvir 100 mg) and Hepatitis B (Tenofovir 300 mg) and thus determining preventive role of these antiviral drugs in Covid-19 infection.

1.3. Materials & Methods: It was prospective study conducted at Department of Medical Gastroenterology, Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, over a period of nine months. All the registered patients who were on treatment with oral antiviral drugs for Hepatitis B (HBV) or Hepatitis C (HCV) since 1st March 2020 were followed for nine months and it was determined that what percentage of patients developed Covid-19 infection.

1.4. Results: Out of two thousand patients of Chronic Hepatitis C, total four patients developed Covid-19 infection but two of them were yet to be started on treatment and rest two had completed antiviral treatment one year back. In case of Chronic Hepatitis B, out of five hundred patients, four patients developed Covid-19 infection but two of them were on alternative medications and rest two were on tablet Entecavir and not Tenofovir. Thus, no patient who was on treatment with Sofosbuvir, Daclastavir, Velpatasvir or Tenofovir developed Covid-19 infection.

2. Introduction

COVID-19 is a devastating global pandemic around the world. While the majority of infected cases appear mild, in some cases individuals present respiratory complications with possible serious lung damage. There are no specific treatments for COVID-19 as yet, though a number are under evaluation, including experimental antiviral drugs. Human pathogenic coronaviruses (SARS-CoV and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels [1-3]. The ability of SARS-CoV2 to enter and infect the human nervous system, based on the strong expression of the ACE2 target throughout the brain [4], should be also considered. *In vitro* and limited clinical data suggest potential benefit for chloroquine and hydroxychloroquine. On the other hand, although *in vitro* and limited clinical data suggest potential benefit for Lopinavir & Ritonavir, and its actual role in the treatment of COVID-19 is still unclear, some preclinical data suggested potential benefit. However, more recent data has failed to confirm their efficacy for COVID-19 treatment [5] While the COVID-19 outbreak continues to spread around the world, the absence of a clinically proven antiviral therapy is a serious challenge for the treatment of severe COVID-19 cases [6].

3. Review of Literature

Researchers from Johannes Gutenberg University Mainz (JGU) in Germany simulated the way that about 42,000 different substances listed in open databases bind to certain proteins of SARS-CoV-2, and thereby inhibit the penetration of the virus into the human body or its multiplication. They found that compounds from the four hepatitis C drugs simeprevir, paritaprevir, grazoprevir, and Velpatasvir have a high affinity to bind SARS-CoV-2 very strongly and may therefore be able to prevent infection. Sofosbuvir and daclatasvir, two antiviral drugs used to treat hepatitis C, were associated with faster recovery, shorter hospitalization and improve survival among people with moderate or severe COVID-19, researchers reported at the COVID-19 Conference that concluded the 23rd International AIDS Conference (AIDS 2020: Virtual). Dr Andrew Hill of Liverpool University admitted that generic versions of sofosbuvir and daclatasvir could potentially be an affordable and widely accessible treatment for the new coronavirus. Hepatitis C virus (HCV) and the new coronavirus – officially named SARS-CoV-2 – are both single-stranded RNA viruses and this has led to suggestion that the same antiviral drugs might work against both.

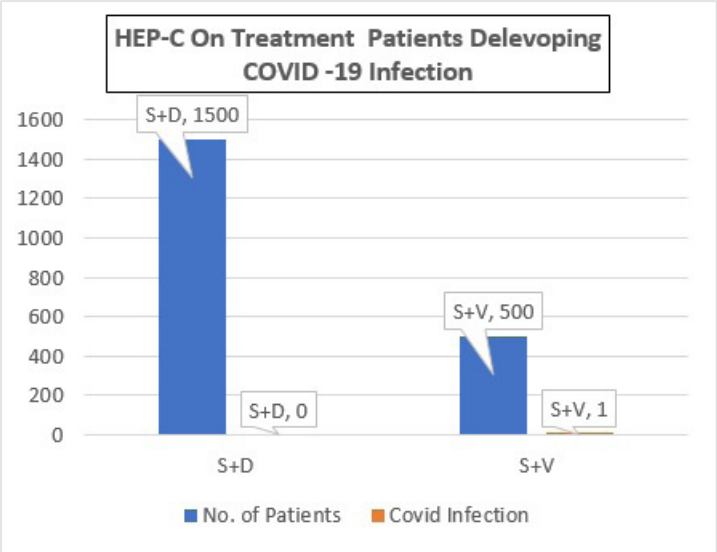
Dr Anahita Sadeghi of Tehran University of Medical Sciences has done a randomized trial evaluating sofosbuvir plus daclatasvir for adults with moderate or severe COVID-19 at four university hospitals in Iran. Sofosbuvir inhibits HCV's NS5B enzyme, the RNA-dependent RNA polymerase, the virus uses to copy its genetic material. Daclatasvir is an HCV NS5A inhibitor. Prior laboratory studies have shown that sofosbuvir and daclatasvir are active against SARS-CoV-2 *in vitro*, and daclatasvir appears to penetrate well into the lungs. Both drugs have been shown to be safe and well tolerated for hepatitis C treatment. The trial enrolled 66 patients with fever and low oxygen levels who tested PCR positive for SARS-CoV-2 and had diagnostic chest CT scans indicating COVID-19. Just over half were men and the median age was approximately 60 years. Co-morbidities were common, including diabetes, hypertension, chronic pulmonary disease and obesity. Those with poor kidney function or multi-organ failure were excluded. The participants were randomized 1:1 to receive sofosbuvir plus daclatasvir with lopinavir/ritonavir for 14 days or standard-of-care treatment consisting of lopinavir/ritonavir with or without hydroxychloroquine. Sadeghi reported that 88% of people taking sofosbuvir plus daclatasvir experienced clinical recovery – defined as normalization of fever, respiratory rate and oxygen saturation – compared with 67% of those on standard therapy. The time to recovery was significantly shorter in the sofosbuvir plus daclatasvir arm (six versus 11 days, respectively). The study also showed that three people taking sofosbuvir plus daclatasvir (9%) required mechanical ventilation compared with seven standard-care recipients (21%); three (9%) versus five (15%) patients in the respective groups died.

4. Aims and Objectives

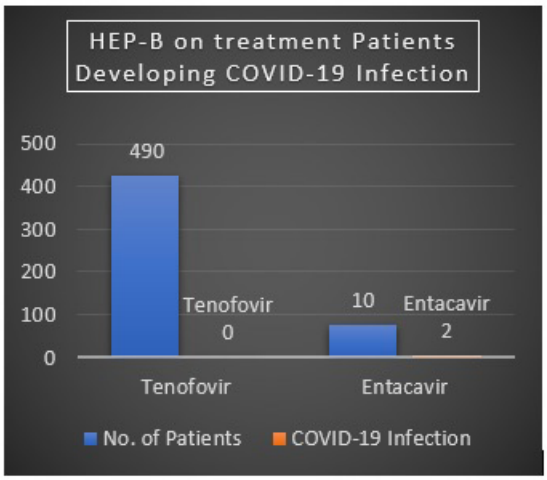
To determine the prevalence of Covid 19 infection in patients taking oral antiviral drugs for Hepatitis C (Sofosbuvir 400 mg, Daclastavir 60 mg, Velpatasvir 100 mg) and Hepatitis B (Tenofovir 300 mg) and thus determining preventive role of these antiviral drugs in Covid-19 infection.

5. Material and Methods

It was prospective study conducted at Department of Medical Gastroenterology, Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, over a period of nine months (Bar Chart 1). All the registered patients who were on treatment with oral antiviral drugs for Hepatitis B (HBV) or Hepatitis C (HCV) since 1st March 2020 were followed for next nine months and it was determined that what percentage of patients developed Covid-19 infection. Total two thousand and five hundred patients were enrolled in the study, out of them two thousand patients were on treatment with oral antiviral for HCV infection and five hundred were on treatment for HBV. The permission for conducting of above study was given by Director General Health Services, Haryana and PGIMS, Rohtak (Bar Chart 2).



Bar Chart 1: Showing Details of Hepatitis C Patients



Bar Chart-2: Showing Details of Hepatitis B Patients

6. Stastical Analysis

All the data was entered in Microsoft Excel and was analysed using SPSS 15.0 version.

7. Observations & Results

Out of two thousand patients of Chronic Hepatitis C, total four patients developed Covid-19 infection but two of them were waiting to start their treatment and rest two had completed antiviral treatment one year back. In case of Chronic Hepatitis B, out of five hundred patients, four patients developed Covid-19 infection but two of them were on alternative medications and rest two were on tablet Entecavir and not Tenofovir. Thus, no patient who was on treatment with Sofosbuvir, Daclastavir, Velpatasvir or Tenofovir developed Covid-19 infection (Table 1).

Table 1: Showing Development of Covid-19 Infection in Patients

Total Patients Enrolled	Chronic Hepatitis -C		Chronic Hepatitis- B	
	S+D	S+V	Tenofovir	Entecavir
2500	1500	500	490	10
Patients who developed COVID-19 infection	NIL	1	NIL	2

8. Discussion

According to [7, 8], SARS, MERS and SARS-CoV-2 coronaviruses, like Hepatitis C virus (HCV) and the Flaviviridae (9), are positive-sense single-strand RNA viruses and these viruses share a similar replication mechanism requiring a RNA-dependent RNA polymerase (RdRp). So, there is a strong possibility that Sofosbuvir, Ribavirin, AZT (and other HCV/HIV nucleoside/nucleotide analogues such as Remdesivir) can tightly bind to SARS-CoV-2 RdRp. In a recent *in silico* (preliminary) study, sequence analyses as well as homology modeling were used to build a new SARS-nCoV RdRp model which then targeted by anti-polymerase drugs, including the approved drugs Sofosbuvir and Ribavirin (10). The docking scores suggested possible eligibilities of Sofosbuvir, Ribavirin, (and Remdesivir) as potent drugs against the new coronavirus. These theoretical data needed to be confirmed by the experimental observations. Using polymerase extension experiments, *in vitro*, Chien M, et al. also demonstrated that the biologically activate triphosphate forms of four well-known nucleotides/nucleoside analogue anti-viral (anti-HCV/HBV, anti-HIV/AIDS) drugs; Sofosbuvir, Tenofovir alafenamide, Alovudine were incorporated by RNA-dependent RNA polymerase (RdRp) enzymes of SARS-CoV as well as SARS-CoV-2, and permanently blocked further incorporation (further polymerase extension was terminated). They considered all these compounds as permanent/strong terminators for the SARS-CoV-2 RdRp [7, 8]. Due to widely availability of these FDA approved drugs (Sofosbuvir, Tenofovir), they expressed hope that the drugs would be more evaluated quickly in laboratory and clinical trials for COVID-19 treatment.

Hill and Sadeghi also described findings from a meta-analysis of three clinical trials (including this one) conducted in Tehran and two other Iranian cities. In Abadan, participants were randomized to receive sofosbuvir plus daclatasvir plus hydroxychloroquine or else lopinavir/ritonavir plus hydroxychloroquine plus ribavirin. In Sari, they were randomized to receive either sofosbuvir plus daclatasvir plus ribavirin or else lopinavir/ritonavir plus hydroxychloroquine. The pooled analysis included 176 participants. Again, about half were men, the median age was approximately 60 years and co-existing conditions were common. The recovery rate was 94% for those taking sofosbuvir plus daclatasvir compared with 70% for those taking standard-of-care regimens, and the time to recovery was significantly shorter in the sofosbuvir plus daclatasvir group. Five (5%) and 17 (20%) patients died in the respective groups, also a significant difference. A larger randomized, placebo-controlled trial called DISCOVER will compare sofosbuvir plus daclatasvir with lopinavir/ritonavir versus lopinavir/ritonavir alone in 600 people with moderate to severe COVID-19 who have had symptoms for seven days or less. In addition, a network of five clinical trials has been established to test sofosbuvir plus daclatasvir in over 2000 patients with COVID-19 in Iran, Brazil, Egypt and South Africa [11]. Sofosbuvir exhibits potent antiviral activities, >90%, even against liver cirrhosis, as well as prior null response to ribavirin and interferon [12]. Moreover, sofosbuvir is fast response and during the mean 0.8 and 2 days, it exerts it 99 and 99.9 % potency [13]. Sofosbuvir offers high healing rate, low side effects, significant efficacy, short administration period, good tolerability and potent resistance defense [14].

The motivation from above mentioned trials led to conducting of present study at Department of Medical Gastroenterology which is also Model Treatment Centre (MTC) under National Viral Hepatitis Control Program (NVHCP) where free diagnostic and treatment facility is provided to patients of hepatitis C & B. As there were number of patients of hepatitis C & B who were coming regularly for treatment which was provided uninterrupted even during Covid-19 Pandemic. All these patients were meticulously followed for eight months for development of Covid-19 infection. The data of all these patients was regularly updated when they came on follow up and also repeated telephonic contact was also maintained with all these patients by staff of Medical Gastroenterology Department.

During nine-month period, total two thousand and five hundred patients on treatment with oral antiviral drugs for hepatitis C & B were followed. Two thousand patients were of chronic hepatitis C and five hundred were of Chronic Hepatitis B. Out of two thousand patients of Chronic Hepatitis C, fifteen hundred were on Sofosbuvir 400 mg & Daclastavir 60 mg combination. The rest five hundred patients were on Sofosbuvir 400 mg & Velpatasvir 100 mg combination. Only one Chronic Hepatitis C cirrhotic patient on treatment with combination of Sofosbuvir 400 mg, Velpatasvir 100 mg & Ribavarin 1000 mg/day developed Covid-19 infection during first month of treatment. There were four more patients of chronic hepatitis C who developed Covid-19 infection but two of them were yet to be

started on treatment and rest two have completed their treatment one year back.

In case of chronic hepatitis B, out of total five hundred patients, four hundred and ninety were on treatment with Tenofovir 300 mg and ten patients were on Entecavir 0.5 mg. In Tenofovir group none patient developed Covid-19 infection whereas in Entecavir group two patients developed Covid-19 infection but till date only Tenofovir has been hypothesized to be effective in Covid-19 infection and not Entecavir.

9. Conclusion

Many smaller drug trials done in different countries highlight role of oral antiviral drugs used in treatment of hepatitis C and B in Covid-19 infection have shown optimistic results. Our study can be taken as indirect evidence of effectivity of above antiviral drugs in treatment of Covid-19 infection but this requires large scale studies directly evaluating the role of these antiviral drugs in treatment of Covid-19 infection.

10. Limitation of Study

The present study is an indirect evidence for role of oral antiviral drugs used for treatment of hepatitis C & B in Covid-19 infection but for establishing effective role of these drugs, large scale drug trials directly on Covid-19 infected patients are required.

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