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Original article

Comparative study between the therapeutic effect of remdesivir versus hydroxychloroquine in COVID-19 hospitalized patients

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ABSTRACT

Background: Up till now, no evidence based studies have recommended specific therapeutic modality to treat corona virus disease-19 (COVID-19). Many regimens were tested since the outbreak has started. Among commonly tested drugs are hydroxychloroquine, an antimalarial agent, which was proposed based on its anti-inflammatory as well as antiviral effects and remdesivir, an antiviral that showed invivo and invitro activity against the formerly known corona-viruses The Food & Drug Administration (FDA) approved using remdesivir in the treatment of severe cases of COVID-19. **Objectives:** To evaluate the effectiveness of remdesivir versus hydroxychloroquine against SARS-CoV-2 in terms of infectivity period in hospitalized COVID-19 patients. **Methods:** Fifty patients that were clinically diagnosed with Covid-19 admitted to Tanta University Isolation Hospital from June - September, 2020 were included in this study and divided into 2 groups. Group I had hydroxychloroquine as the main therapeutic agent in their treatment regimen, while group II had the antiviral remdesivir instead. Laboratory testing involved nasopharyngeal swabbing which was transported immediately to Tanta University Hospital laboratory for Real-time PCR. **Results:** There was a significant better outcome and shorter infectivity period in group 2 who received the antiviral remdesivir. **Conclusions:** Remdesivir showed significant better outcome in COVID-19 hospitalized patients, as it reduced period needed for clinical improvement while administration of hydroxychloroquine was not associated with better outcome or increased risk to the patients.

Introduction

The global outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared by the World Health Organization (WHO) as a pandemic in 2020 when about 120,000 announced infections and about 4000 deaths were reported in more than 100 countries [1, 2]. In Egypt, the officially reported COVID-19 confirmed cases were 94,316 with 4,834 deaths on August 2020 [3].

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The information on the patient features of COVID-19 infection and the risk factors of disease severity in Egypt is scarce [4].

Clinical presentation varies widely among infected individuals. However, most infected subjects may remain asymptomatic or develop mild to moderate illness that recover without need for hospitalization or specific treatment. However, about 10-15% of infected adults develop severe pneumonia that requires supplementary O_2 therapy while 5% may progress to critical forms showing acute respiratory distress syndrome (ARDS) necessitating artificial ventilation. Moreover, disseminated intravascular coagulation (DIC) and multi-organ failure may lead to higher mortality rate in those critical cases [5].

Detection of the viral nucleic acid (RNA) in upper respiratory specimens using amplification tests such as real-time polymerase chain reaction (RT-PCR) is considered the gold standard method in the diagnosis of COVID-19 infection. In areas with widespread SARS-CoV-2 transmission especially in communities with limited laboratory resources, detection of a single target nucleic acid sequence by RT-PCR is considered sufficient for diagnosis [6].

Up till now, no evidence based studies have recommended a specific drug or a successful therapeutic regimen to appropriately manage COVID-19. However, many treatments regimens have been tested in many countries since the outbreak has started [7].

Aminoquinolines like chloroquine and hydroxychloroquine (HCQ) which are commonly used as anti-malarial agents and in the management of some rheumatic and autoimmune diseases have been introduced as possible effective drugs against COVID-19 based on their anti-inflammatory as well as antiviral effects [8].

When compared to chloroquine, HCQ may show a greater in-vitro activity against SARS-CoV-2 [9]. It is thought to have a role in impairing the terminal glycosylation of the angiotensin-converting–enzyme 2 (ACE2) receptor, which is thought to be the main the binding site of the SARS-CoV-2 spike protein inhibiting its endo-lysosomal process [10].

Among other commonly tested drugs, remdesivir which is an antiviral agent, has showed in-vivo and in-vitro activity against the formerly known coronaviruses in experimental animals e.g. Severe Acute Respiratory Syndrome Corona Virus 1 (SARS-CoV1) and Middle East Respiratory Syndrome Corona Virus (MERS-CoV), which are to a great extent structurally similar to the COVID-19 causing coronavirus (SARS-CoV-2) [11]. Therefore, Food & Drug Administration (FDA) approved using the antiviral remdesivir (GS5734™) in the management of critical and severe COVID-19 cases [12].

Remdesivir is a parentral pro-drug that act as an analog of adenosine. It was first used during the epidemic of Ebola in 2013. After being metabolized to the active form, it can interfere with the RNA polymerase leading to pre-mature termination of the process of RNA transcription [13].

In this study, we aimed to evaluate the effectiveness of remdesivir versus hydroxychloroquine as common approved therapeutic agents against SARS-CoV-2 in terms of infectivity period interpreted by calculating the time needed for clinical improvement and the period from the first confirmed positive PCR result to the first confirmed negative one in adults with COVID-19 who required hospitalization.

Methods

Study population, setting, and data collection

This study was done as a part of the outbreak investigation conducted at Tanta University Hospitals, Egypt and supported by the Ministry of Higher Education (MHE). Patients who were admitted to Tanta University Isolation Hospital ICU between June and September, 2020 with laboratory confirmed SARS-CoV-2 infection were included.

Out of eighty-six patients with clinically diagnosed Covid-19 who were admitted to Tanta University Isolation Hospital during the period of the research, a total of thirty-six patients were excluded from this study either because lack of positive PCR confirmation or failure to complete the suggested treatment regimen as being transferred to other health facilities or death shortly after admission, Thus, fifty patients were included in this study as illustrated in the study flow chart **(Figure 1)**. Informed consents were obtained from all participants in the study and it was approved by the ethical committee of Faculty of Medicine, Tanta University. Data from electronic medical records was obtained e.g. demographic data, clinical manifestations and PCR results on admission.

Recent travelling history was obtained showing that included patients had not travelled recently to an endemic area or country at that time, such as countries of South-East Asia. However, most of patients (85%) reported recent contact with a clinically suspected COVID-19 patient who was not PCR confirmed. The most common clinical manifestations on admission were fever, shortness of breath and cough. Co-existing chronic medical conditions were common in critically ill patients such as diabetes mellitus, hypertension, respiratory asthmatic condition, current or former smokers and chronic obstructive pulmonary disease.

Specimen collection and testing

Clinical specimens for COVID-19 diagnostic testing were obtained according to the Centers for Disease Control and Prevention (CDC) guidelines [14, 15]. Management and laboratory investigation of cases were immediately initiated on admission. Laboratory testing involved nasopharyngeal swabbing that was transported immediately to Tanta University Hospital laboratory. Real-time PCR was done with RT-PCR Detection Kit System, primers and probes provided under supervision of MHE. The PCR conditions used were exactly as described in **Corman and his colleagues** [6].

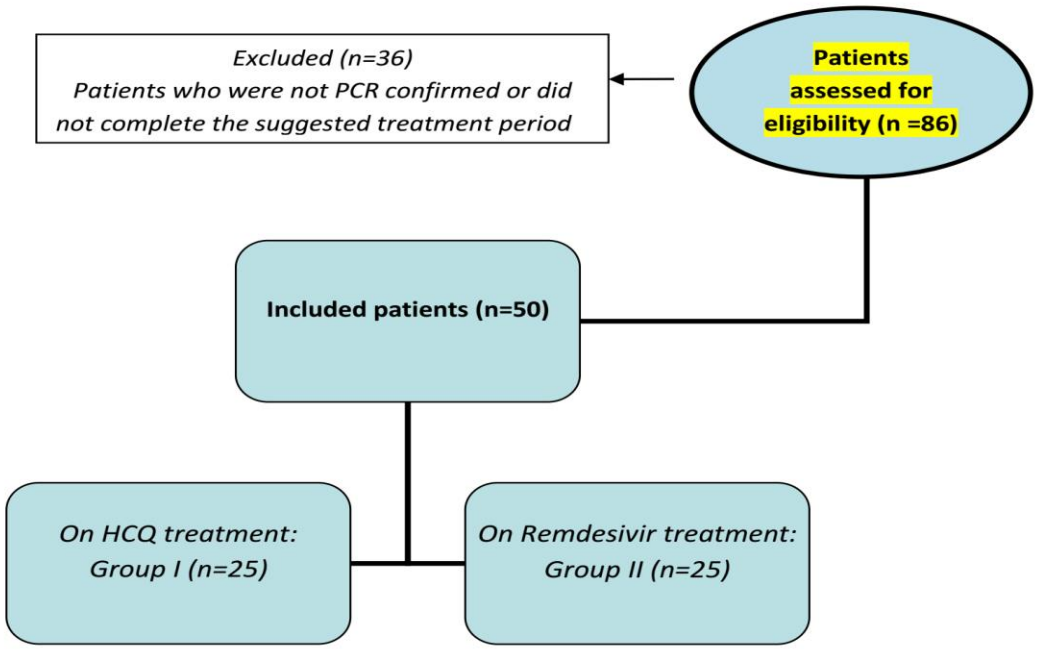
A guidance developed by the Egyptian Ministry of Health (MOH) at that time suggested HCQ as a therapeutic agent for SARS-CoV-2 infected patients who were classified as moderate-to-severe cases [16] defined as O_2 resting saturation > 93% on room air. The suggested HCQ regimen was (800 mg) on the first day as a loading dose, then half that dose (400 mg/day) for the next 6 days. To prevent the occurrence of secondary bacterial infection, azithromycin was used in combination with HCQ. The use of HCQ was discontinued on July 10, 2020 and the antiviral "remdesivir" was added to the MOH treatment protocol [17]. For either regimen, all patients received their first dose during the first twenty-four hours of hospital admission and patients suffering from ARDS with progressive increase in IL6 level received immune-modulatory agents e.g. IL6 inhibitor.

To exclude the impact of some variants like coexisting chronic conditions and the use of immune-modulatory agents in some patients, the Sequential Organ Failure Assessment (SOFA) score was used [18]. It was also used for assessment of the final patients' outcome. The score is a calculation of different six sub-scores for six body systems (respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems) [19]. The Score usually ranges from 0-24. A Score >=2 or a change of 2 or more points is associated with increase in mortality rate by 20% [20].

Statistical analysis

Analysis was performed with T test. Statistical Package for Social Sciences (SPSS) version 23 was used for data analysis. Data were expressed in number (No.), percentage (%), mean (x), and standard deviation (SD). *P*-value < 0.05 was considered statistically significant.

Figure 1. The study flow chart.



Results

Demographic and clinical characteristics of the patients

Out of the 50 patients included in this study, half of which (25 patients) received HCQ in their treatment regimen (group I) while the other half received the antiviral Remdesivir (group II). The mean age of the patients (±SD) was 44.04 ± 16.549 for group I and 44.80 ± 15.663 for group II with 52% of them were men. The baseline characteristics of patients according to therapeutic agent used is shown in **(Tables 1&2)**.

Microbiological results

All patients had SARS-CoV-2 infection that was laboratory-confirmed by RT-PCR assay using a nasopharyngeal swab at Tanta University Lab. **Table 3** shows the correlation between infectivity period (duration of PCR positivity) in relation to the treatment regimen used in both groups. There was a significant difference between the two groups with better outcome and shorter infectivity period in group 2 who received the antiviral remdesivir. **Figure 2a** shows negative SARS-CoV-2 real-time PCR report while **figure 2 b** shows positive SARS-CoV-2 real-time PCR report.

Table 1. Distribution of baseline characters (age) in relation to treatment regimen.

Groups	Age (years)		T-test	
	Range	Mean ± SD	T	*p* value
Group I (n= 25)	23-77	44.04 ± 16.549	0.167	0.868
Group II (n= 25)	22-77	44.80 ± 15.663		

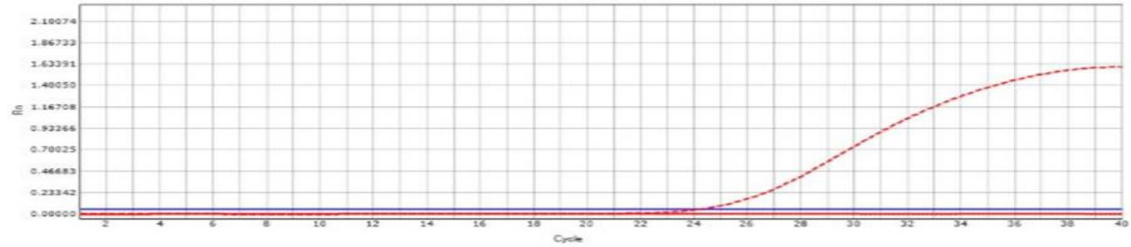
Table 2. Distribution of baseline characters (sex) in relation to treatment regimen.

Sex	Group I		Group II		Total	
	No.	%	No.	%	No.	%
Male	12	48	14	56	26	52
Female	13	52	11	44	24	48
Total	25	100	25	100	50	100

Table 3. Correlation between the infectivity period (PCR positivity) in relation to the treatment regimen used.

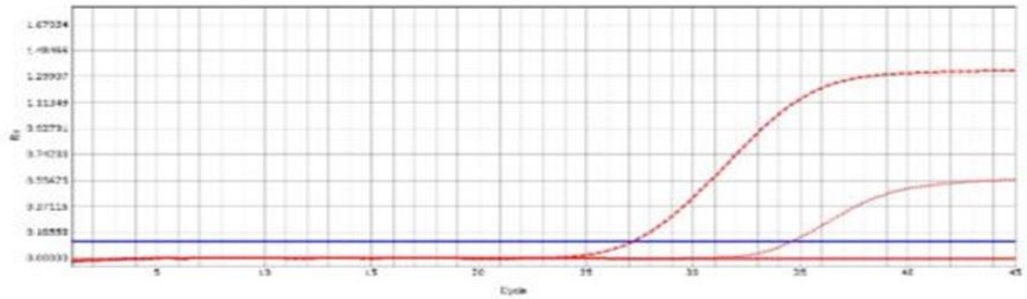
Groups	Infectivity period		T-test	
	Range	Mean ± SD	T	*p* value
Group I (n= 25)	7-35	11.88 ± 5.848	2.791	0.008*

Figure 2a. Negative SARS-CoV-2 real-time PCR report.



Test Item	Test Result	Threshold	Unit	Conclusion
RdRp	No Ct	38	Cycles	Negative
N	No Ct	38	Cycles	Negative
IC	25.45	38	Cycles	Positive

Figure 2 b. Positive SARS-CoV-2 real-time PCR report.



Test Item	Test Result	Threshold	Unit	Conclusion
RdRP	No Ct	38	Cycles	Negative
N	34.61	38	Cycles	Positive
ic	27.16	38	Cycles	Positive

Discussion

Finding an appropriate antiviral therapeutic agent is essential for undertaking this COVID-19 global pandemic. Many introduced drugs have shown an in-vitro activity against the closely related beta coronaviruses. They have also shown some sort of in-vitro activity against SARS-CoV and MERS-CoV, and sometimes can be also used synergistically with certain antivirals as ribavirin [21, 22].

This cross-sectional observational study involved a moderate number of hospitalized COVID-19 patients divided into two groups. Group I received the antimalarial HCQ as the main therapeutic agent while group II received the antiviral remdesivir. We observed a significant better clinical and laboratory patients' outcome on using the antiviral "remdesivir" in the management protocol in critical COVID-19 patients evidenced by the shorter infectivity and PCR positivity period together with faster improvement of the clinical symptoms when compared to using the HCQ protocol.

Many clinical trials have investigated the use of remdesivir in COVID-19 patients. The broadest ones are the random clinical trials ACTT-1 and SOLIDARITY [23, 24]. ACTT-1 reported a reduced time of clinical improvement and a better mortality outcome but that was evidenced only in patients on supplemental O_2 not on artificial ventilation machines. On the other hand, SOLIDARITY did not report any better mortality outcome on using remdesivir. This can be explained by the different primary endpoints of trials, design variation and what they aimed to investigate. As ACTT-1's primary endpoint was mainly concerned with the detection of the period needed to clinical improvement not the mortality outcome while SOLIDARITY was mainly concerned with mortality outcome and was not designed to investigate the time of clinical improvement or comparing the outcome of the drug in ventilated patients versus the non-ventilated ones. Moreover, there was difference in the geographical distribution as ACTT-1 investigated patients living in North America, while SOLIDARITY investigated those living in Africa, Asia and South-America.

Our results are also concomitant with a previous study which indicated that HCQ therapy wasn't connected to lower or more threat of the participants recommending further random clinical trials of HCQ in COVID-19 patients [25].

Moreover, another limited, random Chinese trial revealed no significant clinical improvement in patients who received HCQ (400 mg/day) compared to patients receiving non-specific therapy. The trial reported that by the seventh day, 93% of the non-specific therapy group showed negative swabbing results compared to 86% of HCQ receiving patients [26].

In the same context, another clinical trial which aimed to test 2 doses of HCQ on Covid patients and had a plan of including more than 400 patients in the trial but they ceased when 80 patients suffered from excessive QT wave prolongation in the ECG with indication of higher mortality rate on higher doses of HCQ [27].

On the other hand, an early French study showed a benefit of HCQ in treatment of 26 patients however, their results are difficult to interpret because of the small sample size, lack of a random patient selection and the exclusion of some patients from the study without clear causes [28].

Also, another random Chinese trial in Wuhan, in which group I included patients with mild symptoms receiving non-specific therapy in the form of supplementary O_2, antibiotics, immunoglobulins with or without corticosteroids while group II received HCQ (400 mg/day). Physicians reported earlier clinical recovery manifested by faster subsiding of fever and cough with better results of the chest imaging in group II than in the group I [29].

Conclusion

To conclude, it appears that remdesivir provides a general beneficial therapeutic effect to hospitalized COVID patients, as it can reduce the mean time needed to clinical recovery especially when administrated in patients with mild to moderate forms of the disease or when administrated early in the severe forms of the disease. Hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk to the patients. Further random clinical trials of HCQ in COVID patients are needed.

Given the observational design of our study, we can't rule out the beneficial or harmful aspects of using HCQ as we mainly aimed to evaluate the effectiveness of remdesivir versus HCQ as common approved therapeutic agents against SARS-CoV-2. However, our findings don't encourage the use of HCQ as a solitary anti-COVID agent.

Moreover, we recommend further research of some points to overcome the limitations of our study such as using larger sample size and a multi-centric study that should help supporting and generalization of data.

Conflict of interest: no conflict of interest.

Authors' Contribution

All authors contributed equally to this work.

Financial disclosure

This study was done as a part of the outbreak investigation conducted at Tanta University Hospitals, Egypt and supported by the Ministry of Higher Education (MHE). Patients with laboratory-confirmed SARS-CoV-2 infection, who were admitted to Tanta University Isolation Hospital ICU between June and September, 2020 were included.

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