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Pharm Sci 2020-Coronavirus Disease 2019 Pandemic Hopes Ride High on Targeting Known Drugs against Unkown- PGIMER, India

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Introduction

In December 2019, a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak occurred in Wuhan, China, which rapidly spread to other parts of the world. The WHO has therefore declared the CoV disease (COVID) as a pandemic on March 11, 2020, and it needs to be tackled down at the earliest. The virus exhibits a very high transmission rate which can be witnessed by an increase in the number of new cases everyday across the globe. As of April 11, 2020, globally, the number of confirmed cases is in excess of 16 lakhs, with more than 99,000 deaths.

Till date, no specific and effective therapy exists against COVID-19. In view of this pandemic, there is an urgent need to find the potential treatment options against this novel CoV. Hence, a movement of repositioning of the drugs has been tried to tackle the problem. In the current SARS-CoV-2 outbreak, a number of drugs have been in trial to evaluate their efficacy against the virus. Of all the drugs, antimalarial drug has gained much popularity because of its antiviral effect.

Chloroquine (CQ) was one of the front-line drugs in the prophylaxis and treatment of malaria for many decades. Unfortunately, as CQ-resistant Plasmodium falciparum strains emerged, it led to the decline in the efficacy of the drug. Apart from the efficacy of CQ against various bacteria and fungi, the drug also exhibits efficacy against different viruses such as HIV,

rabies virus, and poliovirus. With regard to CoV, the potential therapeutic benefit of CQ was observed against SARS-CoV. As per the preliminary reports from Chinese authorities, around 100 patients were treated with CQ. These patients showed more speedy fever decline, improvement in lung computed tomography images, and it took less time to recover compared with control groups, with no serious adverse effects. Therefore, Chinese medical advisory board has suggested the inclusion of CQ in the guidelines for SARS-CoV-2 treatment. The virus requires low pH for replication including fusion and uncoating. CQ alkalizes phagolysosome which hinders these pH-dependent steps. During the outbreak of SARS in 2003, many molecules apart from CQ were tested to evaluate their effectiveness against the virus. By inhibiting pH-dependent enzymes like proteases or glycosyltransferases, CQ was able to disrupt the viral proteins maturation and posttranslational modification of viral receptors like angiotensin-converting enzyme 2 (ACE2) in case of SARS-CoV. In an in vitro study, CQ was able to act at both entry as well as postentry stages of viral infection in Vero E6 cells. On oral administration, CQ gets distributed in the entire body including the lungs. The EC90 value of CQ in Vero E6 cells

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against COVID-19 was 6.90 µM, which may be clinically attainable as established in the plasma of rheumatoid arthritis patients who received 500 mg of CQ.

Being an analog of CQ, hydroxychloroquine (HCQ) has got fewer side effects and drug–drug interactions. In a study by Yao et al., HCQ showed a better activity against SARS-CoV-2 in vitro when compared to CQ. It also showed a better antiviral activity as demonstrated by the EC50 values for HCQ being lesser than the EC50 values for CQ. Furthermore, HCQ has showed anti-SARS-CoV activity in vitro in the previous SARS outbreak. In a few patients infected with SARS-CoV-2, an increase in the levels of interleukin (IL)-6 and IL-10 has been observed which may later lead to cytokine storm, subsequently leading to multi-organ failure and death. Both CQ and its analog HCQ are known to suppress an increase in immune factors, thereby exhibiting an immunomodulatory effect. Based on these findings, HCQ may serve as a therapeutic option against SARS-CoV-2 infection because of its antiviral effects and its ability to suppress the cytokine storm by virtue of its immunomodulatory effects. However, there are limited data regarding their use in SARS-CoV-2; hence, clinical trials are ongoing to evaluate their effect in these patients.

A study conducted by Jun et al. showed that there was no statistically difference in negative nucleic acid throat swabs on day 7 between HCQ group and control group; in fact, the negative throat swab was more in the control group, and worsening of a patient in HCQ group was observed. A small sample size of just 30 in the study could be responsible for such results. Another study conducted by Gautret et al. found that the use of HCQ reduced the viral load significantly in patients suffering from

COVID-19. The study showed a synergistic effect in the reduction of viral load on combining HCQ and azithromycin when compared to HCQ alone. Previously, azithromycin has shown some benefits in preventing severe respiratory tract infections when given to patients with a viral infection. However, even here, the sample size was quite small, so more studies are required with a high sample size to generate much more robust evidence.

However, one cannot underestimate the side effect profile of CQ and HCQ. CQ is known to cause dizziness, loss of appetite, headache, arrhythmia, and leukopenia while treating malaria. Retinal toxicity has been observed with long-term use of CQ and HCQ. Another concern is the risk of QT prolongation. Azithromycin has shown to have proarrhythmic potential. In a retrospective study conducted by Ray et al., it was concluded that a slight increase occurred in cardiovascular related deaths during the 5-day treatment with azithromycin that was more prominent in patients having increased baseline risk of cardiovascular disease. The risk is more in patients having a higher baseline risk like those with pre-existing cardiovascular pathology as well as concomitant use of drugs leading to QT prolongation. So, is it really safe to use both HCQ and azithromycin drugs in combination for treating COVID-19 is a question that needs to be answered. Both the drugs are metabolized in the liver with few metabolites excreted through renal route and therefore raises an alarm against the usage of these drugs in patients with hepatic and renal failure. According to a study by Zhang et al., COVID-19 patients had an increased incidence of hepatic abnormalities during the course of the disease, which may be probably due to the effect of SARS-CoV-2 on the liver or medications used in these patients. HCQ is

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metabolized into three active metabolites, of which it has been shown that desethylhydroxychloroquine (active metabolite) is mainly associated with the treatment effect in rheumatoid arthritis patients. The metabolites of HCQ are known to accumulate in the lung tissue; however, the antiviral activity of these metabolites still needs to be explored. HCQ is also known to cause hypoglycemia that may be fatal if administered in patients with or without antidiabetic medications. Azithromycin has shown to have a antiviral activity against Zika and Ebola virus in vitro. Azithromycin has also shown to have an anti-rhinoviral property in bronchial epithelial cells by increasing the interferon-stimulated gene production.

Among the lack of clinical evidence, the question arises that are these drugs really safe for the prophylaxis of healthcare workers? Asymptomatic close household contacts? These drugs are not recommended in children below 15 years. Although disease severity is not much in children compared to adults, they still can be carriers and affect the adult population. So, the question is how can this problem be tackled? What should be the alternative treatment to contain this infection among children? Solutions to all these questions can be given only when the grey area will be explored with clinical research. Now, let us focus on the special cases where these drugs are contraindicated. Glucose-6-phosphate dehydrogenase deficiency is one of the main contraindications for CQ use. In a meta-analysis by Pradeepkumar et al., the overall magnitude of the frequency of G6PD in the Indian population is around 8.5%, which constitutes roughly around 11 crore people, considering the Indian population to be approximately around 138 crores. So, what are the alternative therapeutic options for G6PD patients and patients with renal and hepatic dysfunction? Therefore, it is always advisable to undergo screening for G6PD deficiency and porphyria before taking CQ/HCQ. Apart from all the queries, there is also a concern about CQ overdose as the media has reported three cases of CQ poisoning. Hence, self-medication and prophylactic use in community is not advisable. Moreover, active surveillance and careful monitoring of patient is essential to prevent any adverse events. A recent study has shown encouraging results with the use of convalescent plasma therapy in severe COVID-19 patients, as all the ten patients included in the study met with the primary and secondary endpoints. Hence, convalescent plasma therapy might be a promising solution to the ongoing pandemic; however, there is a need for more data to generate robust evidence.

Coronavirus Disease-2019 Pandemic: Are Angiotensin-Converting Enzyme Inhibitors and Ibuprofen a Double-Edged Sword?

During the previous SARS outbreak, it was found that SARS-CoV binds to ACE2 cell receptor expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. It has been confirmed that SARS-CoV-2 also uses the same receptor and mechanism to enter the host cell. The spike (S) proteins are situated on the exterior of the betacoronaviruses anchor to the ACE2 receptors located in the lower respiratory tract to gain entry into the lungs. Single N501T mutation in the spike protein of SARS-CoV-2 might have considerably improved its binding affinity for ACE2. Viral pneumonia and fatal respiratory failure may develop in a span of 10–14 days, especially in susceptible individuals. Patients on ACE inhibitors and angiotensin receptor blockers (ARBs) will have an increased expression of ACE2 receptors. ACE2 upregulation can also be seen with ibuprofen and thiazolidinediones like pioglitazone in a rat

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model of high fat-induced nonalcoholic steatohepatitis. This might facilitate the S protein of CoV to anchor to these receptors which might lead to severe disease outcomes in SARS-CoV-2-affected patients. In a mouse model of atherosclerosis, ACE2 upregulation is also observed by statins like atorvastatin. In a study by Guan et al. comprising of 1099 patients, more severe disease were observed in patients with diabetes, hypertension, chronic renal disease, and coronary artery disease who might have been on ACE inhibitors and ARBs. As ACE2 decreases inflammation and it is suggested as a possible treatment in inflammatory lung diseases, diabetes mellitus, hypertension, and cancer, it might lead to a conflict. Hence, further exploration into ACE2 polymorphisms and susceptibility to SARS-CoV-2 infection in the Asian population is to be looked upon.

Once SARS-CoV-2 virus gains entry into cell through ACE2 receptors, it causes downregulation of the expression of ACE2 so that the enzyme is incapable of exerting protective effects in organs, thereby leading to an increase in the levels of angiotensin II levels. Furthermore, it has been hypothesized but not yet proven that persistent angiotensin II activity might be one of the factors attributable to organ injury in COVID-19. COVID-19 patients seem to have raised plasma angiotensin II levels, which correlated with the total viral load as well as the degree of lung injury. A study by Khan et al. showed that administration of recombinant ACE2 appeared to restore ACE2, therefore causing a decline in angiotensin II levels in patients with ARDS. Abrupt withdrawal of these drugs could prove to be fatal, especially in patients with underlying cardiac pathology. Hence, in view of these mixed results and in absence of any high-level evidence regarding the use of these drugs in COVID-19, these drugs should not be discontinued. The elderly usually suffer from cardiovascular diseases and majority of them are on ACE inhibitors and statins. So, are these really beneficial or actually posing a threat to elderly by increasing the chances of infection by COVID-19 still remains unexplored. The main problem is the lack of proper evidence due to numerous small trials with different methodologies that most often do not give a clear and strong evidence. The WHO has therefore initiated “WHO Solidarity trial” which involves participation of various COVID-19-affected countries. This is a large international study designed to generate robust data to find out the potential therapy against COVID-19. Hence, let us all join hands together and fight against this pandemic. There is always light at the end of the tunnel…

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