Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infectionwith reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc)

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A B S T R A C T

Background and aims: Multiple issues in management of COVID have emerged, but confusion persists regarding rational interpretation. Aim of this brief review is to review these issues based on current literature.

Methods: This is a narrative review with Pubmed and Google Scholar search till 23 March 2020. Search terms were, COVID-19, treatment of coronavirus, COVID 19 and following terms; chloroquine, hydroxychloroquine, ibuprofen, ACE-inhibitors or angiotensin receptor blockers, cardiovascular disease, diarrhoea, liver, testis and gastrointestinal disease.

Results: We discuss evidence regarding role of chloroquine and hydroxychloroquine in treatment and prophylaxis, use of inhibitors of the renin angiotensin system, safety of ibuprofen, unusual clinical features like gastrointestinal symptoms and interpretation of tests for cardiac enzymes and biomarkers.

Conclusions: While our conclusions on management of COVID-19 patients with co-morbidities are based on current evidence, however, data is limited and there is immediate need for fast track research.

1. Introduction

We recently published an article highlighting the special concerns while managing patients with diabetes in the times of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of the (Corona Virus Disease 2019) COVID-19 pandemic [1]. More data has accumulated since then about this ever-evolving pandemic and several new concerns and concepts have emerged. We considered it worthwhile to highlight some of these issues and try to arrive at some rational conclusion based on the current evidence. Detailed articles on each of below mentioned issues will be published shortly.

2. Search methodology

We systematically searched the PubMed database and Google Scholar till March 23, 2020 using the keywordsCOVID-19, treatment of coronavirus, COVID 19 and following terms; chloroquine, hydroxychloroquine, ibuprofen, ACE-inhibitors or angiotensin receptor blockers, cardiovascular disease, diarrhoea, liver, testis and gastrointestinal disease.We also accessed the and retrieved the full text of the relevant cross references from the search results.

3. Role of chloroquine and hydroxychloroquine (HCQ)

Antiviral properties of chloroquine *in vitro* have been observed for more than half a century [2]. It exerts its antiviral effect by several mechanisms: reducing endocytosis of virus by stabilising the lysosomes, inhibiting the viral replication, and inducing the production of non-infectious particles by inhibition of glycosylation of the envelope glycoproteins [3]. Additionally, it exerts anti-inflammatory effects by inhibiting the release of proinflammatory

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cytokines, especially tumor necrosis factor-alpha which may ameliorate the immune reaction seen with viral infections.

In vitro activity of chloroquine (CQ) has been demonstrated against several viruses including Vesicular Stomatitis virus [4], Mouse Hepatitis virus, Nipah virus, Ebola virus, Influenza virus, and more recently, SARS coronavirus [5,6]. However, except for human immunodeficiency virus and hepatitis C virus, these effects have not been replicated in clinical studies in humans. CQ did not prevent influenza infection in a randomized, double-blind, placebo-controlled clinical trial [7]. Further, there was no effect on patients with dengue infection in a randomized controlled trial [8]. Of concern was the observation that despite having antiviral activity *in vitro*, CQ increased viral replication and exacerbated fever in animal models of chikungunya virus infection [9]. Also, patients with chikungunya virus infection had more chronic arthralgia when treated with CQ *vs.* those treated with placebo [10]. The reasons for this discrepancy between *in vitro* and results from clinical studies are not very clear. One possible mechanism would be the failure of the drug to concentrate in target tissues. Also 50% effective concentration [EC50] of chloroquine for anti-viral effects is about three times higher than that necessary to inhibit chloroquine-sensitive malarial parasites [11].

Against this background, CQ was evaluated in SARS CoV-2 infection and showed very good *in vitro* efficacy [12]. The clinical evidence was recently published from France. In this study of 36 patients, 20 patients were treated with hydroxychloroquine (HCQ), out of which 6 also received azithromycin, and 16 patients served as controls. At day 6 post treatment the proportion of patients who were negative for SARS CoV-2 was 100%, 57% and 12.%% for those treated with HCQ and azithromycin combination, HCQ only and controls, respectively [13].Though this is a small study, the results are very encouraging. Further, a report from China showed good efficacy of CQ in patients with COVID-19, though there was no access to detailed data [14].Concurrently, several trials are planned to study its role in prevention and treatment of COVID-19 and at present, it is difficult to make recommendations based on these preliminary data.

3.1. Practical recommendations based on current evidence

In view of good tolerability of HCQ and low cost, it could be offered as an off-label treatment to the patients with moderate to severe COVID-19 infection. These issues have been discussed in detail in another article in this special issue [15].

Though there is no evidence of the role of chloroquine in prophylaxis against CVID-19, Indian Council of Medical Research (ICMR) has recommended prophylaxis with CQ or HCQ in asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19 and asymptomatic lhousehold contacts of laboratory confirmed cases [16].

4. Use of ibuprofen and other NSAIDs

A doctor from France cited four cases of young patients with COVID-19 and no underlying health problems who went on to develop serious symptoms after using non-steroidal anti-inflammatory drugs (NSAIDs) in the early stage of disease. This observation prompted the advice against the use of ibuprofen in this condition [17]. World Health Organisation (WHO) first recommended against using ibuprofen in COVID-19, however went back against its own advice and updated its advice soon to say that "based on currently available information, WHO does not recommend against the use of ibuprofen" [18]. It is interesting to note that several previous studies have shown a complicated course with increased incidence of empyema, lung cavitation and prolonged stay in the intensive care unit when nonsteroidal anti-inflammatory drugs (NSAIDs) were used in patients with pneumonia [19].

4.1. Practical recommendation based on current evidence

Overall, it seems reasonable, but not mandatory, to avoid ibuprofen and other NSAIDs in COVID-19 infection and use acetaminophen instead for control of fever and pain.

5. Use of drugs acting on renin angiotensin system

Angiotensin converting enzyme-2 (ACE-2) is the receptor for SARS CoV-2 as well as other coronaviruses and is expressed in type 2 alveolar epithelial cells and endothelium. The S-glycoprotein on the surface of coronavirus binds to ACE2. This leads to a conformational change in the S-glycoprotein and allows proteolytic digestion by host cell proteases (TMPRSS2) ultimately leading to internalization of the virion [20].Viral S-glycoprotein, TMPRSS2 and ACE-2 inhibition are potential targets of therapy and possibly vaccine development.

As ACE-2 is the binding site for SARS CoV-2, its blockade is thought to be beneficial in preventing/treating this infection. A retrospective analysis showed reduced rates of death and endotracheal intubation in patients with viral pneumonia who were continued on ACE inhibitors [21]. Mice with coronavirus induced lung injury showed improvement when treated with an angiotensin receptor blocker, losartan [22].As far as CVID-19 infection is concerned, the data on RAS activation or the effect of its blockadeis limited at present. Hypokalaemia and hypertension? could be a marker of RAS activation and high incidence of hypokalaemia has been reported in patients with COVID-19 infection [23].

Despite these small studies suggesting the benefit of drugs acting on RAS pathway, there is some data, albeit scarce, from animal models and human studies that treatment with ACE inhibitors and ARB could causeup regulation of ACE2 [24]. Ibuprofen and thiazolidinediones have also been shown to do the same [25,26]. Increased expression of ACE2 could theoretically increase the risk of infection with SARS CoV-2. This could be a concern in people with diabetes who are at already elevated risk of infections because of many other factors.However, there is no evidence to support this hypothesis currently. In a retrospective analysis of 112 COVID-19 hospitalised patients with cardiovascular disease in Wuhan, there was no significant difference in the proportion of ACEI/ARB medication between non-survivors and survivors [27]. This issue will be discussed in detail in another article to be published in special issue shortly.

5.1. Practical recommendation based on current evidence

In view of lack of robust evidence for either benefit or harm, it is reasonable for patients to continue using ACE inhibitors and ARB, as recommended by European Society of Cardiology Council on Hypertension, European Society of Hypertension and American Heart Association [28–30].

6. Extrapulmonary manifestations

ACE-2 receptor, the binding site for SARS CoV-2 is expressed in several extrapulmonary locations, the chief amongst them being the gastrointestinal epithelium, renal tubules and Leydig cells in testis [31]. This raises concerns about some of the extrapulmonary manifestations and possible complications.

6.1. Gastrointestinal tract and liver

A significant number of patients with COVID-19 have reported diarrhoea, vomiting and abdominal pain [32]. This is not unexpected as ACE-2 is highly expressed in the small intestinal epithelium [33].These observations underscore the importance of considering COVID-19 while evaluating a patient with fever, cough and diarrhoea.

ACE-2 receptor expression has also been seen in bile duct epithelial cells. Liver function test abnormalities have been observed in patients with COVID-19 [34]. Steatosis and liver injury have been reported [35]. These could be because of the direct effects of virus or adverse effects of drugs.

6.2. Kidneys

Patients with chronic kidney and those who have received renal transplant are at increased risk of COVID-19 infection and severity. Moreover, there are frequent renal function abnormalities and increased incidence of acute kidney injury in patients with COVID-19.It is not known yet whether this occurs from the effects of sepsis or is a direct nephrotoxic action of virus. Patients with acute kidney injury have a higher mortality and renal function monitoring should be a part of managing these patients.

6.3. Cardiovascular system

Patients with underlying cardiovascular disease are among the highest risk individuals for severe COVID-19 disease and death [36]. Cardiac troponin Ilevels are significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of disease [37]. This may be similar to what is observed in many patients with acute respiratory illnesses; or it may indicate myocardial injury because of the virus as ACE-2 receptors are widely expressed on cardiomyocytes. American College of Cardiology recommends measuring troponin if the diagnosis of acute MI is being considered on clinical grounds and an abnormal troponin should not be considered evidence for an acute MI without corroborating evidence [38]. Similarly, patients with COVID-19 infection have elevated natriuretic peptides, significance of which is uncertain. Hence an elevated level of natriuretic peptides in COVID-19 should not be taken as an indicator of heart failure.

6.4. Testis

Orchitis was reported in infection with SARS CoV earlier [39]. ACE-2 receptors are present in Leydigcells in testis.At present, there is no data about clinical significance of these receptors; however, reproductive function may need to be followed up in men who have recovered from this infection.

7. Conclusion

There are several unresolved clinical issues and dilemmas in the clinical management of COVID-19. This is not an expected considering the rapidity with which this disease has emerged and is progressing. We have attempted to go through the data available at present and arrive at some reasonable conclusion. However, these recommendations are not final as the evidence is accumulating daily and our understanding of the virus, the disease, its clinical presentation and management is rapidly evolving.

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