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Review Article

Update on Clinical Severity and Management of Novel Corona Virus Disease (2019-nCoV)

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Abstract

The world has witnessed many episodes of varied viral epidemics from last two decades by the name of severe acute respiratory syndrome (SARS) in 2002, H1N1 influenza in 2009, Middle East respiratory syndrome (MERS) in 2012 and the latest by COVID in 2019 (ongoing). The impact of 2019-nCoV is multidimensional being highly pathogenic and pandemic it has led to public health emergency of global concern, international unprecedented lockdown and global economy slipping into recession. The exploded case numbers overwhelmed the health sector forcing doctors to make agonizing decisions. Herein, we present an overview of available information on the etiology, transmission, symptoms, viral replication, epidemiology, and testing with special emphasis on clinical severity and management of COVID-19.

Keywords: *COVID-19; Case Fatality Rate; 2019-nCoV; Replication-Transcription Complex; NSAIDS; Antiviral*

Introduction

Coronavirus disease of 2019 reported first time in Wuhan, China in December 2019 is caused by recently identified β-coronavirus [1]. The World Health Organization (WHO) named virus as 2019 novel coronavirus (2019-nCoV) and the disease as coronavirus disease 2019 (COVID19). As of 31st of March, a total number of 81,500 cases have been reported in China including 3,310 deaths and a total number of 859,929 infected cases including 42,344 deaths worldwide. Coronavirus diseases are zoonotic diseases originated possibly from bat transmitted to humans where it produced a wide range of clinical features from asymptomatic carriers to viral pneumonia patients affecting respiratory, gastrointestinal, cardiovascular and neurological systems [2]. The clinical features of COVID19 absolutely rely on the immune status of infected person; case fatality rates are significantly higher in immunocompromised patients. The disease has been labeled as pandemic by WHO as it has affected 203 countries and territories around the world. COVID19 has shifted from the country of origin to various European countries and US. Wave is spreading to France, Italy, Spain and lately US with high mortality. The COVID19 being a novel disease has posed severe challenges for public health, research, and medical fraternity [3]. The objective of this review article was to have a preliminary opinion about COVID-19, its clinical severity and possible treatment options.

Literature search strategy (Methodology)

A systematic literature search of PubMed and Embase (Elsevier) databases was performed on March 12 - 18, by means of keywords "corona virus," "COVID-19", "2019-nCoV, replication-transcription complex and Case fatality rate". Considering the importance of the theme and to enhance the sensitivity of the search, a classical literature search was performed using the similar keywords on Google Scholar to hit the published articles in recent past. Additionally, the publication database of WHO on novel corona virus was searched for potentially relevant publications (WHO website). With consideration of the date of the first confirmed reports of COVID-19, we restricted our search to articles published in 2020. Because of the large number of records identified from the gray literature, the Google Scholar search was limited to titles. However, no additional limits were applied in the PubMed or Embase search.

Etiology

Corona virus disease /COVID- 19/ nCoV-2019 is a zoonotic disease caused by a virus belonging to the family of *Coronaviridae.* From past two decades trio related attacks of coronaviruses have been established around globe. The earliest being the severe acute respiratory syndrome (SARS-CoV) originated in the Guangdong province of China in the year 2002 followed by Middle-East respiratory syndrome (MERS-CoV) appeared in Saudi Arabia and nowadays the larger part of world is under the grip of corona virus disease COVID-19 that emerged in Wuhan, Hubei province of China in the month of December 2019. The initial infection was reported at Huanan seafood market possibly due to animal contact which led to widespread human to human transmission [4-7].

The coronaviruses are divided into four genera's: alphacoronovirus, betacoronovirus, gammacoronovirus and deltacoronovirus. Alpha and beta are infecting mammals with identified species of HCoV-NL 63, HCoV-229E and HCoV-OC43, HCoV-HKU1, SARS-CoV MERS-CoV respectively (Table 1) [8]. Coronaviruses are enveloped positive sense RNA viruses possessing spikes extending from their surface. The virus is laced with large RNA genome possessing a unique replication stratagem [9]. The genomic sequencing of CoVID-19 showed analogy with SARS-CoV amounting to 79.6% of sequence identity. However, a comparison has showed 380 aminoacid substitutions between them that may have caused pathogenic and functional divergence of nCoV-2019 responsible for invasiveness of 2019-nCoV [10]. The reservoir is presumed to be the bat as the novel coronavirus of humans exhibited 96% whole genome level similarity to bat coronavirus [5].

<table>
<tr><th></th><th>Genera's</th><th>Hosts</th><th>Species</th></tr>
<tr><td rowspan="4">Coronaviruses</td><td>Alphacoronavirus</td><td rowspan="2">Mammals</td><td>HCoV-NL 63
HCoV-229E</td></tr>
<tr><td>Betacoronavirus</td><td>HCoV-OC43
HCoV-HKU1
SARS-CoV
MERS-CoV</td></tr>
<tr><td>Gammacoronavirus</td><td rowspan="2">Birds</td><td>IBV</td></tr>
<tr><td>Deltacoronavirus</td><td>PDCV</td></tr>
</table>

Table 1: *Coronavirus genera's, hosts and species (Abbreviations: HCOV: Human Coronavirus; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; IBV: Infectious Bronchitis Virus; PDCV: Porcine Delta Coronavirus).*

Transmission

CoVID 19 has raised grave concerns among developed and developing countries merely not due to its invasiveness but due to mode of transmissibility of this virus. The virus spreads by droplet infection (sneezing, coughing) and close contact with infected person or asymptomatic carriers. Nasocomial outbreaks have also been reported infecting many health care workers which were not attributed as a major amplifier indeed family clusters were supposed to be the major contributing cause of this spread among health care workers in China. Therefore, for transmission by direct contact or contact with fomites, close and unguarded exposure is needed [11]. The incubation period of 2019-nCov was anticipated to be 1 to 14 days besides 3 - 4 days incubation period is usually suggested.

The viral transmissibility can be assessed by R_0 value/reproduction number. It is a mathematical term which provides an estimate of contagious nature of an infection. The value of R_0 is a gauge to measure number of individuals which can take disease from a single contagious individual. The diseases with R_0 value greater than 1 can cause epidemics or pandemic. The R_0 value estimates for the 2019-nCoV ranges from 2.24 - 5.5 [12,13]. Coronavirus affected person can spread the disease to 2.24 to 5.5 individuals.

Much of the information gathered pertaining to transmission of disease during Wuhan outbreak was followed by activated emergency response besides much remains to be learnt regarding features of virus to refine the risk evaluations and comeback [14].

Clinical severity

The case study conducted by Chinese center for disease control and prevention till February 11, 2020 analyzed 72,314 cases (Table 2). 62% were the confirmed cases diagnosed by positive viral nucleic acid test; 22% were suspected cases diagnosed by signs and symptoms; 15% diagnosed cases based on symptoms and relevant lung imaging features; 1% asymptomatic cases diagnosis made by viral load test only. The majority of cases were in the age group of 30-79 years and lowest number of cases (2%) recorded below 19 years of age. The disease showed a mild course (no pneumonia/mild pneumonia) in 81% of infected cases, 14% positive cases showed severe course of disease exhibiting viral pneumonia and requiring hospitalization and 5% cases were critical (septic shock, multiple organ failure) requiring critical care services [15].

Age distribution (N = 44 672)	Total cases (72314)	Case-fatality rate	Spectrum of Disease (N = 44 415)
80 years: 3%	Confirmed cases 62%	2.3% (1023 of 44 672 confirmed cases)	Mild: 81%
30-79 years: 87%	Suspected Cases 22%	14.8% in patients aged 80 years (208 of 1408)	Severe: 14%
20-29 years: 8%	Diagnosed Cases 15%	8.0% in patients aged 70-79 years (312 of 3918)	Critical: 5%
< 20 years: 2%	Asymptomatic Cases 1%	49.0% in critical cases (1023 of 2087)	

Table 2: *Table showing age distribution, total cases, case fatality rate and spectrum of disease (Findings from the Chinese center for disease control and prevention) [15].*

The case fatality rate (CFR) calculated in China till February 11, 2020 due to coronavirus infection arrived out to be 2.3% and the mortality rate as of 3 March 2020 estimated by WHO globally is 3.4%. The CFR showed a positive correlation with age, CRF was maximum

14.8% in patients aged 80 years, 8% in patients aged 70 - 79 years. Nearly half of critical patients die, the infected patients with other co-morbid conditions viz hypertension, diabetes, COPD are at higher risks [16]; In China as of February 29, 2020 showed increased CFR with age; individuals below 30 years were 0.6 times and individuals above 59 were 5.1 times more likely to die after developing the symptoms of disease. The risk of infection is raised (approximately 4% per year among individuals aged 30 - 60 [16].

The case fatality rate (CFR) is the representation of the proportion of cases that eventually die from a disease and can be estimated once the epidemic/pandemic is over, with the formula: deaths/cases. In case of COVID-19, the epidemic is still ongoing and to arrive at real CFR value at this point of time can be misleading [17]. However to arrive at crude case fatality rate during the course of epidemic Ghani., *et al.* [18] formula can be used:

CFR = Deaths at day X/Cases at day X- (T)

(where T is the average time period from case confirmation to death).

Using a conservative estimate of T = 7 days as the average period from case confirmation to death, the estimated value of CFR as on 31st of march 2020 will be:

CFR = Deaths at day 31st of March/Cases at day 25th of March

CFR = 42,309/ 471,035 = 0.089 or 8.9%.

The case fatality arrived at will be higher than the true value However, it is likely that the true number of cases will be substantially greater than reported as it excludes the unreported asymptomatic infections. Therefore, to arrive at accurate CFR large scale serological surveys is needed.

Symptoms

Respiratory and gastrointestinal systems get largely affected in this disease. The symptoms of nCoV-2019 during its various stages of illness have been reported to be fever, cough, myalgia, fatigue, shortness of breath, muscle ache, headache, sore throat, confusion, chest pain, sputum production diarrhea, nausea and vomiting [19-24]. Among these the most common symptoms at the onset of disease were fever and dry cough [19,20]. The other symptoms less commonly reported by several papers are myalgia, fatigue, shortness of breath, muscle ache, headache, sore throat, confusion, chest pain, sputum production, diarrhea, nausea and vomiting [19,21-24].

Most of the infected cases had underlying chronic comorbidities like hypertension, diabetes, cardiovascular disease, renal diseases [19,23,25]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the drugs of choice for pulmonary hypertension, diabetic hypertension, cardiovascular disease and chronic kidney diseases. Such drugs are known to elevate the number of ACE2 receptors in experimental models. The corona virus is believed to bind with these receptor in lungs located on cell membrane. This will provide more binding sites to virus and hence it is hypothesized nCoV-2019 patients with such comorbid conditions have increased risk of severe disease outcomes [26].

Imaging studies (chest CT) conducted at various stages of disease showed bilateral pneumonia and consolidative pulmonary opacities in majority of cases, ground-glass opacity in few cases and pneumothorax in very few cases. The follow up imaging studies showed increased lung opacity which indicates mild or moderate progress of disease. Some patients developed ARDS in which few developed sepsis and died in a short period of time due to multiple organ failure [21,22,24,27-29].

Viral entry and replication

The exact mechanism of nCoV-19 pathogenesis is still unidentified, however it is suggested the nCoV-19 binds on the same membrane receptor to which SARS-CoV-1 and MERS-CoV do. This is possibly due to certain genetic resemblance of nCoV-19 with the duo [30,31].

Kuhn., *et al.* [32] has established angiotensin-converting enzyme 2 (ACE 2) located on the membranes of host cells is a functional receptor for SARS-CoV. The viral envelop spike glycoprotein (S1 domain protein) binds specifically on the plasma membrane with ACE 2 receptors. A transmembrane protease serine protease 2 (TMPRSS2) and cathepsin triggers the cleavage of S protein, which mediates the endocytosis of SARS- CoV [33].

The positive sense RNA genome of virus after entering in to the cell translates in to structural proteins and two polyproteins (pp1a and pp1ab) leading to replication of viral genome, which codes for non structural proteins thereby forming replication-transcription complex (RTC) in membrane vesicle. The RTC replicates continuously and forms a set of subgenomic RNAs. The enveloped glycoproteins are directed towards endoplasmic reticulum or golgi apparatus, where genomic RNA and nucleocapsid protein forms nucleocapsid. The vesicles containing the virus particles detach from golgi, fuse with plasma membrane and throw the virus by exocytosis [30,34,35].

Epidemiology

On 31 December 2019 the Health Commission of Hubei province (China) reported chain of cases presented with pneumonia of unknown etiology. The province reported 27 cases in the first encounter which rose to 41 with one death as on 11 January 2020 [36]. The occupation of some of the active cases was venders selling animals (recently slaughtered or live) in the seafood market of Huanan. This was followed by the reports of cases in family clusters and transmission to health care workforce. Chan., *et al.* [36] established human to human and nosocomial transmission of this disease in family clusters, hospitals and geographical regions by the travelers. In The lower respiratory tract samples, virus isolated was subsequently sequenced and named as novel corona virus (2019-nCoV) [37]. The disease swiftly spread to most parts of the worlds with higher number of cases in USA, Italy, Spain, China, Germany, France, Iran, UK, Switzerland, and Turkey numbering 189445, 105792, 95923, 81554, 71808, 51487, 44606, 25150, 16597, and 13531 respectively as of 31st of March 2020 (Figure 1c). The total corona cases as of now is 859,929 out of which 178,364 (20%) cases recovered/discharged, 42,344 (5%) are the total deaths and 639,222 (75%) are active cases, in which 606,152 (71%) mild condition and 33,070 (4%) with serious condition (Table 3) (Figure 1a and 1b) (Worldometer figures).

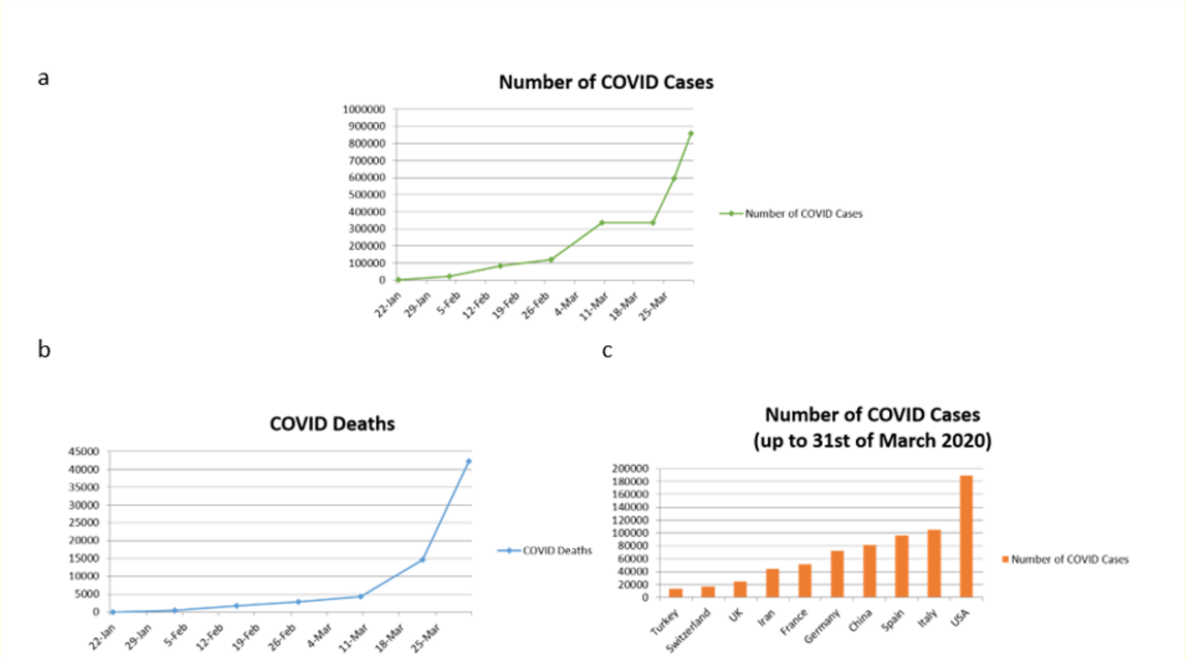

Figure 1: *a) Graph showing COVID-19 Case Matrix (Total number of cases reported as of 31st of March 2020). b) Graph showing COVID-19 Case Matrix (Total number of deaths reported as of 31st of March 2020). c) Graph showing total number of cases of COVID-19 among top 10 effected countries as of 31st of March 2020).*

Total Coronavirus Cases	Recovered/Discharged Cases	Total Number of Deaths	Active Cases	
			Mild Condition	Serious Condition
859,929	178,364 (20%)	42,344 (5%)	606,152 (71%)	33,070 (4%)

Table 3: *Table showing case matrix as of 31st March 2020.*

Testing for 2019-nCoV

The COVID-19 outbreak has generated panic, brought economies at halt, overwhelmed healthcare throughout the world. There is no certainty among the number of infected cases and number of cases screened for testing. Some countries like Spain adapted for mass testing and some have minimal testing resources. The countries ought to adapt similar type of approach by ensuring strict surveillance and testing measures, which is further subjected to their economic condition.

Sample collection: Preferably nasopharyngeal/oropharyngeal swabs are collected adopting strict preventive measures; sensitivity is more with nasopharyngeal swabs. Additional samples including the lower respiratory tract secretions like bronchoalveolar fluid, sputum can be taken from patients with pneumonia [38]. Like MERS and CoV-SARS, the nCoV-2019 has also been detected in blood and urine; so additional samples in this form may also be collected [38,39].

Nucleic acid amplification tests (NAAT)

This test is being conducted for detecting the nCoV-2019 unique RNA sequence. The extraction of viral RNA requires biosafety cabinet (BSL-2). The viral RNA extracted from the samples is amplified by real time reverse transcription-polymerase chain reaction [40]. E (envelope), N (nucleocapsid), S (spike) and RdRP (RNA dependent RNA polymerase) structural protein genes are the targeted viral nCoV-2019 genes [41]. The further confirmation can be obtained by nucleic acid sequencing if and when required.

Antigenic/serological rapid testing

The serological tests requiring serum are based on the detection of viral proteins or antibodies generated against the virus. Western blot and ELISA would be the potential tests of this area that can be employed for cost cutting and performing point of care testing based on antigen kits of nCoV-2019. Tian., *et al.* [42] recently identified nCoV-2019 RBD can be recognized by monoclonal antibody CR3022. Serological type of antibody tests do not always detect early viral infection and are less reliable than PCR; however they may detect antibodies even in asymptomatic carriers. Theoretically detection of positive cases may be much appropriate by combination of tests i.e. NAAT and serology [43].

Management

Place of care

Home treatment: Home treatment can be appropriate under certain circumstances keeping in view the burden of pandemic on existing health care system. Patients with mild symptoms if adequately isolated can be offered home care only. These patients can be monitored for any clinical deterioration that may need urgent hospitalization with a focus on prevention of local transmission. In case of comorbidities (Cardiovascular disease, Diabetes mellitus, Hypertension, Chronic lung disease, Cancer, and Chronic kidney disease) a risk-based approach is needed as only mild symptoms in this group of patients may prompt hospitalization [7,15].

Home management is supportive with adequate hydration, antipyretics and analgesics if needed. These patients should stay separately from other family members in the household and wear a facemask when in same room as other family members. It's important to disinfect frequently touched surfaces at home.

There is limited data on the duration of isolation in patients managed at home. As per World Health Organization (WHO), home isolation in a documented COVID-19 should continue for two weeks after resolution of symptoms [44]. However, the United States Center for Disease Control and Prevention (CDC) recommends test-based and non-test-based strategies. In the former, home isolation can be discontinued when there is resolution of fever without any need for antipyretics, improvement in respiratory symptoms along with two negative nasopharyngeal swabs collected over 24 hours or more apart. The later strategy warrants discontinuation of home isolation if seven days elapse since first appearance of symptoms and at least 3 days pass after resolution of fever and improvement in respiratory symptoms. In some cases of laboratory confirmed COVID 19 but without any symptom when tested, isolation may be discontinued when at least seven days has elapsed since the first positive test (CDC accessed on March 25, 2020).

Hospital care

Severe COVID 19 illness needs hospitalization with emphasis on isolation and supportive care. Such patients often need oxygen support as high flow nasal oxygen or noninvasive positive pressure ventilation with many safety concerns as they are potential aerosol generating procedures. Development of acute respiratory distress syndrome (ARDS) warrants invasive ventilation. Extracorporeal membrane oxygenation (ECMO) is recommended by WHO in patients with severe ARDS refractory to maximal medical management but is technically a demanding procedure that can be initiated in specialized centers only [45].

Anti-inflammatory agents-glucocorticoids and NSAIDs

Despite no strong evidence of benefit, glucocorticoids were widely used in patients with SARS. However, in patients of COVID 19 pneumonia WHO and CDC recommends against use of glucocorticoids unless otherwise indicated like exacerbation of chronic obstructive pulmonary disease [46]. Many anecdotal reports of patients receiving NSAIDS during disease course and later developing exacerbation and severe symptoms of disease lead to many clinicians advising against use of NSAIDS particularly Ibuprofen early in the course of disease notwithstanding the fact that there is no clinical or population-based data supporting this observation [47]. Nevertheless, European Medicines Agency (EMA) and WHO do not recommend against use of NSAIDs when clinically indicated [48].

Novel approaches

A lot of antiviral agents and antibiotics are undergoing international clinical trials based on anecdotal reports and case series describing potential efficacy against COVID 19. However, at the time of writing this manuscript there are no controlled data supporting their use.

Chloroquine/hydroxychloroquine

After *in vitro* studies showed chloroquine block the COVID 19 infection, a number of clinical trials conducted quickly in China (data not published) on both chloroquine and hydroxychloroquine demonstrated significant effect in terms of clinical outcome and viral clearance compared with controls [49]. In a breakthrough publication, Chinese experts recommended chloroquine treatment for COVID 19 cases without contraindication to chloroquine [50]. Hydroxychloroquine (HCQ) has better clinical safety profile and early results of an ongoing open label study in France showed efficient viral clearance by HCQ and a synergist effect with azithromycin [51]. However, the study had a small sample size with limited long-term outcome follow up without any scientific basis for using azithromycin. In a pilot study conducted over 30 COVID 19 patients at Shanghai, the proportion of patients with nasopharyngeal viral clearance at day 7 was not different with hydroxychloroquine (400 mg daily for five days) compared with standard of care [52], thus clinical data evaluating chloroquine and HCQ is sparse. Nevertheless, emergency authorization was issued by US FDA for their use in adults and adolescents hospitalized for COVID 19 who are not eligible to enter a clinical trial. Possible drug toxicity includes QTc prolongation and retinal toxicity. Many dosing regimens are being used but optimal dose is uncertain; FDA suggests HCQ 800 mg Day1 followed by 400 mg daily and chloroquine 1 g day 1 followed by 500 mg daily each for 4 to 7 days. Others use HCQ 400 mg twice daily day 1 followed by daily for 5 days, 400 mg twice daily on day 1 then 200 mg twice daily for four days, and 600 mg twice daily on day 1 then 400 mg daily for four days. Recently HCQ was recommended as prophylaxis in health care workers treating COVID 19 patients in India [53].

Remdesivir

Both *in vitro* and animal studies have demonstrated Remdesivir, a nucleotide analogue to be effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and related coronaviruses (including SARS and MERS-CoV) [45,49]. The compassionate use of remdesivir was described in a case report of one of the first COVID 19 case in US [55]. Presently it is being evaluated in several randomized trials for moderate to severe COVID 19. Remdesivir is an intravenous agent and side effects include nausea, vomiting, and transaminase elevations.

IL-6 pathway inhibitors

Monoclonal IgG1 humanized antibody against IL-6 receptor, commonly used for the treatment of rheumatoid arthritis are being widely investigated in a number of clinical trials involving COVID 19 patients. This comes after demonstration of cytokine storm as one of the pathogenic mechanisms of COVID 19 ending up in multi organ failure syndrome (MODS) with high mortality [56]. Treatment guidelines from National Health Commission of China includes IL-6 receptor blocker tocilizumab for severe COVID 19 patients with elevated IL-6.

Lopinavir-ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, having *in vitro* inhibitory activity against SARS-CoV, the causative agent of SARS in humans and by combining it with ritonavir plasma half-life is increased due to inhibition of cytochrome P45. An open label study in 2004 suggested a reduction in the risk of adverse clinical outcomes and viral load among SARS patients receiving lopinavir-ritonavir (400 mg and 100 mg, respectively) as compared to ribavirin alone [57]. Both *in vitro* and animal models have shown lopinavir activity against Middle East respiratory syndrome coronavirus (MERS-CoV) [58]. In a randomized, controlled, open-label trial (LOTUS China) involving 199 COVID 19 patients there was no difference in the clinical outcome or mortality in seriously ill patients as compared to standard care alone [59]. However, there was significant albeit modest between group differences in the median time to clinical improvement during modified intention-to treat analysis.

Favipiravir

Favipiravir, an RNA polymerase inhibitor active against influenza is being studied in COVID 19 patients. There was a faster viral clearance rates and more rapid radiographic improvement in non-severe disease in comparison to lopinavir-ritonavir [60]. Nevertheless, the results should be taken with a pinch of salt in view of non-randomization and open label nature of study.

Convalescent plasma

Seminal study by Shen., *et al.* involving 5 critically ill patients of COVID 19 with convalescent plasma raised the possibility that this modality may be helpful in severe COVID 19 and ARDS, but requires randomized clinical trials [61]. Notwithstanding the fact and in absence of existent cure, US FDA is granting clinicians permission for use of investigational convalescent plasma under single-patient emergency Investigational New Drug Applications (INDs).

Conclusion

COVID-19 is purely a challenge for research community. World is formulating counter measures to prevent and limit the spreads of this disease. The scientist are putting utmost efforts to understand the disease and conducting randomized controlled trials on drugs which has shown some positive results in small case series and case reports. The pivotal role of researchers is to develop a vaccine that could serve as a promising long term solution.

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