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COVID-19: THE PANDEMIC OUTBREAK OF 2019-20

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ABSTRACT

In the last Fifty years, several distinct coronaviruses have emerged which causes a diverse variety of human and veterinary ailments. Apparently in 2019 during the month of December in Wuhan, china a new strand of coronavirus which was formerly named as "2019-novel coronavirus (2019-nCoV)" and now is addressed as SARS-CoV2 (Severe acute respiratory syndrome coronavirus -2). The disease caused by SARS-CoV2 called Covid-19; it is a new public disaster, transmitted from one human to another through various body fluids predominantly through contaminated droplets. Covid-19 is forbearing in most people; it can advance to pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction in some (usually the elders and those with comorbidities). COVID-19 was called a pandemic by the World Health Organization (WHO) on March 11, 2020. One concern would be how capable the health care systems of the world are to respond to an epidemic of this magnitude. In different regions, rapid identification, and control of the virus at the entry points is crucial throughout in order to prevent widespread population transmission. Based on current published evidence, a summary of various curbing measures with prevention and tenacity of SARS-Cov2 is provided in this review article. Through this review we also provide information about the clinical trials for vaccines and treatment filed by different pharma companies which is one of the most awaited and dominant research in current scenarios around the globe.

INTRODUCTION

Corona viruses are of order Nidovirales, family Coronaviridae and subfamily Coronavirinae, in accordance with the International Committee's classification for Virus Taxonomy (ICTV). Viruses have Ribonucleic Acid genome (RNA) which is single stranded ranging approximately twenty-six to thirty-two kilobases (kb) in dimensions and therefore has the largest RNA genomes.[(1)] The SARS-CoV 2 has an encapsulated virion including a single positive-sense RNA measuring approximately 50–200 nm in diameter. The club-shaped spikes of glycoprotein in the membrane end up giving the virus a chaplet-like feature. Dissemination rates for SARS-CoV 2 are unidentified; yet there is proof of transmission through human-to-human contact.[(2)]Spike protein of Indian SARS-CoV 2 genome displayed 2 dissimilarities when compared with the genome of the pneumonia virus from seafood of Wuhan (Wuhan Hu-1). Further a stretch of three nucleotides containing tyrosine amino acid at 144 position was observed to be terminated in the spike gene of Indian SARS-CoV 2 spike from case 1 in comparison with

the spike gene of other SARS-CoV 2.[3] Such viruses are expected to continue to evolve and develop due to their propensity to mutate, recombine, and infect numerous organisms. Coronaviruses lead to several diseases in birds and mammals varying from redness inflammation necrotizing enteritis in cattle and swine to potentially fatal human respiratory infection.[4] Coronaviruses (CoV), a huge strain of viruses which causes a huge range of diseases spanning from flu to more serious conditions, namely Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Covid-19 is a disease which was never discovered previously in human beings.[5]Multiple cases of unidentified pathogenesis pneumonia were recognized in Wuhan town, China throughout December in the year of 2019. The city of Wuhan is a major infrastructure centre with a community of nearly 11 million.[6]SARS-CoV 2 seems to have a contrasting sequence of coronavirus-specific nucleic acids from all of known human coronavirus strains, quite indistinguishable to certain coronaviruses discovered in bat species.[7]Real-time reverse-transcription PCR assays (quantitative) were employed to detect two distinct regions of the viral genome (ORF1b and N).The primers and set of probes were developed to respond to a novel coronavirus and to similar viruses, such as coronavirus SARS-CoV. Both RT-PCR assays were utilized to examine the respiratory samples of two alleged patients. Preliminary findings from RNA samples which were serially diluted, indicated that N gene assay was effective to about 10 times in detection of positive specimens than the ORF-1b gene assay.For the screening test of Covid-19, RT-PCR precisely N-gene is recommended which is based on their diagnostic results, and indeed the Orf1b assay is prescribed as a confirmatory test.[8] Researchers exploring how coronaviruses such as COVID-19 invade living cells has shown that SARS-CoV 2 spike (S) glycoprotein attaches to ACE2 (angiotensin-converting enzyme 2) of the plasma membrane protein to reach cells. SARS-CoV 2 was shown to adhere to ACE2 through the S protein over its membrane. The S-protein is splintered as subunits, S1 and S2, after infection. S1 comprises the receptor binding domain (RBD) that allows coronaviruses to link explicitly with the ACE2 peptidase domain (PD). S2 then potentially plays a part in the fusion of membranes.[9] Thus, leading to distinct symptoms such as In severe disease: Compliance with any of the following criteria: Laboured breathing, Pulmonary rate above 30 bpm, Hypoxia, Bronchial infiltration of the lungs developed greater than 50 percent in the span of 24-48 hours. In critical stages: Either of the following conditions: Lung failure, Widespread infection, Certain organ incompetence involving intensive care unit (ICU) admittance.[10]

MITIGATION OF COVID-19

Clinical care of doubtful cases of SARS-CoV 2 should focus on quick identification of the disease condition, isolation and acquisition of adequate infection management measures, and the provision of optimized supporting care for doubtful/confirmed cases. The WHO guideline "Clinical management of severe acute respiratory infection when SARS-CoV 2 infection is suspected" for precautionary measures focuses largely on not indulging in a closer contact with persons suffering with acute respiratory infections, routine washing of hands and preventing unnecessary contact with the animals, Often disinfect the surrounding and surfaces. In patients with respiratory distress, the patient must be assessed for the existence of shock. Empirical antimicrobial coverage (to cover up probable causative organisms that may be accountable for severe acute respiratory infection) should be given. Special attention should be given to identifying and managing septic shock.[11]

TENACITY OF SARS-CoV 2 ON VARIOUS OBJECTS

On plastic and stainless-steel SARS-CoV 2 was much more robust than on carton and copper. Hardly any viable SARS-CoV 2 determined on copper after 4 hours and no viable SARS-CoV 2 determined on carton after twenty-four hours. SARS-CoV 2 half-lives is equal to 1.1 hours in aerosols. All viruses had maximum survival on stainless steel and plastic; SARS-CoV 2's approximate mean half-life were around 6.8 hours on plastic surface and on stainless steel for about

5.6 hours.[12]Lifespan of SARS-CoV 2 on a given surface depends on innumerable factors including surrounding temperature, humidity, and surface type. It was found in the study that after 3-hour incubation no infectious virus could be recovered from the printing and tissue papers, whereas on day 2 no virus could be detected from the wood and cloth. Conversely, SARS-CoV 2 on smooth surfaces was more stable. On day 4 no virus could be noticed on smooth surfaces like glass and banknote, similarly virus could not be perceived on day 7 from stainless steel and plastic. Considerably, a noticeable level of virus on the outermost layer of a surgical mask could still be present on day 7 was found to be more stable for 4 hours and 24 hours respectively, on copper and cardboard. SARS-CoV 2 is more stable at 40°C but heat sensitive. At 40° C, the infectious titre reduction after 14 days was around 0.7 log-units. When the temperature of incubation was increased to 70° C, virus inactivation time was reduced to 5 minutes.[13]

CURBING MEASURES AND PIPELINES FOR THERAPEUTICS

Non-pharmacological strategies namely fluid, oxygen and ventilating support are efficacious. Extra Corporeal Membrane Oxygenation (ECMO) is potentially beneficial. [14] Purported medications include an inhibitor of spike protein griffithsin, analogues of nucleoside such as remdesivir, ribavirin also certain proteolytic agents namely ritonavir. Chloroquine, Interferon, and immunoglobulins are immunomodulatory and several other host-targeting factors.[15]Other options of the treatment utilized either infrequently or in experimental condition, are SiRNA, factor-alpha tumour necrosis inhibitors, antibodies neutralizing, pentoxifylline. However, the level of effectiveness is not appropriate and thus not suggested for routine care.[11]

Antivirals Agents and Chloroquine

Antiviral activity is exhibited by a nucleoside analogue Ribavirin, against some coronaviruses, in the SARS-CoV epidemic, several patients were treated with ribavirin alongside corticosteroids and became a standard treatment regimen for SARS-CoV. Lack of control group impeded the assessment of true effect size. An increase in viral load after the treatment was shown by numerous patients on the combination of ribavirin and corticosteroid. Hence its use diminished over a certain time period.[16]HIV management is done by ritonavir boosting along with lopinavir.[17] For treating SARS-CoV 2, lopinavir + ritonavir is the suggested protease inhibitor as per the current guidelines.[18]Prescribed doses of Ritonavir/Lopinavir for SARS-CoV 2 are 50 mg/200 mg two tablets for fourteen days and are to be administered in every twelve hours or if found to be symptomless the doses should be considered for seven days and 100 mg ritonavir/400 mg lopinavir to be administered through nasogastric tube in the form of suspension to the unconscious patients or the patients who cannot take tablets through oral route tablets for fourteen days and are to be administered in every twelve hours.[19]SARS-CoV 2 contains two types of proteases, which includes CL-like and the papain like proteases, it is essential for cleaving the polyproteins and thus resulting in the release of the non-structural proteins (NSP1-16), which perform prominent functions in the life cycle of CoVs. Lopinavir was the strongest inhibitor and saquinavir was weakest inhibitor of CoV protease amidst the protease inhibitors.[20]

Immunoglobulins

No mutations were observed in the SARS-CoV-2 epitopes, and so immune modulation of these would provide protection against COVID-19.[21]Further immunomodulation escalation is advisable on the occurrence of critically ill SARS, displaying the signals of degeneration and attention may be given to intravenous (i.v) immunoglobulin.[22]I.V immunoglobulin may be beneficial for the patients with deficient response to initial empirical therapy.[23]

Interferon

Interferons (IFNs), used predominantly to treat hepatitis B, are broad-spectrum antivirals. In SARS-CoV-2 patients,

the usefulness was noticed on the IFN-α + high dose corticosteroid group in contrast with ribavirin or interferon (IFN) alone.[24]These results are also favoured by several experimental studies, and little disease-associated oxygen saturation impairment was exhibited by the collaborated use of IFN-α and corticosteroid (corticosteroid arm n=13; corticosteroid + IFN-α arm n=9). IFN-α is suggested along with lopinavir + ritonavir combination to treat SARS-CoV-2.[18]

Host-directed therapies

Compounds with their ability to bind to the coronavirus's Spike (S) protein, makes it ineffective to the host cells.[18]Host-directed therapies are essentially aimed at improving the status of the host, improving the immune response of the host, or managing host-related factors linked with viral replication.[25] Metformin, atorvastatin, fibrates, and nutritional supplements may help to treat acute respiratory distress syndrome (ARDS) by boosting immunity, apart from the immunomodulators. Although, evidence of usefulness is disclosed in SARS-CoV or MERS-CoV.[26]

Antibodies

Both the SARS-CoV and SARS-CoV 2, through ACE-2 receptor-mediated entry, enter the host cell particularly through AT2 (Alveolar Type 2) cells present in the lungs. This receptor's downstream signaling mediates the process of endocytosis, and AP2 (Activating Protein 2)-associated protein kinase 1 (AAK1) plays a vital role in the process. Thus, AAK1 is an essential goal. Considering the profile of the adverse events, it was established that the most important agent was Janus kinase inhibitor baricitinib. Besides AAK1, baricitinib also links to another endocytosis regulator protein (cyclin G-associated kinase).

Accordingly, it was recommended by the authors that baricitinib may be assessed in both the in vitro conditions and the SARS-CoV-2 clinical trial settings.[27]It is recommended to produce filtered and extremely refined preparations that accommodate a higher titre of neutralizing antibodies to counter SARS2-CoV-2 as they are safer and have greater activity than convalescent sera. To produce serum or for the isolation of antibody, people who recover from COVID-19 may be approached for the donation of blood through apheresis. Given the current blood banking practices, a screening protocol will be employed on the donated blood products for the assessment of pathological agents and each serum will be evaluated for content of antibody and activity of neutralization for SARS-CoV2.[28]

BCG Vaccine

Three preprints were yielded by the review (manuscripts posted online prior to the peer review), the occurrences of COVID-19 cases in countries using the BCG vaccine with countries which are not using the vaccine was compared by the authors, and noticed that, till date less cases of COVID-19 were reported in the countries that regularly utilized the vaccine in neonates. Such ecological studies are susceptible to notable favouritism from numerous confounders, including variations in the burden of national demographics and disease, testing rates for infections with COVID-19 viruses, and pandemic stage in each country.

Critical types of tuberculosis in children are impeded by the BCG vaccination and the divergence of local supplies may result in unvaccinated neonates which causes the enhance disease and tuberculosis deaths. BCG vaccination for preventing COVID-19 is not proposed by WHO, in case of the lack of evidence. Neonatal BCG vaccination in countries or settings that have higher tuberculosis occurrences is continuously suggested by WHO. There is still no proven appropriate medication as regards therapeutics. China alone has registered more than 200 clinical trials for assessment of potential SARS-CoV 2 vaccine.[29]Clinical trials filed by various pharmaceutical companies and research centres stating their type in order to combat Covid-19 are enlisted in Table 1.

Table 1: Clinical Trials Registered by Different Research Organisations

Organization	Type	Target	References
Gilead	Treatment	Remdesivir	(30)
Sanofi	Treatment + Vaccine	Plaquenil©	(31)
Pfizer &Biontech	Treatment + Vaccine	New Mrna vaccine	(32)
Johnson & Johnson	Vaccine	Covid-19 vaccine	(33)
Abbvie	Treatment	Lopinavir/ritonavir combination	(34)
Vaccitech	Vaccine	Lopinavir/ritonavir combination	(35)
Regeneron	Treatment	Monoclonal antibody therapy	(36)
Takeda	Treatment	Polyclonal antibody therapy	(37)
Hoth Therapeutics	Vaccine	Self-assembling vaccine (SAV)	(38)
Calcimedia Inc.	Treatment	Covid-19 Pneumonia	(39)
Amgen Inc.	Treatment	Antibody drug	(39)
CytoDyn Inc.	Treatment	Leronilab	(39)
Dynavax Technologies Corp	Adjuvant Technologies Corp.	Covid-19 vaccine	(39)
Heat Biologics Inc.	Vaccine	Covid-19 vaccine	(39)
Novavax	Vaccine	Covid-19 vaccine	(39)
Roche Holding AG	Treatment	Actemra	(39)
Vaxart	Vaccine	Covid-19 vaccine	(39)
Vir Biotechnology Inc.	Treatment	Monoclonal antibody therapy	(39)
Murdoch childrens research institute & royal children's hospital	Vaccine	BCG Vaccine	(40)

CONCLUSION

The outbreak of the novel Corona virus has led the world's population in quandary and subsequently created a massive demand for the development of therapeutic agent being target specific to COVID-19. There is a tremendous scope for research and development pertaining to the novel virus detected in December 2019.

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