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Review Article

Corona Virus Infection (Novel CoVid 19) - Update on specific and supportive medications

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Abstract

Coronavirus belongs to the family of Coronaviridae and is structurally enveloped with positive sense single strand. The virus undergoes replication by transcription of a minus strand template by RNA dependent RNA polymerase. The search is ongoing for the specific targeted treatment of corona virus infection. Among the available drugs to treat viral infections, there are few with promise to treat or reduce viral load. Never the less prevention is the best method to tackle the viral infection. The drugs used in the treatment of CoVid 19 according to the evidence available from the past with management of Severe Acute Respiratory Syndrome Corona Virus (SARS Covid 2) and Middle East Respiratory Syndrome Corona Virus (MERS Covid). The options available for treatment of Covid 19 are antiviral drugs and supportive interventions. The currently available drugs used in viral infections are explored for their additional benefit in treating CoVid 19 along with the immune boosters which include vitamins, essential minerals and biological response modifiers.

Keywords: Covid 19, potential drugs, Severe Acute Respiratory Syndrome, Middle Eastern Respiratory Syndrome, Immune boosters

Introduction

World health organization (WHO) identified and coined the name 2019- novel coronavirus (2019-nCov) in the beginning of January 2020 to a cluster of pneumonia cases caused by a novel virus which first occurred in Wuhan city in China later renamed it as coronavirus disease (COVID-19).[1] By July 2020, COVID-19 became pandemic including 215 countries/ territories with 1,36,99,622 cases infected including 5,86,977 deaths worldwide.[2] The viral genome analysis has revealed that the novel corona virus is close to severe acute respiratory syndrome corona-virus (SARS-CoV) in evolutionary development and diversification.[1] Coronavirus belongs to the family of Coronaviridae and structurally enveloped with positive sense single strand. The virus undergoes replication by transcription of a minus strand template by RNA dependent RNA polymerase.[3] The crucial and essential structures for completion of replication cycle in virus are spike, envelope, membrane and nucleocapsid proteins which are translated from sub genomic mRNAs (sgmRNAs).[4] Human coronavirus variants such as HCoV- 229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 are known to communicate a disease to human beings, but few corona viruses from animal reservoirs can be transmitted to man to lead outbreaks in the human species.[5-11] since these pandemics occur time and again, it is important to review the therapeutics and supportive treatment aspect of the Covid 19.

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Clinical presentation

After acquiring Covid 19 infection the symptoms usually start appearing in the initial 5 to 6 days according to WHO reports.[12] The incubation in few patients with Covid can range from 5 to 40 days making the mean incubation period to 14 days.[13] The severity of infection depends on the age, comorbid conditions such as diabetes mellitus, hypertension, congestive cardiac failure and compromised immune system. The incubation period ranges from 11 to 20

days in elderly individuals(70 years).[13] The presentation of the disease could be mild and self-limiting in few patients and others it could cause fever, sore throat and shortness of breath due to severe bronchospasm. The WHO report based on the survey done in China suggests that the most common presentation is fever (88%) followed by dry cough and sore throat (68%), fatigue (38%) and diarrhea (4%).[14,15] The most common system involved with corona virus infection is respiratory system, however in few patients cardio vascular system and cerebrovascular system are involved in the form of mild to severe chest discomfort or myocardial is chaemia and headache respectively.[16] The lining cells of the throat, trachea, bronchus, bronchioles and lung, transform the cells into major site for viral replication that produce enormous amounts of viruses that further infects other cells in the body. The raised body temperature, malaise and tiredness are due to the immune system response to the virus, due to which cytokines are released in to the body. The optimum cytokine release converts into excessive inflammation in due course leading to exacerbated symptoms that the body may not come up.[17] The other major organs which get affected by the virus are kidneys and testis due to expression of ACE2 affecting renal tubular cells and testicular cells.[18] Recently the gastrointestinal manifestations such as diarrhea, vomiting, loss of appetite have been reported with increased mortality and morbidity compared to patients who are devoid of these symptoms.[19]

Treatment

The search is ongoing for the specific targeted treatment of corona virus infection. Among the available drugs to treat viral infections, there are few with promise to treat or reduce viral load. Never the less prevention is the best method to tackle the viral infection. The drugs used in the treatment of covid 19 according to the evidence available from the past with management of Severe Acute Respiratory Syndrome Corona Virus (SARS Covid 2) and Middle East Respiratory Syndrome Corona Virus (MERS Covid) can be broadly divided as specific and supportive drugs as shown in the table 1.

Table 1: Drugs available for the treatment of covid 19

Specific treatment	Supportive treatment
Antiviral drug • Lopinavir+ritonavir • Ribavirin • Remdesvir • Nelfinavir • Umifenovir (Arbidol) • Darunavir • Cobicistat • Chloroquine • Favipiravir	1. Immunomodulators • Hydroxychloroquine • Chloroquine • Interferons • Thymosin with corticosteroids • Baricitinib • Itolizumab 2. Immune boosters • Vitamins – vitamin A, C, B complex and Vitamin E • Omega 3 fatty acids • Micronutients- Iron, selenium, Zinc • Indian traditional medicines

Specific treatment

The combination of lopinavir and ritonavir in the ratio of 4:1 area known protease inhibitor which prevents viral replication by producing immature, non-virulent viral particles. Their use in the treatment of HIV infection, SARS and MERS is established and has been tried in COVID 19.[20,21,22] A study conducted in Hong Kong University has shown promising results in the improvement in clinical symptoms of Covid 19 with this combination hence recommended as per the recent guidelines.[23,24] Ribavirin is a nucleoside analog which inhibits RNA polymerase and shows activity against SARS-COV, MERS and hepatitis C virus.[25] However due to lack of stronger evidence and the adverse effects of ribavirin such as myelosuppression, haemolysis, teratogenicity, mutagenicity and central nervous system related adversities such as depression, irritability, its use is not recommended.[26,27] Remdesvir is an adenine analog used in HIV infection which in addition has shown activity against SARS COV and MERS COV. Studies have established remdesvir as one of the promising drugs for SARS COV which in turn can be tried in the treatment of COVID 19.[28,29] Nelfinavir and

darunavir are used in HIV and SARS COV infections therefore can be opted for the COVID 19 treatment.[30] Umifenovir (Arbidol-ARB) a broad spectrum antiviral drug is used in the treatment of influenza and hepatitis C. It acts by inhibiting the viral fusion with the target cell membrane thereby blocking the viral entry. It was first developed in Russia and used in the treatment of flu caused by influenza and respiratory syncytial virus.[31] Few studies conducted invitro, demonstrated its activity against SARS COV.[32,33] Nitric oxide (NO) is released by NO synthase from arginine and a vital colorless gas to maintain endothelial function. In addition to its vasodilatory property, NO reduces inflammation and maintain airways as a result there can be relief in patients with acute respiratory distress. Organic NO donor has shown to inhibit SARS CoV replication as the concentration increases. Due to these evidences it could be a potential treatment for COVID 19.[34,35] Cobicistal along with chloroquine has been tried in the treatment of COVID 19. It is developed by ritonavir for the treatment of HIV and similar to ritonavir has shown activity against COVID 19 and is under trial NCT04252274. Favipiravir has been effective in inhibiting replication of influenza, ebola, yellow fever, chikungunya, norovirus, enterovirus and SARS CoV. It acts on viral genetic copying to prevent its replication without affecting the host cellular RNA or DNA synthesis.[36-38] Clinical studies are ongoing on the use of favipiravir along with interferon and other agents. Recently Drug Controller General of India (DCGI) has approved the use of Favipiravir 1800mg on day followed by 800mg twice daily for 14 days and Remdesvir.[39] DCGI also gave approval for itolizumab for the treatment of moderate to severe covid 19 infection associated with cytokine release syndrome. The drug acts by regulating and rebooting the immune system to defend covid infection.[40]

Supportive Treatment

Immunomodulatory

Chloroquine is one of the oldest and cost effective drugs used in the treatment of malaria. It was used in the treatment of SARS CoV2, as inhibiting glycosylation of Angiotensin Converting Enzyme 2 (ACE 2) receptor makes the cell resistant to the virus. Hydroxychloroquine has similar mechanism of action as chloroquine with better gastrointestinal absorption and less side effect profile. The additional immunomodulatory property of hydroxychloroquine increases lysosomal enzyme pH in antigen presenting cell and blocks toll like receptor 9 and thereby inhibits the activation of dendritic cells and inflammation.[41] These two drugs can reduce the severity of Covid 19 infection thereby reduce the morbidity and mortality. A study conducted on more than 100 Chinese patients infected with Covid 19, suggested on starting the early treatment with chloroquine or hydroxychloroquine can reduce the severity of the symptoms, admission to intensive care unit, pneumonia and radiological improvement. Due to virus negative sero conversion the spread of the infection reduces.[42] The use of hydroxychloroquine among health care providers was recommended by multiple nations in order to prevent spread of infection. Indian Council of Medical Research (ICMR) has recommended use of hydroxychloroquine as prophylaxis for SARS CoV2 after reviewing the report from invitro testing conducted in National Institute of Virology, Pune and Pharmacovigilance Program of India. Never the less, contraindications and adverse effects such as retinopathy, bull's eye maculopathy, diametric defects in retina, cardiomyopathy, exacerbations of congestive cardiac failure and QT prolongation due to hydroxychloroquine should be kept in mind before prescribing to the health care providers and other frontline protectors like nurses, anganwadi workers and security personnel.[43]

Interferons (IFNs) specifically Alfa and Beta have reported to boost innate immunity of the host against viral infection. Invitro studies have reported that interferon α and β, but not γ could inhibit replication of SARS CoV2.[44] Animal studies conducted on monkeys demonstrated reduced viral replication and minimum lung destruction with 3 days prior treatment with interferon compared to control group.[45] Further during pilot clinical trial using synthetic recombinant IFN with or without ribavirin on humans reported reduction in the severity of infection and mortality with SARS CoV2 and MERS- CoV.[46] These evidences at various levels with interferons against Corono group of virus could make it a potential drug for the prophylaxis of COVID 19. Thymosin α-1 (Ta1) has a role in restoring immune response due to its immunomodulatory action and its ability to prolong and potentiate the thymocyte function. The thymocyte cells treated with thymosin α-1 are resistant to the glucocorticoid induced damage. It could enhance the immunity in SARS CoV2 infected patients. Corticosteroids are used in the treatment of COVID 19 patients to reduce the inflammation, in addition prior use of Ta1 could be recommended to reduce the thymocyte damage due to steroids.[47,48] Baricitinib is janus kinase inhibitor which binds to cyclin G associated kinase is effective in reducing inflammation and preventing viral replication by inhibiting viral entry. The dose required is minimal (2 mg to 4 mg once daily) as compared to other AP2-associated protein kinase 1 (AAK1) inhibitors such as sunitinib and erlotinib (used in cancer

chemotherapy). Thus could be a potential drug for the prophylaxis of COVID 19.[49, 50]

Immune boosters

Adequate vitamin A in human beings is known to protect the body against infection. The deficiency in vitamin A is associated with diarrhea and severe forms of measles in children.[51] A study has reported that in birds feed with vitamin A rich diet had less infection with infectious bronchitis compared to the group with Vitamin A deficient group.[52] The mortality and morbidity are less in infections such as Human Immunodeficiency Virus infection, diarrhea, measles and its associate pneumonia. Vitamin A acts by inhibiting viral replication through the activation of immune cells and making the cells resistant to the infection. As it improves immune system, vitamin A could be a supportive option for reducing morbidity due to CoVid19.[53]

Vitamin B complex especially the B2 and B3 are linked with reduction of infection with staphylococcus aureus through myeloid specific transcription factor and inhibit neutrophil infiltration into the lungs. Thus it reduces inflammation in the lungs associated with ventilator induced injury. Vitamin B6 is connected with required protein metabolism and many other reactions in the body to maintain immunity. Thus as prophylactic measure vitamin B complex could be started in CoVid 19 patients.[54,55] Vitamin C or ascorbic acid is well known for its antioxidant property which also supports immune system functions and offers protection against many infections. Intake of vitamin C is reported to reduce flu like symptoms like stuffy nose, inflammation in the nose and sinuses due to its additional action against histamine receptors. Since it can effectively prevent and control lower respiratory tract infection, we can start vitamin C in CoVid 19 patients for better outcome.[56] Vitamin D is synthesized in our body in presence of sunlight which is considered as an hormone to maintain calcium balance in the body. Vitamin D is essential for the absorption of calcium never the less it does help in the maturation of immune cells. People with less exposure to sunlight such as long working hours indoor, elderly individuals with movement limitation and prolonged winter season have been reported with vitamin D deficiency.[57] The first case of CoVid 19 started in winter in Wuhan (China) and affected in temperate countries like united kingdom, Europe (Italy, Spain), United States of America and many others. The morbidity and mortality was high in these countries compared to the tropical countries such as India, Iran, Turkey, Saudi Arabia, Pakistan and Qatar. The virus could have been more virulent in people with vitamin D deficiency. A study has reported infection with Covin coronavirus in calves with vitamin D deficiency.[58] Vitamin D supplementation could be supportive treatment for CoVid 19. Vitamin E is another lipid soluble vitamin essential for our body. It exists in eight varients (alpha, beta, gamma, delta tocopherol and alpha, beta, gamma, delta tocotrienol) among which only alpha tocopherol has distinct function in human beings. It is a potent antioxidant and plays a pivotal role in reducing oxidative stress. Vitamin E deficiency is associated with increased virulence in certain virus in human beings and animals.[58, 59]

Omega 3 and Omega 6 derived metabolites have immunomodulatory action by competing with the enzymes such as cyclooxygenase, lipoxygenase and cytochrome P450 in production of inflammatory mediators like prostaglandins, leukotrienes, maresins, protectins and resolvins.[60] They promote the anti-inflammatory mediators and reduce pro inflammatory cytokines. The protectin D1 derived from omega 3 fatty acid may inhibit the growth and multiplication of influenza virus probably is beneficial in CoVid 19 treatment.[61]

All the micronutrients with special emphasis on selenium, zinc and iron has an important role in the body's defense mechanism against infection or inflammation. Deficiency of selenium is associated with oxidative stress which could be an aggravator for a simple self-limiting virus infection. Oxidative stress could create an environment for the rapid replication of virus thereby making the virus highly virulent. A study has reported selenium could increase the immune response in the chickens infected with coronavirus causing infectious bronchitis.[62] Zinc is dietary trace element which plays a vital role in development of immune cells thereby boosting the immunity. Zinc supplementation in children has reported to reduce the severity of measles manifestations. Another evidence reported that zinc along with pyrithione could inhibit replication of RNA virus and SARS CoV.[63] Iron is required for the general wellbeing of the human beings. Deficiency of the same could lead to recurrent acute respiratory tract infection.[64]

The traditional medicine is usually mixture of herbs taken either in the form of decoction or powders mixed in appropriate media. Rasayana is one such mixture which has antioxidant property in order to reduce stress, inflammation, microbial growth and multiplication. Decoction of herbs likeT. cordifolia, Z. officinale, C. longa, Ocimum sanctum, Glycyrrhiza glabra, Adhatoda vasica, Andrographis paniculata, Swertia chirata, Moringa oleifera, Triphala and Trikatu could be beneficial to asymptomatic patients with CoVid 19.[65]

Conclusion

Previous experience with SARS and MERS, the potential drugs that could target CoVid 19 are available. Along with the specific drugs, the supportive intervention to be considered to boost the immunity of the affected person as well as the general population to reduce the morbidity.

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