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Review Article

Pharmaceutics for effective drug dosage

Impact of Azithromycin and 8-Hydroxychloroquine in 2019 Novel Coronavirus (COVID-19) Pandemic: A Systematic Review

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Abstract: As we know novel coronavirus is an emergent nuisance in this stipulated period. Corona virus is a group of enveloped viruses, with non-segmented, single stranded & positive sense RNA genomes. Human Corona virus is mainly subdivided into four categories such as 229E, NL63, OC43, HKU1. Epidemiologically it has a greater prevalence in the modern era. The features encountered in the clinical course of the disease are multifarious spanning from cough, sneezing, fever, breathlessness. It may take 2-14 days for a person to notice symptoms after infection. Azithromycin and 8 Hydroxychloroquine both plays an instrumental role for management of COVID-19. Azithromycin is a macrolide antibiotic and it binds with a 50s ribosome then inhibits bacterial protein synthesis. On the other hand 8-Hydroxychloroquine was approved by United State in the year of 1955 .Basically it is used as a antimalarial drugs . Briefly, in inflammatory conditions it binds with toll like receptor & blocks them. 8- hydroxychloroquine increases lysosomal pH in antigen presenting cells . In inflammatory conditions it blocks toll like receptors on plasmacytoid dendritic cells. In our review we focused on the role of Azithromycin, and 8-hydroxychloroquine in Covid-19 .

Key Words: Coronavirus, COVID-19, HKU1, Azithromycin, Hydroxychloroquine, RNA genomes

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1. INTRODUCTION

As we know, COVID-19 is an emergent problem in this present scenario. Coronavirus has been associated with a plethora of species of animals including humans. The molecular mechanism of replication as well as the pathogenesis of several corona viruses has been actively studied since the year of 1970. The term corona virus was discovered in the year of 1968, "corona" - like or crown like morphology were observed for these viruses under the electron microscope.[1]In the year of 1975, coronavirus family was addressed through International Committee on the Taxonomy of Viruses. Since December 2019 an occurrence of unidentified pneumonia was reported in Wuhan, Hubei province in People's Republic of China A(PRC).[2] Repeatedly symptoms were similar to the symptoms of viral pneumonia.[3] On respiratory sample analysis and Polymerase Chain Reaction (PCR) at Centers for Disease Control (CDC) it was declared that the pneumonia later came to be known as Novel Corona virus Pneumonia (NCP).[4] The virus belonged to the β corona virus which is a large group of viruses prevalent in nature. On the other hand, SARS-Cov-2 has a plethora of potential natural hosts, intermediate hosts and final host's. [5] Epidemiologically has a greater prevalence in the global perspective. In India 5,425 persons were affected from this disease and 126 were dead. In this present scenario whereas 525 has recovered with the help of Azithromycin and Hydroxychloroquine in a combined therapy. [2] In China 81, 907 people suffered from this disease & 3,336 people died. In Italy there are 1,5322 peoples are affected by COVID -19 and 52,165 are recovered now.[6] 30,224 peoples were affected, of them only 52, 165 recovered, However 1, 5447 were dead by this disease .[7] In the USA 4, 68,865 are associated with novel corona virus -19, and recovered only 25,343 .Since 16,498 died from this disease. [83] In Pakistan there are 5,230 people were associated from this disease, only 1,028 recovered and 91 died. In Bangladesh 1,020, active cases, 52 recovered and 39 death were reported.[9] The World Health Organization (WHO) R &D blueprint and its working group conveyed an informal consultation on prioritization of vaccine candidates against SARS-CoV-2 in Geneva on January 30, 2020 and identified at least five leading candidate vaccines for SARS CoV-2. As of February 13, 2020 , the WHO expert group had not released a prioritization list, nor did the US Clinical Trials registry show any registered clinical trials on vaccines against SARS-COV-2 . Among the different candidates in the pipeline , nucleic acids and viral vectors were being tried .[10] INO 4800 is one of the leading candidates developed by Inovio Pharmaceuticals and Beijing Advaccine Biotechnology based on a DNA plasmid vaccine Electroporation device . Inovio aims to begin phase I clinical trials in the US simultaneously with Beijing Vaccine in China. Clover Biopharmaceuticals is developing a recombinant subunit vaccine based on the trimeric S protein. All the vaccine studies are presently in the preclinical phase.[11]

1.1 GENETIC STRUCTURE AND PATHOGENIC MECHANISM OF SARS-COV-2: A LACUNAE REVISITED

Coronavirus (COV) is a single stranded RNA virus having a diameter of 140 nm. This virus consists of four types alpha-coronavirus, β –coronavirus δ&γ – coronavirus. 6 strains of corona virus were previously known to human society, such as SARS-COV-2 is known as the seventh member of the coronavirus family which is associated with the human beings after SARS-CoV and MERS-CoV .[12] , SARS-CoV-2 like SARS-CoV and MERS –CoV belongs to the β –coronavirus. There is a high similarity in receptor binding domain (RBD) in the spike proteins.[13] On repeated analysis it came to be known that SARS-COV-2 utilizes angiotensin converting enzyme 2 (ACE) which is located in the lining of endothelial cell in pulmonary circulation as receptor .[14]The corresponding receptor on target cell gets recognized through S protein on the surface and gets inside the cell, resulting in infecting the human body. On development of a new model it is observed that SARS-CoV-2 binds with ACE2 with above 10 folds higher affinity rather than SARS-CoV.[15] Briefly, Spike glycoprotein of SARS-CoV-2 contains two specialized regions namely S1 subunit & S2 subunit, which consists of 1400mino acids. Basically S1 domain is associated with receptor binding. On the other hand S2 domain is linked to viral and host cell membrane fusion .[16] Briefly S1 domain Consists of the N –terminal domain (NTD) & a specialized receptor binding domain (RBD), which contains a core domain & external subdomain (ESD) .[17]Whereas another specialized domain that is S2 , contains three functional domains such as fusion peptides (FP), heptads repeat (HR)1& HR2. [18] The CoVs are widespread in nature and their zoonotic transmissions into the human populations which leads to the pandemic disease. After entering into the respiratory tract this virus infects luminal macrophages and epithelial cells.[19]

1.2 TRANSMISSION OF SARS-COV-2: A BRIEF OVERVIEW

Bats are recognized as the natural hosts of SARS-COV-2 . Along with bats, pangolins & snakes are recognized as intermediate hosts. On the basis of studies done in Institutes Pasteur of Shanghai , it showed that bats are the natural hosts of SARS-CoV-2. Peking University also suggests that SARSCoV-2 infection occurs primarily by Bats. Another study at Wuhan Institute of Virology show the sequence similarity between SARS – CoV -2 and bat corona virus ORFs gene is as high as 96% by using the method of sequencing technology. Other studies observed that typical novel corona virus granules revealed that the pangolin is the potential intermediate hosts carrying the SARS –CoV-2 virus.[820] Transmission and close contact are the most common pathways for spreading of SARS-CoV-2[219] . Pregnant women are suffering from SARS-CoV-2 infection as well. From the epidemiological investigation report , above 65 years aged persons mainly suffer from this disease.[22] The features encountered in the clinical course of the disease are multifarious spanning from fever , cough , sneezing . The median incubation period was 3 days based on clinical features and median time required from the showing of the first symptom to the taking place of death was seen to be 14 days. The maximum latency period of SARS-CoV -2 infection is recently observed to be as high as 24 days which is the risk factor for viral transmission. [23]

1.3 CLINICAL MANIFESTATION

The most common clinical features of SARS-CoV-2 infection were fever (87.9%) ,cough (67.7%) , fatigue (38.1%) , diarrhea (3.7%) and vomiting (5.0%), breathing problem , abdominal pain , Dyspnea , Anorexia as shown in table no (1).[2413]

Table No (1): Clinical Manifestation	
Symptoms	**Rate**
Fever	87.9%
Cough	67.7%
Fatigue	38.1%
Dyspnea	40.00%
Anorexia	42.00%
Productive Sputum	28.01%
Myalgia	23.01%
Dizziness	9.5%
Diarrhea	8.45%
Headache	6.9%
Vomiting	4.02%
Abdominal pain	2.3%
Sore Throat	16.11%

1.4 MODERN TREATMENT STRATEGY

Management of this COVID-19 includes both non pharmacological aspects & pharmacological aspects. Under non pharmacological aspects, maintenance of social distance, washing of hand by sanitizer, home quarantine practices are needed. On the other hand Azithromycin, Hydroxychloroquine plays an important role as per pharmacological aspects which is deployed as Fig 1.[2]

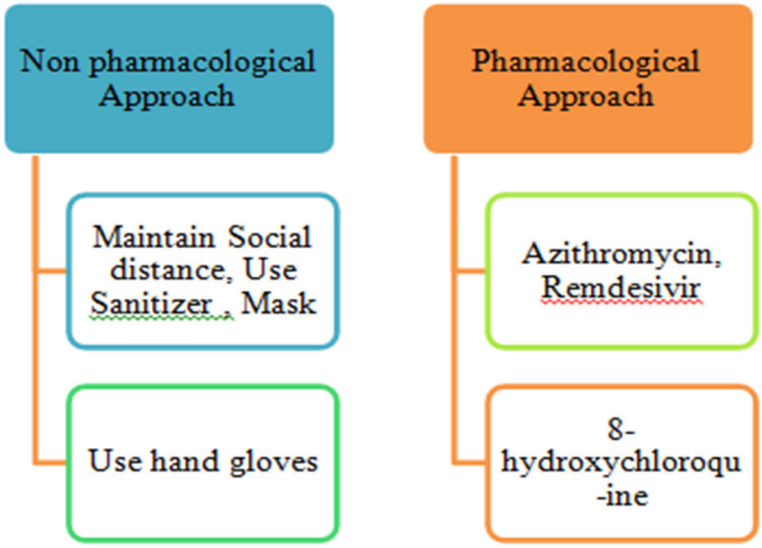

Fig:1 Modern Treatment Strategy

Azithromycin shows an interesting immune modulatory profile by inhibiting several cytokine associated in COVID-19 severe respiratory syndrome .[26] Briefly, Azithromycin decreases the production of IL-1β, IL-6, IL-8, IL-10, IL-12 and IFN∞. Hydroxychloroquine is a major Pharmacological agent which helps to treat this disease.[27,14]Hydroxychloroquine also has immunomodulatory effects and it has been reported to decrease IL-1, IL-2,IL-6,IL-17,IL-22, IFN-∞ and tumor necrosis factor .[28] Azithromycin and Hydroxychloroquine when administered as a combination therapy both [29] decreases the production of inflammatory cytokines namely IL-1 and IL-6.Many experimental studies showed that Azithromycin have immunomodulatory effects . In mammalian cells Azithromycin activates intracellular mitogen activated protein kinase (MAPK) , in specific extracellular signal –regulated kinase ½ (ERK1/2) and the NF-κB pathway downstream of ERK. Because these pathway are associated with inflammatory cytokine production , cell proliferation and mucin secretion. Due to this reason Azithromycin have been proved to have the ability to manage several chronic lungs diseases namely cystic fibrosis (CF) , non –CF bronchiectasis, chronic obstructive pulmonary disorders ,chronic rhinosinusitis, sepsis and diffuse panbronchiolitis. The main clinical evidence concerning the advantages of Azithromycin with or without Hydroxychloroquine or Chloroquine in COVID-19 infection comes from an open label non randomized clinical trial in France recruiting 42 hospitalized persons associated with COVID-19 over 14 days. Patients were treated with Hydroxychloroquine 600 mg daily with add – on – Azithromycin 500 mg per day followed by 250 mg per day for next 4 days in six patients to prevents bacterial super infection. However there is a big difference between Hydroxychloroquine & Azithromycin. Hydroxychloroquine may decrease IL-2 levels but Azithromycin is not associated with it.[30]On the other hand Azithromycin may decrease IL-8 levels but Hydroxychloroquine does not decrease IL-8 levels. Another

point is that *Prevotella* cells which have been located in abnormal quantities in patients with severe disease , could internalize SARS-Cov2 and increase its pathogenecity [31]*Prevotella* spp. are commensal anaerobic bacteria which is found in lungs and they are engaged in idiopathic inflammatory lungs disease and increase the production of IL-6 , IL-8 production . Since Azithromycin is the first line drug to fight against *Prevotella* infections and decrease *Prevotella* induced inflammation .[32] Azithromycin has a large spectrum antiviral activity and its obstruct the virus entry into the cells .On the other hand it enhance immune response against viruses by different actions. The immunomodulation properties of Azithromycin are another reason for use against inflammatory manifestations leading to interstitial lungs diseases .Azithromycin is widely distributed in tissue, especially in lungs where average concentrations in both extracellular fluids and within cells are much higher compared to plasma. Pivotal point is that Azithromycin is only a weak cytochrome P450 inhibitor .Along with the above mentioned, Ritonavir ,Lopinavir , neuraminidase inhibitors , nucleoside analogues these antiviral drugs are used in this present scenario for management of COVID- 19 as per as pharmacological aspects . [33,34]The COVID-19 infection is a major health problem in developed and developing countries .However there is no specific vaccine or drugs to manage this disease . Only Remdisivir has been recently authorized for use in USA and Japan. Most of the established antiviral drugs such as lopinavir, Ritonavir, Chloroquine or its derivative 8-hydroxychloroquine has shown antiviral activity against SARS-COV2.[35]Azithromycin is a broad spectrum macrolide antibiotic & has anti inflammatory properties. However ,its commonly used for bacterial respiratory infections and could potentially treat or prevent co-infection with SARS-CoV-2. Azithromycin also have antiviral activity against some RNA viruses which is another advantage of Azithromycin.[36] On the other hand , Hydroxychloroquine plays an important role in management of COVID-19 and it has lot of advantages. Different studies have shown that Hydroxychloroquine increases the intracellular pH and inhibits lysosomal activity in antigen presenting cells (APC) ,including plasmacytoid dendritic cells and B cells also block major histocompatibility complex (MHC) class II-mediated antigen presentation to CD^{4+} and thus prevents the differentiation of these T cells. Such mechanisms of Chloroquine and 8-Hydroxychloroquine also prevent the antigen processing and suppressing inflammatory signaling pathways and markedly reduce the production of pro-inflammatory cytokines namely TNF-∞,IL-6.[37]

2. CONCLUSION

As we know, novel coronavirus is a big problem in the present scenario. A wide range of veterinary diseases has emerged due to different coronaviruses over the last 50 years. Various researches on coronaviruses will probe aspects of viral replication and pathogenesis in the coming future. To understand the predictability of the source and time of the occurrence of the epidemic spreading between species and understanding the propensity of these viruses. Finally defining the method of action of the coronaviruses causing disease and understanding the immune pathological response in the host will emphasize the development of the ability to formulate efficacious vaccines resulting in reducing the disease tragedy.

3. AUTHOR CONTRIBUTION STATEMENT

Mr. Srikanta Chandra, Ms. Preeta Bose, Mr. Muniraj Bhattacharya conceived the presented idea. Mr. Arun Dutta Mr. Jyotirmay Samanta and Ms. Jyoti Saxena developed the work and contributed equally to the final manuscript.

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5. CONFLICT OF INTEREST

Author declare no conflict of interest.

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