COVID -19: Too Many Hypothesis Too Little Evidence

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Abstract: This Current pandemic of COVID-19 is challenging scientific community with lot many hypothesis. The clinical and epidemiological conclusions of COVID -19 are still uncertain due to its higher transmission rate. From all the corners of the world is sharing their understandings on COVID-19 but the interpretation of those understandings is still ambiguous. There is an urgent need for the scientific community for imperative discussion of those hypothesis on COVID-19. In this prospective discussion we analyzed various hypothesis on COVID-19 with existing clinical facts. Including clinical management, epidemiology and controlling strategies.

Key words: COVID-19, hypothesis, prospective, discussion.

1 Introduction

Coronavirus Disease (COVID-19) is an infectious disease caused by novel corona virus which is emerged from Wuhan, China in December 2019[1]. The clinical presentation of severe acute respiratory syndrome coronavirus disease (SARS-CoV2- Causative virus) resembles viral pneumonia [1]. This enveloped positive RNA virus shows lower respiratory symptoms including cough, shortness of breathing and fever within 11.5 days post infection. This ongoing pandemic attributed to > 200,000 mortality, > 1,962,235 infected cases and widespread to > 200 nations. It witnessed the world needs more scientists who can effectively translate their expertise, the findings and projections at this time undoubtfully help the scientific community to relay further [1]. However, these projections may lead a kind of uncertainty about COVID-19 that will cause misrepresentations of risk to common community. Hence, the hypothesis and clinical opinions on this infection are taken for prospective discussion with available facts.

2 Clinical management

2.1 Hydroxychloroquine(HCQ) as a game changer

Since from outbreak of COVID-19 this drug played global political responses of unconceivable proportions. The president of United States shown his trust of HCQ for his people using ready for retaliation. This molecule exhibits blocking replication of enveloped viruses including coronavirus at late stage by interfering pH dependent steps of viral entry. Effective concentration 50 (EC50) value of 6.25 micromole of HCQ at 24 hrs was reported to have a promising effect on COVID-19 prevention in *in vitro* experiments [2]. Mode of action perhaps blocking endosomal maturation in intermediate stages of endocytosis which leads to failure in transport of virions to releasing site. Other than direct antiviral potentials, HCQ may possess anti-inflammatory potentials in autoimmune conditions. It plays vital role in attenuating release of pro-inflammatory mediators [3]. Further, HCQ treatment shows viral nasopharyngeal carriage clearing of SARS-CoV-2 in COVID-19 patients in three to six days [4]. Single dose of 800mg of HCQ provides more than higher level of EC 50 at lung fluids. However, FDA suggested 200mg for 22 days were found to be effective in prevention of lung damage of COVID-19 patients. Antimalarial agents most commonly produce cardiotoxicities including cardiomyopathy, atrioventricular block and majorly in the case of HCQ produces QT prolongation which is potential indicator of *torsade de pointes*. There are two trials in progress in Shanghai Public Health Clinical Center and University of Oxford which are currently in the process of recruiting patients with COVID-19 [5]. Indian council of medical research expresses that there is no satisfactory results attained with HCQ for COVID-19 patients. On the other hand United States and Brazil appreciate India's decision of exporting HCQ. However, more trials are the only way to decide the safety and efficacy of HCQ further.

2.2 Azithromycin with chloroquine

The pharmacokinetics of azithromycin and chloroquine does not have any interactions as such [6]. Further, chloroquine is also a well-known candidate for phase IV potassium channel repolarization delay. Hence, it has increased chance of prolongation of QT intervals. Further, the genetic polymorphism plays crucial role in the release of cytochrome P450 enzyme 2D6 (CYP2D6), a metabolizing enzyme of

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Chloroquine [7]. This will allow the chance of suspect of death reports from Africa and Arizona due to chloroquine. However, there is no evidence of Azithromycin and/or chloroquine for fetus toxicity [8]. On the other hand there should be Azithromycin and/or chloroquine optimization need for their employability in COVID-19 therapy for pregnant patients; else it will negatively impact the course of the disease. Chloroquine may augment the inflammatory response due to T-helper cell proliferation. On the other hand, the immunomodulatory effect of chloroquine may give a great prescribing push for COVID-19. However, more robust randomized trials needed for proving the effect [9].

2.3 Ayurveda's Immunity Boosting

The global ayurveda's birth place INDIA's Ministry of AYUSH recommend few care guidelines for preventive health measures and boosting immunity with special reference to respiratory health. These are supported by Ayurvedic literature and scientific publications. The practices include, consuming *chyavanprash* (A herbal immune booster) 10 g and/or drinking herbal tea contain basil, cinnamon, black pepper and dry ginger for two to three times a day. Further, golden milk (Milk with, turmeric) also suggested by many Ayurveda literature against viral infections. However, these suggestions are chiefly employed to feel symptomatic relief and boosting immunity needs more evidences against COVID-19. Further, these Ayurveda supplements can be suggested along with ongoing other system of medicines [10].

2.4 Antiviral with NSAIDS

Traditionally NSAIDs were used for flu like fever in clinical practice. Indomethacin exhibits promising anti-viral property against coronavirus, by interfering with viral multiplication. The cyclooxygenase inhibition effect helps to block viral RNA synthesis at cytoprotective dose of Indomethacin which was demonstrated *In vivo* and *In vitro* experiments [11]. However, the augmented evidences suggest that children treated with NSAIDs for viral infections produces emphysema [12] which may lead to lethality in case of lower respiratory tract targeting disease like COVID-19. Naproxen shows potential interference in RNA synthesis process with influenza infections [13], selective JAK-STAT signaling inhibitors like baricitinib, fedratinib, and ruxolitinib were reported for effectiveness in elevated interferon-γ cases of COVID-19 [14]. Combining Baricitinib with antivirals is consciously practiced for COVID-19 due its favoring pharmacodynamics property. Further, aberrant host inflammatory response of these combination plays vital role in COVID-19 [15].

2.5 Africa's response and herbal remedy for COVID-19

The East African country Ethiopian Ministry of Innovation and Technology and Ministry of Health has announced that they took the initiative to develop a "new drug" for COVID-19 in collaboration with a team of traditional medicines experts. The primary concern of the critics from scientific community is that fear of leading the public to believe the treatment against corona is low hanging fruit but actually. However, the preliminary data, scientific explanation about the effectiveness and tolerability of the alleged inhibitors by the scientists [16]. The government of Zimbabwe believes herbal treatment can be the answer to the deadly coronavirus. Hence, the government has authorized herbalists to treat coronavirus patients. However, medical experts have urged the government to stick to WHO guidelines on how to contain the virus [17]. Madagascar's president has endorsed a controversial "miracle cure" to tackle the coronavirus. There is no scientific evidence though that the herbal remedy is effective. Also, Burkina Faso will make face masks mandatory as of April 27, but they're still hard to come by [18].

2.6 Off label antivirals

Majority of antiviral agents administered immediately after symptoms of COVID to reduce viral load in respiratory secretions from 5-6 days to up to 14 days. Further, antivirals can be also prescribed as prophylactic purpose to reduce the risk of contact infection [19]. The off label claim of lopinavir/ritonavir combination along with oseltamivir relatively shown good recovery in COVID-19 related pneumonia in few cases in china. The influenza agent favipiravir also reported effective in current pandemic. Radiological investigations on favipiravir (600 mg twice daily) plus interferon treated subjects shown greater viral shedding [20]. Remdesivir an anti-Ebola agent also prescribed for MERS and SARS in cells. But, there is no concrete evidence for its therapeutic ability. Though there are few studies with off label COVID-19 claims but with this minor populations and lack of randomization in available trials. Further, the available studies have not considered the stage and differences in severity of the disease as well as the differences in age of the two groups. Hence, this lead lack of blinding of outcomes to the researchers all cast doubt on the findings.

2.7 Corticosteroids

Generally corticosteroids are mostly effective in controlling immunopathological damage but simultaneously produce viral rebound in most of respiratory viral diseases. Higher viral RNA load was reported with SARS-CoV patients treated with corticosteroids [21]. Latest study with COVID-19 pneumonia early and low dose of corticosteroid therapy for short duration of 2-4 days reported with earlier improvement of clinical symptoms [22]. COVID -19 patients who received corticosteroids for earlier symptoms were reported for requirement of mechanical ventilation and renal replacement therapy [23]. The ultimate fact of viral load increment upon corticosteroids administration is well known in previous outbreaks of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) [23].

2.8 Cuba's interferon alpha-2b

HIFN-2b molecule is a glycoprotein consisting of 166 amino acids with O-glycosylated threonine at position 106. Augmented evidences suggested that HIFN alpha- 2b hindering JAK-STAT signal transduction by inhibiting extracellular signal-regulated kinase (ERK) mitogen ERK kinase (MEK) pathway. Young and middle aged COVID-19 patients may not requires HIFN-2b owing to their good

immune conditions. However, aged patients who are susceptible to bad immunity perhaps require HIFN-2b for avoiding complications. South America and African countries have plan to start HIFN-2b vaccination to attain earlier control of COVID-19.

2.9 Convalescent plasma therapy

Convalescent plasma (CP) therapy, played significant role in past decades as classic adaptive immunotherapy in prevention and treatment of many infectious diseases. The efficiency in treatment of SARS and MERS and H1N1 pandemic is well known [24]. However, the CP therapy was unable to show significance in Ebola virus disease, perhaps absence of data of neutralizing antibody titration for stratified analysis [25]. Chiefly the scope of CP therapy for COVID-19 might be promising due to virological similarity with SARS and MERS. Pilot studies suggested potential therapeutic effect in reducing viral load by neutralizing antibodies for severe patients [26]. However, multiple population randomized trails are warranted at the earliest to make CP as promising

3 EPIDEMIOLOGY

3.1 Elderly are more prone

Older adults are at higher risk for developing more serious complications from COVID-19 illness. Researchers report elderly people's elevated risk of serious illness and death from the new coronavirus: Covid-19 kills an estimated 13.4% of patients 80 and older, compared to 1.25% of those in their 50s and 0.3% of those in their 40s.The fatality rate for people over 80 from COVID-19 is almost 15% according to data from China [27]. The main reason why older adults are at higher risk is that they don't have as strong an immune system so they are more vulnerable to infectious disease. The other reason why older people are more prone to fatality from COVID-19 is that they are more likely to have conditions such as heart disease, lung disease, diabetes or kidney disease, which weaken their body's ability to fight infectious disease.

3.2 Co-morbidities vs COVID-19

The number of comorbidities is a predictor of mortality in COVID-19. Diabetes has been reported to be a risk factor for hospitalisation and mortality of the COVID-19 infection [28]. A study in 52 intensive care patients revealed that diabetes was comorbidity in 22% of 32 non-survivors [29]. In another study of 173 patients with severe disease, 16.2% had diabetes, and in further study of 140 hospitalised patients, 12% had diabetes [30, 31]. When comparing intensive care and non-intensive care patients with COVID-19, there appears to be a twofold increase in the incidence of patients in intensive care having diabetes [32]. Mortality seems to be about threefold higher in people with diabetes compared with the general mortality of COVID-19 in China [33]. Indeed, people with diabetes are a high-risk group for severe disease. Notably, diabetes was also a risk factor for severe disease and mortality in the previous SARS, MERS coronavirus infections and the severe influenza A H1N1 pandemic in 2009. [33-35]

Diabetic patients are at increased risk of infections including influenza and complications such as secondary bacterial pneumonia. This is most likely because they have impaired immune-response to infection both in relation to cytokine profile and to changes in immune-responses including T-cell and macrophage activation. Poor blood sugar control impairs several aspects of the immune response to viral infection and also to the potential bacterial secondary infection in the lungs. It is likely that many of the patients with diabetes in China have been in poor metabolic control when infected by COVID-19 [36,37].

In addition to diabetes, the other most common comorbidity COVID-19 is hypertension [38]. Out of 1,590 COVID-19 cases in a nationwide analysis in China nearly 17% was found to be hypertensive cases. The severity of the disease was also reported to be higher for hypertensive cases compared with those non-hypertensive cases [39]. It was also suggested that comorbidities such as COPD, other cardiovascular and renal diseases, and malignancy predisposed to adverse clinical outcomes in patients with Covid-19. However, the strength of association between different comorbidities and the prognosis was less consistent when compared with the literature reports [40-43]

It has been well accepted that some comorbidities frequently co-exist. For instance, diabetes and COPD frequently co-exist with hypertension or coronary heart diseases. Therefore, patients with co-existing comorbidities are more likely to have poorer baseline well-being. Importantly, it was verified that the significantly escalated risk of poor prognosis in patients with two or more comorbidities as compared with those who had no or only a single comorbidity. The category and number of comorbidities should be taken into account when predicting the prognosis in patients with Covid-19. [44, 45]

3.3 Vaccination against tuberculosis prevents mortality

The WHO clears with its statements that no evidence that Bacille Calmette-Guérin vaccine (BCG) protects people against infection with COVID-19 virus. However, this tubercular vaccine reported effective against leprosy with non-specific immunity boosting, the common logic behind is both are mycobacterial infections. The correlation of BCG vaccinated COVID-19 positive cases suggested that fall in mortality and morbidity and may be played vial role in controlling this pandemic [46]. BCG vaccinated mice shown increased IFN-Y production from CD4+ cells, this so called trained immunity produces epigenetic changes. Including increasing secretion of pro-inflammatory cytokines. This may drive the scientific community like to tempt to pronounce the statements BCG vaccine as "silver bullet". Further, we observe the slow spreading rate of COVID-19 in BCG vaccine mandate countries [47]. But another 90 days may require to have strengthen this statement. The COVID-19 data of south Asia and Africa may be contributed to lower number of testing. Additionally, there are couple of trials are registered for BCG for COVID-19 the results of these trials may give us better concussion [47].

3.4 SARS-CoV-2 cross immunity to south Asians, Africans, and South Americans

The spike protein of SARS-CoV, HCoV-NL63 and SARS-CoV-2 possess quite similar in structure among them. The hypothesis of antibody dependent enhancement in south Asians, due to previous exposure of Dengue and Zika virus is may be the reason of slow in doubling rate of COVID-19 in South Asians. But this statement not ends unless this pandemic completes its turn. Other observations on slow spreading of COVID-19 in South Asia, Africa and South America make us to suspect cytokine storm. But this is too early to conclude. The pandemic is not over yet [48]

4 Conclusion

Numerous understandings and hypothesis from various parts of the world signifies clearly, that the COVID is yet to be understood by scientific community. However, researchers are continuously working for vaccine development for this ongoing pandemic. Majorly CHINA, INDIA and AMERICA are actively participated in vaccine development race. Our understanding suggests that this pandemic deemed to be over in 12 to 30 months in this world. At all the outset we have to live with COVID-19 and this is "not the first nor the last".

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