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Review Article

CORONA VIRUS DISEASE-19 PANDEMIC - THERAPEUTICS AND NOVEL DEVELOPMENT

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ABSTRACT

Every individual must follow the slogan of front line worker as "we stay at work for you, you stay at home," This means to protect the healthcare worker who are working in the frontline to save life of the corona virus disease (COVID)-19 patient of the different phases, other should stay home safe and secured; however, if we could not protect them than the matter will be serious to everyone to control the situation of this pandemic and many life can be lost. Thus, it is suggested to the young asymptmatic people to remain quarantine and isolated until the incubation period be over, it could be as long as 41 days or as short as 6 days but average time necessary is 14 days. There are no drugs or other therapeutics presently working to knock out COVID-19 pandemic. However, drugs employed in the treatment of hospitalized patient are on the basis of previous exposure of congruent strain of virus; in addition, supportive care management such as supplemental oxygen and mechanical ventilation procedure is highly being used to the critical patient. This review highlights step to step treatment plan, employed therapeutics, mechanism, efficacy, and new development of the clinical trial results if any.

Keywords: Coronavirus disease-19, Drugs, Pandemic.

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INTRODUCTION

Although there are no any drugs precisely made for coronavirus disease (COVID)-19, repurpose drugs are in use for the patient that is seriously sick from COVID-19. Human was previously in exposure to SARS-CoV in 2002–2003 and Ebola virus in 2014, this virus was posseing similar genetics about 70–80% therefore on the basis of their knowledge doctors and scientist opt to select the drugs type that might work in the COVID-19, later same will be examined through clinical trial to assign as the officially approved COVID-19 drugs if found statistically significant. Possible COVID-19 therapeutics option are: Chloroquine and hydroxychloroquine and azithromycin, Remdesivir, Tocilizumab, Lopinavir-ritonavir, Baraticinib, convalescent plasma therapy, Angiotensin converting enzyme 2, nonsteroidal anti-inflammatory drugs, glucocorticoids, glutathione therapy, Ivemectin.

STEP TO STEP TREATMENT PLAN TO COVID-19

The COVID-19 patient varies from Asymptomatic to Critcall ill as on their pathophysiological mechanisms, accordingly therapeutics plan is progressed.

THERAPEUTICS FOR ASYMPTOMATIC PHASE

The asymptomatic does not have specific drugs or therapy, instead isolation, maintaining hygiene, and consuming fluid to hydrate themself is recommended. The serious features are they could be super spreader, prone to generate the pandemic by carrying virus on their body but do not exhibit any sort of sign and symptom and walk around as if they were not infected. They incubate the virus and easily transmit to another host thus be serious spreader. It was reported that virus can reside in asymptomatic patient for long time and when they actively sneeze or cough the droplets so formed as a result could fly as far as 26 ft. and settle on the surface contaminating it where it can remain viable more than 9 days depending on the surface they settle down.

In some people no sign and symptoms were seen might be because of their silence to the host immunity response, and remaining inside the body as if they behave inanimate object. This is the period where patient incubate virus. Study has reported that there is human to human transmission from asymptomatic patient hence are transmissible host, if the transmitted person be vulnerable like 60 years of age or having some sort of already existed comorbidity than virus in very short time exhibit symptoms and even become fatal, for instance, a kidney patient in UK after getting transmission died in 3 days aftermath reverse-transcription polymerase chain response positive.

Asymptomatic patient main job is only to limit the transmission and thus not providing new host for the virus, assuming that the virus could show any sort of activity in the asymptomatic host after it get favorable condition, test is the first criteria solely to know about the person infectivity It is strictly advised to asymptomatic patient to stay at home and prevent your relative, community, and healthcare worker and isolate ownself waiting for the incubation period be over and impending danger to come up.

Consume adequate amount of fluid, fruit, vegetables, and hydrate oneself to boost immunity toward the virus. The asymptomatic patient should think of the burden that he or she has to prevent other from getting infected, wearing mask especially with no any filterable pore with in the mask will be priority for the asymptomatic patient moreover keeping onself in isolation using separate bathroom, utensil clothes is must.

THERAPEUTICS FOR SYMPTOMATIC PHASE OR ORANGE GROUP

Symptomatic patient responsibility is to stop the virus to soar up or alternatively to reduce the viral load so they do not shift to critically ill patient instead aim is to get free of virus. Entry of virus to the lung through mouth, nose, eyes encounter macrophage and get adhered to bind with angiotensin 2 converting enzyme (ACE2) receptor, virus spike protein seek ACE2 receptor of the host cell, and cause symptomatic feature of that particular area such as in mouth, nose, lungs, blood vessel, gastrointestinal tract (GIT) and immune cell itself, producing symptoms such as loss of taste and smell, dry cough, hypertension, diarrhea, and fever.

The symptomatic patient exhibit certain medical criteria such as high respiratory rate, high fever, shortness of breath, computed tomography scan image of pulmonary infiltration, ground glass opacity, pneumonia, fibrosis, and low oxygen saturation which led them to become immediately critical ill patient.

This type of patient need immediate hospalization and start up with some drugs as a therapeutics measures or in the repurpose of the old drugs medication that is learned from 2002 to 2003 SARs epidemic, will be applied for treating the patient with old drugs, though there is no clinical trial for the drugs to be approved for the treatment but for the time of desperate emergency. Chloroquine, hydroxychloroquine, and azithromycin, remdesivir and other drugs are given to the patient in the hope that the drugs are useful and patient gets improved in its condition. Mild symptoms of fever are treated with paracetamol and lot of fruits and vegetables especially patient recover in a week.

CHLOROQUINE AND HYDROXYCHOLOROQUINE

Chloroquine is an old FDA approved antimalarial drugs and hydroxy derivative of chloroquine is Hydroxy chloroquine is immunosuppressive drugs use for the treatment of autoimmune disease such as Lupus and rheumatoid arthritis also they showed broad spectrum antiviral activity [1,2]. It has been demonstrated that these drugs do have effect on the post and well as entry stage of viral infection as study demonstrated to function on ACE2 receptor of host epithelia cell [3,4].

The entry of SARS-CoV-2 is initiated by recognizing ACE2 receptor on the host cell that is present in Lung, GIT, Heart, Kidney, etc., bind there by its S1 domain and fuse by S2 domain [5,6]. The priority to stop the binding of the Spikes protein is the basis to block the virus and thus prevent virus not to enter the cells [7,8].

Efficacy to use the drugs on this specific disease has been demonstrated by different report, Wang *et al*. *in vitro* infection demonstrated that chloroquine is highly effective in the control of 2019-nCoV and is recommended to examine it in the COVID-19 patient [5]. In addition, the one study carried out in 100 patient of COVID-19 demonstrated that chloroquine phosphate could be used to ameliorate and control the disease as its treatment is preventing the exacerbation of pneumonia, lung injury, shortening the disease course, and promoting virus negative conversion [9]. However, attention should be paid to the potential detrimental effects of chloroquine observed in the previous attempts to treat viral diseases. At present, the clinical trials to evaluate the efficacy and safety of chloroquine in the treatment of COVID-19 are ongoing [10]. The use of chloroquine in the treatment of COVID-19 should refer to the most recent announcements if any. However, its adverse effect such as serious cardiac arrythmia, QTc prolongation has to be considered before its administration. Hydroxychloroquine is found to be superior more potent in managing the COVID-19, recommended dose of it is 400 mg BD for 1st day followed by 200 mg d for another 4 days [11]. Till date, no clinical data for this drug are available but its clinical trial to procure data is in progress which provides preliminary result about the effectiveness of this drugs.

A study in France showed in patient treated with oral hydroxychloroquine and Azithromycin 600 mg daily in 10 days course just in 3–6 days significantly decreased the mortality rate which was just 0.5%. It is that Azithromycin inhibits bacterial pneumonia by inhibiting 50 S ribosome thus it hypothesized that hydroxychloroquine or chloroquine is given with Azithromycin in combination while treating COVID-19 since such combination may both act as an antiviral therapy against SARS-CoV-2 and prevents bacterial super-infections [12]. Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

MECHANISM OF ACTION

These drugs are approved antimalarial drugs as well as used in Lupus and Rheumatoid arthritis so it very much to be careful on their demand, must meet who are already need of it for such disease.

Antiviral activity of chloroquine and hydroxychloroquine in terns of COVID-19 is expected to as; by glycosylation of ACE2 receptor thus prevent the binding of virus spikes on the receptor. Obstructing the virus fusion with the endosome by altering the PH, or impairment on acidification to endosome or prevent virus/cell fusion by increasing endosomal pH thus Impeding the packaging of the virus, also they work as ionophore for Zn allowing it to easy access to cell and thus inhibit viral replication cycle.

CRITICALLY ILL PATIENT OR RED GROUP

Remdesivir

Remdesivir is a RNA viral drugs that inhibit RNA dependent RNA polymerase enzyme reduce viral replication and thus virus load under experimental setting, thus prevents lung damage, was readily in use during 2003–2004 SARS outbreak, Correspondingly 2014 Ebola virus outbreak treatment was also issued by this drugs and is currently under clinical development [12-14]. In Ebola virus long time use of remedisivir is safe without or with not noted adverse effect, however till April 1, 2020 remedisivir was under double blind clinical trial for the study of safety and efficacy of the drugs.

In China, participant for the trial chosen was mild to moderate or severe hospitalized who was loaded with 200 mg on day 1 followed by 100 mg i. v. once daily maintenance dose for 9 days [15,16]. The results of these Chinese clinical trials showed, drug was not successful to show approving result means it did not improve the patient condition or reduce the pathogenic load. Hope dashed as the remdesivir drug failed in its first randomized clinical trials performed in China.

Researcher and Scientist were in a great hope that the remdesivir drug could be effective in the treatment of COVID-19, but this potential anti-viral drugs for the corona virus in its first randomized clinical trial failed, the reasoning given is they could not finish the trial because of not having enough patient for the trial to complete.

It showed that researchers studied 237 patients, administering the drug to 158 and comparing their progress with the remaining 79, who received a placebo. After a month, 13.9% of the patients taking the drug had died compared to 12.8% of those receiving the placebo. The trial was stopped early because of side effects. “Remdesivir was not associated with clinical or virological benefits,” but the same drug in USA is proven to be significant treating the patient of COVIDA-19, 30% patient are recovering in faster rate on this clinical trial drugs result, this is the drugs of Ebola virus but it is to premature to declare this drug as cure for COVID-19.

Remedisivir is the first drug officially announced by US to treat the COVID-19 and is based on the clinical trial that showed 30% faster improvement.it is given intravenously for severely sick for 10 days and moderately sick for 5 days.

Mechanism of action

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases is a nucleoside analogue that mimicks adenine nucleoside, during replication it hinder by inserting itself in place of adenosine stop the replication.

FIRST DRUG OF FDA AUTHORISATION FOR COVID-19 IN USA

Remedisivir the previously used Ebola virus drug became the first authorized drug for the treatment of COVID-19 in USA on the basis of clinical trial of fast recovery 11 days compared with non-user (Placebo) 15 days. Though 11 days (31% Dr. Fauci’s report) does not seem likely of clear cut knockout for 100% but it is now strictly proven that the drug can block this COVID-19. The drug interferes with the virus’s genome, disrupting its ability to replicate, but is not a proven “Magic Bullet.”

It is also mentioned that people who were under this drug trial less likely to die, that is mortality rate was 8.0% for those receiving

remdesivir versus 11.6% for the placebo group and it took 90 days to get authorization since clinical trial begun. Report suggest that it is administered intravenously and 10 days for severe and 5 days for less severe patient in hospitalization scenario. Although chloroquine and hydroxychloroquine the antimalarial drugs is being in use for the treatment in different country, these drugs do not have absolute clinical data of its alone efficacy cardiac arrhythmia as an adverse effect was reported, this remdesivir now have the data for its fast recovery rate; hence, it become the first drug authorized for the treatment in the United States as well more data regard to use of this drug is expected from other country too. (This is my understood review from published journal article). However, this same drug is failed to approve by China clinical trial as they say due to not having enough patient they did not get the result as it was hoped statistically for remdesivir and concluded that trial without its concrete conclusion but it came out as failure to appear effective for COVID-19.

In Conclusion, This would be an important step in options available to clinicians to treat those hospitalized with COVID-19. The data show that many hospitalized patients will die, so although the effectiveness of remdesivir is limited, it may be a useful addition as an option for treatment.

LOPINAVIR/RITONAVIR

Different antiviral drugs are the experimental option for the COVID-19 similar is lopinavir/ritonavir which is antiviral drugs used in the treatment of HIV virus and they also disrupt replication cycle, their effect is to cease acute respiratory distress syndrome (ARDS), reports suggest that their efficacy is decrease ARDS is higher when used in combination with ribavirin [17]. On the contrary, there are documented report they Lopinavir/ritonavir administered 400 mg followed by 100 mg twice daily to severe hospitalized adult patient did not show any benefit compared to standard care [17] despite adverse effect were noted such as anorexia, nausea, abdominal discomfort, diarrhea, or acute gastritis. There is also risk of hepatic injury, pancreatitis, cutaneous eruption severe as well there is CYP3A inhibition that cause drugs interaction, this adverse effect need to be noticed for prolonged use for its out come [18]. Future trials with severe illness might help to elucidate the possibility of benefit of lopinavir/ritonavir treatment, although no significant improvement to the patient with COVID-19 were observed compared to standard therapy some modification was seen in ARDS, mortality hence it is encouraged to use the drugs in research setup to further evaluate its effectiveness.

CYTOKINE, STORM DAMPENING THERAPY

Aggravated immunoresponse toward virus resulted into own tissue damage noted during the treatment of hospitalized severe COVID-19 patient. The activation of immune cell such as leukocyte causes flood of cytokine release known as Cyrokine Storm and these cytokine worsen the disease by own tissue damage.

People with immune system suppressed or deficient or old age people get critical illness by COVID-19. Some of these people have very low CD4+ T cell and thus weakened immuno system [19,20]. Therefore to modulate the immunoresponse and prevent from own damage a variety of therapeutic proposition has been made [21].

NEW DEVELOPMENT FOR POSSIBLE ANTIINFMMATORY DRUGS COVID-19

Colchine is used as an anti-inflammatory agent in rheumatic and cardiovascular disorders and successful in neutrophilic disorder therapeutic doses of the drug reduce C-reactive protein to levels below 2 mg/L, is protective to myocardial damage with frequent side effect diarrhea [22]. Impending Storm ahead as c-reactive protein (CRP), interleukin (IL)-6 and more serious flood of cytokine storm cause ARDS, led the patient die. Colchicine can suppress these inflammatory hence could be one of the possible therapeutics to ameliorate hyperinflammation in COVID-19. Colchicine is effective in suppressing inflammation by various mechanisms. However, inhibition of neutrophil chemotaxis appears to be its main anti-inflammatory effect [23]. Kiraz *et al*. studied the effect of colchicine on inflammatory cytokines and selectins in familial Mediterranean fever patients in a previous study. In this study, IL-6, IL-8, tumor necrosis factorα, and E and L-selectin levels were significantly reduced after 2 months of treatment with colchicine [24]. However, poisoning caused by colchicine overdose is a life-threatening disease; therefore, it should be used with extreme caution in patients with renal or hepatic impairment. It is mainly excreted by the biliary system, intestines, and kidneys. Colchicine is metabolized by cytochrome 3A4 [25]. This cytochrome can be inhibited by various drugs that lead to colchicine poisoning during concomitant administration.

Possible ameliorative effect of colchicine on the prevention of cytokine storm and its associated hyper inflammation in patient with COVID-19.

Tocilizumab

There is aggravated response of immune system in COVID-19 patient, releasing flood of cytokine known as "Cytokine storm" characterized by excessive IL-6, IFN, and other cytokines that damages own tissue of lungs which will lead to ARDS or multiple organ failure [26].

Different therapeutics are in progress to counter the flood of cytokines activity, one in clinical trial is Tocilizumab a humanized monoclonal antibody that blocks IL-6 and prescribed in anti-inflammatory condition Rheumatoid arthritis as well have effect on cytokine release syndrome [27]. As is similar scenario observed in COVID-19 patient; therefore, it could be one. Of the possible immunotherapeutic agent for the patients with mild to severe extensive lung lesions characterized by increased in level of IL-6 and other cytokines. The efficacy of tocilizumab in COVID-19 patients still needs to be investigated and no precise data is available.

In Addition to, baricitinib is another Monoclonal antibody assumed to be applicable to counter the cytokine storm as being one of the inhibitor of cytokine release license for the treatment of rheumatoid arthritis with efficient efficacy and safety rerecord. Moreover it seems to have anti-viral effects by its affinity for AP2-associated protein AAK1, reducing SARS-CoV-2 endocytosis. The use of baritinicib therapy may limit the cytokine-release syndrome associated with COVID-19 and it may be useful because it acts against a wide-range of cytokines [28].

COVALESCENT PLASMA THERAPY

In COVID-19, one of the measure adopted in management is transfusion of plasma from the already recovered COVID-19 patient, This works in the principle that CP, obtained from recovered COVID-19 patients who had established humoral immunity against the virus, contains a large quantity of neutralizing antibodies capable of neutralizing SARS-CoV-2 and eradicating the pathogen from blood circulation and pulmonary tissues [29]. The only risk of this transfusion is the transmission of the potential pathogen, to filter this effect Methylene blue photochemistry was applied so as to inactivate the potential residual virus and to maintain the activity of neutralizing antibodies as much as possible, a method known to be much better than ultraviolet C light [30] a single dose 200-mL CP was observed to be tolerated, with the clinical symptoms, oxyhemoglobin saturation improved accompanied by virus within 3 days periods.

Effectiveness of CP therapy is considered if immune response, and plasma from recently recovered patient were recruited as a suitable donors. The study accomplished demonstrated that the donor age should be lower than the recipient (42.0 y vs. 52.5 y) and recently within 21 days passed of recovered of the infection with neutralizing antibody titer above 1:640.Treatment time point is the main factor associated with its efficacy, the outcome is more promising if the mean

time from onset of illness of plasma transfusing is 16.5 days [31]. Only especially critical sick patient experiencing significant lung injury and in rarer case is if antibody dependent antiviral system get suppress which could leads to logarithmic intracellular growth of virus [32].

Above mentioned efficacy result came out in the patient that all were received antiviral despite the drugs uncertainty of efficacy. As a result unknowingly the chance that the drugs have contributed or synergized the therapeutic effect of CP [33]. Furthermore, Glucorticood were provided to some patient who might have interfered with immune response and delay virus clearance. Dynamic changes of cytokines were not investigated in the study. This study did not investigated dynamic changes of cytokines during treatment.

In conclusion, CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. With rapid increase of lymphocyte counts and a decrease of CRP, with remarkable absorption of lung lesions in CT.

ACE2

ACE2 is a enzyme that is homologue with ACE belonging to same family but physiologically they serve function opposing to each other, ACE is weaponized to cleave Angiotebsin-I to Angiotensin-II, thus formed Ang-II binds to AT1R leading to smooth muscle contraction and thus blood vessel constriction thus raising blood pressure. By Contrast, ACE2 convert Angiotensin II to Angi-1-7 that activates Mas receptor and cause dilation of blood vessel hence works as a potent vaso dialtor. it means ACE2 counter regulates RAS system [34,35].

Both animal experiment and human observation documented that there were ACE2 upregualtion in the patient who were taking Losrtan or olmesartna to lower blood pressure that work by blocking AT1R, this increase in expression of ACE2 were observed in chronic treatment condition of 28 days both in heart and kidney, SARS -CoV-2 initiate its pathological journey by binding to ACE2 recptor of host cell.

It is obvious that binding of SARS-CoV-2 Spike protein to its ACE2 receptor downregulate it which in turn leads to excessive accumulation of Angio-II, as there is less conversion enzyme left after infection thus less Angiotensin 1-7, which play role in lung injury and angiotensin-stimulated AT1R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology [36]. Therefore, higher ACE2 expression following chronically medicating SARS-CoV-2 infected patients with AT1R blockers seems as if it protecting lung damage therefore, it could be one proposal to use olmesartan to protect rather than discontinuing.

Now with this it can be sum up as ACEIs/ARBs upregulate the expression and activity of ACE2 in lungs, they may play a dual role in COVID-19. On the one hand, the higher level of ACE2 might increase the susceptibility of cells to SARS-CoV-2. On the other hand, the activation of ACE2 might ameliorate the acute lung injury induced by SARS-CoV-2 [21].

Now the furious question is whether to discontinue the treatment receiving patient of Losartan or olmesartan the antihypertensive drugs, I believe the answer is no, because the use of these drugs have double edge swords in COVID-19. In one side, due to upregulation of ACE2 there might be increased risk of COVID-19. On the other hand it might mitigate the possibility of severe lung damage precipitated by infection [37].

However, it would be unwise to discontinue these medications assertively because the protective role of ACE2 in the respiratory system is supported by ample of evidence, whereas the increased danger of infection is still a hypothesis. Besides, patients with COVID-19 also showed potential cardiac injuries and the RAS activation.

Some author even suggest that to infuse soluble ACE2 to the patient to protect so that it binds with COVID-19 thus will not get opportunity to bind with cell ACE2 as they will be busy to confront with injected soluble ACE2 and this will not get entry into the host cells.

NSAIDS AND CORTICOSTEROIDS

There is no concrete evidence of allowance or disapproval in the use of NSAIDS however some reports emerge out as it has beneficial result if used utilized in the early acute phase of infection in regulating or suppress cytokine storm early phase which not only specific to COVID-19 [38]. However in other viral disease like Dengue WHO does not recommend corticosteroid as the "glucocorticoid-mediated stimulation of the hypothalamic-pituitary adrenal axis can also drive lymphocytopenia, or it may promote exaggerated pro-inflammatory responses that eventually cause a worsening of the pathogenic condition." These are unprecedented times for the medical community and although evidence suggests a potential role for the use of NSAIDs and corticosteroids in COVID-19 treatment, caution should be exercised until further evidence, specific to this infection strain, emerges. The same guidance stands for cancer patients who are not advised to change their medication routine unless told otherwise by their doctor [39].

There is no particular data available for the use of ibufropen the NSAIDS worsenong of COVID-19 in fever and pain management, despite the recommendation is use of paracetamol for the fever is wise and further data or study for this future use of safety and efficacy is remained to be understood. Reports state that first week of corona virus infection is virus driven so virus need to handle by immune response accurately so it is not wise to use immune suppressive agent such as corticosteroid but on the contrary second week is Immune system driven which itself damage own tissue hence it will be fruitful to the patient in the second week suppress the over reactive immune cells [40].

GLUTATHIONE THERAPY

Infection with COVID-19 potentially can result in severe outcomes and death from "cytokine storm syndrome," resulting in novel coronavirus pneumonia with severe dyspnea, ARDS. A case report observing two patients with Covid-19 given 2 g of PO or IV glutathione was used in both patients and improved their dyspnea within 1 h of use. Repeated use of both 2000 mg of PO and IV glutathione was effective in further relieving respiratory symptoms. Oral and IV glutathione, glutathione precursors (N-acetyl-cysteine) and alpha lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia [41].

IVERMECTIN AND DOXYCYCLINE

Bangladeshi Doctor has reported of their observation that Ivermectin and Doxycycline could be effective combinations of drug in the treatment of COVID-19, they claim they have report that patient got recovered in 3–4 days after its treatment, this is similar observatory reports as made by the France doctor who treated COVID-19 Parient with Hydroxy Chloroquine and Azithromycin [42].

CONCLUSION

It is wise to be away from this novel coronavirus as no cure specific to the disease is possible yet. However, vaccine is in the course to develop.

Frequent hand washing with soap or use of sanitizer, remaining 2 m distance apart and wearing mask in public place is only the methods used as preventive and safe methods although many drug trials are under process yet there is no specific drug to control this virus and cure the disease.

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