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A COMPARISON ANALYSIS ON REMDESIVIR, FAVIPIRAVIR, HYDROXYCHLOROQUINE, CHLOROQUINE AND AZITHROMYCIN IN THE TREATMENT OF CORONA VIRUS DISEASE 2019 (COVID-19) - A REVIEW

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ABSTRACT

Background: This comparative study is to ascertain the efficacy and results proven drug used in the management of the novel corona virus disease 19 since most patients admitted are recovering while there is no clinically approved or certified drug or group of drugs used worldwide for this fatal disease that is of great global public health concern. **Methods:** Literature review was prominently used by researchers from accredited research centers library, google scholar, PubMed, Elsevier, and other peer reviewed scientific articles and journals. Search terms included coronavirus, 2019-nCoV, SARS-CoV-2, and COVID-19 in combination with treatment, pathogenesis, pathophysiology and pathmorphology. The search resulted in 2210 articles. With respect to time and convenience looking in how the need for better profiling of COVID-19 education for the general public, the researchers also included case reports and case series. The authors independently reviewed the titles and abstracts for inclusion. Additional relevant articles were identified from the review of citations referenced. Many research works done by scientist and

practitioners in affected countries were reviewed further especially some through active probing through interviews via emails to some authors for clarification and analyses of the most drugs (remedesvir, favipiravir, hydroxychloroquine, chloroquine, Azithromycin etc.) used routinely with effective outcomes sampled and discussed on how it really works on the disease causing agent SARS COV 2 in corona virus disease 19 (COVID-19). **Results:** There are no clinically certified effective therapies that treat COVID-19 diseases although there is a growing and advancing knowledge regarding SARS-CoV-2 and its mechanism of invading the human system. Since the outbreak there has been numerous treatment plans with polypharmacies practice as the main routine due to how wild and unpredictable the virus is and the complex nature of its invasion and cells destruction bring about different symptoms in the very particular organ and systems it invades and affects. The researchers found that although hydroxychloroquine, favipiravir and remdesivir where commonly used in pacesetter countries of the COVID19 disease in Asia notably china, Japan, Europe: Italy, Spain, and the united states of America but remdesivir and favipiravir are seen to be most promising although showed side effects, it had prominent efficacy and efficiency although not yet certified as the main anti-viral agent for COVID 19. Furthermore, the researchers find that with the recovering rates of patients who were given remdesivir and favipiravir were increasing with short recovery rate as against the usual 11 to 14 days and saw little or no efficacy and efficiency difference between the two anti-viral agents. In addition, the researchers found that there has been no monotherapy success in the treatment of COVID 19 worldwide, all treatments have been polytherapies with supportive and conventional care. **Conclusion:** The researchers see the threat and fatal distress of the COVID 19 pandemic to the world and assures the science community and the general population that there is constant work been done to find solutions and a potent and efficient drug or vaccine for the pandemic and all should maintain the world health organization's preventive measures of constant hand washing with soap under running water, the use of alcohol based hand sanitizers and face mask till a certified drug of choice is approved for use by the world.

KEYWORDS: SARS-CoV-2, COVI-19, Remdesivir, Favipiravir, Hydroxychloroquine, Chloroquine, Azithromycin.

INTRODUCTION

Corona virus disease 2019 (COVID – 19) is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARA COV – 2: formerly

called 2019 – nCoV) which was first identified amid outbreak of respiratory illness cases in Wuhan city, Hubei province china. It was named COVID 19 by the world health organization and declared an outbreak and global health emergency.

Signs and Symptoms

Presentations of COBID 19 have ranged from asymptomatic, mild symptoms to severe ones with mortality. Very known symptoms include fever (> 38 degree Celsius), dry cough, muscle aches, general bodily pains, fatigue.

The very uncommon symptoms may include headaches, sputum production, diarrhea, dyspnoea, haemoptysis, lymphopenia and more seriously respiratory distress and pneumonia. Loss of smell and has now been reported by most recovered people.

Route of transmission

This is usually through respiratory droplets from coughing and sneezing.

Epidemiology

As of time of this research the world wide infection of COVID 19 stood at two million seventy eight two hundred and seventy seven (2,078,277), those recovered stood at five hundred and twenty five thousand three hundred and sixteen (525,316) while death stood at one hundred and thirty eight hundred and one (138,101) Incubation period of COVID 19 range from 1 – 14 days post exposure to the virus but in some rare cases it is able to extend to 25 to 30 days.[1]

Pathophysiology of COVID 19

The virus invades the respiratory system through the oropharyngeal route. When people develop cough and fever is as a result of the infection reaching the respiratory tree thus the air passages that conduct air between the lungs and the outside.

The lining of the respiratory tree becomes injured causing inflammation. This in turn irritates the nerves in the lining of the airway. When the air passages become infected, they respond by pouring out inflammatory material into the air sacs that are at the bottom of the lungs and this outpouring causes pneumonia. The lungs filled with inflammatory material are unable to get enough oxygen to the blood stream, reducing the body's ability to take oxygen and get rid of carbon dioxide and this causes death. When infection in the lungs and it involves the air sacs the body's response is first to try and destroy the virus and limit replication.

There may be first responder mechanism which can be impaired in people with underlying heart and lung conditions, diabetes and most importantly in the elderly. Usually is binding of a receptor expressed by host cells. At this stage the epithelial cells of the lungs become the primary target. With human to human transmission SARS COV occurs by binding between the receptor binding domain of the virus spikes and the cellular receptor which has been identified as angiotensin – converting enzyme 2 (ACE2) receptor.

Severe pneumonia, RNAaemia combined with the incidence of ground glass opacities and acute cardiac injury during radiology investigations.

The virus invasion causes high blood levels of cytokines and chemokines like IL1RA, IL7, IL 8, IL9, IL10. Basic FGF2, GCSF, GMCSF, IP10, MCP1, PDGFB, VEGFA and others. In some patients there are high values of blood C – reactive protein, high erythrocyte sedimentation rate and D – dimmer.[2,3,4]

Treatment pattern

There have been randomized trials on many drugs on patients around the globe where COVID-19 is wide spread that is both herbal and orthodox medications yet none have been clinically accepted and certified to be used worldwide. Is because of this that the researchers realized four particular drugs been used in various countries affected with COVID 19 and the success rate kept increasing and improving. Almost all affected countries with steady clinical improvement in morbidity and reduced mortality used these set of drugs (REMDESIVIR, FAVIPIRAVIR, HYDROXYCHLOROQUINE, CHLOROQUINE) while others added AZITHROMYCIN and CORTOCOSTEROIDS as polytherapies. The researchers shall base their analysis and findings on only remdesivir, favipiravir, hydroxychloroquine, chloroquine and Azithromycin.

SARS CoV-2: Virology and Drug Targets

SARS-CoV-2 is purely a single-stranded RNA - enveloped virus, which mainly targets cells through the viral structural spike protein that binds to the Angiotensin - converting enzyme 2 (ACE2) receptor. Following the theory of receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS 2, facilitates cell entry via the Spike protein. Once inside the cell, viral polyproteins are synthesized that encode for the replicase - transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase enzyme. Structural proteins are

synthesized leading to completion of assembly and release of viral particles. Drugs which show high probability of acting as good targets include nonstructural proteins (e.g., 3-chymotrypsin-like protease, papain like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathway.[5]

REVIEW OF POTENTIAL PURPOSEFUL DRUGS

Favipiravir

Favipiravir, sometimes back was known as T-705. It is a prodrug of a purine nucleotide called favipiravir ribofuranosyl-5′-triphosphate. The nucleotide contains active agent which inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity, however, the agent also demonstrated broad activity against other RNA viruses. It undergoes an intracellular phosphoribosylatioin to be an active form, favipiravir – RTP 9favipiravir ribofuranosyl – 5 – triphosphate) which is recognized as a substrate by RdRp and inhibits the RNA polymerase activity. Since the catalytic domain of RdRp is conserved among the various types of RNA viruses, this mechanism of action underpins a broader spectrum of anti-viral activities of favipiravir.[6]

Favipiravir is effective against a wide range of types and subtypes of influenza viruses including strains resistant to existing anti influenza drugs. In vitro, the EC50 of favipiravir against SARSCoV- 2 was 61.88 μM/L in Vero E6 cells. Various dosing regimens have been proposed based on the type of infectious indication. Dosing variations are likely due to the lower favipiravir EC50 values described against influenza compared with Ebola and SARS-CoV-2.

Doses at the higher end of the dosing range should be considered for the treatment of COVID-19. A loading dose is recommended (2400mg to 3000mg every 12 hours in 2 doses) followed by a maintenance dose (1200mg to 1800mg every 12 hours). The half-life is approximately 5 hours. The agent has a mild adverse effect profile and is overall well-tolerated, although the adverse event profile for higher-dose regimens is limited. Favipiravir is currently available in Japan for the treatment of influenza, but not available in the United States for clinical use. Limited clinical experience has been reported supporting the use of favipiravir for COVID-19. In a prospective, randomized, multicenter study, favipiravir (n = 120) was compared with Arbidol (n = 120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with

moderate infections (71.4%favipiravir and 55.9%Arbidol, P =.019).No significant differences were observed in the severe or severe and moderate (combined) arms.73 These data support further investigation with RCTs of the efficacy of favipiravir for the treatment of COVID-19.

Favipiravir has widely been used in Wuhan china and japan for treating COVID -19 patients and has shown some efficacy and effectiveness. Research shows the ministry of sciences and technology in china has accredited favipiravir for COVID-19 although there is limited data and its methodology to back such claims but is really making some efficacy in both Japan and Wuhan china.[5]

According to Zhang Xinmin an official of the ministry of science and technology China a hospital in Shenzhen treated patients with favipiravir tested negative for the virus after a median four days rather than 11 days it took members of the study's control group to test negative. A study carried out in Wuhan, indicates that patients taking the drug allegedly recovered from fever nearly two days earlier than those who did not take the medication.[8]

Such results be it preliminary and unconfirmed as they may be would seem to confirm with the way favipiravir works, unlike most influenza treatments which inhibit the spread of the virus across cells by blocking the enzyme neuraminidase, favipiravir works by inhibiting the replication of viral genes within infected cells,, there by mitigating the virus ability to spread from one cell to another. This also means that patients who in practical terms take the drug while their viral load is low or moderate may prevent it from making them any sicker. And there is some evidence that favipiravir can achieve these same effects in viruses other than influenza.[5,7]

REMDESIVIR

Is a broad-spectrum antiviral originally designed for Ebola treatment but was ineffective in most preclinical trials in university of North Carolina and Vanderbilt University before the pandemic it showed a promising character against a wide range of viruses including corona viruses. Remdesivir, formally known as GS-5734, is a monophosphate prodrug that undergoes metabolism to an adenosine analogue which incorporates into nascent viral RNA chains and results in pre mature termination. Currently, remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent invitro activity against several nCoVs, including SARS-CoV-2 with EC50 and EC90 values of 0.77 μM and 1.76 μM, respectively. In murine lung infection models with MERS-CoV, remdesivir prevented lung

hemorrhage and reduced viral lung titers more than comparator agents. The safety and pharmacokinetics of remdesivir were evaluated in single- and multiple-dose phase 1 clinical trials. Intravenous infusions between 3mg and 225mg were well tolerated without any evidence of liver or kidney toxicity. Remdesivir demonstrated linear pharmacokinetics within this dose range and an intracellular half-life of greater than 35 hours. Following multiple-dose administrations, reversible aspartate aminotransferase and alanine transaminase elevations occurred. The current dose under investigation is a single 200mg loading dose, followed by 100-mg daily infusion. No hepatic or kidney adjustments are recommended at this time, but initiation is not recommended in patients with an estimated glomerular filtration rate less than 30 mL/min.

Remdesivir was recently given on a compassionate use basis to 53 critically ill patients hospitalized in the United States, Canada, Europe and japan. Clinical improvement was observed in 68% of the patients treated, according to an analysis made in the New England journal of medicine. Each patient was given at least one dose of remdesivir and evaluated during a median follow up of 18 days. According to the study results 36 patients (68%) had an improvement in oxygen support class including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated.

An estimated total of about 25 patients (47%) were discharged and 7 patients (13%) died, mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation. Remdesivir is the only antiviral drug of promising effects and seven clinical trials on going to determine its safety and effectiveness against the COVID 19. That been said there is an existing data of about 25% patients receiving remdesivir having severe side effects including multiple organ dysfunction syndrome, septic shock, acute kidney injury and low blood pressure. Another 23% demonstrated evidence of liver damage on lab tests.[9]

AZITHROMYCIN

Azithromycin belongs to a macrolide antibiotic with a 15-member lactone ring. It is believed to have high potential for tissue penetration and antimicrobial activity against a wide range of gram negative and gram-positive bacteria. It has the following anti-inflammatory effects; reduction in pro inflammatory cytokine production 1 and hastening of macrophages phagocytosis ability. Strong antiviral activity actions have been reported on azithromycin. Because of its already mentioned antibacterial and anti-inflammatory effects, it is therefore

used for chronic obstructive pulmonary diseases (COPD), asthma, intestinal lung diseases, bronchiectasis and cystic fibrosis. Although Azithromycin is an antibacterial agent patient with viral pneumonia from COVID 19 can also develop a secondary bacterial infection that may need to be treated with antibiotic and verily are these common as a complication in the diseases of COVID 19 reported.[10]

It is said that Azithromycin may work synergistically with other antiviral treatment. Some research has proven that in vitro laboratory azithromycin has demonstrated antiviral activity against zika virus and against rhinoviruses which cause common cold.

Studies indicate that from a very small clinical trial which enrolled 20 patients with COVID 19 in France, patients were treated with hydroxychloroquine alone or in combination with azithromycin. Viral loads were significantly reduced in patients receiving hydroxychloroquine than those who did not and it cleared the virus more quickly than those who did not receive hydroxychloroquine BUT the virus elimination was even more efficient in 6 patients in the trial who received both azithromycin and hydroxychloroquine.

There is hope for such a combination trials with azithromycin and hydroxychloroquine but more research needs to be done the areas since the sample size for the France trials was small and efficacy tracing of azithromycin only on COVID 19 needs to be experimented and in more patients and effects well documented.[11]

CHLOROQUINE

This is a widely used anti-malarial and autoimmune disease drug. It is known to be a cheap drug used for more than 50 years but is also known to have potentially serious heart side effects disrupting heart rhythms given higher doses as revealed in a study done in brazil by medRxiv where 450mg twice a day for one day and them one a day for four more days and 600mg twice a day for 10 days and this resulted in about 25% of patients in the latter 600mg group developing heart rhythm problems and more deaths occurring in that group. It blocks any viral infection by increasing endosomal P^H required for the virus or cell fusion as well as interfering with the glycosylation of cellular receptors of SARS CoV.[12] In addition to the antiviral activity, chloroquine has immune – modulating activity which may synergistically enhance its antiviral effect *in vivo.*[13] Chloroquine is usually distributed to the whole human system including the lungs after oral administration. Some studies done shows the EC90 value of chloroquine against 2019 – nCoV is Vero E6 cells was higher. Dosing of

chloroquine to treat COVID-19 has consisted of 500mg orally once or twice daily. However, a paucity of data exists regarding the optimal dose to ensure the safety and efficacy of chloroquine. Hydroxychloroquine dosing recommendations for SLE generally are 400mg orally daily. However, physiologically based pharmacokinetic modeling study recommended that the optimal dosing regimen for hydroxychloroquine in COVID -19 treatment is a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily. In contrast, alternative recommendations are made for 600mg total daily dose based on safety and clinical experience for Whipple disease. Further studies are needed to delineate the optimal dose for COVID -19. Chloroquine and hydroxychloroquine are relatively well tolerated as demonstrated by extensive experience in patients with SLE and malaria. However, both agents can cause rare and serious adverse effects (<10%), including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy. Baseline electrocardiography to evaluate for prolonged QTc is advisable prior to and following initiation of these medications because of the potential for arrhythmias, especially in critically ill patients and those taking concomitant QT - interval prolonging medications such as azithromycin and fluoroquinolones. No significant adverse effects have been reported for chloroquine at the doses and durations proposed for COVID-19. Use of chloroquine and hydroxychloroquine in pregnancy is generally considered safe. A review of 12 studies including 588 patients receiving chloroquine or hydroxychloroquine during pregnancy found no overt infant ocular toxicity.[5]

HYDROXYCHLOROQUINE

So far study results for hydroxychloroquine are inconclusive. Results from the primary controlled study of hydroxychloroquine for treating COVID – 19 showed no significant difference in outcomes between those two received it through standard care. In step with a study from Shanghai public health clinical center in china, 30 patients hospitalized with confirmed COVID 19 between February 6 and February 25, have half the patients who randomly received 400mg of hydroxychloroquine per day for five days additionally to plain care et al. up to the mark group who only received standard care saw disease progression as statistically similar although there was evidence of a discount in viral load.

On the contrary initial results from a placebo-controlled trial of hydroxychloroquine at rennin hospital of Wuhan university in Wuhan china indicate that patients hospitalize with mild COVID 19 recovered more quickly with addition of the drug than placebo at the beginning of

a customary treatment pattern. Within the trail 62 patients at the hospital were randomized to receive either a placebo or 200mg of hydroxychloroquine twice daily for five days additionally to plain care. 31 of the patients given hydroxychloroquine reported a standard blood heat and cessation of cough much quicker in comparison to 31 patients given a placebo. Within the same study a bigger number of patients on hydroxychloroquine also demonstrated an improved chest CT, 61% showing significant improvement.

No high-quality evidence exists for the efficacy of chloroquine/hydroxychloroquine treatment of SARS or MERS. A news briefing from China reported chloroquine was wont to treat a series of quite 100 COVID-19 cases leading to improved radiologic findings, enhanced viral clearance, and reduced disease progression.

However, the trial design and outcomes data haven't yet been presented or published for referee, preventing validation of those claims. A recent open-label nonrandomized French study of 36 patients (20 within the hydroxychloroquine group and 16 within control group) reported improved virologic clearance with hydroxychloroquine, 200 mg, orally every 8 hours compared with control patients receiving standard supportive care. Virologic clearance at day 6, measured by nasopharyngeal swabs, was 70% (14/20) vs 12.5% (2/16) for the hydroxychloroquine and control groups, respectively (P =.001).

The authors also reported that addition of azithromycin to hydroxychloroquine in 6 patients resulted in numerically superior viral clearance (6/6, 100%) compared with hydroxychloroquine monotherapy (8/14, 57%). Despite these promising results, this study had several major limitations: a little sample size (only 20 within the intervention arm and only 6 receiving hydroxychloroquine and azithromycin); the removal of 6 patients within the hydroxychloroquine group from analysis because of cessation of treatment resulting from critical illness or intolerance of the medications; variable baseline viral loads between hydroxychloroquine monotherapy and combination therapy groups; and no clinical or safety outcomes reported. These limitations including concerns of additive cardiotoxicity with combination therapy don't support adoption of this regimen without additional studies. Another prospective study of 30 patients in China randomized patients to hydroxychloroquine, 400 mg, daily for five days plus standard of care (supportive care, interferon, and other antivirals) or standard care alone during a 1:1 fashion; there was no difference in virologic outcomes. At day 7, virologic clearance was similar, with 86.7%vs

93.3%clearance for the hydroxychloroquine plus standard of care group and standard care group, respectively (P >.05).[5,14]

Limitation of Study

Due to the everyday changing in treatment pattern of the COVID 19 and the everyday trials, researchers had little literature review that added much of clinical observation and practice as to the care of persons infected with the COVID -19 disease. Secondly the need to publish the little wok piece to enable scientist and researchers to use it as a measure and build on it for a wider and broader research in the pursuit of a suitable and efficient and accurate drug for SARS CoV 2 and COVID as a whole to save the world from such a pandemic.

Recommendations

The researchers recommend the science community to carefully study the antiviral effect and the synergistic activity of AZITHROMYCIN if it can add up to and supplement remdesivir and favipiravir in the treatment of COVID 19 since the cardio toxicity effect of chloroquine seems to be severe.

CONCLUSION

The researchers see the threat and fatal distress of the COVID-19 pandemic to the world and assures the science community and the general population that there is constant work been done to find solutions and a potent and efficient drug or vaccine for the pandemic and all should maintain the world health organization's preventive measures of self-isolation, avoiding crowded places for now, constant hand washing with soap under running water, the use of alcohol based hand sanitizers and face mask till a certified drug of choice is approved for use by the world.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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