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Antagonist Co-Administration of Antiviral Remdesivir with Chloroquine in Patient with COVID-19 Taking ACEI Drug in Hypertension

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Abstract: Coronaviruses a positive-sense single-stranded RNA genome ,belong to a family of enveloped viruses that infect humans and animal. They are cause respiratory diseases like severe acute respiratory syndrome coronavirus(SARS), .Middle East respiratory syndrome (MERS) and the emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), the causative agent of the disease "COVID-19". The protocols of therapy for treatment COVID-19 is used some drugs like hydroxychloroquine, chloroquine phosphate, remdesivir, andlopinavir/ritonavir. The FDA emergency revoked use the combination of hydroxychloroquine and chloroquinein the cure of COVID-19. It has been noted that the patients suffer from cardiovascular disease are increased risk of severe COVID-19. This may be due to the use of angiotensin-converting enzyme(ACE) inhibitors or blockers of angiotensin receptor (ARBs) in diabetic, hypertensive, or patients suffer from heart failure. This may be explained by the fact that ACE inhibitors and ARBs drugs enhance ACE2 blockers in epithelial cells lining the lung, where SARS-CoV-2is more likely to infect these cells via ACE2 receptors. Similarly, ACEI and ARBs drugs are shown to interact with several antiretroviral drugs leading to increase viral load. The chloroquine have antagonistic effect with remdesivir which leads to decrease therapeutic activity of remdesivir.

Results: The results of obvious studies may highlighted the risk of combination therapy of hydroxychloroquine and chloroquine with ACEI and probably with ACE2.

Purpose: The objective of this review is to highlight on the risk of combination use of antiviral drug – Remdesivir – with antimalarial drug – Chloroquine – in patient treated with antihypertensive angiotensin converting enzyme inhibitors drug (ACEI)

Keyword: COVID-19, SARS, Remdesivir, Chloroquine, Antagonist effect, ACEI.

1. Introduction

Early 1960s, Coronaviruses are discovered and thought are responsible for slight disease, as common cold, like HCoV 229E and HCoV OC43. They are a belong to a group of enveloped viruses which is a positive-sense single-stranded RNA genome that cause disease to humans and animals (Andersen et al .,2020). Between all families of coronaviruses, this type are responsible for severe acute respiratory syndrome coronavirus (SARS), coronavirus that related toMiddle East respiratory syndrome (MERS) and the emerged severe acute respiratory syndrome coronavirus2 (SARS-CoV-2), that causes

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"COVID-19". Respiratory and intestinal regions can infected by Coronaviruses in animals and humans and causes SARSthat pandemic in 2002 and at 2012 cause MERS outbreak (Son, 2019). These considers zoonotic infections thatresulted mortality more than 10% and 35%, respectively. Most recently, China reported to the World HealthOrganization (WHO) cases of pathogenic viral pneumonia in Wuhan, Hubei Province, China caused by SARS-like pathogen which named later as SARS-CoV-2 (Zhou, 2020). Officially ,this outbreak is confirmed by the WHO on March 11, 2020 as a global pandemic (WHO, 2020) spreading everywhere including the Middle East and Iraq.

2. Therapy for COVID-19

Due to its new discovery, the treatments for COVID-19 vary among many countries and there wasn't protocol available by the WHO to follow. Recommendation were directed to managing of symptoms, developing preventive measures particularly targeting pediatric patients, pregnant women with chronic diseases and patients with underlying co-morbidities. Currently, WHO licensed a new treatment for COVID-19 (remdesivir)according to patient's clinical condition, and in severe cases WHO is recommended and should be given empiric antimicrobialtherapy, together with mechanical ventilation. Subsequently, various therapeutic protocols were implemented for treatment of COVID-19, which is hydroxychloroquine, chloroquine phosphate, and remdesivir \or lopinavir (Chen et al., 2020, Safa Tahmasebi et al., 2020, Colson et al.,2020).

3. Angiotensin converting enzyme (ACE)

The reninangiotensin system (RAS) demonstrated a significant role when there is incidence of hypertension. Meanwhile, the inhibitors of ACE (ACEIs) and the antagonists of angiotensin receptor (ARBs) had an antihypertensive activity. COVID-19 that enters thehost cells via receptors of angiotensin-converting enzyme 2 (ACE2), that is expressed in many organs of human particularly in the epithelial cells lining the lung and small intestine. In addition, coronaviruses also infect the upper respiratoryand gastrointestinal tract of mammals (Guan et al.,2020). The COVID-19 enter via the same cell entry receptor ACE2 by interact with it in humans, and can use Chinese horseshoe bats receptors , or ACE2 of pig but not receptors of mouse species ACE2 to enter cells via this receptor (Wan et al.,2020). Moreover, ACE2 receptors are important site for binding to the spike (s-glycoprotein) of coronaviruses (Wrapp et al.,2020). Therefore, uses ACEI and ARB as antihypertensive drugs for treatment patients suffer from COVID-19 could be increased the complication by combination antiviral therapy.

4. Remdesivir

Remdesivir was proved by the FDA as a promising anti-COVID-19 therapy due to its antiviral activity for inhibition the replication of SARS-CoV-2 *in vitro* and it is the first treatment agent for COVID-19 to be recommended (FDA,2020). Remdesivir is a nucleotide analogue used as a substrate for large numbers of complexes of viral RNA-dependent RNA polymerase (RdRp) leading to inhibit synthesis of RNA of virus by a special mechanism that delayed the termination of chain in all types of coronaviruses like (MERS-CoV, SARS-CoV and SARS-CoV-2) (Figure 1) (Gordonet al.,2020). In addition, the use of Remdesivir drug can reduced viral loads in the lung and lung damage after incubaions with MERS-CoV in nonhuman study (Wit et al.,2020).

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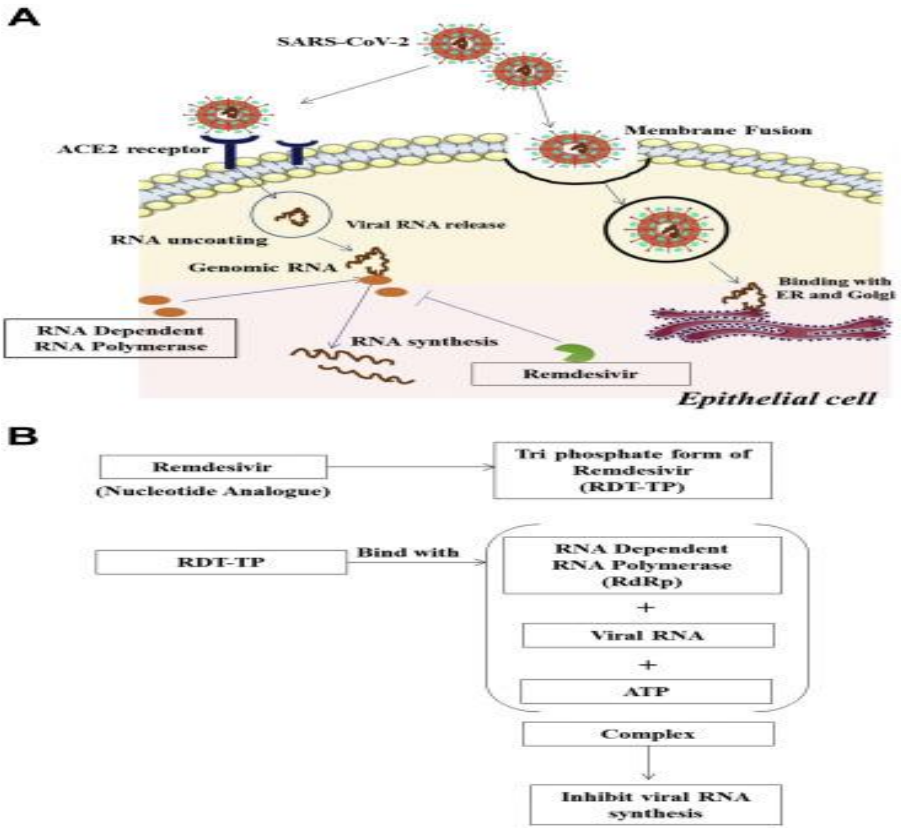

Figure (1). The mechanism of action of Remdesivir against Coronavirus

Chloroquine\Hydroxychloroquine

Chloroquine is consider as aminoquinolone derivative which was used in first time in 1940s for treatment malaria disease. Chloroquine and hydroxychloroquine(Chloroquine derivatives)have also been used in the treatment of a many medical cases such as HIV/AIDS, rheumatoid arthritis also systemic lupus erythematosus(Chen et al.,2011). The mechanism of action of Chloroquine can be achieved through protonation the membranes of cell and diffusion through endosomes,lysosomes, and Golgi vesicles;the chloroquine trapped inside organelle leading to pH rise. This raised of pH inside endosomes, prevent the particles of virus of using its activity needed for fusion then enter to the cell (Ducharme and Farinotti, 1996). It is shown that Chloroquine can't affect the expression levels of ACE2 on cell surfaces, its stopped the glycosylation termination of ACE2-. If the ACE2 not glycosylated, it render it low efficient for interaction with the spike protein of SARS-CoV-2, and lead to inhibit the viral entry (Wang et al.,2020). The FDA authorized use of hydroxychloroquine drug and chloroquine for treatment the pandemic COVID-19 was introduced in 15 June 2020 (FDA, 2020)and which have approval much earlier in 1949 (FDA, 2020).

6. Interaction of Remdesivir and Chloroquine

The combination therapy in which remdesivir was given with either chloroquine phosphate or with hydroxychloroquine sulfate is no supported by a non-clinical laboratory study. Such recommendation is based on the conclusion made that the co-administration reduces remdesivir's antiviral activity. The FDA declares the anti-viral effect was only seen in a non-clinical setting. It has not been observed

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among clinical observation carried out on COVID-19 patients (FDA, 2020). During an *in vitro* study of the co-administration of these drugs, established "antagonistic effect according to dose-dependent for chloroquine on the activation of metabolic intracellulary and activity as antiviral drug of remdesivir (Wang at al.,2020)." In addition, when remdesivir and chloroquine phosphate were incubated together at appropriate concentrations at clinical in HEp-2 cells that infected with respiratory syncytial virus (RSV), the antiviral activity of remdesivir was antagonized (Muratov, and Zakharov, 2020).

7. Antagonistic effect between Remdesivir\and Chloroquine

The Previous studies have shown that the remdesivir has a significant antagonistic activity against malarial drugs, ex: hydroxychloroquine, mefloquine, and the amodiaquine (Figure 2). The effects of hydroxychloroquine usage (10 μM and lower) have completely removed the antiviral function of in vitro remdesivir (Tesia Bobrowskia et al.,2020). A higher dose of hydroxychloroquine, on the other hand, demonstrated synergism with remdesivir. This differential effect of interaction (low-concentration antagonism and high-concentration synergism) indicates that there are interaction between remdesivir and **chloroquine** (Tesia Bobrowskia et al.,2020).

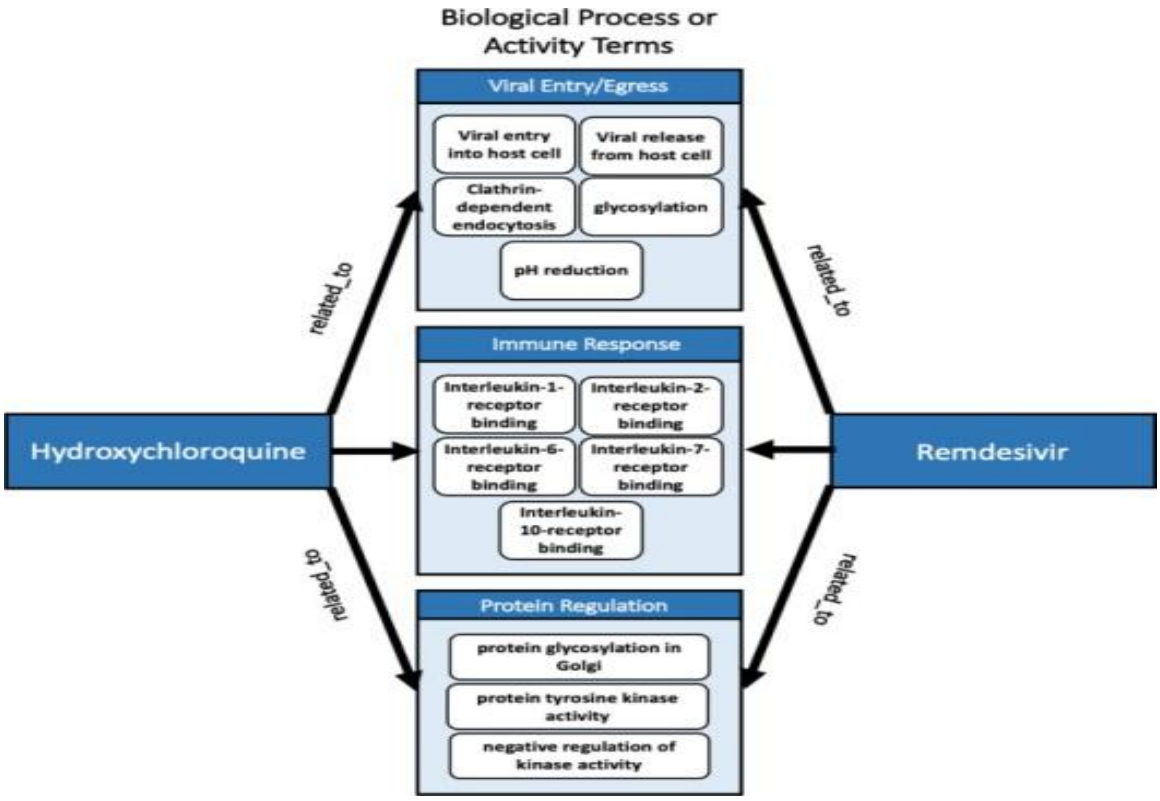

Figure (2). Antagonist effect between the Remdesivir and Chloroquine

Both the hydroxychloroquine\ and remdesivir are associated with several factors that penetrate the host cell, such as' clathrin-dependent endocytosis.' "inflammatory response"; "reduction of pH"; "negative regulation of activity of kinase"; and "activity of protein tyrosine kinase." Investigation of these pathways will establish the common interactions with both drugs to identify potential targets where the

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two drugs could interact and induce antagonist effect in one or more of these biological processes (Chen et al.,2016). Hydroxychloroquine is a well-known serine-threonine kinase (GSK-3β) inhibitor which is used to control the viruses replication like dengue-2 and SARS-CoV. Similarly, SARS-CoV N protein phosphorylation controlled by GSK-3 (Wu et al.,2009), thus leading to downregulation of RNA synthesis (Embi et al.,2020). Remdesivir, on the other hand, has no known activity or association with kinase activity. The activity of the RNA-dependent RNA polymerase is known for inhibition (RdRp) of the SARS\CoV-2. As a result, further analysis by computers revealed that hydroxychloroquine's inhibition the GSK-3βmay have important role in the antagonistic effect against remdesivir (Cuartas-López and Gallego-Gómez,2020).

8. Interaction between antihypertensive and Chloroquine

It is known that a number of antihypertensive drugs may interact with several antiretroviral drugs. Pharmacokinetic interactions with diuretics, kidney-excreted β-blockers, ACEI, and ARBs other than losartan and irbesartan are less than expected. Furthermore, calcium channel blockers (CCBs) are normally metabolized in the liver by the CYP3A4 enzyme, with the possibility of association with antiviral drug groups of NNRTIs and PIs (Baekken et al.,2008). There is much more risk of extreme Corona virus19 in cardiovascular disease patients. In patients suffering from diabetes, hypertension, or heart disease, this increased risk may be due to the use of ACEIs or ARBs. The fact that these drugs may be increased the ACE2 expression , which also can expressthe susceptible cells to SARS-CoV-2 infection through ACE2 receptors, can explain this sort of association (Fang, 2020, Cao et al.,2020). The compounds that can increase level of the expression of the ACE2 receptors have for that reason, Scientific and medical experts have received a key emphasis where increased the ACE2 receptors expression andcanmake SARS-CoV2 more infectious, which can lead to increased viral load, morbidity and mortality (Vaduganathan et al.,2020; Zaid et al., 2018) . ACE2 inhibitors can affect mRNA expression of ACE2 and ACE2 activity in tissues. Inhibition of Corona virus by targeting cellular ACE2 receptor is thus theoretically exciting, but the practical results do not inherently serve the disease control strategy and may potentially increase mortality (Chen et al.,2020). The study on the use of ACE inhibitors for all patients with pre-existing hypertension and COVID-19 infection is worth remembering (Sun et al.,2020). In hypertension, ACE inhibitors have a correct balance between the formation of ACE2 and ANG II, where such inhibitors can decrease the ACE2 receptors regulation via reduce formation of ANG II in patients with Coronavirus, resulting in increased viral load (Glowacka et al .,2010). There are other variables, such as nicotine and vitamin D, in addition to ACEI and ARBs via increased potassium intake (Badreh et al.,2019). In addition, ACE2 RNA expression levels in human lung tissue showed that expression ofACE2 viral receptor is aggregation in a limited numberof alveolar type II cells (AT2) (Gonzalez et al.,2019). Interestingly, AT2 cells not only expression the receptors of viral, but also cause expression for more than 20 other genes strictly linked for replicationand propagation of viruses. This relationship between these cells (AT2) and other SARS-CoV2 susceptibility coreceptors can serve to develop a new treatment strategy against worldwide epidemics in the near future (Glowacka et al.,2010).

9. Conclusion

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As ACEI increases expression of ACE receptors, this leads to increase viral loads and exacerbate disease progression. Further, the chloroquine and its derivatives have antagonist effect with remidesvir which lead to decrease therapeutic activity of remedisvir against COVID-19. These findings indicate that combination therapy of chloroquine (in low dose) with ACEI and remedisvir cannot be advised for patients with hypertension history and infected with COVID-19. Therefore, manymore clinical studies are required to assess susceptibility of Coronavirus and for corresponding single or combination therapies in patients suffer from hypertension cured with ACEI inhibitors drugs.

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