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Insight into Literatures of COVID-19 and Possible Repurposed Pharmacological Drugs

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Abstract

COVID -19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has threatened worldwide populations with high morbidity and mortality. In search for countermeasures, tremendous scientific work and publications have been released. Based on that, we reviewed the most relevant scientific articles and reports published by the PubMed, World Health Organization, American Food and Drug Administration and many scientific journals including those from Europe, China and Korea to summarize drugs used in treatment of COVID19 from a pharmacological view. This review displays and summarizes the recent literatures on COVID-19 and repurposed drugs focusing on their mechanism of actions. Since there are no specific antiviral drugs have been approved for SARS-CoV infections, weak base drugs with known mechanism of actions through in vitro studied have been utilized. These weak base drugs such as chloroquine, hydroxychloroquine, azithromycin, ciprofloxacin become protonated and ionized in acidic endosomes /lysosomes by different degrees leading to increase in their pH and subsequently suppression of the enzyme functions and viral processing. In addition, corticosteroids have been used in severely ill COVID-19 patients for their immune-modulation properties. Nevertheless, these drugs still need confirmation for their use by randomized clinical trials.

Conclusion: These drugs have shown effectiveness in suppressing virus development and propagation at the outbreak in spite not being undergone randomized clinical trials.

Keywords: SARS-CoV-S infection, Chloroquine/hydroxychloroquine, Azithromycin, Corticosteroids.

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لمحة عن مرض كوفيد 19 والأدوية العلاجية الممكنة والمعاد استخدامها

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ملخص الدراسة

المقدمة: إن مرض COVID -19 الذي يسببه فيروس الالتهاب الرئوي الحاد سارس كورونا 2 (SARS-CoV-2) يهدد البشرية في جميع أنحاء العالم بارتفاع معدلات الوفيات والمراضة. وفي البحث عن التدابير المضادة لهذا المرض، تم إصدار منشورات علمية بأعداد هائلة. واستناداً إلى ذلك، قمنا بمراجعة أهم المقالات والتقارير العلمية ذات الصلة التي نشرت في مقالات Pub Med، ومنظمة الصحة العالمية، وهيئة الأغذية والعقاقير الامريكية، والعديد من المجلات العلمية بما في ذلك تلك الصادرة عن أوروبا والصين وكوريا لتلخيص الأدوية المستخدمة لعلاج كوفيد19 من وجهة نظر دوائية. يستعرض هذا المقال ويوجز ما نشر علميا عن COVID 19 والأدوية المعاد استخدامها مع التركيز على آلية عملها. ونظرا لعدم توافر أدوية مضادة للفيروسات محددة تمت الموافقة عليها لعدوى السارس - CoV مسبقا، فقد تم استخدام عقاقير ضعيفة القاعدية وذات آلية معروفة في الدراسات المختبرية. هذه القواعد الضعيفة مثل الكلوروكين، هيدروكسي كلوروكوين، أزيثروميسين، وسيبروفلوكساسين، تصبح بروتونية ومتأينة في lysosomes الحمضية / وإندوسومات بدرجات مختلفة مما يؤدي إلى زيادة في قاعدتيها وبالتالي قمع وظائف الانزيمات والمعالجة لتكاثر الفيروس. بالإضافة إلى ذلك، فقد تم استخدام الكورتيكوستيرويدات في الحالات الشديد ة لمرضى COVID-19 وذلك لخصائصها في تعديل وكبح التفاعلات المناعية. ومع ذلك، تحتاج هذه الأدوية الى تأكيد لاستخدامها من خلال التجارب السريرية العشوائية.

الاستنتاج: أظهرت هذه الأدوية فعالية في قمع تطور الفيروس وانتشاره عند تفشي الوباء على الرغم من عدم خضوعها لتجارب سريرية عشوائية.

الكلمات المفتاحية: عدوى السارس-COV-S، الكلوروكين/هيدروكسي كلوروكوين، أزيثروميسين، كورتيكوستيرويدات.

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Introduction

The pandemic outbreak of coronavirus disease 2019 (COVID-19) has represented a challenge for health care system in almost every country. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], has threatened worldwide populations with high morbidity and mortality, so the urgent need to understand SARS-CoV-2 as a virus, COVID-19 as a disease and possible approaches for its management and prophylaxis has led to worldwide collaborative actions. A tremendous scientific work and publications have been released based on development of countermeasures, comprising therapeutics with the goals of lessening disease severity and to come up with prophylaxes including vaccines [2].

At the time of the COVID-19 outbreak, there are no specific antiviral drugs or vaccine against it. The first option at that time was to use broad spectrum antiviral drugs such as Nucleoside analogues and also HIV-protease inhibitors till availability of specific agents [3]. Remdesivir, an investigational drug, has been tested and shown efficacy against 2019-nCoV infection in vitro [4]. Clinically, administration of Remdesivir to a hospitalized patient with pneumonia and COVID-19 has shown improvements in clinical signs of the disease and recovery as reported in a case study by Sodani *et al* [5]. Clinical trials have shown the effectiveness of Remdesivir in shortening the time to recovery in adults who hospitalized with COVID-19 and lower respiratory tract infection [6]. Further ongoing clinical trials are required for evidence of its place in treatment of SARS-COV-2 infection.

In march 2020, the Food and Drug Administration (FDA) in the United States approved the emergency use of chloroquine phosphate (CQ) and hydroxychloroquine sulfate (HCQ) in treating COVID-19 mainly for adolescents and adults who have been hospitalized and who cannot be a part of clinical trials [7]. Later on, the combination of HCQ and azithromycin have shown benefits based on the finding of viral load reduction in patients with COVID - 19 in initial clinical trials [8]. In line with the use of antimicrobial agents in viral infections, ciprofloxacin has also shown the same mechanism like azithromycin and CQ against SARS-CoV-2 in vitro which required validation of its effect in COVID-19 patients [9]. The aim of this review is to demonstrate the recent published scientific reports on SARS-CoV-2 infection and the repurposed drugs focusing on their mechanism of actions. Therefore, we reviewed the most relevant scientific articles and reports published in Pup med, WHO, FDA, and many scientific journals including those from Europe, China and Korea.

Aspects of SARS-CoV-2 Infection

Coronaviruses are grouped into alpha, beta, gamma, and delta [10]. Among them four types can cause mild respiratory symptoms like the common cold, including 229E, OC43, NL63, and HKU [11], while SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 can cause severe respiratory diseases [12].

Once inside the infected cell, viruses in general can trigger a series of host responses including autophagy, apoptosis and innate immunity [13]. It has been reported that almost 80% of SARS-CoV-2 infected persons are associated with mild clinical symptoms while the rest may encounter acute respiratory distress syndrome (ARDS) or death [13].

In sighting the pathophysiology of SARS-CoV-2 one can reveal that it almost resembles SARS-CoV but with aggressive inflammatory response resulting in air way damage [14]. Thus, the disease severity is due to both the viral infection and the host response including increment of severity with the age [15]. In terms of immune-pathology, the disease course can be seen as **infectious phase**, **immune response** and **hyperinflammatory phase** during which infected patients recover or become severely ill or the uncontrolled inflammation may lead to cytokine storm with multi-organ failure ending with death [14].

Infectious Phase

Early studies have shown that SARS-CoV infection starts with binding to ACE2 expressing cells such as airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung [16,17]. Recently, it has been reported that SARS-CoV-2 uses the same targets and bind to ACE 2 cell surface receptors as the SARS-CoV [18]. Once SARS-CoV-2 enters the host cell, the receptor ACE2 are cleaved and shaded by ADAM metallopeptidase domain 17(AMAD17) [19]. Thus, SARS-COV-2 infection suppresses ACE 2 expression. Since ACE 2 is a counter regulator of RAS [20], its downregulation leads to dysfunction of RAS with increasing Ang 2 activity including impacts on blood pressure, fluid/electrolyte balance and enhancement of inflammation and vascular permeability in the airways [21]. Therefore, it reflects its pathological aspects.

The spike (S) protein expressed on the surface of the virus particles attaches to host ACE 2 receptor. Receptor-mediated conformational changes [22] induce exposure of cleavage site within viral glycoprotein that follows by proteolytic (cathepsin, TMPRRS2 or furin-like protease) cleavage of S protein into subunit 1 (S1) and subunit 2 (S2). S1 includes the receptor-binding domain (RBD) which attaches to ACE2 receptor on host cells starting the infection process [1]. This binding triggers endocytosis of the SARS-CoV-2 virus, and then exposes it to endosomal proteases [22]. On the other hand, S2 contains the fusion peptide (FP) region that facilitates fusion with the host cell membrane in acidified endosomes releasing the viral genome into the host cytoplasm where replication occurs.

Immune Response

At this stage, the infected cell senses the existence of virus replication through specific intracellular pattern recognition receptors (PRRs) that detect virus formed aberrant RNA structures [23]. Interaction between PRRs such as Toll-like receptors (TLRs) and aberrant viral RNA activates IRFs (interferon regulator factors) and NF-$_k$B (nuclear factor kappa-light-chain-enhancer of activated B cells) [11,13] which **launch** two general antiviral programs. The first represents a

cellular antiviral defense that induces the interferons (IFNs; mainly IFN I and IFN III) [24] and the second involves the *recruitment* of specific leukocytes (monocytes and macrophages) in the affected area releasing pro-inflammatory cytokines, including IL1, IL6, TNFα, and chemokines (proteins promote motility and directional migration) like CCLs [25]. This process aims at clearing the pathogen and most patients with adequate immunity recover.

Blanco-Melo *et al*. (2020) reviewed the host response to SARA-CoV-2 and demonstrated a failure to launch a robust IFN I and IFN III responses to SARA-CoV-2 in spite virus replication, which is accompanied with a higher recruitment of effector cells [14]. Thus, this waning immune response enables a sustained viral replication which may explain why individuals with comorbidity or older populations may frequently experience serious courses of COVID-19 [26].

Inflammatory Responses Early Response

As in case of any viral infection, when the ACE 2 expressing cells are infected with SARS-CoV-2, the virus actively replicates and then releases new viruses. The SARS-CoV-2 replicative cycle can injure the infected cells leading to their death [27]. In air way epithelial cells, SARS-CoV-2 infection and replication can cause a highly inflammatory type of programmed cell death called pyroptosis [28] that is associated with vascular leakage, as has been evident in patients with SARS-CoV [29]. During pyroptosis, an important cytokine (IL1β) is released which has been shown to be elevated in patients infected with SARS-CoV-2 [15]. Cells undergo pyroptosis release the damage associated molecules such as ATP, nucleic acid and cell contents which trigger a local immune response recruiting macrophages and monocytes. These cells release cytokines which induce and prime T and B cell for immune response. Often, in most cases, the infection does resolve by this pathway, but in some patients, disfunction of immune response can occur leading to severe lung damage.

Secretion of these cytokines and chemokines attracts monocytes and T-lymphocytes from the blood into the infected site [26]. So, as a part of explanation of lymphopenia and increased neutrophil-lymphocyte ratio might be the infiltration of lymphocytes with recruitment of the immune cells from the blood into the air way. In addition, some studies reported lymphopenia might be due to the direct virus killing of lymphocytes where they reported its presence in macrophages [30], T lymphocytes and monocytes derived dendritic cells [31]. This has been seen in almost 80% of patients infected with SARS-CoV-2. In most cases, the migrated immune cells clear the infection in the lung or elsewhere, then the immune response withdraws and the patients recover.

Late response

Occasionally, in some patients, the occurrence of a dysfunctional immune response triggers a cytokine storm that induces widespread inflammation in the lung. In accordance with this, the observation was that patients with severe COVID-19 requiring intensive care in hospital showed higher blood

plasma levels of IL (IL 2, IL 6, IL 7. IL 10) macrophage inflammatory protein 1α (MIP1α), tumor necrosis factor (TNF) and granulocyte colony- stimulating factor (G- CSF) [12]. Moreover, the peripheral blood of patients with severe but not mild COVID-19 shows a higher percentage of inflammatory monocytes which release inflammatory cytokines contributing to cytokine storm.

Repurposed drugs Chloroquine / Hydroxychloroquine

Chloroquine and its hydroxyl derivative, hydroxychloroquine, are amphiphilic weak bases that share properties in pharmacology and chemistry [32]. They were predominantly used for treatment and prevention of malaria as well as inflammatory diseases [33]. Both drugs have shown pleiotropic actions including antiviral actions [34] promoted their involvement in treatment of COVID-19.

Chloroquine, the first potent antimalaria, was synthetized as an analogue to quinine [35]. Later on, hydroxychloroquine has proposed as a safer alternative to chloroquine by adding a hydroxyl to chloroquine. Both have good absorption profile with nearly 75% in fasting subjects [36-38]. Their absorption is unaffected by food. Since absorption is determined by the extent and the rate, interindividual variability in the extent of absorption has been reported, which in part account for the individual variability in chloroquine and hydroxychloroquine effectiveness and toxicity [37,38]. Nevertheless, the peak plasma concentration of the drug reaches in 4-12 hours after a single dose and the steady state level is usually achieved after 4-6 weeks of regular doing [39]. On chronic use their metabolites including desethylhydroxy-chloroquine affect the plasma levels. Due to extensive distribution and tissue uptake and also volume of distribution the elimination half-life ranges between 40-50 days [40]. Excretion is mainly through renal with limited excretion by the bile, sweat and saliva. Acidification of urine enhances its elimination. Thus, the pharmacokinetics of 4-aminoquinolines is complex because of differential sequestration and accumulation in various tissues [36].

Mechanisms of Chloroquine/ Hydroxychloquine Action the Primary mechanism of Action

The primary mechanism of action of chloroquine is based on its weak basic feature (also called cationic amphiphilic character) which allows the drug to be protonated in acidic medium. This protonation which depends on the Pka (it is a measure for a chemical species to donate or accept a proton; and in case of chloroquine, it accepts a proton in acidic medium) of the drug leads to increase in the pH of the affected targets or organelles producing pleiotropic effects (such as blockade of enzyme functions, inhibition of protein and cytokines production) that have been utilized in research in targeting host functions required for viral replication that might be of benefit in different clinical conditions.

Chloroquine and hydroxy-chloroquine have the same mechanism. Chloroquine is a weak base with Pka of 8.1and 10.1 due to its two-positive nitrogen ions in the molecule [41]. So, in plasma at a physiological pH 7.4, 18% of

chloroquine is monoprotonated (means protonation of one nitrogen only) but still lipid soluble and can cross cell membrane. On the other hand, lysosomes have a pH between 4 and 5 that is maintained by an active transport of protons from the cytosol into the lysosomes [42]. Chloroquine is bi-protonated in lysosomes, and sequestered where it cannot diffuse back out into the cytoplasm [43] leading to accumulation. This action increases the pH of the lysosomes from the base line four to six [41], Figure 1.

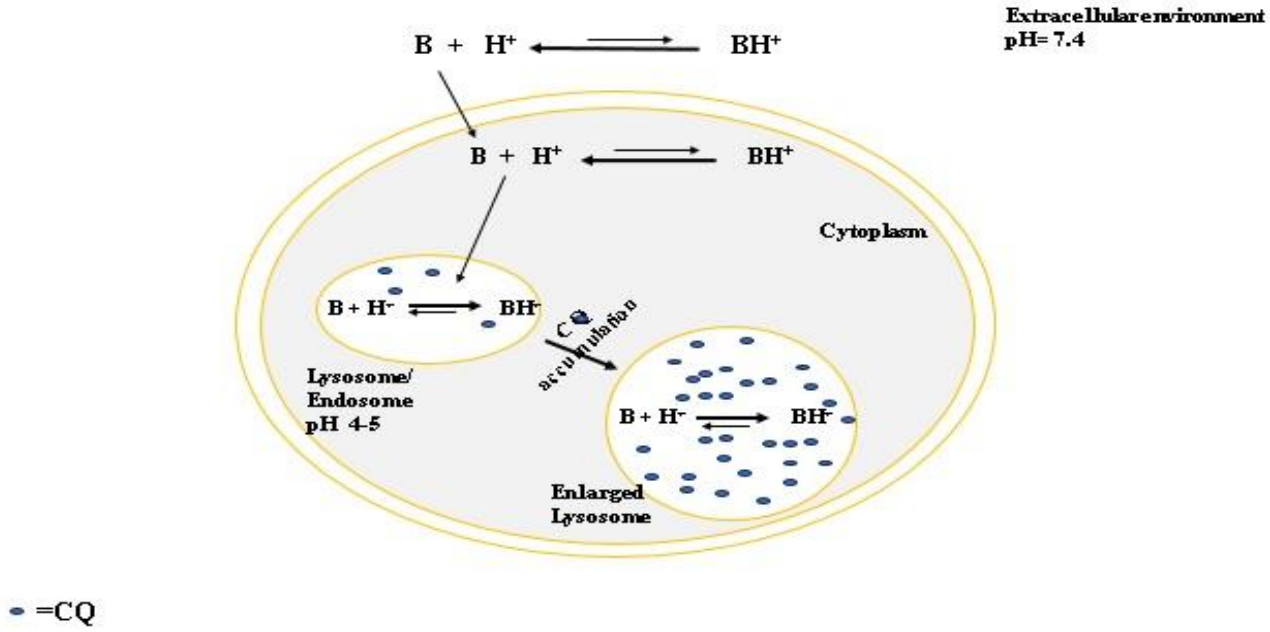

Figure 1: Simplified Depiction of the Primary Mechanism of Action of Chloroquine

Chloroquine molecules are a weak base presented in an amphiphilic form with Pka 8.1 & 10.1, in physiological medium (pH 7.4) depending on Pka some molecules attract protons (H+) and become monoprotonated but still lipid soluble and enter the cell or lysosome/endosome (B). In lysosome where pH is lower (4-5), they become di-protonated and more ionized (BH+) and cannot leave the lysosome, accumulate and the lysosome enlarges with increase in the pH. Thus, enzymes function and viral or pathogen processing are inhibited.

Antimalaria Mechanisms

Based on the primary mechanism, chloroquine is one of the autophagy inhibitors antimalaria drugs. The antimalaria mechanism of action of chloroquine ensues when it accumulates in the food vacuole of the parasite after protonation where it increases the pH and suppresses the enzyme heme-polymerase which acts to change the released toxic heme into non-toxic hemozoin. Then, the free heme lyses the cell membrane leading to parasite death and the housing red blood cells, too [40].

Immunomodulation Mechanisms

With the discovery of hydroxychloroquine benefits in autoimmune-disorders many in vitro and in vivo studies investigated its

possible mechanistic activity on innate and adaptive immunity. It has been found that it preferentially targets autoimmunity without interfering with adaptive immunity that is necessary for fighting off the pathogens [44]. It is well known in immune responses that PRRs in the infected cell recognize the abnormal pathogenic products such as viral RNA and activates antiviral or antipathogenic program including NF-kB in antigen presenting cells that release pro-inflammatory cytokines like IL1, IL6 and TNF. Chloroquine blocks this pathway by increasing pH and suppression of enzyme functions and cytokines production [45], Figure 2.

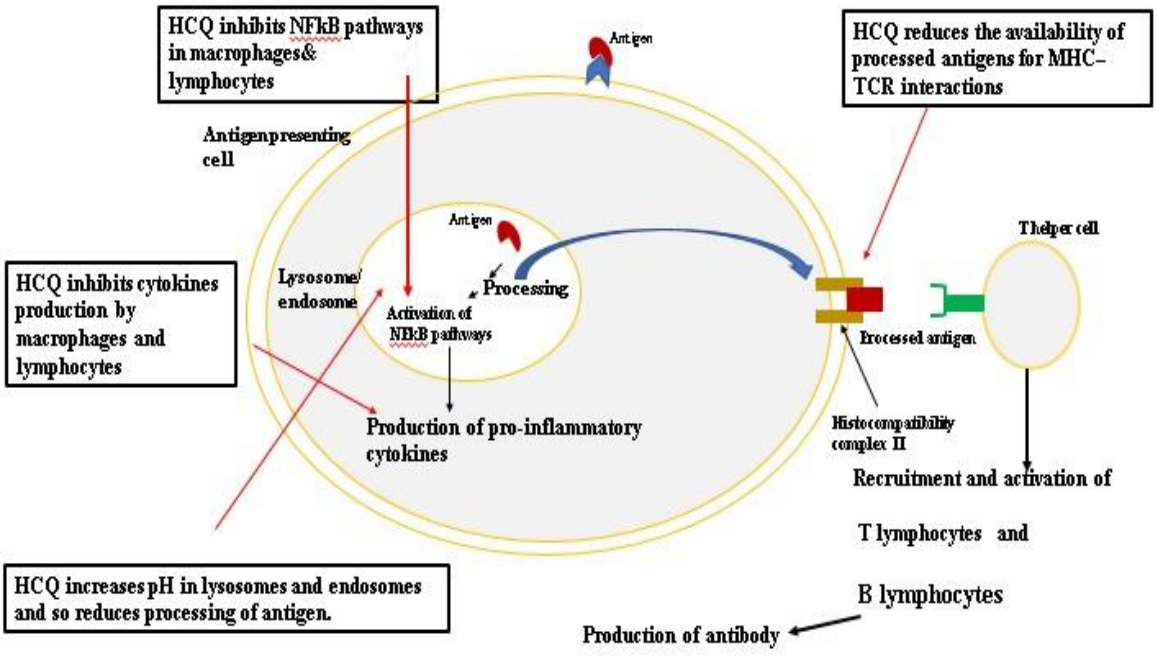

Figure 2: Proposed Antiviral and Immunological Actions of Chloroquine /Hydroxychloroquine

MHC=Major histocompatibility complex II, TCR= T cell receptor

Moreover, the acidic environment in lysosomes of immune cells is necessary for digesting and processing the antigenic peptide that is eventually presented to T-cell through major histocompatibility complex (MHC) where the interaction between MHC and T-cell receptor (TCR) forms complex (MHC-TCR) [40]. This leads to downstream activation of T- and B-cells with production of targeted T-cells (NKC) and autoantibodies. Here also chloroquine reduces the processing of antigenic peptide and also the availability of processed peptide for MHC-TCR interaction, Figure 2. The benefits of chloroquine have been shown in patients with lupus when long term use of chloroquine is associated with reduced pro-inflammatory cytokines [46]. Silva *et al*. (2013) demonstrated chloroquine induced reduction in cytokines release in patients with

systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [47].

Antiviral Mechanisms

The history of chloroquine activity as antiviral stands from long time laboratory studies in various cell cultures and animal experimentations where it shows inhibition of replication of human immunodeficiency virus (HIV), human influenza A, Zika, Ebola, dengue virus and SARS-CoV-2 viruses [4,48-52]. Clinical studies have also shown inconsistent outcomes [53] and even could not confirm significant beneficial effects in a number of viruses, which may be attributed to poor methods and reports as well as urgency of the outbreak situation. So, high quality designed randomized controlled clinical trials of chloroquine and hydroychloroquine might be the standard key for elaboration of strong evidence [45].

The antiviral mechanism of these drugs stands for their primary mechanism of action (protonation in acidic organelles) related to their basic structure where in addition to elevation of endosomes/lysosomes pH, CQ and HCQ inhibit autophagosome-lysosome fusion and inactivate enzymes that viruses require for replication [30]. Besides that, CQ is able to change the glycosylation of ACE2 receptor and spike protein leading to prevention of SARS-CoV entry [50]. Moreover, elevation of lysosomal pH inhibits MHC class II-dependent antigen processing and presentation by monocytes as well as MHC class II presentation to CD4 T cell [54]. This might be of beneficial effects in autoimmune-diseases due to reduced production of cytokines, lymphocytes and nature killer cell (NKC) activity [55].

Chloroquine/ Hydroxychloroquine and COVID-19

In search for urgent treatment for COVID-19 outbreak, CQ presents as an existing drug, offers a pragmatic alternative that has shown to be beneficial in shortening the course of SARS-CoV2 disease, alleviate inflammation in response to infection, improves lung function and decreases viral replication [55,56]. CQ/HCQ involvement in the treatment of COVID-19 is based on various studies that examined the antiviral activity of CQ and its derivatives in vitro, some examples are present in Table 1, [4, 57-60]

Table 1: Antiviral Activity of Chloroquine/Hydroxychloroquine in Vitro Studies

Author/year/reference	coronavirus type	Study	Outcome
Vincent et al ./2005/[57]	SARS-CoV	In a pre-and post-infection, Vero cells were infected and treated with CQ and ammonium chloride	-In pre-treatment tail, a concentration dependent decrement in SARS-CoV infection was found -in post treatment, CQ at higher concentration abolish almost completely the infection and its spread to nearby cells in culture.
Yao et al /2020/[58]	SARS-CoV-2	Pharmacological activity of CQ and HCQ were studied in Vero cells and pharmacokinetics was tested too.	Both drugs showed antiviral activity in vitro with superiority to HCQ. They decreased viral replication.
Wang et al /2020/[4]	SARS-CoV-2	The study tested the antiviral activity of CQ in VeroE6 cells with other compounds.	CQ showed time dependent antiviral activity at entry and at post entry stages in Vero cells.
Keyaerts et al/2004/[59]	SARS-CoV	Activity and toxicity of CQ against SARS-CoV were tested in Vero E6 cells.	A higher concentration of CQ was needed 3-day post-infection to inhibit viral replication.
De Wilde et al/2014/[60]	SARS-CoV MERS-CoV	A library screening for FDA approved compounds against MERS-CoV in Vero cells.	CQ inhibits MERS-CoV replication in vitro, and blocked the replication of SARS-CoV, too.

The drugs are associated with common adverse reactions such as GIT effects (nausea, vomiting and diarrhea), prolongation of QT intervals and induction cardiovascular disorders in susceptible individuals [61].

Azithromycin (Az)

The broad-spectrum macrolide azithromycin was chemically synthetized in 1980 to extend the macrolide antibacterial activity [62]. It shows good therapeutic effects in treatment of bacterial infections in respiratory and gastrointestinal tract as well as genitourinary tract with safe profiles where it acts by inhibition of bacterial protein synthesis through binding to 50S ribosomal subunit of the microorganisms [63].

Findings of early clinical studies by Gautret *et al* (2020) showed the benefit of azithromycin in treatment of COVID-19, Table 2, [8,64]. For more data and details on clinical and in vitro studies can be found in Ref by Damle *et al* [65]. For determination of the validity of this benefit, different investigations have been performed in vitro and in vivo to demonstrate the potential antiviral activity of this drug, although it is not approved as antiviral agent. Several in vitro studies have shown its antiviral activity against different viruses [66,67] including Zika virus. Schogler *et al* (2015) demonstrated

the mechanisms of antiviral action of azithromycin in cystic fibrosis bronchial epithelial cells in vitro in which after pre-treatment with azithromycin, rhinovirus (RV) replication was reduced without induction of cell death, while RV-induced PRRs, IFN and IFN-stimulated gene mRNA levels were increased [68]. Similarly, Li *et al*. showed that azithromycin upregulates the expression of PRRs, host type I and III interferons (IFN I and IFN III) and IFN-stimulated genes in response to ZIKA virus or other viruses [66].

Table 2: Early Studies on Azithromycin in Patients with SARS-Cov-2 Infection

Study design	Drugs used	Study outcome	Remarks	Reference
open-label non-randomized clinical trial	hydroxychloroquine (HCQ) alone or in combination with azithromycin (Az)	reduced viral load in coronavirus disease 2019 (COVID-19) patients.	-A single-arm, nonrandomized study in Marseilles, France -AZ was added to prevent bacterial superinfection in a subset of patients, while untreated patients from another center and those refusing treatment served as unmatched controls	[8]
uncontrolled observational cohort study	Hydroxychloroquine combined with azithromycin	-improvement in all cases (80 COVID-19 patients) except of 86-year patient with advanced irreversible state - a rapid fall in viral load tested by quantitative PCR (qPCR) was reported	-single-arm study - advised to perform an ECG at the treatment begin for patients with co-morbidity	[64]

The question is why azithromycin is added to chloroquine in coronavirus-2 infection. In a small uncontrolled study of hydroxychloroquine to COVID-19 patients, the investigators noticed the achievement of a virologic response by reducing viral load in six patients receiving azithromycin for prevention of bacterial infection [8]. Several studies support its benefits in COVID-19 patients [65]. In line with this and to explore its mechanisms, it has been reported that azithromycin as well as ciprofloxacin alter the pH within intracellular organelles which accounts for their actions in respiratory epithelia in cystic fibrosis [9] (previously though to kill the

microbe pseudomonas by antibacterial actions). This action as previously mentioned, is attributed to chloroquine [69]. Moreover, Az inhibits autophagy in respiratory epithelial cells [70]. These effects in part overlap with chloroquine action which enable azithromycin and ciprofloxacin to be involved in treatment of COVID-19, theoretically any weak basic drugs that disturb the acidic environment of lysosomes and Golgi network can be a candidate for use in COVID-19. Altogether, the antiviral activity of azithromycin lies in increment of the pH in endosomes and lysosomes of infected cells leading to inhibition of viral replication and boosting the host own innate immune response to the virus [65].

Corticosteroids (CS)

Corticosteroids are pharmacological active agents suppress immune responses. Their effects are dose and duration dependent. By almost understanding the course of COVID-19, several researchers and scientists suggested that CS may be effective in COVID-19 and their effects vary according to the course of the disease. Thus, CS appeared in COVID-19 treatment guidelines [71,72] for those hospitalized with severe illness.

As mentioned before, three phases can be differentiated in COVID-19; early phase of infection, pulmonary and hyperinflammation phase [73]. In the early stage (almost seven days), infection occurs due to the virus while in the second and third stages, varied intense inflammatory responses seem to be causative, 7-15 days from disease onset. Some patients admitted to the intensive care unit 7-15 days after symptoms onset might develop critical illness. So, those critically ill patients are in the hyperinflammatory state [74]. Since corticosteroids are anti-inflammatory agents, it is suggested to have beneficial effects in this phase. A supporting view might be that reported by Xu *et al* (2020) in which patients died by COVID-19 showed pathological finding of pulmonary edema and hyaline membrane formation [26] which could be attributed to proteases and reactive oxygen species secreted by infiltrated inflammatory cells and the virus as well [75]. In fact, these responses limit gas exchange causing breathing difficulty and low blood gas that have been noticed in severely ill COVID-19 patients and exposed them to secondary infection.

It has been reported that the early use of anti-inflammatory drugs is not necessary and may worsen the course of viral infection [76]. This can be partly explained by the two overlapping pathological stages; firstly; it is triggered by the virus and the secondly by the host response [73] which then can be separated into early host response with dominant local inflammation and late systemic inflammation with multiorgan dysfunction [73]. Once CS are used in critically ill patients, it should not be rapid discontinued but gradually tapering to preserve the improvement gained by their administration [74].

Although, treatment with CS is based on protocols that are recommended by the Corticosteroid Guideline Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) for critically ill patients even those with acute respiratory distress syndrome (ARDS) [77], still some questions about efficacy, time of initiation, and appropriate duration

of use are unanswered [71,72]. Nevertheless, CS have shown to reduce mortality in COVID-19 patients with life threatening cytokine storm [78].

Conclusion

The rapid use of old drugs with known mechanism of actions which made them candidates for treatment of COVID 19 has suppressed the outbreak of SARS-CoV-2 infections mainly in patients with severe disease, but still needs confirmation by randomized clinical trials and validation of their efficacy in vivo.

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