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Internal Medicine: Open Access

Review Article

Treatments against SARS-CoV-2, Current Perspectives: A Review

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ABSTRACT

This review is intended to provide a comprehensive overview of plausible therapies for SARS-CoV-2. Literature on drugs such as PLpro protease inhibitors, CLpro 3, RNA helicase, and Spike protein is reviewed. Likewise, the efficacy of interferons (innate immunity) and also of monoclonal antibodies (adaptive immunity) is evaluated. In addition, preliminary results on the use of active principles extracted from plants that may have antimicrobial properties are included. A review of the literature is made, which provides data on drugs with potential use to counteract COVID-19, which have been carried out over the course of months, huge *in vitro* and clinical trials, in controlled and randomized studies, on how positions like Hydroxychloroquine and Chloroquine. Guidelines agreed by medical institutions and advances, findings so far, will also are evaluated.

Keywords: SARS-CoV-2; COVID-19 therapy; COVID-19 treatments

INTRODUCTION

SARS-CoV-2 is an enveloped, positive RNA virus, included in the order Nidoviridae and of the Coronaviridae family, with a genome of around 32 kilo bases [1-3]. With the ability to adapt to diverse contexts and species, due to its recombination capacity, its genome has high mutant potential, which increases the possible range of host range and varied tropism for different types of tissues. A classification of four genera, δ, β, γ α, is usually attributed. Type's β and α are transmitted to humans, also with zoonotic behavior in bats, type β generates a complex of acute and severe symptomatic manifestations at the respiratory level [4,5]. Its transmission can be through the air, by inhalation, when speaking with the release of droplets to a person who is in close contact with the patient, or through the formation of aerosols when coughing or sneezing. The means of entry can be the nose, mouth, mucosa of the eye. Fomites are also a medium of transmission, which include contact with objects or surfaces [6-8].

The installed disease state comprises a constellation of multiple affected organs, including the cardiorespiratory system, cough, shortness of breath, like a picture of pneumonia that may well progress rapidly over a period of days and atypical, to severe deterioration of the gastrointestinal respiratory function; Diarrhoea, and central nervous system. Also included are alterations of the circulatory system, with the appearance of coagulopathies, or hematopoietic, lymphopenia. And systemic symptoms of fever, general malaise, feeling of fatigue, or pain in multiple areas of the body, including the articular ones [9,10].

The initial approach to the clinical picture is oriented to the control of the symptoms, rising in the aggressiveness scale according to the needs of the patient, or the evolutionary course of the disease [11].

It is estimated that pre-existing chronic respiratory symptoms, and concomitant with high air pollution, can exacerbate inflammatory responses, which worsen and pose a worse prognosis, and a higher fatality rate [12-15].

Therapies proposed for treatment include drugs of different categories according to the symptom-oriented intervention focus, namely Favipiravir, Remdesivir, Ritonavir, Lopinavir, and Hydroxy Chloroquine (HCQ), Chloroquine (CQ) [16-21]. The response to treatment of possible patents is evaluated, describing the range of options available at the time [3].

We proceeded with exploration of databases in Science, Elsevier, Oxford, Wiley, CDC, NEJM, JAMA, BMJ, using terms such as SARS-CoV-2, therapy, patents. Tracing studies in the preliminary results phase, excluding duplicates, incomplete texts, access-only payment. At first, both descriptors in title and in the

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Received: August 03, 2021; **Accepted**: August 24, 2021; **Published**: August 31, 2021

Citation: Carlos MV, Lina MV (2021) Treatments against SARS-CoV-2, Current Perspectives: A Review. Intern Med. 11: 347.

summary of the collected texts were examined, then extensive sections of content were evaluated, of which the objectives of the study were identified, and therapy proposals measured in their effectiveness. The PRISMA methodology was used as an article evaluation route. Classifying the search results, according to the type of treatment or established therapeutic target, the time range for the selection of texts includes the date of publication in the period 2020-2021, cocktail of drugs, active principles, and their derivatives, structure molecular.

By cataloging drugs according to whether they act on the virus itself, blocking signaling pathways at some stage of the synthesis and replication of genomic material, its RNA, or inhibiting a crucial viral enzyme necessary for receptor coupling, virus-cell binding, and reproduction, or that reinforce the cellular immune defense system, both at the level of innate and adaptive response, counteracting immediate infection, and replication; use of interferons. The antiviral role of a drug can be to reinforce the innate defense system or attack some component of the viral structure. In both cases the objective is to counteract the replication load [22,23].

The ability of the virus to enter a cell or to bind to a certain protein can be inhibited. SARS-CoV-2 uses the Angiotensin-Converting Enzyme 2 (ACE2) receptor as an entry target, unlike MERS-CoV, which binds to the Dipeptidyl Peptidase Receptor 4 (DPR4) [24].

The Angiotensin Converting Enzyme 2 (ACE2), in addition to being an entry route, also exerts a mediating effect on the innate response system, stimulating the production of cytokines both in favor of inflammation, as well as anti-inflammatory in nature. Participating in this way, in the activation downstream in the cascade of immunological events in response to SARS-CoV-2.

A first line of treatment is given to the development of wide-ranging antimicrobial strategies, such as the use and reuse of antivirals within which a wide spectrum fits, such as those prescribed for pneumonic pathology, whether they are Ribavirin inhibitors or interferons. Some avant-garde projects are aimed at the discovery or synthesis of new compounds with antiviral effect, for example β-1b (Betaferon). Database screening of molecules that demonstrate inhibition of the cytopathic viral effect, or a certain blocking profile of certain pathological characteristics. Another strategy has been the search for a better understanding of the genetic information of the virus. Elucidate how the virus reacts to a different treatment. The determination of its response profile and the immunopathological reaction according to the effects of a specific antiviral, opens horizons of therapeutic alternative, among these, the use of viral protease inhibitors, interferons and specifically directed Monoclonal Antibodies (MAbs).

MONOCLONAL ANTIBODIES

As a treatment regimen, passive immunization using MAbs can theoretically counteract viral replication, neutralizing or prophylactically decreasing the rate of rapidity of spread. Thus, target points are structural proteins of the virus. The potential of MAbs to have a favorable impact on the clinical condition has been demonstrated by *in vivo* and *in vitro* studies. An example of this fact has been the development of monoclonal antibodies directed to the peak protein in SARS-CoV-1 and MERS-CoV in DPP4 mouse models [24].

MAbs can be manufactured with the ability to bind to the peak protein in specific regions of their gene product, thereby interfering with their binding to the ACE2 receptor, and consequently, subsequent steps in the immune response cascade [25].

XenoMouseTM mice have been reported with fragments of loci in the heavy and light chain of Immunoglobulin [IG], containers of repeat sets and homologs of human genes with the potential to manufacture MAbs with antigen specificity [26].

Likewise, it has been possible to produce MAbs with specific binding to the S2 domain of the peak protein, with an effective neutralizing capacity in both MERS-CoV and SARS-CoV-1, which block the formation of syncytia between those cells that express infected the S protein and the ACE2 receptor.

INTERFERONS

Interferons (IFN) produced in cells stimulated in response to the detection of a pathogen, act on the cells themselves and their neighbors. INFs α and β type I produced promptly by innate response to a viral attack have been shown to be immunomodulators that inhibit the replication of SARS-CoV, in *in vitro* studies and *in vivo* models. While Ribavirin, IFN-α-2a, shows an inhibitory effect against MERS-CoV. Interferons α-n3 (Alferon), α-n1 (Wellferon), (Multiferon) have shown inhibitory effects on replication, in the treatment of Vero E6 cells from samples of patients with MSS, on the one hand, they interfere with the cytopathic effect, and on the other, they do not show cytotoxicity related to IFN concentration. Other studies, however, do not show a significant difference with placebo in items such as viral load reduction or clinical improvement [25,27].

PROTEASE INHIBITORS

Protease inhibitors have within their target, type 3C protease (3CLpro), whose structure is conserved in all CoV types [28]. One sample is Benzhydrylpiperazine, a non-peptidic SARS-CoV-1 inhibitor, which decreases the volume of the protease interaction zone, occupying hydrophobic bonding spaces. Inhibitory potential has been found in Acamprosate sodium, with an inhibition rate that exceeds that of the previous drug. Isatin-5-amide, derivatives of isatin with a quantitative measure of semi-maximum inhibitory concentration of 0.95 μM, has been used for the same purpose, yielding greater potency and selectivity against 3CLpro SARS-CoV-1 [29]. In another study, a constant IC50 between 0.516 and 5.954 μM was obtained *in vitro*, using asymmetric aromatic disulfides with a competitive action to 3CLpro, inhibiting the replication rate [30]. Likewise, compounds with methyl and ethyl ester groups have shown the ability and specificity to form covalent bonds with protease, resulting in inhibition. Quercetin has also shown antioxidant activities that reduce the formation of free radicals and an inhibitory effect of the inflammatory cascade, which affects respiratory function.

Viral helicase (nsP13) is a protein that participates in the progress of viral replication; it has been targeted by substances such as Baicalein, with the ability to inhibit the hydrolysis of nsP13. Compounds such as Amento flavone have also shown an inhibitory effect, preventing the RNA of helicase from unwinding. Icariin interferes with the ATP hydrolysis of nsP13. It has been found that the substitution of armethyl in the 7-OH position of Quercetin also has inhibitory activity, as does the Aryl Diketoacid Derivative (ADD), an analog of pyrophosphate, hindering the unwinding of the double strand of viral DNA, hydrolyzes Nucleoside Triphosphate (NTP), releasing nucleic acid. The compound Kanamycin has shown inhibitory activity of Papain-Like Protease (PLpro) in Mers-CoV [3].

Protein S, a type I surface glycoprotein, binds receptors on the cell membrane, fusing it with the viral membrane. Synthetic compounds have been tested that block this fusion at the entry level, thereby reducing viral load [3].

NATURAL PRODUCTS

Among Natural Products (NP) with chemical profiles and antiviral and anti-inflammatory properties, the polyphenolic antioxidant Catechin, flavonoid family, flavan-3-ols subgroup has been studied [3]. At concentrations lower than 30 μg/mL, it showed *in vitro* the maintenance of viable cells, and inhibition of viral replication. Epigallocatechin Gallate (EGCG) Epigallocatechin-3-Gallate, an ester of Epigallocatechin and Gallic acid, has shown a broad-spectrum inhibitory effect on viral infections. Resveratrol 3,5,4'-trihydroxy-trans-stilbene is a Stilbenoid, it has been recognized antioxidant effects and *in vitro* studies it demonstrated potential inhibitor of gene expression and protein synthesis of nucleocapsid N, of cell apoptosis in the MERS, post infection [3].

Baicalein, 5, 6,7-trihydroxydoflavone, a flavonoid derived from fungi Scutellaria baicalensis and Scutellaria lateriflora, with antiviral activity is presented as a therapeutic alternative to correct lymphopenia. Bryostatin-1 (BRIO-1), polyacetylated macrolactone inactivates Protein Kinase C (PKC), under study for its potential as a negative regulator of the cell cycle, by inducing p21, dephosphorylates CDK2 by inactivating it could be used to support the management of the clinical picture of SARS-CoV, including atypical pneumonia.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Hydroxychloroquine as a therapeutic agent for acute respiratory syndrome has been studied in clinical trials, also in controlled trials. The evidence at the moment shows, as a result, important side effects, some of which could be adverse, for cardiac function, arrhythmias and QTc prolongation.

Chloroquine belonging to the group of 4-Aminoquinolines has a half-life of 3.2 hours, reaching plasma levels of between 34 to 79 ng/ml, after 2 to 5 hours.

The toxicity profile of Hydroxychloroquine (RS) -2 –[{4-[(7-chloroquinolin-4-yl) amino] pentyl} (ethyl) amino] ethanol, is lower than that of chloroquine, its mechanism of action interact with DNA, alters the assembly of the α and β chains of the Major Histocompatibility Complex or MHC II, obstructing antigen recognition, and thus, reducing the stimulation of the autoimmune action of TCD4 +, also inhibiting the polymerization of the group, and impacts broad networks of the immunogenic spectrum, with immunoregulatory effects. The maximum plasma concentration of Hydroxychloroquine is reached in a range of 2-4.5 hours. Undesirable effects are consisting of gastrointestinal disorders such as Diarrhoea, nausea. Changes in the retina, atrophy and irregular pigmentation, effects that appear to be dose dependent, with loads above 800 mg. Narrowing of the arteries, edema, opaque deposits of the epithelium, and visual disturbances such as scotomas. However, they are disorders of cardiac function, such as variations in the conduction of the electrical charge impulse, dangerous prolongation of the QTc, and cause for alarm. Electrocardiographic monitoring data, as a dependent variable of comorbidities and concomitant use of medications for chronic pathologies, can be stochastically modulated, by intervening factors, in addition to the use of Hydroxychloroquine. A QTc of 16 ms (95% CI: 9-23 ms) was associated with 600 mg of chloroquine, in healthy patients, while an increase of 28 ms (95% CI: 18-38 ms) was correlated with 1500 mg. These results have been reported in cases of patients who use Chloroquine or Hydroxychlorotine long-term, for prolonged periods. These drugs have shown pharmacological interaction with Ampicillin (Chloroquine reduces its plasma levels), Antacids (they decrease the absorption of Chloroquine), for its part, Cyclosporine, increases the concentration of Chloroquine, Mefloquine (increases the probability of suffering seizures). Other drugs that show interaction are Azithromycin, Cyclosporine, Insulin and Amiodarone, among others.

The use of Hydroxychloroquine concomitant with the administration of Azithromycin has reported an increase in the QTc interval, prolonging it significantly up to 40 to 60 ms above. There is also a possible hemolytic anemia, associated with those with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.

SARS-CoV-2 uses the Angiotensin Converting Enzyme 2 (ACE-2) receptor to enter the cell. Chloroquine inhibits the SARS-CoV-2-ACE2 binding by interfering with terminal glycosylation. Hydroxychloroquine inhibits gangloside binding by preventing the virion-ACE2 bonding relationship. These drugs are added in the Lysosome and Endosome compartments, to the body of the endocytic vesicle. The pH within these compartments becomes more basic, the maintenance homeostasis of these organelles is lost in this new, more basic environment, thereby altering the integrity of the vesicular membrane. Endocytosis processes, in terms of invagination, material transport, and recycling, become dysfunctional, due to loss of the action capacity of the proton pump ATPase in the transport of hydrogen ions, affecting viral replication. SARS-CoV-2 loses potential for entry through membranous organelles, and for propagation, due to degradation of hydrolytic enzymes. The viral genome is exposed to an environment that alters the stability of its genomic structure.

By means of immunofluorescence techniques, it has been shown that the exposure of a cell to the chloroquine agent minimized the replication of SARS-CoV-2, post-exposure. Chloroquine levels of 8.8 ± 1.2 μM reduced the virus replication rate by half, in *in vitro* studies. 6.5 ± 3.2 μM concentrations of Chloroquine in Vero cells also showed this behavior. The prophylactic administration of Hydroxychloroquine in an interval of 48 hours, experimental studies have reported a mean effective inhibition concentration of 5.47 μM for Chloroquine and 0.72 μM for Hydroxychloroquine.

Both in clinical trials and *in vitro* studies of cell lines the viral multiplication rate has decreased with the treatment of these two antiviral agents. Migrating endosomes lead to failures in the transport of ingested materials, as well as in recycling. However, case studies and randomized trials of small cohorts have not yielded a determination of statistical significance to support their results. When making comparisons of patients who were treated with Hydroxychloroquine with patients without such treatment, the group differences, the p value is not less than the level of significance required to reject the null hypothesis that the study drug is not effective. The evaluation in terms of clinical criteria and viral load measurement do not show differences in results. Although there have been isolated studies and case reports of clinical improvement and radiological findings, the administration of Chloroquine is not more effective than the standard choice of treatment. The statistical test does not corroborate the aforementioned findings.

Clinical trials, with small patient samples with open-label, non-piecemeal, unblinded, and randomized controlled study designs, do not report clinical or viral titer results from nasopharyngeal swab samples that show significant differences. Original studies have been published, with Azithromycin and Hydroxychloroquine combination trials showing reports of seroconversion and negative PCR tests on the sixth day of joint administration of these drugs, in addition to clinical improvement in respiratory function and greater probability of survival, and no requirement intensive care. Dosing with different regimens, which included cocktails of antiviral, antimicrobial, and anti-inflammatory medication, accompanied by ventilatory support, and to randomized patients with pneumonia states has shown a reduction in radiological compromise and subjective improvement and in pulmonary ventilation parameters, as well as a decrease in signs and symptoms such as cough, after treatment. The possibility of biased allocation, the participation of confounding variables and poorly defined evaluation criteria must be taken into account when distinguishing differential effects in randomly chosen patients and the use of controls.

In prospective cohort studies, with a small number of patients, dosage regimens that vary in quantity and time range have been established. Establishing in advance comorbidities that could be relevant, as a differential variable, or a new diagnosis, no negative nasopharyngeal swabs were observed at six days of treatment. Some patients worsened requiring an intensive care unit, and one death. References to previous research do not show a statistical estimate from which effect size can be extracted. Samples of participants in these studies were configured without calculation of statistical samples, they do not allow making inferences or extrapolations from the population, or deriving clinical treatment guidelines.

The probability of adverse events such as Arrhythmias and QTc prolongation, due to the use of Chloroquine and Hydroxychloroquine, could increase depending on the concomitant use of other categories of drugs such as Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs), which requires a strict evaluation of cardiac function during clinical trials studying the efficacy of these Aminoquinolones.

The study of Antiretrovirals belonging to the group of protease inhibitors, such as Ritonavir/Lopinavir, in association or not, with Aminoquinolones, has not shown significant differences in terms of clinical improvement in clinical trials. These drugs can increase the plasma levels of Chloroquine, by inhibiting the metabolism of the CYP2D and enzyme, increasing the risk of Arrhythmias and Cardiomyopathies.

The pharmacological arsenal can be categorized into groups according to which it inhibits viral replication, such as Ritonavir (protease inhibitor), and Lopinavir. Another category is the use of plasma transfer from convalescent patients, temporarily and artificially introducing passive immunity. The use of Anti-inflammatory drugs is currently being considered to support symptomatic management, such as the Recombinant Humanized Monoclonal Antibody Tocilizumab, which blocks the binding of IL-6 with its receptor, obstructing its signaling pathway Lenzilumab; IgG1 Kappa class, targeting Colony-Stimulating Factor 2 (CSF2)/Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), in preclinical evidence, interferes with the systemic inflammatory pathway, which involves GM-CSF in association with Chimeric Antigen Receptor (CAR-T), which activates Myeloid cells that produce Monocyte Chemoattractant Protein 1 (MCP-1) and its receptor (CCR2). Other drugs such as Valsartan and Losartan, type 1 Angiotensin II receptor antagonist (AT1) Anti-Hypertensives.

CONCLUSION

The evidence of toxicity, in clinical trials of the use of Hydroxychloroquine (HCQ) and Chloroquine (CQ), in the long term, does not support their use, *in vitro* it seems that CQ increases the pH inside the endosomes, interfering with the introduction of virus, deactivating the point of binding to ACE2. The data showed here invite further studies and therapeutic patent proposals. Finding that, to a large extent, the response to COVID-19 has been supportive therapy.

DECLARATION OF INTERESTS

The authors declare that they have no financial interests or personal relationships that may have influenced the work reported in this document.

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