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"COVID KIT" AND ITS CLINICAL MANIFESTATIONS: A SYSTEMATIC REVIEW

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Abstract: Introduction: With the emergence of Covid-19 and the rapid evolution of the pandemic, the lack of proven effective medicines brought about the need to adopt off-label treatments, with the aim of reducing patients' symptoms, the time of disease evolution and the rate of mortality. Hydroxychloroquine (HCQ), chloroquine (CQ), azithromycin (AZT) and ivermectin (IVT) were the most used medications in Brazil and became popularly known as the "Covid Kit". Objectives: This study was carried out between June 2021 and October 2022 and aimed to evaluate the effectiveness of HCQ, CQ, AZT and IVT, alone or in combination, in the treatment of patients with COVID-19, in addition to verifying possible adverse effects, through a systematic review based on studies carried out on patients with Covid-19 who used these medications as treatment. Methodology: This review used the Cochrane Handbook methodological model. The methodology of the scientific articles that were used for data extraction was evaluated for quality using the Heyland qualification (EQM), considering EQM 8 to be of high quality. The databases used were Pubmed, MEDLINE and Portal Capes. Result: It was found that there are no benefits in the use (in safe doses) of HCQ/CQ, AZT and IVT alone or in combination, in relation to the evolution of the disease, reduction of symptoms and mortality. Despite the initial need to test experimental therapies, the "Covid Kit" currently does not prove to be more effective than usual symptomatic care.
Keywords: COVID-19; therapy; efficiency; adverse effects.

INTRODUCTION

On December 30, 2019, in China, the first cases of atypical pneumonia with an unidentified etiology were reported. After 8 days, the severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2), a new betacoronavirus, was recognized and the disease was named COVID-19 (CEVIK; BAMFORD; HO, 2020). On March 11, 2020, the WHO declared COVID-19 a pandemic (LIU; KUO; SHIH, 2020).

Coronaviruses (CoVs) of the Coronaviridae family are highly pathogenic enveloped positive-sense single-stranded RNA viruses. The entry routes of SARS-CoV into the human body are: respiratory tract, airways and alveolar epithelial cells, vascular endothelial cells and alveolar macrophages. Although SARS-CoV-2 has similarities to SARS-CoV in its genomic structure, tissue tropism and viral pathogenesis, the new beta coronavirus is apparently more transmissible and produces heterogeneous immune responses, and is still poorly understood (HARRISON; LIN; WANG, 2020).

The most common initial symptoms of the disease are: fever, dry cough, myalgia, fatigue, dyspnea and anorexia, which can also lead to diarrhea and nausea. In CT scan results of hospitalized patients, a bilateral distribution of irregular shadows and ground-glass opacity is typically found, which generally relates to the main complications of COVID-19: respiratory distress syndrome, arrhythmia and shock (WANG). et al., 2020). In addition to the usual evolution of the disease, studies indicate that there are several complications that manifest themselves in the long term, such as myocarditis (HARRISON; LIN; WANG, 2020).

The profile of critical patients, with more ICU admissions, was mainly elderly people with other underlying diseases (such as Diabetes and obesity) (WANG et al., 2020), however, with the progression of the pandemic it became clear that not only the senile population was at risk, but also children, young people and adults (HARRISON; LIN; WANG, 2020).

With the emergence of COVID-19, off-

label use of medications became an option, as there were no elucidated and specific drug therapies for the disease. The use of a medication in therapy for a purpose other than that for which it was produced is a common practice in medicine, especially in pediatrics, a specialty that includes few specific pharmacological studies for each age group (GUIMARAES; SOUSA; PINTO, 2021).

Based on the implementation of off-label drug therapy in other countries, in Brazil, Chloroquine (CQ), Hydroxychloroquine (HCQ), Azithromycin (AZT) and Ivermectin (IVM) were widely used in COVID-19 therapy and received the popular name of "Covid Kit".

CHLOROQUINE AND HYDROXYCHLOROQUINE

In 1935, CQ began to be used to treat malaria (GOLAN et al., 2014). It is effective against erythrocytic forms of P. vivax, P. ovale, P. malariae, P. knowlesi and strains of P. falciparum sensitive to CQ. Furthermore, CQ and HCQ are used for the treatment of hepatic amebiasis and are secondary drugs for rheumatoid arthritis, systemic lupus erythematosus, discoid lupus, sarcoidosis, porphyria cutanea tarda and severe light-triggered polymorphic eruption (BRUNTON et al., 2012).

CQ (Figure 1), a 4-aminoquinoline derivative, consists of a weak base that spreads freely across the membrane of the parasite's food vacuole (GOLAN et al., 2014). The d-, l- and dl- forms of CQ have equal potency, but the d-isomer has lower toxicity than the l-isomer in mammals. HCQ (Figure 2), in which one of the N-ethyl substituents of CQ is β-hydroxylated, is essentially equivalent to chloroquine in its action against P. falciparum malaria (BRUNTON et al., 2012).

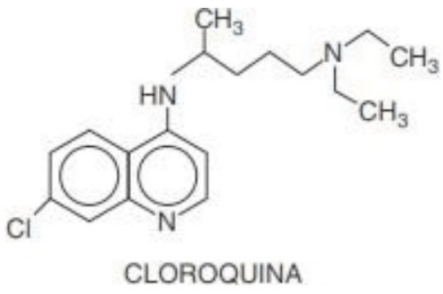


Figure 1: Chemical structure of chloroquine

Source: BRUNTON et al., 2012

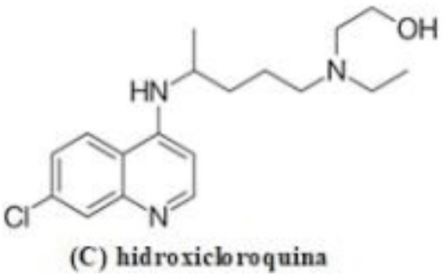


Figure 2: Chemical structure of hydroxychloroquine

Source: ROLIM *et al.*, 2021

These drugs are widely distributed and absorbed by different tissues (liver, lung, kidney tissue, melanin-containing tissues, and nervous tissue).

Because of this, a loading dose is necessary to obtain effective plasma concentrations (BRUNTON et al., 2012).

HCQ is chosen for the treatment of mild forms of rheumatoid arthritis and lupus erythematosus because, when high doses are required, it can cause less ocular toxicity when compared to CQ. When administered orally, the concentration of CQ required to alkalize human cell lysosomes is much higher, conferring the safety of this medication when compared to other routes of administration (BRUNTON et al., 2012).

On the other hand, CQ, when administered in doses greater than the therapeutic dose, presents toxicity mainly related to the cardiovascular system and the central nervous system (CNS), including: vasodilation,

hypotension, suppression of myocardial function, cardiac arrhythmias and risk of cardiac arrest. Confusion, convulsions and coma can be consequences of overdose (from 30mg/kg ingested in a single dose) (BRUNTON et al., 2012; GOLAN et al., 2014).

Because it has a low cost and is available for purchase, chloroquine is used worldwide for suicide, a reflection of its high toxicity when poorly administered. Accidental ingestion by children can also be fatal. (BRUNTON et al., 2012; GOLAN et al., 2014).

Regarding drug therapy care, HCQ and CQ must be used with caution in the presence of advanced liver failure or severe gastrointestinal, neurological or blood disorders. When there are complications of renal function, the dose must be adjusted to avoid high plasma concentrations. CQ can cause serious reactions in patients with psoriasis or another exfoliating skin condition. Furthermore, it reduces the effectiveness of the yellow fever vaccine when administered simultaneously (BRUNTON et al., 2012).

CQ presents a drug interaction when administered together with amiodarone or halofantrine, CQ interacts by opposing the action of anticonvulsants, increasing the risk of ventricular arrhythmias. By increasing plasma levels of digoxin and cyclosporine, CQ may increase the risk of toxicity from these agents (BRUNTON et al., 2012).

AZITHROMYCIN

Antibiotic commonly used in outpatient therapy for the treatment of respiratory tract infections due to its high effectiveness against Streptococcus pneumoniae, Haemophilus influenzae and atypical pathogens. Also used in the treatment of pneumonia, pharyngitis, skin infections, acute exacerbations of chronic bronchitis, for the treatment of sexual diseases that are transmissible, mainly during pregnancy, uncomplicated non-gonococcal urethritis and chancroid, acute otitis media, acute streptococcal pharyngitis and acute bacterial sinusitis (BRUNTON et al., 2012).

The synthetic derivative of erythromycin, AZT, is a macrolide antibiotic that contains a 15-member lactone ring, to which one or more deoxysugars is fixed (Figure 3) (BRUNTON et al., 2012).

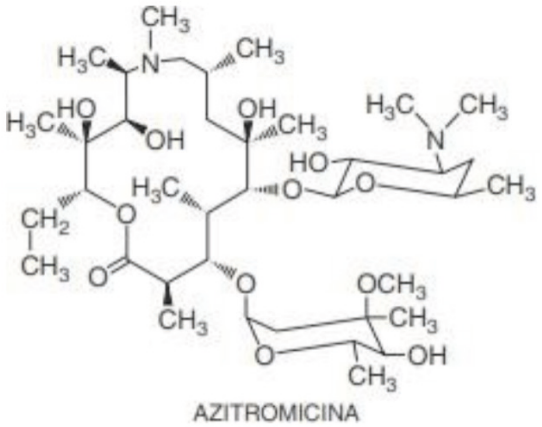


Figure 3: Chemical structure of azithromycin

Source: BRUNTON et al., 2012

After oral administration, this medication is quickly absorbed and distributed throughout the body, with the exception of the brain and cerebrospinal fluid. Thus, the serum concentration of this medication remains below the tissue concentration and secretions, as its pharmacokinetic properties present extensive tissue distribution and high concentrations of the drug inside cells. The main route of elimination of this antibiotic is through biliary excretion, there is still little hepatic metabolism into inactive metabolites and 12% is excreted in its unchanged form in the urine (BRUNTON et al., 2012).

The main adverse effect of AZT is severe hepatotoxicity induced by telithromycin. Such cases generally present a short latency period between the use of the drug and hepatotoxicity, with the possibility of death or liver transplantation. The association of AZT must be avoided with drugs that have been

proven to interact with erythromycin, such as: Ciprofloxacin, Clopidogrel, Fluconazole, nifedipine, carbamazepine, digoxin, ergotamine, simvastatin and loratadine, as it can enhance or decrease the effects of such medications (BRUNTON et al., 2012).

IVERMECTIN

IVT (22,23- dihydroavermectin B1a) is a semi-synthetic analogue of avermectin B1a (abamectin) - used as an insecticide to control crops. IVT is a white, odorless powder, with high lipid solubility and low water solubility (Figure 4) (BRUNTON et al., 2012).

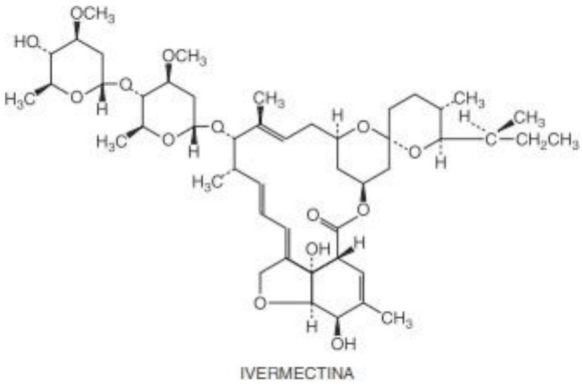


Figure 4: Chemical structure of ivermectin

Source: BRUNTON et al., 2012

IVT is a drug used to control and treat a wide variety of infections caused by parasitic nematodes, such as: in the treatment of onchocerciasis, lymphatic filariasis; strongyloidiasis; ascariasis; enterobiasis. IVT is the first treatment option for cutaneous larva migrans caused by hookworms in dogs or cats, in addition to being efficient as a treatment for scabies (BRUNTON et al., 2012).

Possibly the most likely mechanism of this medication is through binding to chloride channels present in the nerve or muscle cells of nematodes, causing hyperpolarization as a result of the increase in the intracellular concentration of chloride. This induces paralysis of the parasite, immobilizing it (BRUNTON et al., 2012).

This drug has low affinity for receptors present in the CNS, which explains the small number of central neurological side effects (BRUNTON et al., 2012).

The WHO does not recommend the use of IVT by pregnant women, women who are breastfeeding in the first week after birth, children less than 90 cm in height (approximately 15 kg of body weight) and patients in serious condition (WHO, 2006). This drug is contraindicated in patients with blood-brain barrier abnormalities (BRUNTON et al., 2012).

Given the widespread use of these medications in Brazil as a therapy for Covid-19, both in seriously ill patients and as a prophylaxis, and the potential risks that the use of these medications outside of their specific indications present, this work aimed to identify the possible consequences, beneficial or not, of using the "Covid Kit" in patients diagnosed with Covid-19. Furthermore, disseminate the results obtained as a way of assisting rational medication prescription by qualified health professionals.

METHODOLOGY

The research design followed the Cochrane Handbook model for systematic reviews as a methodological model (HIGGINS; GREEN, 2011). The results were expressed according to the main items for presenting systematic reviews (PRISMA) (MOHER et al., 2015). The research is sourced from the Pubmed, MEDLINE and Portal Capes databases, where clinical articles will be identified based on the search terms early treatment in Covid19, AZT, CQ/HCQ, IVM, SARS-COV-2. The methodology of the scientific articles was evaluated for quality, for data extraction, through the Heyland qualification (EQM) (HEYLAND et al., 2014), considering the EQM 8 to be of high quality. The characteristics of the

scientific articles included in the research were extracted by two independent reviewers using a standardized form, including information about authorship; year of publication; study design (crossover or parallel); therapeutic scheme; duration; therapeutic agents; double-blind, single-blind or open study; sample size; health impacts; characteristics relating to participants, funding body and study location. Scientific articles were subjectively assessed for risk of bias: presence of randomization (selection bias); how randomization was performed (selection bias); double-blind or single-blind study; how many participants entered and remained in the study (attrition bias) and whether efficacy and survival data were properly reported (information bias) (HIGGINS; GREEN, 2011).

RESULTS

A total of 28 articles on AZT, 40 on CQ and HCQ and 45 on IVT were selected, totaling 113 articles from the Pubmed, Medline and Portal Capes databases until August 2022. The search was carried out in English and Portuguese, using the following keywords: azithromycin + COVID-19; chloroquine + COVID-19; hydroxychloroquine + COVID-19, ivermectin + COVID-19, adverse effects, prophylaxis, treatment.

Of this sample, 73 were excluded, as they did not fit into the research due to the following factors: 36 systematic reviews or meta-analyses; 10 letters to the editor or editorial; 9 included other medications in the treatment; 6 duplicates; 4 with inconsistencies in the design; 3 used an unusual route of administration of the medication; 3 in vitro studies and 2 observational studies.

Therefore, the systematic review included 40 articles. All clinical trials maintained the same inclusion and exclusion criteria for the research design (Flowchart 1). Randomized clinical trials, natural trials, comparative retrospective cohort studies, pilot studies, proof of concept and retrospective analyzes were considered.

With parallel, crossover, open, phase II, IIb or III, double and single-blind, placebo-controlled or no comparison group, multicenter, adaptive platform or cluster study designs. Furthermore, the study follow-up time ranged from 5 days to 10 months and 9 days, 37 of which were prospective and 3 retrospective ones. The sample size ranged from 26 to 7763 patients, one of which was carried out with 1483 high-risk healthcare professionals.

The study locations varied: 7 studies were carried out in Brazil; 6 in the USA (3 in the USA and Canada); 3 in the United Kingdom, 3 in France, 3 in Spain, 2 in Denmark, 2 in Egypt, 2 in India, 2 in Argentina and 1 in China, Iraq, Nigeria, Lebanon, Italy, Malaysia, Turkey, Iran, Bangladesh and Colombia.

The articles included in the search considered isolated or combined therapy with AZT, CQ/HCQ and IVT. Thus, 3 used isolated therapy with AZT, 8 combined AZT with CQ/HCQ, 1 combined AZT + CQ/HCQ + IVT; 13 maintained isolated therapy with CQ/HCQ and 1 combined CQ/HCQ with IVT; finally, 14 articles demonstrated the isolated use of IVT (Figure 5).

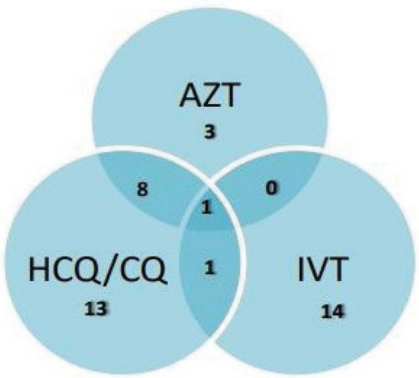
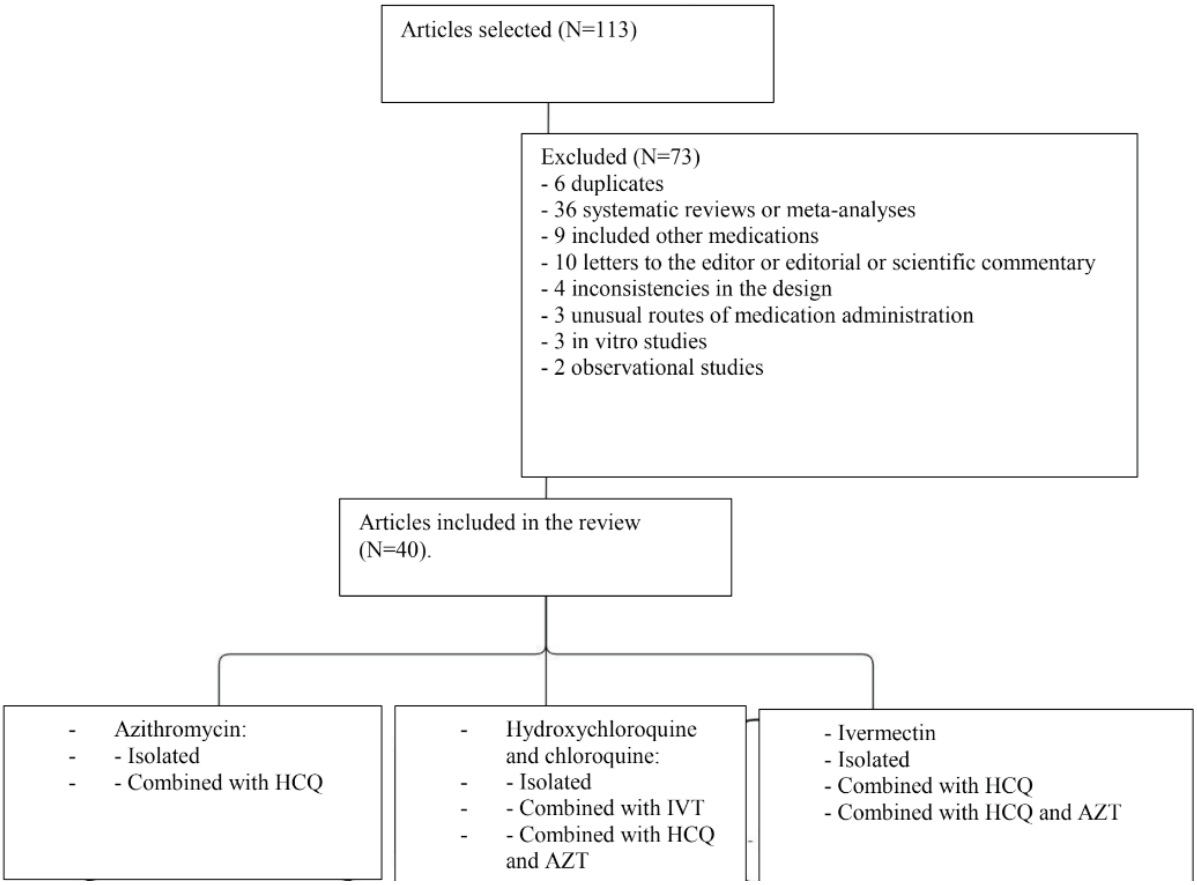


Figure 5: Venn diagram with the 40 selected articles and the type of therapy used (isolated or combined)

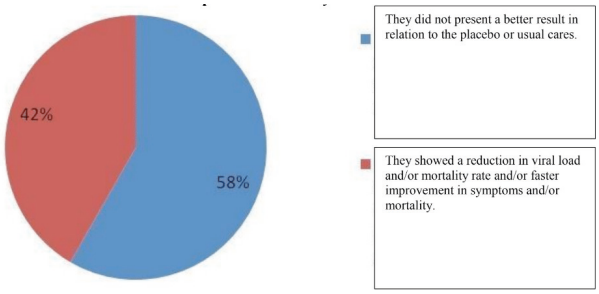
Source: own authorship



Flowchart 1: Number of articles selected, excluded and included. Exclusion and inclusion criteria

Source: own authorship

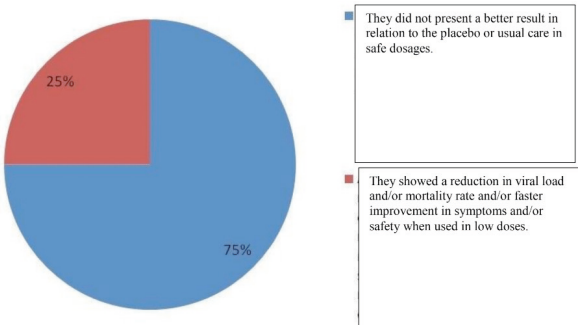
Of the 12 articles that included AZT as a treatment, 5 (42%) showed a reduction in viral load and/or faster improvement in symptoms and/or a decrease in mortality rate and in 7 (58%) there was no better result in relation to placebo or usual care (Graphic 1).



Graphic 1: Azithromycin results

Source: own authorship

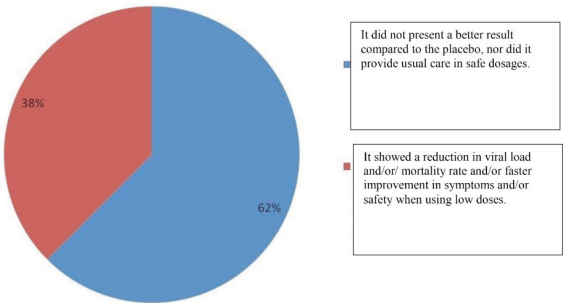
In the 24 articles that addressed CQ/HCQ therapy, only 6 (25%) demonstrated a reduction in viral load and/or mortality rate and/or faster improvement in symptoms, while for 18 (75%) of the results in compared to placebo or usual care, there was no improvement (Graphic 2).



Graphic 2: Chloroquine/hydroxychloroquine results

Source: own authorship

Regarding the administration of IVT, 16 articles were analyzed and 6 (38%) showed positive results in reducing viral load and/or mortality rate and/or faster improvement in symptoms, and 10 (62%) did not bring benefits in relative to placebo or usual care at safe dosages (Graphic 3).



Graphic 3: Ivermectin Results

Source: own authorship

The characteristics of the scientific articles included in the research are summarized in the table below (Table 1):

DISCUSSION

ISOLATED THERAPY

AZT

AZT is the second most prescribed treatment for COVID-19, according to a survey of more than 6,000 doctors in 30 countries (Sermo, 2020). Three studies evaluated the isolated use of AZT in the treatment of Covid-19 and both had similar results, as the medicine did not bring benefits compared to usual care or placebo.

The objectives of clinical trials have ranged from determining whether AZT leads to the absence of symptoms (Oldenburg et al., 2021); evaluate the effectiveness of AZT in suspected COVID-19 among patients at increased risk of complications (Butler et al., 2021) and estimate the safety and effectiveness of AZT in patients with COVID-19 admitted to hospital (Abaleke et al., 2021).

The interventions used in the patients studied involved placebo or a single 1.2g oral dose of AZT (Oldenburg et al., 2021); AZT 500 mg orally, nasogastric tube or intravenous injection once daily for 10 days or until discharge compared to usual care (Abaleke et al., 2021) and daily dose of AZT 500 mg for 3

Table 1. Characteristics of scientific articles included in the research						
Author, Year	Design and type of study/clinical trial	Time of study	Therapeutic agents	Initial sampling	Place of study	Results
Oldenburg et al. (2021)	Randomized, parallel	10M9D	AZT	604 P	USA	Patients who received treatment with AZT did not have a better result in relieving symptoms within 14 days than those who received placebo.
Butler et al. (2021)	Randomized, controlled, open	6M	AZT	2265 P	UK	There was no evidence of any difference in improvement between the two study groups (with and without AZT use/usual care)
Furtado etal. (2020)	Randomized and open	1M21D	AZT +HCQ	447 P	57 centers in Brazil	In patients with severe COVID-19, adding AZT to standard treatment (which includes HCQ) did not improve clinical outcomes.
Abbas et al. (2020)	Natural, quasi-experimental, no comparison group	2M24D	AZT +HCQ	161 P	Baghdad, Iraq	HCQ and AZT are useful in treating most patients and have reduced their signs and symptoms. They cause some controllable side effects, mainly related to heart rate.
Arshad etal. (2020)	Retrospective, comparative cohort study	1M22D	HCQ, HCQ +AZT, AZT	2541 P	Southeast Michigan	Treatment with HCQ alone and in combination with AZT was associated with reduced mortality in COVID-19
Gautret etal. (2020)	Non-randomized and open	14D	HCQ +AZT	36 P	Marseille, France	HCQ treatment is significantly associated with reduction/disappearance of viral load and its effect is reinforced by AZT
Abaleke etal. (2021)	Randomized, controlled, open and adaptive platform	7M20D	AZT	7763 P	176 UK hospitals	AZT did not improve survival or other prespecified clinical outcomes. Its use in hospitalized patients must be restricted to patients in whom there is a clear antimicrobial indication.
Lagier et al. (2020)	Retrospective analysis	1M24D R+	AZT eHCQ	3737 P	Marselha, France	Early treatment with at least 3 days of HCQ-AZ leads to a significantly better clinical outcome and a faster viral load reduction than other treatments
Borba et al. (2020)	Parallel, double-blind, randomized, phase IIb	13D	CQ	81 P	Manaus, Brazil	The higher dosage of CQ must not be recommended for critically ill patients due to its potential safety risk, particularly when taken with AZT and oseltamivir.
Réa-Neto etal. (2021)	Randomized, open, controlled, phase III.	3M21D	CQ ouHCQ	142 P	48 hospitals in France	For severe COVID-19, the use of CQ/HCQ plus standard care resulted in signifcant worsening of clinical status, increased risk of renal dysfunction, and increased need for invasive mechanical ventilation
Dubée et al. (2021)	Randomized, double-blind, placebo-controlled	1M19D	HCQ	250 P	48 hospitais da França	It did not achieve enough power to make a statement about the effectiveness of HCQ in mild to moderate patients. No effect of HCQ was observed on clinical outcome or viral clearance.
Grau-Pujol et al. (2021)	Randomized, double-blind, placebo-controlled	3M	HCQ	269 PSAR	3 hospitals in Barcelona	Although the effectiveness of HCQ pre-exposure in preventing COVID-19 cannot be assessed, our study showed that low-dose HCQ is safe.
Sivapalan etal. (2021)	Randomized, double-blind, placebo-controlled	8M15D	AZT eHCQ	117 P	6 hospitals in Denmark	The combination of AZT and HCQ did not improve survival or length of stay in patients with COVID-19.
Rodrigues et al. (2021)	Randomized, double-blind, placebo-controlled	1M1D	AZT eHCQ	84 P	Hospital Santa Paula, Brazil	There was no benefit in primary and secondary outcomes in treatment using HCQ/AZT or placebo in patients with early and mild COVID-19.

Rajasingha m et al.(2020)	Randomized, double-blind, placebo-controlled	3M7D	HCQ	1483 PSAR	United States and Canada	Pre-exposure prophylaxis with HCQ once or twice weekly did not reduce confirmed COVID-19 or COVID-19 compatible illness among healthcare workers.
Abd- Elsalam et al. (2020)	Randomized and controlled	4M	HCQ	194 P	3 hospitals in Egypt	Adding HCQ to standard treatment did not add significant benefits, did not decrease the need for ventilation and did not reduce mortality rates in patients with COVID-19.
Mitjà et al. (2021)	Cluster randomized, open	1M11D	HCQ	754 P	Catalunha, Spain	Post-exposure therapy with HCQ did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in healthy people exposed to a PCR-positive patient.
Self et al. (2020)	Single-blind, randomized, placebo-controlled	2M17D	HCQ	479 P	34 hospitals in the USA	Among adults hospitalized with COVID-19 respiratory illness, HCQ treatment, compared with placebo, did not significantly improve clinical status at day 14
Skipper etal. (2020)	Randomized, double-blind, placebo-controlled	1M28D	HCQ	491 P	USA and Canada	HCQ did not substantially reduce symptom severity in outpatients with mild and early COVID-19
Boulware etal. (2020)	Randomized, double-blind, placebo-controlled	2M	HCQ	821 P	USA and Canada	After high-risk or moderate-risk exposure, HCQ did not prevent illness consistent with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days of exposure
Cavalcanti et al. (2020)	Controlled, randomized, open, three-group	2M4D	AZT eHCQ	667 P	55 hospitals in Brazil	Among patients hospitalized with mild to moderate Covid-19, the use of HCQ, alone or with AZT, did not improve clinical status at 15 days compared with standard care.
Horby et al. (2020)	Open, controlled and randomized platform study	2M11D	HCQ	4716 P	176 UK hospitals	Among patients hospitalized with Covid-19, those who received HCQ did not have a lower incidence of death within 28 days than those who received usual care.
Chen et al. (2021)	Retrospective cohort study	26D R+	HCQ eCQ	63 P	Wuhan, China	Administration of HCQ/CQ is not related to fewer cases of mortality in the late phase of COVID-19.
Hernandez-Cardenas et al. (2021)	Double-blind, randomized, controlled, parallel, phase III	3M4D	HCQ	214P	Ixtapaluca and Oaxaca, Mexico	No beneficial effects or significant harm could be demonstrated.
Krolewieckiet al. (2021)	Parallel, randomized, controlled, open, single-blind	5D	IVT	45 P	Argentina	Concentration-dependent antiviral activity of IVT in patients infected with SARS-CoV-2
Camprubí etal. (2020)	Crossed, Open	20D R+	IVT	26 P	HC, Barcelona	No differences were found between groups
Babalola etal. (2021)	Parallel, randomized, controlled, double-blind	7M	IVT	62 P	HU Lagos, Nigeria	Statistically significant and dose-dependent effect to reduce time to negativity in positive patients
Galan et al. (2021)	Phase II, double-blind, randomized study	2M15D	CQ HCQ IVT	168 P	Roraima	CQ, HCQ or IVT demonstrated a favorable safety profile, but do not reduce the need for supplemental oxygen, ICU admission, invasive ventilation or death in patients hospitalized with the severe form.
Samaha etal. (2021)	Randomized, controlled	3M	IVT	100 P	Lebanon	It appears to bring clinical benefits in the treatment of asymptomatic positive individuals.

Buonfrate etal. (2022)	Randomized, double-blind, phase II, dose finding, proof of concept	9M25D	IVT	93 P	Italy	There was no significant reduction in viral load between ivt and placebo. High-dose IVT was safe but not effective in reducing viral load
Lim et al. (2022)	Randomized, open	4M24D	IVT	490 P	Malaysia	IVT treatment during initial disease did not prevent progression to severe disease.
Reis et al. (2022)	Double-blind, randomized, placebo-controlled and adaptive platform	4M14D	IVT	3515 P	Brazil	It did not result in a lower incidence of medical admissions or prolonged emergency room observation among outpatients with early diagnosis.
Okumuş etal. (2021)	Phase III, randomized, controlled and single-blind	5M	IVTHCQ AZT	66 P	Türkiye	Increased clinical recovery, improved prognostic laboratory parameters and decreased mortality rates even when used in patients with severe COVID-19.
Mohan et al. (2021)	Pilot, double-blind, randomized, placebo-controlled, parallel	2M1D	IVT	157 P	NCI, New Delhi	In mild and moderate patients, a single oral administration of IVT did not significantly increase RT-PCR negativity or viral load decline on day 5 of enrollment.
						compared to placebo.
Shahbaznej ad et al.(2021)	Double-blind, randomized, controlled	2M8D	IVT	70 P	Mazandaran, Iran	A single dose can improve important clinical symptoms in patients with COVID-19, such as dyspnea, cough and lymphopenia.
Ahmed etal. (2021)	Randomized, double-blind and controlled	5D	IVT	72 P	Dhaka, Bangladesh	It has been shown to be safe and effective in treating adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings
Ravikirti etal. (2021)	Double-blind, parallel, randomized and controlled	2M30D	IVT	115 P	East India	The inclusion of IVT cannot be recommended with certainty as it showed only a marginal benefit in successful hospital discharge, with no other benefits observed.
Abd- Elsalam etal. (2021)	Randomized, open, controlled, parallel.	1M	IVT	164 P	Egypt	The use of IVT did not reach significance for the outcomes. However, a tendency to reduce hospital stay was observed
Vallejos etal. (2021)	Randomized, double-blind and controlled	6M3D	IVT	501 P	Corrientes, Argentina	IVT had no significant effect on preventing hospitalization. Those who received IVT required early ventilatory support. No significant differences in other secondary outcomes.
López- Medina etal. (2021)	Double-blind, randomized	5M6D	IVT	400 P	Cali, Colômbia	Among adults with mild COVID-19, a 5-day course of IVT, compared to placebo, did not significantly improve time to symptom resolution

Table 1: Consider the items: EM = months; E = days; R+ = retrospective; TO = patients; PSAR = high-risk healthcare professionals.

Source: own authorship

days or care alone usual (Butler et al., 2021).

The profile of patients in studies involving AZT was patients aged approximately 43 to 65 years. In Oldenburg et. al (2021) there was a female majority, as well as for Butler et al., 2021 who restricted the study to patients aged 65 or over or 50 years old with at least one known comorbidity, 14 days of illness or suspected COVID-19. In the platform study by Abaleke et al., (2021), the majority of patients were male and had an average age of 65.3 years.

For the three articles selected with isolated AZT therapy, its use did not increase the probability of the patient becoming asymptomatic more quickly (Butler et al. 2021; Oldenburg et al., 2021) there was no reduction in the severity of symptoms as it was not associated with reduction in mortality, length of hospital stay, or risk of being ventilated or dying for those not on ventilation at baseline (Abaleke et al., 2021; Butler et al., 2021). Therefore, there was no difference between the groups receiving AZT and those receiving usual care or placebo (Abaleke et al., 2021; Butler et al., 2021; Oldenburg et al., 2021). Furthermore, studies have demonstrated an increased risk related to the inappropriate use of antibiotics and the consequent increase in antimicrobial resistance (Butler et al., 2021), which can also cause gastrointestinal adverse events (Oldenburg et al., 2021).

CQ AND HCQ

In the US, prescriptions for short-acting HCQ or CQ (<28 days) increased by nearly 2,000% between 2019 and 2020, followed by a decline, likely due to off-label use for treating COVID-19. (VADUGANATHAN et al., 2020). Of the 13 articles selected for isolated therapy with CQ and HCQ, 1 article observed only CQ, 10 considered only HCQ, 2 used HCQ and CQ.

Borba et. al (2020) evaluated the safety and effectiveness of CQ in the treatment of Covid-19. Participants were assigned to receive high (600mg) or low (450mg) doses of CQ. Placebo pills were used in the low-dose group to standardize treatment and mask the study group and participants. It was not possible to independently evaluate the toxic role of CQ because all patients were already using AZT, according to the hospital protocol. They concluded that high doses of CQ must not be recommended in critically ill patients due to potential safety risks, especially when taken with AZT and oseltamivir. Furthermore, no apparent benefit of CQ was observed in relation to patient mortality.

The studies involving HCQ aimed to determine whether HCQ reduces the risk of adverse outcome or the severity of symptoms in patients with COVID-19 (Dubée et al., 2021; Hernandez-Cardenas et al., 2021; Skipper et al., 2020); test the safety and efficacy of HCQ added or not to some standard treatment (Abd-Elsalam et al., 2020; Horby et al., 2020; Self et al., 2020); evaluate pre-exposure of healthcare professionals to HCQ (Grau-Pujol et al., 2021; Rajasingham et al., 2020) and, therefore, HCQ as a prevention of COVID-19 (Boulware et al., 2020; Mitjà et al., 2021).

The interventions used in randomized trials were varied. Most authors controlled the study through the use of placebo pills under the same conditions as those who actually received the treatment (Boulware et al, 2020; Dubée et al., 2021; Grau-Pujol et al., 2021; Hernandez -Cardenas et al., 2021; Rajasingham et al., 2020; Self et al., 2020; Skipper et al, 2020). Others used as a comparison only previously established standard treatments or usual care (Abd-Elsalam et al., 2020; Horby et al, 2020; Mitjà et al., 2021) which could include, for example: paracetamol, oxygen, fluids, antibiotic empirical, oseltamivir and invasive mechanical ventilation with hydrocortisone for severe cases (Abd-Elsalam et al., 2020). The dosage ranged from 200 mg to 800 mg,

being administered in different ways, as well as the treatment time, which ranged from days to weeks or until the patient was discharged.

Participants in HCQ research were patients and, in some studies, healthcare professionals. Ages ranged from 39 to 77 years old, with 5 of the 10 articles having a greater participation of females, 3 of males; 1 article did not specify and 1 had equal participation of men and women.

For trials involving early HCQ treatment, participants were exposed to SARS-CoV-2, as Rajasingham et al. (2020), that 91% of healthcare professionals reported more than 14 hours of direct contact with patients per week and 79% of participants routinely performed aerosol-generating procedures. The study by Mitjà et al. (2021) included asymptomatic adults who had a recent history of close contact with a patient with PCR-confirmed Covid-19, without similar symptoms and at increased risk of infection (healthcare worker, household contact, worker or nursing home resident). Skipper et al. (2020) entered non-hospitalized adult patients who needed to have 4 days or less of symptoms and PCR-confirmed SARS-CoV-2 infection or compatible symptoms after a high-risk exposure to a person with COVID-19. For Boulware et al. (2020) 87.6% reported a high-risk exposure to a confirmed Covid-19 contact at a distance of less than 6 feet for more than 10 minutes without wearing a face mask or eye shield or wearing a face mask but without eye protection.

The 10 articles that involved HCQ therapy demonstrated that the medication was ineffective for clinical progression, (Abd-Elsalam et al., 2020; Self et al., 2020; Skipper et al., 2020; Dubée et al., 2021; Hernandez-Cardenas et al., 2021;) speed of viral elimination (Dubée et al., 2021), transmission of SARS-Cov-2 (Mitjà et al., 2021), severity of symptoms (Skipper et al., 2020), pre-exposure prophylaxis. (Abd-Elsalam et al. 2020; Boulware et al., 2020; Rajasingham et al., 2020) or incidence of death (Horby et al., 2020).

Furthermore, mild adverse effects related to the use of HCQ were demonstrated in Mitjà et al. (2021). In Dubée et al., 2021, patients with conditions that put them at risk of increased HCQ toxicity were excluded, therefore this administration was shown to be safe, but the question of whether COVID-19 could be prevented with pre- exposure to HCQ was not answered in this article. For Hernandez-Cardenas et al. (2021) no beneficial effects or significant harm could be demonstrated using relatively low doses of HCQ.

The clinical trial by Réa-Neto et al. (2021) evaluated the effectiveness of CQ or HCQ plus standard treatment for five days compared to standard treatment alone in patients with severe COVID-19. The median age of patients was 53 years and 66.7% of patients were male. CQ was available to patients in public hospitals in Brazil, while in private centers, there was only HCQ. The dosages were chosen so that they had a lower incidence of adverse effects and were those recommended by the Brazilian Ministry of Health. The addition of CQ/HCQ to standard care in patients with severe COVID-19 resulted in clinical worsening and a higher incidence of invasive mechanical ventilation and renal dysfunction, although there was no difference in mortality.

The retrospective study by Chen et al. (2021) aimed to evaluate the efficacy and safety of HCQ/CQ in COVID-19. 11 patients received HCQ and 3 CQ. The average age was 62.20 years with a predominance of males. It was identified that the administration of HCQ/CQ was not related to fewer cases of mortality, nor to a reduction in the time of COVID-19 infection. Furthermore, HCQ, unlike CQ, has been proven to be a safe and tolerable drug in patients with COVID-19.

IVT

According to Scaramuzzo (2021), IVT showed an 829% increase in sales from 2019 to 2020. This can pose health risks, as excessive exposure to the antiparasitic can lead to outbreaks of scabies - increasing the risk of infant mortality due to secondary infections (Oliveira-Filho et al., 2021). In this work, 14 articles were selected to evaluate the effectiveness of IVT and, for the most part, no positive results were obtained.

Of these, 10 clinical trials sought to evaluate the effectiveness of standard doses, 2 included research on the antiviral effect, 3 tested safety, 1 researched early treatment, 2 included the speed of virus elimination and 1 prevention through the use of IVT in patients with mild to severe COVID-19.

The interventions used were diverse among the selected articles. The doses ranged from 200mcg/kg to 600 mg/kg and for some it was established according to the patients' body weight, as in Samaha et al. (2021), where patients weighing 45 to 64 kg received IVT 9 mg, 65 to 84 kg IVT 12 mg and, above 85 kg, IVT 150 mcg/kg. The treatment time was 5 to 14 days and most studies compared IVT to placebo, many with previously established standard treatment associated (HCQ and AZT, lopinavir/ritonavir, doxycycline, zinc and vitamin C supplements). Lim et al. (2022) had as a standard symptomatic therapy and monitoring of signs of early deterioration based on clinical findings, laboratory test results and chest images.

The patients participating in the study had a demographic profile ranging from 31.78 to 62.5 years old and 8 articles were carried out with mostly male participants, 4 with the predominant female gender and 2 articles brought equal numbers of men and women to the research. Furthermore, the studies were differentiated according to the severity of patients with COVID-19, as in Mohan et al. (2021), where the proportions of asymptomatic, mild and moderately ill patients were similar across the three study groups. Some even used risk factors to randomize their participants (Reis et al., 2022).

From the articles that considered isolated therapy using IVT, the conclusions were more varied than those that used AZT, CQ and HCQ as therapy. Some studies have demonstrated an effect on reducing infection time (Ahmed et al., 2021; Krolewiecki, 2021; Samaha et al., 2021), modifying prognostic factors (Babalola et al., 2021), reducing symptoms and hospital admissions; (Samaha et al., 2021; Shahbaznejad et al., 2021) also reported that IVT is a safe medicine (Babalola et al., 2021; Mohan et al., 2021; Shahbaznejad et al., 2021) even at high doses (Buonfrate et al., 2022). Furthermore, the effectiveness of this medication is proportional to the doses administered (Babalola et al., 2021; Camprubí et al., 2020; Krolewiecki, 2021).

On the other hand, other research concluded that the single dose did not improve the clinical and microbiological outcomes of patients with severe COVID-19 in late stages of infection (Camprubí et al., 2020) and did not prevent progression to severe disease in early stages (Camprubí et al., 2020) and did not prevent progression to severe disease in early stages (Lim et al., 2022). Furthermore, it was not possible to conclude that IVT can be prophylactic (Babalola et al., 2021), that it is effective in reducing viral load (Buonfrate et al., 2022; Mohan et al., 2021) or that there is a significant difference in negativity of RT-PCR. (López-Medina et al., 2021; Mohan et al., 2021) In the randomized study by Reis et al. (2022), IVT administration did not result in a lower incidence of medical hospitalization or prolonged observation among outpatients at high risk for serious illness.

For Ravikirti et al. (2021), IVT must not

be recommended in the treatment regimen of patients with COVID-19 and, according to Vallejos et al. (2021), patients who received the antimalarial needed invasive mechanical ventilation at the beginning of their treatment. López-Medina et al. (2021) also demonstrated other related adverse events, the most common being headache, reported by 52% who received IVT. The serious adverse event was multiple organ failure, occurring in 4 patients (2 in each group studied). Therefore, the use of IVT did not reach significance for any of the outcomes (Abd-Elsalam et al., 2021) and had no significant effect on preventing hospitalization of patients with COVID-19 (Vallejos et al., 2021).

COMBINATION THERAPY

Furtado et al. (2020) enrolled hospitalized patients with suspected or confirmed COVID-19 and at least one additional severity criterion in their study.

Patients used AZT 500 mg once a day for 10 days plus standard treatment or standard treatment without macrolides (HCQ 400 mg twice a day for 10 days). Patients could be enrolled if treated for COVID-19 infection with one of these drugs, as long as the duration of treatment was not more than 48 hours. The median age was 59.8 years and 66% of patients were men. In conclusion, for patients admitted to hospital with severe COVID-19, adding AZT to a standard with HCQ did not result in clinical improvement or reduced mortality.

In Abbas et al. (2020) all patients were treated according to the treatment protocol that is based on severity status: HCQ and AZT for Covid-19 patients without pneumonia; HCQ + AZT + Tamiflu for Covid-19 patients with pneumonia in the ward; HCQ + AZT + Kaletra for Covid-19 patients with pneumonia in the ICU. The average age of the participants was 44.3 years. This natural trial showed that the HCQ and AZT regimen were helpful in treating the majority of patients and reduced their signs and symptoms. There were some manageable side effects, mainly those related to heart rhythm.

In the retrospective study by Arshad et al. (2020), four treatment groups were used: HCQ alone, HCQ + AZT, AZT alone and none of the treatments. Overall, 2541 consecutive patients were included in the analyzes with a mean age of 64 years. In this multi-hospital evaluation, when controlling for COVID-19 risk factors, treatment with HCQ alone and in combination with AZT was associated with reduced mortality.

Gautret et al. (2020) carried out a study with patients with an average age of 45.1 years. 20 patients were treated with oral HCQ 200 mg, three times a day for ten days, among these patients, 6 received AZT in combination (500 mg on day 1 followed by 250 mg per day for another 4 days). On day 6 post-enrollment, 100% of patients treated with a combination of HCQ and AZT were virologically cured compared to 57.1% of patients treated with HCQ alone and 12.5% in the control group. There were adverse effects reported in another article by the author.

Sivapalan et al. (2021) investigated whether adding 15-day treatment with AZT and HCQ to the standard of care could decrease the length of hospitalization and the risks of non-invasive ventilation, intensive care unit admission, and death. Patients were randomized to one of two treatment arms: AZT plus HCQ and placebo. For the study, they used recommended doses of both medications and respected their contraindications when recruiting participants, therefore, no changes in heart rate were observed. Participants had a median age of 65 years and 56% of them were male. Combining these drugs did not increase the likelihood of survival or hospital discharge for patients with COVID-19.

Lagier et al. (2020) performed a

retrospective analysis of patients treated with HCQ and AZT for at least three days and patients treated with other regimens. The average age of patients was 45 years and 45% were men. Although a retrospective analysis, the results suggested that early diagnosis, isolation and early treatment of patients with COVID-19 with at least 3 days of HCQ and AZT lead to a significantly better clinical outcome and faster viral load reduction than other treatments.

In Rodrigues et al. (2021), participants in the treatment group received HCQ or AZT. The study population were adult patients aged <65 years, without comorbidities and onset of mild symptoms 2-5 days before enrollment. Viral clearance rates did not change through treatment with HCQ or AZT, although there were no major cardiovascular events observed in participants without comorbidities, secondary outcomes were also not improved compared to placebo.

Cavalcanti et al. (2020) conducted a study in which patients received standard treatment (control group), standard treatment plus HCQ (HCQ alone group), or standard treatment plus HCQ/CQ/AZT. The average age of patients was 50 years and 58% were men. In this study involving patients hospitalized with mild to moderate Covid-19, there was no significant difference in the clinical status outcome between the groups. Patients who received HCQ with AZT or alone had more frequent events of QTc interval prolongation and elevated liver enzyme levels than patients who did not receive either agent.

Okumuş et al. (2021) used the reference treatment recommended by the Turkish Ministry of Health, consisting of HCQ, favipiravir and AZT. In addition to the reference treatment, patients in the study group received IVT treatment. The average age of the control group was 58.17 years, while that of the study group was 66.23 years. This study suggested that IVT could be used in the treatment of COVID-19 disease or an additional option to current treatment. Even when used in critically ill patients with COVID-19, it can provide increased clinical recovery, improved prognostic laboratory parameters and decreased mortality rates.

Galan et al. (2021) evaluated the safety and efficacy of CQ, HCQ or IVT in severe forms of COVID-19, in addition to identifying predictors of mortality. The average age was 53.4 years and the majority of participants were men. Groups were randomized to receive CQ, HCQ, or IVT. According to hospital protocol, all patients without contraindications received prophylactic doses of enoxaparin, those who met the criteria for acute respiratory distress syndrome used AZT and ceftriaxone, and oseltamivir was also prescribed when suspected influenza infection. In this study, the conclusion was that the use of CQ, HCQ or IVT was not related to a reduction in the need for supplemental oxygen, ICU admission, invasive ventilation or death, but at the doses used, the medications were safe. Age over 60 years, obesity, diabetes, extensive lung involvement and low oxygen saturation at hospital admission were independent risk factors for mortality.

CONCLUSION

With the rapid advancement of Covid-19 and the severity of the disease, which led to overcrowding in hospitals, there was a need to use experimental treatments. However, over time, with the identification of the virus, disease progression and preliminary results regarding drug therapy and hospital support, the protocols adopted must have been adjusted and based on evidence-based criteria. However, what was seen in Brazil, and in many countries, the use of the medicines covered in this study was indiscriminately adopted by the population, without scientific

basis and qualified professional monitoring. Furthermore, many hospitals continued to base their protocols on this medication kit.

In order to demonstrate the safety and effectiveness of this treatment, this systematic review brought together clinical trials with different treatment protocols, approaches (treatment and prophylaxis) and severity of COVID-19 disease. Of the 40 articles selected involving the medicines from the so-called "Covid Kit", 30 concluded unsatisfactory results in relation to the use of the medicines, whether due to ineffectiveness, risks of serious adverse effects and low safety. Furthermore, those who reported positive effects highlighted a dose-dependent benefit, which entails less safety and risk of toxicity in the therapy.

From the analysis of the results obtained in this study, it was found that there is no satisfactory data regarding the safety and effectiveness of the use of HCQ/CQ, AZT and IVT in the prophylaxis or treatment, alone or in combination, of Covid-19 regarding the evolution of the disease, reduction of its symptoms and mortality rate

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