Review Article

Diagnosis and Critique of Drugs Used in Treating Coronavirus Disease in 2019 in Nigeria: A Review

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ABSTRACT

Background and Objectives: Drugs used in treating patients who contracted the coronavirus disease of 2019 (COVID-19) include chloroquine or hydroxychloroquine (CQ, HCQ), antiviral, steroid, and antibiotic. Treatment outcomes were characterized by positive and adverse reactions as therapeutic options were based on clinical trials coupled with diagnostic constraints. This study assesses the diagnostic processes and critically examines the drugs used in the clinical settings to treat COVID-19 in Nigeria.

Methods: The search was conducted on various databases with a focus on diagnoses and drugs used to treat COVID-19. Articles that did not meet selection criteria were excluded and the data collected from sampled articles were collated, analyzed, and evaluated.

Results: The finding showed a lack of sufficient evidence-based data to support the use of CQ/HCQ, remdesivir, lopinavir/ritonavir, and antibiotics, such as azithromycin as treatment options for COVID-19, even though patients responded partly to the drugs probably due to their action mechanisms.

Conclusion: There is a lack of evidence-based scientific data to guide the definitive treatment of COVID-19 patients during the pandemic. Drugs used in the emergency were based on clinical trials. The efficacy of the drugs depends partly on the innate capability of the immune system of an affected individual.

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Introduction

The emergence of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19 by the World Health Organization (WHO) started with a lower respiratory tract infection in Wuhan, China in December 2019 [1]. The COVID-19 spread from China to various countries to start a pandemic. According to the Nigeria Center for Disease Control (NCDC), the first case of COVID-19 was identified in Lagos, Nigeria on February 27, 2020 [2].

Experts in healthcare services were faced with the challenge of diagnosing and treating COVID-19 due to the absence of data to guide the processes [3]. However, with the increase in diagnosis and isolation of SARS-CoV-2 among humans, there were discoveries about the disease that led to the regular review of its case definition [4]. In developed and developing countries, the medical laboratory testing process for the diagnosis of SARS-CoV-2 was characterized by various challenges [4]. Inadequate testing capacities occupy a part of the challenges associated with the worldwide management of COVID-19 [5].

When the first case of COVID-19 was detected in a foreign person who came to Nigeria from Italy, the laboratory scientists who specialized in molecular testing were few. Similarly, no specific drug existed for the definitive treatment of COVID-19, and various drugs were used to treat patients based on clinical trials [6]. Drugs used in different health facilities in Nigeria have limited scientific acceptability for treating COVID-19, and there was no extensive research on their use for that purpose, even though the country's drug regulatory agencies authorized their use for the treatment of COVID-19 patients [7].

As a result of this problem, the drugs used for the treatment of COVID-19 patients were characterized by positive and adverse reactions due to the exploration of therapeutic options of drugs during clinical trials. Drugs used in clinical trials to treat COVID-19 in Nigeria included 4-aminoquinoline and its derivatives (chloroquine [CQ] or hydroxychloroquine [HCQ]), azithromycin, zinc, vitamin C, remdesivir, lopinavir-ritonavir, and dexamethasone [8] due to inability to promptly contain the COVID-19 pandemic worldwide, WHO considered the lack of data responsible to guide the treatment, in addition to inadequate testing materials and no definitive case definition for the disease [9].

In Nigeria, the pace and process of diagnosis was slow at the outset of the COVID-19 pandemic, no specific antiviral drug for definitive treatment of the infected persons, and drugs used across the states of the federation were not supported with extensive research work for the treatment of COVID-19. This constitutes problems for healthcare professionals and infected patients. Based on these challenges, this review is carried out to fill the knowledge gap.

Accordingly, this study aims to evaluate the diagnosis processes and critically examine the effects of the practical application of the drugs on COVID-19 patients. The justification for this study is to critique the outcomes of the therapeutic options in terms of the drug's pharmacokinetics, pharmacodynamics, drug's efficacy, and safety in COVID-19 patient treatment. The significance of this review is that the findings can be useful to the stakeholders and medical experts in addressing the definitive treatment of COVID-19.

Materials and Methods

Resources, sample selection, and data analysis

This study on the critique of diagnosis and drugs used in treating COVID-19 with practical application was conducted in October 2020 in Nigeria. The databases of learned journals and literature were assessed with a focus on studies that collected primary data on drug treatment of COVID-19. Relevant articles on COVID-19 diagnostic testing and COVID-19 drug treatment were identified. The search was conducted on the following databases: EBISCO, PubMed, Cochrane, CINAHL, Willey online library, Directory of Open Access Journals, ScienceDirect, and Web of Science. The keywords used for the search were as follows: "COVID-19 diagnosis," "COVID-19 drugs," "chloroquine or hydroxychloroquine treatment," "azithromycin," "remdesviri," "Zinc and vitamin C," and "COVID-19 rtPCR testing."

Results

The total number of relevant articles was 40 out of 59; however, 19 articles were investigated based on the purpose of the review as shown in Figure 1.

The inclusion criteria were as follows; peer-reviewed articles in English on COVID-19 diagnosis, treatment, safety, and efficacy of the drugs, and articles related to treatment protocols adopted in treating COVID-19 patients. Meanwhile, the exclusion criteria were duplicated studies and articles on the historical trajectory of COVID-19. Also, systematic review or meta-analysis studies

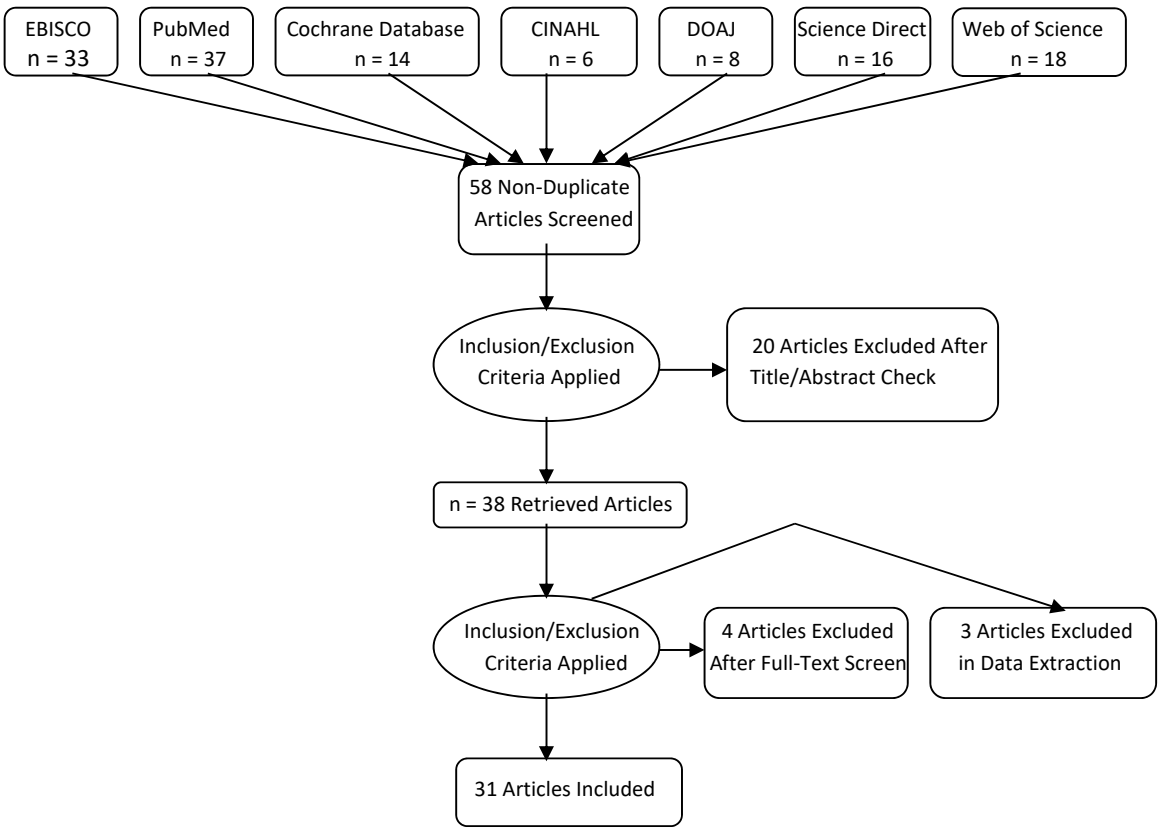

Figure 1. Flow chart of the selected articles

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in which primary data were not collected and studies not published in learned journals were excluded.

Discussion

Evaluation of COVID-19 diagnosis

Diagnosis of COVID-19 is the process of understanding whether a patient has SARS-CoV-2 present in their collected specimen. The specimen for testing in the molecular laboratories to identify COVID-19 included sputum, aspirate, lavage, swab from the oropharyngeal region, whole blood, urine, and stool; however, if a patient is deceased, materials from the autopsy is considered [9]. In a study conducted in Wuhan, China, among 425 cases, the incubation period for COVID-19 was between 1 to 14 days, though it varies widely between individuals worldwide [9].

The purpose of diagnosing COVID-19 is essential at every step to monitor, screen, and determine the pattern of the disease. Significantly, SARS-CoV-2 continues to mutate about the timing and compartmentalization, and this characteristic of viral shedding about optimal specimen collection is not well understood. The diagnostic methods included laboratory investigations using molecular methods of real-time polymerase chain reaction testing, imaging such as computed tomography scan, x-ray, and magnetic resonance imaging to detect the virus and assess the status of the lung and other internal organs.

Molecular laboratory testing for COVID-19

The real-time polymerase chain reaction testing method was recommended by WHO for coronavirus segregation in molecular laboratories, and it was adopted in Nigeria to isolate SARS-CoV-2, and the principle of the diagnosis was based on the detection of COVID-19 protein. According to the NCDC, at the outset of the pandemic, there were few molecular laboratories available to conduct testing for COVID-19. Currently, the number of designated laboratories being funded by the government has increased across the states of the federation. There were also private molecular laboratories that operated on fees for services. The limited number of molecular laboratories at the outset of the pandemic constitutes

a problem as specimens collected were transported to the available molecular laboratories, leading to delays in decision-making.

Furthermore, the logistic problem partly resulted in the poor quality of the specimen, and consideration of whether there is adequate human DNA in the sample [10]. The most challenging of the test is the mutation of SARS-CoV-2 or real-time polymerase chain reaction testing method inhibition. The negative results may not rule out COVID-19; therefore, re-testing is encouraged and laboratory scientists were advised to perform entry testing and or validation on functionality or potential contaminants [10]. Similarly, chest computed tomography scans and x-rays without significant abnormality were witnessed in COVID-19 patients' imaging results. These results do not rule out COVID-19 which is dependent on the innate immune system of an individual which plays a vital role in the diagnosis and response to treatment [10].

Critique of the drugs used in treating COVID-19

Pharmacokinetics of the drugs

Before the COVID-19 pandemic, 4-aminoquinoline and its derivatives (CQ or HCQ) were previously used to treat malaria in children and adults in Nigeria before its withdrawal [11]. Recently, rheumatoid arthritis, autoimmune, and systemic lupus erythematosus diseases have been treated with CQ or HCQ [11]. The plasma concentration of CQ or HCQ administered orally will reach its peak in 2 to 4.5 h, and 75% to 100% get absorbed into the gastrointestinal tract as it binds to the plasma protein and slowly reaches a steady state of concentration [11, 12]. The highest blood CQ or HCQ concentration can be reached within 1 to 2 h after taking the medication. The bioavailability of CQ or HCQ can reach 50% after oral administration [12]. The kidney mainly excretes 40% to 50% of CQ or HCQ, the rest is excreted through fecal matter and the plasma CQ or HCQ elimination half-life is about 32 days and this pharmacokinetic mechanism of action might be responsible for its potency on COVID-19 [12].

The use of remdesivir which is an antiviral drug was suggested by the NCDC, through the National Agency for Food and Drug Administration and Control [13], which is the constituted regulatory agency for Food and Drug Administration and Control in Nigeria (NAFDAC) emphasized the use of CQ or HCQ, the agency encouraged clinicians conducting the trial to continue based on the immune modulation effect of the drug in human [13]. Wang et al. [14] stated that the administration of 10 mg/kg remdesivir intravenously will remain in active form in the blood at 10 μM and confer 100% protection against Ebola disease. Hence, based on the effectiveness of the drug on Ebola, it was recommended by WHO for clinical trials in the treatment of COVID-19 in Nigeria. Data shows that the EC90 value of remdesivir against novel COVID-19 in vitro E6 was 1.76 μM, thereby inhibiting viral replication by terminating ribonucleic acid (RNA) transcription prematurely in vivo during its pharmacokinetics activities [14].

According to Cavalcanti et al. [15], azithromycin which is an antibiotic has a bioavailability of approximately 37% but decreases significantly by 50% with food following oral administration, and the peak plasma concentrations are 0.35-0.45 mg/L within approximately 2 h. Similarly, the peak plasma concentration of zinc and the time to reach are 3.87 μg/mL and 2 h for ZnY [16]. However, for vitamin C (ascorbic acid), the half-life in adult humans is about 10 days with 1 mg/kg body weight; therefore, a body pool of 22 mg/kg will be reached at plasma ascorbic acid concentration of 50 μmol/L and this timeline inhibits the action of COVID-19 [17]. Hence, the pharmacokinetics implication of those drugs used in treating COVID-19 is the time course advantages of the coronavirus.

Pharmacodynamics of the drugs

Remdesivir, an adenosine analog acts by incorporating itself into the nascent viral RNA chains and causes premature termination of COVID-19, and it also functions at a stage of post-virus entry as a nucleotide analog [14]. Remdesivir inhibited SARS-CoV-2 efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to COVID-19 [14]. Azithromycin, a macrolide, binds to the 50 S ribosome and inhibits bacteria protein synthesis, and quorum sensing, and reduces the formation of biofilm translation [15]. Zinc restores mucosal barrier integrity and promotes the production of antibodies and circulation lymphocytes against intestinal pathogens, while vitamin C acts physiologically as a reductant and enzyme cofactor [15-17]. Also, the use of intravenous corticosteroids, vitamin C, and thiamine proved effective in preventing progressive organ dysfunction, thereby reducing patient morbidity, severe sepsis, septic shock, and mortality [17].

According to Quiros Roldan et al. [18], the mechanism of action of CQ or HCQ on SARS-Cov-2 is based on the following two long-standing hypotheses. Firstly, CQ or HCQ elevates the pH of endosomes/lysosomes and their immune modulation. The CQ or HCQ in its unprotonated

form cross-cell membrane and gets trapped in the endosomes/lysosomes, thereby alkalizing the environment, and blocking viral entry into vulnerable host cells. Secondly, when endosomes fuse with lysosomes, the CQ or HCQ high pH can prevent SARS-Cov-2 envelop from breaking, thereby preventing liberation of RNA into the host cells, and inhibit viral replication as relevant enzymatic functions are compromised by elevated pH [18]. The body metabolic conversion of CQ or HCQ occurs in the liver and its main metabolite is desethylchloroquine that have a low clearance rate in the blood at around 96 mL/min; however, at the time the half-life can range from 40 to 50 days [18].

Efficacy of the drugs

The efficacy of 4-aminoquinoline was noted to produce a significant effect in terms of clinical outcome and viral clearance in COVID-19 treatment [19]. CQ or HCQ inhibits the exacerbation of pneumonia, improves lung imaging, and brings about virus-negative results, shortening the disease course [19]. Experts concluded that CQ or HCQ has potent activity against COVID-19 and should be added to the guidelines for the prevention and treatment of COVID-19 patients [20]. The intravenous hydrocortisone alone and in combination with high-dose vitamin C, and thiamine affected the patient's survival the septic shock, suggesting that adding vitamin C in the treatment of sepsis is efficacious and beneficial in treating COVID-19 in adults and children patients with or without pneumonia [21].

In an observational study conducted among 481 hospitalized COVID-19 patients in Catalonia, Spain, no evidence was found that azithromycin alone or in combination with other drugs had any significant clinical efficacy on COVID-19 patients as it was associated with poorer clinical outcomes compared with marched patients in the controls group [22]. The implication of the reduction in the efficacy of azithromycin found by the researchers may likely be due to drug interaction effects because of the combined therapy adopted in the management of COVID-19 patients.

Similarly, the efficacy of zinc on COVID-19 patients' treatment outcome was disputed in a randomized clinical trial which showed that high doses of zinc gluconate alone or combined with ascorbic acid did not significantly shorten the duration of symptoms compared with no combination of zinc [22]. The finding on the efficacy of zinc implies that there is a likelihood of antagonist reaction with ascorbic acid and or other drugs combined in the treatment of COVID-19 patients as zinc and vitamin C are both anti-oxidants.

Conversely, remdesivir and lopinavir/ritonavir were found to be highly effective in the control of COVID-19 in vitro with safety tract records that showed their efficacy against COVID-19 [23]. On the efficacy of dexamethasone on COVID-19 patients, the finding of the study conducted in the UK reported that a lower mortality rate was recorded among hospitalized patients who were given dexamethasone and receiving either invasive mechanical ventilation or oxygen alone at randomization compared to patients who are not receiving respiratory support [23].

Safety of the drugs

The safety records of CQ or HCQ when used to treat patients with malaria in Nigeria showed that it was safe except for mild side effects, such as gastrointestinal reactions (vomiting and diarrhea), dizziness, headache, tinnitus, taste and smell disturbance, and irritability [24]. Since these effects are usually mild, they disappear once the treatment is stopped. Conversely, the safety issues of the use of CQ or HCQ have been disputed due to its cardiac toxicity and prolongation of the QT interval in COVID-19 patients treated with this drug [24]. Also, it has been hypothesized that short CQ or HCQ treatments might cause harmful effects in treating COVID-19 patients because the drug may impair innate immunity and deprive the host of self-defense against COVID-19 [25].

According to Zhang et al., the adverse drug reaction of CQ/HCQ results in more severe side effects, such as retinopathy which is a serious clinical problem that results in irreversible damage to the vision, and cardiotoxicity due to the accumulation of excessive lysosomal disorder which may be related to long-term use and eventually lead to arrhythmia and or cardiomyopathy, or in the case of excessive ingestion of chloroquine it causes poisoning [19]. On the nervous system, there is currently no experimental evidence that CQ/HCQ and their metabolites affect its conduction properties [26, 27].

Remdesivir and lopinavir/ritonavir are antiviral drugs already in use with their safety established, and during the COVID-19 pandemic, the evidence encouraged their safe administration to hospitalized patients without significant grade 3 or 4 adverse effects reported [28]. Similarly, vitamin C and zinc are oxidizing agents, and their safe use in the management of viral infections is to boost the immune system while dexamethasone's safe administration to COVID-19 patients is not disputed as a treatment for inflammatory problems [29].

Practical application of drugs treatment in COVID-19

The treatment approach for COVID-19 patients is fundamental to discriminate between anecdote and reliable evidence-based drugs for clinical decision-making. In Nigeria, the analysis of the NCDC reported data indicating low morbidity and mortality rate which are indices for measuring treatment response to a disease. The comparison of the data of COVID-19 patients' response to CQ or HCQ treatment in Nigeria to other countries shows the effectiveness of CQ or HCQ on COVID-19. Based on available data from the NCDC, the total number of deaths recorded from COVID-19 since the first case was identified on February 27 until October 31, 2020, equal to 1130 out of 61 992 confirmed cases, and 57 465 recovered from the infection compared with the population of approximately 200 million people in the country. Accordingly, the CQ or HCQ and antiviral therapeutic regimen is effective for Nigerians.

Besides the above-mentioned statistics, the bioavailability of CQ or HCQ administered orally will reach its peak in 2 to 4.5 h and it is an added advantage in COVID-19 treatment [23]. The drug can have an active effect on the gastrointestinal tract as it binds to the plasma protein and slowly reaches a steady state of concentration in a short time. Researchers have established that CQ or HCQ is effective against SARS-CoV-2 through increasing the body pH to a high level, prevention of viral entry into the cells, impaired replication, and a pleiotropic action on the human immune system through its immunomodulatory activity [23].

WHO supported the use of the antiviral drug (remdesivir) for the treatment of SARS-CoV-2 to date. Several antiviral drugs have been used in the treatment of COVID-19 patients which included lopinavir/ritonavir (400/100 mg) orally every 12 h in a randomized, controlled open-label trial [23]. Remdesivir pre-clinical trial suggested the drug is an inhibitor of RNA polymerase against multiple RNA viruses; therefore, it was effective for both prophylaxis and therapy of HCoV infections and in macaques infected with SARS-CoV-2 and the same for lopinavir/ritonavir [30].

According to Cavalcanti et al., CQ or HCQ in combination with antibiotics, such as macrolides should be prohibited to avoid the risk of promoting QT prolongation that can lead to tip torsion [15]. Also, the interval between the therapeutic and toxic doses of CQ or HCQ is narrow, and acute poisoning is associated with a potential cardiovascular disease that is life-threatening [24].

Cavalcanti et al. conducted a study on 667 participants in Brazil to determine the efficacy of chloroquine with or without azithromycin; accordingly, 504 patients were confirmed cases of COVID-19 that were included in the modified intention-to-treat analysis compared with standard care. The finding showed that the proportional odds of having a higher score on the 7-point ordinal scale at 15 days of treatment as compared with standard care were not affected by HCQ alone or HCQ+azithromycin [15].

Furthermore, the study showed prolongation of QT interval and frequent elevation of liver enzyme levels were recorded in patients receiving HCQ alone or with azithromycin compared to those participants who were not receiving either of the drugs [24]. This finding implies that the use of HCQ alone or with azithromycin did not improve the clinical status of the patients after 15 days as compared with the standard care for COVID-19 patients in Brazil [24]. This was not the case in Nigeria probably because CQ was already in use and it was an effective drug for treating malaria before the outset of the COVID-19 pandemic though its use had reduced drastically probably due to resistance occurring or the side effects [30]. Recently, CQ or HCQ was found to have immunomodulatory properties that probably result in its effectiveness in treating COVID-19 patients in Nigeria. COVID-19 therapeutics investigated to date include anti-inflammatory agents, antivirals, and antithrombotics as therapies for acute and chronic conditions [31].

Conclusion

The drugs used in the treatment of COVID-19 patients during the pandemic were purely based on clinical trials though in emergencies like that of the COVID-19 pandemic, the scientists posit that whatever drugs that work for an individual have to do with the innate capability of their immune system. It was then argued that treatment of COVID-19 might probably be related to the host characteristics, degree of severity, diversity, environment, and available treatment options.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, study design and preparing the content of the manuscript: Tajudeen Olusegun Rasheed, Revision of the manuscript: Bilawu Yisa Abiodun; Final approval: Wael Mohamed Noaman Higazy.

Conflict of interest

The authors declared no conflict of interest.

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