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Review Article

Ototoxic and Vestibulotoxic Effects of Chloroquine/ Hydroxychloroquine and Remdesivir in the Treatment of COVID-19: Update Review

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ABSTRACT

Introduction: Antiviral drugs have been extensively used as a potential treatment during the COVID-19 pandemic. Based on previous studies, there were concerns about some of these drugs' ototoxic and vestibulotoxic effects. Still, these concerns were exacerbated by the widespread use of these drugs at the beginning of the COVID-19 pandemic. Therefore, this article was done to comprehensively review the effects of ototoxicity and vestibulotoxicity of chloroquine (CQ)/hydroxychloroquine (HCQ) and remdesivir with different administration models and compare with the COVID-19 treatment guidelines in the world and Iran.

Materials and Methods: This study collected the related published studies in PubMed, Scopus, Google Scholar, and Web of Science with the main keywords "chloroquine", "hydroxychloroquine", "remdesivir", "ototoxicity", "vestibulotoxicity", and "COVID-19".

Results: The dose or duration of used HCQ/CQ drugs that caused ototoxic or vestibulotoxic effects in some diseases was reported mainly more than in COVID-19 guidelines, especially in Iran. These findings align with a recent study on slight HCQ-induced ototoxicity in patients with COVID-19 at low doses and short lengths of use. No evidence of possible cochlear damage after taking remdesivir is reported.

Conclusion: It seems that the concern about the ototoxic effects of some drugs used in the COVID-19 pandemic should be according to some factors that affect the pharmacological effects of drugs, such as dose, length of use, and co-administration of drugs. Therefore, lower dosage and length of use in some administration models in COVID-19 treatment, such as Iran, are associated with limited and reversible ototoxicity effects. However, further studies are needed.

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1. Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) disease or COVID-19 pandemic appeared in China in December 2019. Compared to other common viral infections, this disease has spread rapidly, and its ability to be transmitted by asymptomatic individuals was peculiar [1]. Although vaccination is underway in most countries, the outbreak of COVID-19 has not yet stopped [2]. Several antiviruses were used during the pandemic period, including chloroquine (CQ) and its analog hydroxychloroquine (HCQ), and remdesivir [3]. CQ and HCQ have long been used as critical antiviral drugs to treat malaria [4]. Hydroxychloroquine is utilized to remedy childhood arthritis, rheumatoid arthritis, manifestations of lupus, pulmonary hemosiderosis, and some autoimmune diseases via intervention with the relationship of cells in the immune system; thus, obstructing the virus from infecting the cell and reproducing inside the cell [5-10]. In February 2020, the National Health Commission in China recommended the CQ/HCQ for COVID-19 treatment [2]. The same year, the Food and Drug Administration (FDA) approved their use to treat hospitalized patients with COVID-19 [11]. Therefore, this drug is widely suggested in the diagnosis and treatment protocols of COVID-19 globally [1, 12-14]. This choice was made mainly because of its history of impact on the SARS-CoV1 virus [15]. Although several clinical trials have shown the positive effects of CQ/HCQ on alleviating illness duration and improving pulmonary pneumonia [16, 17], some randomized clinical trials do not support the efficacy of HCQ in treating COVID-19 and suggest ceasing its prescription [14]. CQ and HCQ were widely used during the COVID-19 pandemic, but studies showed dose-dependent side effects of CQ. Thus, higher doses of this drug are associated with more severe destructive effects, while lower doses have relatively few harmful effects [18]. Decreased visual acuity, diplopia, retinal toxicity, hallucinations, bleaching of the hair, skin lesions, and hypotension are the adverse effects of this drug [19, 20].

On the other hand, HCQ is a more soluble and less toxic metabolite of CQ, which causes fewer side effects and is safer [21]. Other side effects of these drugs, which have raised concerns about their widespread use during the COVID-19 pandemic, are ototoxicity and vestibulotoxicity [14, 22-24]. This concern is due to the ototoxic and vestibulotoxic effects of CQ in the treatment of malaria, Lupus Erythematosus [4, 20, 25-29], and HCQ in the treatment of systemic lupus erythematosus, human immunodeficiency virus (HIV), idiopathic pulmonary fibrosis, and rheumatoid arthritis reported by the patient or audiological assessment [5-10]. Ototoxicity refers to the toxic capacity of drugs that can harm cochlear, vestibular, and auditory nerve cells and is generally associated with symptoms, such as sensorineural hearing loss, tinnitus, and imbalance [30]. These symptoms can arise during or after the end of therapy and they can be bilaterally symmetrical or asymmetrical [31].

Although the World Health Organization's (WHO) guideline published on December 17, 2020, did not strongly recommend CQ/HQ usage with any severity and symptoms of the disease [32], many people worldwide have used this drug during the COVID-19 pandemic. Therefore, considering the widespread prescription of CQ/HCQ at the beginning of the COVID-19 pandemic, it is unclear whether we should be concerned about the ototoxic effects of the drug in COVID-19 patients. Another antiviral drug extensively prescribed and used to treat COVID-19 is remdesivir. It is a new antiviral drug from the family of nucleoside analogs initially known by the code GS-5734. It was developed to treat Ebola virus disease and Marburg virus infections. However, it gradually became clear that it had antiviral properties against other RNA monoclonal viruses, such as respiratory syncytial virus, blood virus, Nipa virus, and the coronavirus family [26, 33]. The recommendation to use remdesivir in COVID-19 treatment was approved on November 20, 2020, based on review articles and meta-analyzes of four clinical trials [34]. However, there are more unknowns about its underlying effects, including the need for mechanical ventilation, age group of children and the elderly, duration of hospitalization, long-term safety, and uncommon but significant side effects [35]. Since some review articles refer to this drug as an ototoxic drug, concerns about its impact on hearing can be another concern for its side effects [22]. Therefore, this article was done to comprehensively review the effects of ototoxicity and vestibulotoxicity CQ/HCQ and remdesivir with different administration models and compare them with the COVID-19 treatment guidelines in the world and Iran.

2. Materials and Methods

The databases included PubMed, Scopus, Google Scholar, and Web of Science. The search strategy was the combined MeSH terms and keywords of chloroquine or hydroxychloroquine, remdesivir, ototoxicity, hearing loss, vestibulotoxicity, tinnitus, COVID-19, and SARS-CoV-2. The search period was between 1968 and 2022. The selection process of the article was based on its relevance to the subject of the article. Thus, articles with one of the drugs in their title or abstract, along with the keywords hearing, ototoxicity, and vestibulotoxicity, were considered strongly related.

3. Results

In Table 1, administration models of some drugs in COVID-19 treatment in the world and Iran are mentioned. Also, Fourteen research articles related explicitly to the ototoxicity due to CQ/HCQ drugs are listed in Table 2. Different models of administration of HCQ/CQ and Remdesivir drugs and the results of the studies conducted in the tables in the discussion section will be discussed.

4. Discussion

Firstly, in this section, we started the treatment approach to COVID-19 in the world and Iran. Then, studies on the effect of CQ/HCQ and remdesivir on the auditory and vestibule systems with a focus on dose and length of use are reviewed.

Treatment approaches for COVID-19 in the world and Iran

The suggested prescription was oral HCQ 800 to 1600 mg on the first day, divided into one to three doses. Then, 200 to 800 mg orally once a day divided into one to three doses for 5 to 21 days [34]. HCQ prescription values can also vary depending on the severity of the disease and the administration models are listed in Table 1 [36]. In the latest guideline published by WHO, the administration of HCQ is not strongly recommended [37]. In the global guidelines for the treatment of COVID-19, the HCQ form is mostly given, and CQ is used sparingly, but 250 mg CQ tablets are considered equivalent to 200 mg HCQ. Remdesivir is recommended only in critical cases. People who need supplemental oxygen but are not under invasive mechanical ventilation (extracorporeal membrane oxygenation (ECMO)) benefit most from prescribing this drug. The recommended dose of remdesivir for patients who need mechanical ventilation and/or ECMO ventilation is given in Table 1. However, if the patient needed mechanical ventilation, 200 mg was injected on the first day and 100 mg in the same way on the second to fifth days. If the patient did not recover, the same treatment was given for another five days [38]. This injection is 5 mg/kg in children weighing more than 3.5 to 4 kg as a single dose on the first day and then 2.5 mg/kg on the second day [39].

As seen in Table 1, in versions 1-3 of the diagnostic therapeutic flowchart for COVID-19 (DTFC) in Iran, firstly, HCQ 200 mg (or CQ 250 mg) was administered twice daily for 5 to 14 days. In DTFC5-6 (April 29, 2020), the prescribed dose of these drugs was doubled on the first day (400 mg), but the maximum duration of use of this drug was set at ten days. On June 28, 2020, based on DTFC update 7, the dose of HCQ/CQ did not change but was administered only to high-risk populations in an outpatient setting [12].

Table 1. Administration models of some drugs in COVID-19 treatment in the world and Iran

Drug	Statements	Administration Models
HCQ	Globally	800 to 1600 mg on the 1st day, then 200 to 800 mg daily for 5-21 days Prescription according to the severity of the disease: Mild: 800 mg once at 1st dose, then 200 mg twice daily for 4-7 days without optional additional medicine. Pneumonia: 200 mg twice a day for 5–20 days plus lopinavir 400 mg twice a day/ritonavir 100 mg twice a day Severe: 400 mg twice on the 1st day and then 200 mg twice a day on days 2–5 plus remdesivir
	Iran	DTFC 1-3: 200 mg twice daily for 5-14 days DTFC5-6: 400 mg twice daily for a maximum of 10 days DTFC5-7: 400 mg twice daily on the 1st day, then 400 mg daily for 7-12 days in hospitalized patients DTFC update 9: Same protocol, Prescribing only for high-risk individuals DTFC update 10: Same protocol, case-by-case basis Prescription according to the severity of the disease: Non-severe: 200 twice daily on the 1st day plus lopinavir/ritonavir (200 mg/50 mg) for 5-14 days. Hospitalized patients: 400 mg twice daily on the 1st day, then 200 mg twice daily for 7-14 days. Very severe: Not recommended
CQ (Its prescription is not common)	Globally	Mild: 1000 mg at 1st dose, then 500 mg twice a day, then 300 mg twice a day until day 5. Pneumonia: 500 mg twice a day for 7 days. Severe: 600 mg at 1st dose, then 300 mg, and then 300 mg twice a day on days 2–5
	Iran	Similar to the HCQ prescription protocol (250 mg of CQ is considered equivalent to 200 mg of HCQ)
Remdesivir	Globally	Critical cases: 200 mg on the 1st day injected within 30-120 minutes, then 100 mg on days 2-10
	Iran	Pulmonary involvement: Similar to the administration model in the world

Abbreviations: HCQ: Hydroxychloroquine; CQ: Chloroquine; DTFC: Diagnostic therapeutic flowchart for COVID-19. JMR

According to DTFC1-4, two disparate treatments were proposed based on disease severity in in-patient settings. For patients in the non-severe category of the disease, a combination of HCQ 200 mg (or chloroquine phosphate 250 mg) twice daily only on the first day plus lopinavir/ritonavir (200 mg/50 mg), two tablets twice daily for 5-14 days was recommended. In conclusion, DTFC5-7 recommends only HCQ 200 mg (or CQ 250 mg), two tablets twice daily on the first day, and one tablet twice daily for a minimum of 7 and a maximum of 14 days in hospitalized patients. In patients categorized as very severe, the administration of HCQ/CQ is not recommended [12]. In the DTFC5-9 update (December 2, 2020), HCQ/CQ is recommended only in patients without hospitalization, specifically in the first week of the onset of symptoms [40]. According to the latest guidelines published in Iran, DTFC update 10 (May 24, 2021), HCQ is recommended on a case-by-case basis, and lopinavir and ritonavir are not recommended [41].

Remdesivir can only be prescribed in children and adults with COVID-19 approved by pulmonary involvement and need support for respiratory disorders, not only in critical conditions in Iran. The prescribed dose is the same as other protocols globally [38, 42].

Administration models of CQ and HCQ (dose and length of treatment) and ototoxicity and vestibulotoxicity effects

The physiopathology of the ototoxic effects of HCQ and CQ is not known precisely. The studies suggest that it is probably related to the destruction of stereocilia, neuronal loss, vascular injury, and degenerative changes in both planum semilunatum and stria vascularis. Therefore, quinine-related compounds revealed long-term retention in the inner ear's melanocytes, explaining the late onset of lesions and symptoms [43]. As shown in Table 2, the results of our search showed that 14 studies were conducted on the effect of using CQ and HCQ on auditory and vestibular organs, and only one of them examined the effects of HCQ ototoxicity along with the possibility of hearing damage caused by COVID-19 itself. Of these, ten studies were case reports (four studies about CQ and six studies about HCQ) and there were two observational studies, one case-control study, and one cohort study [4-10, 20, 25, 27-29, 44-47]. In short-term use of 1200 mg CQ (high dose) in the first dose and 600 mg every 12 hours to 2 days, out of 30 patients with malaria, only two patients showed bilateral high-frequency hearing loss (8 to 12 kHz) at behavioral thresholds. Otoacoustic emissions (OAEs) and auditory brainstem response (ABR) were also abnormal, but after one month, the results were reversible (typical). One person also showed dizziness and nystagmus, which resolved spontaneously after treatment [4]. Another observational study was conducted in 1985 by Bernard on 74 patients (18-50 years). Of these, 70 had rheumatoid arthritis, and four had lupus treated with CQ. The study lacked dose and duration of drug consumption reports. However, as the author stated in the results section that abnormal results in ABR were observed after about eight months of treatment in 13 patients with rheumatoid arthritis that resolved after CQ discontinuation, it seems that the duration of treatment is long. Only two patients developed episodic imbalance and tinnitus during treatment [25]. A case study was conducted by Borba et al. (2004) on monitoring the ototoxic effects of CQ use in children treated for systemic lupus erythematosus during pregnancy. Nine children whose mothers used CQ during pregnancy (dose of 250 mg at least during the first trimester of pregnancy (56% during the whole gestational period)) did not show hearing loss in pure tone audiometry in comparison to the control groups [44]. However, a single case report declared the entire lack of inner and outer hair cells throughout the length of the cochlea in a deaf child whose mother took CQ during pregnancy (dose of 250 mg/day during the first trimester of pregnancy). This study did not mention the absence of other risk factors for hearing loss in children [28]. Hearing loss in two children whose mothers used CQ during pregnancy was seen in another study (chloroquine phosphate 250 mg until the sixth week of her pregnancy) [48]. Hearing loss after consuming CQ was observed in two adult cases and in one of them (a 52-year-old man) after the injection of the dose of 1 g of CQ, which was bilateral and accompanied by tinnitus, and in another case, after CQ treatment and lasted for seven months [27, 46].

So far, six case reports (7 patients) have been published about hearing loss and tinnitus after taking HCQ [5-10]. Two of these reports were on children. In one of them (a 7-year-old child with idiopathic pulmonary hemosiderosis), severe unilateral progressive hearing loss was observed in audiometry with no response in ABR after two years of HCQ consumption (200 mg daily), and in the second case (an 11-year-old child with systemic lupus erythematosus), hearing loss, especially at low frequencies, was reported after two months of taking this drug (100 mg daily dose) [5, 9]. In other reported cases, the primary dose of HCQ was 400 mg/day, and the duration of the drug prescription was from one month to three years [6-8, 10]. In a 57-year-old man, bilateral sensorineural hearing loss (moderate to severe) was observed after one month of HCQ use, but the hearing improvement was observed two months after drug discontinuation [8]. In another case (a 34-year-old woman with rheumatoid arthritis), mild hearing loss was observed after five months of using HCQ,

which improved after discontinuation of the drug [10]. Also, Johansen et al. reported two samples of irreversible hearing loss after years of using HCQ in a man and a woman aged 44 years old, although the details are unclear [7]. The most relevant study that directly addressed the effects of HCQ consumption on the hearing system of COVID-19 patients was conducted recently. The findings of this cohort study showed that both COVID-19 adult patients with a history of HCQ (HCQ+) and patients without drug use (HCQ-) had poor pure tone audiometry (PTA) thresholds and decreased transient evoked otoacoustic emissions (TEOAE) amplitudes at high frequencies in comparison to the control group. Despite further damage to the cochlear structure in HCQ+ patients, these results were not reflected in their PTA thresholds. Also, the damage was somewhat reversible. In this study, HCQ (400 mg) was taken as tablets twice daily on the first day, followed by one tablet twice a day for a maximum of six days [47].

Remdesivir, ototoxicity, and vestibulotoxicity

Remdesivir was approved by FDA On October 22, 2020, as the first antiviral treatment for COVID-19 [49]. It seems that this drug has efficiency even against newer coronavirus strains, including B.1.17 and B.1.351, which is considerable in this respect [50]. In a longitudinal study of 137,870 patients admitted to US hospitals between February 1, 2020, and February 28, 2021, 21.2% had taken remdesivir [51]. Meanwhile, some review studies suggest that the drug may be ototoxic [22, 52]. However, to the best of our knowledge, no original study has confirmed the ototoxicity of remdesivir at any dose and duration of use. Also, Cianfrone et al. (2011) did not mention this antiviral drug among the drugs that can lead to ototoxicity and vestibulotoxicity effects [53]. Although no evidence has been reported on the possible cochlear and vestibular damage after taking medicine, and investigations are ongoing.

Comparison between administration models of CQ, HCQ, and remdesivir regarding ototoxicity and what was used in the COVID-19 pandemic

Two approved treatments are mentioned in the latest update of the guideline for treating diseases caused by SARS-CoV and MERS-CoV (August 17, 2021). One of these treatments is a class of antiviral drugs whose effectiveness has been proven or is being studied, and a newer category is anti-SARS-CoV-2 monoclonal antibodies [54]. Antivirals have been widely used in treating COVID-19 since the beginning of the pandemic. At the same time, studies were conducted on the side effects of their use, and concerns about the ototoxic effects of some of them were published, which, based on previously published articles on the treatment of other diseases, showed ototoxic effects. Some essential drugs were CQ, HCQ, and remdesivir [22, 23, 53, 55].

As mentioned, a review of studies, which are primarily case reports, shows that the use of high doses or more prolonged use of CQ/HCQ than the values prescribed in the treatment of COVID-19 can lead to high-frequency hearing loss and ABR abnormalities in some cases [4, 5, 8-10, 46], which has been accompanied by vestibular symptoms in rare cases (only after CQ consumption) [25, 28, 46]. Although the hearing loss was reversible or partially reversible in some cases [4, 8, 10, 25], the hearing loss that occurred when the drug was used for several years was not reversible after stopping the medication [7]. Regarding the effects of CQ ototoxicity during pregnancy on children, a case-control study did not show a significant difference in the thresholds of PTA in children whose mothers had a history of using this drug with the group without a history of use [44]. However, there are very few case report studies that the ototoxic effects of this drug (especially in the first trimester of pregnancy) can lead to hearing loss [28]. Therefore, it should be considered in prescribing this drug during pregnancy.

Regarding the use of HCQ, two hearing loss cases in children have been reported, in both of which the drug doses used were less than the prescribed dose in the treatment of COVID-19 in adults. Nevertheless, the duration of drug use was longer than the treatment period for COVID-19 (two months and two years) [5, 9]. HCQ/CQ must not be in the treatment protocols of children with COVID-19 [39]. In adult cases with hearing loss, the dose of HCQ was mainly 400 mg per day, but the duration of use was from one month to three years [6-8, 10]. According to the global prescribed HCQ protocol, the first dose was initially estimated at 800-1600 mg per day, and in the following days, 200 to 400 mg per day [34]. In Iran and many countries, the lower limit of dosage is considered. Thus, 800 mg (1000 mg CQ) on the first day and 400 mg (500 mg CQ) on the following days are recommended. The prescribed dose of these drugs in the COVID-19 flowchart treatment until the sixth version in Iran was lower than the lower limit of WHO guidelines (400 mg on the first days and 200 mg of HCQ on the following days) [12, 36]. It seems that only the prescribed dose on the first day of treatment of COVID-19 is higher than the doses used in other studies that led to hearing loss, such as in malaria treatment. Also, it should be noted that two out of three cases of hearing loss in the treatment with CQ in malaria disease were children and effective results were obtained [20, 29, 46].

Table 2. Published studies on ototoxicity and vestibulotoxicity of CQ and HCQ drugs

Author (s)	Disease	Study Design	Sample Size/Age (y)	Type of Drug	Dose and Duration of Used	Audiological or Vestibular Test	Results	Durability
Matz 1968 [28]	Systemic lupus erythematosus in mother	Case report	1/7	CQ	250 mg/day, during the 1st trimester of pregnancy	PTA/vestibular examination	Profound bilateral sensorineural hearing loss, a complete absence of inner and outer hair cells in a deaf child. disequilibrium with a tendency to fall to the left, a marked bilateral vestibular paresis	Irreversible
Dwivedi and Mehra 1978 [46]	Malaria	Case report	1/52	CQ	1000 mg, a single dose	PTA, caloric test	Bilateral complete sensorineural deafness, caloric test with ice-cold water did not show any response in either ear	Irreversible
Mukherjee and Enugu 1979 [29]	Malaria	Case report	1/ 6	CQ	250 IM mg/day, Seven days	PTA	Severe unilateral sensorineural hearing loss and abnormal gait	Reversible after prednisolone prescription
Bernard 1985 [25]	Rheumatoid arthritis and systemic lupus erythematosus	Observational study	74/18 -50	CQ	250 mg/day, At least 12 months	PTA, speech audiometry, and ABR	No hearing change in pure tone audiometry after taking the drug, abnormal results of ABR two patients reported transient episodes of tinnitus and imbalance	In 13 patients, eight months of treatment, the symptoms were resolved after discontinuation of chloroquine
Hadi et al. 1996 [20]	Malaria	Case report	1/2.5	CQ	65 mg single IM dose	ABR, PTA	Severe hearing loss (no response bilaterally), Abnormal gait	Hearing thresholds were followed up to 7 years and did not recover (irreversible). Gait returned to normal after 9 months (reversible)
Borba et al. 2004 [44]	Systemic Lupus Erythematosus during the 1st trimester of pregnancy	Case-control study	9/mean of age 7.5	HCQ	250 mg/day, during the 1st trimester of pregnancy (mean time of CQ use was 6.1 months)	PTA	No significant difference in the PTA threshold between the case and control groups	-

Author (s)	Disease	Study Design	Sample Size/Age (y)	Type of Drug	Dose and Duration of Used	Audiological or Vestibular Test	Results	Durability
Subramaniam and Vaswani 2015 [4]	Malaria	Prospective observational study	30/14-58	HCQ	1200 mg and then 600 mg every 12 hours for two days	PTA, OAE, and ABR	Two patients showed bilateral high-frequency hearing loss OAE and ABR findings were abnormal	Thresholds were normal after one month (reversible)
Johansen and Gran 1998, [7]	Systemic lupus erythematosus	Case report	2/44	HCQ	No report	PTA	Sensorineural hearing loss after several years	Irreversible
Seçkin et al. 2000 [10]	Rheumatoid arthritis	Case report	1/34	HCQ	400 mg/day, 5 months	PTA	Mild hearing loss with tinnitus	Normal audiogram two months after the discontinuation of the drug (reversible)
Coutinho and-Duarte 2002 [5]	Pulmonary haemosiderosis	Case report	1/7	HCQ	200 mg/day, two years	PTA, ABR	Unilateral progressive hearing loss in audiometry and abnormal ABR	No report
Lim and Tang, 2011 [9]	Systemic lupus erythematosus	Case report	1/11	HCQ	100 mg/day, two months	PTA	Hearing loss, especially at low frequencies in both ears	
Khalili et al. 2014 [8]	Rheumatoid arthritis (HIV)	Case report	1/57	HCQ	400 mg/day, one month	PTA	Bilateral sensorineural hearing loss (moderate to severe)	Recovery of audiometric thresholds two months after the discontinuation of the drug (reversible)
Fernandes et al. 2018 [6]	Systemic lupus erythematosus	Case report	1/51	HCQ	400 mg daily, 3 years	PTA	Bilateral moderate sensorineural hearing loss and tinnitus	Irreversible
Rahimi et al. 2022 [47]	COVID-19	Cohort study	30/23-48	HCQ	800 mg/day and then 400 mg, day, 4-6 day	PTA TEOAE	No significant difference in PTA threshold between HCQ+ and HCQ- cases Further damage to outer hair cells (OHCs) due to lower TEOAE amplitude in the HCQ+group	Partial reversible

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Abbreviations: CQ: Chloroquine, HCQ: Hydroxychloroquine, PTA: Pure tone audiometry, TEOAE: Transient evoked otoacoustic emissions, ABR: Auditory brainstem response.

The maximum duration of administration of this drug in the treatment of COVID-19 is 21 days [37]. The period of use of these drugs in COVID-19 flowchart therapy in Iran is a maximum of ten days, and the shorter duration of use of medicine can reduce the cumulative effects of the drug [56]. Both CQ and HCQ are considerable for their long terminal and elimination half-lives of 22 and 20–60 days, respectively [57]. Therefore, the mentioned drugs' use in treating COVID-19, especially in Iran, is less than those used to treat other diseases, such as systemic lupus erythematosus [6]. The results of a recent study on COVID-19 patients could support these findings. Because this study was performed in Iran, the dose of HCQ and the duration of its use are safer than other protocols; thus, the results showed mild effects of HCQ in addition to the impact of COVID-19 on patients. This difference is not seen in the audiometric results of patients.

However, more damage to OHCs, especially at high frequencies, was evident in drug users in TEOAE results. The study noted that due to dose-dependent effects, there is a possibility of more apparent damage at higher doses [47].

Generally, the mechanisms of ototoxicity caused by different drugs are different. About the antimalarial drug "quinine", its exact mechanism is not clear. But vasoconstriction in the cochlea, decreased cochlear blood flow, and damage to OHCs are reported in guinea pigs [58]. Reversible inhibition of mechanoelectrical transducer (MET) channels associated with a reduction in hair cell motility is also supposed to be involved in hearing impairment. The first point that should be considered regarding the damage caused by this drug was a high dependency on the dose [31]. The second point, in terms of the side effects of drugs, is that some factors modify drug effect and dosage. Thus, they can change pharmacodynamics and pharmacokinetics. One of the factors is physiological factors, including age, gender, and species. Very young (neonatal) and very old humans and animals require low dosages compared to those required by adults. Also, the aging process can increase or decrease sensitivity to a medication independent of pharmacokinetic changes [59]. In most elderly cases, according to the pharmacokinetics hypothesis, higher drug concentrations at the sites of action lead to increased end-organ response [60]. Also, Lien et al. (2021) stated that females were more likely to experience adverse drug reactions, including ototoxic effects [61]. Genetic, pathological, environmental, and therapeutic factors affecting the particular frequency of drug administration are other influential factors that must be considered when interpreting the ototoxic effects of drugs [56]. The simultaneous administration of drugs should be considered due to cumulative effects and ototoxicity. Thus, Alvan et al. (2016) emphasized not using quinine at the same time as other ototoxic drugs [62]. In the COVID-19 treatment flowchart, whenever CQ/HCQ is used concomitantly with another drug, a lower dose is prescribed, but the combined effects of the drugs cannot be assured. However, the ototoxic drugs lopinavir and ritonavir are currently not prescribed in combination with CQ/HCQ [36, 55]. Some evidence suggests that taking these drugs may increase serum HCQ levels and increase the risk of ototoxicity [63]. Although no research has yet been published on the ototoxic effects of this drug alone or in combination with other drugs, caution should be exercised. However, the use of HCQ has decreased today and it is recommended only at the beginning of the disease [41].

In severe cases, in addition to CQ/HCQ, remdesivir was prescribed. However, the dose of HCQ was reduced to only five days. In severe cases, HCQ was not prescribed in Iran. Consistent with published systematic reviews and meta-analyses, the use of remdesivir increases the rate of recovery in moderate and severe patients [64]. Although no evidence of remdesivir toxicity effects has been found so far, it can be considered safe until writing this article.

The third point that should be mentioned, besides the effects of medications used in the COVID-19 treatment, is the nature of the SARS-CoV-2. Although a few studies have not reported hearing loss in COVID-19 [65], most studies have shown that this disease could lead to sudden sensorineural hearing loss, high-frequency hearing loss, tinnitus, and dizziness like other viral diseases known in this field, such as herpes simplex virus and cytomegalovirus infections by causing inflammatory processes and cytokine storms [47, 66-68]. In the meta-analysis published by Almufarrij and Munro (2021), the pool rate of 7.6%, 14.8%, and 7.2% for hearing loss, tinnitus, and rotatory vertigo, respectively, were reported. Thus, hearing loss and vertigo after contracting COVID-19 can occur following vestibular neuritis or labyrinthitis [68]. This effect is more pronounced in the severe form of the disease [66, 67]. During COVID-19 treatment, these effects are difficult to distinguish from the damage caused by ototoxic drugs. Although Rahimi et al. (2022) showed cochlear damage caused by SARS-CoV-2, in addition to the effects of ototoxicity by designing a study with two COVID-19 patient groups with and without HCQ medication and a healthy group [47]. Therefore, it seems that SARS-CoV-2 with its mentioned mechanisms also leads to damage to the hearing system, but there are not many studies in this field [47]. Using OAE, which can

indicate the condition of the OHCs [47] and audiometry can be recommended for hearing monitoring in patients with COVID-19, especially for the severe form [69]. Although high-frequency audiometry is an ideal option, conventional audiometry can also be used as a screening tool in general due to its availability and low cost [36].

5. Conclusion

Although WHO does not strongly recommend CQ/HCQ, many patients used them during the COVID-19 pandemic. Therefore, there were concerns about their effects in addition to the impact of COVID-19 on the hearing and balance system. Based on the findings of studies, it seems that the ototoxic and vestibulotoxic effects of CQ/HCQ, like the effect on other organs, depend on the dose and length of use. The dose and especially the period of use of these drugs with ototoxic and vestibulotoxic effects were mainly higher than the administration models published in the treatment of COVID-19 (especially in Iran). Also, harmful effects can be reversible. Therefore, there is less concern about the ototoxicity of these drugs in countries that use a safer administration model. However, due to the simultaneous use of several ototoxic drugs during the COVID-19 pandemic, the combined effects of these drugs should be considered. A few studies have been performed on the impact of these drugs during the COVID-19 pandemic and the evaluation of the auditory and vestibular systems in patients with a history of COVID-19 who report hearing loss and dizziness symptoms after taking the drug is necessary. There is currently no evidence that remdesivir affects the hearing system; however, further research is needed.

Ethical Considerations

Compliance with ethical guidelines

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

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Authors' contributions

Conceptualization: Vida Rahimi; Methodology: Vida Rahimi and Elham Tavanai; Writing: Vida Rahimi, Elham Tavanai and Mohammad Ehsan Khalili; Supervision: Ghassem Mohammadkhani.

Conflict of interest

The authors declared no conflict of interest.

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