

OTOTOXICITY OF DRUGS USED IN THE TREATMENT OF COVID-19

Magdalena Beata Skarzynska^{1,2,A-E}, Bartłomiej Krol^{3,F}, Natalia Czajka^{3,E-F},
Lukasz Czajka^{1,2,E-F}

Contributions:

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B Data collection/entry
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D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

¹ Otorhinolaryngology, Institute of Sensory Organs, Poland

² Otorhinolaryngology, Center of Hearing and Speech, Poland

³ Otorhinolaryngology, Institute of Physiology and Pathology of Hearing, Poland

Corresponding author: Magdalena Beata Skarzynska, Institute of Sensory Organs, Center of Hearing and Speech, 05-830 Kajetany, 7 Mokra St., Poland;
email: m.skarzynska@csim.pl, phone: + 48 22 4635346

Abstract

Background: Actual level of knowledge of treatment of COVID-19 disease caused by a type of coronavirus is that the disease cannot at present be cured by targeted therapy. Worldwide research is aiming to find a specific treatment, such as a vaccine or drug, for this type of coronavirus; this may help improve the situation, but it is highly expensive and time-consuming. The purpose of this paper is to review drug therapies approved in different parts of the world to treat COVID-19 and draw attention to ototoxicity as one of the adverse side-effects.

Material and methods: Review of current literature was done in the scientific databases PubMed, ResearchGate, GoogleScholar, and ScienceDirect. Studies were reviewed with reference to the inclusion criteria, then graded to assess the internal and external validity, leaving 50 studies for review.

Results: According to scientific reports, possible antiviral pharmacological agents to treat COVID-19 consist of chloroquine, hydroxychloroquine, azithromycin, oseltamivir, and tocilizumab. In some cases, certain combinations may lead to additive ototoxicity as an adverse effect. Ototoxicity may be manifested by sensory and nervous hearing loss, tinnitus, imbalance, and cochlear-mandibular symptoms, which are sometimes temporary but sometimes permanent.

Conclusion: Drug ototoxicity is well known as a cause of cochlear hearing loss, and so the use of new pharmacotherapy methods and drug combinations in the fight against the new coronavirus may have harmful effects. Ototoxicity needs to be taken into account.

Key words: drugs • hearing loss • ototoxicity • chloroquine • COVID-19 • SARS-CoV-2.

OTOTOKSYCZNOŚĆ LEKÓW STOSOWANYCH W LECZENIU COVID-19

Streszczenie

Wprowadzenie: Aktualny stan wiedzy na temat leczenia choroby COVID-19 wywołanej przez rodzaj koronawirusa wskazuje, że choroby tej nie można obecnie wyleczyć za pomocą terapii celowanej. Prowadzone na całym świecie badania mają na celu znalezienie przyczynowego sposobu leczenia – szczepionki lub leku działającego na tego typu wirusa. Proces badań naukowych i klinicznych nad szczepionką lub nowym lekiem jest procesem zarówno bardzo kosztownym, jak również czasochłonnym. Celem niniejszego artykułu jest przegląd terapii farmakologicznych w leczeniu COVID-19 aktualnie stosowanych w różnych częściach świata oraz zwrócenie uwagi na ototoksyczność jako jedno z działań niepożądanych stosowanej farmakoterapii.

Materiał i metody: Przeglądu aktualnej literatury dokonano na podstawie naukowych baz danych: PubMed, ResearchGate, GoogleScholar i ScienceDirect. Wyniki przeglądu poddano analizie pod kątem kryteriów włączenia, a następnie oceniono trafność wewnętrzną i zewnętrzną materiału. Ostatecznie do analizy pozostawiono 50 badań.

Wyniki: Według doniesień naukowych do farmakoterapii COVID-19 możliwe jest wykorzystanie takich substancji czynnych jak: chlorochina, hydroksychlorochina, azytromycyna, oseltamivir i tocilizumab. Ich niektóre kombinacje mogą skutkować wystąpieniem ototoksyczności jako działania niepożądanego. Ototoksyczność może objawiać się: utratą słuchu odbiorczego i przewodzeniowego, szumami usznymi, zaburzeniami równowagi; może być przejściowe lub trwałe.

Wnioski: Ototoksyczność leków jest znanym działaniem niepożądanym wielu grup leków oraz może być przyczyną utraty słuchu. Dlatego stosowanie farmakoterapii i nowych schematów leczenia w walce z koronawirusem, wywołującym chorobę COVID-19, wymaga zwrócenia uwagi na możliwe działania niepożądane, w tym skutki ototoksyczne.

Słowa kluczowe: leki • utarta słuchu • ototoksyczność • chlorochina • COVID-19 • SARS-CoV-2

Background

Introduction

At the beginning of 2020, we faced one of the biggest public health crises, one which has had broad economic effects on all industries and on human freedom (1). At the end of 2019, disturbing information began to emerge

from the city of Wuhan (in the Hubei province of China with a population over 11 million) about cases of a previously unknown disease whose clinical symptoms resembled pneumonia (2). The cases later turned out to be triggered by a new coronavirus and led to a rapid spread of the virus (3). The Chinese scientific and clinical community developed methods of diagnosing the new disease by providing a new virus sequence. The development of a reverse

transcriptase polymerase chain reaction (RT-PCR) test for COVID-19 allowed the disease to be diagnosed (4,5). However, the low availability of tests and the large number of false-negative results at the beginning of the epidemic's development hindered rapid diagnosis of new cases. Radiological examination remains the standard for diagnosing COVID-19 disease. Computed tomography of the chest allows detection of the disease in its early stages (6–9).

On 12 January 2020 the World Health Organization (WHO) classified the new virus as a novel coronavirus, nCoV-2019. On 11 February 2020, WHO classified the disease caused by the coronavirus under the name COVID-19 (10,11). In addition, the International Committee on Virus Taxonomy called acute respiratory coronavirus 2 2019-nCoV (SARS-nCoV-2) syndrome (12,13). About a month later, on 11 March 2020, WHO announced a coronavirus-related pandemic, thus establishing the highest degree of threat to international public health (14).

According to data on the WHO website, as of 25 May 2020 there were more than 5 250 000 confirmed cases of virus infection in 216 countries. The most registered cases were in China, but the virus also reached Europe, where the northern part of Italy became the main epicenter of the disease. However, the pandemic continues and new confirmed cases are reported daily (15).

Due to the lack of available pharmacological treatments or vaccines and the progressive nature of the pandemic, scientists and doctors have tried new therapies to combat the developing pandemic (9). However, the latest reports on the drugs employed show they carry risks, in particular ototoxic effects. The purpose of this review is to provide timely information on therapies for the new coronavirus, in particular the risks of ototoxic effects of the drugs used in current COVID-19 pharmacotherapy.

Outbreak and etiology

According to sources, the first cases of infection with a new type of virus concerned the residents of Wuhan from the Chinese province of Hubei, who visited the local fish market, from where they became infected with the new virus (4,16). On 1 January 2020, the fish market was closed and was subjected to detailed analysis of infection factors (3).

The available research methods for the new pathogen enabled a full genome analysis to be published on 7 January 2020. As a result of this analysis, the causative agent was identified as a new coronavirus that shows about 90% homology with the coronavirus group identified in bats and about 70% homology with SARS-CoV (3,4,11). The virus is surrounded by single-stranded RNA resembling a corona. Its genome codes for the four main structural proteins on its envelope (6,11). A particularly important protein in terms of viral transmission is the peak protein (S), which binds to the angiotensin 2 converting enzyme (ACE2) and participates in the entry of the virus into the host cell (17–19). It is worth mentioning that from an interview with a patient infected with nCoV-2019, we know that bats were not available at the market at the time, since winter is a hibernation period for many species of bats (3). This suggests that at least

one other species might have participated in the expansion of the virus from bat to human (11). SARS-CoV-2 virus belongs to the beta subtype of coronaviruses (there are α , β , γ , and δ groups). The β -coronaviruses are particularly dangerous due to the fact that they can cause pneumonia and severe respiratory disorders (20). In recent years, there have been two epidemics caused by influenza viruses from the coronavirus group. The first was at the turn of 2002/03 in China (the SARS epidemic) and another in 2013 in Saudi Arabia (the MERS epidemic) (21–23, 129). Analysis of the nCoV-2019 genome shows genomic similarities to SARS, with a similarity of 45–90%; the similarity to MERS is 20–60% (18,24,25).

Clinical picture of the disease

COVID-19 disease has a diverse character, ranging from cases that pass asymptotically to those in which patients have acute respiratory failure and multiple organ dysfunction (12,20,26). The most common accompanying clinical manifestations of the disease are fever (but not in all cases), cough, headache, sore throat, fatigue, myalgia, or dyspnea (3,9,20). These symptoms may resemble those of influenza. About a week after infection, patients may experience exacerbation of their symptoms, including respiratory failure, which is particularly dangerous for people with comorbidities (11,27–29). The *New England Journal of Medicine* provided clinical features of infections developed in China based on data from 552 hospitals in 30 provinces, and only 6.1% of patients required hospitalization in intensive care units. The median age of incidence was 61 years (IQR 53.3–71.0), and the median incubation period was 4 days (IQR 7.0–7.5). Of clinical importance, among patients requiring hospitalization in ICU wards, the most common comorbidities were hypertension, diabetes, and COPD (30).

Treatment of COVID-19

Currently, no treatment methods have been developed for the new coronavirus, and according to WHO development of a COVID-19 vaccine may take 18 months (18). Thus, there is an urgent need to develop an effective and safe antiviral therapy, since the WHO does not recommend the use of antibiotics without confirmation of microbial infection (31). The model of currently accepted therapy for COVID-19 disease is one of only treating symptoms and giving general support. In this regimen, proven antiviral drugs as well as anti-inflammatory drugs have been found useful (32). This is confirmed by an analysis carried out by Zhou and colleagues on a group of 191 patients in Wuhan treated for COVID-19 (33). From the data collected by them we know that the pharmacotherapy regimen differed significantly in the group who survived and were released from hospital ($n = 137$) and in those who died ($n = 54$). This diversity may be associated with the co-morbidity of diseases and the representation of specific infection symptoms in given patient groups. The vast majority of patients (95%) were treated with antibiotics. Antiviral drugs were used in a significantly smaller number of patients (21%). In addition, some patients were also treated with corticosteroids and intravenous immunoglobulins. Importantly, the doses of these drugs were significantly different between

survivors and those who died: in the survivor group 48% and 67% of patients received corticosteroids and intravenous immunoglobulins, respectively, whereas in the non-survivor group the figures were 23% and 7%, respectively. These differences were also observed in high-flow oxygen therapy and mechanical ventilation, which mainly involved patients in the group that died (33).

In addition to widespread basic pharmacotherapy, for “complicated” patients there is also a need for supportive care (32). This therapy often involves continuous renal replacement therapy (CRRT), invasive mechanical ventilation, and even extracorporeal membrane oxygenation (ECMO) (34,35). The similarity in the genomic sequence of the new 2019-nCoV coronavirus to the SARS-CoV and MERS-CoV virus sequences allowed researchers to use already known drugs and therapies, although the assessment of the effectiveness of some of these drugs remains controversial (11). Among the drugs tested were ribavirin, penciclovir, nitazoxanide, and nafamostat. Research has drawn attention to the promising therapeutic effect of chloroquine (and its safer analog hydroxychloroquine) and the antiviral drug remdesivir (34,36). The chloroquine dosage was 250 mg twice a day for 7–10 days with the possibility of increasing the dose to 500 mg twice a day (37,38). For hydroxychloroquine, a loading dose of 400 mg twice a day is recommended on the first day, followed by a maintenance dose of 200 mg for the next 4 days (39). In addition to drug treatment, it must be remembered that the key element in rational disease therapy is to stop the spread of the disease by isolating the patient, protecting other patients and medical staff (9,32).

Ototoxicity as an adverse effect of drugs

One sign of ototoxicity is a sudden increase in hearing thresholds or worsening in hearing over a period of time. Ototoxicity is defined as an adverse pharmacological reaction that can affect the auditory nerve or the inner ear and is characterized by cochlear or vestibular dysfunction (40). Ototoxicity is an adverse side-effect of a drug that can have longlasting consequences for the future quality and standard of living of the patient, but in some cases the benefits of using the drug outweigh the risk of loss of hearing. Ototoxicity is particularly dangerous for elderly people as well as for young children. For children, ototoxicity can have significant impacts on their future psychosocial development and whole adult life. Known ototoxic drugs include the aminoglycoside antibiotics, cytostatics (platinum derivatives), loop diuretics, nonsteroidal anti-inflammatory agents (NSAIA), and anti-malarial drugs (41,42). Importantly, ototoxic side-effects can sometimes disappear after pharmacotherapy is stopped, but in some cases it may be irreversible. For example, the ototoxicity of certain groups of drugs, such as aminoglycoside antibiotics like gentamycin, used in children to treat infection, can cause permanent hearing loss (43).

According to clinical protocols and the recommendations of scientific societies, monitoring for early detection of ototoxicity allows treatment regimens to be changed and hence can minimize, or even prevent, ototoxicity leading to balance impairments and/or hearing loss (40,44,45). According to the American Academy of Audiology (AAA), sensorineural

degradation and auditory damage can lead to permanent hearing loss and tinnitus. Audiological monitoring for ototoxicity should be performed for a number of reasons. First, audiological testing allows hearing impairment to be detected as soon as possible before a severe handicap occurs. Second, early detection of a change in hearing may lead to reconsideration of the drug regimen (46). Third, it is important to bear in mind that a drug may become ototoxic not alone but in combination with a few other drugs, so that a cumulative adverse effect may build up.

Material and methods

A database search was conducted to identify the relevant literature. This involved Medline, US National Library of National Institutes of Health (PubMed), ResearchGate, GoogleScholar, and ScienceDirect. Since the literature is scarce, we did not limit the time-frame of our search. The database search was conducted using the terms: ototoxicity, COVID-19, SARS-CoV-2, nCoV-2019, chloroquine, hydroxychloroquine, azithromycin, tocilizumab, oseltamivir. The inclusion criteria were articles written in Polish, German, French, Spanish, or English concerning treatment of COVID-19 and ototoxic effects of the drugs used. The records were reviewed by title and abstract, analyzing the full texts if there were any doubts as to the suitability of the work for inclusion. After excluding articles relating to treatments not covered by this article, topics outside its scope, and works in other languages, 50 articles were considered appropriate for the current review.

Results

Examples of drugs used in treatment of COVID-19 which have ototoxicity as a side-effect

Chloroquine and hydroxychloroquine (37,47–51, 130)

Chloroquine (CQ) and its hydroxychloroquine analogue (HCQ) have long been known and widely used as anti-malarial drugs. They are also used in autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, and discoid lupus due to their immunomodulatory properties (52,131,135). However, recent reports suggest these two substances have potential antiviral properties (53). These drugs are widely used in therapy, and their action is considered safe, although they do have documented side-effects, and the border between a therapeutic dose and a toxic dose is narrow. Overdose may be associated with cardiovascular disorders dangerous to patient health (48).

Chloroquine is one of the antimalarials listed in WHO's *Model List of Essential Medicines (2019)*. According to the list, CQ is strictly recommended for use in the prevention and treatment of *Plasmodium vivax* infection in areas where resistance has not yet developed. Chemically, CQ is 4-aminoquinoline [(7-chloro-4-(4-diethylamino)1-methylbutylamino) quinoline]. It is widely used to treat all types of malaria, except for disease caused by chloroquine-resistant *P. falciparum*. It is highly effective against erythrocytic forms of *P. vivax*, *P. ovale*, and *P. malariae*, sensitive strains of *P. falciparum*, and gametocytes of *P. vivax* (54). CQ inhibits the parasitic enzyme heme polymerase which converts the toxic heme into non-toxic

hemazoin and inhibits ferriprotoporphyrin IX (a heme-detoxifying enzyme), thereby resulting in the accumulation of toxic heme within the parasite (55). It may also interfere with the biosynthesis of nucleic acids. In humans, CQ inhibits thiamine uptake, acting specifically on thiamine transporter 2 (*SLC19A3*) (52,56). According to clinical trials, CQ may have a beneficial effect as an antiretroviral (HIV-1/AIDS and chikungunya fever) and as a radiosensitizing/chemosensitizing agent assisting cancer therapies (57).

CQ is a weak base and acts to raise pH inside the protozoan organism that causes malaria. In rheumatology and dermatology, CQ inhibits phospholipase A2, phagocytosis, and peroxide synthesis; it also acts on lysosomes, raising intracellular pH in vacuoles – which leads to reduced activation of lymphocyte CD4, suppression of cytokine release from monocytes, and production of antibodies (58). CQ is a synthetic 4-aminoquinoline formulated as the phosphate salt for oral use. The pharmacokinetic properties of chloroquine are medium protein binding (50%) and a bioavailability after oral administration of 89%. It is rapidly and almost completely absorbed from the gastrointestinal tract, reaching a maximum plasma concentration in about 3 h, and is rapidly distributed to tissues. It has a very large apparent volume of distribution of 100–1000 L/kg and is slowly released from tissues and metabolized to diethylchloroquine. Clearance of CQ is 1.8 mL/min/kg body mass. CQ is principally excreted in the urine with an initial half-life of 3–5 days but a much longer terminal elimination half-life of 1–2 months (59).

The exact mechanism of CQ's antiviral activity in the context of treating SARS-CoV-2 infections has not been developed. However, from the point of view of developing new therapies, it is promising as a new potential therapeutic molecule (60). It has been demonstrated that CQ is an inhibitor of endocytosis of nanoparticles (14–2600 nm, spherical or discoidal), which may be one of the key properties underlying its activity against the virus. SARS-CoV-2 is a spherical nanoparticle of size 60–140 nm. In addition, an important property of CQ is its ability to suppress the endocytosis of viral particles by reducing the expression of a protein that mediates the entry of viral particles into the host cell (60). This mechanism involves increasing the endosomal pH required for fusion of the virus to the host cell. This is possible due to the physical and chemical properties of CQ: it is weakly alkaline in water, and after entering the cell it can accumulate cellular structures – lysosomes or Golgi structures – interfering with their acidification (60–63). In addition, CQ inhibits the terminal glycosylation of the angiotensin 2 converting enzyme receptors on the surface of Vero E6 cells, thereby inhibiting the pH-dependent binding of virus receptors and ACE2 (34,37). Reports of biological and comparative analyses of SARS-CoV and nCoV-2019 SARS-CoV cells indicate, importantly, a similarity in the peak protein (S) which is involved in the process of infection with the virus and its subsequent replication in host cells (61).

As reported by Wang et al., CQ may inhibit viral replication in the Vero E6 cell line induced by SARS-CoV (34). In addition, it shows its activity at the cell entry stage as well as after infection with the 2019-nCoV virus. Additional

to its antiviral activity, CQ affects immunity, which can potentially support antiviral activity. An important advantage of this drug is also its good bioavailability throughout the body, including the lungs after oral administration, which may be key from the perspective of use of CQ in the fight against the new virus (37). CQ and HCQ are commonly used substances; however, frequent or non-rational therapeutic use may give rise to harmful effects due to ototoxicity.

CQ or 4-aminoquinoline and HCQ are related to quinine, and are drugs which have long been used and proven effective in the treatment of rheumatoid arthritis, connective tissue diseases, and other autoimmune diseases (52,64). The emergence of the new nCoV-2019 coronavirus and data on the potential antiviral activity of these drugs have directed researchers to use these drugs in the treatment of COVID-19 disease (34). Confirmation of this use was the approval of CQ by the US FDA (and in other countries by national bodies responsible for drug safety) as an adjunct drug in the treatment of beta-coronavirus infections such as SARS-CoV, MERS-CoV, and SARS-CoV-2 (65).

It should be noted that from the point of view of the use of these drugs in pharmacotherapy against COVID-19, these substances have demonstrated and well-known side-effects, such as gastrointestinal disorders and skin rashes (66). It should be emphasized that these drugs are particularly dangerous for those patients in which retinopathy can occur. This condition is associated with long-term intake of the drug or with high dosages, and so pharmacotherapy requires constant monitoring.

In addition to the side-effects already described, it is worth noting that these drugs are closely related to quinine, which has proven ototoxic effects (51, 134). Patients who have been treated with CQ or HCQ have reported symptoms such as sensorineural hearing loss, tinnitus, imbalance, and cochlear-mandibular symptoms. Sometimes these have been transient, but cases with permanent auditory or vestibular dysfunction have been reported (52, 132, 133). The mechanism of ototoxicity is unknown; however, toxicity is associated with long-term exposure or high doses, resulting in drug accumulation. It can also occur as an accumulation of side-effects from simultaneously administered drugs. These substances accumulate in tissues in a form selectively bound to melanocytes, which are present in high levels in retinal cells, hair follicles, and glands. In terms of the ototoxicity of CQ and HCQ, melanocytes are well represented in the inner ear, especially in well vascularized areas. This means that accumulation of drugs can lead to vascular damage and degenerative changes in the planum semilutatum and stretch marks (67). It is known that ototoxicity is correlated with the accumulation of CQ and HCQ, and as a result may contribute to the destruction of stereocilia, reduction in number of neurones, and changes in support structures, leading to ischemia of the auditory system (64,68,69,136). Ototoxicity of CQ may manifest as both auditory and vestibular dysfunction. It is typically mild to moderate, bilateral, and symmetric. Hearing is usually restored after cessation of the drug, but when similar adverse effects occur during simultaneous intake of other drugs the effect may be irreversible (52,57,70–73).

According to clinical national protocols for SARS-CoV-2 treatment, the CQ dose was set at 250 mg twice a day for 7–10 days, with the possibility of increasing the dose to 500 mg twice a day (37,38). Some clinical recommendations for curing pneumonia during progress of SARS CoV-2 infection consist of CQ at a dose of 500 mg twice a day in combination with oseltamivir at a dose of 150 mg twice a day (74). For HCQ, a loading dose of 400 mg twice a day is recommended on the first day, followed by a maintenance dose of 200 mg for the next 4 days (39). This scheme of administration should be supported by using azithromycin at a dose of 500 mg once a day as well as standard antibiotic therapy of piperacilone with tazobactam (4.5 g four times a day) or meropenem at a dose of 2 g three times per day in justified cases (75). In severe cases, intravenous administration of methylprednisolone should be considered at a dose of 40 mg twice a day. GSK (glycorticosteroids) may mask the symptoms of infections (75).

Azithromycin

In addition to the use of CQ and HCQ, the latest publication from a French team of scientists provides information on the experimental benefits of including therapy with HCQ/azithromycin, which was administered as HCQ 200 mg three times a day for 10 days combined with azithromycin at a dose of 500 mg on the first day and 250 mg for the next 4 days (76). As known from other studies, azithromycin is active *in vitro* against Ebola and Zika, and is also used to prevent severe respiratory infections in patients suffering from viral infections (77,78). Although the application profile of azithromycin in the treatment of COVID-19 seems invaluable, we would like to highlight the potential ototoxicity risk caused by this macrolide antibiotic. The first cases of ototoxicity of macrolide antibiotics were reported in the 1970s. However, in the case of azithromycin alone, it was described in patients treated for AIDS who had received a combination of drugs including a high dose of azithromycin; it was followed by several patients who reported spontaneous hearing loss confirmed by tonal audiometry. However, these cases involved temporary hearing loss which receded over time (79). The next publication presented the case of a healthy woman who after low doses suffered irreversible sensorineural hearing loss (80,81). The mechanism of azithromycin ototoxicity is unknown, but it is thought it may be similar to the ototoxic effects of quinine, salicylate, and erythromycin. In audiometric testing, they all show similar frequency shifts. In addition, the bactericidal action of azithromycin is associated with its blocking of ribosome subunits, rapid distribution throughout the body, and a significant intracellular concentration, all of which may contribute to its ototoxicity (81).

Tocilizumab

A recent report describes the use of a new drug in the fight against the COVID-19 pandemic. In early March, China approved the use of a new biological drug, tocilizumab, which was used on people with severe coronavirus complications (82). Tocilizumab is a humanized monoclonal antibody against interleukin-6 (IL-6R) approved in 2010 in the United States, where it is used in the treatment of rheumatoid arthritis (82). Results on a small group of patients

infected with the nCoV-2019 virus, recently published, demonstrate that tocilizumab improves patient health and improves prognosis (83). This was confirmed by the approval of the Chinese National Health Commission to use tocilizumab in patients with COVID-19, in particular those with severe lung damage and high levels of Interleukin-6, and these outcomes in turn led to the start of fresh clinical trials (84–87). Again, it is worth drawing attention to the potential ototoxic effects of this drug. Although a mechanism for ototoxicity has not been documented, the characteristics of the drug indicate the possibility of it being ototoxic, with symptoms in the form of dizziness, ringing and buzzing in the ears, and even hearing loss (88,89). The literature reports one confirmed case of a 72-year-old woman who experienced severe dizziness and malaise after the third infusion of tocilizumab. The therapy was discontinued, although no investigation of the cause and mechanism of the dizziness was made (90).

Oseltamivir

The search for effective therapies for pneumonia of unknown etiology during the Chinese influenza season (which was later confirmed to have been triggered by nCoV-2019) contributed to the trial of a new treatment regimen consisting of the use of an antibiotic (oral and intravenous) and a broad spectrum antiviral drug, oseltamivir. Patients with confirmed infection with the new nCoV-2019 coronavirus, as well as patients with suspected infection, received oseltamivir twice daily at a dose of 75 mg. The factor that directed researchers to the trial of this COVID-19 therapy was that oseltamivir belongs to the group of drugs, neuroaminidase inhibitors, which had already demonstrated their effectiveness in treatment of the MERS-CoV virus. It was known to have certain similarities in the structure of its genome to the nCoV-2019 virus (20,91,92). However, further research and analysis of the new coronavirus showed that the nCoV-2019 coronavirus does not produce neuroaminidases and that oseltamivir does not show specific activity. Oseltamivir is used to treat influenza and is well tolerated by patients; however, side-effects such as gastrointestinal disorders, headaches, and rashes are observed, and what is important for our analysis has been the occurrence of dizziness (93). In a review of ototoxic effects of drugs, oseltamivir was classified as a group of drugs with possible audiological effects causing hearing impairment and others known to contribute to dizziness (94). The mechanism responsible for the occurrence of dizziness is unknown, but these effects are acknowledged in the drug's safety data sheet (95,96).

Remdesivir

Remdesivir is an antiviral, adenosine nucleotide analogue drug placed on the market in 2017. Originally used to treat the Ebola virus, it also has an active effect on Marburg virus, type 3 virus, Nipah virus, Hendra virus, and measles, mumps, and pneumovirus. Furthermore, based on animal studies, it has demonstrated *in vitro* and *in vivo* activity against the coronavirus SARS-CoV and the coronavirus of the respiratory syndrome in the Middle East (MERS-CoV), to which SARS-CoV-2 shows similarity in structure. The mechanism of action consists in binding to RNA-dependent viral polymerase, which in turn inhibits

virus replication as a result of early completion of RNA transcription (97–99). In vitro, the drug demonstrated its activity against SARS-CoV-2, which was subsequently confirmed in preclinical studies carried out on a group of monkeys where a lower level of the virus was recorded in the test group compared to the control group (34,100–102). Positive effects of Remdesivir therapy were confirmed in a multinational randomized placebo-controlled clinical trial in 1063 patients. Drug administration in a group of patients resulted in a faster recovery time in 31% of them as well as a lower percentage of deaths. In another clinical trial conducted in China, no statistically significant changes in clinical improvement were observed (34,102). Another study confirmed that the administration of Remdesivir reduced oxygen support in treated patients (103). In the context of ototoxic effects, no literature data concerning this drug has been found.

Discussion

SARS-CoV-2 treatment protocols

As a result of the lack of development of an unambiguous and specific treatment regimen, the FDA currently has not registered an official documented and safe method of treatment of COVID-19. The medical practice in research on the disease currently uses a number of drugs with originally different indications and, above all, the therapy consists of symptomatic treatment. Using various pharmacotherapy

models, clinical trials are designed and conducted in order to learn about treatment mechanisms important from the therapeutic perspective. The data obtained will allow the development of a cure for COVID-19. The results of the studies published today provide experimental knowledge that can only be used in well-designed studies to ensure maximum patient safety. Scientific publications inform that the established model of pharmacotherapy is selected according to the classification of the patient's health condition where the symptoms of the disease are represented. Depending on the scale of disease symptoms, the drugs used are selected. Table 1 lists the drugs discussed here taking into account the clinical form of the disease and the drug administration model (104–108).

Early symptoms of ototoxicity and predisposing conditions indicating ototoxic risk

Transient evoked otoacoustic emission (TEOAE) and distortion product otoacoustic emission (DPOAE) tests are considered to be the gold standard in testing for ototoxicity. These tools allow quick assessment of high frequency cochlear function. Clinical studies confirm a tight relationship between otoacoustic emissions and ototoxicity of a drug. Otoacoustic emissions can even allow ototoxicity to be detected right from the beginning of treatment, sometimes even before any audiometric deficit is detected (94). Over the past decades, three main approaches to ototoxicity monitoring via audiology have emerged:

Table 1. Examples of treatments for COVID-19

Drug	Clinical form of disease	Treatment	Optional additional medicine
Chloroquine	Mild	Chloroquine phosphate 1000 mg at the time of diagnosis, then 500 mg twice a day, then 300 mg twice a day until day 5.	Lopinavir 400 mg twice a day Ritonavir 100 mg twice a day
	Pneumonia	Chloroquine phosphate 500 mg twice a day for 7 days in adults aged 18–65 and over 50 kg; 500 mg twice daily for 1–2 days, followed by 500 mg for 3–7 days in adults below 50 kg	
	Severe	First dose of 600 mg, then 300 mg 12 h later and then 300 mg twice a day on days 2–5	Remdesivir
Hydroxychloroquine	Mild	800 mg once at 1st dose, then 200 mg twice daily for 4–7 days	
	Pneumonia	200 mg twice a day for 5–20 days	Lopinavir 400 mg twice a day Ritonavir 100 mg twice a day
	Severe	An absorbent dose of 400 mg twice a day and then 200 mg twice a day on days 2–5	Remdesivir
Azithromycin	Pneumonia	500 mg orally once on the first day, followed by 250 mg orally on days 2–5	Hydroxychloroquine
Tocilizumab	Pneumonia/ severe	Single dose 8 mg/kg IV, max. 800 mg. In case of intensified or no improvement of clinical symptoms, a single repeated dose after 12 h	
Oseltamivir	Not determined	300 mg (or 4–6 mg/kg) per day in combination with optional drugs	Protease inhibitors; Favipiravir; Hydroxychloroquine
Remdesivir	Critical	Patients requiring invasive mechanical and/or ECMO ventilation: IV 200 mg for 30–120 min on day 1; days 2 to 10, 100 mg IV for 30–120 min. Patients not requiring invasive mechanical ventilation and/or ECMO: 200 mg IV for 30–120 min on day 1, followed by 100 mg IV for 30–120 min on days 2 to 5. In the absence of improvement, treatment may be extended by another 5 days	Chloroquine; Hydroxychloroquine

1. Otoacoustic emissions (OAEs)
2. High frequency audiometry (HFA)
3. Basic audiological assessment.

The superiority of the first and the second assessments has been confirmed in clinical trials.

Audiological assessment may be used in combination or separately. Ideally, it would be best if baseline testing were performed prior to ototoxic therapy, but unfortunately this is frequently impossible. Ototoxic therapy is in some cases life-saving, and so there is no time for prior preparation and evaluation (e.g. baseline hearing testing) before or after treatment. Comparisons of hearing thresholds over the course of therapy are therefore impossible. Audiological assessment is particularly crucial for the elderly and remains an important part of ototoxicity monitoring (109–111). However, basic audiological assessment limits testing to 8 kHz and unfortunately does not permit the earliest detection of ototoxicity.

ABR (auditory brainstem response) audiometry is one of the most sensitive tests in detecting very early manifestations of cochlear damage caused by CQ when it is still in a reversible stage. Additionally, ABR can be done in patients who are unconscious or in a medically induced coma (52). According to the authors, the reversibility of CQ ototoxicity is debatable. However, it is strongly suggested that, to reduce the risk of ototoxicity, the most important factor is to stop therapy, although this is often difficult or impossible.

High Frequency Audiometry (HFA)

According to published clinical studies, the earliest adverse effects of ototoxic drugs tend to be seen as diminished responses of the outer cells of the basal cochlear turn. HFA is an audiological assessment comprising air-conduction threshold testing for frequencies above 8 kHz (ranging from 16 to 20 kHz) (112–118). However, elderly patients with hearing loss may not have measurable hearing thresholds at such high frequencies (119–121). Ototoxicity tends to be progressive (i.e., proceeding from high to low frequencies) and is usually bilaterally symmetric.

Otoacoustic emissions (OAEs)

The OAEs most commonly used in clinical practice are transient OAEs (TEOAEs) and distortion product OAEs (DPOAEs) and both can be used to detect ototoxic changes. According to authors, DPOAEs can detect ototoxic changes earlier than TEOAEs, especially since DPOAEs can be measured at higher frequencies than TEOAEs. DPOAEs are more sensitive to the first affected (higher) cochlear frequencies, and DPOAEs can often be recorded in the presence of quite severe sensorineural hearing loss (122–126).

Practical recommendations for monitoring ototoxicity

According to the AAA (American Academy of Audiology), the two most widely used 'adverse event' scales for hearing are the ototoxicity grades of the National Cancer Institute

(NCI) Common Terminology Criteria for Adverse Events (CTCAE) and Brock's Hearing Loss Grades.

The NCI CTCAE ototoxicity grades are as follows:

1. For children: threshold shift or loss of 15–25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear (same for adults) – grade 1;
2. For children: threshold shift or loss of >25–90 dB, averaged at two contiguous test frequencies in at least one ear (same for adults) – grade 2;
3. For children: hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., >20 dB bilateral HL in the speech frequencies; >30 dB unilateral HL; and requiring additional speech/language related services). For adults: >25–90 dB, averaged at three contiguous test frequencies in at least one ear – grade 3;
4. For children: means indication for cochlear implantation (CI) and requiring additional speech/language related services. For adults: profound bilateral hearing loss >90 dB HL – grade 4.

The Brock's Hearing Loss Grades, which were originally designed for children receiving platinum-based chemotherapeutics, are:

Degrees 0: Hearing thresholds <40 dB at all frequencies; **1:** Thresholds 40 dB or greater at 8 kHz; **2:** Thresholds 40 dB or greater at 4–8 kHz; **3:** Thresholds 40 dB or greater at 2–8 kHz; **4:** Thresholds at 40 dB or greater at 1–8 kHz.

Unfortunately, audiological assessed patients can include those on platinum-based chemotherapy and under aminoglycosides treatment, and, as a result, patients under anti-malaria therapy who suffer from SARS-CoV-2 may be overlooked. In ototoxicity monitoring, it is essential to be proactive and absolutely crucial to obtain a baseline evaluation. It is important to note that, if the desired baseline testing cannot be performed for the reasons stated above, it can prove beneficial to ask the patient or a family member about the availability of prior audiometric records. Noise-exposed workers are likely, for example, to have access to such information.

In summary, a medical professional needs to take a number of factors into consideration before treating SARS-CoV-2 with a potentially ototoxic combination of medicines. Of course, SARS-CoV-2 may be a severe and life-threatening illness and, logically, saving lives is indisputable. However, bearing in mind the future years of a cured patient, some indications of audiometric risk should be taken into account. Individuals with preexisting auditory disorders should be treated with caution, and if hearing deficits occur then, according to the FDA recommendation from 2018, CQ usage should be discontinued. Other indications for caution are hepatic disease (alcoholism, other hepatotoxic drugs) since CQ may, according to pharmacokinetics and pharmacodynamics, accumulate in the liver. Other precautions surround the taking of other drugs which may lead to ototoxicity, such as aminoglycosides, cytostats, loop diuretics, macrolides, salicylates, and glycopeptides. Also at risk are patients with renal impairment, children less than 3 years old, those over 65 years, pregnant women,

and patients who have been given ototoxic drug in the past or to whom ototoxic agent will be administered for longer than 14 days (127,128).

Conclusion

The outbreak of the new nCoV-2019 coronavirus pandemic, which the entire scientific community is obliged to deal with, has created a sudden need to develop new forms of pharmacotherapy. However, research into the development of vaccines and novel therapeutic substances is a lengthy and costly process. A significant step on the way to the development of disease treatments was obtaining the full genomic sequence of the virus, announced in early January 2020, which has provided key information about its similarity to the already known SARS-CoV and MERS-CoV viruses. This scientific evidence has led to work on screening potential therapeutic molecules using currently available drugs in new experimental doses or treatment models. In analysis of treatments to date, we have acquired knowledge about the results of administering to patients anti-malarial drugs like CQ and HCQ (obtained during the SARS-CoV and MERS-CoV epidemics), antiviral drugs like ostelamivir, monoclonal antibodies such as tocilizumab, as well as antibiotics like azithromycin.

In our review, we have analyzed available publications, clinical cases, and scientific evidence in the context of approved and accepted methods of COVID-19 pharmacotherapy and the consequences of their use. On this basis, we have set out evidence of possible ototoxic side-effects as a result of treating COVID-19 with certain drugs. There are possible long-term effects, notably a deterioration in the hearing of treated patients. Drug ototoxicity is a well-known cause of cochlear hearing loss, caused by a variety of commonly used drug groups, and unfortunately these include those used to treat COVID-19. Reports of clinical cases have been

characterized by elevated hearing thresholds resulting in temporary or, in extreme cases, permanent hearing loss. In addition, there are reports of cases where patients are left with tinnitus, imbalance, dizziness, or cochlear symptoms. Currently used clinical protocols combine the use of several drugs with known ototoxic effects, thus increasing the possibility of adverse effects and contributing to the development of additive ototoxicity.

The overriding motivation of doctors and research teams is to develop treatments for patients with COVID-19. However, based on an analysis of the available literature, we have drawn attention to the possible long-term effects of some forms of therapy, effects which are potentially damaging to the health of patients. Currently available methods of audiological testing allow very quick ways of gauging the ototoxicity of drugs. We propose that various audiological testing methods be introduced to monitor patient populations treated for nCoV-2019 infection. The techniques used and the test schedules might be adapted depending on the drug used, the patient's age, and the ability to conduct behavioral and audiological tests. Importantly, audiological tests can also be performed on unconscious patients or patients in a pharmacological coma. It should be underlined that ideally the tests should be performed before and after pharmacotherapy so that comparisons can be made.

In addition, a number of scientific publications indicate a positive therapeutic value of the COVID-19 pharmacotherapy methods mentioned in our analysis. They justify ongoing research on the effectiveness and adverse effects of these drugs. It is also necessary to understand the molecular mechanisms underlying the action of the drugs. Understanding these mechanisms may contribute to the development of new therapeutic molecules and methods of pharmacotherapy for treating nCoV-2019 infection – and of course its possible mutations.

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