® Postepy Hig Med Dosw (online), 2020; 74: 348-353
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 22.07.2020
Accepted: 04.08.2020
Published: 20.08.2020

SARS-CoV-2 infection and some controversies concerning therapy with chloroquine and hydroksychloroquine: case report and selected literature review

Zakażenie SARS-CoV-2 i kontrowersje dotyczące stosowania chlorochiny i hydroksychlorochiny: opis przypadku i wybrane dane z literatury

Hubert Ciepłucha, Brygida Knysz

Department of Infectious Diseases, Liver Diseases and Acquired Immune Deficiencies Wroclaw Medical University, Poland

Summary

Covid-19 is caused by a new virus and no effective therapy is available. The following article presents the case of a 47-year-old woman with SARS-CoV-2 infection. The infection was initially mild but because of exacerbation of the symptoms: cough, fever, headache, extreme weakness she was admitted to the hospital. The chest X-ray revealed pneumonia due to Covid-19, that is why CT was not done. Due to persistent symptoms of infection, therapy containing chloroquine and azithromycin was introduced, obtaining a very quick improvement in the condition of the infected patient. Because of ambiguous opinions of the efficacy of these two drugs in the therapy of SARS-CoV-2 infection, the authors wonder whether the improvement was either a result of the treatment with chloroquine and azithromycin or because of the natural Covid-19 course. The following part of the article briefly reviews research and world reports as well as problems connected with chloroquine and hydroxychloroquine therapy in patients with Covid-19. The current positions of the World Health Organization (WHO) and the Food and Drug Administration (FDA) in terms of the topic were also presented. It was also pointed out the way unprecedented before the therapy has been introduced based on several and variable report about the efficacy and safety of these drugs.

Keywords:

GICID 01.3001.0014.3589
DOI: 10.5604/01.3001.0014.3589
Word count: 3 844
Tables: –
Figures: 2
References: 37

Author's address: Hubert Ciepłucha, Department of Infectious Diseases, Liver Diseases and Acquired Immune Deficiences, Wroclaw Medical University im. Piastów Śląskich Wrocław, ul. Koszarowa 5, 51-149 Wrocław; e-mail: hub.cieplucha@gmail.com

Abbreviations: **AZ** – azithromycin, **CQ** – chloroquine, **CRP** – C-reactive protein, **HCQ** – hydroxychloroquine, **N** – standard.

INTRODUCTION

Covid-19 is a new disease known in many respects only since January 2020. One of the most important aspects is the symptomatology of this disease and treatment. There is currently no widely available effective antiviral drug in the world. Many drugs are under clinical studies, and remdesivir is strongly recommended for the therapy of Covid-19 as well as dexamethasone, especially in those with severe disease [3, 8, 35, 36]. Hopes for effective treatment appeared after the publication of the results of the use of chloroquine among patients with Covid-19 [16], and then hydroxychloroquine with azithromycin in France [18]. This was the reason for the worldwide discussion about safety and efficacy regarding these two drugs, as well as the reliability of the data obtained. Despite doubts on the part of the authorities, these results led to immediate use of these drugs all over the world.

In Poland, chloroquine is registered as a supportive treatment in patients hospitalized for Covid-19 [6].

The following is a case of a patient with Covid-19, who was been treated with chloroquine.

A CASE REPORT

A 47-year-old woman with no significant medical history and a diagnosis of SARS-CoV-2 infection established five days earlier (third day of illness) was admitted to the J. Gromkowski Provincial Specialist Hospital in Wrocław as a result of exacerbated symptoms: weakness, shortness of breath, severe headache and muscle aches, persistent cough, and fever. It was established from the medical history that she had contact with people with Covid-19.

On admission, the patient was in an overall stable condition, heart rate was 120 bpm, saturation 96%. On auscultation, a follicular murmur was found with single crackles located at the basal of both lungs.

Laboratory tests performed at the emergency room found the following: partial respiratory alkalosis (pH 7.63, pCO2 19.0 mmHg; [HCO3-] 20.0 mmol/L); eosinopenia (10/μL eosinophils); decrease in lymphocyte percentage; increase in the percentage of monocytes and a slight increase in the percentage of neutrophils (neutrophils 71%; monocytes 11.9%; eosinophils 0.2%; lymphocytes 16.6%). A slight increase in D-dimer-523.0 ng/ml and C-reactive protein 45 mg/L levels were also found. Infections with influenza A and B viruses were excluded.

The chest X-ray taken on the day of admission showed a weakly limited area of reduced peripheral transparency in the lower right field and slightly increased densities at the base of the upper lobe of the right lung. Because of the X-ray picture indicating SARS-CoV-2 pneumonia CT was not done. During the first four days of hospitalization, the patient's condition did not improve. She was still feverish to 38.4°C, heart rate was constantly accelerated to

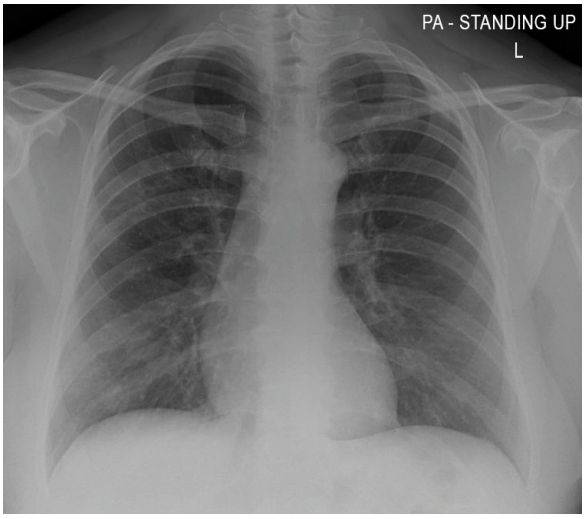

Fig. 1. X-ray of the patient's lungs on the day of admission. There are inflammatory changes in the area of the lower pulmonary fields.

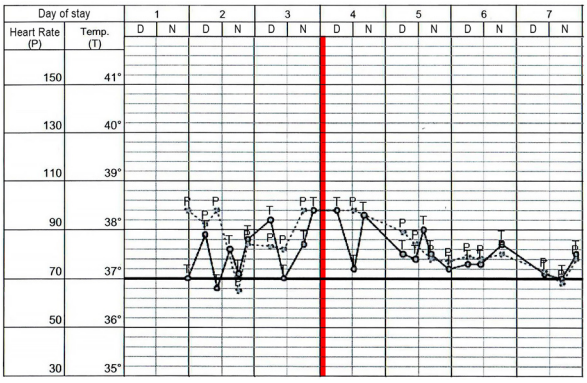

Fig. 2. Graph presenting the patient's heart rate and temperature depending on the day of hospitalization. The day of adding chloroquine to the therapy is marked in red.

110/min, saturation was 98%. During this period, the patient received antitussive, analgesic, and antipyretic treatment. Despite the intravenous supply of paracetamol and the preparation with metamizole, the patient's condition did not improve.

As a result of persistent weakness, fever, severe headache, unresponsiveness to treatment, auscultatory changes in the lungs, coughing attacks, after obtaining the patient's informed consent, experimental pharmacotherapy of SARS-CoV-2 infection with chloroquine (CQ) 500 mg/day was implemented for 5 days in two divided doses. Azithromycin (AZ) containing pharmacotherapy (initially 500 mg once, then 250 mg once daily) was added.

Starting from the fifth day of hospitalization (day 13 of illness), a gradual improvement in the patient's clinical condition was observed. There were no side effects of chloroquine. On day 7 of hospitalization (day 15 of

illness), a throat swab was taken for SARS-CoV-2, and a positive result was still obtained. In contrast, laboratory tests showed an improvement in the blood smear, but still elevated levels of C-reactive protein (CRP 52.5 mg/L). In capillary blood gas, alkalosis (pH 7.46, [HCO3-] 24.2 mmol/L) was observed and oxygen saturation was 97%. Heart rate was not accelerated.

In the next days of hospitalization, further improvement of the patient's condition was observed: pain relief and normalization of body temperature. On the fourteenth day of hospitalization (22nd day of illness), no auscultatory changes were found over the lung fields. On the fifteenth day of stay (day 23 of the disease), the first negative result for SARS-CoV-2 infection (RT-PCR) was obtained, which was confirmed by another negative result within 24 hours. In laboratory tests from that day, only a slight deviation from the norm was observed in the automatic blood smear. The CRP concentration was normal. The chest X-ray did not reveal any changes. The patient was discharged on the sixteenth day of hospitalization (24 day of illness) in good general condition.

DISCUSSION AND SHORT DATA REVIEW

The patient described above presents an example of a disease of prolonged duration with typical severe symptoms. Due to persistent symptoms, she was admitted to the hospital around the eighth day of illness, i.e. at the time when further serious complications of Covid-19 could develop. The patient developed pneumonia, which was confirmed by an X-ray of the chest. On the basis of positive data from some reports [2, 6, 19, 26], azithromycin and chloroquine were administered.

The reason for using chloroquine in therapy was the persistence of significantly exacerbated symptoms of Covid-19. Also, no contraindications to the therapy were found: the patient had not been seriously ill thus far and had not taken any preparations that could interact with chloroquine [6, 7, 29]. The ECG did not reveal a deviation from the norm. Based on the observation of the single case presented above, it cannot be clearly answered whether the improvement in the patient's condition was associated with the inclusion of chloroquine one day earlier or was the result of a natural, typical course of the disease. In the presented case, CQ could have an anti-inflammatory effect, accelerating healing, which could be demonstrated by the improvement the next day after using the drug [25, 33].

On the other hand, it cannot be excluded that the disease would have a similar course without the administration of CQ [14]. Prognostic parameters such as D-dimer level, CRP level, deviations in blood counts were positively promising. In light of the divergent results on the efficacy and safety of CQ and HCQ, below we present a brief overview of the most important information about CQ and HC Q in Covid-19 therapy and doubts whether to use them.

DATA REVIEW

Occurrence of new coronavirus SARS-CoV-2, the causative agent of a new disease in human beings, Covid-19, with high mortality rate prompted an intensive search for a new drug, sometimes among old, well-known ones that have any antiviral activity. The first reports about chloroquine and hydroxychloroquine (HCQ) and their efficacy in Covid-19 treatment came from China [18]. HCQ is different from CQ because of the added hydroxyl group, thus decreasing its toxicity [6, 8]. These two old drugs have been known from the 1930s–1940s as antimalarial drugs, which were later also used in the treatment of rheumatoid arthritis because of their immunomodulatory and anti-inflammatory properties [21, 28, 31]. There were some studies performed in the past that investigated both in vitro and in vivo antiviral efficacy of CQ [21, 34, 35]. The data from in vitro studies indicated their antiviral mechanism based on inhibiting viral entry and also preventing autophagosomal degradation [23, 35]. Despite the fact that antiviral activity of CQ in vitro studies has been found, in vivo it was not confirmed against Ebola, flu, HIV, Zika and especially chikungunya, where in human studies CQ exerted a harmful effect by exacerbating the symptoms [11, 12, 15, 33]. In HIV positive patients, hydroxychloroquine use was connected with the fall of the CD4 T cell count [32].

There are some research studies in vitro indicating the antiviral activity of CQ in SARS-CoV [34] and MERS-CoV (Middle East respiratory syndrome coronavirus) [13]. Also, according to SARS-CoV-2, it was seen in vitro studies that CQ could be effective in inhibiting viral replication [35]. Because there is a great similarity between SARS-CoV-1 and SARS-CoV-2, it was recognized that chloroquine could be effective in Covid-19 therapy. The first clinical trials evaluating the efficacy and safety of CQ and HCQ have been initiated in China but after then many trials were established all over the world [2, 4, 9, 10, 18, 20, 26, 36].

There was a great debate on the use of HCQ with AZ after the results of a French non-randomized study were published, indicating that the use of HQ, especially with AZ, has shortened the time of virus detection in the nasopharyngeal swabs [19]. However, many controversies have remained, because of the methodological mistakes and the conclusions were questionable.

In another French study, retrospective observation of 1.061 SARS-CoV-2 positive patients who received HCQ and AZ revealed good clinical outcome, low fatality rate and safety of this drug combination. The author also recommended generalization of safe and well-tolerated drugs in outpatient departments in patients with mild symptoms, indicating special attention to drug-drug interactions [26].

The other two non-randomized studies from USA on large groups of patients did not confirm the efficacy of HQ

[20, 30] as well as recently published data obtained from patients hospitalized with mild-to-moderate Covid-19, the use of HCQ with or without AZ did not improve the clinical course [5].

Alexander P.E et al. conducted an analysis of 6 studies, 3 randomized control trials and 3 observational studies in terms of efficacy and safety of CQ and HCQ (with azithromycin). In conclusion, they found very poor methodology and reporting [1], making it difficult to establish reliable results.

There was a discussion regarding the results of the worldwide multicenter observational study that was summarized by Mehra et al. [24]. Almost 100.000 hospitalized patients were included. There were groups among them receiving CQ, HCQ, each of these drugs together or without macrolide. The authors concluded that there was no benefit of the therapies mentioned above. The survival among hospitalized patients was decreased and ventricular arrhythmias were more often observed [24].

In response to the data, the WHO has stopped recruiting patients to the HCQ arm in the SOLIDARITY study [27]. After the Mehra publication, an open letter signed by more than 140 clinicians, medical researchers, statisticians, and ethicists from across the world was sent to the authors and Richard Horton, the editor of the Lancet. Concerns regarding the statistical analysis and data integrity were mentioned and a request was made to Lancet for it to reveal the peer review comments that led to this manuscript being accepted for publication. Finally, because the validity of the data presented by Mehra et al. were uncertain, the authors asked the Editor to retract the paper [25]. After then, for a short time the WHO accepted studies with HCQ in the therapy of Covid-19.

There are also many reports about the safety of CQ and HCQ in SARS-CoV-2 infected patients. The opinions are different, but in general the adverse effects are major problems [22, 27]. There is a question whether to use these drugs or not, which dose is optimal and how long the therapy should be continued [4, 7, 20, 29]. Around 18.9% of patients have to stop therapy with CQ or HCQ because of ECG abnormalities [7].

Although these drugs are well tolerated in those treated with CQ or HCQ because of different diseases [28, 31] there are scanty information about cardiac adverse effects in SARS-CoV-2 positive patients. The doctors must be aware of the risk of cardiological complications [4, 7, 20, 29].

FDA announced on the 24 of April 2020 drug safety communication and cautioned against use of hydroxychloroquine or chloroquine outside of the hospital or a clinical trial due to a risk of serious heart rythm problems in patients with Covid-19 treated with hydroxychloroquine or chloroquine often in combination of azithromycin and other QT drug prolonging medicines. These two drugs can cause QT interval prolongation and ventricular tachycardia [16]. Especially patients with heart and kidney diseases are at risk for these heart problems. FDA experts also indicated increased use of these drugs through outpatient prescriptions [16]. Previously, they authorized their temporary use during the COVID-19 pandemic for treatment of hospitalized patients when clinical trials were not available [17].

The same day a small clinical study with CQ immediately interrupted in Brazil by the safety monitoring board was published in JAMA [4]. The aim of the study was to evaluate the efficacy and safety of two different CQ doses in patients with severe SARS CoV-2 infection. The death rate in a group receiving higher doses 600 mg twice a day for 10 days was 39.0% (16/41 individuals). Side effects, such as QTcF greater than 500 milliseconds and ventricular tachycardia before death, were more often observed in the higher dosage group [4].

CONCLUSION

Since the very beginning of the pandemic, many studies on the efficacy and safety in the treatment of Covid-19 have been started. Different new data are reported almost every day, more or less reliable, which are also spread by social media and journalists. These are all read by many people, by scientists but also by lay people interested in the topic and afraid of contracting Covid-19 and dying. There has been wide use of different drugs, out of label because of information about their effectiveness announced by any media. Medical doctors and scientists have a great responsibility to present confirmed data and information about the disease and the drugs and avoid the use of drugs if there is only little information about them. Moreover, the information is changing rapidly, even influencing the decision of the WHO.

This is why it is necessary to conduct randomized, multicenter double blind clinical trials to obtain objective data in terms of Covid-19 therapy. On the 4th of July, the WHO stopped for the second time the HCQ arm of the SOLIDARITY trial because of the lack of effectiveness and serious adverse events [37].

REFERENCES

[1] Alexander P.E., Borg Debono V., Mammen M.J., Iorio A., Aryal K., Deng D., Brocard E., Alhazzani W.: COVID-19 coronavirus research has overall low methodological quality thus far: Case in point for chloroquine/hydroxychloroquine. J. Clin. Epidemiol., 2020; 123: 120–126

[2] Arshad S., Kilgore P., Chaudhry Z.S., Jacobsen G., Wang D.D., Huitsing K., Brar I., Alangaden G.J., Ramesh M.S., McKinnon J.E., O'Neill W., Zervos M., Henry Ford COVID-19 Task Force: Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int. J. Infect. Dis., 2020; 97: 396–403

[3] Beigel J.H., Tomashek K.M., Dodd L.E., Mehta A.K., Zingman B.S., Kalil A.C., Hohmann E., Chu H.Y., Luetkemeyer A., Kline S., de Castilla D.L., Finberg R.W., Dierberg K., Tapson V., Hsieh L., et al.: Remdesivir for the Treatment of Covid-19 — Preliminary Report. N. Engl. J. Med., 2020, https://www.nejm.org/doi/full/10.1056/NEJMoa2007764 (17.07.2020)

[4] Borba M.G., Val F.F., Sampaio V.S., Araújo Alexandre M.A., Cardoso Melo G., Brito M., Gomes Mourão M.P., Brito-Sousa J.D., Baiada-Silva D., Guerra M.V., Abrahão Hajjar L., Costa Pinto R., Silva Balieiro A.A., Fonseca Pacheco A.G., Santos J.D., et al: Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A randomized clinical trial. JAMA Netw. Open, 2020; 3: e208857

[5] Cavalcanti A.B., Zampieri F.G., Rosa R.G., Azevedo L.C., Veiga, V.C., Avezum A., Damiani L.P., Marcadenti A., Kawano-Dourado L., Lisboa T., Junqueira D.L., de Barros e Silva P.G., Tramujas L., Abreu-Silva E.O., Laranjeira L.N., et al.: Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N. Engl. J. Med., 2020, https://www.nejm.org/doi/10.1056/NEJMoa2019014 (29.07.2020)

[6] Charakterystyka produktu leczniczego Arechin, 250 mg, tabletki. http://www.urpl.gov.pl/sites/default/files/Arechin%20Charakterystyka%20Produktu%20Leczniczego.pdf

[7] Chatre C., Roubille F., Vernhet H., Jorgensen C., Pers Y.M.: Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. Drug Saf., 2018; 41: 919–931

[8] Colson P., Rolain J.M., Lagier J.C., Brouqui P., Raoult D.: Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int. J. Antimicrob. Agents, 2020; 55: 105932

[9] Colson P., Rolain J.M., Raoult D.: Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int. J. Antimicrob. Agents, 2020; 55: 105923

[10] Cortegiani A., Ingoglia G., Ippolito M., Giarratano A., Einav S.: A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J. Crit. Care, 2020; 57: 279–283

[11] De Lamballerie X., Boisson V., Reynier J.C., Enault S., Charrel R.N., Flahault A., Roques P., Le Grand R.: On chikungunya acute infection and chloroquine treatment. Vector Borne Zoonotic Dis., 2008; 8: 837–839

[12] Delvecchio R., Higa L.M., Pezzuto P., Valadão A.L., Garcez P.P., Monteiro F.L., Loiola E.C., Dias A.A., Silva F.J., Aliota M.T., Caine E.A., Osario J.E., Bellio M., O'Connor D.H., Rehen S., Santana R., de Aguiar R., et al.: Chloroquine, an endocytosis blocking agent, inhibits Zika virus infection in different cell models. Viruses, 2016; 8: 322

[13] de Wilde A.H., Jochmans D., Posthuma C.C., Zevenhoven-Dobbe J.C., van Nieuwkoop S., Bestebroer T.M., van den Hoogen B.G., Neyts J., Snijder E.J.: Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East Respiratory Syndrome coronavirus replication in cell culture. Antimicrob. Agents Chemother., 2014; 58: 4875–4884

[14] dos Santos W.G.: Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed. Pharmacother., 2020; 129: 1104934

[15] Dowall S.D., Bosworth A., Watson R., Bewley K., Taylor I., Rayner E., Hunter L., Pearson G., Easterbrook L., Pitman J., Hewson R., Carroll M.W.: Chloroquine inhibited Ebola virus replication in vitro but failed to protect against infection and disease in the in vivo guinea pig model. J. Gen. Virol., 2015; 96: 3484–3492

[16] FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Drug Safety Communication; https://www.fda.gov/media/137250/download (24.04.2020)

[17] FDA issues emergency use authorization for chloroquine, hydroxychloroquine for COVID-19 patients. www.trussvilletribune.com/2020/03/30/breaking-fda-issues-emergency-use-authorization-for-chloroquine-hydroxychloroquine-for-covid-19-patients/ (19.07.2020)

[18] Gao J., Tian Z., Yang X.: Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci. Trends, 2020; 14: 72–73

[19] Gautret P., Lagier J.C., Parola P., Hoang V.T., Meddeb L., Mailhe M., Doudier B., Courjon J., Giordanengo V., Vieira V.E., Dupont H.T., Honore S., Colson P., Chabriere E., La Scola B., et al.: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. Int. J. Antimicrob. Agents, 2020; 56: 105949

[20] Geleris J., Sun Y., Platt J., Zucker J., Baldwin M., Hripcsak G., Labella A., Manson D.K., Kubin C., Barr R.G., Sobieszczyk M.E., Schluger N.W.: Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N. Engl. J. Med., 2020; 382: 2411–2418

[21] Inglot A.D.: Comparison of the antiviral activity in vitro of some non-steroidal anti-inflammatory drugs. J. Gen. Virol., 1969; 4: 203–214

[22] Juurlink D.N.: Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ, 2020; 192: E450–E453

[23] Keyaerts E., Vijgen L., Maes P., Neyts J., Van Ranst M.: In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem. Biophys. Res. Commun., 2004; 323: 264–268

[24] Mehra M.R., Desai S.S., Ruschitzka F., Patel A.N.: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet, 2020, doi.org/10.1016/S0140-6736(20)31180-6 (22.05.2020)

[25] Mehra M.R., Ruschitzka F., Patel A.N.: Retraction. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis Lancet, 2020; 395: 1820

[26] Million M., Lagier J.C., Gautret P., Colson P., Fournier P.E., Amrane S., Hocquart M., Mailhe M., Esteves-Vieira V., Doudier B., Aubry C., Correard F., Giraud-Gatineau A., Roussel Y., Berenger C., et al.: Early treatment of 1061 COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med. Infect. Dis., 2020; 35: 101738

[27] Q&A: Hydroxychloroquine and COVID-19; https://www.who.int/news-room/q-a-detail/q-a-hydroxychloroquine-and-covid-19 (15.07.2020)

[28] Rainsford K.D., Parke A.L., Clifford-Rashotte M., Kean W.F.: Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology, 2015; 23: 231–269

[29] Roden D.M., Harrington R.A., Poppas A., Russo A.M.: Considerations for drug interactions on QTc in exploratory COVID-19 treatment. Circulation, 2020; 141: e906–e907

[30] Rosenberg E.S., Dufort E.M., Udo T., Wilberschied L.A., Kumar J., Tesoriero J., Weinberg P., Kirkwood J., Muse A., DeHovitz J., Blog D.B., Hutton B., Holtgrave D.R., Zucker H.A.: Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA, 2020; 323: 2493–2502

[31] Schrezenmeier E., Dörner T.: Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat. Rev. Rheumatol., 2020; 16: 155–166

[32] Tsai W.P., Nara P.L., Kung H.F., Oroszlan S.: Inhibition of human immunodeficiency virus infectivity by chloroquine. AIDS Res. Hum. Retroviruses, 1990; 6: 481–489

[33] Vigerust D.J., McCullers J.A.: Chloroquine is effective against influenza A virus in vitro but not in vivo. Influenza Other Respir. Viruses, 2007; 1: 189–192

[34] Vincent M.J., Bergeron E., Benjannet S., Erickson B.R., Rollin P.E., Ksiazek T.G., Seidah N.G., Nichol S.T: Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J., 2005; 2: 69

[35] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M., Shi Z., Hu Z., Zhong W., Xiao G.: Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 2020; 30: 269–271

[36] Wang Y., Zhang D., Du G., Du R., Zhao J., Jin Y., Fu S., Gao L., Cheng Z., Lu Q., Hu Y., Wang K., Lu Y., Li H., Wang S., et al.: Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2020; 395: 1569–1578

[37] WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19 (19.07.2020)

The authors have no potential conflicts of interest to declare.