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International Journal of Antimicrobial Agents 55 (2020) 105969

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Drug repositioning is an alternative for the treatment of coronavirus COVID-19

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ARTICLE INFO

Keywords:
Repositioning
COVID-19
SARS-CoV-2

ABSTRACT

Given the extreme importance of the current pandemic caused by COVID-19, and as scientists agree there is no identified pharmacological treatment, where possible, therapeutic alternatives are raised through drug repositioning. This paper presents a selection of studies involving drugs from different pharmaceutical classes with activity against SARS-CoV-2 and SARS-CoV, with the potential for use in the treatment of COVID-19 disease.

The recent spread of the novel coronavirus, SARS-CoV-2 has created a worldwide public health emergency. In December 2019, the outbreak of this emerging disease (COVID-19) began in Wuhan, China. It quickly spread, and a pandemic was declared by the World Health Organization in March 2020 [1,2].

Repositioning drugs already approved for use in humans is a useful tool to search for new therapeutic options, particularly in the current global crisis [3]. Thus, drug repositioning, also known as redirecting, repurposing, and reprofiling [4,5], emerges as an effective possibility for generating new treatments against COVID-19. Repositioning is defined as a new use of a drug, in addition to its original indication(s), and is an option for rapid identification of new therapeutic agents. The availability of drug-related information, such as pharmacokinetics, pharmacodynamics and toxicity [6], is an important advantage in the research efforts to quickly find an effective treatment for this deadly virus.

Table 1 presents a selection of recent studies that investigated the antiviral activity of several pharmacological classes, including antimalarial drugs and antibiotics, as options for repositioning as treatments of coronavirus (SARS-CoV, SARS-CoV-2 and HCoV-OC43) [7–10]. A search was conducted on three databases (PubMed, SCOPUS and Web of Science) between March 15 th and March 27 th, 2020 using the following search strategy: [(repositioning) AND (repurposing) AND (redirecting) AND (reprofiling) AND (rediscovery) AND (COVID-19) AND (CORONAVIRUS) AND (treatment)] with review filters appropriate for individual databases. The inclusion criterion was studies that included the repositioning of drugs with antiviral activity against coronavirus. Duplicate cases were excluded, as were studies that did not address the issue.

The analysis revealed seven studies that address drug repositioning against SARS-CoV-2; the target drugs were chloroquine, hydroxychloroquine associated with azithromycin, teicoplanin, remdesivir, nitazoxanide and metformin. Several authors report the potential of chloroquine as a therapeutic option against this virus: in vitro it presented an EC_{50} of 1.13 µm and in vivo it caused a negative conversion of the virus in more than 100 patients who were participating in multicenter clinical trials conducted in China [7,8]. In the in vitro study performed by Liu et al. (2020), both chloroquine and hydroxychloroquine inhibited the virus from entering the cell and, at later cell stages of SARS-CoV-2 infection, blocked virus transport between cell organelles, which is considered a determining step for the release of viral genome in cells in the case of SARS-CoV-2. However, chloroquine was observed to have a higher efficacy [9].

Teicoplanin, on the other hand, presented an in vitro IC_{50} of 1.66 µM, a relatively low active concentration, which is promising for its use against SARS-CoV-2; however, this requires further in vivo verification and incorporation in clinical trials [10].

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https://doi.org/10.1016/j.ijantimicag.2020.105969
0924-8579/

Table 1
Studies of the repositioning of drugs with effects against coronavirus.

Drug	Class	Original indication	New indication in repositioning	Type of study	Active concentration	Probable mechanism of action	Reference
Amodiaquine	4-amino-quinoline	Antiparasitic agent	SARS-CoV	In vitro	EC_{50} = 1.274	-	Dyall et al. 2014 [13]
Captopril	ACE-2 inhibitor	Hypertension	SARS-COV-2	Hypo-thesis	-	Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia	Sun et al. 2020 [14]
Chloroquine	4-amino-quinoline	Antimalarial	SARS-CoV	In vitro	EC_{50} = 6.538	-	Dyall et al., 2014 [13]
			SARS-CoV	In vitro	IC_{50} = 8.8 µM	-	Keyaerts et al., 2004 [15]
			SARS-CoV	In vitro	EC_{50} = 4.1 µM CC_{50} ≥ 128 µM	-	de Wilde et al., 2014 [16]
			SARS-CoV-2	In vitro	EC_{50} = 1.13 µM	Probably blocks virus infection by increasing endosomal pH required for virus/cell fusion, and interferes with glycosylation of cellular receptors of SARS-CoV	Wang et al., 2020 [7]
			SARS-CoV-2	In vitro	EC_{50} = 2.71 µM	Blocks virus transport between cell organelles	Liu et al., 2020 [9]
			SARS-CoV-2	In vitro	EC_{50} = 5.47 µM		Yao et al., 2020 [17]
			SARS-CoV-2	Comput-ational	-	-	Gordon et al., 2020 [18]
			SARS-CoV-2	In vivo	-	-	Gao et al,, 2020 [8]
			HCoV-OC43	In vivo	EC_{50} = 0.3 µM	Probably affects endosome-mediated fusion	Keyaerts et al., 2009 [19]
Cyclosporin A	Calcineurin inhibitors	Immuno-supressant	SARS-CoV	In vitro	16 µM	Likely that the drug interferes with functional interactions between viral proteins and one or multiple members of the large cyclophilin family	de Wilde et al., 2011 [20]
			SARS-CoV	In vitro	EC_{50} = 3.3 µM	Affects replicative protein	Pfefferle et al., 2011 [21]
Chlorpromazine hydrochloride	Antipsychotic	Schizophrenia	SARS-CoV	In vitro	EC_{50} = 8.8 µM CC_{50} = 24.3 µM	-	de Wilde et al., 2014 [16]
Clomipramine	Neurotransmitter inhibitor	Antidepressant	SARS-CoV	In vitro	EC_{50} = 13.2 µM	-	Dyall et al., 2014 [13]
Disulfiram	Tiuram dissulphide	Chronic alcohol dependence	SARS-CoV	In vitro	IC_{50} = 24.1 µM	Competitive inhibitor of SARS-CoV papain-like protease	Lin et al, 2018 [22]
Enalapril	ACE-2 inhibitor	Hypertension	SARS-COV-2	Hypo-thesis	-	Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia	Sun et al., 2020 [14]
Gemcitabine hydrochloride	DNA metabolism inhibitor	Anticancer	SARS-CoV	In vitro	EC_{50} = 4.9 µM	-	Dyall et al., 2014 [13]
Hydroxychloroquine	4-amino-quinoline	Antimalarial	SARS-CoV	In vitro	EC_{50} = 7.9 µM	-	Dyall et al., 2014 [13]
			SARS-CoV-2	In vivo	0.46 µg/mL (serum concentration)	-	Gautret et al., 2020 [11]

(*continued on next page*)

Table 1 (*continued*)

Drug	Class	Original indication	New indication in repositioning	Type of study	Active concentration	Probable mechanism of action	Reference
			SARS-CoV-2	In vitro	$EC_{50} = 2.71\,\mu M$	Blocks virus transport between cell organelles	Liu et al., 2020 [9]
			SARS-CoV-2	In vitro	$EC_{50} = 0.72\,\mu M$	-	Yao et al., 2020 [17]
Dasatinib	Kinase signaling inhibitor	Anticancer	SARS-CoV	In vitro	$EC_{50} = 2.1\ \mu M$	-	Dyall et al., 2014 [13]
Imatinib mesylate	Kinase signaling inhibitor	Anticancer	SARS-CoV	In vitro	$EC_{50} = 9.8\ \mu M$	-	Dyall et al., 2014 [13]
Loperamide	Opioid	Antidiarrheal	SARS-CoV	In vitro	$EC_{50} = 5.9\ \mu M$ $CC_{50} = 53.8\ \mu M$	-	de Wilde et al., 2014 [16]
Mefloquine	Aminoquinoline	Antiparasitic agent	SARS-CoV	In vitro	$EC_{50} = 15{,}5\ \mu M$	-	Dyall et al., 2014 [13]
Metformin	Biguanide	Diabetes	SARS-CoV-2	Comput-ational	-	-	Gordon et al., 2020 [18]
Nitazoxanide	Nitrothiazole	Antimalarial	SARS-CoV-2	In vitro	$EC_{50} = 2.12\,\mu M$	-	Wang et al., 2020 [7]
Promethazine hydrochloride	Neurotransmitter inhibitor	Antihistamine	SARS-CoV	In vitro	$EC_{50} = 7.5\ \mu M$	-	de Wilde et al., 2014 [16]
Remdesivir	Nucleoside analog	Clinical development for treatment of Ebola virus infection	SARS-CoV-2	In vitro	$EC_{50} = 0{,}77\ \mu M$; $IC_{50} > 100\ \mu M$	Adenosine analogue incorporates into nascent viral RNA chains and results in premature termination	Wang et al., 2020 [7]
Tamoxifen	Estrogen receptor inhibitor	Breast cancer	SARS-CoV	In vitro	$EC_{50} = 92.8\ \mu M$	-	Dyall et al., 2014 [13]
Terconazole	Sterol metabolism inhibitor	Antifungal	SARS-CoV	In vitro	$EC_{50} = 92.8\ \mu M$	-	Dyall et al., 2014 [13]
Toremifene	Estrogen receptor inhibitor	Breast cancer	SARS-CoV	In vitro	$EC_{50} = 11.9\ \mu M$	-	Dyall et al., 2014 [13]
Teicoplanin	Glycopeptide antibiotic	Bacterial infection	SARS-CoV-2	In vitro	$IC_{50} = 1.66\,\mu M$	Inhibited entry of 2019-nCoV pseudovirus, which provides a possible strategy for prophylaxis and treatment for 2019-nCoV infection	Zhang et al., 2019 [10]

(-) Not determined

Gautret et al. (2020) conducted a clinical trial using hydroxychloroquine in patients infected with SARS-CoV-2. The initial results show a significant reduction in viral carriage and the use of hydroxychloroquine in conjunction with azithromycin was more efficient in eliminating the virus [11]. There is also expectation for the results of the WHO solidarity initiative, which consisted of a worldwide call for a clinical study to simultaneously research the efficacy of four drugs, including remdesivir, chloroquine and hydroxychloroquine, for the treatment of patients affected with COVID-19 [12]. Thus, drug repositioning is a promising alternative for the treatment of COVID-19 disease, and a more complex investigation of the antiviral effect of these molecules against SARS-CoV-2 is encouraged.

Declarations

Funding: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Competing Interests: The authors report no conflicts of interest.

Ethical Approval: Not required

References

[1] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020 (March 11, 2020), Accessed 17 March 2020.
[2] Wang LS, Wang YR, Ye DW, Liu QQ. A review of the 2019 novel coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020.
[3] Baron SA, Devaux C, Colson P, Raoult D, Rolain MJ. Teicoplanin: an alternative drug for the treatment of coronavirus COVID-19? Int J Antimicrob Agents 2020. doi:10.1016/j.ijantimicag.2020.105944.
[4] Serafin MB, Hörner R. Drug repositioning, a new alternative in infectious diseases. Braz J Infec Dis 2018;22(3):252–6. doi:10.1016/j.bjid.2018.05.007.
[5] Foletto VS, Serafin MB, Bottega A, da Rosa TF, de S, Machado C, Coelho SS, et al. Repositioning of fluoxetine and paroxetine: study of potential antibacterial activity and its combination with ciprofloxacin. Medicinal Chemistry Research 2020;29:556 –53.
[6] Zheng W, Sun W, Simeonov A. Drug repurposing screens and synergistic drug-combinations for infectious diseases. Br J Pharmacol 2018;175(2):181–91. doi:10.1111/bph.13895.
[7] Wang M., Cao R., Zhang L. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Research 2020;30:269–71. https://doi.org/ 10.1038/s41422-020-0282-0
[8] 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(1):72–3. doi:10.1101/2020.02.05.935387.
[9] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. Cell Discov 2020;6:16. doi:10.1038/s41421-020-0156-0.

[10] Zhang J, Ma X, Yu F, Liu J, Zou F, Pan T, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. BioRxiv 2020. doi:10.1101/2020.02.05.935387.
[11] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, 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. doi:10.1016/j.ijantimicag.2020.105949.
[12] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 27 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—27-march-2020 (March 27, 2020), Accessed 27 March 2020.
[13] Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East Respiratory Syndrome coronavirus infection. Antimicrob Agents Chemother 2014;58(8):4885–93. doi:10.1128/AAC.03036-14.
[14] Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(0):E014. doi:10.3760/cma.j.issn.1001-0939.2020.0014.
[15] 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(1):264–8. doi:10.1016/j.bbrc.2004.08.085.
[16] de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, et al. 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(8):4875–84. doi:10.1128/AAC.03011-14.
[17] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020.
[18] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, O'Meara MJ, et al. A SARS-CoV-2-human protein-protein interaction map reveals drug targets and potential drug-repurposing. BioRxiv 2020. doi:10.1101/2020.03.22.002386.
[19] Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Van Ranst M, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009;53(8):3416–21. doi:10.1128/AAC.01509-08.
[20] de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, Thiel V, Narayanan K, Makino S, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol 2011;92:2542. doi:10.1099/vir.0.034983-0.
[21] Pfefferle S, Schöpf J, Kögl M, Friedel CC, Muller MA, Carbajo-Lozoya J, et al. The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. PLoS Pathog 2011;7(10):e1002331. doi:10.1371/journal.ppat.1002331.
[22] Lin MH, Moses DC, Hsieh CH, Cheng SC, Chen YH, Sun CY, et al. Disulfiram can inhibit MERS and SARS coronavirus papain-like proteases via different modes. Antiviral Res 2018;150:155–63.