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The broad spectrum host-directed agent ivermectin as an antiviral for SARS-CoV-2?

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**A B S T R A C T**

FDA approved for parasitic indications, the small molecule ivermectin has been the focus of growing attention in the last 8 years due to its potential as an antiviral. We first identified ivermectin in a high throughput compound library screen as an agent potently able to inhibit recognition of the nuclear localizing Human Immunodeficiency Virus-1 (HIV-1) integrase protein by the host importin (IMP) α/β1 heterodimer, and recently demonstrated its ability to bind directly to IMPα to cause conformational changes that prevent its function in nuclear import of key viral as well as host proteins. Cell culture experiments have shown robust antiviral action towards a whole range of viruses, including HIV-1, dengue, Zika and West Nile Virus, Venezuelan equine encephalitis virus, Chikungunya, pseudorabies virus, adenovirus, and SARS-CoV-2 (COVID-19). Close to 70 clinical trials are currently in progress worldwide for SARS-CoV-2. Although few of these studies have been completed, the results that are available, as well as those from observational/retrospective studies, indicate clinical benefit. Here we discuss the case for ivermectin as a host-directed broad-spectrum antiviral agent, including for SARS-CoV-2.

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1. Introduction

The work identifying ivermectin, a macrocyclic lactone 22,23-dihydroavermectin B produced by the bacterium Streptomyces avermitilis, and subsequently demonstrating its activity as a novel therapeutic against "infections caused by roundworm parasites" was recognized, along with the seminal work on the antimalarial artesunate, with the award of the 2015 Nobel Prize for Physiology or Medicine [1,2]. Soon after its discovery in 1975, ivermectin was approved as a treatment for parasitic infection indications in animals (1981), and subsequently for human use to treat onchocerciasis (river blindness) 6 years later. It has since been approved for treatment of a range of human nematode (roundworm) infections that cause river blindness, filariasis, ascariasis and strongyloidiasis, as well as pediculosis and scabies, caused by ectoparasites, and also for rosacea [1,3]. Because of its importance in treating all of these indications, ivermectin is firmly on the World Health Organisation’s List of Essential Medicines [6], with millions of doses prescribed worldwide every year.

Starting in 2012, ivermectin’s antiviral properties have been progressively documented towards a number of RNA viruses, including human immunodeficiency virus (HIV)-1, influenza, flaviruses such as dengue and Zika, and most notably, SARS-CoV-2 (COVID-19) [4,5,7-17], as well as DNA viruses such as pseudorabies, polyoma and adenoviruses [18-20]. Ivermectin’s antiviral activity is based on its ability to bind to and inhibit the transport function of the host importin α (IMPα) protein [11,15,20]; IMPα is known to mediate nuclear import of various viral proteins and key host factors, although other actions of ivermectin have been proposed which may also contribute to its activity [eg. [12,21,22]]. In light of the possibility that ivermectin has potential to be a key weapon to help control the SARS-CoV-2 pandemic, this review briefly examines the weight of evidence for ivermectin’s broad-spectrum antiviral activity through its action on host factor IMPα, [6,17].
2. FDA-approved anti-parasitic ivermectin

Ivermectin has had an immense impact as a therapeutic to control various parasitic diseases [1–6], its antiparasitic mode of action believed to be through potentiating GABA-mediated neurotransmission, and by binding to invertebrate glutamate-gated Cl− channels to effect parasite paralysis and death [23]. The selectivity of ivermectin stems from the fact that it does not readily penetrate the central nervous system (CNS) of mammals, where GABA functions as a key neurotransmitter [23]. Doses up to 2000 μg/kg can be well tolerated in patients with parasitic infections [23,24], with analysis of the first 11 years of mass global ivermectin administration indicating a very low incidence of serious adverse side effects [4,25], with no resistance in humans yet confirmed in over 25 years. Ivermectin is in fact usually administered as a single oral yearly dose (eg. 150 or 200 μg/kg, respectively) to treat onchocerciasis and strongyloidiasis, with filariasis similarly treated with a once yearly dose (300–400 μg/kg) in endemic areas, or alternatively bi-yearly (150–200 μg/kg) [26]. Clearly, ivermectin is a safe, efficacious antiparasitic likely to remain an integral part of the WHO List of Essential Medicines [6] long into the future [1,4].

3. Ivermectin as an IMPα targeting agent

Transport into and out of the nucleus is an integral part of normal eukaryotic cell function, as well as in the case of viral infection, since viruses commonly hijack the system in order to antagonize the cellular antiviral response that is driven to a large extent by nuclear factors such as transcription factors [14,27]. The key signal-dependent mediators of this transport are the members of the IMP superfamily of proteins, of which there are multiple α and β forms [14,27]. Nuclear transport mediated by the IMPα/β heterodimer is the best characterized pathway by which host proteins enter the nucleus through nuclear envelope-embedded nuclear pores; host proteins transported into the nucleus include members of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducers and activators of transcription (STATs) inducible transcription factor families that play key roles in the response to infection. Specific viral proteins [see [27,28]] also use this pathway (see Fig. 1). Briefly, IMPα within the IMPα/β heterodimer performs the adaptor role of signal-specific recognition of the nuclear import cargo, while IMPβ1 performs the main transport roles of binding to/translation through the nuclear pores, and subsequent release of the nuclear import cargo within the nucleus upon interaction with another transport factor, the monomeric guanine nucleotide binding protein Ran (not shown in Fig. 1) [see 27]. Specific high affinity recognition by IMPα is critical to nuclear localization of various viral proteins such as dengue non-structural protein (NS) 5, as shown in mutagenic studies [32]; significantly, dengue virus with impaired NS5 interaction with IMPα is severely attenuated, underscoring the critical importance of the NS5-IMPα interaction for dengue infection. The importance of this interaction to dengue infection is the basis for the fact that multiple distinct small molecules that disrupt IMPα recognition of dengue NS5 are able to limit dengue infection [eg. [7,8,11,31,33]]. Significantly in the case of ivermectin, this activity extends to a large number of different viruses (see below) [7–17], including SARS-CoV-2 [18].

We identified ivermectin in 2011 in a high throughput screen using bacterially expressed proteins and a 1200-compound library of small molecules for inhibitors of HIV-1 Integrase (IN) recognition by IMPα/β1 [34]; specific inhibitors targeting IMPα/β1 directly (such as ivermectin) and not IN (such as budesonide) were identified using a nested counter-screening strategy [34,35]. Of several compounds now confirmed to be active against IMPα/β1 and possessing antiviral activity as a consequence [7,14,31,36], ivermectin is the best characterized, shown to have broad-spectrum activities (summarized in Tables 1–3). It was initially shown to inhibit nuclear import not only of IN, but also of simian virus SV40 large tumour antigen (T-ag) and other IMPα/β1- (but not IMPα/β1-) dependent cargoes, consistent with the idea that IMPα (not IN) is the direct target of ivermectin [34,35]. Subsequent work has confirmed this, with ivermectin’s ability to inhibit the nuclear accumulation of various different host, including NF-κB p65 [37,38] and viral proteins demonstrated in transfected and infected cell systems (see Table 1) [14,34]. ivermectin’s ability to inhibit binding of IMPα to the viral proteins NS5 and T-ag has also been confirmed in a cellular context using the biomolecular fluorescence complementation technique [11] (Table 1).

Although targeting of IMPα by ivermectin was implicated by many years of research (see also below), direct binding was only recently formally demonstrated using a set of biophysical techniques, including thermostability, analytical ultracentrifugation, and circular dichroism (CD) [11]. Importantly, the CD/thermostability studies indicate that binding of ivermectin to IMPα induces structural changes which are likely the basis of ivermectin inhibition of IMPα binding to viral nuclear import cargoes. Strikingly, the structural change also appears to impair heterodimerisation of IMPα with IMPβ1 [11 - see however 20]; thus, ivermectin inhibits nuclear import not only by preventing signal recognition by IMPα, but also by ensuring that the IMPα/β1 complex essential to mediate subsequent transport through the nuclear pore is prevented from forming (see Fig. 1).

4. Ivermectin’s broadspectrum antiviral activity

Consistent with the fact that many viruses are known to rely on IMPα/β1-dependent nuclear import of specific viral proteins for robust infection, including many viruses for which the lifecycle is entirely carried out in the cytoplasm [14,27,28], a body of in vitro studies have confirmed ivermectin to be active in limiting infection by a range of different RNA viruses [10,14], including HIV-1 [7], DENV (all 4 serotypes) and related flaviviruses [8,11,12], influenza, and alphaviruses such as Venezuelan equine encephalitis virus (VEEV) and Chikungunya [9,15,16] (see Table 2); it is also active against DNA viruses [18–20]. Exciting recent studies indicate it is a potent inhibitor of SARS-CoV-2 [17].

A striking aspect of this antiviral activity is that, where determined, the EC50 for viral inhibition as assessed by a range of different techniques is in the low μM range (see right column, Table 2), interestingly aligning perfectly with its activity in inhibiting recognition of viral nuclear import cargoes by IMPα (see Table 1). The clear implication is that the mechanism of inhibition of infectious virus production in the case of all of the viruses listed in Table 2 is largely through targeting IMPα to prevent its role in nuclear import, and of viral proteins in particular (see Fig. 1). Significantly, two other small molecules (GW5074 and gossypol) that appear to target IMPα in a very similar way to prevent its nuclear import function [31 and unpublished] have comparable antiviral properties [13,31,36], consistent with the idea that the host protein IMPα is a key contributor to infection by a number of medically important viruses.

5. Ivermectin in the clinic as an antiviral?

As in many other disciplines, one of the biggest challenges in antiviral research is to transition from laboratory experiments to preclinical/clinical studies, with the question of dosing in the case of ivermectin for viral infectious indications contentious [see 6,39,40]. It is important, firstly, to stress the obvious in this context:
that the antiviral activities of ivermectin documented in Table 2 have been derived from laboratory experiments that largely involve high, generally non-physiological, multiplicities of infection, and cell monolayer cultures, often of cell lines such as Vero cells (African green monkey kidney cells impaired in interferon α/β production) that are not clinically relevant. Clearly, the results in Table 2 for low uM EC50 values reveal robust, dose-dependent antiviral activity in the particular model system used, but it would be naïve to believe that it is necessary to achieve uM concentrations of ivermectin in a patient for maximum clinical benefit.

In fact, a key consideration in clinical intervention using ivermectin is its host-directed (IMPα-directed) mechanism of action. Host-directed agents that impact cellular activities that are essential to healthy function must be tested with caution; although ivermectin has an established safety profile in humans [24,26], and is FDA-approved for a number of parasitic infections [1,3,5], it targets a host function that is unquestionably important in the antiviral response, and titration of a large proportion of the IMPα repertoire of a cell/tissue/organ is likely to lead to toxicity. With this in mind, where a host-directed agent can be a "game-changer" in treating viral infection may well be in the initial stages of infection or potentially even prophylactically by keeping the viral load low so that the body’s immune system has an opportunity to mount a full antiviral response [11,17].
Ivermectin’s potential as an antiviral to treat infection can of course only be demonstrated in clinical studies. Preclinical studies in a lethal Pseudorabies (PRV) mouse challenge model showed that dosing (0.2 mg/kg) 12 h post-infection protected 50% of mice, which could be increased to 60% through administration of ivermectin at the time of infection [18]. Clinical data for a phase III trial against DENV infection similarly indicate antiviral activity, with daily dosing (0.4 mg/kg) found to be safe, and virological efficacy demonstrated, although it was concluded that dosing regimen modification was required to achieve clinical benefit [41]. These studies underline ivermectin’s real potential as an antiviral able to reduce viral load in a clinical context.

### Table 1

*In vitro effects of ivermectin on IMPs.*

| Cargo Protein | Virus | Host |
|---------------|-------|------|
| IMPβ1 (IC50 7 μM) [11] | HIV IN (IC50 5 μM) [34] | IMPβ1 (IC50 7 μM) [11] |
| DENV1 NS5 (IC50 2 μM) [8] | DENV1 NS5 (IC50 1 μM) [7,8,11] | DENV V (IC50 15 μM) [13] |
| SV40 T-ag [34] | SV40 T-ag [11,20] | Adenovirus EIA [20] |
| TRF1 [7,34] | HIV-EN [7] | SV40 T-ag [7,16,34] |
| p53 [7] | DENV2 NS5 [7] | VEEV Capsid [16] |
| NF-kB (LPS-induced) [37,38] | VEEV Capsid [16] | adenovirus EIA [1] |
| adenovirus EIA [1] | PSV UL42 [18] | hCMV ppUL44, pUL5 [7] |
| adenovirus EIA [1] | VEEV Capsid [9] | adenovirus EIA [1] |

*Abbreviations: HIV-1, human immunodeficiency virus; DENV, dengue virus; VEEV, Venezuelan equine encephalitis virus; PSV, Pseudorabies virus; hCMV, human cytomegalovirus; T-ag, SV40 large T-antigen; DENV, dengue virus; TRF1, telomere repeat factor 1; LPS, lipopolysaccharide.*

### Table 2

*In vitro* antiviral action of ivermectin.

| Virus | Inhibitory Concentration/Fold reduction (Assay) |
|-------|-------------------------------------------------|
| SARS-CoV-2 | EC50 = 2.2/2.8 μM/5000-fold reduction (qPCR/released/cell-associated virus) [17] |
| Lentivirus | 50 μM > 2-fold reduction (luciferase) [7] |
| HIV-1 (VSV-G-pseudotyped NL4-3.Luc.R-E-HIV) | 0 μM total inhibition (luciferase) [10] |
| Orthomyxovirus | EC50 = 5.0/0.5 μM (CPE/qPCR) [12]/3 μM > 50,000-fold reduction (pfu) [15] |
| Influenza VLPs (avian influenza A/MxA escape mutants) | EC50 = 2.33 μM (CFI, 2 hosts) [8]/EC50 = 0.7 μM (qPCR) [12] |
| Flaviviruses | EC50 = 0.4/0.6 μM (pfu/qPCR) [11]/50 μM total inhibition (pfu) [7] |
| YFV (17D) | EC50 = 2.1/1.7 μM (CFI, 2 hosts) [8] |
| DENV1 (EDEN-1) | EC50 = 1.7 μM (CFI) [8] |
| DENV2 (NGC) | EC50 = 19 μM (CFI) [8] |
| DENV2 (EDEN-2) | EC50 = 4 μM (qPCR) [12] |
| DENV3 (EDEN-3) | EC50 = 10 μM (pfu/qPCR) [11] |
| DENV4 (EDEN-4) | EC50 = 1/0.5 μM (pfu/qPCR) [11] |
| WNV (NY99) | EC50 = 1.3/1.6 μM (pfu/qPCR) [11] |
| WNV (MRR61C) | EC50 = 1.9/0.6 μM (luciferase, 2 hosts)/3 μM > 5000-fold reduction (pfu) [15] |
| ZIKV (Asian/Cook Islands/2014) | 3 μM > 1000-fold (pfu) [15] |
| Alphaviruses | 3 μM > 200-fold (pfu) [15] |
| Chikungunya virus (CHIKV-Rhuc) | Est. EC50 = 2 μM (TCID/luciferase) [13] |
| Sindbis (HR) | EC50 = 80 μM (luciferase, 2 hosts)/3 μM > 5000-fold reduction (pfu) [15] |
| Semlicki Forest Virus | EC50 = 1 μM c. 20-fold (pfu) [9] |
| VEEV (TC83) | Est. EC50 = 2 μM (TCID/luciferase) [13] |
| Hendra (Hendra virus/Australia/Horse/1994) | EC50 = 2.5 μM; 10 μM 20-fold reduction (qPCR) [20] |
| DNA viruses | EC50 = 10 μM c. 8-fold reduction (qPCR) [20] |
| Adenovirus (HAdV-C5) | Est. EC50 = 1.5 μM (pfu/CPE/qPCR) [19] |
| Adenovirus (HAdV-B3) | Est. EC50 = 0.8 μM 1000-fold (pfu) [15] |

*Abbreviations: HIV-1, human immunodeficiency virus; VLP, virus like particle; PSV, Pseudorabies virus; YFV, yellow fever virus; DENV, dengue virus; ZIKV, zika virus; WNV, West Nile virus; TCID; pfu, plaque forming unit (infectious virus assay); CPE, cytopathic effects; qPCR, quantitative polymerase chain reaction; CFI, cell fluorescence-based immunofluorescence assay.*
Table 3
Summary of Current Clinical Trials using Ivermectin for SARS-CoV-2.

| Title                                                                 | Status | Interventions | Start | Locations                           |
|----------------------------------------------------------------------|--------|---------------|-------|-------------------------------------|
| 1 Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19 | R      | Ivermectin 0.6 mg/kg QD plus SC vs. SC | 18.5.20 | CEMIC, Buenos Aires, Ciudad De Buenos Aires, Argentina |
| 2 Ivermectin and Nitazoxanide Combination Therapy for COVID-19        | NY     | Ivermectin 0.2 mg/kg once plus NZX 500 mg BID for 6 days vs. SC | 20.5.20 | Tanta University, Egypt |
| 3 Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19 Infection | R      | Ivermectin 12−15 mg/day for 3 days vs. Placebo | 12.5.20 | Sheba Medical Center, Ramat-Gan, Israel |
| 4 Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection | A      | Ivermectin 12 mg (<80 kg) or 18 mg (>80 kg) once vs. HCQ 400 mg BID for 1 day then 200 mg BID for 4 days vs. Placebo | 4.5.20 | Jose Manuel Arreola Guerra, Aguascalientes, Mexico |
| 5 Efficacy of Ivermectin in Adult Patients With Early Stages of COVID-19 | R      | Ivermectin 0.3 mg/kg daily for 5 days vs. Placebo | 20.6.20 | Colombia |
| 6 Ivermectin In Treatment of COVID 19 Patients;                      | R      | Ivermectin (dose undefined) vs. SC | 9.6.20 | Isolation and referral hospitals for COVID 19 patients, Cairo, Egypt |
| 7 Efficacy and Safety of Ivermectin and Doxycycline in Early Combination of Antiviral Drugs in Patients With COVID-19 Infection; | NY     | Ivermectin 0.2 mg/kg once plus 200 mg DOX day 1 followed by 100 mg | 16.6.20 | ICDDR, Dhaka, Bangladesh |
| 8 Efficacy of Ivermectin as Add on Therapy in COVID19 Patients        | C      | Ivermectin 0.2 mg/kg once weekly plus HCQ 400 mg vs. Placebo | 18.4.20 | General Directorate of Medical City, Baghdad, Baghdad, Iraq |
| 9 COVID/IVERMECTIN: Ivermectin for Treatment of COVID-19 (COVER)      | C      | Ivermectin 1.2 mg/kg QD for 5 days vs. Placebo | 20.6.20 | Negrar, Verona, Italy; Bologna, Italy; Milan, Italy; Rovereto, Italy; Turin, Italy; Barcelona, Spain; Madrid, Spain |
| 10 Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected With SARS-CoV-2 With or Without Symptoms (SILVERBULLET); | NY     | Ivermectin 12 mg/day for 3 days plus paracetamol 500 mg QID for 14 days vs. Placebo plus paracetamol 500 mg QID for 14 days | 20.6.20 | Investigacion Biomedica para el Desarrollo de Farmacos S.A. de C.V., Mexico |
| 11 Sars-CoV-2/Covid-19 Ivermectin Navarra-ISOGlobal Trial (SAINT);   | A      | Ivermectin 0.4 mg/kg once vs. Placebo | 14.5.20 | Clínica Universidad de Navarra, Pamplona, Navarra, Spain |
| 12 A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh; | C      | Ivermectin 0.2 mg/kg once plus DOC 100 mg BID for 10 days plus HCQ 400 mg day 1 then 200 mg BID for 9 days plus ATM 500 mg BID for 5 days | 2.5.20 | Chakoria Upazilla Health Complex, Cox’s Bazar, Bangladesh |
| 13 Ivermectin vs Combined Hydroxychloroquine and Antiretroviral Drugs (ART) Among Asymptomatic COVID-19 Infection (IDRA-COVID19); | NY     | Ivermectin 0.6 mg/kg daily for 3 days vs. HCQ 400 mg | 20.7.20 | Siriraj Hospital, Bangkok Noi, Bangkok, Thailand |
| 14 IVERMECTIN Aspirin Desametastone and Enoxaparin Against COVID-19 As Treatment of Covid-19; | A      | Ivermectin 5 mg/ml oral to be repeated 1 week later | 1.5.20 | Hospital Eurnekian, Buenos Aires, Argentina |
| 15 A Preventive Treatment for Migrant Workers at High- Risk of Covid-19; | C      | Ivermectin 12 mg once vs. HCQ 400 mg day 1 then 200 mg BID for 42 days vs. Zinc 80 mg/day plus vitamin C 500 mg/day for 42 days vs. Vitamin C 500 mg/day for 42 days | 13.5.20 | Tuas South Dormitory, Singapore, Singapore |
| 16 New Antiviral Drugs for Treatment of COVID-19;                    | NY     | Ivermectin (dose undefined) plus NZX (dose undefined) plus ribavirin 200 mg or 400 mg vs. Control (untreated) | 20.5.20 | Mansoura University, Mansoura, Select A State Or Province, Egypt |
| 17 Early Treatment With Ivermectin and LasaTAN for Cancer Patients With COVID-19 Infection (TITAN); | R      | Ivermectin 12 mg once plus losartan 50 mg/day for 15 days vs. Placebo | 20.7.20 | Instituto do Cancer do Estado de Sao Paulo, Brazil |
| 18 Ivermectin in Treatment of COVID-19;                             | R      | Ivermectin daily (dose undefined) for 3 days plus SC vs. SC | 31.5.20 | Waheed Shouman, Zagazig, Sharkia, Egypt |
| 19 Efficacy of Ivermectin in COVID-19;                              | R      | Ivermectin 12 mg once plus SC vs. SC | 15.4.20 | Combined Military Hospital Lahore, Lahore, Punjab, Pakistan |
| 20 Ivermectin and Doxycycline in COVID-19 Treatment;                | R      | Ivermectin (dose undefined) plus DOC (dose undefined) vs. CQ (dose undefined) | 1.6.20 | Sherief Abd-Elsalam, Sharkia, Egypt |
| 21 The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment; | R      | Ivermectin (dose undefined) vs. Ivermectin (dose undefined) vs. Nitazoxanide (dose undefined) | 16.6.20 | Tanta University, Tanta, Egypt |
| 22 Prophylactic Ivermectin in COVID-19 Contacts;                    | C      | Ivermectin (dose undefined) vs. Ivermectin (dose undefined) vs. CQ (dose undefined) | 31.5.20 | Zagazig University, Zagazig, Sharkia, Egypt |
| 23 Max Ivermectin- COVID 19 Study Versus Standard of Care Treatment for COVID 19 Cases; A Pilot Study; | C      | Ivermectin (dose undefined) vs. Ivermectin (dose undefined) vs. CQ (dose undefined) | 25.4.20 | Max Super Specialty Hospital, Saket (A unit of Devki Devi Foundation), New Delhi, Delhi, India |

(continued on next page)
| Title, URL | Status | N<sup>a</sup> | Interventions<sup>b</sup> | Start | Locations |
|-----------|--------|--------------|-------------------------|-------|-----------|
| **24** A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19 (IFORS); https://ClinicalTrials.gov/show/NCT04441466 | R | 64 | Ivermectin 0.1 mg/kg once vs. Ivermectin 0.1 mg/kg day 1 and repeated after 72 h vs. Ivermectin 0.2 mg/kg once vs. Ivermectin 0.2 mg/kg day 1 and repeated after 72 h vs. SC | 1.7.20 | Hospital Universitário da Universidade Federal de São Carlos (HU-UFSCar), São Carlos, São Paulo, Brazil |
| **25** Novel Agents for Treatment of High-risk COVID-19 Positive Patients; https://ClinicalTrials.gov/show/NCT04374019 | R | 240 | Ivermectin 12 mg (~75 kg) or 15 mg (~75 kg) daily for 2 days vs. HCQ 600 mg/day for 14 days plus ATM 500 mg/day 1 then 250 mg/day for 4 days vs. Camostat Mesilate 200 mg TID for 14 days vs. Artemesia annua 50 mg TID for 14 days vs. SC | 1.5.20 | University of Kentucky Markey Cancer Center, Lexington, Kentucky, United States |
| **26** Ivermectin-Azithromycin-Cholecalciferol (IvAzCol) Combination Therapy for COVID-19; https://ClinicalTrials.gov/show/NCT04397946 | C<sup>c</sup> | 30 | Ivermectin 6 mg/day on days 0, 1, 7 and 8 plus ATM 500 mg/day 4 days plus Cholecalciferol 400 IU BID for 30 days vs. Control (untreated) | 15.3.20 | Outpatient treatment, Mexico City, Mexico |
| **27** USEFULNESS of Topic Ivermectin and Carrageenan to A<sup>d</sup> Prevent Contagion of Covid 19 (IVERCAR); https://ClinicalTrials.gov/show/NCT04424580 | | 1195 | Ivermectin (topical for oral mucosae) plus iota carrageenan (topical for oral mucosae) 5 times per day plus PPE vs. PPE only | 1.6.20 | Hospital Eurnekian, Buenos Aires, Argentina |
| **28** Novel Regimens in COVID-19 Treatment; https://ClinicalTrials.gov/show/NCT04382846 | NY | 80 | Ivermectin plus CQ (dose unlisted) vs. Ivermectin plus NZX (dose unlisted) vs. Ivermectin plus NZX plus ATM (dose unlisted) vs. NZX and ATM (dose unlisted) | 8.5.20 | Tanta University, Egypt |
| **29** Anti-Androgen Treatment for COVID-19; https://ClinicalTrials.gov/show/NCT04444249 | R | 254 | Ivermectin 0.2 mg/kg QD plus ATM 500 mg QD vs. Ivermectin 0.2 mg/kg QD plus ATM 500 mg QD plus Dutasteride 0.5 mg QD | 26.6.20 | Coprometria Institute, Brasilia, Brazil |
| **30** A Real-life Experience on Treatment of Patients With COVID 19; https://ClinicalTrials.gov/show/NCT04345419 | | 120 | Ivermectin (dose unlisted) vs. CQ (dose unlisted) vs. Favipiravir (dose unlisted) vs. NZX (dose unlisted) vs. Niclosamide (dose unlisted) vs. other drugs (oseltamivir or combination of above, dose unlisted) | 16.6.20 | Tanta University Hospital, Tanta, Egypt |
| **31** Worldwide Trends on COVID-19 Research After the Declaration of COVID-19 Pandemic (observational); https://ClinicalTrials.gov/show/NCT04460547 | NY | 200 | Completed interventional vs. completed observational studies on Ivermectin, Convalescent Plasma, HCQ, DAS181, or Interferon J1A | 25.7.20 | Qassim University, Saudi Arabia |
| **32** Trial of Combination Therapy to Treat COVID-19 Infection; https://ClinicalTrials.gov/show/NCT04482866 | NY | 300 | Ivermectin (dose unlisted) day 1 and plus DOC (dose unlisted) for 10 days plus Zinc for 10 days plus Vitamin D3 for 10 days plus Vitamin C for 10 days vs. Placebo | 22.7.20 | ProgeniBiome, California, USA |
| **33** Randomised clinical trial of ivermectin for treatment and prophylaxis of COVID-19; https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001994-66/ES | O | 266 | Ivermectin (dose unlisted) vs. Placebo | 8.5.20 | Fundació Assistencial Mútua Terrassa, Spain |
| **34** Multicenter, randomized, double-blind, placebo-controlled study investigating eficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (COVID-19) and manifested clinical symptoms; https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002091-12/BE | | 120 | Ivermectin 0.4 mg/kg plus SC vs. Placebo plus SC | 5.5.20 | Bulgaria (9 sites) |
| **35** Efficacy of hydroxychloroquine, ciclesonide and ivermectin in treatment of moderate covid-19 illness: an open-label randomised controlled study [EHYCVER-COVID]; http://ctri.nic.in/Clinicaltrials CTRI/2020/04/024948 | NY | 120 | Ivermectin 12 mg/day for 7 days vs. Ciclesonide 0.2 mg/kg BID for 7 days vs. HCQ 400 mg BID Day 1 then 200 mg BID for 6 days vs. SC | 15.5.20 | New Delhi, India |
| **36** A Phase IIIb open label randomized controlled trial to evaluate the efficacy and safety of ivermectin in reducing viral loads in patients with hematological disorders who are admitted with COVID 19 infection; http://ctri.nic.in/Clinicaltrials CTRI/2020/04/025068 | NY | 50 | Ivermectin 3 mg (15-24 kg) or 6 mg (25-35 kg) or 9 mg (36-50 kg) or 12 mg (51-65 kg) or 15 mg (66-79 kg) or 0.2 mg/kg (80 kg) once vs. SC | 27.5.20 | Christian Medical College Vellore, Tamil Nadu, India |
| **37** Intervventional study to assess the efficacy of ivermectin with standard of care treatment versus standard of care in patients of COVID-19 at R D Gardi Medical College, Ujjain, India; http://ctri.nic.in/Clinicaltrials CTRI/2020/04/025234 | NY | 50 | Ivermectin 12 mg/day for 2 days plus SC vs. SC | 24.5.20 | R D Gardi Medical College, Ujjain, Madhya Pradesh, India |
| **38** Study to assess the efficacy of Ivermectin as prophylaxis of COVID 19 among health care workers and COVID 19 contacts in Ujjain, India; http://ctri.nic.in/Clinicaltrials CTRI/2020/04/025262 | NY | 2000 | Ivermectin 12 mg/day (adult) or 6 mg/day (children) for 2 days vs. Control | 27.5.20 | R D Gardi Medical College, Ujjain, Madhya Pradesh, India |
| **39** Randomised Controlled Trial of Ivermectin in hospitalised patients with COVID19 (RIVET-COV); http://ctri.nic.in/Clinicaltrials CTRI/2020/04/025333 | NY | 60 | Ivermectin single dosing of 0.2 mg/kg vs. Ivermectin 0.4 mg/kg vs. Ivermectin 0.8 mg/kg vs. Ivermectin 1.6 mg/kg vs. Ivermectin 2 mg/kg vs. SC | 25.6.20 | New Delhi, India |
| **40** A Prospective, randomized, single centred, open labelled, two arm, placebo-controlled trial to evaluate efficacy and safety of Ivermectin drug in patients infected with SARS-CoV-2 virus; http://ctri. nic.in/Clinicaltrials CTRI/2020/04/025960 | NY | 100 | Ivermectin 12 mg/day for 3 days vs. SC | 18.6.20 | Symbiosis University Hospital and Research Centre, Maharashtra, India |
| **41** A Clinical Trial to Study the Efficacy of “Ivermectin” in the prevention of Covid-19. A Single Arm Study; http://ctri.nic.in/Clinicaltrials CTRI/2020/04/026232 | NY | 50 | Ivermectin 0.2 mg/kg once | 10.7.20 | DVFM, Andhra Pradesh, India |
| Title, URL | Status N<sup>1</sup> | Interventions<sup>2</sup> | Start | Locations |
|------------|-----------------|----------------------|-------|-----------|
| 42 Ivermectin Nasal Spray for COVID19 Patients; https://clinicaltrials.gov/ct2/show/NCT04510233 | NY 60 | Ivermectin nasal spray (1 mL) in each nostril BID vs. Placebo | 10.8.20 | Tanta University, Tanta, Egypt |
| 43 Outpatient use of ivermectin in COVID-19; https://clinicaltrials.gov/ct2/show/NCT04530474 | NY 200 | Ivermectin 0.15–0.2 mg/kg (max 12 mg) once vs. Placebo | 26.8.20 | Temple University Hospital, Philadelphia, USA |
| 44 Ivermectin to prevent hospitalizations in COVID-19; https://clinicaltrials.gov/ct2/show/NCT04529525 | R 24 | Ivermectin 12 mg (48-80 kg) or 18 mg (80-110 kg) or 24 mg (>100 kg) at inclusion and again at 24h vs. Placebo | 21.8.20 | Ministry of Public Health, Province of Corrientes, Argentina |
| 45 Clinical trial of ivermectin plus doxycycline for the treatment of confirmed Covid-19 infection; https://clinicaltrials.gov/ct2/show/NCT04523831 | C 400 | Ivermectin 6 mg and DOC 100 mg BID for 5 days vs. Placebo | 19.8.20 | Dhaka Medical College, Dhaka Bangladesh |
| 46 Pilot study to evaluate the potential of ivermectin to reduce COVID-19 transmission; https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001474-29/ES | O 24 | Ivermectin (dose unlisted) vs. Placebo | 8.5.20 | Clinica Universidad de Navarra, Pamplona, Spain |
| 47 Dose-Finding study of ivermectin treatment on patients infected with Covid-19; A clinical trial; https://en.irct.ir/trial/47012 | A 125 | Ivermectin 0.2 mg/kg single dose plus SC vs. Ivermectin 0.2 mg/kg day 1, 2, 5 plus SC vs Placebo plus SC vs. Ivermectin 0.4 mg/kg day 1 and 0.2 mg/kg day 2, 5 vs. SC | 4.5.20 | Qazvin University of Medical Sciences, Qazvin, Iran |
| 48 In vivo use of ivermectin (IVR) for treatment for corona virus infected patients: a randomized controlled trial; http://www.chctrc.org.cn/showprojen.aspx?proj=54707 | NY 60 | Ivermectin single dose 0.2 mg/kg vs. Placebo | 10.6.20 | Rayak Hospital, Riyaq, Lebanon |
| 49 A randomized clinical trial study, comparison of the therapeutic effects of ivermectin, Kaletra and Chloroquine with Kaletra and Chloroquine in the treatment of patients with coronavirus 2019 (COVID-19); http://en.irct.ir/trial/48444 | A 60 | Ivermectin oral (6 mg) TID vs. Placebo | 30.5.20 | Ahvaz Razi Hospital, Ahvaz, Iran |
| 50 A double-blind clinical trial to repurpose and assess the efficacy and safety of ivermectin in COVID-19; https://www.clinicaltrialsregister.eu/ctr-projen.aspx?proj=45707 | R 45 | Ivermectin 6 mg every 3.5 days for 2 weeks vs. Placebo | 23.4.20 | Lagos University Teaching Hospital, Lagos, Nigeria |
| 51 Effectiveness of Ivermectin in the Treatment of Coronavirus Infection in Patients admitted to Educational Hospitals of Mazandaran in 2020; https://en.irct.ir/trial/49174 | R 60 | Ivermectin 0.2 mg/kg single dose plus SC vs. Placebo | 21.5.20 | Bouali Hospital, Sari, Iran |
| 52 Sub-cutaneous Ivermectin in Combination With and Without Oral Zinc and Nigella Sativa: a Placebo Randomized Control Trial on Mild to Moderate COVID-19 Patients; https://clinicaltrials.gov/ct2/show/NCT04472585 | NY 40 | Ivermectin 0.2 mg/kg subcutaneous injection every 2 days plus SC vs. Ivermectin 0.2 mg/kg subcutaneous injection every 2 days plus 80 mg/kg Nigella Sativa oral QD plus SC vs. Ivermectin 0.2 mg/kg subcutaneous injection every 2 days plus 20 mg Zinc Sulfate oral TID plus SC vs. Placebo 7.9.20 Ponti Province of Corrientes, Argentina | 14.7.20 | Shaikh Zayed Hospital, Lahore, Pakistan |
| 53 Pragmatic study "CORIVIR": Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19); https://www.clinicaltrialsregister.eu/ct2/show/NCT04502211 | O 45 | Ivermectin 0.2–0.4 mg/kg (regime unlisted) vs. HCQ 400 mg vs ATM 500 mg vs Placebo | 22.7.20 | Hospital Universitario Virgen de las Nieves, Granada, Spain |
| 54 Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel at All Levels of Care, During the 2020 Pandemic: A Randomized Clinical Controlled Trial; https://clinicaltrials.gov/ct2/show/record/NCT04527221 | NY 550 | Ivermectin 0.2 mg/kg weekly for 7 weeks vs. Placebo | 7.9.20 | Pontificia Universidad Javeriana, Valle Del Cauca, Colombia |
| 55 Ivermectin Inhalation Forms in the Management of COVID-19 Egyptian Patients; https://clinicaltrials.gov/ct2/show/NCT04510233 | NY 60 | Ivermectin nasal spray BID (dose unlisted) vs. Placebo | 10.8.20 | Tanta University, Tanta, Egypt |
| 56 Safety and Efficacy of Ivermectin and Doxycycline in NY Treatment of Covid-19; https://clinicaltrials.gov/ct2/show/NCT04551755 | NY 188 | Ivermectin 12 mg first dose then 12 mg after 12 h plus DOC 100 mg BID for 10 days vs. Placebo | 16.9.20 | Bangladesh Medical College Hospital, Dhaka, Bangladesh |
| 57 Comparative Study of Hydroxychloroquine and Ivermectin in Covid-19 Prophylaxis; https://clinicaltrials.gov/ct2/show/NCT04384458 | R 400 | Ivermectin (dose based on weight, unlisted) QD for 2 days repeated every 14 days for 45 days plus 20 mg BID active Zinc versus HCQ 400 mg BID on day 1, QD on days 2–5 followed by QD every 5 days for 50 days plus 20 mg BID active Zinc | 12.5.20 | Drug Research and Development Centre, Federal University of Ceará, Ceará, Brazil |
| 58 Assessment of response of ivermectin on virological clearance in COVID 19 patients; http://ctri.nic.in/Clinicaltrials; CTRI/2020/08/027394 | NY 56 | Ivermectin 0.2 mg/kg single dose vs. Placebo | 26.8.20 | Maulana Azad Medical College, New Delhi, India |
| 59 Evaluation of the effect of ivermectin on patients with COVID-19; http://en.irct.ir/trial/50305 | C 130 | Ivermectin 0.2 mg on day 1 followed by 3 mg BID days 2–4 plus HCQ sulfate and ATM alone | 23.8.20 | Tehran University of Medical Sciences, Tehran, Iran |
| 60 Prophylactic Ivermectin in COVID 19 Contacts http://ctri.nic.in/Clinicaltrials; CTRI/2020/08/027282 | NY 180 | Ivermectin 12 mg once vs. Ivermectin 36 mg once vs. Placebo | 20.8.20 | Government Institute of Medical Sciences Greater Noida, Uttar Pradesh, India |

(continued on next page)
6. Ivermectin as a therapeutic for SARS-CoV-2 infection?

The current SARS-CoV-2 pandemic has eclipsed the porcine flu epidemic in terms of numbers of infections (currently >70 million) and deaths (>1.6 million, with >310,000 of these in the US alone) worldwide. The search for antivirals through repurposing existing drugs has proved challenging (eg. see Ref. [42,43]), one important aspect of repurposing being the perceived need to achieve therapeutic levels in the lung. Published pharmacokinetic modelling based on both the levels of ivermectin achievable in human serum and lung levels of ivermectin can be measured, indicates that concentrations of ivermectin 10 times higher than the c. 2.5 μM EC50 indicated by in vitro experiments (Table 2) are likely achievable in the lung in the case of SARS-CoV-2 [39]; modelling based on different assumptions predicts lower values, but highlights the long-term stability of ivermectin in the lung (over 30 days) based on data from animals [40]. It should also be noted that liquid formulations for intravenous administration of long-acting ivermectin have been described, with aerosol administration also in development, to enable ivermectin administration to achieve even higher concentrations to tackle SARS-CoV-2, whilst the use of ivermectin in combination with other agents may enhance efficacy at lower doses.

Ivermectin as a treatment for SARS-CoV-2 in humans has already been approved in a number of states and countries, including the Republic of Peru [44] and Northeastern Beni region of Bolivia [45]. Importantly, close to 70 trials worldwide are currently testing the clinical benefit of ivermectin to treat or prevent SARS-CoV-2 (see Table 3); these include variations on dosing regimens, combination therapies (preliminary results for NCT04523831 in Table 3, #45) [46,47], and prophylactic protocols. With respect to the latter, preliminary results from recently completed study NCT04422561 (Table 3, #22, and footnote) examining asymptomatic family close contacts of confirmed COVID patients, reveal that two doses of ivermectin 72 h apart result in only 7.4% of 203 subjects reporting symptoms of SARS-CoV-2 infection, in contrast to 101 control untreated subjects, of whom 58.4% reported symptoms; evidence of prophylaxis by ivermectin.

| Title, URL | Status | Interventions | Start | Locations |
|------------|--------|--------------|-------|-----------|
| Ivermectin as a possible treatment for COVID-19; http://crii.mnc/clinicaltrials NCT/2020/08/07225 | NY | Ivermectin 12 mg QD on days 1–2 vs. Placebo | 18.08.20 | AAIMS, Patna, India |
| Evaluating the effect of Ivermectin on covid 19 patients; http://en.itrc.ir/trial/49935 | R | Ivermectin 14 mg every 12 h for 36 h then again on day 7 vs. Placebo | 06.08.20 | Ahvaz University of Medical Sciences, Ahvaz, Iran |
| Evaluate the Efficacy of Siddha Treatment in Patients with Novel Coronavirus Infectious Disease; http://ctri.in/clinicaltrials NCT/2020/08/026999 | R | Ivermectin 12 mg once plus DOC 100 mg BID for 5 days plus Vitamin C 500 mg QD plus Zinc QD plus SC vs. Siddha traditional medicine protocol for 7 days | 05.08.20 | Indian Medicine and Homeopathy Department, Tamil Nadu, India |
| Ivermectin treatment in the effect of patients with covid-19; http://en.itrc.ir/trial/49180 | R | Ivermectin 0.2 mg/kg QD for 2 days vs. antiviral drugs (eg. HCQ) as per SC | 20.07.20 | Mashhad University of Medical Sciences, Mashhad, Iran |
| Randomized phase IIa clinical trial to compare the efficacy of ivermectin versus placebo to obtain negative PCR results in patients with early phase Covid-19; PER-034-20 | R | Ivermectin 0.3 mg/kg QD for 3 days vs. Placebo | 17.07.20 | Universidad Peruana Cayetano Heredia, Lima, Peru |
| Evaluation of ivermectin effects on Covid-19; http://en.itrc.ir/trial/49280 | R | Ivermectin 0.15 mg/kg/day plus SC vs. SC | 22.08.20 | Kermanshah University of Medical Sciences, Kermanshah, Iran |
| A placebo-controlled, randomized, double-blind study in Covid-19 patients with ivermectin; An inVestiget iniTaTedi trial (CORVETTE-01); jRCT2031200120 | R | Ivermectin 0.2 mg/kg once vs. Placebo | 16.09.20 | Kitasato University Hospital, Kanagawa, Japan |
| A single-centre, open-label, randomized controlled study of ivermectin treated mild to moderate COVID-19 cases; Debidwar Upazila Health Complex | Ch | Ivermectin 0.2 mg/kg once plus SC vs. SC | 01.05.20 | Debidwar Upazila Health Complex, Comilla, Bangladesh |

* R, Recruiting; NY, Not yet recruiting; A, Active not recruiting; C, Completed; E, Enrolling by invitation; O, ongoing.

** Numbers of participants.

† SC, standard care, QD, once per day; BID, twice daily; QID, 4 times daily; TID, 3 times daily; PPE, personal protective equipment; versus, HCQ, hydroxychloroquine; DOC, doxycycline; CQ, chloroquine, ATM, Azithromycin, NZX, Naxoxide

‡ Raw data for asymptomatic family close contacts of confirmed COVID patients show that 2 doses of ivermectin 72 h apart resulted in only 7.4% of 203 subjects reporting symptoms of SARS-CoV-2 infection, in contrast to 101 control untreated subjects, of whom 58.4% reported symptoms; evidence of prophylaxis by ivermectin.

§ Recovery rate of the 28 patients that received ivermectin/SC vs. SC 22.08.20 Kermanshah University of Medical Sciences, Kermanshah, Iran

¶ Recovery rate of the 28 patients that received ivermectin/AM/cholecalciferol was 100%, with mean symptom recovery 3.6 days (negative PCR confirmed day 10). Imaging on day 10 showed improvement in all patients with pneumonia. Authors conclude the combination therapy might mitigate disease progression without significant adverse effects but further studies required (preferably controlled) [46].

‖ Preliminary results for 1195 subjects consistent with prophylaxis effected by ivermectin/carrageenan topical combination [47].

¶¶ Raw data shows a significant reduction in the number of 183 patients with late clinical recovery (requiring >12 days to show clinical improvement) in the ivermectin/DOC group compared to placebo (23 versus 37.2%), as well as a significant reduction (8.7 versus 17.8%) in patients showing clinical deterioration (from mild/moderate to moderate/severe), and a significant reduction (7.7 versus 20%) in persistent Covid-19 positive patients at 14 days compared to 180 control patients; evidence of efficacy for ivermectin/DOC.

‖‖ No statistically significant clinical benefit in 32 treated subjects compared to 30 subjects given placebo, but authors concluded study requires confirmation with larger numbers of subjects [48].
significant differences for patients with severe pulmonary involvement (mortality rates of 38.8 versus 80.7%). Although these early results are consistent with efficacy, it is clear that only the results from large rigorous randomized clinical trials (Table 3) will definitively establish ivermectin’s utility to treat or prevent SARS-CoV-2 infection. It is to be hoped that the results from these trials will emerge in the next few months to document ivermectin’s credentials or otherwise as a viable therapeutic for COVID-19 infection, and potentially infection by many other viruses.

Author contributions

Conceptualization, D.A.J.; writing—original draft preparation, D.A.J., K.M.W.; review and editing, D.A.J., K.M.W. Both authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A. Crump, S. Omura, Ivermectin, wonder drug from Japan: the human perspective, Proc. Jpn. Acad. 87 (2011) 13–28.
[2] https://www.nobelprize.org/prizes/medicine/2015/press-release/.
[3] A. González Canga, A.M. Sahagún Prieto, M.J. Diez Libiana, N. Fernández Martínez, M. Sierra Vega, J.J. García Vieitez, The pharmacokinetics and interactions of ivermectin in humans— a mini-review, AAPS J. 10 (2008) 42–46.
[4] A. Crump, A.S. Omura, Ivermectin: panacea for resource-poor communities? Trends Parasitol. 30 (2014) 445–455.
[5] World Health Organization’s list of essential Medicines, 21st List 2019, https://www.who.int/medicines/areas/essentialmeds/list/2019.06-eng.pdf.
[6] B.S. Kumar, M. Jayaraman, S. Haran, K. Kehn-Hall, L. Brunt, M. Miyara, A nicotinic hypothesis for COVID-19 with preventive and therapeutic implications, Comptes Rendus Biol. 343 (2020) 33–39.
[7] V. Y. L., V. Bui, W. R. Dang, L. Qiu, J. Ren, C. Yan, Z. Yang, X. Wang, Ivermectin inhibits DNA polymerase $\mu$A of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo, Antivir. Res. 159 (2018) 55–62.
[8] S.M. Bennett, L. Zhao, C. Bosard, M.J. Imperiale, Role of a nuclear localization signal on the minor capsid proteins VP2 and VP3 in BEFV nuclear entry, Virology 474 (2015) 110–116.
[9] C. Rong, T.M. Tressier, M.J. Dodge, J.B. Weinberg, J.S. Mymrky, Inhibition of human adenovirus replication by the importin $\alpha$1 nuclear import inhibitor ivermectin, J. Virol. (2020) in press, doi: 10.1128/JVI.00710-20.
[10] J.-P. Changeux, Z. Amoura, F.A. Rey, M. Miyara, A nicotinic hypothesis for COVID-19 with preventive and therapeutic implications, Comptes Rendus Biol. 343 (2020) 33–39.
[11] R.M. Krause, B. Buisson, S. Bertrand, P.J. Corringer, J.L. Galzi, J.-P. Changeux, D. Bertrand Ivermectin, A positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor, Mol. Pharmacol. 53 (1998) 283–294.
[12] A. Loukas, P.J. Hotze, Chemotherapy of helminth infections, in: L.L. Brunton, J.S. Lazo, K.L. Parker (Eds.), Goodman & Gilman’s the Pharmacological Basis of Therapeutics, eleventh ed., McGraw Hill, New York (NY), 2006, pp. 1073–1093.
[13] M. Maru, D. Camprubi, A. Requena-Méndez, B. Buenfate, G. Girol, J. Ramengo, J. Garidon, J. Munioz, A. Krolewiecki, Safety of high-dose ivermectin: a systematic review and meta-analysis, J. Antimicrob. Chemother. 75 (2020) 827–834.
[14] N.A.Y. Twum-Danso, S.E.D. Meredith, Variation in incidence of serious adverse events after onchocerciasis treatment with ivermectin in areas of Cameroon co-endemic for loiasis, Trop. Med. Int. Health 8 (2003) 820–831.
[15] C.A. Guzzo, C.I. Furtek, A.G. Porras, C. Chen, R. Tipping, C.M. Clineschmidt, D.C. Scherb and J.H.S. Kieck, L. L. Lasser, Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects, J. Clin. Pharmacol. 42 (2002) 1122–1133.
[16] A. Fulcher, D.A. Jans, Regulation of nuclearcytoplasmic trafficking of viral proteins: an integrational role in Alethogenesis? Biochem. Biophys. Acta Mol. Cell Res. 1813 (2011) 2176–2190.
[17] L. Caly, K.M. Wagstaff, D.A. Jans, Nuclear trafficking of proteins from RNA vi- ruses: potential target for anti-virals? Antivir. Res. 93 (2012) 202–206.
[18] M. Frenman, B. Yount, M. Hese, S.A. Kopecky-Bromberg, P. Palese, R.S. Baric, Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/golgi membrane, J. Virol. 81 (2007) 9812–9824.
[19] J.J. Wu, F. Ye, N. Zhu, W. Wang, Y. Deng, Z. Zhao, W. Tan, Middle East respiratory syndrome coronavirus ORF4b protein inhibits type I interferon pro- duction through both cytoplasmic and nuclear targets, Sci. Rep. 5 (2015) 17554, https://doi.org/10.1038/srep17554.
[20] S.N.Y. Yang, S.C. Atkinson, J.E. Fraser, C. Wang, B. Maher, N. Roman, J.K. Forwood, K.M. Wagstaff, N.A. Borg, D.A. Jans, Novel flavivirus antiviral that targets the host nuclear transport importin $\alpha$1 heterodimer, Cells 8 (2019) 2B.
[21] M.J. Pryor, S.M. Rawlinson, R.E. Butler, C.L. Barton, T.A. Waterhouse, S.G. Vasudevan, P.G. Bardin, P.J. Wright, D.A. Jans, A.D. Davidson, Nuclear localization of dengue virus nonstructural protein 5 through its importin $\alpha$1 heterodimer, J. Antimicrob. Chemother. 81 (2016) 2176–2190.
[22] S.T. Yen, C.A. Guzzo, J.-P. Changeux, Z. Amoura, F.A. Rey, M. Miyara, A nicotinic hypothesis for COVID-19 with preventive and therapeutic implications, Comptes Rendus Biol. 343 (2020) 33–39.
[23] N.A.Y. Twum-Danso, S.E.D. Meredith, Variation in incidence of serious adverse events after onchocerciasis treatment with ivermectin in areas of Cameroon co-endemic for loiasis, Trop. Med. Int. Health 8 (2003) 820–831.
[24] C.A. Guzzo, C.I. Furtek, A.G. Porras, C. Chen, R. Tipping, C.M. Clineschmidt, D.C. Scherb, J.H.S. Kieck, L. L. Lasser, Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects, J. Clin. Pharmacol. 42 (2002) 1122–1133.
G. Tachedjian, D.A. Jans, Molecular dissection of an inhibitor targeting the HIV integrase dependent preintegration complex nuclear import, Cell Microbiol. 20 (2018) e12953. https://doi.org/10.1111/cmi.12953.

[36] A.J. Lopez-Denman, A. Russo, K.M. Wagstaff, P.A. White, D.A. Jans, J.M. Mackenzie, Nucleocapsid-plasmid shuttling of the West Nile virus RNA-dependent RNA polymerase NS5 is critical to infection, Cell Microbiol. 20 (2018) e12848. https://doi.org/10.1111/cmi.12848.

[37] X. Ci, H. Li, Q. Yu, X. Zhang, L. Yu, N. Chen, Y. Song, X. Deng, Ivermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway, Fund. Clin. Pharmacol. (2009) 449–455. https://doi.org/10.1111/j.1472-8206.2009.00644.x.

[38] X. Zhang, Y. Song, X. Ci, N. An, Y. Ju, H. Li, X. Wang, C. Han, J. Cui, X. Deng, Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice, Inflamm. Res. 57 (2008) 524–529, https://doi.org/10.1007/s00011-008-8007-9.

[39] U. Arshad, H. Pertinez, H. Box, L. Tattham, R.K.R. Rajoli, P. Curley, M. Neary, J. Sharp, N.J. Liptrott, A. Valentijn, C. David, S.P. Rannard, P.M. O’Neill, G. Aljayyoussi, S.H. Pennington, S.A. Ward, A. Hill, D.J. Back, S.H. Khoo, P.C. Bray, C.A. Biagini, A. Owen, Prioritisation of anti-SARS-cov-2 drug repurposing opportunities based on plasma and target site concentrations derived from their established human pharmacokinetics, Clin. Pharmacol. Ther. (2020), https://doi.org/10.1002/cpt.1909.

[40] V.D. Schmith, J.J. Zhou, L.R. Lohmer, The approved dose of ivermectin alone is not the ideal dose for the treatment of COVID-19, Clin. Pharmacol. Ther. (2020), https://doi.org/10.1002/cpt.1889.

[41] E. Yamashita, F.A. Saleh-arong, P. Avirutnan, N. Angkasekwinai, D. Mairiang, US Food and Drug Administration, FDA Cautions against Use of Hydroxychloroquine-Chloroquine%20-%2020May2020_ReRedacted.pdf. May 20, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/OSE%20Review_Hydroxychloroquine-Chloroquine%20-%2020May2020_ReRedacted.pdf.

[42] X. Zhang, Y. Song, X. Ci, N. An, Y. Ju, H. Li, X. Wang, C. Han, J. Cui, X. Deng, Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice, Inflamm. Res. 57 (2008) 524–529, https://doi.org/10.1007/s00011-008-8007-9.

[43] X. Ci, H. Li, Q. Yu, X. Zhang, L. Yu, N. Chen, Y. Song, X. Deng, Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway, Fund. Clin. Pharmacol. (2009) 449–455. https://doi.org/10.1111/j.1472-8206.2009.00644.x.

[44] C.S. Podder, N. Chowdhury, M.I. Sina, W.M.M.U. Haque, Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study, IMC J. Med. Sci. 14 (2020), 002.

[45] M.S.I. Khan, M.S.I. Khan, C.R. Debnath, P.N. Nath, M.A. Mahtab, H. Nabeka, S. Matsuda, S.M.F. Akbar, Ivermectin Treatment May Improve the Prognosis of Patients with COVID-19, Archivos de Bronconeumologia, 2020, https://doi.org/10.1016/j.arbres.2020.08.007.

[46] M. Alam, R. Murshed, E. Bhiuyan, S. Saber, R.F. Alam, R.C. Robin, A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline, Bangladesh Coll. Phys. Surg. 38 (2020) 10–15, https://doi.org/10.3329/jbpcs.v38i0.47512.

[47] G. Espitia-Hernandez, L. Munguia, D. Diaz-Chiguer, R. Lopez-Elizalde, F. Jimenez-Ponce, Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: a proof of concept study, BioMed. Res. 31 (2020) 129–133.

[48] M.S.I. Khan, M.S.I. Khan, C.R. Debnath, P.N. Nath, M.A. Mahtab, H. Nabeka, S. Matsuda, S.M.F. Akbar, Ivermectin Treatment May Improve the Prognosis of Patients with COVID-19, Archivos de Bronconeumologia, 2020, https://doi.org/10.1016/j.arbres.2020.08.007.

[49] J.C. Rajter, M.S. Sherman, N. Fatteh, F. Vogel, J. Sacks, J.J. Rajter, Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 (ICON study), Chest (2020). https://doi.org/10.1016/j.chest.2020.10.009.

[50] M. Alam, R. Murshed, E. Bhuiyan, S. Saber, R.F. Alam, R.C. Robin, A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline, Bangladesh Coll. Phys. Surg. 38 (2020) 10–15, https://doi.org/10.3329/jbpcs.v38i0.47512.

[51] J.C. Rajter, M.S. Sherman, N. Fatteh, F. Vogel, J. Sacks, J.J. Rajter, Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 (ICON study), Chest (2020). https://doi.org/10.1016/j.chest.2020.10.009.

[52] M.A. Rahman, S.A. Iqbal, M.A. Islam, M.K. Niaz, T. Hussain, T.H. Siddiquae, Comparison of viral clearance between ivermectin with doxycycline and hydroxychloroquine with azithromycin in COVID-19 patients, Bangladesh Coll. Phys. Surg. 38 (2020) 5–9, https://doi.org/10.3329/jbpcs.v38i0.47514.