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

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ABSTRACT

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.

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 artemisin, 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) infestations 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 WHO (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, flaviviruses 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 [11,18,20]; 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].

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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/β1 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-kB) 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/β1 heterodimer performs the adaptor role of signal-specific recognition of the nuclear import cargo, while IMPβ1 performs the main transport roles of binding to/translocation 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, underlining 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 counterscreening 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 IMPβ1-) 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-kB 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 uM 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:

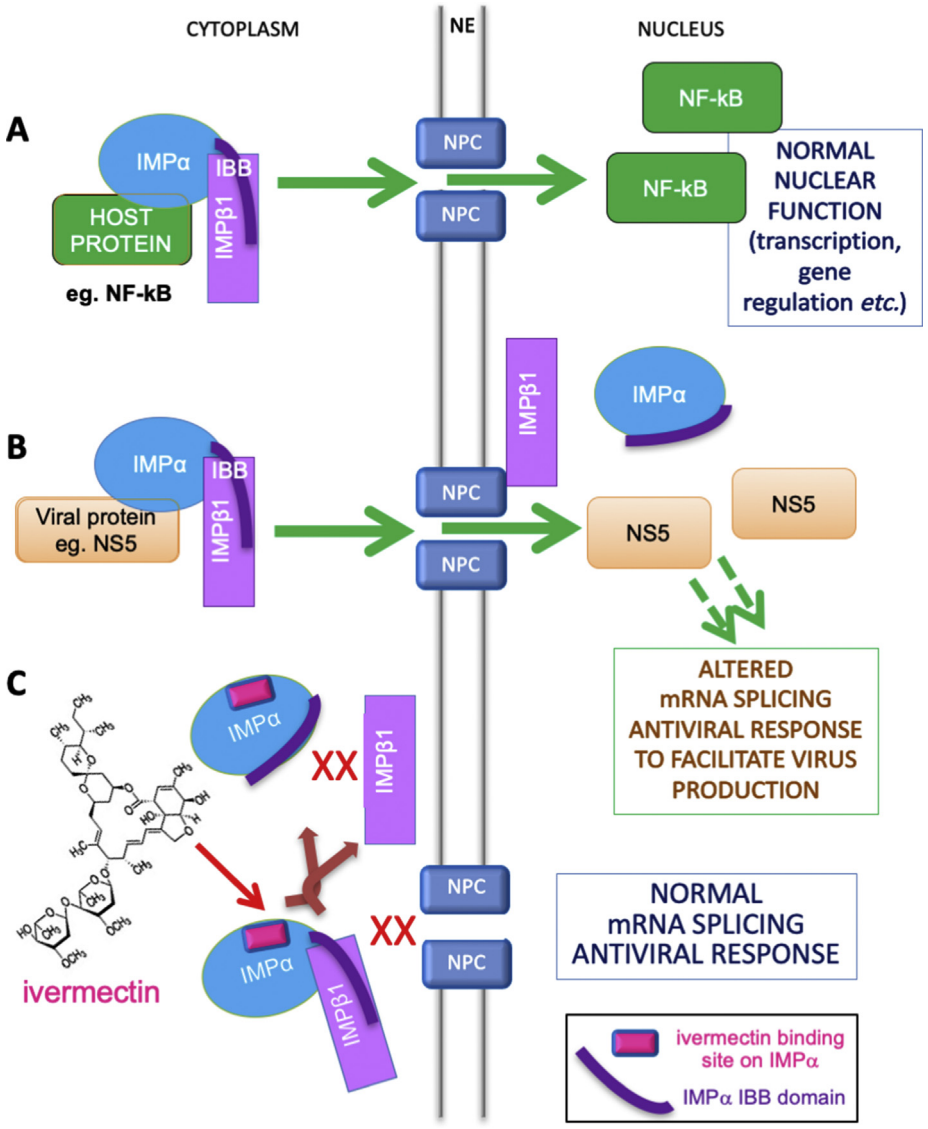

Fig. 1. Model of IMPα's role in nuclear transport of host and viral proteins, and mechanism of inhibition by ivermectin. **A.** Host proteins such as members of the NF-κB transcription factor family localize in the nucleus through IMPα/β1, where the "IBB" (IMPβ-binding) region of IMPα (purple curved line) is bound by IMPβ1 to enable cargo recognition by IMPα within the heterodimer. Subsequently, IMPβ1 mediates transport of the trimeric complex into the nucleus through the nuclear envelope (NE)-embedded nuclear pore (NPC, nuclear pore complex). Release within the nucleus enables the transcription factor to carry out normal function in transcriptional regulation, including in the antiviral response. IMPα cannot mediate nuclear import, unless heterodimerised with IMPβ1. **B.** In viral infection, specific viral proteins (eg. NS5 in the case of DENV, ZIKV) able to interact with IMPα utilize the IMPα/β1 heterodimer to access the nucleus and antagonize the antiviral response [14,27,28]. This is critical for optimal virus production as shown by mutagenic and inhibitor studies. The SARS-CoV-2 proteins that may access the nucleus via IMPα/β1 in infected cells has not been examined, but in ORF6 (Open Reading Frame 6) protein from SARS-CoV1 has been shown to bind IMPα [29], and ORF4b from MERS-CoV (Middle Eastern Respiratory Syndrome Coronavirus) are both known to access the nucleus in NLS-dependent fashion [30]. **C.** The small molecule ivermectin (structure shown) binds to IMPα (binding site shown as red lozenge) both within the IMPα/β heterodimer to dissociate it, and to free IMPα to prevent it binding to IMPβ1, thereby preventing NS5 nuclear import [11], contributing to reduced virus production. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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].

Table 1
In vitro effects of ivermectin on IMPα.[a]

Effect on IMPα	Cargo Protein	
	Virus	Host
In vitro		
Inhibits direct binding of IMPα (ALPHASCREEN/AUC)	HIV IN (IC50 5 μM) {34} DENV1 NS5 (IC50 2 μM)) [8] DENV2 NS5 (IC50 1 μM) [7,8,11] Hendra V (IC50 15 μM) [13] SV40 T-ag [34]	IMPβ1 (IC50 7 μM) [11]
Cellular Context		
1) Inhibits binding of IMPα in transfected cell context (BiFC/CoIP)	SV40 T-ag [11,20] DENV2 NS5 ([7,11] Adenovirus EIA [20]	
2) Inhibits nuclear accumulation in a transfected cell context of IMPα/β1- (but not β1-) recognised proteins (CLSM) [7]	HIV-IN [7] SV40 T-ag [7,16,34] DENV2 NS5 [7] VEEV Capsid [16] adenovirus E1A [20] PSV UL42 [18] hCMV ppUL44, pUL5 [7]	TRF1 [7,34] p53 [7] NF-kB (LPS-induced) [37,38]
3) Reduces nuclear localisation in infected cells	VEEV Capsid [9] adenovirus E1A [20]	

[a]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.
[b]Inhibits helicase activity (FRET based assay) of DENV2, YFV and WNV NS3 (IC50 0.2–0.5 μM) [12].

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 2
Documented antiviral action of ivermectin.[a]

Virus	Inhibitory Concentration/Fold reduction (Assay)
Coronavirus	
SARS-CoV-2	EC50 = 2.2/2.8 μM/5000-fold reduction (qPCR/released/cell-associated virus) [17]
Lentivirus	
HIV-1 (VSV-G-pseudotyped NL4-3.Luc.R-E-HIV)	50 μM > 2-fold reduction (luciferase) [7]
Orthomyxovirus	
Influenza VLPs (avian influenza A/MxA escape mutants)	10 μM total inhibition (luciferase) [10]
Flavivirus:	
YFV (17D)	EC50 = 5/0.5 nM (CPE/qPCR) [12]/3 μM > 50,000-fold reduction (pfu) [15]
DENV1 (EDEN-1)	EC50 = 2.3/3 μM (CFI, 2 hosts) [8]/EC50 = 0.7 μM (qPCR) [12]
DENV2 (NGC)	EC50 = 0.4/0.6 μM (pfu/qPCR) [11]/50 μM total inhibition (pfu) [7]
DENV2 (EDEN-2)	EC50 = 2.1/1.7 μM (CFI, 2 hosts) [8]
DENV3 (EDEN-3)	EC50 = 1.7 μM (CFI) [8]
DENV4 (EDEN-4)	EC50 = 1.9 μM (CFI) [8]
WNV (NY99)	EC50 = 4 μM (qPCR) [12]
WNV (MRM61C)	EC50 = 1/0.5 μM (pfu/qPCR) [11]
ZIKV (Asian/Cook Islands/2014)	EC50 = 1.3/1.6 μM (pfu/qPCR) [11]
Alphavirus:	
Chikungunya virus (CHIKV-Rluc)	EC50 = 1.9/0.6 μM (luciferase, 2 hosts)/3 μM > 5000-fold reduction (pfu) [15]
Sindbis (HR)	3 μM > 1000-fold (pfu) [15]
Semlicki Forest Virus	3 μM > 200-fold (pfu) [15]
VEEV (TC83)	1 μM c. 20-fold (pfu) [9]
Henipavirus:	
Hendra (Hendra virus/Australia/Horse/1994)	est. EC50 = 2 μM (TCID/luciferase) [13]
DNA viruses	
Adenovirus (HAdV-C5)	EC50 = c. 2.5 μM; 10 μM 20-fold reduction (qPCR) [20]
Adenovirus (HAdV-B3)	10 μM c. 8-fold reduction (qPCR) [20]
BK polyomavirus (BKPyV)	Est. EC50 1.5 μM (pfu/CPE/qPCR) [19]
Pseudorabies	Est. EC50 c. 0.8 μM 1000-fold [18]

[a]*In vitro*
[b]Inhibits helicase activity (FRET based assay) of DENV2, YFV and WNV NS3 (IC50 0.2–0.5 μM) [12].
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, URL	Status[a]	N[b]	Interventions[c]	Start	Locations
1	Ivermectin Effect on SARS-CoV-2 Replication in Patients With COVID-19; https://ClinicalTrials.gov/show/NCT04381884	R	45	**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; https://ClinicalTrials.gov/show/NCT04360356	NY	100	**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; https://ClinicalTrials.gov/show/NCT04429711	R	100	**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; https://ClinicalTrials.gov/show/NCT04391127	A	200	**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; https://ClinicalTrials.gov/show/NCT04405843	R	400	**Ivermectin** 0.3 mg/kg daily for 5 days vs. Placebo	20.6.20	Colombia
6	Ivermectin In Treatment of COVID 19 Patients; https://ClinicalTrials.gov/show/NCT04425707	R	100	**Ivermectin** (dose unlisted) vs. SC vs. **Ivermectin** (dose unlisted) plus SC	9.6.20	Isolation and referral hospitals for COVID 19 patients, Cairo, Egypt
7	Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection; https://ClinicalTrials.gov/show/NCT04407130	E	72	**Ivermectin** 0.2 mg/kg once plus 200 mg DOC day 1 followed by 100 mg DOC BID for 4 days vs. **Ivermectin** 0.2 mg/kg QD for 5 days vs. Placebo	16.6.20	ICDDR, Dhaka, Bangladesh
8	Efficacy of Ivermectin as Add on Therapy in COVID19 Patients; https://ClinicalTrials.gov/show/NCT04343092	C	100	**Ivermectin** 0.2 mg/kg once weekly plus HCQ 400 mg QD plus ATM 500 mg QD vs. HCQ 400 mg QD plus ATM 500 mg QD	18.4.20	General Directorate of Medical City, Bagdad, Baghdad, Iraq
9	COVidIVERmectin: Ivermectin for Treatment of Covid-19 (COVER); https://ClinicalTrials.gov/show/NCT04438850	R	102	**Ivermectin** 0.6 mg/kg QD for 5 days vs. **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); https://ClinicalTrials.gov/show/NCT04407507	NY	66	**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-ISGlobal Trial (SAINT); https://ClinicalTrials.gov/show/NCT04390022	A	24	**Ivermectin** 0.4 mg/kg once vs. Placebo	14.5.20	Clinica Universidad de Navarra, Pamplona, Navarra, Spain
12	A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh; https://ClinicalTrials.gov/show/NCT04434144	C	116	**Ivermectin** 0.2 mg/kg once plus DOC 100 mg BID for 10 days vs. HCQ 400 mg day 1 then 200 mg BID for 9 days plus ATM 500 mg/day 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); https://ClinicalTrials.gov/show/NCT04435587	NY	80	**Ivermectin** 0,6 mg/kg daily for 3 days vs. HCQ 400 mg BID Day 1 then 200 mg BID for 4 days plus Darunavir/ritonavir (400 mg/100 mg) BID for 5 days	20.7.20	Siriraj Hospital, Bangkok Noi, Bangkok, Thailand
14	IVERMECTIN Aspirin Dexametasone and Enoxaparin as Treatment of Covid 19; https://ClinicalTrials.gov/show/NCT04425863	A	100	**Ivermectin** 5 mg/ml oral to be repeated 1 week later (dose unlisted)	1.5.20	Hospital Eurnekian, Buenos Aires, Argentina
15	A Preventive Treatment for Migrant Workers at High-risk of Covid-19; https://ClinicalTrials.gov/show/NCT04446104	C	5000	**Ivermectin** 12 mg once vs. HCQ 400 mg day 1 then 200 mg/day for 42 days vs. Zinc 80 mg/day plus vitamin C 500 mg/day for 42 days vs. Povidone-iodine throat spray TID 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; https://ClinicalTrials.gov/show/NCT04392427	NY	100	**Ivermectin** (dose unlisted) plus NZX (dose unlisted) 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 LosarTAN for Cancer Patients With COVID-19 Infection (TITAN); https://ClinicalTrials.gov/show/NCT04447235	R	176	**Ivermectin** 12 mg once plus losartan 50 mg/day for 15 days vs. Placebo	20.7.20	Instituto do Cancer do Estado de São Paulo, Brazil
18	Ivermectin in Treatment of COVID-19; https://ClinicalTrials.gov/show/NCT04445311	R	100	**Ivermectin** daily (dose unlisted) for 3 days plus SC vs. SC	31.5.20	Waheed Shouman, Zagazig, Sharkia, Egypt
19	Efficacy of Ivermectin in COVID-19; https://ClinicalTrials.gov/show/NCT04392713	R	100	**Ivermectin** 12 mg once plus SC vs. SC	15.4.20	Combined Military Hospital Lahore, Lahore, Punjab, Pakistan
20	Ivermectin and Doxycycine in COVID-19 Treatment; https://ClinicalTrials.gov/show/NCT04403555	R	40	**Ivermectin** (dose unlisted) plus DOC (dose unlisted) vs. CQ (dose unlisted)	1.6.20	Sherief Abd-Elsalam, Tanta, Egypt
21	The Efficacy of Ivermectin and Nitazoxanide in COVID-19 Treatment; https://ClinicalTrials.gov/show/NCT04351347	R	300	**Ivermectin** (dose unlisted) vs. **Ivermectin** (dose unlisted) plus NZX (dose unlisted) vs. **Ivermectin** (dose unlisted) plus CQ (dose unlisted)	16.6.20	Tanta University, Tanta, Egypt
22	Prophylactic Ivermectin in COVID-19 Contacts; https://ClinicalTrials.gov/show/NCT04422561	C[d]	304	**Ivermectin** (dose unlisted) 2 doses 72 h apart vs. Control (untreated)	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; https://ClinicalTrials.gov/show/NCT04373824	R	50	**Ivermectin** 0.2–0.4 mg/kg daily for 2 days plus SC vs. SC	25.4.20	Max Super Speciality Hospital, Saket (A unit of Devki Devi Foundation), New Delhi, Delhi, India

(*continued on next page*)

Table 3 (*continued*)

	Title, URL	Status[a]	N[b]	Interventions[c]	Start	Locations
24	A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19 (IFORS); https://ClinicalTrials.gov/show/NCT04431466	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 m/kg once vs. **Ivermectin** 0.2 mg/kg day 1 and repeated after 72 h vs. SC	1.7.20	Hospital Univeristário 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	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/NCT04399746	C[e]	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 Prevent Contagion of Covid 19 (IVERCAR); https://ClinicalTrials.gov/show/NCT04425850	A[f]	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/NCT04446429	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	Corpometria Institute, Brasilia, Brazil
30	A Real-life Experience on Treatment of Patients With COVID 19; https://ClinicalTrials.gov/show/NCT04345419	R	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 β1A	25.7.20	Qassim University, Saudi Arabia
32	Trial of Combination Therapy to Treat COVID-19 Infection; https://ClinicalTrials.gov/show/NCT04482686	NY	300	**Ivermectin** (dose unlisted) day 1 and 4 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	ProgenaBiome, 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 efficacy, 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/BG	O	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 (EHYCIVER-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 IIB 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	Interventional 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/2020/04/025224	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/2020/04/025333	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/2020/04/026001	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

Table 3 (*continued*)

	Title, URL	Status[a]	N[b]	Interventions[c]	Start	Locations
42	Ivermectin Nasal Spray for COVID19 Patients; https://ClinicalTrials.gov/show/NCT04510233	NY	60	**Ivermectin** nasal spray (1 ml) in each nostril BID vs. **Ivermectin** oral (6 mg) TID vs. SC	10.8.20	Tanta University, Tanta, Egypt
43	Outpatient use of ivermectin in COVID-19; https://ClinicalTrials.gov/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 hospitilizations in COVID-19; https://ClinicalTrials.gov/show/NCT04529525	R	500	**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/show/NCT04523831	C[g]	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.chictr.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** 0.15–0.2 mg/kg single dose day 1 plus HCQ 200 mg day 1 plus Lopinavir/Ritonavir 400/100 mg days 2–6 vs. HCQ 200 mg day 1 plus Lopinavir/Ritonavir 400/100 mg days 2–6	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; http://isrctn.com/ISRCTN40302986	R	45	**Ivermectin** 6 mg every 3.5 days for 2 weeks vs. **Ivermectin** 12 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. SC	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/study/NCT04472585	R	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 plus SC	14.7.20	Shaikh Zayed Hospital, Lahore, Pakistan
53	Pragmatic study "CORIVER": Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19); https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001971-33/ES	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/NCT04527211	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	**Ivernectin** nasal spray BID (dose unlisted) vs. **Ivermectin** oral 6 mg TID vs. SC	10.8.20	Tanta University, Tanta, Egypt
56	Safety and Efficacy of Ivermectin and Doxycycline in 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, and 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. SC	26.08.20	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 (both according to protocol of Ministry of Health) vs. HCQ sulfate and ATM alone	23.08.20	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	20.08.20	Government Institute of Medical Sciences Greater Noida, Uttar Pradesh, India

(*continued on next page*)

Table 3 (*continued*)

	Title, URL	Status[a]	N[b]	Interventions[c]	Start	Locations
61	Ivermectin as a possible treatment for COVID-19; http://ctri.nic.in/Clinicaltrials CTRI/2020/08/027225	NY	90	**Ivermectin** 12 mg QD on days 1–2 vs. Placebo	18.08.20	AAIMS, Patna, India
62	Evaluating the effect of Ivermectin on covid 19 patients; http://en.irct.ir/trial/49935	R	60	**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
63	Evaluate the Efficacy of Siddha Treatment in Patients with Novel Coronavirus Infectious Disease; http://ctri.nic.in/Clinicaltrials CTRI/2020/08/026999	R	100	**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
64	Ivermectin effect in the treatment of patients with covid-19; http://en.irct.ir/trial/49180	R	40	**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
65	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	68	**Ivermectin** 0.3 mg/kg QD for 3 days vs. Placebo	17.07.20	Universidad Peruana Cayetano Heredia, Lima, Peru
66	Evaluation of ivermectin effects on Covid-19; http://en.irct.ir/trial/49280	R	50	**Ivermectin** 0.15 mg/kg/day plus SC vs. SC	22.08.20	Kermanshah University of Medial Sciences, Kermanshah, Iran
67	A placebo-controlled, randomized, double-blind study in COvid-19 patients with iveRmectin; An inVEstigator iniTiaTEd trial (CORVETTE-01); jRCT2031200120	R	240	**Ivermectin** 0.2 mg/kg once vs. Placebo	16.09.20	Kitasato University Hospital, Kanagawa, Japan
68	A single-centre, open-label, randomized controlled study of ivermectin treated mild to moderate COVID-19 cases; Debidwar Upazila Health Complex	C[h]	62	**Ivermectin** 0.2 mg/kg once plus SC vs. SC	01.05.20	Debidwar Upazila Health Complex, Comilla, Bangladesh

[a] R, Recruiting, NY, Not yet recruiting, A, Active not recruiting, C, Completed, E, Enrolling by invitation, O, ongoing.
[b] Number of patients.
[c] SC, standard care, QD, once per day, BID, twice daily, QID, 4 times daily, TID, 3 times daily, PPE, personal protective equipment, vs. versus, HCQ, hydroxychloroquine; DOC, doxycycline; CQ, chloroquine, ATM, Azithromycin, NZX, Nanozoxide
[d] 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.
[e] Recovery rate of the 28 patients that received ivermectin/AZM/cholecalciferol was 100%, with mean symptomatic 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].
[f] Preliminary results for 1195 subjects consistent with prophylaxis effected by ivermectin/carrageenan topical combination [47].
[g] 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 or 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.
[h] 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].

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 from standard parasitic treatment dosing and robust large animal experiments where lung levels of ivermectin can be measured, indicates that concentrations of ivermectin 10 times higher than the c. 2.5 μM EC_{50} 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 (for 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 stark contrast to control untreated subjects, of whom 58.4% reported symptoms, underlining ivermectin's potential as a prophylactic. Results from retrospective/observational trials [48–52] are also consistent with clinical benefit. Mymensingh Medical College Hospital (Bangladesh) reported that none of 115 subjects receiving a single 12 mg dose of ivermectin developed pneumonia/cardiovascular complications, compared to 9.8% (pneumonia) and 1.5% (ischemic stroke) in 133 control subjects [49]. Further, significantly fewer ivermectin group patients developed respiratory distress (2.6 versus 15.8%), or required oxygen (9.6 versus 45.9%), antibiotics (15.7 versus 60.2%) or intensive care management (0.09 versus 8.3%). Ivermectin-treated patients became SARS-CoV-2 negative significantly faster (median 4 compared to 15 days), had significantly shorter hospital stays (median 9 versus 15 days), and significantly lower mortality (0.9 vs 6.8%). Although combinations of therapies were used, the results for a 196 patient propensity-matched cohort study (ICON - Ivermectin in COvid Nineteen – study) at Broward Health Medical Centre (Florida, USA) [50] indicate significantly reduced mortality (13.3%) in subjects receiving 0.2 mg/kg ivermectin (optional second dose 8 days later), compared to 24.5% mortality in those not receiving ivermectin, with more

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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