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EFFICACY OF IVERMECTIN IN COVID-19: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

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1. INTRODUCTION

In the first months of the COVID-19 pandemic there was almost nothing to offer patients except supportive care, and the temptation to repurpose existing drugs was enormous. Ivermectin was an attractive candidate. It is cheap, available worldwide, and has been given to hundreds of millions of people for onchocerciasis and lymphatic filariasis with an excellent record of tolerability [1, 2]. When a laboratory in Melbourne reported that it sharply reduced SARS-CoV-2 RNA in infected cell cultures, the finding spread quickly through scientific and lay media alike [3]. Within a few months

Abstract

Ivermectin, an antiparasitic with a long safety record, was proposed early in the COVID-19 pandemic as a repurposed antiviral after it inhibited SARS-CoV-2 replication in cell culture. This review, which reports no new data, examines the published randomised controlled trials of ivermectin in COVID-19 together with the pharmacology, meta-analyses and safety literature. Small early trials gave mixed and sometimes favourable signals, whereas larger, better-designed placebo-controlled trials in outpatients found no clinically meaningful benefit on recovery, hospitalisation or death. Favourable pooled estimates depended heavily on low-quality or later discredited studies. Concentrations needed for antiviral effect are hard to reach at approved doses. Ivermectin cannot be recommended for COVID-19 outside trials.

the drug was being used, sometimes in veterinary formulations, in many countries, well before any controlled clinical data existed.

Clinical evidence then arrived in waves. The first wave consisted of small, often single-centre trials with varied designs and endpoints, some of them published as preprints, and several giving encouraging results. The second wave consisted of larger placebo-controlled trials sponsored by academic networks, many with pre-registered protocols and clinically meaningful outcomes [4, 5, 6]. Systematic reviews and meta-analyses were written in between, and they reached different conclusions depending on which trials they trusted [7, 8, 9]. Few drug stories in modern medicine show so clearly how the quality of the evidence, rather than its quantity, decides what can be concluded.

This article reviews the published randomised controlled trials of ivermectin in COVID-19 and the secondary literature around them. It starts with the pharmacological rationale and the question of achievable drug concentrations, then discusses the early and the large trials, the pooled analyses and the integrity problems that complicated them, and the safety literature. The review reports no new data and does not describe its own database search or pooled estimate. Numbers are cited only where they are widely reported in the original trials, and the main aim is to explain why the answer, which is now fairly clear, was reached so slowly.

2. PHARMACOLOGICAL RATIONALE

Ivermectin is a semisynthetic macrocyclic lactone derived from avermectins produced by *Streptomyces avermitilis*, and it acts in invertebrates by binding glutamate-gated chloride channels, causing paralysis of the parasite [1, 10]. It is used at around 150 to 200 µg/kg as a single oral dose for most indications. Its absorption is improved by a fatty meal, it is extensively metabolised by CYP3A4, and its elimination half-life is of the order of a day [10]. Nothing in this profile suggests an antiviral drug, which is why the cell-culture result was surprising, and why it needed careful interpretation before being turned into a treatment recommendation.

Several mechanisms have been proposed for antiviral effects. Ivermectin inhibits importin α/β -mediated nuclear import in laboratory

studies, and this has been linked to activity against some RNA viruses such as dengue and HIV-1 in cell systems [11]. The SARS-CoV-2 report described a very large drop in viral RNA after 48 hours in infected cells, with a half-maximal inhibitory concentration in the low micromolar range [3]. The experiment was a single in vitro system, and it used concentrations that bear little resemblance to what is reached in human plasma after standard dosing. Other proposed actions include anti-inflammatory effects and binding to viral proteins in docking studies, but human evidence for any of these is lacking [12, 13].

The pharmacokinetic argument against clinical activity at approved doses was made early. Plasma concentrations after a standard dose are well below the micromolar range reported to inhibit the virus in culture, and models of lung tissue exposure suggested that antiviral levels would not be reached without dosing far above the approved amount [12, 13, 14]. Ivermectin is highly protein-bound, which further reduces the free fraction available. Higher doses have been given safely to healthy volunteers, in a study that went up to several times the usual dose [15], and this made dose-escalation trials reasonable. But the gap between culture concentrations and tissue exposure was a consistent reason for scepticism about the standard regimens used in most trials [13, 14].

The regimens used in trials varied widely, which complicates any attempt to compare them. Some studies gave a single oral dose in the range of 12 to 24 mg, others 200 to 400 µg/kg daily for three to five days, and a few tested 600 µg/kg for five days, roughly three times the usual antiparasitic exposure per dose [6, 16, 17, 18]. Investigators generally chose the schedule from tolerability data in healthy volunteers [15] and from the modelling work, but there was no dose-ranging in patients with the virus before the larger trials began. As a result, a trial that finds no effect at 400 µg/kg cannot automatically be extended to higher exposures, a caveat that applies to many repurposed drugs. Pharmacokinetic sampling nested within the trials would have made the dose question far easier to settle.

3. RANDOMISED TRIAL EVIDENCE

Early randomised trials were small. A pilot placebo-controlled trial of a single high dose in non-severe outpatients found no clear virological effect, although some symptoms such as cough and loss of smell appeared to improve over the following weeks [16]. A trial in Bangladesh reported faster virological clearance with a five-day course of ivermectin alone than with placebo [19], and a dose-finding study with a high dose given for five days found no overall difference in viral load, with an apparent link between plasma concentration and effect in secondary analysis [18]. These studies were hypothesis-generating at best. Numbers were small, endpoints were surrogate or subjective, and in several of them blinding or randomisation details were incompletely described.

Larger trials then examined clinical outcomes. A randomised trial of 476 adults with mild COVID-19 in Colombia tested a five-day course and found no significant difference in time to resolution of symptoms [4]. The I-TECH trial in Malaysia enrolled adults with comorbidities, gave ivermectin as an add-on to standard care and did not reduce progression to severe disease [20]. Trials from India and Argentina in mild and moderate disease also failed to show benefit on viral clearance or hospitalisation [17, 21]. The results are summarised in table 1. Individually, several of these trials were modest in size, and their confidence intervals were wide enough that a small benefit could not be excluded.

Table 1: Pharmacology, randomised trials and evidence synthesis on ivermectin in COVID-19

Study or topic	Published finding	Ref.
In vitro study SARS-CoV-2 in cells	Large fall in viral RNA at micromolar concentrations	[3]
Pharmacokinetic analyses	Standard-dose plasma and lung levels likely below those active in culture	[12, 13, 14]
Pilot placebo-controlled trial outpatients	No clear virological effect; small symptom differences	[16]
Five-day course Bangladesh	Faster viral clearance in a small trial	[19]

Study or topic	Published finding	Ref.
Colombian trial mild COVID-19	No significant difference in time to symptom resolution	[4]
I-TECH Malaysia	No reduction in progression to severe disease	[20]
TOGETHER Brazil	No reduction in hospitalisation or emergency observation	[5]
ACTIV-6 and COVID-OUT USA	No improvement in recovery or in hypoxaemia, hospitalisation or death	[6, 22]
Meta-analyses	Cochrane and others found no reliable benefit; favourable analyses relied on weak trials	[7, 8, 9]
Data integrity withdrawn study	Duplicated or implausible data in a heavily weighted trial	[23, 24]
Safety self-medication and Loa loa	Poisoning cases; encephalopathy in heavy Loa loa infection	[25, 26]

Choice of endpoint matters as much as choice of dose. Viral load and time to a negative PCR test are attractive in small trials because they respond quickly and need fewer participants, but they correlate imperfectly with how patients feel or whether they are admitted to hospital. Symptom resolution is subjective, particularly when nobody is blinded, and composite outcomes can hide the fact that one component, such as an emergency visit, drives the result. Early trials relied on virological or symptom endpoints [16, 18, 19], whereas the later ones used time to sustained recovery or hospitalisation [4, 5, 6], so the move from small to large trials also involved a move to outcomes that patients and health systems care about.

The platform trials gave the most definitive answers. The TOGETHER trial in Brazil randomised more than 1,300 high-risk outpatients and found that ivermectin did not reduce hospitalisation or prolonged emergency department observation [5]. ACTIV-6, a US trial that eventually enrolled well over a thousand participants for the ivermectin comparison, tested a three-day course at 400 µg/kg and found no improvement in time to sustained recovery [6]. The COVID-OUT trial tested ivermectin alongside metformin and fluvoxamine in a factorial design and found that ivermectin did

not prevent hypoxaemia, emergency visits, hospitalisation or death [22]. These studies used placebo controls, pre-specified outcomes and adequate power for clinically relevant differences, and their protocols and statistical analysis plans were publicly available before results were known.

The context in which trials were run also changed. Early studies enrolled unvaccinated patients infected with ancestral strains, whereas the later ones were conducted amid successive variants, rising vaccination and wider use of other treatments, including corticosteroids for hospitalised patients and, later, antivirals for outpatients [5, 6, 22, 27]. Event rates fell over time, which lowered the power of studies planned with higher assumptions. Platform designs, with adaptive stopping rules and shared placebo groups, were partly developed to cope with this shifting background. None of these changes explains the consistently null findings, but they do mean that the older positive trials cannot be pooled naively with later ones [6, 22].

Several features make the later trials more reliable than the early ones. They were prospectively registered, used central randomisation and blinded placebo, and measured outcomes that matter to patients, such as hospitalisation, recovery and death, and not only viral load or composite scores. Dose and duration were higher than approved antiparasitic regimens in some of them, which answers part of the pharmacokinetic criticism, although not all of it [5, 6, 14]. In this respect the ivermectin story resembles that of dexamethasone, where a large pragmatic trial settled a question quickly, but with a different result: the RECOVERY trial found a mortality benefit in hospitalised patients needing oxygen, showing that a well-run randomised trial can identify real benefit when it exists [27].

The distribution of the evidence by type is shown in fig. 1. Larger trials make up four of the eleven rows of table 1, with two rows each for pharmacology, early trials and evidence synthesis, and one for safety. That balance is informative because it shows how much of the literature rests on a handful of well-designed studies and on commentary

about their interpretation. Where outcomes are given in the original reports, none of the larger trials showed a clinically meaningful reduction in hospitalisation or death, and the point estimates clustered around no effect [4, 5, 6, 20, 22]. It is hard to design an argument for benefit from this pattern without invoking subgroups or special doses.

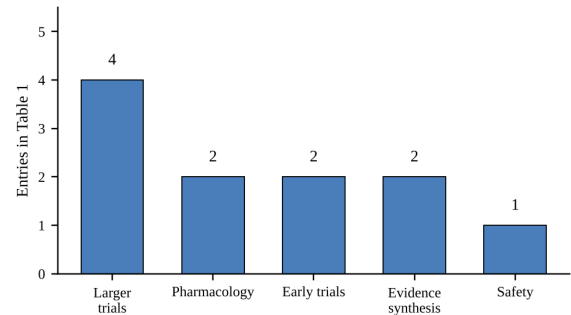


Fig. 1: Number of entries in table 1 by type of evidence

4. EVIDENCE SYNTHESIS AND DATA INTEGRITY

Meta-analyses of ivermectin trials produced strikingly different headlines. A Cochrane review found no reliable evidence supporting use of ivermectin for treatment or prevention of COVID-19 and rated the certainty of the evidence as low or very low [7]. A meta-analysis of randomised trials in Clinical Infectious Diseases similarly found no significant effect on mortality, with wide intervals, and noted the poor quality of the contributing studies [9]. By contrast, an analysis published in 2021 and an accompanying narrative review reported large reductions in mortality and took a favourable view, relying on the early small trials [8, 28]. Differences arose from which trials were included, how risk of bias was judged and how heterogeneity was handled.

Part of the explanation is data integrity. One large Egyptian study that contributed heavily to the favourable pooled estimates was withdrawn from the preprint server after allegations of duplicated data and implausible patient records, and other trials have been questioned for similar reasons [23, 29]. When meta-analyses are repeated after removing studies with serious integrity or bias concerns, the apparent benefit largely disappears [24]. The episode led methodologists to argue that meta-analyses based on summary data alone

are inherently vulnerable, and that reviewers should check the provenance and plausibility of trials before pooling them, using individual participant data where possible [23, 24].

Sensitivity analyses showed how fragile the favourable conclusions were. Removing the withdrawn study from a pooled estimate, or restricting analyses to trials at low risk of bias, moved the mortality estimate toward no effect, and the Cochrane authors rated certainty as low or very low largely because of imprecision and risk of bias [7, 24]. Trial sequential analysis, used in one favourable review, can be helpful for judging whether enough information has accumulated, but it cannot rescue a pool that is dominated by unreliable data [8]. A fair summary is that the quality of the individual trials, not the choice of statistical model, determined what each review found [7, 9].

Methodological frameworks exist for exactly this purpose. Meta-regression can probe heterogeneity but is weak when few trials are available [30], and trial quality is better judged component by component, looking at sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, than by a summed score [31]. Reporting should follow the PRISMA statement [32]. Applied to the ivermectin literature, such assessments tend to flag many of the small positive trials as having some concerns or high risk of bias, mostly through unclear allocation concealment, open-label design and subjective outcomes, whereas the large placebo-controlled trials are generally rated at low risk [7, 31].

5. SAFETY CONSIDERATIONS

At approved doses ivermectin is among the safer antiparasitic drugs, with mild and transient adverse effects such as dizziness, nausea and itching, the last mostly a consequence of parasite death. Higher doses than those approved have been studied. A meta-analysis of studies of high-dose ivermectin found it generally well tolerated, though most subjects were healthy volunteers or people with parasitic infection, not patients with acute viral illness [15, 33]. In the COVID-19 trials, adverse event rates in the ivermectin and placebo groups were similar,

and serious events were uncommon [4, 5, 6]. This reassuring finding applies to supervised dosing of pharmaceutical-grade tablets, which is not how the drug was always taken. For prescribers the safety question arises mainly outside trials.

Pharmacokinetic interactions are a further consideration for off-label use. Ivermectin is metabolised mainly by CYP3A4 and is a substrate of P-glycoprotein, so strong inhibitors of either could raise plasma and possibly central nervous system concentrations, and the safety margin seen in trial volunteers cannot be assumed in patients taking several medicines [10, 15]. Ivermectin has also been combined with doxycycline, hydroxychloroquine, zinc and other agents in uncontrolled regimens, which adds interaction risk and makes attribution of any benefit or harm impossible. Dose conversion errors are a practical hazard when veterinary products are used, because concentrations are far higher than in human tablets [25].

Outside trials, harms were documented. Poison centres in several countries reported increased exposure to ivermectin, with cases of gastrointestinal upset, hypotension, neurological symptoms such as confusion, ataxia and seizures, and hospital admissions following self-medication with veterinary products or excessive doses [25]. Concomitant CYP3A4 inhibitors and other drugs may raise exposure. Another well-established risk is the encephalopathy seen in people with very heavy *Loa loa* microfilaraemia when given ivermectin during mass treatment programmes [26]. In regions where *Loa loa* is endemic, widespread off-label use of ivermectin could therefore carry specific dangers. The overall balance of risk and benefit for COVID-19 is unfavourable [25, 26, 34].

6. LIMITATIONS AND IMPLICATIONS

The literature has limits that affect even the large trials. Most enrolled patients with mild disease, often vaccinated or unvaccinated to differing degrees, and infected with variants that changed through the pandemic, so a small effect in a specific subgroup or at very high dose cannot be completely excluded [5, 6]. Control groups sometimes received other

treatments, adherence was not always verified, and drug levels were rarely measured, which weakens conclusions about exposure-response [14, 18]. Even so, the consistency of null results across trials from different countries and settings argues strongly against a clinically useful effect with the regimens tested.

The implications for practice are straightforward. Ivermectin should not be used to treat or prevent COVID-19 outside well-designed clinical trials, and clinicians should explain this to patients who ask, acknowledging the early excitement while presenting the later data [34]. For research, the experience supports pre-registration, pharmacokinetic study before efficacy trials, platform designs able to give quick answers, data sharing, and scrutiny of data integrity for trials that will feed into guidelines [23, 24, 32]. Repurposing remains a sensible strategy, and several repurposed drugs, such as dexamethasone, have succeeded, but the route to a recommendation should pass through adequately sized randomised trials [27].

It is also worth reflecting on prior probability. A drug that works at micromolar concentrations in a dish but cannot reach those concentrations in the body starts with a low chance of clinical success, and the repeated null results are what that pharmacology would predict [13, 14]. This does not make early testing wrong, since small trials are cheap and some surprises occur. It does suggest that enthusiasm should scale with the strength of the mechanistic and pharmacokinetic case, and that guideline panels are justified in waiting for adequately powered trials before changing practice, as the WHO panel did [34].

Prophylaxis deserves a brief mention because it was promoted separately. Trials of ivermectin to prevent infection in contacts or health workers were few, mostly small and often open-label, and the Cochrane review found the evidence insufficient to support prevention [7]. Standard preventive measures, vaccination in particular, rest on far stronger randomised data, and the suggestion that a drug taken monthly could replace them was never backed by adequately controlled trials. Telling those at risk that an unproven drug

protects them may do harm if it leads to abandoning measures with proven value [34, 35].

A final point concerns communication. Early claims from laboratory studies and small trials travelled faster than the corrections, and a measured scientific position was often portrayed as hostility to a cheap drug. Pharmacists and clinicians are in a good position to explain the difference between an in vitro signal and a clinical effect, and between statistical and clinical significance. Where patients ask about ivermectin, the evidence base is now sufficient for a clear answer, and the broader lesson is that evidence of efficacy should reach a certain standard before any drug is promoted for a new disease [29, 34, 35].

7. CONCLUSION

Ivermectin showed activity against SARS-CoV-2 in cell culture, but the concentrations involved are difficult to reach in patients at approved doses [3, 13, 14]. That mismatch between laboratory promise and pharmacokinetic reality was an early warning that the clinical results would be disappointing. Small early randomised trials gave inconsistent and sometimes favourable signals, while larger placebo-controlled trials in outpatients found no meaningful benefit on recovery, hospitalisation or death [4, 5, 6, 16, 22].

Favourable pooled estimates depended on weak or discredited studies, and when these were handled appropriately the apparent benefit disappeared [7, 24]. Ivermectin is safe at approved doses but has known harms when misused or given to people with heavy Loa loa infection [25, 26]. The practical conclusion for clinicians and patients is simple, and it has been stable for several years. It should not be used for COVID-19 outside trials, and the episode is a useful case for better evidence standards in drug repurposing [23, 34].

8. ABBREVIATIONS

CYP3A4-Cytochrome P450 3A4,
 COVID-19-Coronavirus disease 2019,
 SARS-CoV-2-Severe acute respiratory syndrome coronavirus 2, RCT-Randomised controlled trial,
 WHO-World Health Organization,

PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RNA-Ribonucleic acid, PCR-Polymerase chain reaction

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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