Six RCTs recently published in mainstream scientific journals that confirm major, statistically significant benefits of ivermectin against COVID-19 as reported in several prior RCTs

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Abstract

Major benefits of ivermectin (IVM) treatment for COVID-19 have been known since the results of 20 such randomized controlled trials (RCTs) were reported, as compiled in January 2021. Of the eight of these RCTs that tracked mortality or morbidity in COVID-19 patients with serious cases, seven showed statistically significant clinical improvements. The pooled mortality reduction in these eight RCTs was 78% in the treatment vs. controls groups (one-fifth of the deaths), and the RCT that used the highest dose of IVM reported a 92% reduction in mortality ($p < 0.001$). Three RCTs for IVM prevention of COVID-19 and two animal studies of IVM at low human-equivalent doses likewise reported pronounced efficacy. Here we note the recent publication of six RCTs for IVM treatment or prevention of COVID-19 in mainstream scientific journals that confirm these previously reported findings.

Background

The consistently observed, major benefits of ivermectin (IVM) for COVID-19 treatment have been known since a January 2021 meta-study compiled results of 20 such randomized clinical trials (RCTs).¹ Of the eight of these RCTs that tracked mortality or morbidity in patients with moderate or severe symptoms (4 double-blind,²⁻⁵ 1 single-blind,⁶ and 3 non-blinded⁷⁻⁹), seven showed statistically significant clinical improvements (all but Podder et al.⁸). The pooled mortality reduction in these eight RCTs for the IVM treatment group vs. controls was 78% (mortality of 2.1% for IVM, 9.5% for controls). The RCT that used the highest dose of IVM, 1,600 µg/kg total, had 2 vs. 24 deaths in the treatment vs. control group (n=200 each),⁷ a 92% reduction in mortality ($p < 0.001$).

It is noteworthy that this study and other IVM treatment studies for COVID-19 conducted at higher cumulative doses of 1,500 µg/kg¹⁰ or 3,000 µg/kg¹¹ over 4 or 5 days had only small percentages of mild or transient adverse effects. These findings of IVM safety at higher doses for COVID-19 treatment aligned with those of other studies unrelated to COVID-19 which found IVM well tolerated at much greater than the standard single dose of 200 µg/kg.^{12,13}

Complementing the IVM treatment studies noted above, three RCTs evaluated IVM for prevention in subjects exposed to COVID-19 patients. These studies reported relative COVID-19 incidences of 20%, 16% and 13% compared with incidences in controls, with even lower relative incidences for serious such cases. In addition, two animal studies of IVM treatment at low human-equivalent doses for SARS-CoV-2 in hamsters¹⁴ and for a closely related betacoronavirus in mice¹⁵ likewise found major, highly statistically significant treatment benefits.

Yet some skeptical reviewers had dismissed this overwhelming RCT evidence for clinical efficacy of IVM against COVID-19, claiming insufficient quality of the studies,^{16,17} as had been indicated by the lack of publication of any in mainstream scientific journals. The recent publication of six such RCTs for IVM in top-tier journals, including Lancet eClinicalMedicine¹⁸ and BMC infectious diseases,¹⁹ all reporting major, statistically significant clinical benefits against COVID-19, dismantles these skeptical critiques.

Six recently published studies in mainstream scientific journals

Of the five recently published RCTs that studied IVM treatment of COVID-19 (a sixth studied prevention), Chaccour et al., as previously released in preprint, monitored outcomes for 40 generally young patients with mild COVID-19 symptoms.¹⁸ A single dose of IVM at 400 µg/kg significantly reduced the duration of

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hyposmia/anosmia ($p < 0.001$), but gave only a modest reduction in viral load. Shahbaznejad et al. reported in May 2021 that IVM in a single dose of 200 µg/kg reduced duration of COVID-19 symptoms and hospitalization ($p = 0.02$ for each).²⁰ IVM also reduced duration of coughing ($p = 0.02$) and of shortness of breath ($p < 0.05$). No conclusions could be drawn regarding mortality, since only one patient died, within 24 hours of hospitalization in critical condition, a 78-year old woman in the treatment group with a history of diabetes and heart failure.

Samaha et al., as reported in May 2021, administered a single dose of IVM at 150 µg/kg to 50 asymptomatic patients positively tested for COVID-19, with 50 controls (all subjects also given zinc and vitamin C).²¹ Incidence at +3 days of fever, anosmia and myalgia were each lower in the IVM group ($p \leq 0.002$ each), and viral load as determined by cycle threshold was also lower ($p < 0.001$). Mahmud et al. administered a single dose of IVM at 12 mg plus doxycycline at 100 mg twice daily for five days.²² The IVM treatment group had statistically significant clinical benefits vs. controls by four different measures, $p = 0.001$ to 0.003 , and had a reduced percentage of positive PCR tests at 14 days with $p = 0.002$. Okumus et al. administered IVM at 200 µg/kg for five consecutive days, in addition to the standard of care used for both the treatment and control groups, which included azithromycin.¹⁹ At the end of the five-day study follow-up period compared with controls, spO_2 was increased; CRP, ferritin and D-dimer blood levels were reduced; and percentage of PCR-negative tests were increased, all to statistical significance ($p = 0.032, 0.02, 0.005, 0.03$, and 0.01 , respectively).

Another RCT conducted in Cali, Columbia on patients with median age 37 and generally mild symptoms had no deaths in the IVM treatment group, 1 death in the placebo group, but found no statistically significant difference in outcomes.¹⁰ However, this study was severely compromised by protocol violations including mistaken substitution of IVM for placebo in 38 of the first 75 patients, discovered a month after the fact by the study's lead pharmacist.²³ Extensive use of over the counter IVM, sales of which surged in Cali during the study period, were indicated in the placebo group. Blinding was violated by the use of glucose solution for the first one-third of the patients in the control group, whereas IVM has a bitter taste.²³ The placebo group was then switched to a solution produced by a company, the technology capability of which has been questioned, that initially could not affirm that it could produce such a placebo. Despite the study lead author's cooperation in producing detailed deidentified patient data in response to other queries, he has refused repeated queries to specify the composition of this new placebo solution.²³ Until this question is answered and other procedural violations are clarified, this study's findings cannot be considered reliable.

Among the six recently published RCTs other than that from Cali noted above was a prevention study of April 2021 by Seet et al.²⁴ IVM was administered to 617 subjects, with 2,420 other subjects assigned to either a control group or to one of three other preventative regimens. The subjects were then tracked for onset of COVID-19 symptoms and positive nasopharyngeal PCR tests over a 42-day period. IVM at a dose of 12 mg was given just once on day one, while the three other preventative regimens were each administered daily during this 42-day period. Yet IVM at this single low dose yielded the best clinical results, reducing incidence of symptomatic COVID-19 by 50% ($p = 0.003$) and of ARDS symptoms by 49% ($p = 0.012$) with respect to controls. IVM at that single low dose, however, yielded only a non-significant 8% reduction in relative incidence of positive PCR tests.

More pronounced reduction by single-agent IVM of COVID-19 morbidity v. infectivity

The findings of two of these six recently published RCTs, Chaccour et al.¹⁸ and Seet et al.²⁴ (but not Samaha et al.²¹) fit a pattern exhibited in a prior RCT³ and two animal studies^{14,15} of more pronounced alleviation by IVM as a single agent of COVID-19-related symptoms and morbidities than reductions in viral load. Indeed, one RCT of IVM at an unusually high dose, 3,000 µg/kg total over 5 consecutive days, yielded a statistically significant reduction in viral load in COVID-19 patients vs. controls only for the subgroup of treated patients (45%) in which the highest levels of plasma IVM levels were obtained.¹¹

This disparity between reduction in morbidity vs. infectivity by IVM for COVID-19 may be explainable by the indicated clinically operative biological mechanism of IVM as reported in seven molecular modeling

studies.²⁵⁻³¹ Those studies found that IVM bound strongly to regions of SARS-CoV-2 viral spike protein, one subdomain of which (RBD) controls viral binding and replication via host cell ACE2 receptors, with another subdomain (NTD) governing viral attachments to sialic acid (SA) binding sites on blood, endothelial and other host cells.³² The latter such attachments of SARS-CoV-2 to SA binding sites on red blood cells (RBCs) are responsible for the clumping that is observed *in vitro* when virus is mixed with RBCs in this hemagglutinating virus. Whereas the common cold human betacoronavirus strains contain an enzyme, hemagglutinin esterase (HE), that releases viral-RBC clumps, the three virulent betacoronavirus strains—SARS-CoV-2, SARS-CoV, and MERS—lack HE.³² IVM, if it is found to bind to NTD sites on SARS-CoV-2 spike protein, might thus limit viral virulence by blocking such hemagglutinating bindings.

The biological mechanism of IVM that is operative clinically against COVID-19 remains to be confirmed, as do indications of its greater reduction of morbidity than of infectivity per the studies noted. The recent publication of the six RCTs noted in top-tier scientific journals, however, positively confirms the major, statistically significant clinical benefits of IVM, as previously reported in several prior such RCTs, for COVID-19 treatment and prevention.

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