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The effect of ivermectin on the viral load and culture viability in early treatment of nonhospitalized patients with mild COVID-19 – a double-blind, randomized placebo-controlled trial

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ABSTRACT

Objectives: Ivermectin, an antiparasitic agent, also has antiviral properties. In this study, we aimed to assess whether ivermectin has anti-SARS-CoV-2 activity.
Methods: In this double-blinded trial, we compared patients receiving ivermectin for 3 days versus placebo in nonhospitalized adult patients with COVID-19. A reverse transcriptase-polymerase chain reaction from a nasopharyngeal swab was obtained at recruitment and every 2 days for at least 6 days. The primary endpoint was a reduction of viral load on the sixth day as reflected by cycle threshold level >30 (noninfectious level). The primary outcome was supported by the determination of viral-culture viability.
Results: Of 867 patients screened, 89 were ultimately evaluated per-protocol (47 ivermectin and 42 placeboes). On day 6, the odds ratio (OR) was 2.62 (95% confidence interval [CI]: 1.09-6.31) in the ivermectin arm, reaching the endpoint. In a multivariable logistic regression model, the odds of a negative test on day 6 were 2.28 times higher in the ivermectin group but reached significance only on day 8 (OR 3.70; 95% CI: 1.19-11.49, $P = 0.02$). Culture viability on days 2 to 6 was positive in 13.0% (3/23) of ivermectin samples versus 48.2% (14/29) in the placebo group ($P = 0.008$).
Conclusion: There were lower viral loads and less viable cultures in the ivermectin group, which shows its anti-SARS-CoV-2 activity. It could reduce transmission in these patients and encourage further studies with this drug.

Background

Ivermectin is a Food and Drug Administration-approved broad-spectrum antiparasitic agent, initially approved for humans in 1987 to treat onchocerciasis and awarded the Nobel Prize of Medicine to the discoverers in 2015. Its primary use is treating infections caused by roundworm parasites. However, over the years, the spectrum was extended to include a variety of parasitic skin infections, such as scabies (Laing et al., 2017).

In the last decade, several *in vitro* studies have shown its antiviral activity against a broad range of viruses, mainly RNA viruses, including HIV, influenza, and several flaviviruses such as Dengue virus, Zika, and West Nile Virus (Caly et al., 2012; Götz et al., 2016; Lundberg et al., 2013; Tay et al., 2013; Wagstaff et al., 2012). Ivermectin was tested *in vitro* against SARS-CoV-2 and showed ~5000-fold reduction (99.8%) in viral RNA after 48 hours (Caly et al., 2020). However, it was criticized that the dosing used in the study cannot be achieved with the currently approved dose, and its anti-SARS-CoV-2 activity in humans has never been proven (Bray et al., 2020).

Ivermectin has anti-inflammatory properties (Zhang et al., 2008). Because the excessive inflammatory response to SARS-CoV-2 is thought to be a major cause of disease severity and death in patients with COVID-19, ivermectin may have a different

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value in addition to its antiviral properties (Mehta et al., 2020).

With its good safety profile, ivermectin is a potential treatment against COVID-19 in its different stages. Some clinical studies and meta-analyses have shown beneficial results regarding clinical outcomes and the length of viral shedding; however, most of them lack a high standard of rigorous methodology (Bryant et al., 2021; Hill et al., 2022; Padhy et al., 2020; Zein et al., 2021).

Here we conducted a double-blinded randomized control trial (RCT) to assess whether ivermectin shows anti-SARS-Cov-2 activity as reflected by shortening the viral shedding in nonhospitalized patients in the early stage of COVID-19 infection. In addition, we were able to test and show the impact of ivermectin on culture viability.

Methods

Ethics

Institutional Review Board (IRB) approval was given by the Sheba Medical Center's IRB (7156/20). Written informed consent was received from each participating individual before recruitment. The study is registered at ClinicalTrials.gov: NCT 04429711.

Study design

A double-blinded RCT to evaluate ivermectin's effectiveness in reducing viral shedding among patients with mild to moderate COVID-19. The study was conducted in hotels located in Tel Aviv, Jerusalem, and Ashkelon, Israel, designated as isolation facilities for patients with mild to moderate COVID-19, not requiring oxygen.

Study population

Patients were eligible for enrollment in the study if they were 18 years or older, not pregnant, with molecular confirmation of COVID-19 by RT-PCR, and included only those who received results within the first 3 days from symptom onset. However, because of the delay (3 to 4 days) in testing the participants and the delayed results coming back from the laboratories, we extended the time up to 7 days from symptoms onset. Because our primary outcome was the change in viral shedding (as reflected by cycle threshold [Ct] value), asymptomatic cases were also included within 5 days from molecular diagnosis.

Patients were excluded if they weighed less than 40 kg, had known allergies to the drug, could not take oral medication, or participated in another RCT for treatment of COVID-19. In addition, patients who had postrandomization RT-PCR results with Ct value >35 in the first two consecutive tests were excluded for further analysis. Patients with co-morbidities of cardiovascular disease, diabetes mellitus, chronic respiratory disease (excluding mild intermittent asthma), hypertension, and/or cancer were included and defined as high-risk patients.

Randomization

Randomization in a 1:1 ratio, in a simple randomization method, was done by a computer-generated program using randomization.com (http://www.jerrydallal.com/random/randomize.htm) by the Clinical Research Coordinator (CRC), blinded to the rest of the study team. This CRC was not recruiting patients, and the numbered pill bottles were available only for the recruiting physicians. The envelope with the randomization codes was opened only at the end of the study.

Patients assigned to the intervention arm received ivermectin in a dosage regimen according to body weight; patients weighing between 40-69 kg received four tablets (= 12 mg) daily, and patients weighing $\geq$70 kg received five tablets (= 15 mg) daily, all for 3 days. Patients assigned to the placebo arm received the same number and appearance of pills per weight daily for 3 days. They were guided to take the pills one hour before a meal. The investigators and patients were blinded to the assignment.

Intervention

On the day of randomization and treatment initiation, patients were tested for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs (day zero). Tests were administered every 2 days from day 6 to day 14 unless patients were discharged earlier from the isolation facilities. The protocol was amended at the beginning of September when the Ministry of Health changed the policy of isolation and allowed infected patients to leave the facility 10 days from symptom onset without further testing. At this point, testing on days 2 and 4 were added to the protocol.

Because the results of the test could have been influenced by the examiner who performed the swab and with differences between labs (Basso et al., 2020; Carroll and McNamara, 2021), a small number of trained practitioners were allocated to obtain the swab during the entire trial and were instructed to use a uniform technique. In addition, all RT-PCR tests, including verification that patients were positive on day zero, were conducted by the same lab at the Israel Central Virology Laboratory of the Ministry Of Health (located at Sheba Medical Center).

Patients were followed up daily by telephone until their discharge. Patients were asked whether they took the pills as guided, if they noticed any adverse effects after treatment and whether there were any follow-up of symptoms.

Unexpectedly, some patients isolated in the hotels as verified positive patients were found to be borderline or negative upon our RT-PCR test (Fig. 1). Therefore, a patient who had RT-PCR results with Ct value >35 in the first two consecutive RT-PCR tests were excluded (two consecutive tests were done to be sure that a borderline test was not a very early stage of the disease, but instead, they already were cured or were sent to the hotel by mistaken results). The equivalent number of patients were further recruited. The IRB amended this in November 2020.

Outcomes

The primary clinical endpoint was viral clearance after a diagnostic swab taken on the sixth day (third day after termination of treatment) in the intervention group compared with placebo. Although negative PCR is defined in Israel with Ct >40 and borderline with Ct >35, it was found that reaching this level may take a few weeks. In contrast, at an early stage of the pandemic, significant evidence showed that a noninfectious state is usually achieved at Ct level >30 (Brown et al., 2020; Bullard et al., 2020; Gilad et al., 2021; Poopalasingam et al., 2022; Wölfel et al., 2020), and therefore isolation time in Israel was changed in September 2020 and was reduced to 10 days without looking for complete negative results. Therefore, we defined a negative test at a noninfectious level as measured by RT-PCR of Ct values >30 (less than 3.4×10^4 viral copies per reaction, equal to less than 10^6 copies/ml).

Culture viability analysis: Toward the end of our study (January 2021), the central virology lab established a Biosafety Level 3 (BSL-3) unit, allowing us the ability to culture the virus. Because the positive medium of participating patients was kept at -80°C, we were able to culture it. Thus, an endpoint of culture viability at days two to six postintervention was added.

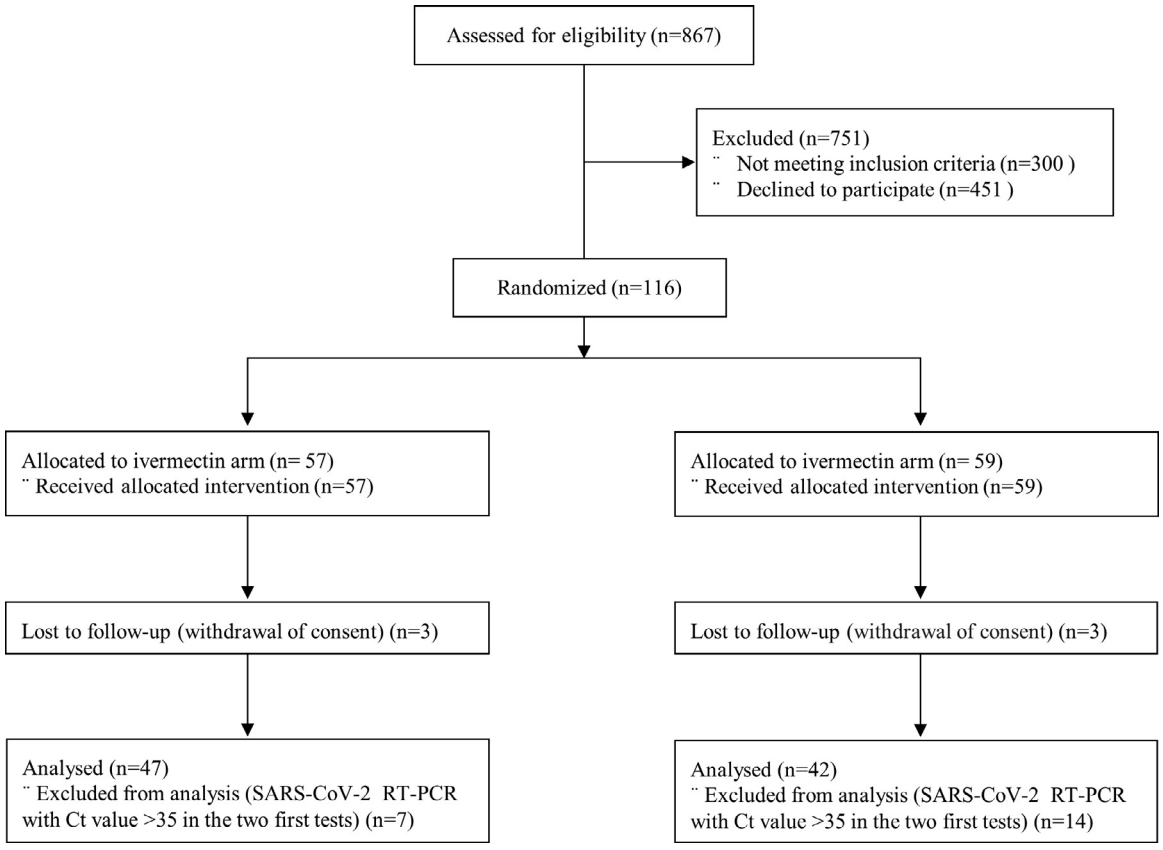

Fig. 1. Enrollment and patient flow.
Ct = cycle threshold; RT-PCR = reverse transcription-polymerase chain reaction.

PCR testing

The SARS-CoV-2 RNA was detected using the Seegene Allplex CoV19 detection kit, according to the manufacturer's instructions (See supplement). The test detects three viral genes: envelope, nucleocapsid, and RNA-dependent RNA polymerase (RdRp). For each sample, the Ct level was defined as the Ct level of the highest viral load (low Ct).

In vitro cultures

Positive samples (Ct values $\leq$30) were stored at -80°C and were thawed for culturing on Vero E6 cells at 37°C for 7 days, as detailed in the Supplementary Methods.

Statistical methods

Sample size: Based on published data from the Ministry of Health at the time of study initiation, we expected less than 10% of patients on day 6 to show a negative RT-PCR test. With the interventional drug, we expected a reduction of at least 25% in the proportion of positive cases. Therefore, considering a potential decrease from 90% to 67.5% (25% decrease), with a power (1-β) of 80% at a significance level of 5% (α = 0.05), a minimal sample size of 96 participants in total, was required to detect a statistically significant difference. Therefore, 48 patients were needed in each study arm.

Statistical analysis: Statistical analysis was done by the Biostatistics and Biomathematics Unit, Gertner Institute, Sheba Medical Center, Tel Hashomer, Israel. The modified intention to treat (mITT) population included all randomly assigned patients who had positive results upon recruitment. However, our primary analysis was done by per-protocol analysis, excluding those lost to follow-up without further test results. Continuous variables are presented as mean ± SD or median and interquartile range. Categorical variables are presented as N (%). Differences between ivermectin and placebo groups were assessed using a chi-square test and *t*-test for categorical and continuous data, respectively. Fisher's exact test was used when cross-tabulation frequencies were less than five. A multivariate logistic regression model was used to determine the impact of ivermectin while controlling for age, sex, weight, and being symptomatic or not on the reduction of viral load on day 6 as reflected by Ct level >30. Results include adjusted odds ratios (OR) and 95% confidence intervals (CI). Kaplan-Meier curves were drawn, and survival analysis was conducted with a log-rank test using the time to negative RT-PCR (Ct level >30) result. For all analyses, significance was set at P <0.05. All data analyses were performed with the SAS 9.4 software (Cary, North Carolina, USA).

Results

From May 15, 2020, to January 25, 2021, 867 patients were screened. Of them, 116 (13.4%) were eligible and were randomized; ultimately, 89 (76.7%) were per-protocol evaluable, 47 in the ivermectin and 42 in the placebo arm (Fig. 1). The last follow-up was ended on January 31, 2021, after reaching our calculated sample size (based on the original 96 patients and the additional 21 patients who were found to be negative immediately after randomization).

The baseline study of mITT and per-protocol population characteristics are listed in Table 1. The median age of the patients was 35 years (range, 20-71), 24.2% (23/95) equal to or older than

Table 1
Baseline study population.

	Modified Intention to treat						Per-protocol (eligible patients)					
	All (n = 95)		Ivermectin group (N = 50)		Placebo group (N = 45)		All (n = 89)		Ivermectin group (N = 47)		Placebo group (N = 42)	
Male gender *n, (%)*	74	(78.7)	38	(77.6)	36	(80.0)	69	(78.4)	36	(78.3)	33	(78.6)
Age *median (IQR)*[a]	35.0	(28.0–50.0)	35.0	(29.0-46.0)	37.0	(27.0-51.0)	35.0	(28.0-47.0)	36.0	(32.0-50.0)	33.5	(26.0-47.0)
Weight *median (IQR)*	79.0	(70.0-88.0)	80.0	(70.0-90.0)	76.0	(68.0-85.0)	79.0	(70.0-86.0)	80.0	(70.0-90.0)	75.0	(67.0-85.0)
Symptomatic *n, (%)*	77	(81.1)	39	(78.0)	38	(84.4)	72	(80.9)	37	(78.7)	35	(83.3)
Days from symptoms onset *median (IQR)*[b]	4.0	(3.0-5.0)	4.0	(3.0-5.0)	4.0	(3.0-5.0)	4.0	(3.0-5.0)	4.0	(3.0-5.0)	4.0	(3.0-5.0)
Ct value on day 0 *median (IQR)*[c]	23.0	(20.0-28.0)	24.0	(20.529.0)	22.0	(19.0-27.0)	23.0	(20.0-28.0)	24.0	(21.0-28.0)	22.0	(19.0-27.0)

No variable was statistically significantly different between the two groups by Fisher exact test for categorical variables or by Kruskal-Wallis test for continuous variables.
[a] Three are missing.
[b] Calculated only for symptomatic patients.
[c] Two are missing.Ct = cycle threshold; IQR = Interquartile range.

50 years, and 8.4% (8/95) equal to or older than 60 years. Most patients were male (78.7%, 74/95). A total of 12 (13.7%,13/95) patients had co-morbidities associated with risk for severe disease (Wu and McGoogan, 2020); 16% (8/50) and 11.1% (5/45) among the ivermectin and placebo groups, respectively, $P = 0.56$.

Most patients were symptomatic (77/95, 81.0%). The most common symptoms of fatigue, fever, cough, headache and myalgia were prevalent in approximately half of the study population (Symptoms detailed in Table S1-supplement). None of these variables were statistically different between the two study arms.

A total of 89 were eligible for analysis per-protocol (Fig. 1 and Table 1).

Study outcome

The mean Ct values of the per-protocol population are listed in Table 2, and the change in Ct values is depicted in Fig. 2. The Ct values of the ivermectin group increased faster (means the viral load decreased faster) compared with the placebo group at the early intervention stage during the first 4 days. Spontaneous recovery also took place in the placebo group; their Ct values increased as well, having similar Ct values since day 6.

As mentioned previously, our calculations were based on negative results reflected in Ct >30. According to per-protocol analysis, the rate of negative RT-PCR for SARS-CoV-2 from day 4 (one day after termination of treatment) through day 10 was higher in patients receiving ivermectin. However, it was statistically significant on days 6 to 8 (Table 3).

In the multivariable logistic regression model, the adjusted OR of SARS-CoV-2 RT-PCR negative test (Ct >30) for treatment with ivermectin compared with placebo at day 6 was 2.28 (95% CI: 0.87-5.95, $P = 0.09$) but reached significance only at day 8 at 3.70 (95% CI: 1.19-11.49, $P = 0.02$) fold higher than for the placebo group, respectively (Table 4).

Table 2
Mean Ct values of per-protocol participants.

	Ivermectin			Placebo			
	N	Mean	SD	N	Mean	SD	*P*
Day 0	47	24.2	5.0	42	22.4	5.0	0.11
Day 2	26	28.8	6.4	19	23.9	6.5	0.02
Day 4	24	32.2	6.0	19	28.2	7.1	0.06
Day 6	36	33.9	5.5	30	31.6	6.9	0.14
Day 8	21	33.0	5.4	21	34.6	5.6	0.36
Day 10	18	34.2	4.1	16	35.0	5.1	0.63
Day 12	15	36.2	4.4	15	36.4	10.3	0.89
Day 14	8	37.6	2.5	12	33.1	4.6	0.02

Ct = cycle threshold; SD = standard deviation.

Kaplan-Meier analysis (Fig. 3) adjusted to symptom onset showed a significant difference between the ivermectin and placebo arms during treatment.

Modified intention to treat analysis shows no significant difference from the per-protocol analysis (Table S3).

Taking an endpoint of Ct level >35 as a negative result and comparing the two groups, the ivermectin group showed that 43% (20/46) reached this point at day 6 versus 33% (13/39) of the placebo group; however, it did not reach statistical significance ($P = 0.34$).

Clinical outcome

Four patients were referred to hospitals during the study period, three from the placebo arm. The first placebo-treated patient was hospitalized for 11 days with prolonged respiratory symptoms and needed oxygen even after his discharge from the hospital. The second was hospitalized for one day because of respiratory complaints. The third one was referred to the hospital because of headache and dizziness and was diagnosed with sinusitis after evaluation (brain computed tomography and magnetic resonance imaging). In addition, one asymptomatic patient became symptomatic in the placebo group. In the ivermectin arm, one patient was referred to the hospital because of shortness of breath on the recruitment day. He continued the ivermectin and was sent back to the hotel in good condition a day later.

Culture positivity rate

A convenient number of 16 samples were cultured on the day of recruitment (day zero). Ct levels ranged from 14-28 (mean 21.5±4.1), and among them, 13/16 (81.2%) was positive. Culture viability was tested further by available samples with Ct ≤30 on days 2, 4, and 6 after intervention (see details Table S2-supplement). Altogether 52 samples were cultured; viable cultures in the placebo group were positive in 14/29 cultures (48.2%), whereas, among the ivermectin group, only 3/23 (13.0%) were found positive ($P = 0.008$).

In a composite calculation, taking into account Ct values >30 together with nonviable culture, the negative results of the ivermectin group reached significance even on day 4 (one day after ending the treatment), with 86% negative patients compared with 59% in the placebo group ($P = 0.04$) (see Table 2B).

Adverse events

Among all the 116 randomized patients, three reported having diarrhea after the treatment, two (3.5%) in the ivermectin group and one (1.7%) in the placebo group. In all cases, diarrhea resolved

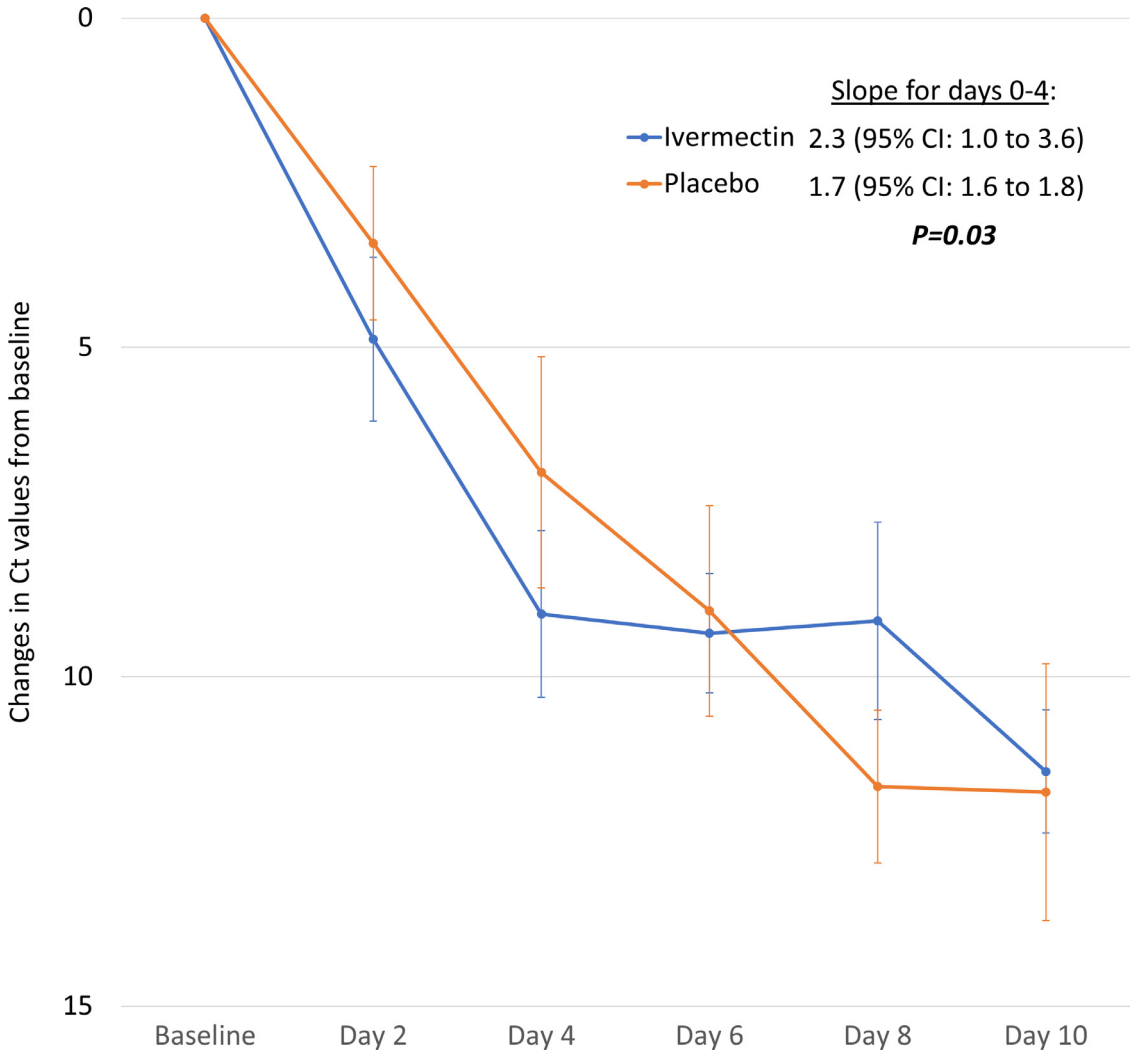

Fig. 2. Changes of cycle threshold (Ct) values from base lines during the first 10 days.
CI = confidence interval; Ct = cycle threshold.

Table 3
Ratios for negative RT-PCR (Ct >30) tests on days four to 10 in per-protocol participants.

Based on RT-PCR (Ct >30) test							
95% CI		OR	*P*-value*	Placebo	Ivermectin	N	
7.92	0.77	2.47	0.12	7/22 (32%)	15/28 (54%)	50	Day 4
6.31	1.09	2.62	0.03	21/42 (50%)	34/47 (72%)	89	Day 6
8.82	1.25	3.32	0.01	25/42 (59%)	39/47 (83%)	89	Day 8
7.72	0.91	2.56	0.07	29/42 (69%)	40/47 (85%)	89	Day 10
Based on RT-PCR (Ct >30) test together with nonviable cultures							
16.1439	1.0688	4.1538	0.03	13/22 (59%)	24/28 (86%)	50	Day 4
20.2129	1.3400	5.2043	0.01	31/42 (74%)	44/47 (94%)	89	Day 6
34.2875	1.4419	7.0313	0.01	32/42 (76%)	45/47 (96%)	89	Day 8
19.7078	0.7135	3.7500	0.14**	36/42 (86%)	45/47 (96%)	89	Day 10

* *P*-value by chi-square test.CI = confidence interval; Ct = cycle threshold; OR = odds ratio; RT-PCR = reverse transcription-polymerase chain reaction.

in 2 days. Two patients in the placebo arm reported a rash during the treatment course, which subsided within one to 2 days. No other adverse effects were reported. All 89 patients eligible for the analysis reported adhering to the treatment as guided.

Discussion

In this double-blind RCT with patients with mild COVID-19, ivermectin significantly reduced the time of viral shedding and affected viral viability when initiated in the first week after evidence of infection. Our primary endpoint was to show the benefit of ivermectin on day 6 (3 days after ending treatment), which was achieved with 72% of samples being noninfectious (Ct >30) in comparison with 50% among the placebo group (OR 2.6). Even on day 4 (one day after treatment ended), the ivermectin group showed an OR of 2.4, although this did not reach significance. In the multivariable logistic regression model, the superiority of iver-

Table 4
Multivariable analysis for negative RT-PCR (Ct >30) test for SARS-CoV-2 results on day 6 and 8 in per-protocol participants.

	Day 6				Day 8			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
Female	1.13	0.32	3.96	0.8491	0.60	0.16	2.33	0.4631
Age	0.97	0.94	1.01	0.1830	0.95	0.91	0.99	0.0281
Weight	1.00	0.97	1.04	0.8347	1.00	0.96	1.03	0.9016
Symptoms	1.14	0.29	4.46	0.8497	0.98	0.20	4.81	0.9768
Ct value at baseline	1.17	1.05	1.31	0.0055	1.20	1.05	1.37	0.0071
Ivermectin	2.28	0.87	5.95	0.0930	3.70	1.19	11.49	0.0235

CI = confidence interval; Ct = cycle threshold; OR = odds ratio; RT-PCR = reverse transcription-polymerase chain reaction.

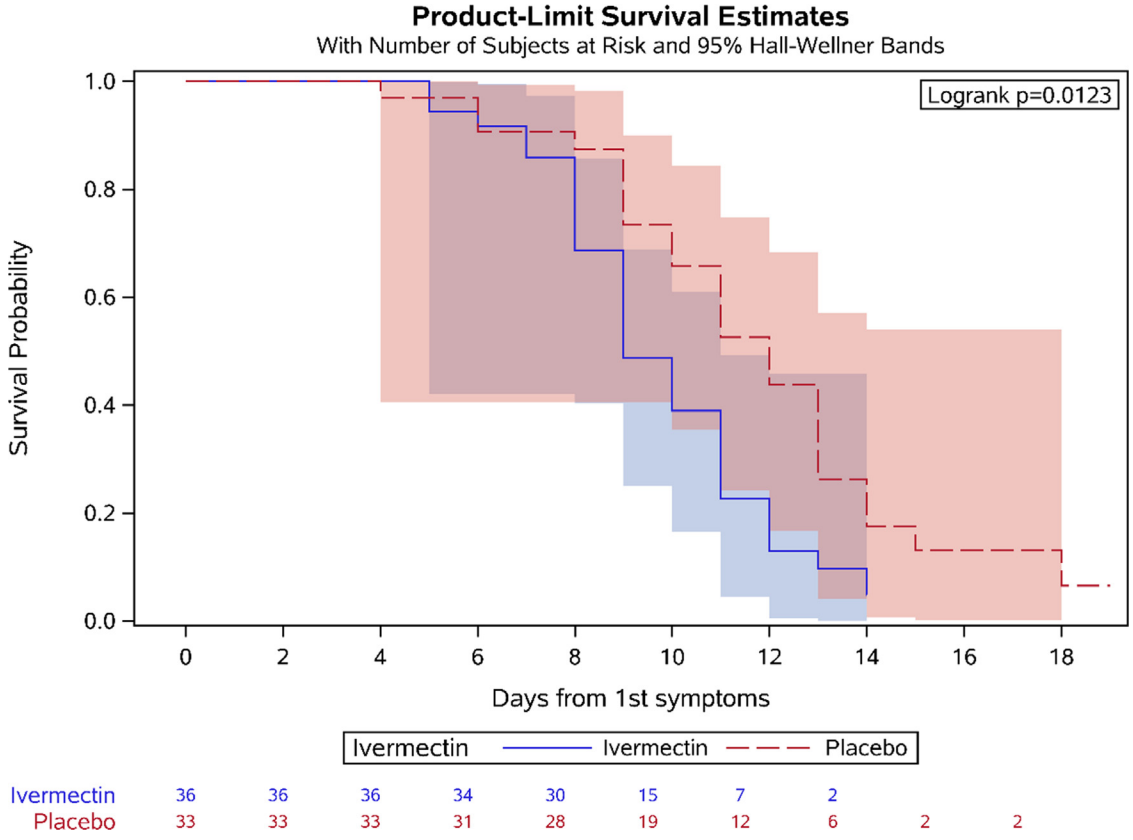

Fig. 3. Kaplan-Meier curve for time to negative (Ct<30) results for symptoms onset (calculation is done for symptomatic patients, N=69).

mectin reached significance at day 8 only, possibly because of the small sample size.

The antiviral activity was also reflected in the Kaplan-Meier curve, where the drug's effect was seen after the second day of treatment (Fig. 3).

To further explore the antiviral activity, we tested the culture viability in both placebo and ivermectin groups. This analysis became available in our institution at the end of the study only, when the BSL-3 lab was established (January 2021). The results show the advantage of ivermectin, where only 13% of samples stayed positive on days 2 to 6. In comparison, 48% stayed positive in the placebo group ($P = 0.008$). The antiviral properties of ivermectin against SARS-CoV-2 were shown in an *in vitro* model (Caly et al., 2020). A major criticism regarding this *in vitro* model was that the ivermectin concentration used was more than 35 times higher than the maximum plasma concentration after oral administration of the approved dose (Bray et al., 2020). Therefore, our study demonstrates the anti-COVID activity of ivermectin in a dosage that can be used in clinical scenarios. The new anti-COVID drug molnupiravir (manufactured by Merck) was tested in a similar design to our protocol and demonstrated, in the same way, its anti-SARS-CoV-2 activity (Fischer et al., 2022). Reduction in viral load was also demonstrated after remdesivir treatment and was considered a marker for antiviral properties (Biancofiore et al., 2022).

The broad-spectrum antiviral activity of ivermectin is considered to be related to its ability to target the host importin $\alpha/\beta 1$ nuclear transport proteins responsible for nuclear entry of cargoes of viral proteins, which in turn block the host antiviral activity (Wagstaff et al., 2012). It also interferes with SARS-CoV-2 cell entry by docking in spike (S) protein and ACE-2 receptor binding sites and interrupting the S protein's priming by the transmembrane protease serine 2 protein (Choudhury et al., 2021; Eweas et al., 2020; Lehrer and Rheinstein, 2020). Furthermore, it may inhibit RNA-virus replication by interacting with RdRp, nonstructural protein 14 (nsp14), nucleocapsid phosphoprotein, membrane (M) protein, main protease (Mpro), papain-like protease (PLpro), 3 chymotrypsin-like proteases, and inhibiting the Karyopherin $\alpha 1$ (KPNA)/Karyopherin $\beta 1$ (KPNB1)-mediated nuclear import of viral proteins (Zaidi and Dehgani-Mobaraki, 2022).

The clinical implication of using ivermectin in preventing hospitalization, reducing mortality, and using it for prophylaxis is an ongoing debate (Santin et al., 2021). Several meta-analyses were

performed that did not resolve the debate and perpetuate the saga (Hill et al., 2022; Schwartz, 2022a; Siedner, 2021). These aspects were beyond the goal of our study; however, shortening the infectiousness period may have an enormous impact on public health, and our study can support this aspect. Considering the two composites, Ct values above 30 and negative cultures in our study demonstrate an almost 90% noninfectious status on day 4 (one day after treatment) and 94% on day 6 among ivermectin users (Table 2). The recommended isolation period was recently reduced to 5-7 days by the Centers for Disease Control and Prevention and many other health authorities, and even the requirement for facial masks is gradually being removed. However, studies have shown that in these 5-7 days, patients are still infectious at a rate of 59%, similar to the results we obtained with our placebo group (Lefferts et al., 2022). Thus, decreasing the drug's viral shedding duration could decrease transmission and improve public health.

Our study has several limitations. First, the sample size was relatively small and was designed to look for differences in viral load but not for clinical deterioration and prevention of hospitalization. Indeed, this was planned as a second stage after proving its anti-COVID activity. The second limitation was that investigators did not physically observe drug therapy. Another limitation was the male predominance in our study. Finally, our study was conducted among nonhospitalized patients with mild symptoms. Therefore, the results cannot be applied to more severe or immune-suppressed populations.

The strength of our study was its double-blind structure with more concrete outcomes such as Ct values and culture viability, where the laboratory personnel was blinded to the patients' assignment.

In conclusion, our study supports the notion that ivermectin has anti-SARS-CoV-2 activity. Therefore, if used at the early stage of disease onset, it may shorten the isolation time and reduce transmission.

Further studies are needed to test its ability to prevent clinical deterioration in high-risk groups and to examine its potential as a prophylactic drug. Vaccines are available, but it will take years before they are distributed worldwide. This drug may also reduce mortality, so urgent intervention with further well-designed studies is needed. Because, in most countries, ivermectin has not been approved for COVID-19 treatment, performing ivermectin versus placebo studies appears unethical when the newer drugs, paxlovid and molnupiravir, have been officially approved by health authorities. However, offering ivermectin to those who refuse the new drugs seems to be a reasonable option. Because eligibility criteria in receiving these early treatments are targeted to high-risk patients only, observing the outcome of these arms of oral treatment: paxlovid versus molnupiravir or ivermectin, might shed light on the value of ivermectin in comparison with the newer drugs (Schwartz, 2022b). In addition, as we know from the treatment of other diseases, a single drug will not be sufficient, but instead, combined therapy, thus proving ivermectin as a drug with anti-SARS-Cov-2 activity may be helpful as a partner drug to combat this virus.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contribution

Conceptualization: ES; Data curation: ES, AB, MM; Formal analysis: ES, AB, MM, OE; Investigation: AB, MM, GH, DL, LR, AS, IN, LK, OE, ES; Methodology: ES, AB, MM, OE; Supervision: ES, AB; Writing - original draft: ES, AB, DL; Writing - review & editing: all authors contributed, reviewed, and approved the last draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.003.

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