The SAIVE Trial, Post-Exposure use of ivermectin in Covid-19 prevention: Efficacy and Safety Results

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INTRODUCTION

Ivermectin (IVM) is a well-known drug currently used to treat several parasitic diseases. It has a proven safety profile over many decades of exposure. It is one of the several drugs explored for its potential therapeutic and preventive role against SARS-CoV-2 infection as previous studies had reported its antiviral effects on both RNA and DNA viruses[1,2]. Caly et al. demonstrated that a single dose of IVM could control the *in vitro* replication of SARS-CoV-2[3]. Several mechanisms of action have been suggested for its effect on SARS-CoV-2[4]. Those mechanisms could lead to an efficient SARS-CoV-2 prevention, independently of virus mutations[5].

Post-exposure prophylaxis (PEP) is a method of preventing SARS-CoV-2 infection after a known exposure to the virus that may limit the spread of infection.

METHOD

The SAIVE Trial (NCT05305560) is a randomized, double blind, multicenter, parallel group, placebo-controlled clinical trial, assessing the efficacy and safety of ivermectin in a post-exposure population. Participants were followed 56 days and RT-PCR tests were performed on days 1, 4, 7, 10, and 28, or when infection was suspected. It was conducted in 11 clinical sites in Bulgaria between March and Oct. 2022.

The primary objective of the SAIVE trial was to evaluate the efficacy of a continuous administration of oral ivermectin as post-exposure prophylaxis against SARS-CoV-2 infection in confirmed contact cases. Additionally, this study would further reinforce the safety of continuous exposure to ivermectin, as evaluated in a previous phase 1 study (NCT04632706).

Out of 400 enrolled, 399 participants were randomized in a 1/1 ratio to ivermectin (200µg/kg on day 1 then 100µg/kg/day up to day 28) or matching placebo. Main inclusion criteria was confirmed contact within 5 days with a positive COVID-19 case (assessed by RT-PCR). Primary endpoint was the proportion of confirmed infections between groups from baseline to day 28. Time to positivity, severity of symptoms after confirmed infection and efficacy as a function of variant type were also assessed during the study.

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RESULTS

Demographics

Distribution between groups was well-balanced. One fifth (respectively 19.5 and 17.1% in ivermectin and placebo groups) of the participants were in the same household as the contact case.

	IVM	Placebo
Age		
Mean/Median	41/40.5	40/39
Min-Max (years)	18-64	19-64
Body weight		
Mean/Median	79/79	79.3/80
Min-Max (kg)	46-132	50-135
BMI		
Mean/Median	26.1/26	26.1/25.9
Min-Max	23.2-41.7	22.8-41.2
Gender		
Male/Female	119/81	109/90
Same Household		
Yes (%) / No (%)	39 (19.5) / 16 (80.5)	34 (17.1) / 165 (82.9)

Efficacy

Statistically significant difference was found between active and control groups in terms of risk of infection with SARS-CoV-2 between D1 and D28 post-treatment initiation. Relative Risk Reduction (RRR) was highly statistically significant with 71.57% difference with respectively 30/200 positive cases in ivermectin group and 105/199 in placebo group (mFAS population (399 patients)) with p<0.0001.

	Positive		Negative		Total	
Treatment	N	%	N	%	N	%
Ivermectin	30	15	170	85	200	100
Placebo	105	52.8	94	47.2	199	100

Statistics	N	value	95% CI	
Odds Ratio (OR)	399	0.158	0.098-0.255	*
Relative Risk (RR)	399	0.284	0.199-0.405	*
Relative Risk Reduction (RRR)	399	0.715	0.594-0.801	*

**Statistically significant*

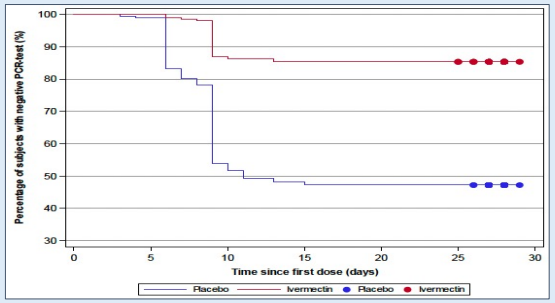
The study also showed statistically significant difference between the two groups in terms of WHO Covid-19 scale[6] for disease progression. This indicates milder symptoms in the ivermectin group compared to placebo, in case of infection.

Variant ID	Ivermectin	Placebo	Total
BA.1.1	10	44	54
BA.5	20	60	80
Variant ID not recorded	0	1	1
Total	30	105	135

Omicron BA.1.1 and BA.5 variants were present during the study and ivermectin demonstrated an equivalent high efficacy whatever the variant with a significant difference (p value<0.0001).

	Variant ID	Ivermectin	Placebo
Viral Load HIGH	BA.1.1	0	40
	BA.5	4	59
	Total	4	99
Viral Load LOW	BA.1.1	10	4
	BA.5	16	1
	Total	26	5

Interestingly, even when contaminated, participants receiving ivermectin had a lower risk of presenting high viral load (log10 RNA copies/mL) as compared to placebo (only 14% of high viral load in IVM group).



A significant delay was observed on Time to Positivity between the groups and most infections occurred between D7 (3 cases in ivermectin group *vs* 38 in placebo group) and D10 (25 cases *vs* 57 respectively) (Hazard Ratio of 0.213 (p-value < 0.0001)).

Safety

No deaths or serious adverse events (SAE) were reported. Of 173 reported Adverse Events (AEs), most were mild and 135 were related to COVID-19. All participants with documented infection received standard care (steroids, anticoagulants – mostly aspirin- vitamins C and D) and were followed until resolution. No participant had severe symptoms, required oxygen, or was hospitalized. There was an excellent tolerance to ivermectin.

CONCLUSION

This study demonstrated highly statistically significant evidence in a large, randomized, double-blind, placebo-controlled study that daily oral treatment with ivermectin reduced the risk of infection following exposure to SARS-CoV-2.

Ivermectin was also shown to be safe in doses and duration higher than currently used in approved indications.

DISCUSSION

Ivermectin demonstrated a significant efficacy in preventing COVID-19 infection in a post exposure setting as compared to placebo group.

The lower viral loads observed with ivermectin could potentially indicate a lower risk of disease severity and a lower contagiousness[7]. We can hypothesize that ivermectin would be a valuable tool in the protection of at-risk populations, in addition to vaccination.

Efficacy of ivermectin administration was similar regardless of the sub-variant during the trial (60% of infections were related to Omicron BA.5 and 40% to BA.1.1) and the significance of results is equivalent to overall RRR on the whole population in both subgroups. This result may indicate ivermectin efficacy on different variants. This could be due to its non-specific mechanisms of action.

Ivermectin should be investigated in further clinical trials in post-exposure context to confirm these results.

The positive outcome of the trial supports the development of a long-acting injectable (LAI) of Ivermectin for this application, allowing a continuous release from a bioresorbable subcutaneous depot for several weeks or months.

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