Open Access

Journal of Clinical Immunology and Microbiology

Research Article

The Use of Oral Human Grade Ivermectin with Supplements Known as Immunomodulators for Treating Patients with COVID-19 Infections at Home

Godofreda R Vergeire-Dalmacion[1*], Pedrosa Glenda[2]

[1]Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila; Manila, Philippines

[2]Division of Educational Leadership and Professional Services, College of Education, University of the Philippines, Diliman; Quezon City, Philippines

[*]**Corresponding Author:** Godofreda R Vergeire-Dalmacion, Department of Clinical Epidemiology, University of the Philippines, Manila, Paz Mendoza Bldg, Ermita Manila, Philippines;
Email: gvdalmacion1@up.edu.ph

Received Date: 11-06-2022; **Accepted Date:** 27-06-2022; **Published Date:** 07-07-2022

Abstract

Several meta-analyses have shown low to moderate certainty for Ivermectin (IVM) to reduce all-cause mortality from COVID-19 infection by 68% and to prevent infection by about 86%.

The aim of our study is to determine the effects of oral IVM for treating mild to moderate COVID infections and the effects of demography, symptomatology, co-morbidities, IVM dose and combination or single immunomodulation supplements on clinical recovery.

Method: An ex post facto research design involving COVID-19 patients treated with ivermectin covering the period of April 2021 to June 2021 was used. The participants were clinicians in Metro Manila who prescribed IVM for home care treatment of their COVID-19 patients.

Out of 338 evaluable patients, 95.6% (323/338) recovered completely, 0.59% (2/338) were still recovering, 2.36% (8/338) were long haulers and 1.47% (5/338) died from the infection. Mild cases received IVM at 0.2 to 0.8 mg/kg body weight (kgbw) and 1.0 to 1.8 mg/kgbw for

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

moderate cases for 5-7 days. The p-values of 0.022 for gender and 0.000 for co-morbidity showed that these factors can significantly affect the recovery of COVID-19 patients. Shortness of breath (p-value of 0.000), muscle pain (p-value =.002) and headache (p-value=0.011) have significant effects on recovery. Among the co-morbidities, hypertension (p-value = 0.000), diabetes (p-value =.006), cardiovascular diseases (p-value = 0.001) and obesity (p-value = 0.014) have statistically significant effects on clinical outcomes. Using Kruskal-Wallis H statistics, the intake of combination immunomodulators has a significant effect on the recovery of COVID-19 patients (p-value of 0.027). Using Mann-Whitney statistics, zinc alone showed a statistically significant effect (p-value of 0.002) for recovering from COVID.

IVM is effective for COVID infections provided it is given early and the dose is adjusted for severity and co-morbidities. The graduated dose regimen of IVM and the predilection of the virus to mutate will become a challenge for designing future randomized clinical trials.

Keywords

Home Care; COVID-19; Ivermectin; Patient-Centered Therapeutic; Viral Mutation

Abbreviations

AES: Acute Encephalitis Syndrome; COVID: Corona Virus Disease of 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; CDC: Center for Disease Control; FLCCC: Frontline Line Critical Care COVID Alliance; EUA: Emergency Use Authorization; NIH: National Institutes of Health; CDC PH: Concerned Doctors and Citizens of the Philippines; SOB: Shortness of Breath

Introduction

The sheer magnitude of the disruptions to human existence brought about by the COVID-19 pandemic pales beyond comparison to any natural or man-made calamities that have besieged our world in the last 50 years or perhaps more. The cause of the Coronavirus-2019 (COVID-19) pandemic was traced back to Wuhan, China in early January 2020 by a novel positive-sense single-stranded genomic RNA virus, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It belongs to the family of Coronaviridae, which is the largest group of viruses causing respiratory and gastrointestinal infections, including the ubiquitous common cold [1]. SARS-CoV-2 contains the largest known RNA genome, with a size of around 30,000 bases long. The genome-based features of SARS-CoV-2 are unique compared

to other well-known -CoVs. These features may explain the reasons behind the heightened infectivity and transmission ability of the virus in humans [2,3].

Much earlier in the pandemic, the role of drug therapies was noticeably dismissed in favor of the a priori belief that only vaccines could and should control the pandemic [4]. This belief was accepted as an immutable truth by many members of the medical community and government despite having only a primitive knowledge of the pathophysiology of the disease and what the virus is capable of doing to the human body, especially to its immune system, as we battle it while awaiting the development of the vaccine. The vital role of vaccines against future biological warfare has always been held by the US government as early as the 9/11 infamous attack [5]. It is unsurprising that US government agencies, particularly the FDA and Centers for Disease Control (CDC), will collaborate with the World Health Organization and Big Pharma to implement mass vaccination for the current pandemic. In order to fully disseminate this narrative, Facebook became the self-appointed fact checker for COVID-19 and its management [6]. The clinical course of COVID-19 infection, although clearer and slightly reassuring now, is still shrouded in many uncertainties and unknown long-term outcomes.

As early as 2011, researchers discovered the anti-viral and anticancer properties of Ivermectin (IVM), an anti-parasitic drug that effectively eradicated River Blindness in Africa. IVM was one of the 480 preselected compounds they studied as probable importin inhibitors. Importin alpha and beta are nuclear cargo proteins that carry viral proteins into the nucleus where they are assembled to become new virions [7]. Only IVM showed positive results, which was later replicated in their studies of HIV and Dengue, both RNA viruses like SARS CoV2. Also, it was shown that IVM could dock to the SARS CoV2 receptor binding domain on the ACE2 receptors [7]. This action of IVM interferes with the attachment of the spike protein of the putative virus into the ACE2 receptors and the subsequent entry of the virus into the human cell membrane. Once inside the cell, the virus' primary objective is to hijack the cellular host's machinery for its replication. IVM's purported mechanisms of action can lower viral load, decrease viral shedding and prevent the further spread of the virus. More recent studies have demonstrated the ability of IVM to inhibit the release of interleukin 6 and TNF, which are responsible for the cytokine storm and mortalities of most COVID-19 cases [8].

In March 2021, as the pandemic raged across continents, Caly published the results of an in vitro study using the anti-parasitic agent against SARS-CoV-2 in Vero cells [9]. This seminal study reported the ability of IVM to significantly reduce the replication of SARS-CoV-2 and established its potential use for treating the early phase of the infection. As the pandemic approached the end of the year, more scientific papers on IVM for treating COVID-19 infections were published, indicating a trend for its efficacy and safety [10]. But the WHO and the US National Institutes of Health (NIH) issued warnings against the use of the drug unless in clinical trials [11]. Following that, the US CDC would soften its recommendation for or against the use of IVM for COVID-19, leaving the decision to the physician and patient. The

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

US FDA could not grant IVM an Emergency Use Authorization (EUA) because it took a neutral stance [12].

Many studies involving small sample sizes and published by mostly independent researchers from low-income and middle-income countries have shown a trend towards the reduction of all-cause mortality, early viral clearance and prevention of COVID-19 cases with the use of IVM [13-15].

Objectives

The aim of our study is to describe the recovery of patients with mild to moderate COVID-19 infections treated with oral human grade IVM combined with supplements and vitamins, which were prescribed for their mechanism of action as immunomodulators. It also aims to statistically test the significant difference between the level of recovery from IVM based on a patient's demography, symptomatology, co-morbidities, side effects of IVM, dosage of IVM and combined or single immunomodulators. Ivermectin, either in capsule or tablet form, was prescribed at the recommended dose by the Frontline Line Critical Care Covid Alliance (FLCCC) as modified by the Concerned Doctors and Citizens of the Philippines (CDC PH) [6].

Methods

We conducted an ex post facto research design involving COVID-19 patients in Metro Manila treated at home with oral ivermectin from April 2021 to June 2021 by doctors who are known prescribers of IVM. The case report forms in an Excel Database were sent to consenting doctors to be filled out. A method similar to crowd sourcing, in this instance, physician sourcing was used to purposively target doctors known to be prescribers of IVM. The form did not require information about the names or addresses of their patients or any data that could violate the latter's privacy. Instructions on how to fill up the form were included in the file, but access to the primary investigator was open to all participating doctors for any questions or clarifications. Henceforth, this study took advantage of the secondary data via non-probability sampling, particularly purposive sampling. The descriptive statistics applied in this research is the mode in order to ascertain the highest number of patients per profile, symptomatology, co-morbidities, side effects of IVM, dosage of IVM, combined and single immunomodulators. Moreover, the mean age was also computed. In testing the significant difference in the level of recovery, the Mann-Whitney U test and Kruskal-Wallis were applied. The Mann-Whitney was analyzed for the profile of patients with two (2) categories only, such as gender, clustering effect, symptoms and comorbidities. Kruskal-Wallis was applied to the profile of patients with more than 2 categories, such as age, side-effects and combined immunomodulators.

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

The data was analyzed via SPSS version 26. All the raw data was reassessed to validate the encoded data by identifying inaccuracies and discrepancies during the encoding process.

Prior to the start of the study, ethics approval was obtained on January 12, 2022 from the Research Ethics Committee of the Asian Hospital and Medical Center.

Ethical Consideration

Because only secondary data was collected, there was no risk, damage, or harm to any person, whether emotional, mental, or physical. The study, which involved the review of existing medical records containing an anonymized list of COVID-19 patients, was done in coordination with consenting physicians who voluntarily participated. Following the rules of the Philippine Data Privacy Act of 2012, the information about the participants and the data that was collected were kept secret.

Patient and Public Involvement

No patients or the public were involved.

Results

A total of 338 patients treated with IVM at varying doses were eligible for analysis. Their mean age is 43 years old and their most common gender is male (count = 172). Their profile consists of their demography, symptomatologies, comorbidities and clusters, which are seen in Table 1. Unlike the early phase of the pandemic in 2020, when patients consulted alone, at the time of our study, many patients came with other family members, with other neighbors, or with co-workers. It was for this reason that the patients were categorized as either part of a cluster or otherwise when consulting individually. Table 1 shows the characteristics of the study population.

Characteristics		**Number of Patients/% of Patients**					***p*-value**
		Recovered (n = 323)	**Recovering (n = 2)**	**Long-Hauler (n = 8)**	**Dead (n = 5)**	**Total (n = 338)**	
Age Category	Below 19	33 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	33 (100.00%)	0.302

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

	19 to 25	30 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	30 (100.00%)	
	26 to 39	95 (96.90%)	0 (0.00%)	1 (1.00%)	2 (2.00%)	98 (100.00%)	
	40 to 59	99 (92.50%)	1 (0.90%)	5 (4.70%)	2 (1.90%)	107 (100.00%)	
	60 to 69	44 (93.60%)	0 (0.00%)	2 (4.30%)	1 (2.10%)	47 (100.00%)	
	Above 69	22 (95.70%)	1 (4.30%)	0 (0.00%)	0 (0.00%)	23 (100.00%)	
Gender	Male	160 (93.00%)	1 (0.60%)	8 (4.70%)	3 (1.70%)	172 (100.00%)	0.022
	Female	163 (98.20%)	1 (0.60%)	0 (0.00%)	2 (1.20%)	166 (100.00%)	
Clustering Effect	Individual	104 (96.30%)	1 (0.90%)	3 (2.80%)	0.00%	108 (100.00%)	0.628
	With Groups	219 (95.20%)	1 (0.40%)	5 (2.20%)	5 (2.20%)	230 (100.00%)	
Symptoms	Without	69 (98.60%)	0 (0.00%)	0 (0.00%)	1 (1.40%)	70 (100.00%)	0.177
	With	254 (94.80%)	2 (0.70%)	8 (3.00%)	4 (1.50%)	268 (100.00%)	
Comorbidity	Without	246 (98.80%)	0 (0.00%)	2 (0.80%)	1 (0.40%)	249 (100.00%)	0.000
	With	77 (86.50%)	2 (2.20%)	6 (6.70%)	4 (4.50%)	89 (100.00%)	

Table 1: Profile of the patients.

Patients who were 25 years old and below had a recovery rate of 100%, which was the highest among the age categories. The test of significant difference on the level of recovery of the patients yielded a level of significance of p-value of 0.302 for age category, 0.628 for clustering effect and 0.177 for symptoms. Thus, age category, clustering effect and symptoms have no significant effects on the recovery of COVID-19 patients. However, the computed p-value of

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

0.022 for gender and 0.000 for comorbidity significantly showed that gender and co-morbidity can adversely affect the recovery of COVID-19 patients. In the same token, among the different variables in the patients' profile, comorbidity has the most significant effect.

Out of 338 evaluable patients, 268 (79%) presented with symptoms as seen in Table 2.

Symptoms		Number of Patients/% of Patients				*p*-value
		Recovered (n = 323)	Recovering (n = 2)	Long-Hauler (n = 8)	Dead (n = 5)	
Fever	Yes (n = 139)	131 (94.20%)	2 (1.40%)	3 (2.20%)	3 (2.20%)	0.33
	No (n = 199)	192 (96.50%)	0 (0.00%)	5 (2.50%)	2 (1.00%)	
Muscle Pain	Yes (n = 103)	93 (90.30%)	1 (1.00%)	5 (4.90%)	4 (3.90%)	0.002
	No (n = 235)	230 (97.90%)	1 (0.40%)	3 (1.30%)	1 (0.40%)	
Sore Throat	Yes (n = 93)	90 (96.80%)	0 (0.00%)	1 (1.10%)	2 (2.20%)	0.525
	No (n = 245)	233 (95.10%)	2 (0.80%)	7 (2.90%)	3 (1.20%)	
Cough	Yes (n = 155)	146 (94.20%)	2 (1.30%)	4 (2.60%)	3 (1.90%)	0.267
	No (n = 183)	177 (96.70%)	0 (0.00%)	4 (2.20%)	2 (1.10%)	
Colds or Runny Nose	Yes (n = 99)	93 (93.90%)	0 (0.00%)	4 (4.00%)	2 (2.00%)	0.345
	No (n = 239)	230 (96.20%)	2 (0.80%)	4 (1.70%)	3 (1.30%)	
Anosmia	Yes (n = 88)	84 (95.50%)	0 (0.00%)	2 (2.30%)	2 (2.30%)	0.935
	No (n = 250)	239 (95.60%)	2 (0.80%)	6 (2.40%)	3 (1.20%)	
Headache	Yes (n = 104)	95 (91.30%)	1 (1.00%)	4 (3.80%)	4 (3.80%)	0.011
	No (n = 234)	228 (97.40%)	1 (0.40%)	4 (1.70%)	1 (0.40%)	
SOB	Yes (n = 69)	58 (84.10%)	2 (2.90%)	5 (7.20%)	4 (5.80%)	0.000
	No (n = 269)	265 (98.50%)	0 (0.00%)	3 (1.10%)	1 (0.40%)	
Diarrhea	Yes (n = 19)	19 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.334
	No (n = 319)	304 (95.30%)	2 (0.60%)	8 (2.50%)	5 (1.60%)	
Ageusis	Yes (n = 69)	65 (94.20%)	0 (0.00%)	2 (2.90%)	2 (2.90%)	0.522
	No (n = 269)	258 (95.90%)	2 (0.70%)	6 (2.20%)	3 (1.10%)	
Dizziness	Yes (n = 7)	7 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.565
	No (n = 331)	316 (95.50%)	2 (0.60%)	8 (2.40%)	5 (1.50%)	

Table 2: Symptoms of patients with COVID-19 infections.

The most common presenting symptom was cough (146), while dizziness (7) was the least common. Patients presenting with diarrhea and dizziness (100%) had the greatest percentage of recovery, while those with the least chance of recovery (84.1%) were those with shortness

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

of breath (SOB). Aside from SOB (p-value = 0.000), the symptoms with significant effects on recovery are muscle pain (p-value = 0.002) and headache (p-value = 0.011).

Table 3 illustrates the type of medical conditions or comorbidities that the patient had at the time of their COVID infections.

Comorbidity * Outcome		**Number of Patients/% of Patients**				***p*-value**
		Recovered (n = 323)	**Recovering (n = 2)**	**Long-Hauler (n = 8)**	**Dead (n = 5)**	
Hypertension	Yes (n = 65)	55 (84.60%)	2 (3.10%)	5 (7.70%)	3 (4.60%)	0.000
	No (n = 273)	268 (98.20%)	0 (0.00%)	3 (1.10%)	2 (0.70%)	
Asthma	Yes (n = 21)	19 (90.50%)	0 (0.00%)	1 (4.80%)	1 (4.80%)	0.234
	No (n = 317)	304 (95.9%)	2 (0.60%)	7 (2.20%)	4 (1.30%)	
Diabetes	Yes (n = 27)	23 (85.20%)	0 (0.00%)	2 (7.40%)	2 (7.40%)	0.006
	No (n = 311)	300 (96.50%)	2 (0.60%)	6 (1.90%)	3 (1.00%)	
CVS e.g., Ischemia, Arrhythmia	Yes (n = 14)	11 (78.60%)	1 (7.10%)	0 (0.00%)	2 (14.30%)	0.001
	No (n = 324)	312 (96.30%)	1 (0.30%)	8 (2.50%)	3 (0.90%)	
Autoimmune	Yes (n = 1)	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.959
	No (n = 337)	322 (95.50%)	2 (0.60%)	8 (2.40%)	5 (1.50%)	
Overweight	Yes (n = 25)	22 (88.00%)	0 (0.00%)	1 (4.00%)	2 (8.00%)	0.051
	No (n = 313)	301 (96.20)	2 (0.60)	7 (2.20)	3 (1.00)	
Obese	Yes (n = 10)	8 (80.00%)	0 (0.00%)	1 (10.00%)	1 (10.00%)	0.014
	No (n = 328)	315 (96.00%)	2 (0.60%)	7 (2.10%)	4 (1.20%)	

Table 3: Comorbidities or associated medical conditions of patients who consulted for COVID-19 infection.

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

The number of cases per comorbidity is not comparable. Ascertaining which comorbidity has the highest or lowest number of recovered patients is not applicable. The test of significant difference has a computed level of significance with a p-value of 0.234 for asthma, 0.959 for autoimmune disease and 0.051 for overweight. Thus, asthma, autoimmune disease and being overweight have no significant effect on the recovery of COVID-19 patients. On the other hand, the p-values of 0.000 for hypertension, 0.006 for diabetes, 0.001 for cardiovascular diseases (e.g., ischemia, arrhythmia) and 0.014 for obesity imply that these illnesses have significant effects on the recovery from COVID-19.

All patients received IVM in either capsule or tablet form, with a dose ranging from 0.2 mg/kg body weight (kbw) to the highest dose of 1.8 mg/kgbw. Only one patient, a male and 35 years old who presented with shortness of breath and the whole range of respiratory symptoms, received the 1.8 mg/kgbw dose. There were only a few patients given more than 1 mg/kg body weight. The usual recommended dose of 0.2 to 0.4 mg/kgbw was given to those with mild symptoms, while those with moderate symptoms were given doses greater than 0.4 mg/kgbw up to 1.2 mg/kgbw. There were only two sources of IVM for this batch of patients because all of the prescribing physicians are members of an advocate group for early treatment of COVID-19 infections. Both sources were compounded while, towards the end of the study, IVM came from the only drug company that was approved to market it locally. Table 4 shows the test of significant differences according to the dosages of IVM. The test statistics used were Kruskal-Wallis H, also known as one-way ANOVA on ranks, which is a rank-based non-parametric test.

Test Statistics	Computed Value
Kruskal-Wallis H	2.014
df	3
Asymp. Sig.	0.57

Table 4: Test of significant difference on the dosage of IVM.

The computed value for the Kruskal-Wallis H test was 2.014 with a p-value of 0.57, which shows that the dosage of IVM has no significant effect on the recovery of COVID-19 patients. Table 5.0 shows the side effects of IVM according to the different clinical outcomes. Mostly, patients did not experience side-effects from IVM (count = 303) and if they did, the side effects were often dizziness and headache.

Side Effects	Number of Patients/% of Patients				
	Recovered (n = 323)	Recovering (n = 2)	Long-Hauler (n = 8)	Dead (n = 5)	Total
Without	303 (95.30%)	2 (0.60%	8 (2.50%)	5 (1.60%)	318 (100.00%)
Headache	7 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (100.00%)

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

Dizziness	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
Diarrhea	3 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
Blurring Vision	2 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)
Elevated Liver Function	2 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)
Dizziness and Headache	3 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (100.00%)
Dizziness and Diarrhea	2 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)

Table 5: Descriptive statistics of the side effects of IVM.

Table 6 displays the result of the Kruskal-Wallis H computed value of 0.983 and a p-value of 0.805, which is showing that the side effects of IVM have no significant effect on the recovery of COVID-19 patients.

Most patients were either already taking or placed on various types of vitamins and supplements which are believed to be capable of modulating the immune responses against the SARS-Cov2 virus. Table 7 shows the descriptive statistics of the combined immunomodulators according to clinical outcomes while Table 8 shows the statistical test for significant effect of combined immunomodulators on the recovery from COVID-19.

Based on Table 8, the greatest number of patients were prescribed Vitamin C, D and Zinc while a few were given Vitamin C and D alone [2]. The analysis of which combination of immunomodulators has the highest percentage of recovered patients cannot be ascertained as there is no comparable number of cases.

Test Statistics	Computed Value
Kruskal-Wallis H	0.983
df	3
Asymp. Sig.	0.805

Table 6: Kruskal-Wallis Statistics of the side effects of IVM.

Immunomodulators	Number of Patients/% of Patients				
	Recovered (n = 323)	Recovering (n = 2)	Long-Hauler (n = 8)	Dead (n = 5)	Total
Vitamin C	24 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	24 (100.00 %)
Zinc	53 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	53 (100.00 %)
Vitamin C and D	2 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (100.00 %)
Vitamin C, D and Melatonin	17 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	17 (100.00 %)

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

Vitamin C, D, Melatonin and Zinc	58 (98.30 %)	0 (0.00 %)	1 (1.70)	0 (0.00 %)	59 (100.00 %)
C, D and Zinc	116 (92.80 %)	1 (0.80 %)	5 (4.00 %)	3 (2.40 %)	125 (100.00 %)
Vitamin C and Zinc	31 (96.90)	0 (0.00 %)	1 (3.10)	0 (0.00 %)	32 (100.00 %)
Vitamin C, Melatonin and Zinc	21 (84.00)	1 (4.00)	1 (4.00)	2 (8.00)	25 (100.00 %)

Table 7: Descriptive statistics of the combined immunomodulators.

Test Statistics	Computed Value
Kruskal-Wallis H	15.753
df	7
Asymp. Sig.	0.027

Table 8: Kruskal-Wallis Statistics of the combined immunomodulators.

Table 8 reveals the Kruskal-Wallis Statistics of the combined immunomodulators, which shows a computed value of 15.753 and p-value of 0.027. Thus, combined immunomodulators have significant effect on the recovery of COVID-19 patients. This results are compared with the effect from a single immunomodulator shown in Table 9.

Immunomodulator * Outcome		Number of Patients/% of Patients					*p*-value
		Recovered	Recovering	Long-Hauler	Dead	Total	
Vitamin C	Without	26 (100.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	26 (100.00)	0.254
	With	297 (95.20 %)	2 (0.60 %)	8 (2.60 %)	5 (1.60 %)	312 (100.00 %)	
Vitamin D	Without	102 (96.20 %)	1 (0.90 %)	1 (0.90 %)	2 (1.90 %)	106 (100.00 %)	0.694
	With	221 (95.30 %)	1 (0.40 %)	7 (3.00 %)	3 (1.30 %)	232 (100.00 %)	
Melatonin	Without	147 (96.70 %)	1 (0.70 %)	2 (1.30 %)	2 (1.30 %)	152 (100.00 %)	0.356
	With	176 (94.60 %)	1 (0.50 %)	6 (3.20 %)	3 (1.60 %)	186 (100.00 %)	
Zinc	Without	152 (99.30 %)	0 (0.00 %)	1 (0.70 %)	0 (0.00 %)	153 (100.00 %)	0.002
	With	171 (92.40 %)	2 (1.10 %)	7 (3.80 %)	5 (2.70 %)	185 (100.00 %)	

Table 9: Effect of a single immunomodulator on the recovery from COVID-19.

Most of the patients were prescribed Vitamin C (Count = 297) and a lesser number of patients were given Vitamin D (Count = 102).

The Mann-Whitney test of significant difference resulted in a level of significance with a p-value of 0.254 for patients with Vitamin C, 0.694 combined with Vitamin D and 0.356 with Melatonin. Consequently, Vitamin C, Vitamin D and melatonin as immunomodulators have no

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

significant effect on the recovery of COVID-19 patients. But there is a level of significance with a p-value of 0.002 for zinc, indicating that the intake of zinc with IVM by patients with COVID-19 infection has a significant effect on their clinical outcomes.

Discussion

The constraint imposed by the Department of Health and the early misinformation from the Director General of the Philippine Drug Regulatory Agency (FDA) effectively discouraged local physicians from using IVM for the early treatment of COVID-19 [16,17]. On the other hand, conducting randomized clinical trials with a placebo as a comparator was considered unethical, adversarial to the government's COVID control program and a logistical nightmare. Despite our study being ex post factor, important hypotheses can still be generated and a positive trend confirmed existing experiences of other researchers of IVM. Nonetheless, we recommend caution in generalizing the results of the study because of the study's high risk for selection bias and lack of a comparator group.

Until now, the standard of care for COVID-19 has been isolating patients and prescribing supportive treatment until their symptoms have resolved. Hospitalization is advised only when the patient's conditions turn worse. The Greek philosopher Celsus, in the proem to De Medicina, wrote that "the art of medicine should be rational and all doctors aspire to rational prescribing." But doctors forget that "rationality is not the same as appropriate" [18]. Rational prescribing should result in appropriate prescribing, but rational prescribing need not be appropriate. This is best exemplified by the fate that befell IVM, which was disapproved for the early treatment and prevention of COVID-19 infection, allegedly due to the low confidence evidence of its efficacy. This pronouncement was based on the contentious paradigm that randomized clinical trials are the best evidence, if not the only evidence, to prove the efficacy of any intervention, regardless of the potential harm or delay it will cause while being investigated. Our health officials, encouraged by the WHO, prescribed isolation and supportive treatment for COVID-19 cases, believing this is a rational approach to managing the COVID-19 infection. During the Delta variant surge, more COVID-19 cases progressed to the severe state requiring hospitalization. Many patients were reported to succumb to the infection while waiting in the parking lot of our local hospitals for vacancies, an intervention that was neither appropriate nor public health in nature [19].

The purported antiviral property of IVM against the influenza virus, Venezuelan equine encephalitis, dengue fever virus and West Nile virus has been consistently shown in many earlier studies [20-23]. Based on these studies, IVM was regarded as a possible candidate for the treatment of COVID-19 infection. Despite the abundance of evidence for IVM, the country's health officials and alleged experts persisted in pushing for mere isolation and mass vaccination once the vaccines became available. However, it should be more reasonable to just

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

allow low and middle-income countries to explore other countermeasures for the COVID-19 infections that are cheap, equally effective, safe and available due to the high probability that vaccines will be expensive and likely inaccessible for poorer countries with constrained budgets and health delivery systems like the Philippines [24]. The safety profile of IVM is firmly established by its regular inclusion for many years in the WHO Essential Medicine List under "Drugs for Several Parasitic Diseases". This includes the current 21st edition of the WHO electronic Essential Medicine List, updated in June 2019 [23].

The varied doses that doctors used for IVM have always been a subject of criticism, but doses always hovered between 0.2 and 0.4 mg/kgbw until the emergence of the Delta variant in the country [25]. By 2021, local prescribers gained more confidence from their unexpected clinical successes with IVM, even for severe COVID-19 cases. IVM was also shown to improve oxygen saturation as low as 90%. For the most part, physicians in the last months of 2020 prescribed IVM using the conservative dose of 0.150 mg/kg as recommended in the package insert for parasitism and the recommended protocol of the US-based FLCCC [6]. During the Delta surge, local prescribers of IVM started giving doses ranging from 0.5 to 0.8 mg/kgbw for severe cases, which apparently resulted in a faster onset of action and resolution of symptoms. In our study, blurred vision occurred in two patients who received high doses of IVM. The elevated liver function tests manifested by two different patients had no baseline values for comparison. Thus, it is unclear whether the deranged liver function tests were due to the IVM, to the COVID infection itself, or to a pre-existing liver problem. In addition, due to the abundance of medical literature confirming the adverse effects of COVID-19 on the clinical course of patients with comorbidities such as diabetes or obesity, the presence of these illnesses eventually becomes a primary consideration for prescribing higher dosages of IVM [27].

Ironically, the use of face shields was imposed in the country without any strong evidence of their efficacy for preventing transmission of COVID infections except for increasing waste and polluting the environment. Yet, in contrast to IVM, the wearing of face shields was indiscriminately enforced up to the second quarter of 2022. In September 2021, in spite of the draconian measures of lockdowns, compulsory face shields, wide scale COVID-19 immunization and restricting mobility of unvaccinated people, the country continued to have an average daily new cases of COVID of about 18,000 in September of 2021 with a mortality rate of 319.67. In contrast, Vietnam, our nearest neighbor, which did not impose the donning of face shields, had at the same time an average daily new COVID cases of around 14,000 and a mortality rate of 127.93. [28] Currently, the Department of Health of the Philippines reported 1,295 new cases of COVID-19 infections from May 30 to June 5, 2022, of which 16 cases were severe or critical and 1 confirmed death [29].

Our study involved 338 COVID cases treated with oral IVM by 8 clinicians. The clinical outcomes measured were full recovery, recovering, long-term and death after treatment. At the

Citation: Vergeire-Dalmacion GR, et al. The Use of Oral Human Grade Ivermectin with Supplements Known As Immunomodulators for Treating Patients with COVID-19 Infections At Home. J Clin Immunol Microbiol. 2022;3(2):1-16.

DOI: https://doi.org/10.46889/JCIM.2022.3205

end of the study, the test of significance showed that gender (p-value = 0.022) and co-morbidity (p-value = 0.000) have effects on the recovery of COVID-19 patients. Clinically, hypertension, CVS diseases, DM and obesity carry statistically significant effects on the clinical outcomes. The age category, clustering effect and symptoms have no statistically significant effect on the recovery of COVID-19 patients. Nevertheless, SOB (p-value = 0.000), muscle pain (p-value = 0.002) and headache (p-value = 0.01) have significant effects on the recovery of COVID-19 patients. The intake of combination immunomodulators has a significant effect on the recovery of COVD-19 patients at a p-value of 0.027 using Kruskal-Wallis H statistics. Using the Mann-Whitney test for single immunomodulators, zinc showed a p-value of 0.002, which indicates a statistically significant effect of zinc on the recovery from COVID-19 [30-32].

Conclusion

The results of our study revealed the effectiveness of IVM for treating COVID-19 infection provided it is given early and the dose is adjusted based on severity and co-morbidities of cases. Patients' Bill of Rights to information and informed consent must be upheld notwithstanding a pandemic. Our results also suggest that government would fare better in controlling the pandemic by implementing focused protection based on age, gender and co- morbidities. The government should adopt a less myopic and terrified approach to managing the pandemic which includes long term lockdowns in various permutations with artificial effects. Opportunities for use and access to IVM and other drugs with preclinical or clinical evidence of antiviral properties should be allowed for the treatment of COVID infections by competent and licensed physicians. Finally, until a sterilizing vaccine is available, the most promising and cost effective treatment to control the pandemic may be a combination drug therapy with or without vaccines provided there is transparency of information on their benefit to risk ratio.

The graduated dosing of IVM to treat COVID-19 based on severity of symptoms and the predilection of the virus to mutate will prove challenging in designing a randomized clinical trial both ethically, morally and scientifically. A more ethical but scientifically sound paradigm to test the effectiveness of treatments for emerging novel infections is imperative because infections are an imminent threat to the security of the world.

Acknowledgement

I would like to express our gratitude for the moral and technical support of the Concerned Doctors and Citizens of the Philippines (CDC PH) especially to Drs. Sham Quinto, Homer Lim, Miles dela Rosa, Rafaal Castillo, Jade del Mundo, Romeo Quijano and Marivic Villa and the Speaking the Truth in Love; Engrs. Ric Casabuena, Manolo Gonzalez and Drs. Jean Tay, Rhodora Reyes and Ma. Luisa Manlapaz.

Author's contribution

GRVD: Sole author and proponent, conceptualized, designed and created the database for the survey, analyzed the data and wrote majority of the paper.

Glenda Pedrosa: Co-author who helped tremendously in cleaning the data, performing the statistical tests and critically appraising the final paper.

Funding statement

The study did not receive any research grant and was done using personal funds of the proponent.

Competing Interest

I declare no conflict of interest. I and my co-author are not connected with any manufacturer or distributor of Ivermectin.

References

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Bio Medica: Atenei Parmensis 2020;91(1):157.
2. Andersen KG, Rambaut A, Lipkin WI. The proximal origin of SARS-CoV-2. Nature Med. 2020;26(4):450-52.
3. Walls AC, Park YJ, Tortorici MA. Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181(2):281-92.
4. Cahut M. COVID-19 pandemic 2020: The search for a vaccine. Medical News Today. 2020.
5. FDA. COVID-19 Vaccines United States: US Food and Drug Administration. 2021.
6. FLCCC Alliance: Ivermectin in COVID-19. [Last accessed on June 24,2022] https://COVID19criticalcare.com/ivermectin-in-COVID-19/
7. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. *In-vivo*. 2020;34(5):3023-6.
8. Zhang X, Song Y, Ci X. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflammation Res. 2008;57(11):524-9.
9. Caly L, Druce JD, Catton MG. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in-vitro*. Antiviral Res. 2020;178:104787.
10. Okumuş N, Demirtürk N, Çetinkaya RA. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infect Dis. 2021;21(1):1-11.
11. WHO. WHO advises that ivermectin only be used to treat COVID-19 within clinical trials: World Health Organization; 2021 [Last accessed on June 24,2022] https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-COVID-19-within-clinical-trials

12. FDA. Emergency use authorization of medical products and related authorities United States: Food and Drug Administrator; 2017 [Last accessed on June 24,2022] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities#criteria
13. Kow CS, Merchant HA, Mustafa ZU. The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis. Pharmacological Reports. 2021.
14. Ewing ET. Measuring mortality in the pandemics of 1918-19 and 2020-21. Health Affairs Organization. 2021.
15. Cascella M, Rajnik M, Cuomo A. Features, evaluation and treatment coronavirus (COVID-19). Statpearls. 2020.
16. Galvez D DOH. FDA: Recent trials indicate Ivermectin cannot treat COVID-19. Inquirer. 2021.
17. FDA Advisory No.2021-0526. Public health warning on the purchase and use of ivermectin veterinary products for COVID-19. https://www.fda.gov.ph/fda-advisory-no-2021-0526-public-health-warning-on-the-purchase-and-use-of-ivermectin-veterinary-products-for-COVID-19/
18. Aronson J. Rational prescribing, appropriate prescribing. Br J Clin Pharmacol. 2004;57(3):229.
19. Ranada P. Metro manila placed under ECQ from August 6 to 20. Rappler. 2021.
20. Götz V, Magar L, Dornfeld D. Corrigendum: Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Scientific Rep. 2016;6.
21. Lundberg L, Pinkham C, Baer A. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce venezuelan equine encephalitis virus replication. Antiviral Res. 2013;100(3):662-72.
22. Tay M, Fraser JE, Chan W. Nuclear localization of Dengue Virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res. 2013;99(3):301-6.
23. Yang SN, Atkinson SC, Wang C. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020;177:104760.
24. David Williams O, Yung KC, Grépin KA. The failure of private health services: COVID-19 induced crises in Low-and Middle-Income Country (LMIC) health systems. Global Public Health. 2021:1-14.
25. WHO Model List of Essential Medicines-21st list. 2019.
26. American Society of Microbiology. How dangerous is the delta variant? (B.1.617.2)? https://asm.org/Articles/2021/July/How-Dangerous-is-the-Delta-Variant-B-1-617-2
27. Townsend MJ, Kyle TK, Stanford FC. Outcomes of COVID-19: disparities in obesity and by ethnicity/race: Nature Publishing Group. 2020.
28. Ranada P. Metro manila placed under ECQ from August 6 to 20. Rappler. 2021.
29. COVID-19 pandemic: Latest Situation in the Philippines-June 2022. [Last accessed on June 24, 2022] https://www.rappler.com/nation/COVID-19-pandemic-latest-situation-philippines-june-2022
30. WMA. WMA declaration of cordoba on patient-physician relationship: world medical association; 2020. [Last accessed on June 24, 2022] https://www.wma.net/policies-post/wma-declaration-of-cordoba-on-patient-physician-relationship/
31. Nikmatul H. Analisis Survival Terhadap Pasien COVID-19 di Kabupaten Dharmasraya Tahun. 2020. Universitas Andalas. 2021.
32. Baraniuk C. COVID-19: How effective are vaccines against the delta variant? BMJ. 2021;374.