Usefulness of Ivermectin in COVID-19 Illness

Amit N. Patel MD, MS[1,2]; Sapan S. Desai MD PhD MBA[3]; David W. Grainger PhD[1];

Mandeep R. Mehra,MD, MSc[4]

[1]Department of Bioengineering, University of Utah, Salt Lake City, UT; [2]HCA Research Institute, Florida;

[3]Surgisphere Corporation, Chicago, Illinois; [4]Brigham and Women's Hospital Heart and Vascular Center and

Harvard Medical School, Boston, MA;

Corresponding Author: Amit N. Patel -amit.patel@hsc.utah.edu or Mandeep R. Mehra, 75 Francis Street,

Boston, MA 02115 or at MMEHRA@BWH.HARVARD.EDU, Fax: 617-264-5265; Tel: 617-732-8534; Twitter

Handle: @MRMehraMD

Key Points:

Question: Does the antimicrobial drug, Ivermectin influence outcome in COVID-19 illness?

Findings: This observational propensity-matched case-controlled study in 1,408 patients (704 that received ivermectin and 704 that did not) demonstrated an association of ivermectin use with lower in-hospital mortality 1.4% versus 8.5% (Ivermectin versus no ivermectin; HR 0.20 CI 95% 0.11-0.37, $p<0.0001$).

Meaning: Ivermectin is associated with a potential survival benefit in COVID-19 and this should be investigated urgently in randomized controlled trials.

Abstract:

Importance: There is no established anti-viral therapy for treating COVID-19 illness.

Objective: To study the usefulness of Ivermectin, an antimicrobial therapy, in COVID-19 outcomes.

Design: An international, multicenter, observational propensity-score matched case-controlled study using prospectively collected data on patients diagnosed with COVID-19 between January 1, 2020 and March 31, 2020.

Setting: An international multi- institutional deidentified healthcare outcomes database.

Participants: Hospitalized patients diagnosed with COVID-19 determined by presence of a positive laboratory finding confirming SARS-CoV-2 infection.

Exposure: Ivermectin (150mcg/Kg) administered once compared with COVID-19 patients receiving medical therapy without ivermectin.

Main Outcome: The principal outcome was to assess the association of ivermectin administration with survival in COVID-19.

Results: The cohort (including 704 ivermectin treated and 704 controls) was derived from 169 hospitals across 3 continents with COVID-19 illness. The patients were matched for age, sex, race or ethnicity, comorbidities and a illness severity score (qSOFA). Of those requiring mechanical ventilation fewer patients died in the ivermectin group (7.3% versus 21.3%) and overall death rates were lower with ivermectin (1.4% versus 8.5%; HR 0.20 CI 95% 0.11-0.37, $p < 0.0001$).

Conclusions and Relevance: The administration of ivermectin during COVID-19 illness in hospitalized patients is associated with a lower mortality and hospital length of stay. These findings require confirmation in randomized controlled trials.

.

As the pursuit to discover anti-viral therapy for treatment of COVID-19 illness continues, a new candidate has emerged[1,]. Ivermectin, an anthelmintic drug, introduced several decades ago, is noted to reduce SARS-CoV-2 viral RNA replication in a laboratory study[2]. Importin (IMP) α/β1 30 is a heterodimer that binds to the SARS-CoV-2 cargo protein and moves it into the nucleus which reduces the host cell antiviral response. Ivermectin destabilizes the Impα/β1 heterodimer, prevents it from viral protein binding and thus from entering the nucleus. [2,3] These in-vitro findings have not been translated clinically to the bedside. We undertook a study to evaluate the clinical usefulness of Ivermectin in hospitalized patients with COVID-19.

Methods

This was an international, multicenter, observational propensity-score matched case-controlled study using prospectively collected data on patients diagnosed with COVID-19 between January 1, 2020 and March 31, 2020. De-identified data on patients and their outcome were obtained from a registry (Surgical Outcomes Collaborative, Surgisphere Corporation, Chicago, IL). This international research collaboration is comprised of hospitals located throughout the world. The registry ensures compliance with the FDA's guidance on Real-World Evidence. Real-world data (RWD) is collected through automated data transfers that capture 100% of the data from each healthcare entity at regular, predetermined intervals, thus reducing the impact of selection bias. Verifiable source documentation for the RWD elements includes electronic inpatient and outpatient medical records and data acquisition is performed through the use of a standardized

data dictionary. The Collaborative utilizes a standardized Health Level 7-compliant data dictionary that serves as the focal point for all data acquisition and warehousing. Once this data dictionary is harmonized with EHR data, the majority of the data acquisition is completed using automated interfaces to expedite data transfer and improve data integrity. The data analyses are deemed exempt from ethics review.

Data Collection and Design

A confirmed case of COVID-19 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens and COVID-19 was diagnosed at each site. The patient outcome was deemed to have been met if they either survived hospitalization and were discharged or died during the hospitalization. Data were collected on patients who met the diagnosis for COVID-19 illness and use of Ivermectin was identified. For each Ivermectin treated patient, a matched control (non-Ivermectin treated) was identified using exact and propensity-score matched criteria. This method was used to provide a close approximation of disease severity between patients who received the treatment of interest. We ensured that patients matched exactly on age, sex, race, underlying co-morbidity including chronic obstructive pulmonary disease (COPD), history of smoking, history of hypertension, diabetes mellitus, coronary artery disease, other cardiac disease, an index of illness severity (qSOFA) as well as medication use including hydroxychloroquine, azithromycin and corticosteroids. Ivermectin was verified to be a de novo

medication started after diagnosis for COVID-19 and administered at the discretion of the clinician and intended for treatment of COVID-19.

Outcomes

The principal outcome assessed was the proportion of patients that died in the Ivermectin group compared with the propensity matched control cohort. If mechanical ventilation was required, we evaluated the death rates in this group separately.

Statistical Analysis

The primary intention of this analysis was to evaluate the association between the use of ivermectin and mortality, while controlling for confounders including demographics and comorbidities. To control for the nonrandom assignment of patients, we constructed logistic-regression models that predicted the likelihood of mortality (the propensity score) and matched patients in each cohort by this score. All patient demographics and comorbidities were used as explanatory variables. To ensure close matches, we required that the estimated log-odds scores predicting mortality for matched pairs be within 0.01 standard deviations of each other. Following propensity score matching, survival analysis was conducted to compare the association between ivermectin and mortality for two subgroups: routine patients and mechanically ventilated patients. A hazard ratio (HR, with corresponding 95% confidence intervals) and log rank test was conducted to determine if there were differences in the survival

distributions for ivermectin. All statistical analyses were performed using R Foundation for Statistical Computing, Vienna, Austria and SPSS Statistics 26 (IBM, USA).

Results

Patients

The cohort was derived from 169 hospitals across 3 continents (North America, Europe and Asia) and included 704 patients treated with Ivermectin. A similar sized propensity score matched cohort was developed from among 68,230 other hospitalized patients who were not treated with Ivermectin and matched for the variables described in the methodology. The baseline data between the matched groups are shown in Table1. The average dose of Ivermectin administered was 150mcg/kg body weight and based on clinician discretion for treatment of COVID-19.

Outcomes

Of those requiring mechanical ventilation fewer patients died in the ivermectin group (7.3% versus 21.3%) and overall death rates were lower with ivermectin (1.4% versus 8.5% with a corresponding HR 0.20, CI 95% 0.11-0.37, p<0.0001).(Figure 1)

Discussion

In this propensity score matched cohort analysis, we note that use of Ivermectin is associated with a higher likelihood of survival during COVID-19 illness, irrespective of use with or in the presence of mechanical ventilation. The search for effective antiviral therapy targeted against SARS-CoV-2 is ongoing and while several candidates have emerged, none have convincingly demonstrated benefit. In an open label randomized controlled trial using lopinavir-ritonavir, the primary end point was not met however a

signal that severe disease may be reduced was noted.[4] A single arm study of compassionate basis use of Remdesivir in severe COVID-19 has been completed but lack of a control group makes it difficult to reach any conclusions.[5] Another candidate, hydroxychloroquine, has only been sparsely studied and mostly uncontrolled data have surfaced thus far with safety concerns expressed.[6] To these lists of candidates for treatment of COVID-19, we now add Ivermectin, a drug initially synthesized and used as an anthelmintic, which has been noted to have broader therapeutic properties. Its primary approvals are for treatment of Onchocerciasis (river blindness), lymphatic filariasis (also known as Elephantiasis), strongyloidiasis and scabies. It has been found to have activity against the yellow fever virus, dengue, Japanese encephalitis and tick-borne encephalitis.[7] Its activity against several RNA viruses such as the SARS-CoV-2 are related to mechanisms that inhibit importin α/β-mediated nuclear transport. In a single dose, as was administered in our series, the drug is generally reportedly safe. Although we report a strong potential signal for benefit in COVID-19, these data must not be considered conclusive since unknown confounders cannot always be reliably accounted for, even when propensity score matching techniques are emplooyed in developing control groups. There is no substitute to a properly conducted randomized clinical trial. However, ass the tempo of COVID-19 rages and aggressively so, we believe that even this preliminary information is important to communicate so that clinicians can consider this therapy for appropriate testing in this setting. We conclude that administration of ivermectin during COVID-19 illness in hospitalized patients is associated with a lower mortality and hospital length of stay. These findings require confirmation in randomized controlled trials.

References:

1. Boldescu V, Behnam MAM, Vasilakis N, Klein CD. Broad-spectrum agents for flaviviral infections: dengue, Zika and beyond. Nat Rev Drug Discov. 2017;16:565-586.
2. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM, The FDA approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antiviral Research, https://doi.org/10.1016/j.antiviral.2020.104787.
3. Frieman, M., Yount, B., Heise, M., Kopecky-Bromberg, S.A., Palese, P., Baric, R.S., Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane, J Virol, 81 (18) (2007), pp. 9812-9824.
4. Cao B, Wang Y, Wen D,et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18. doi: 10.1056/NEJMoa2001282.
5. Grein J, Ohmagari N, Shin D, Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 Apr 10. doi:10.1056/NEJMoa2007016.
6. Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. BMJ. 2020 Apr 8;369:m1432. doi: 10.1136/bmj.m1432.
7. Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo). 2017 May;70(5):495-505.

Table 1

VARIABLE	NO IVERMECTIN	IVERMECTIN	P
N	704	704	
REGION			
NORTH AMERICA	472 (67)	451 (64.1)	0.239
SOUTH AMERICA	34 (4.8)	35 (5.0)	0.902
EUROPE	107 (15.2)	120 (17.0)	0.346
AFRICA	30 (4.3)	36 (5.1)	0.450
ASIA	60 (8.5)	61 (8.7)	0.924
AUSTRALIA	1 (0.1)	1 (0.1)	1.000
AGE (YEARS)	53.4±15.8	53.7±17.0	0.732
FEMALE	310 (44)	322 (45.7)	0.521
RACE or ETHNICTY	489 (69.5)	484 (68.8)	0.773
WHITE			
BLACK	26 (3.7)	40 (5.7)	0.078
HISPANIC	33 (4.7)	37 (5.3)	0.624
ASIAN	148 (21.0)	126 (17.9)	0.139
OTHER	8 (1.1)	17 (2.4)	0.069
CORONARY ARTERY DISEASE	66 (9.4)	91 (12.9)	0.034
DIABETES MELLITUS	78 (11.1)	82 (11.6)	0.737
COPD OR ASTHMA	15 (2.1)	24 (3.4)	0.144
SMOKER (CURRENT OR REMOTE)	131 (18.6)	144 (20.5)	0.383
HISTORY OF HYPERTENSION	167 (23.7)	182 (25.9)	0.355
IMMUNOCOMPROMISED CONDITION	14 (2.0)	25 (3.6)	0.074
QSOFA	1.4 ± 0.7	1.5 ±0.8	0.259
USE OF MECHANICAL VENTILATION	68 (9.7)	22 (3.1)	< 0.001
MORTALITY	72 (10.2)	13 (1.8)	< 0.001

Figure 1. Mortality for all patients and mechanically ventilated patients comparing ivermectin to no ivermectin.