Cover Letter

Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management

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Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19 with significant public health impact (1). Several therapeutic agents have been evaluated for the treatment of Covid-19, however, none have yet been shown to be effective (2,3)

Recently some reports on HCQ [4-6], Azithromycin [7] and Ivermectin [8] have shown therapeutic effects against novel coronavirus infection.

Ivermectin is an antiparasitic drug with a broad spectrum antiviral effect (9). Recently, in vitro study showed reduction of viral RNA in Vero-hSLAM cells 2 hours postinfection with SARS-CoV-2 clinical isolate Australia/VIC01/2020 (8). The authors hypothesized that the effect was likely due to the inhibition of IMP α/β1- mediated nuclear import of viral proteins.

Because of the broad spectral antiviral activities of IVM and it is safety profile, It may offer a therapeutic potential to COVID-19. This study was designed to assess effectiveness and safety of add-on use of IVM to HCQ and AZT in COVID 19 patients.

Patients and Methods

Study design

This pilot interventional single center study with a synthetic controlled arm (SCA) was conducted at Al-Shifa'a Hospital Center from first of April to the end of May 2020. Synthetic controlled arm was used due to difficulty of using placebo for our patients and the strong preference for the investigational product in this pandemic Covid-19 disease to improve drug development and reduce patients burden. SCA is an external control constructed from patient-level data from previous patients records to match the baseline characteristics of the patients in an investigational group and augment a single-arm trial to estimate treatment effects. The SCA in this

trial included previous patients who were treated by HCQ and AZT according to the Iraqi Ministry of Health protocols for treatment of covid-19.

Ethical approval of the study was taken in accordance with the Declaration of Helsinki and its amendments and the Guidelines for Good Clinical Practices issued by the Committee of Propriety Medicinal Product of the European Union from Iraqi ministry of health and the study was registered with No. 497 at April 2020. Also, this study was registered in ClinicalTrials.gov website under identifier number: NCT04343092. Informed consent was obtained from the participants to admit the study.

Participants

Inclusion criteria

Inclusion criteria were the following: 1) men and women with age at least 18 years 2) mild to moderate COVID-19 diagnosed by positive polymerase chain reaction (PCR) testing <=3 days from enrollment 3)Patient acceptance and willingness to comply with planned study procedures and to complete the follow up. 4) hospital admission 5) no participation in other clinical trials, such as antiviral trials, during the study period. 6) Able to provide informed consent

Mild and moderate COVID-19 were defined according to World Health Organization (WHO) interim guidance (16). Mild COVID-19 was defined as symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. The symptoms included: fever, cough, fatigue, anorexia, shortness of breath, myalgias. Other non specific symptoms such as soar throat, nasal congestion, headache, diarrhea nausea, vomiting, loss of smell, loss of taste, Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, and absence of fever. Moderate COVID-19: included adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 $\geq$ 90% on room air.

Exclusion criteria

Exclusion criteria were the following: 1) severe COVID-19 defined as respiratory distress ($\geq$30 breaths/min; in resting state, oxygen saturation of 93% or less on room air; or arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) of 300 or less. 2) Life threatening COVID-19 was defined as

respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring. 3) hypersensitivity or severe adverse events to IVM, 4) Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) 4) pregnancy 5) breast feeding.
6) history of severe asthma.

Intervention

Patients received IVM 200 Mcg single dose at the admission day as add on therapy to Iraqi Ministry of Health protocol for treatment of mild to moderate COVID-19 [HCQ 400mg BID for the first day then 200mg BID for 5 days plus AZT 500mg single dose in the first day then 250mg for 5 days]. We evaluated these patients for cure by clinical assessment and PCR swab testing. Nasopharyngeal or oropharyngeal swabs specimens were collected on days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 , and 23 for viral RNA detection and quantification till two successive days of negative PCR swab testing at least 24hrours apart. Virological testing was done at Alshifa'a Hospital Laboratory Center using ABI 7500Dx Real-Time PCR System instruments (Applied Biosystems), USA.

Outcomes

The primary outcome was percentage of the cured patients within 23 days. Cure of the patients was defined by assessing proportion of patients who were symptoms free to be discharged from the hospital and included body temperature returned to normal for longer than 3 days, respiratory symptoms significantly improved, and 2 consecutive negative PCR test results from nasopharyngeal swabs at least 24 hours apart. The secondary outcomes were time to cure in both groups. Time to cure is evaluated by measuring time from admission of the patient to the hospital till discharge after being free of symptoms and negative PCR swab. Once nasopharyngeal and oropharyngeal swab viral PCR testing yielded negative results 2 times consecutively, no further testing was performed. Also safety outcomes included treatment-emergent adverse events, serious adverse events, and premature discontinuations of study were recorded if present.

Sampling method and sample size calculation

A convenient consecutive sample of patients were enrolled in the study. The sample size calculated for this pilot trial was 30 patients : 15 in the active arm (IVM group) and 15 in the controls (SCA) according to pilot study sample size rule of thumb to get medium effect size of $0.3 \leq \delta/\sigma < 0.7$ with a statistical power of 90%. (17)

Statistical analysis

Statistical analysis was done using R packages software for IOS. The normality of continuous variables was analyzed using Shapiro Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) if were normally distributed and median (interquartile range) if not normally distributed. Categorical variables were presented as number and percentages. Difference between normally distributed continuous variables was measured using Student's t-test and Mann-Whitney U test if not normally distributed. Difference between categorical variables was evaluated by Chi square test. Effect size for non normally distributed variables was measured using Vargha and Delany A test. Kaplan Meier survival curve analysis with and log rank testing was used. The standardized mean difference effect size is small if value 0.2- 0.5; medium if value 0.5-0.8, and large effect size if value 0.8-1.4 P value less than 0.05 was considered statistically significant.

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