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Effectiveness of VIUSID® and ASBRIP® in Hospitalized Patients Infected by SARS-CoV-2 and Mild-to-Moderate Respiratory Illness. An Observational Prospective Study

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Abstract

Background: The emerging SARS-CoV-2 infection has been associated with moderate and severe disease in patients with a weaker cellular immunity which might result in prolonged period of hospitalizations. Viusid® has shown recognized immunoregulator properties, including an important modulation on IFN-δ, TNF-α, IL-1β and IL-6 levels in patients with infectious diseases. Our observational study was aimed to evaluate the effectiveness of Viusid® along with Asbrip®, an upper respiratory antiseptic, in patients with mild to moderate symptoms related with SARS-COV-2 infection.

Methods: An observational study was conducted to evaluate the efficacy of Viusid and Asbrip® in patients with mild to moderate symptoms of respiratory disease caused by the emerging SARS-CoV-2 infection in 2019 at the Teodoro Maldonado Carbo University Hospital in Guayaquil, Ecuador. A total of 53 subjects were enrolled in our observational study. Of them, 44 were non-responders to the protocolized standard therapy for 46 ± 23 days. All of them received the protocolized standard therapy along with Viusid® 30 ml and Asbrip® 10 ml every 8 h for 21 days and assessed clinically until the hospital discharge.

Results: The results of the trial show that non-responders to the protocolized COVID-19 therapy patients taking Viusid® and Asbrip® experienced a significant improvement in their symptoms over a relatively shorter period of time. The average length of stay in the hospital with no changes was reduced once they were assigned to Viusid® and Asbrip® (15 ± 5 days). New hospitalizations were protocolized with the adjuvant therapy with an average length of stay in the hospital of 14 ± 6 days.

Conclusions: Viusid® in conjunction with Asbrip® might reduce the length of patient hospitalization in patients with SARS-COV-2 infection.

Keywords: COVID-19 • Immunomodulator • Glycyrrhizic Acid • Supportive Care • Length of stay

Abbreviations: ALT/AST: Alanine Aminotransferase/ Aspartate Aminotransferase Ards: Acute Respiratory Distress Syndrome; CRP: C-Reactive Protein; HIV-1: Human Immunodeficiency Virus Type 1; ICU: Intensive Care Unit; IFN-δ: Interferon Gamma; IL-6: Interleukin 6; IL-1β: Interleukin 1 Beta; IL-10: Interleukin 10; RT-PCR: Reverse Transcription Polymerase Chain Reaction; SARS: Severe Acute Respiratory Syndrome; TLR: Toll-Like Receptor; TNF-α: Tumor Necrosis Factor Alpha; WHO: World Health Organization

Introduction

Over the course of the pandemic, the treatment protocol for patients with COVID-19 evolved and became more specialized as the mechanisms of pathogenesis became apparent [1,2] and based on comorbidities of the infected patients [3-5]. One of the main questions has been how the immune system of those infected responds to SARS-CoV-2 and what differences lie between those with COVID-19-associated symptoms and those who are asymptomatic [6].

Different studies have described immunological differentiation between respondent patients and those who have subsequently perished, highlighting among other factors a lymphocyte deficit, as well as a decrease in the cellular immune response in the initial phase of viraemia based on CD3+, CD4+ and CD8+ or an increase in C-Reactive Protein (CRP) levels [7-10] in patients with a poorer prognosis, extending the length of patient hospitalization in moderate to severe phases of the disease [11-14]. The possible long- term effects from the disease post-recovery, such as potential neurological, cardiovascular or hematological side effects, are not yet fully established, given the prolonged use of the drugs administered during treatment and the complications of the disease itself, such as renal failure or cardiovascular disorders [15-17].

Immunomodulatory and immunosuppressive therapies are playing a key role in the development of early cellular immune response [18], as well as in the regulation of alterations in inflammatory response, cell infiltration or platelet dysfunction and coagulation [19] within COVID-19 therapies.

The use of oral and/or nasal antiseptics has been studied in patients with COVID- 19, with good results in prevention and control of the viral load [20, 21]. Therefore, Asbrip® (*Catalysis S.L.,* Spain; **Table 1**) may have benefits in the control of SARS-CoV- 2 infections as an antiseptic, antitussive and expectorant.

Viusid® (*Catalysis S.L., Spain;* **Table 2**), has been described as an antioxidant, antiviral, immunomodulator and hepatoprotector used to treat different pathologies with alterations in the immune response, overproduction of cytokines and proinflammatory interferons, especially in patients with COVID-19, liver damage and hematological alterations such as anemia [22-26].

Viusid® contains glycyrrhizinic acid as one of its main ingredients, which has

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Table 1. Composition of Asbrip®.

Composition	Concentration (mg/100 ml)
Malic acid	2,000
Carnitine L-Fumarate	1,000
Vitamin C (L-Ascorbic acid)	200
Eucalyptus Oil (*Eucalyptus globulus Labill.*)	100
Sodium benzoate	100
Potassium sorbate	100
Mint flavor	25
Water qsp	100 ml

Table 2. Composition of Viusid® oral solution.

Composition	Concentration (mg/30 ml)
Glucosamine sulphate Potassium chloride	600
L-Arginine	600
Malic acid	600
L-Glycine	300
Licorice extract (*Glycyrrhiza Glabra L.*).	30
Sodium benzoate	30
Potassium sorbate	30
Vitamin C (L-Ascorbic acid)	18
Lemon flavor	15
Sucralose	7.2
Zinc sulphate	4.5
Pantothenic acid (D-Calcium Pantothenate)	1.8
Vitamin B6 (Pyridoxine Hydrochloride)	0.6
Folic Acid (Pteroylmonoglutamic Acid)	60 µg
Vitamin B12 (Cyanocobalamin)	0.3 µg
Water sqp.	30 ml

been described as an antiviral molecule [27-30] and an immune response modulator through the inhibition of prostaglandin E2 in tissue damage [31], a TLR4 and TLR2 expression modulator by disruption of lipid rafting [32-34], and an inhibitor of hyperphosphorylation of the SRC family of protein kinases [35,36] during replication of different virus families [37,38]. Given these properties and mechanisms of action described above, glycyrrhizinic acid has been a target molecule for application in COVID-19 as part of stabilization therapy and patient treatment [39-45]. Viusid also contains zinc, which has antiviral properties by stimulating the cellular immune response and regulating the inflammatory response [46-48] which is of special interest in respiratory infections thanks to the maintenance of the respiratory epithelium [49] such as COVID-19 [50-52] where regulation of viral replication has also been observed by inhibiting SARS-CoV RNA polymerase [53-55].

Therefore, we sought to explore the clinical effectiveness of Viusid® and Asbrip® in COVID-19 hospitalized patients who had mild to moderate respiratory illness.

Materials and Methods

Trial products

Asbrip® (Table 1) *and Viusid*® (Table 2), both formulated and produced by Catalysis S.L. in Spain, were the products tested. Both were donated to the Hospital de Especialidades Teodoro Maldonado Carbo by Jaspharm Cia. LTDA.

Test subjects

A total of 56 patients diagnosed with COVID-19 in the province of Guayas and non-responders to the standard therapy for Covid-19 were included in the study according to the following criteria:

Inclusion criteria:

1. Patients ≥ 18 years of age and both sexes.
2. Subjects with mild to moderate symptoms of respiratory disease caused by coronavirus 2019 infection, as defined below: mild illness (no complications).
3. Diagnosed with COVID-19 by standardized RT-PCR test and mild symptoms characteristic of the disease, such as fever, runny nose, mild cough, sore throat, malaise, headache, muscle pain or discomfort, but no difficulty breathing and no signs of more severe lower airway illness.

Exclusion criteria:

1. Subjects showing signs of Acute Respiratory Distress Syndrome (ARDS) or respiratory failure requiring mechanical ventilation at the time of examination.
2. History of severe chronic respiratory disease and need for long-term oxygen therapy.
3. Subjects who showed signs of clinical jaundice at the time of the examination.
4. History of moderate and severe liver disease (Child-Pugh score >12)
5. History of uncontrolled diabetes.
6. History of severe chronic kidney disease or those requiring dialysis.
7. Any uncontrolled active systemic infection requiring admission to an Intensive Care Unit (ICU).
8. Patients with malignant tumors or other serious systemic diseases.
9. Patients participating in other clinical trials.
10. Patients with a history of allergic reactions attributed to chemically or biologically similar compounds to Viusid or Asbrip did not qualify.
11. Patients unable to give informed consent or to comply with test requirements. Informed consent was explained in detail, accepted, and signed by those involved in this study.

For the study purposes, subjects infected with HIV-1 were eligible for the study if their viral load was undetectable and they were on a stable antiretroviral regimen. Researchers were required to review the subjects' medical records to confirm suppression of HIV-1 RNA within the past 3 months. In addition, empirical antibiotic treatment for secondary bacterial infections was permitted during the study. No pregnant women were included and those of childbearing age were verified to be either abstinent or using a contraceptive method.

Treatment plan

The treatment regimen for the trial was as standardized by the Ecuador Ministry of Health in accordance with the WHO, for patients diagnosed with COVID-19, based on the phase of the disease [59]. For this purpose, a patient's medical history was retrieved that included all symptoms and signs related with COVID-19 infection. Drugs used in different clinical and preclinical trials such as corticosteroids, anti-inflammatories, anticoagulants or antithrombotics, antibiotics and antivirals were used within the standard protocol. In this study standard therapy was considered for the conventional treatment paracetamol 1gr every 8 h; Acetyl cysteine 200 mg every 8 h; Azithromycin 500 mg every 8 h; and dexamethasone 8 mg per day administered for 3 days for moderate dyspnea.

Furthermore, trial patients received 30 ml of Viusid® and 10 ml of Asbrip® orally every 8 hours for 21 days.

RT-PCR analysis

All patients with suspected infections had upper respiratory throat swab samples taken at admission, which were then shipped to designated

authorized laboratories to detect the SARS-CoV-2. Nasopharyngeal swabs samples were vortexed and centrifuged at 250×g for 10 min. SARS-CoV-2 RT-PCR tests were performed on days 1, 7, 14 and 21 from the beginning of the treatment or for longer if the patient continued with a positive result. Patients only returned home when nucleic acid tests were negative on both respiratory tract samples during isolation.

Measurements

Demographics variables as age, gender, and initial clinical symptoms and vital signs were measured on the first day of admission. The symptoms associated with COVID-19 were systematically evaluated during the trial period by means of an assessment test on each patient in both groups. Assessed symptoms consisted of fever, tiredness, cough, mild dyspnea, moderate dyspnea, anosmia and dysgeusia. They were evaluated according to whether they presented the symptom (1) or not (2).

Differences in duration of hospitalization, number of patients whose condition deteriorated and required ICU admission, length of ICU stay, mortality rate and results of the 21-day follow-up after discharge were also evaluated as outcome measures.

Safety

Possible adverse events associated with Viusid® and Asbrip® were systematically monitored during the trial period by means of an assessment test on each patient in the intervention group. Assessed symptoms consisted of palpitations, tachycardia, sickness, heartburn, diarrhea, dizziness, insomnia, nervousness, and/or others. They were evaluated according to whether they presented the adverse event (1) or not (2).

Statistical analysis

The baseline characteristics were summarized as percentages for categorical variables and as mean ± SE for continuous variables. The $\chi 2$ test was applied to categorical variables. The two-sample *t*-test was used to compare means, and the Mann-Whitney *U*- test if they were not normally distributed. All confidence intervals, significance tests, and resulting P values were two-sided, with an alpha level of 0.05. Statistical analyses were performed using SPSS Inc. for Windows, release 20, Chicago, IL.

Ethical appropriateness

At the time the trial was designed, the regulations did not contemplate a review by an Human Research Ethics Committee (HREC), as it is a natural product (not biological / not drug). It was approved by the Research Coordination and the highest authority of the hospital in charge of the General Management at the *Hospital de Especialidades Teodoro Maldonado Carbo*, in Guayaquil (Ecuador). Other elements that complete the rigor of the study such as informed consent, monitoring, and statistical analysis were complied with in accordance with current regulations. Patients were informed of monitoring methods before providing written consent, and data were collected and anonymized for analysis.

Results

All patients received standard treatment, including paracetamol, azithromycin, chloroquine, corticoids, NSAIDs and assisted ventilation. Since the clinical symptomatology continued and RT-PCR tests for SARS-CoV-2 were positive, they were included in the trial.

Patients received the protocolized standard therapy with Viusid® and Asbrip® study products. Patients ranged from 25 to 97 years of age.

45 of 56 patients were non-responders to the standard therapy, hospitalized for 47 ± 22 days with no improvement in the stage of the disease or the symptoms associated with COVID-19.

Effect of Viusid plus Asbrip on regression of COVID-19

Daily controls were conducted with ongoing monitoring of the trial patients. The results for clinical symptomatologic indicators such as fever, cough, fatigue, dyspnea, anosmia or ageusia were determined as 1 if the patient presented the symptom or 2 if the patient did not present the symptom.

By the end of the 21-day follow up, 100% of patients tested negative for SARS-CoV- 2 RT-PCR.

The progression of the characteristic Covid-19 symptoms was analyzed in the intervention group, observing a significant improvement in each one **(Figure 1)** from enrollment to 21 days of treatment. Some patients experienced

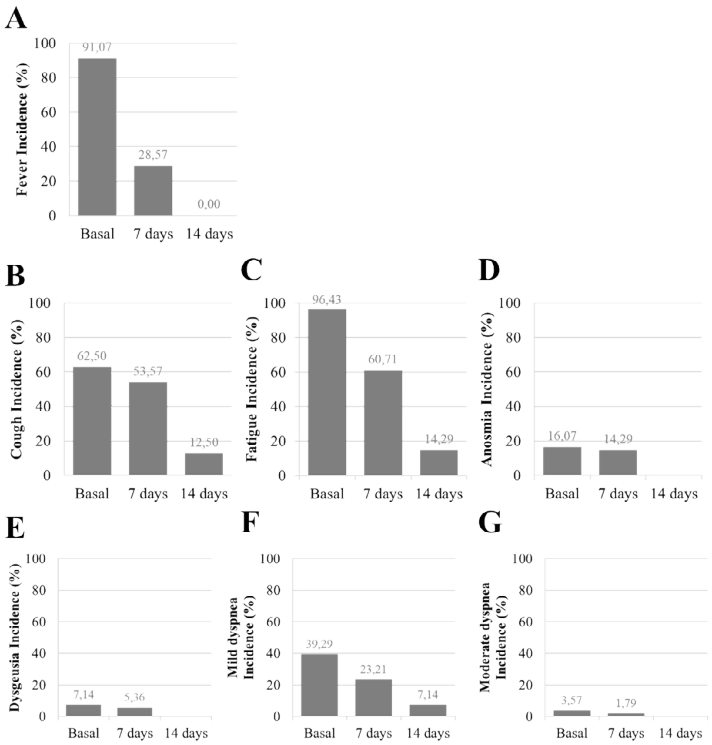

Figure 1. Progression of COVID-19 symptoms in patients in the Viusid® and Asbrip® clinical trial intervention group. The progression of fever (A); cough (B); fatigue (C); anosmia (D); dysgeusia (E); mild (F) and moderate dyspnea (G); were described, with the percentage of patients presenting the symptom in grey. Consultations were carried out on days 0, 7 and 14 of treatment.

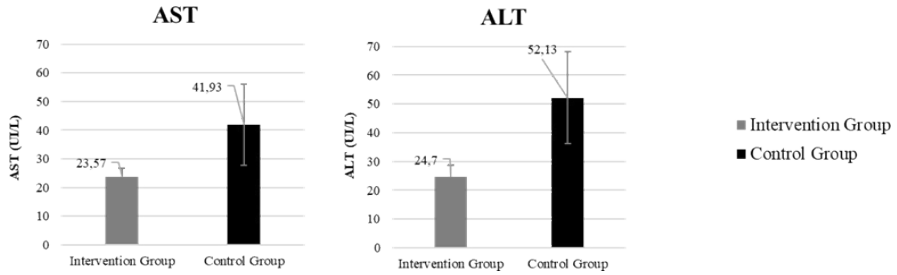

Figure 2. Biochemical profile of COVID-19 patients 30-days post-recovery. The treatment group appears in grey and the historical group in black.

persistent cough (12.50%), fatigue (14.29%) and mild dyspnea (7.14%) with negative RT-PCR for Covid-19.

Progression of the time spent in hospital by COVID-19 patients

One of the critical aspects which showed up in the pandemic refers to the saturation of heath resources in Hospitals by the incoming of COVID-19 patients. That circumstance represented a bottleneck along the first wave of the pandemic and is becoming progressively relevant along the second wave, especially in certain European countries. As a decrease in hospitalization time may favor the overall management of the pandemic, one of the objectives of the study was the evaluation of the intervention treatment with Viusid and Asbrip on hospitalization time. Hospitalization periods for COVID-19 non- responders to the therapy patients in the Viusid® and Asbrip® intervention group was 15 ± 5 days after 46 ± 23 days receiving standard treatment without the use of coadjuvants with no response. Concerning the new hospitalized patients that received the adjuvant therapy from the hospitalization day, they were hospitalized for 14 ± 6 days.

Analysis of biochemical parameters in COVID-19 patients

A biochemical analysis was performed on both trial patient groups 1-month post- recovery, establishing liver function by ALT/AST, creatinine, ferritin, and fibrinogen levels. Only significant differences were observed for ALT/AST levels (**Figure 2**) within the normal range (10 U/L to 34 U/L; 8 U/L to 37 U/L respectively), significantly lower than those in the historical group from the hospital who exceeded the normal range.

Discussion

The results of this study showed that the Viusid® and Asbrip® intervention products were safe since they did not show significant alterations in biochemical laboratory parameters (hematic biometry, liver enzymes, renal function, metabolic parameters) or adverse effects, in trial patients undergoing treatment, with morbidities or in healthy individuals receiving preventive care. Nor did they show negative interaction with the drugs used in the established protocol for COVID-19 patients.

In the results, the shortened hospital stays of SARS-CoV-2 infected patients are noteworthy, which is significantly lower in the Viusid® and Asbrip® coadjutant treatment group. This appears to underline the benefit of immunomodulators and oral antiseptics within the protocols for treating COVID-19. More patients would be advisable in order to verify these results with Viusid® and Asbrip®. Therefore, further studies are required to reinforce the data presented here, which indicate, to improve hospitalization time, in-patient hospital turnover, reduce toxicity associated with the standard protocols, facilitating the recovery and reduce the cost of treatment.

It should be noted that the trial group at the time of selection had already spent several weeks receiving treatment with no response neither improvement.

Conclusions

The presented phase II study indicates that Viusid® and Asbrip® intervention products are safe and effective in the treatment of patients with COVID-19. Safety was demonstrated via the absence of both clinical and biochemical side effects, while clinical efficacy stems from shortened in-hospital stays.

Author's contribution

Guarantor of the article: Please include here the full name of the MD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Wilson I. Benites

Specific author contributions: All authors made substantial contributions to the intellectual content of the paper and approved the final version of the manuscript.

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Potential conflict of interests

The authors whose names are listed immediately below certify that they have no affiliations with/or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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