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VIUSID AND ASBRIP COMBINATION VERSUS REMDESIVIR IN THE MANAGEMENT OF MILD-TO-MODERATE COVID-19

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Аннотация. Пандемия COVID-19 поставила перед здравоохранением всех стран мира актуальную задачу по созданию эффективных лечебно-профилактических подходов против новой коронавирусной инфекции. Появляется все больше свидетельств того, что некоторые компоненты растительного происхождения могут обладать активностью против SARS-CoV-2. Цель настоящего исследования состояла в том, чтобы оценить эффективность комбинации Виусида (основной ингредиент — глицирризиновая кислота) и Асбрипа (основной ингредиент — масло эвкалипта) по сравнению с Ремдесивиром у пациентов с COVID-19 легкой и средней степени тяжести. В многоцентровое открытое рандомизированное исследование включены 80 госпитализированных пациентов. Было три группы лечения: Виусид и Асбрип (V+A); Ремдесивир и V+A (COMBO) и Ремдесивир (REM). Первичным показателем исхода была продолжительность пребывания в стационаре. К концу госпитализации были обнаружены значительные различия между группами лечения, включая продолжительность пребывания в стационаре 10,1 [8,76–11,4], 11,3 [9,31–13,3], 12,9 [11,8–13,9] для V+A, Combo и REM, соответственно (V+A vs Combo p = 1,0, V+A vs REM p = 0,004 и Combo vs REM p = 0,018), лихорадка во время пребывания в стационаре 2,56 [1,92-3,20], 2,80 [2,15-3,45], 3,97 [3,23–4,70] для V+A, Combo и REM, соответственно (V+A vs Combo p = 1,0, V+A vs REM p = 0,022 и Combo vs REM p = 0,053). Кроме того, были обнаружены различия в некоторых маркерах воспаления, что отражает цитокиновый шторм при COVID-19. Препараты растительного происхождения «Виусид» и «Асбрип» продемонстрировали эффективность при легкой и средней степени тяжести COVID-19 и могут использоваться в качестве лечения у таких пациентов. Несмотря на то, что полученные результаты выглядят многообещающе, необходимы дальнейшие более масштабные исследования Виусида и Асбрипа, чтобы поддержать их более широкое использование для лечения COVID-19.

Ключевые слова: виусид, асбрип, ремдесивир, коронавирус, COVID-19

Abstract. The COVID-19 pandemic has posed an urgent task for public health in all countries of the world to create effective therapeutic and prophylactic approaches against a new coronavirus infection. There is growing evidence that some plant-origin components may have activity against SARS-CoV-2. The aim of the present study was to evaluate the efficacy of Viusid (the main ingredient is Glycyrrhizinic Acid) and Asbrip (the main ingredient is Eucalyptus oil) combination compared to Remdesivir in patients with mild-to-moderate COVID-19. 80 hospitalized patients were included into the multicenter open label randomized study. There were three treatment arms: Viusid and Asbrip (V+A); Remdesivir and V+A (COMBO) and Remdesivir (REM). The primary outcome measure was the length of hospital stay. By the end of the hospitalization, there were significant differences found between the treatment arms including the length of hospital stay 10.1 [8.76-11.4], 11.3 [9.31-13.3], 12.9 [11.8-13.9] for V+A, Combo and REM, respectively (V+A vs Combo p = 1,0, V+A vs REM p = 0.004 and Combo vs REM p = 0.018), fever during hospital stay 2.56 [1.92-3.20], 2.80 [2.15-3.45], 3.97 [3.23-4.70] for V+A, Combo and REM, respectively (V+A vs Combo p = 1.0, V+A vs REM p = 0.022 and Combo vs REM p = 0.053). In addition, there were differences in some inflammatory markers, which reflects a cytokine

storm in COVID-19. Viusid and Asbrip plant-derived products demonstrated effectiveness in mild-to-moderate COVID-19 and may be used as a regimen in such patients. Even though the obtained results look promising, further larger studies of Viusid and Asbrip are required to support their wider use for COVID-19 treatment.

Abbreviations: GA - Glycyrrhizinic Acid

Keywords: viusid, asbrip, remdesivir, coronavirus, COVID-19

Introduction. The infection caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) continues its march around the globe. As of March 2022, the COVID-19 pandemic has infected more than 474 million people and killed over 6.1 million since its onset at the end of 2019 (1). Kazakhstan accounts for more than 1.304 million cases of COVID-19 and 13.6 thousand deaths (March 23, 2022) (2).

Coronaviruses of the Coronaviridae family, which occur in the human population and cause acute respiratory infections, periodically cause outbreaks of severe infections, in particular a severe acute respiratory syndrome (causative agent - SARS-CoV) or the Middle East respiratory syndrome (the causative agent - MERS-CoV). The new coronavirus SARS-CoV-2, a member of the Betacoronavirus family, can transmit very quickly from people to people compared to its predecessors SARS-CoV and MERS-CoV, and the lethality of this virus greatly exceeds that of the influenza virus (3).

This pandemic has posed an urgent task for public health in all countries of the world to create effective therapeutic and prophylactic drugs against the new coronavirus infection. Despite some vaccines are available, there is a need in new therapy options for COVID-19. These options should possess not only the antiviral properties but have anti-inflammatory activity because of the cytokine storm caused by SARS-CoV-2. SARS-CoV-2 – associated cytokine storm is considered to be associated with COVID-19 severity and the leading cause of death (4). The only drug officially approved for use for COVID-19 treatment in Kazakhstan is Remdesivir (REM), but it is indicated for severe and critical disease and, as it has been shown, provides benefits not to all patients with some inconsistency in clinical trials results (5). There is growing evidence that some plant-origin components may have activity against SARS-CoV-2 (6,7). Among them is Licorice derived Glycyrrhizinic Acid (GA) that may inhibit inflammatory pathways in COVID-19 (8), featuring inhibitory activity against virus spike protein (9). Another candidate is Eucaliptus oil (eucaliptol) that can bind the virus main protease (10).

Recently, it has been shown that combination of Viusid (the main ingredient is GA) and Asbrip (the main ingredient is Eucalyptus oil) could decrease the length of hospital stay and improve the recovery rate in COVID-19 patients (11,12). The aim of the present study was to evaluate the efficacy of Viusid and Asbrip combination compared to Remdesivir in patients with mild-to-moderate COVID-19.

Materials and methods. Study population. The eligibility criteria for inclusion into the study were as follows: male and female hospitalized patients who had signed an informed consent, aged 18-85 years, with RT-PCR confirmed COVID-19, fever, CT-scan percentage area of lung involvement with ground-glass opacities <50, respiratory rate <20–30/min, SpO2 ≥95%. The exclusion criteria were as follows: oxygen support (ventilation and non-invasive), no previous use of Remdesivir, Viusid and Asbrip, uncompensated or exacerbated concomitant diseases or conditions that may complicate or make a patient's participation in the study impossible, or make it difficult to explain clinical findings, any known intolerability to any of the study regimens' components, a patient's family or official relations with a member of staff of the clinical site, a patient's failure to assess his/her physical and/or emotional condition, a patient's failure to comply with the study requirements, a patient's refusal to participate in the study, as well as pregnancy or breastfeeding. The present study was approved by the Ethics Committee of the Astana Medical University, protocol #16 dated June 17, 2021. All patients were enrolled between June 2021 and September 2021. The study was conducted according to the Declaration of Helsinki. All patients participated voluntarily, provided a written informed consent, and agreed that the results of the study would be published. The study was retrospectively registered under the study registration number NCT04980534 at ClinicalTrials.gov on July 28, 2021.

Study design and treatment. The present study was multicenter, open-label, randomized clinical trial in three parallel groups with a minimum 5-day treatment period. No follow-up period was intended. The following visits were scheduled: Visit 1– the first day of hospitalization; Visit 2 – the day of discharge. The following primary endpoint was used: mean length of hospitalization. The indications for discharge were: normal body temperature for 2 days, normal appetite for 4 days, normal CBC, no requirement in oxygen support, decrease in or normal CRP, any

decrease in IL-6, ferritin and D-dimer level lower than the doubled normal value. Secondary endpoints included: mean levels of CRP, IL-6, ferritin and D-dimer. Levels of CRP, IL-6, ferritin and D-dimer were determined centrally at OLYMP diagnostics lab (https://www.kdlolymp.kz/). Following lab kits were used: CRPL3 ref 08057575 Roche (CRP), Elecsys IL-6 ref 05109442 Roche (IL-6), FERR4 ref 08057648 Roche (ferritin), HemosIL D-Dimer HS 0020007700 Instrumentation Laboratory (D-dimer), SARS-CoV-2 Nucleic Acid Detection Kit Zybio (SARS-CoV-2 PCR). The protocols of the manufacturers were followed.

The study was conducted at three centers: 1. The City Center For Infectious Diseases (Nur-Sultan City, Kazakhstan); 2. The Clinics of Astana Medical University (Nur-Sultan City, Kazakhstan); 3. The City Children's Hospital #1 (Nur-Sultan City, Kazakhstan). Patients were randomly assigned to one of the three comparison groups:

1. Viusid (4.5 g sachets with powder for dilution) 1 sachet bid and Asbrip 10 ml bid for the total length of hospitalization (V+A);
2. Remdesivir IV 200 mg on the first day and then 100 mg daily for the next 4 days AND Viusid (sachets with powder for dilution) 1 sachet bid and Asbrip 10 ml bid for the length of hospitalization (COMBO).
3. Remdesivir IV 200 mg on the first day and then 100 mg daily for the next 4 days (REM).

Viusid and Asbrip are complex medicinal preparations (as registered in Kazakhstan), their compositions are presented in Table I and Table II.

A total of 80 patients were enrolled in the study; 30 in the REM group, 25 in each V+A and COMBO groups. Sequentially numbered opaque sealed envelopes were used as the randomization method. The study centers were provided with an excess amount of Remdesivir, Viusid and Asdrip and an excess number of envelopes.

Patients from all the groups were allowed to use anti-inflammatory/apyrogenics (acetaminophen, ibuprofen, metamizole) or antiviral (umifenovir) treatment prior to the present study. In addition to their study regimens, patients were administered with acetaminophen, ibuprofen, metamizole, prenoxdiazine, butamirate, acetylcysteine, carbocysteine, ambroxol, and dexamethasone and antibiotics if needed.

Statistical analysis was performed using StatSoft Statistica 10.0 software (http://statsoft.ru/). Baseline characteristics are presented as mean and (standard deviation), unless otherwise stated; when comparisons between the groups or within a group were made, the data are presented as mean and [95% confidence interval (CI)]. Categorical variables are expressed as absolute numbers and percentages. The differences of quantitative variables (independent) between the two groups were compared using the Mann-Whitney U test and the differences within each group (pairwise)

Table I.

Composition of Viusid per sachet

Glycyrrhizinic Acid	46.9 mg
Glucosamine	690 mg
Arginine	720 mg
Glycine	393 mg
Ascorbic Acid	43 mg
Pyridoxine Hydrochloride	0.59 mg
Calcium Pantothenate	2.2 mg
Folic Acid	0.068 mg
Cyanocobalamin	0.000395 mg
Malic Acid	704 mg
Zinc sulfate	5 mg

Table II.

Composition of Asbrip per 100 ml

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

were compared using the sign test. The differences of categorical variables were compared using the Yates corrected Chi-square or two-sided exact Fisher test. As there were three comparisons (each group with other one) Mann-Whitney U test, Chi-square, exact Fisher test p values were tripled according to the Bonferroni correction. P<0.05 was considered to indicate a statistically significant difference.

Results

80 patients were enrolled in the study; of which 30 in the REM group, 25 in each V+A and COMBO groups. The initial clinical characteristics of the subjects are provided in Table III. No significant differences were found between the compared groups at baseline. 76 (95%) of patients received antibiotics during hospital stay (most often ceftriaxone, levofloxacin).

By the end of the hospitalization, there were significant differences found including the length of hospital stay, fever during hospital stay (fig. 1), and some inflammatory markers, which reflects a cytokine storm in COVID-19 (Table IV). CT-scans were not repeated in this study.

When comparing the results within each of the groups (when hospitalized and at discharge), the majority of the inflammatory markers have decreased significantly: ferritin p < 0.001, p < 0.001, p = 0.006; CRP p < 0.001, p < 0.001, p = < 0.001, IL6 p < 0.001, p < 0.001, p < 0.001; D-dimer p < 0.001, p < 0.001, p = 0.855 for groups V+A, Combo and REM, respectively.

All treatment regimens were well tolerated with similar types and rates of adverse events across three groups. These events most probably were associated with the disease itself, rather than with the medications used. In this study, the most frequent adverse events were: fatigue, dyspnoea, headache, anosmia, headache, body pain, diarrhea, and anorexia (Table V).

Discussion. This is the first study to show that the combination of Viusid and Asbrip containing amino acids, vitamins, micronutrient elements, and naturally-occurring biologically-active macromolecules are able to decrease the length of hospital stay and hospital fever days compared to Remdesivir in pa-

Table III.

The patients' baseline characteristics for each group

Characteristic	V+A	Combo	REM
Age	49.9 (15.3)	53.8 (13.9)	54.9 (15.2)
CT scan percentage area of lung involvement with ground-glass opacities	23.8 (11.7)	25.3 (11.8)	26.1 (10.9)
Ferritin μg/l	519.1 (165.7)	527.9 (162.9)	531.5 (252.4)
CRP mg/l	49.7 (34.2)	79.3 (12.9)	52.2 (26.6)
Il-6 pg/ml	78.8 (64.0)	79.9 (188.0)	61.7 (31.0)
D-dimer μg/ml	0.28 (0.2)	0.27 (0.11)	0.26 (0.31)

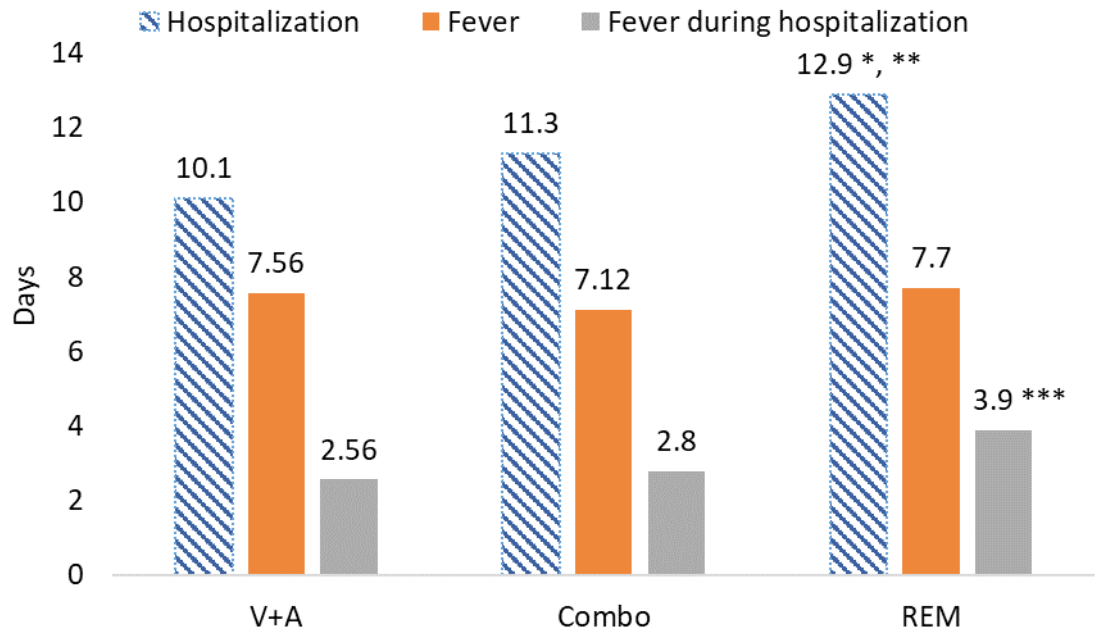

Table IV.

Markers of inflammation at discharge for each group

Marker	V+A	Combo	REM
Ferritin μg/l	300.4 [234.7-366.1]	331.9 [162.3-501.7]	399.4 [324.3-474.6]*
CRP mg/l	24.3 [17.2-31.4]	25.1 [22.9-27.2]	38.6 [29.5-47.7]**
Il-6 pg/ml	24.3 [12.3-36.4]	18.4 [10.7-26.1]	24.1 [16.6-31.6]
D-dimer μg/ml	0.13 [0.11-0.15]	0.11 [0.09-0.13]	0.15 [0.06-0.24]***

*p = 0.018 vs Combo, **p = 0.05 vs V+A, ***p = 0.012 vs V+A

Table V.

The most frequent adverse events in study arms

Event: absolute (%)	V+A	Combo	REM
Fatigue	20 (80)	15 (60)	20 (67)
Dyspnoea	14 (56)	15 (60)	22 (73)
Anosmia	10 (40)	17 (68)	20 (67)
Headache	22 (88)	25 (100)	25 (83)
Body pain	20 (80)	18 (72)	28 (93)
Diarrhea	8 (32)	12 (48)	20 (67)
Anorexia	10 (40)	10 (40)	17 (57)

tients with mild-to-moderate COVID-19. Moreover, their use was accompanied by a more prominent decrease of the most inflammatory markers studied.

At present, there are very few options for COVID-19 treatment that have shown efficacy in clinical trials. It makes the search for new treatments urgently needed. Available vaccines are the best choice for prevention but not for absolute protection. Even vaccinated people often have mild-to-moderate symptoms. As Remdesivir is indicated in severe and critical cases, there are no available options in mild-to-moderate cases. In the present study, we evaluated the efficacy of Viusid and Asbrip in patients with mild-to-moderate COVID-19 compared to Remdesivir in the manner of a randomized trial. The obtained results show that the combination of these plant-derived products is effective and safe. Of special interest is the fact that Viusid and Asbrip combination led to a more marked and faster (because of a shorter hospital stay) impact over inflammatory markers. Previously, it has been shown that Licorice derived GA have anti-inflammatory activity via several pathways including those typical for COVID-19 (8,13,14). The first work regarding these properties of GA was published in 2005 by Zhiqian Yu and colleagues (15). They assumed that its anti-inflammatory activity against LPS-induced platelet responses and lethality could be promising in SARS. Later, the inhibitory activity of GA regarding inflammatory pathways in COVID-19 was shown (8). The first report about the antiviral activity of GA against SARS associated coronavirus was published in 2003 by J. Cinatl, and since that time GA have been considered as a promising agent to combat coronaviruses (16). Later, some other mechanisms of action of GA were discovered, including inhibition of CoV-2 spike protein inhibition (9). Together with the known ability of Eucaliptus oil (eucaliptol) to inhibit the virus main protease (10), these data suggest that the combination of GA and Eucaliptus oil could be helpful to combat COVID-19. It should be noted that these agents are not toxic and have a good safety profile. In conclusion, Viusid and Asbrip plant-origin products have demonstrated effectiveness and safety in treatment of patients with mild-to-moderate COVID-19 and may be used as a regimen in such patients. They provide a shorter hospital stay and a more prominent decrease in inflammation with good tolerability. Even though the obtained results look promising, further larger studies of Viusid and Asbrip are required to support their wider use in combatting COVID-19.

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Availability of data and materials. The data generated in the present study may be requested from the corresponding author.

Authors' contributions. Marina Morenko was involved in study design and interpretation of final results, patient selection and follow up. was involved in study design, protocol and procedure development and writing the manuscrip Kseniya Shnayder was involved in study design, protocol and procedure development, patients' selection and interpretation of final results. performed statistical analysis and was a major contributor in writing the manuscript. Tatyana Tsechoeva was involved in study design, protocol and procedure development, interpretation of final results, and patient selection. Zauresh Smagulova was involved in study design and interpretation of final results. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate. The present study was approved by the Ethics Committee of the Astana Medical University, protocol #16 dated June 17 2021. All patients were enrolled between June 2021 and September 2021. Under the Declaration of Helsinki, all patients provided written informed consent to participate in the study.

Patient consent for publication. All patients provided written informed consent for publication of the results.

Competing interests. Authors declare that they have no competing interests.

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