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Original Article

The effectiveness of dual antiviral treatment against COVID-19

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ABSTRACT

This study evaluates the effectiveness of combination antiviral therapy for COVID-19 using Umifenovir and Oseltamivir compared with standard treatment. A total of 85 outpatients with confirmed COVID-19 were randomly assigned to two groups: 43 patients received combination antiviral therapy (Umifenovir 200 mg 4 times daily, Oseltamivir 75 mg twice daily for 7 days), and 42 received standard therapy based on WHO recommendations. The study spanned 16 months. Primary endpoints included the number of patients with fever, cough, sore throat, diarrhea, and the need for hospitalization or intensive care at 1, 2, and 3 weeks post-infection. The secondary endpoint was a negative PCR test at 7, 14, and 21 days.

Results showed that 72% of patients in the antiviral group and 67% in the control group had alpha and omicron variants. Patients receiving combination therapy showed a significantly faster resolution of fever and cough within the first two weeks. Viral elimination by the end of the second week occurred in 95% of patients in the combination group, compared to 79% in the control group ($P<0.05$). The therapy was well-tolerated, and the combination was twice more effective in symptom relief, virus clearance, and reducing the need for hospitalization. Combination therapy with Umifenovir and Oseltamivir presents a promising treatment approach for outpatient COVID-19 cases.

Keywords: Treatment of COVID-19, Antiviral therapy of COVID-19, Umifenovir in the treatment of COVID-19, Oseltamivir in the treatment of COVID-19

Introduction

COVID-19 has a significant impact on both the health of the population [1, 2] and social life [3], as well as the practice of doctors of various specialties [4, 5].

SARS-CoV-2, a beta coronavirus B that was identified in the second half of 2019 and caused the COVID-19 pandemic, belongs to the family of RNA viruses [6]. It is logical to assume that antiviral drugs that destroy RNA should be effective in COVID-19 [7]. However, the evidence base for the use of Oseltamivir and other antiRNA drugs is insufficient to recommend their use [8, 9]. This is probably due to their late appointment from the onset of COVID-19, i.e. already in the hospital and in patients with complications [10, 11].

A recent systematic review of randomized clinical trials to evaluate the efficacy of antiviral therapy for COVID-19 12449 patients analyzed revealed, 1) antivirals were more effective when administered early in the disease course 2) no antiviral treatment demonstrated efficacy at reducing COVID-19 mortality 3) sofosbuvir/daclatasvir results suggested clinical improvement, although statistical power was slow 4) remdesivir exhibited efficacy in reducing time to recovery, but results were inconsistent across trials [12].

The presence of risk factors in the patient, such as concomitant chronic diseases, and the timeliness of the appointment of antiviral drugs are of decisive importance [13, 14]. Thus, Chuah CHetal (2021) showed that among patients with COVID-19 at high risk of disease progression, early treatment with oral favipiravir did not prevent disease progression from non-hypoxia to hypoxia [15].

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The working hypothesis for this study was the expected efficacy of antiviral drugs administered no later than the first 48 hours from the clinical onset of COVID-19 [16, 17]. To improve the effectiveness of therapy, given the accumulated experience of insufficient effectiveness of monotherapy with Oseltamivir or Umifenovir, it was proposed to use their simultaneous administration [18, 19]. Previously, we have reported on the effectiveness of combination therapy as a therapeutic approach to improve the effectiveness of treatment in the treatment of severe migraine as an example [20].

The study aims to evaluate the effectiveness of the etiotropic treatment of COVID-19 using a combination of Umifenovir and Oseltamivir.

Materials and Methods

Ethics approval

Local Ethics Commission (21.02.2020 №1) and Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine (24.04.2020 №16) approved the study.

Study design

The presented study is a pragmatic, two-center, open, initiative, randomized, prospective trial in two parallel groups of outpatients with COVID-19: 1) patients who received antiviral therapy with a combination of Umifenovir / Oseltamivir, 43 people 2) a comparison group who received standard therapy according to WHO recommendations [21], 42 people. The patients in the groups were homogeneous in terms of age, sex, etiologic agent, and clinical manifestations.

The selection into the groups was determined by random selection based on patients' desire to follow WHO recommendations or try the proposed protocol approved by the ethical committee. The investigator did not have any information regarding the treatment regime and could only analyze data from groups 1 and 2. Family doctors (Kyiv's region) prescribed drugs to patients. The duration of the study was 16 months from 02.2020 to 06.2021.

Study protocol

A POEM (Patient Based Evidence That Matters) design [22] was used for subjects with COVID-19.

Dosage regimen in the antiviral therapy group

Umifenovir 200 mg 4 times a day, Oseltamivir 75 mg twice a day, duration of administration is 7 days.

Study group

Patients with a confirmed COVID-19 PCR test.

The Centers for Disease Control and Prevention classification was used to identify COVID-19 types [23]. There are the following:

- British variant with a 50% higher possibility of the surrounding infection. There is a possibility of a more severe course of the disease. This results in higher hospitalization and mortality rates. Does not influence the monoclonal antibody's treatment. At a minimal degree is neutralized by reconvalecent and postvaccine sera.
- South – African variant with a 50% higher possibility of the surrounding infection. Significantly worse reaction to treatment with a combination of bamlanivim and monoclonal antibody etesevivam while other variants of antibody treatment are available. At a worse degree, are neutralized by reconvalescent and postvaccine sera.
- Japanese-Brazilian variant which does not influence the infection of surrounding. Poor reaction to the treatment by bamlanivim and monoclonal antibody etesevivam while other variants of antibody treatment are available. At a worse degree, are neutralized by reconvalescent and postvaccinal sera.
- Indian variant with increased spreading ability. Potential decrease of neutralization by some methods of monoclonal antibody treatment. Potential decrease of neutralization after postvaccine serum.
- OMICRON with increased spreading ability. Potential decrease of neutralization by some methods of monoclonal antibody treatment. Potential decrease of neutralization after postvaccinal serum.
- EPSILON with ~20% increased transmission. Decreased sensibility to a combination of bamlanivim and etesevivam. Its clinical consequences are unknown. Alternative methods of monoclonal antibody treatment are available. Neutralization by reconvalescent and postvaccinal sera is decreased.

  British variant which, doesn't influence the possibility of the surrounding infection. Potentially is worse neutralized by methods of monoclonal antibody treatment. Potentially is less neutralized by reconvalescent and postvaccine sera, and
- Indian variant, which doesn't influence the possibility of the surrounding infection. Potentially is worse neutralized by methods of monoclonal antibody treatment. Potentially is less neutralized by reconvalescent and postvaccine sera.

Sampling method

unlikely sampling; minimum age: 16 years old, maximum age: 90 years old; gender: male, female. The average age was 47±3,1 years.

Inclusion criteria

People with COVID-19 requiring outpatient treatment.

Exclusion criteria

People with COVID-19 requiring hospital treatment.

Primary endpoint

number of patients with fever (above 37.2°C), number of patients with cough, number of patients with sore throat, number of patients with diarrhea, and number of patients requiring hospitalization and intensive care unit at 1, 2, and 3 weeks after the onset of COVID-19.

Secondary endpoint

negative PCR test at 7, 14, and 21 days from the onset of COVID-19.

Informed consent form - all patients gave oral consent to the provision of personal data.

Statistical evaluation of the results of the study was carried out in the package of medical statistics [24]. All statistical analyses and graphs were performed using the MedCalc Statistical Software version 22.007 (MedCalc Software Ltd). A multivariate Cox proportional hazards regression model was used for the primary outcomes. We calculated hazard ratios (HR) with 95% confidence intervals (CI) to evaluate the associations between groups. All statistical analyses and graphs were carried out using the Prism 5.0 software package. The data obtained are presented as mean values with their STDEV (standard deviation of the mean) error (M±STDEV). The test for normal distribution of data has been performed. Correlation analysis was done using the Pearson test. Log-rank tests were conducted to determine the statistical significance of differences between the two groups. A multivariate Cox proportional hazards regression model was used for the primary outcomes. We calculated hazard ratios (HR) with 95% confidence intervals (CI) to evaluate the associations between groups. The differences were considered significant at $p < 0.05$. Pearson correlation coefficient for the linear correlation between two variables was calculated. The level of $p < 0.05$ was considered statistically significant.

Results and Discussion

The diagnosis of COVID-19 was established in all examined people **(Table 1)**.

Table 1. Characteristics of coronavirus type in the persons under examination

Type of virus/group	Main group, n=43	Group of comparison, n=42
Alpha, abs, %	14	16
Beta, abs, %	3	4
Gamma, abs, %	2	1
Delta, abs,%	7	9
Omicron, abs, %	17	12

The table shows the relative homogeneity of patients receiving therapy. Most of the examined had alpha and omicron types: 72% in the main group and 67% in the comparison group.

The comparative effectiveness of treatment outcomes in groups is shown in **Table 2**. None of the patients died.

Table 2. Evaluation of the results of the primary endpoint in the studied groups

Feature characteristics/Number of patients %	Onset	1 week	2 weeks	3 weeks	Reliability
fever (above 37.2C)					
Main group, =43	40 (93%)	5 (12%)	1 (2%)	0	1 week: Fisher's test (two-tailed) 0.10248 P≤0,05; RR 0,465 95% CI 0,177–1,225, NNT 7,312
Comparison group, =42	37 (88%)	11 (26%)	4 (10%)	0	2 weeks: Fisher's test (two-tailed) 0.20201 P>0,05; RR 0,244 95% CI 0,028–2,096, NNT13,892
Cough					
Main group, =43	37 (86%)	29 (67%)	4 (9%)	1 (2%)	2 weeks: Fisher's test (two-tailed) 0.2042 P>0,05; RR 0,250 95% CI 0,076–0,822, NNT4,667
Comparison group, =42	38 (90%)	32 (74%)	12 (29%)	4 (10%)	3 weeks: Fisher's test (two-tailed) 0.20201 P>0,05; RR 0,244 95% CI 0,028–2,096, NNT 13,892
throat pain					
Main group, =43	39 (91%)	4 (9%)	1 (2%)	0	1 week: Fisher's test (two-tailed) 0.156 P>0,05; RR 0,558 95% CI 0,176–1,767, NNT 13,579
Comparison group, =42	37 (88%)	7 (16%)	0	0	
Diarrhea					

Main group, =43	3 (7%)	0	0	0	
Comparison group, =42	3 (7%)	0	0	0	
Need hospitalization and intensive care unit.					
Main group, =43	2 (5%)	0	0	0	2 weeks: Fisher's test (two-tailed) 0.24118 P>0,05
Comparison group, =42	2 (5%)	2 (5%)	2 (5%)	1 (2%)	

As follows from **Table 2** data, the clinical symptoms in both groups were similar and did not have significant differences in the frequency of detection. Fever and the presence of cough underwent significantly faster resolution during the first two weeks in people receiving combined antiviral therapy. Moreover, the need for hospital stay was eliminated for two hospitalized from this group, in contrast to people who received standard therapy.

An explanation for this change in scores can be found in **Table 3**, which compares the score for the secondary endpoint.

Table 3. Data of PCR diagnostics in the patients under examination

Test period/group	Main group, n=43	Comparison group, n=42	Significance of differences
Debut of the disease	43 (100%)	42 (100%)	Fisher's exact test 1.0, P≥0.05
7 days, abs, %	38 (88%)	38 (90%)	Fisher's exact test 1.0, P≥0.05
14 days, abs, %	2 (5%)	9 (21%)	Fisher's exact test (two-tailed) 0.02608 P<0,05 RR 0,217 95% CI 0,005–0,946, NNT 5,960
21 days, abs %	1(2%)	1 (2%)	Fisher's exact test 1.0, P≥0.05

There are significant differences in the elimination of coronavirus between the groups **(Table 3)**. These differences are only documented at the end of the second week of infection observation.

In assessing the clinical picture in comparison of the groups, the following differences were also observed: volume (58%), headache (44%), attention disorders (27%), and back (24%) were less in people of the first group.

No serious adverse reactions beyond those indicated in the manufacturer's instructions were revealed. None of the patients discontinued treatment due to side effects. Patient tolerability of the double combination, which was defined as the patient's non-refusal was 98%, and unwillingness to continue to take the combination was demonstrated by one person (2%). 6 people (14%) from the group taking combined antiviral therapy required a reduction in the dose of Oseltamivir from two to 1 capsule (75 mg) due to the occurrence of side effects (nausea, pain in the projection of the kidneys).

To date, highly effective etiotropic therapy for coronavirus infection has not been proposed in the available literature. Hardly had we named the highly effective treatment for COVID-19. This is due both to the changing properties of the virus and to the ignorance of the obvious previously known approach, which consists of the direct destruction of the agent in two or three ways at the same time. One universal agent is not known, and that is what is important, to be highly effective. Therefore, we used these known truths for the proposed approach to the treatment of coronavirus infection, namely two etiotropic agents against the RNA virus. Our data allowed us to state that this approach turned out to be pragmatic, justified, effective, and not the most expensive. The use of a double combination allowed us to achieve significantly faster elimination of the virus by the end of the second week from the onset of the disease and to stop clinical symptoms faster. According to the signs of improvement in the clinical condition, we did not achieve statistically significant differences, except for the normalization of temperature, but the identified trend towards a better clinical condition is obvious. Probably, an increase in the statistical groups will allow the demonstration of statistically significant results.

Umifenovir, known for more than 40 years as a direct antiviral molecule, has already demonstrated its efficacy in the treatment of COVID-19 [25]. In 2013, Umifenovir was included in the Anatomical Therapeutic Chemical Classification System) WHO and assigned the international ATX code as a direct-acting antiviral (J05A - Direct acting antivirals) - the fourth class of antiviral drugs used to prevent and treat influenza.

Umifenovir is effective in severe COVID-19 as in fewer hospital deaths for severe and critical patients with COVID-19 [26].

Ming Li *et al*. showed that Umifenovir is advantageous over chloroquine in terms of the SARS-CoV-2 negative conversion and the length of hospital stay in COVID-19 patients [27]. Chang Chen *et al*. [28], comparing Umifenovir and favipiravir, demonstrated that the latter can be considered the preferred treatment due to its faster rate of clinical recovery within 7 days and more effective reduction in the frequency of fever and cough, except for some side effects associated with antiviral drugs.

Fang Jie *et al*. [29] evaluated the combination of Umifenovir showing that the early combined usage of LHQW and Umifenovir may accelerate recovery and improve the prognosis of patients with moderate COVID-19.

There are also direct comparisons between Umifenovir and Oseltamivir. Qibin Liu *et al*. [30] found Umifenovir promising and associated with reduced mortality (95% CI, 0x075 to 0x446;

P<0.001) which was also associated with faster lesion absorption after adjusting for patient's characteristics and concurrent Oseltamivir and Lopinavir use 2=00.

Among the many publications, we want to draw your attention to two excellent reviews devoted to an in-depth analysis of the effectiveness of drugs for the treatment of COVID-19 [31, 32]. These papers represent a summary of the evidence obtained from randomized trials, except for case descriptions and self-citations. More than 20 therapeutic approaches, which include antiviral therapy, immunobiological drugs, and accompanying agents, are reviewed in these two publications. Without setting ourselves the goal of a detailed retelling of these works, we consider it important to note that the research thought of researchers is multifaceted and aimed at finding and obtaining the most effective approaches to treatment. A number of these approaches have indeed proved to be very effective, mainly in cases of hospitalizations and severe cases of coronavirus infection. For our study, however, these treatment regimens rather represent state-of-the-art luxury therapy. We were looking for affordable funds for outpatient practice, setting the goal of highly effective inexpensive treatment at the prehospital stage, which would avoid complications of coronavirus infection and prevent its severe course.

The analysis of these publications was the basis for planning a study with the use of a combination of Umifenovir and Oseltamivir in a reduced dosage. These data allowed, on the one hand, to confirm its effectiveness, on the other hand, they demonstrated a significantly better effect compared to standard non-isotropic therapy. At the same time, the tolerability of the combination of drugs did not reduce the succession to treatment, which may be due to the worst tolerability of Oseltamivir.

The results obtained showed that the failure of a single drug can be leveled when using combination therapy. The effectiveness of treatment is obviously due to the higher rate of elimination of coronavirus. This ultimately led to a faster resolution of clinical symptoms in the group of people who received the combination of Umifenovir and Oseltamivir and reduced the need for hospital stay. At the same time, an important aspect is the prevention of post-COVID syndrome and the formation of complications, which often occur with COVID-19 [33, 34].

The development of new approaches to COVID-19 treatment involves the evaluation of the effectiveness of modern antiviral drugs. For example, three novel antivirals (molnupiravir, fluvoxamine, and Paxlovid) are effective in reducing mortality and hospitalization rates in patients with COVID-19 [35, 36].

The limitations of this study: small statistical groups, lack of double-blind study.

Conclusion

1. Combination therapy for COVID-19 with Umifenovir 200 mg 4 times a day and oseltamivir 75 mg twice a day for 7 days, administered in the first 48 hours from the onset of infection, leads to twice rapid elimination of the virus and relief of clinical symptoms, minimizing the hospitalization of outpatients with COVID-19.
2. Combination therapy with Umifenovir 200 mg 4 times a day and Oseltamivir 75 mg twice a day for 7 days is well tolerated and effective in the prehospital setting, representing a pragmatic low-cost approach for outpatient COVID-19 treatment.
3. Further research is needed to evaluate the possible recommendations of the proposed treatment regimen for widespread use in COVID-19.

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Conflict of interest: None

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Ethics statement: Local Ethics Commission (21.02.2020 №1) and Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine (24.04.2020 №16) approved the study. The study was approved by the local Institutional Ethics Committee in keeping with 99 the principles of the Declaration of Helsinki. In accordance with Ministry of Health 100 regulations, the Institutional Ethics Committee did not require written informed 101 consent because data were collected anonymously from the electronic medical 102 records without active patient participation.

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