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Coronavirus Pandemic

Efficacy of favipiravir in COVID-19: A retrospective two center comparative study

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Abstract

Introduction: Favipiravir (FVP) is an antiviral, targeting RNA-dependent RNA polymerase. We aimed to evaluate the efficacy of FVP as a treatment for COVID-19.

Methods: We conducted a retrospective study in two centers (San Martino University Hospital in Genova, Italy, and Marmara University Pendik Training and Research Hospital, Turkey). Adult patients (inpatients) diagnosed with COVID-19 between March and June 2020 were included. All patients in the Italian center received the standard of care (SoC) treatment, while in the Turkish center patients received FVP in addition to SoC.

Results: Six hundred-nineteen patients were analyzed (225 from Turkey, all treated with FVP, and 394 from Italy, none treated with FVP). Propensity score-matching was done in 142 patients (71 from the SoC group vs. 71 from the SoC + FVP group). A Higher requirement of NIV/CPAP (n = 38; 53.5%) was registered in the SoC group compared to the SoC + FVP group (n = 9; 12.7%). A higher frequency of intubation was registered in the SoC + FVP group (n = 25; 35.2% vs n = 13, 18.3%). There was a trend towards better survival in SoC + FVP treated patients with HR = 0.64 (95% CI 0.30-1.34). At 28 days the OS was, respectively, 70.3% (95% CI: 53.2-82.1) vs 80.3% (95% CI: 69.0-87.8).

Conclusions: The addition of FVP to SoC did not show a significant difference in survival and invasive and noninvasive (CPAP/NIMV) mechanical ventilation compared to standard of care in moderate and severe COVID-19-infected patients.

Key words: Favipiravir; efficacy; COVID-19; antiviral.

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Introduction

The pandemic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019. Unfortunately, there was no specific treatment for COVID-19, although numerous immunotherapies, antivirals, and anti-inflammatory drugs were being investigated. There were limited studies that demonstrated efficacy for treatment or prevention of COVID-19 until 2020 [1,2]. Today, there are more than 18,000 papers on COVID-19 prevention strategies, including vaccines, and/or treatments' efficacy. SARS-CoV-2 infection can be grouped based on severity of illness as asymptomatic, mild, moderate, severe, or critical [3]. In addition to supportive care, steroid therapy and anticoagulation are the main therapeutic options for those with moderate or severe infection. The clinical efficacy of some antivirals has not been confirmed, while for others there are contradictory data or studies are ongoing. For example, remdesivir showed in vitro activity against SARS-CoV-2 [4,5] and has been approved by the Food and Drug Administration (FDA) for patients ≥ 12 years with COVID-19 [6], but no benefit on mortality was documented in a large trial, and WHO does not support its use [7,8]. In addition to WHO studies, other studies have shown that remdesivir is either not effective at all or does not reduce mortality in moderate-severe cases [9–11]. In recent studies, new therapeutical alternatives such as nirmatrelvir/ritonavir (paxlovid) were used for the treatment of COVID-19 infection [12,13]. It is also not widely available in many countries due to limited resources or health policy. In addition, monoclonal antibodies such as bamlanivimab-etesevimab, casirimivab-imdevimab, and sotrovimab

have received emergency approval for selected patients but are of limited availability in many countries [14–16]. Vilobelimab is the latest monoclonal antibody that FDA approved usage on April 4, 2023 [17]. A definitive cure treatment has still not been defined. Therefore, alternative antivirals are needed. Influenza B and SARS-CoV-2 are RNA viruses depending on RNA-dependent RNA polymerase (RDRP) [18], and favipiravir (FVP) is an antiviral drug targeting RDRP, approved in Japan for influenza A treatment [19,20]. Early trials in China and Russia suggested some benefits of FVP [21], and it continued to be evaluated in various studies [22].

This study aimed to evaluate the clinical efficacy of FVP as a treatment for COVID-19.

Methodology

Patients and data collection

We conducted a retrospective two-center study to evaluate the efficacy of oral FVP combined with standard of care (SoC) in adult patients with COVID-19. We included all consecutive adult (≥ 18 years of age) patients with SARS-CoV-2 infection diagnosed with RT-PCR who had a WHO clinical progression scale for COVID-19 of ≥ 5 (need for oxygen support by mask or nasal prongs) [23] admitted to one of two participating hospitals (San Martino University Hospital in Genova, Italy and Marmara University Pendik Training and Research Hospital, Turkey) between March and June 2020. Pregnant patients were excluded from the study.

Patients in the Turkish center received FVP (1600 mg twice on the first day, followed by 600 mg twice daily for five days) and SoC. In Turkey, the standard care comprised hydroxychloroquine (800 mg loading and 400 mg maintenance dose for 5 days), antibiotics, supportive oxygen, and low-molecular-weight heparin prophylaxis, dexamethasone in case of severe COVID-19 pneumonia and systemic inflammation (6 mg/day for 5 days), tocilizumab in steroid unresponsive cases (intravenously (iv) at the dose of 8 mg/kg, maximum 800 mg). In Italy, the SoC included oral hydroxychloroquine 400 mg bid, unless glucose-6-phosphate dehydrogenase deficient, darunavir/ritonavir 800/100 qd until March 24th, short-term antibiotic coverage, supportive oxygen, low-molecular-weight heparin prophylaxis unless contraindicated, tocilizumab in case of severe COVID-19 pneumonia and systemic inflammation since March 11th (iv at the dose of 8 mg/kg, maximum 800 mg, or subcutaneously 162 mg in case of temporary shortage), and methylprednisolone (1 mg/kg for 5 days intravenously, then 0.5 mg/kg for 5 days) since March 16th.

Patients were evaluated at the baseline for basic parameters, body temperature, the saturation of arterial blood (SpO_2), computerized chest tomography (CT) or chest x-rays, blood biochemistry, coagulation function, C-reactive protein (CRP), and IL-6.

Statistical analyses

The primary endpoint was overall survival (OS) at 28 days after hospital admission. Firstly, to define risk factors associated with unfavorable OS, univariable and multivariable Cox proportional hazard regression model were used. The baseline variables used in the multivariable analyses were: age, gender, Charlson comorbidity index, ratio of partial pressure of arterial oxygen to fractional concentration of oxygen-inspired air (PaO_2/FiO_2), time from symptoms onset to hospital admission, ferritin, C-reactive protein (CRP) and LDH levels on admission. To avoid overfitting, only those characteristics that showed a p value ≤ 0.15 at univariable analysis and after inclusion in the multivariable model were considered, with age and gender forced into the model. For a better interpretation and to avoid the influence of outliers on estimation, the IL-6, ferritin, CRP, and d-dimer were log-transformed before the analysis due to the highly skewed distribution.

Subsequently to minimize baseline differences between patients from the two centers, a 1:1 propensity-score (PS) matching with exact matching on age was performed. PS was derived by a logistic regression model including the same baseline variables used for the Cox regression analysis: age, gender, Charlson comorbidity index, ratio of partial pressure of arterial oxygen to fractional concentration of oxygen-inspired air (PaO_2/FiO_2), time from symptoms onset to hospital admission, ferritin, C-reactive protein (CRP) and LDH levels on admission. The positivity assumption of PS was checked after the calculation.

Non-invasive ventilation (NIV)/Continue positive airway pressure (CPAP) was considered as a time-dependent adjustment.

To assess the balance of covariate distribution between the two groups, Cohen's standardized mean differences (SMD) were calculated between the two groups in the original samples and after weighting. An SMD < 0.10 was not considered a significant clinical difference between the two groups.

The Cox proportional hazard regression model was used to calculate the adjusted HR of FVP plus SoC vs SoC patients in the matched cohort. Cumulative

probability of failure, intended as requirement of ventilation (Non-invasive ventilation (NIV)/Continue positive airway pressure (CPAP)/intubation) or death, was calculated by the mean of Kaplan-Meier (KM) survival curves.

All results were reported as HR with a 95% confidence interval (95% CI). A $p < 0.05$ was considered significant. Stata (v.16; StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) was used for the computation

Ethics Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the local Ethics Committees (approval ID: 09.2021.560).

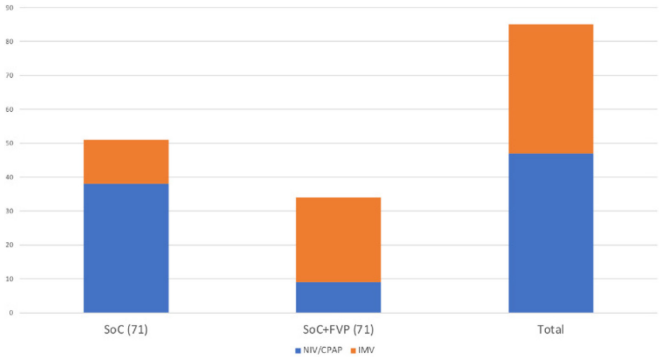
Results

Data from a total of 619 patients with COVID-19 pneumonia admitted to the two hospitals were analyzed (225 from Turkey, all treated with FVP, and 394 from Italy, none treated with FVP). The principal characteristics, including concomitant therapies, of the two cohorts are shown in Table 1.

Cohort matching and the impact of treatment on the overall survival

To account for numerous differences between the cohorts, a matched analysis was performed. The distribution of the patients' characteristics according to propensity score-matched analytic samples (71 from SoC group vs. 71 from SoC + FVP group) is shown in Table 2.

Figure 1. Ventilation requirement among patients.



Outcomes: ventilation and death in the propensity score matched cohorts

The patients who were intubated and needed NIV/CPAP are shown in Figure 1. A total of 47 (33.1%) patients needed NIV/CPAP during follow-up. Higher frequency was registered in SoC group (n = 38; 53.5%) than in SoC + FVP group (n = 9; 12.7%). NIV/CPAP was required in the median within one day from hospitalization (IQR: 0-5), and with a median duration of 4 days (IQR: 2-7), without significant differences between the two groups ($p = 0.16$). CPAP, considered a time-dependent variable, did not result, however, significantly associated with OS at univariable analysis (HR = 0.78; 95% CI: 0.18-3.37; $p = 0.75$).

In total, 38 patients (26.8%) were intubated during the follow-up in the median after four days (IQR: 2-8) from hospitalization. A higher frequency of intubation was registered in SoC + FVP group (n = 25; 35.2% vs n = 13, 18.3%) while patients in SoC group were

Table 1. Demographic and clinical characteristics of the two cohorts.

	SoC (n = 394)	Soc + FVP (n = 225)	*p*
Demographics			
Period of observation	03-03-20/30-04-20	15-04-20/30-06-20	
Age	70.1 (13.1); 28-102	60.4 (15.4); 21-96	< 0.001
Gender (F/M), n (%)	125/269 (31.7/68.3)	81/144 (36/64)	0.28
Laboratory findings			
PaO_2/FiO_2, median (IQR)	207 (137-270)	326 (266-355)	< 0.001
LDH (U/L), median (IQR)	349 (266-438)	290 (230-400)	< 0.001
D-dimer (mg/L), median (IQR)	1062 (667-1673)	700 (500-1300)	< 0.001
Ferritin (mg/L), median (IQR)	832 (435-1439)	239 (101-467)	< 0.001
PCT (mg/L), median (IQR)	102 (50-140)	58 (22-113)	< 0.001
ALT (U/L), median (IQR)	33 (22-54)	24 (16-38)	< 0.001
AST (U/L), median (IQR)	39 (27-59)	36 (26-52)	0.12
Fibrinogen (mg/dL), mean (SD)	6.20 (1.97)	5.25 (1.52)	< 0.001
Lymphocytes ($\times 10^3$/mL) mean (SD)	0.94 (0.81)	1.11 (0.68)	0.008
Creatinine (mg/dL), mean (SD)	1.15 (0.75)	1.06 (1.00)	< 0.001
Charlson index, median (IQR), range	4 (2-6); 0-14	2 (1-4); 0-12	< 0.001
Treatment			
Tocilizumab, n (%)	146/394 (37.1)	60 (26.7)	0.01
Steroid, n (%)	296 (75.1)	55 (24.4)	< 0.001
Steroid + tocilizumab, n (%)	114 (28.9)	33 (14.7)	< 0.001
Clinical data			
Symptoms days onset to hospital admission (days)	6.7 range: 0-36	3.1 range 0-27	< 0.001

F: Female; M: Male; LDH: Lactate dehydrogenase; PCT: Procalcitonin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; SoC: Standart of Care; FVP: Favipiravir.

intubated earlier (median: 2 days; IQR: 1-9) than in SoC + FVP group (median: 5 days; IQR: 3-8).

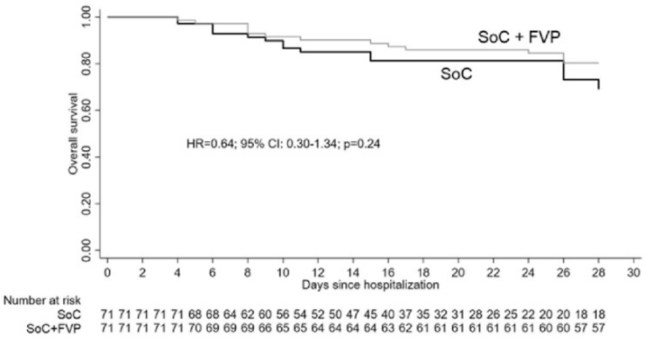
Tocilizumab was administered mainly intravenously (n = 46; 82.1%), in median within two days from hospital admission (IQR: 1-6), similar to steroids (median: 2.5 days (IQR: 1-6)) in SoC group. In the Soc + FVP group, both tocilizumab (median: 4 days; IQR: 2-6) and steroids (median: 5 days; IQR: 4-13) were started later than in SoC group (median difference: 2 days; IQR: 1-3 for tocilizumab; median: 2 days; IQR: 2-6 for steroids).

Although there was a trend towards better survival in FVP-treated patients with HR = 0.64 (95% CI 0.30-1.34) it was not statistically significant (Figure 2). A total of 29 deaths after a median follow-up of 28 days were registered. At 14 days the OS was 85.3% (95% CI: 74.3-91.8) in SoC group vs 90.1 (95% CI: 80.4-95.2) in SoC + FVP group. At 28 days the OS was, respectively, 70.3% (95% CI: 53.2-82.1) vs 80.3% (95% CI: 69.0-87.8).

Discussion

Despite vaccination efforts against COVID-19, the requirement for safe, efficient, and reliable treatment alternatives is still a critical point of clinical research. There have been a lot of repurposed drug studies for COVID-19 treatment, and while some are not used anymore, the effectiveness of some is still being investigated. As conclusive therapeutic approaches for proven COVID-19 continue to be a challenge, there is a significant interest in repurposing existing antiviral agents [24]. FVP, as a ribonucleotide analog and RNA polymerase inhibitor, inhibits SARS-CoV-2 in vitro [4]. In the present study, we evaluated FVP efficacy in patients with COVID-19 who were admitted to the hospital. The efficacy was assessed according to the need for ventilation support (NIV/CPAP), intubation, and survival ratios.

Figure 2. Kaplan-Meier analysis on OS in matched patients receiving SoC and SoC + FVP.



After propensity score matching to control for differences between the two cohorts, NIV/CPAP requirement was registered less frequently in SoC + FVP group (n = 9; 12.7%) compared to the SoC cohort (n = 38; 53.5%). Similarly, in another study that compared FVP and arbidol, FVP was associated with a higher 7 day clinical recovery rate (71.43% vs. 55.86%) and the NIV requirement rate was lower in FVP than the arbidol group (8.16% vs. 17.12%) [25].

Our analysis showed the need for intubation was not reduced in SoC + FVP group (18.3% vs. 35.2%), but the SoC group was intubated in median 3 days earlier than SoC + FVP group. And patients received steroids and tocilizumab later in SoC group compared with the SoC + FVP group. The reason why patients in the SOC group were intubated earlier and received tocilizumab and steroids treatment later than the SoC + FVP group

Table 2. Characteristics of the propensity score matched groups.

	SoC (n = 71)	SoC + FVP (n = 71)	SMD
Age, mean (SD); range	67.8 (12.4); 39-96	67.8 (12.4); 39-96	0.00
Gender (F/M), n(%)	24/47 (33.8/66.2)	26/45 (36.6/63.4)	0.059
PaO_2/FiO_2, mean (SD)	241.0 (85.9)	250.7 (102.7)	0.10
LDH, mean (SD)	343.9 (132.0)	365.8 (181.7)	0.13
D-dimer, mean (SD); median (IQR)	2042 (4594); 886 (530-1708)	2059 (3593); 1000 (500-1900)	0.004
Ferritin, mean (SD); median (IQR)	879.6 (875.2); 616.2 (342-1124)	461.7 (526.7); 281 (116-582)	0.57
PCR, mean (SD); median (IQR)	104.3 (94.0);78.9 (36.2-137)	101.1 (81.7); 86.0 (34-154)	0.036
ALT, mean (SD)	45.5 (33.2)	35.3 (41.4)	0.27
AST, mean (SD)	48.6 (37.3)	47.6 (35.4)	0.028
Fibrinogen, mean (SD)	6.10 (2.11)	5.63 (1.60)	0.25
Lymphocytes, mean (SD)	1.09 (1.09)	1.11 (0.63)	0.018
Creatinine, mean (SD)	1.00 (0.34)	0.97 (0.40)	0.095
Charlson index, mean (SD); median (IQR)	3.8 (2.7); 3 (2-6)	3.9 (2.6); 4 (2-5)	0.048
Time from symptoms onset to hospital admission (days), mean (SD); range	4.2 (3.6); 0-14	4.4 (4.4); 0-12	0.039
Tocilizumab*, n(%)	29 (40.9)	27 (38.0)	0.067
Steroid*, n(%)	54 (76.1)	21 (29.6)	1.12
Combined, n(%)	22 (31.0)	13 (18.3)	0.38
Other, n(%)	10 (14.1)	-	

*Including also combined treatment; SMD: Standardized Mean difference; F: Female; M: Male; LDH: Lactate dehydrogenase; PCT: Procalcitonin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; SoC: Standart of Care; FVP: Favipiravir.

may be due to their older age and later hospital admission, and waiting to evaluate a response to intubation respectively. Khamis *et al.* conducted a study showing no significant difference was detected between FVP and the hydroxychloroquine group in the need for intubation [26]. In another study, only two of the 22 (6%) patients in FVP and one patient (%3) in the baloxavir marboxil group needed intubation [27]. Solaymani *et al.* showed that there was no influence on ICU admission with FVP compared with lopinavir/ritonavir (31 admissions to ICU vs. 25), and they did not detect a reduction in the need for intubation (27 intubation vs. 17) or in-hospital mortality (26 death vs. 21) in FVP group [28]. Taking into account these results, FVP does not seem to reduce the rate of intubation in COVID-19 patients.

In our matched cohort, although there was a trend towards better survival in the SoC + FVP group at 14 days (90.1% vs 85.3%) and 28 days (80.3% vs 70.3%) respectively, it was not statistically significant. In a live systematic review, it was shown that FVP was not effective on fatality rate and mechanical ventilation requirement in moderate to severe COVID-19 patients [29].

In addition, a randomized trial did not show virological benefit from the early prescription of the FVP compared with the late prescription in asymptomatic or mildly symptomatic patients [30]. Our patients took FVP medium on the 4th day of hospital admission, so we could not compare early and late-onset FVP therapy.

The limitations of our study include first of all retrospective design and comparison between two centers from different countries in which different policies for hospital admission and treatment might be in place. However, similar SoC was used during the study period in both centers and the propensity score matching allowed us to possibly account for most of the difference and provide two uniform cohorts, although it limited significantly the number of patients included. The second limitation is the short period of time of observation/data collection.

Conclusions

In conclusion, the addition of FVP to SoC did not show a beneficial effect on intubation (CPAP/NIMV or IMV), nor survival in hospitalized COVID-19 patients. Randomized controlled studies are needed to describe the efficacy of FVP.

Authors' Contributions

ETT, ZO, MB, and VK participated in the planning of this study. ETT, BES, MM, AS, SD, ST participated in the data collection and reporting, reading and approving the final manuscript. AS participated in the data analysis.

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