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FULL PAPER

Tenofovir disoproxil fumarate in the treatment of COVID-19: Evaluation of 78 patients

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SUMMARY

One of the drugs that has been suggested for the treatment of SARS-CoV-2 infection is tenofovir disoproxil (TDF). Herein, it was aimed to evaluate the outcomes of TDF receiving COVID-19 cases in terms of day 7-10 PCR negativity and day 30 survival. Patients who received TDF due to PCR-confirmed COVID-19 between 27.04.2021 and 31.12.2021 were included in our study. The primary outcome was considered to be 7-10 days of PCR negativity, while the secondary outcome was considered 30-day survival after diagnosis of COVID-19. Patients who died before completing the treatment period (7-10 days) were also considered as PCR failures. Data were analyzed both in terms of intention to treat basis and in the subgroup that survived to the end of treatment. A total of 78 patients (30 women, mean age: 61.15±18.5 years) met the inclusion criteria. In the intention to treat analysis group, one-month-mortality was 44.87% (35/78) in the overall cohort. In the end of treatment analysis group, one-month-mortality was 29.5% (18/61) in the overall cohort. Day 7-10 PCR negativity was detected in 55.7% of the overall EOT cohort. Our data suggest that TDF may be an alternative salvage treatment option in antiviral unresponsive patients. We suggest evaluating TDF in well-designed controlled trials involving treatment-naïve cases.

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INTRODUCTION

In December 2019, a new coronavirus, named SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2), was found in patients with pneumonia in China (Elfiky, 2020; Park *et al*., 2020). SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus that belongs to the Betacoronavirus family. It has a RNA-linked RNA polymerase (RdRp) in its structure to copy its genome (Elfiky, 2020; Park *et al*., 2020; Zanella *et al*., 2021; Wang *et al*. 2021). Spreading rapidly around the world, Covid-19 was declared a pandemic by the World Health Organization on March 11, 2020 (WHO, 2020). According to WHO data, as of August 8, 2023, 768,983,095 cases were diagnosed with Covid-19 and 6,953,743 deaths occurred (WHO, 2022). The number of cases and deaths continues to increase.

Key words:
Favipiravir, liver transplantation, pregnancy, tenofovir.

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Many vaccine and drug studies are being carried out for the treatment of SARS-CoV-2 infection, which has already caused the death of millions of people (Park *et al*., 2020; Zanella *et al*., 2021).

Although remdesivir (RDV), a nucleotide analog, is one of the antiviral treatments approved by the FDA, it has been evaluated by WHO as having limited benefit (FDA, 2022). Remdesivir, on the other hand, acts as a delayed terminator that inhibits SARS-CoV-2 RdRp. Similarly, other drugs that inhibit SARS-CoV-2 RdRp are favipiravir, molnupiravir, tenofovir disoproxil (TDF), and sofosbuvir (Wang *et al*., 2021). During 2021, in the COVID-19 Guidelines of the Turkish Ministry of Health, favipiravir was recommended for patients diagnosed with COVID-19.

TDF has been used for many years in the treatment of HIV and Hepatitis B virus (Park *et al*., 2020). It is effective *in vitro* against COVID-19. Besides, in a study evaluating the clinical efficacy of TDF, it was compared with hydroxychloroquine, a molecule that has an immunomodulatory effect and was found to inhibit the growth of SARS-CoV-2 *in vitro* (Park *et al*., 2020; Cornejo-Giraldo *et al.,* 2021). The primary results of the study, length of hospital stay, intensive care unit (ICU) and/or mechanical ventilator (MV) need, and

mortality were evaluated. The difference in TDF use (68 cases) compared with hydroxychloroquine (36 cases). In the estimation model of the treatment effects by regression adjustment, it was found that TDF decreased the stay by −6.38 days (C.I.: −12.34 to −0.42, p = 0.036); the need for ICU / MV at −41.74% (C.I.: −63.72 to −19.7, p = 0.000); and mortality by −35.22% (C.I.: −56.47 to −13.96, p = 0.001) (Cornejo-Giraldo *et al.,* 2021). Herein, the aim was to evaluate the outcomes of TDF receiving COVID-19 cases in terms of day 7-10 PCR negativity and day 30 survival.

MATERIALS AND METHODS

Patients who were consulted to Infectious Diseases and Clinical Microbiology Consultants and started TDF due to PCR confirmed COVID-19 from 27.04.2021 to 31.12.2021 were included in the study. Cases aged <18 were excluded.

The TDF was given as used by Cornejo-Giraldo et al., i.e., 245 mg q24 h and 245 mg q48 in case of chronic renal failure (Cornejo-Giraldo *et al.,* 2021). Primary outcome was considered to be day 7-10 PCR negativity while secondary outcome was considered to be day 30 survival after COVID-19 diagnosis. Patients who died before completing the treatment period (7-10 days) were also considered as PCR failure. Data were analyzed both in terms of intention to treat analysis and in the subgroup who survived until the end of treatment.

COVID-19 disease severity was evaluated according to IDSA Guidelines for the Treatment and Management of COVID-19 (Bhimraj *et al.,* 2023).

Group 1: Mild-to-moderate COVID-19 (SpO_2 ≥94% on room air and not needing supplemental oxygen) with risk factors for progression to severe disease, hospitalization or death [a] (a few of the risk factors are: age >60 years, Body Mass Index (BMI) >25, diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, cancer, or immunocompromised patients).

Group 2: Severe but not critical COVID-19 (SpO_2<94% on room air or needing low-flow supplemental oxygen).

Group 3: Critical COVID-19 needing high-flow oxygen and/or non-invasive ventilation.

Group 4: Critical COVID-19 needing mechanical ventilation or external corporeal membrane oxygenation.

In addition to the above-mentioned classification, patients who could not be classified according to this guideline (without risk factors, SpO_2 ≥94% in room air and not needing supplemental oxygen) were considered to be Group 0.

One-month mortality rate (OMM) referred to all-cause mortality 30 days after the first dose of tenofovir.

The study was approved by the Scientific Research Platform of the Ministry of Health (2021-12-30T21_31_56).

RESULTS

A total of 78 patients (30 female, mean age: 61.15±18.5 years) fulfilled the study inclusion criteria. When the comorbidities of the 78 patients included in the study were evaluated, 33 (42.3%) had hypertension, 22 (28.2%) had diabetes, 14 (17.9%) had coronary artery disease, seven (9%) had congestive heart failure, seven (9%) had chronic renal failure, six (7.7%) had chronic liver disease, five (6.4%) had chronic obstructive pulmonary disease, three (3.8%) had collagen tissue disease. Furthermore, three (3.8%) had solid organ malignancy and three (7.8%) had hematological malignancy. There were six (7.7%) organ transplant patients in total: three kidney transplants and three liver transplants.

Favipiravir was started as the first line COVID-19 oriented antiviral therapy in 73 patients (93.6%) and TDF was started after failure with favipiravir.

COVID-19 treatments other than favipiravir and TDF in the overall cohort were evaluated: corticosteroid (60-76.9%), vitamin C (45-57.7%), IVIG (33-42.3%), famotidine (15-19.2%), tocilizumab (11-14.1%), and plasma (3-3.8%).

Five patients (6.4%, three cases due to pregnancy and two due to underlying liver disease) received TDF as the first line therapy. TDF treatment was started before completion of favipiravir in five patients (due to liver function tests >x5 elevation in 4 patients and due to allergic reaction in 1 patient). The mean duration of previous favipiravir treatment in the overall cohort was 9.26±4.17 days (min: 1, max: 18). The mean duration of TDF treatment was 6.38±1.79 days (min:1, max:9).

a. Intention to treat analysis (ITT)

A total of 17 patients (21.8%) died before the end of TDF treatment (within <7 days).

ITT based mortality analysis revealed an OMM of 44.9% (35/78) in the overall cohort. Considering the OMM in all COVID-19 disease severity groups, it was found to be 0% (0/7) in group 1, 58.3% (7/12) in group 2, 42.9% (9/21) in group 3, and 70.4% (19/27) in group 4. In addition, OMM was found to be 0% (0/11) in groups with no risk factors other than these groups and SpO_2 ≥94% in room air (*Table 1*).

The possible causes of death in the overall cohort were as follows: septic shock in 22 (62.9%) patients, cardiopulmonary arrest in 6 (17.1%) patients, cardiac shock in two (5.7%) patients, pneumothorax in two (5.7%) patients, and hemorrhagic shock in two patients (5.7%). No possible cause of death could be found in one patient.

b. End of treatment analysis

A total of 61 patients (25 females, mean age: 58.86±18.25 years) could complete the TDF treatment at least seven days. Fifty-seven cases used favipiravir treatment before TDF (mean 9.21±3.93 days min: 1, max: 16), while it

Table 1 - *Intention to treat analysis results of TDF.*

	Number of patients	*Day 7-10 PCR negativity*	*One-month-mortality*
Group 0 (SpO_2 ≥94% on room air and not needing supplemental oxygen and no risk factors)	11	n=9 (81.8%)	n=0 (%)
Group 1: Mild-to-moderate COVID-19 (SpO_2 ≥94% on room air and not needing supplemental oxygen) with risk factors for progression to severe disease, hospitalization or death	7	n=4 (57.15%)	n=0 (0%)
Group 2: Severe but not critical COVID-19 (SpO_2 <94% on room air or needing low-flow supplemental oxygen)	12	n=6 (50%)	n=7 (58.3%)
Group 3: Critical COVID-19 needing high-flow oxygen/ or non-invasive ventilation	21	n=7 (33.3%)	n=9 (42.9%)
Group 4: Critical COVID-19 needing mechanical ventilation or ECMO	27	n=8 (29.6%)	n=19 (70.4%)
Patients started after favipiravir	73	n=32 (43.8%)	n=39 (53.4%)
Favipiravir naive patients	5	n=2 (40%)	n=4 (80%)
Total number of patients	78	n=34 (43.6%)	n=43 (55.1%)

*Required any level of supplemental oxygen on day 1 or during tenofovir treatment.

Table 2 - *End of treatment analysis of TDF.*

	Number of patients	*Day 7-10 PCR negativity*	*One month-mortality*
Group 0 (SpO_2 ≥94% on room air and not needing supplemental oxygen and no risk factors)	11	n=9 (81.8%)	n=0 (0%)
Group 1: Mild-to-moderate COVID-19 (SpO_2 ≥94% on room air and not needing supplemental oxygen) with risk factors for progression to severe disease, hospitalization or death	7	n=4 (57.15%)	n=0 (0%)
Group 2: Severe but not critical COVID-19 (SpO_2 <94% on room air or needing low-flow supplemental oxygen)	10	n=6 (60%)	n=5 (50%)
Group 3: Critical COVID-19 needing high-flow oxygen/ or non-invasive ventilation	18	n=7 (38.9%)	n=6 (33.3%)
Group 4: Critical COVID-19 needing mechanical ventilation or ECMO	15	n=8 (53.3%)	n=7 (46.7%)
Patients started after favipiravir	57	n=32 (56.1%)	n=39 (68.4%)
Favipiravir naive patients	4	n=2 (50%)	n=4 (100%)
Total number of patients	61	n=34 (55.7%)	n=43 (70.5%)

was started as the first line antiviral therapy in four patients (6.6%, three due to pregnancy and one liver transplantation history). The mean duration of TDF treatment was 7.19±0.57 (min:7, max: 9) days.

EOT based mortality analysis revealed an OMM of 29.5% (18/61) in the overall cohort. Considering the OMM in all COVID-19 severity groups, it was found to be 0% (0/7) in group 1, 50% (5/10) in group 2, 33.3% (6/18) in group 3, and 46.7% (7/15) in group 4. In addition, OMM was 0% (0/11) in groups with no risk factors other than these groups and SpO_2 ≥94% in room air.

Day 7-10 PCR negativity was detected in 55.7% in the overall EOT cohort. Day 7-10 PCR negativity was 81.8% (9/11) in group 0, 57.15% (4/7) in group 1, 60% (6/10) in group 2, 38.9% (7/18) in group 3, 53.34% (8/15) in group 4.

Three pregnant patients (mean age: 38.66±0.57 years) who received TDF treatment for seven days were evaluated separately as a subgroup. All were followed up in the ICU via noninvasive mechanical ventilator support (Group 3). The day 30 survival of the patients was 100% (3/3) while the PCR negativity on day 7-10 was 66% (2/3).

DISCUSSION

Despite a huge amount of research, vaccination and efforts, COVID-19 continues around the world, with

higher mortality rates in some patient subgroups and in the unvaccinated population (Nadir, 2023; Park *et al*., 2020; WHO, 2022).

TDF studies in addition to Cornejo-Giraldo *et al.* on which our study was based, are limited in the literature (Cornejo-Giraldo *et al*., 2021). In the study conducted by Park *et al*., ferrets infected with SARS-CoV-2 were treated with lopinavir-ritonavir, hydroxychloroquine sulfate, and TDF-emtricitabine, and their clinical scores and viral loads were evaluated. Better clinical scoring was seen in all treatment arms than in the control group. Nasal wash samples were examined to evaluate their viral load, and, on the eighth day, decreased virus titers were found in the TDF-emtricitabine group compared to the control group (Park *et al*., 2020). In the open-label phase 2 study by Parienti *et al*., outpatient SARS-CoV-2 cases were divided into two groups (those receiving 7-day TDF-emtricitabine and standard care). The viral loads of the patients were evaluated on days 4 and 7, and a statistically significant decrease was found on day 7. No patient died in either group (Parienti *et al*., 2021). Our study aligns with the findings mentioned above. In the subgroup where PCR positivity persisted post-favipiravir, we observed a PCR negativity rate of 41.4% (12/29) among those requiring high-flow oxygen, non-invasive ventilation, or mechanical ventilation. This rate was 70.38% (19/27) in the group who were either in room air or needed low levels of supplemental oxygen. Additionally, the PCR negativity rate was 50% (n=2/4) in patients who began and completed TDF treatment as the first-line approach, and these had a 0% (n=0/4) OMM. Furthermore, we noticed a 55.7% PCR negativity rate at days 7-10 in the overall EOT cohort, with 67.9% in the COVID-19 severity group 0+group 1+group 2 and 45.5% in the group 3+ group 4.

In the presented cohort, TDF was used since there was no antiviral treatment (including remdesivir and hyperimmuneglobulins in our center) except favipiravir during the study period. Remdesivir was available for a very short period of time in March (before this cohort's first case). Favipiravir was used for up to 14 days according to data of Zhao *et al.* (Zhao *et al*., 2021; Express Pharma, 2022) and TDF was started in case of persisting PCR positivity. PCR negativity was important throughout the study period for healthcare workers (comprising the outpatient group in our study) as well as ICU patients for transfer in in-hospital services or ICUs.

In a recent review on COVID-19 in pregnant women, it was emphasized that the need for intensive care and mechanical ventilation in pregnant women was significantly higher than in non-pregnant women (Taylor *et al*., 2021). The safety of TDF was evaluated in HIV-infected pregnant women (n=1886) who received TDF during pregnancy. Major congenital malformation was detected in 37 of 866 (4.27%) infants exposed to TDF, while major congenital malformation was detected in 38 of 1020 (3.73%) infants exposed to antiretrovirals other than TDF. It was determined that the use of TDF in the first trimester did not increase the risk of major congenital malformations in the newborn compared to other ARTs (Hernández-Díaz *et al*., 2021). In our study, TDF, which is known to be safe, was preferred in pregnant patients. The OMM of the pregnant patients was 0% (n=0/3).

Our study is subject to several limitations:

i) it was a retrospective cohort study,
ii) the majority of cases were not antiviral naïve,
iii) favipiravir was the first line antiviral, as it was the only one available in our country during the study period,
iv) the TDF cohort lacked a comparable control group, mainly due to the unavailability of any other antiviral during the study period,
v) viral culture could not be performed in any case,
vi) OMM is not an ideal indicator for outpatient COVID-19 cases; however, we chose to analyze the OMM,
vii) we aimed to analyze the antiviral effect of TDF by examining day 7-10 COVID-19 PCR negativity; however, this could have been influenced by the duration of the COVID-19 infection or might not affect the clinical outcomes in all cases.

Despite these disadvantages, to our knowledge this is the largest dataset in terms of COVID-19 vs TDF and TDF vs ICU cases including cases needing MV.

In conclusion, our data suggest that TDF can be considered an alternative salvage antiviral treatment for patients who are unresponsive to favipiravir and other antiviral drugs, as well as for antiviral-naive patients. However, we recommend that our findings be tested in controlled trials involving a larger number of antiviral-naive patients and those who are refractory to favipiravir or other antivirals.

Conflicts of interest

The authors have no conflicting interests to declare.

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