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Evaluation of the Relationship between Favipiravir Use Status and Telogen Effluvium in Patients Diagnosed with COVID-19

COVID-19 Tanısı Alan Hastalarda Favipiravir Kullanım Durumu ile Telogen Effluvium Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Aim: Favipiravir (FVP) is a competitive inhibitor of viral RNA-dependent RNA polymerase and is also a purine nucleoside analogue. It produces antiviral activity against the SARS-CoV-2 virus and has been used to treat COVID-19. Telogen effluvium (TE) is a widespread, non-scarring shedding due to the early entry of hair during the telogen phase. The most prevalent causes are drugs, physiological and emotional stress, surgery, high fever, chronic infections, diet, iron deficiency, and smoking. In this study, we investigated whether there was a significant difference in terms of TE by questioning the patients who had coronavirus in the last 1 year, and who received and did not receive FVP treatment.

Material and Method: Patients between the ages of 18 and 65, who applied to the Dermatology and Venereal Diseases Outpatient Clinic of Karaman Training and Research Hospital with a complaint of hair loss and who were diagnosed with COVID-19 over the past year, were included in this study. We confirmed the diagnosis of TE by using trichoscopy on patients with a positive pull test. We investigated whether there was a difference in terms of TE and other types of hair loss between patients who received FVP treatment and those who did not. For the study Karamanoglu Mehmet Bey University ethics committee approval was obtained (June 29, 2022).

Results: As a result of comparing the patients' gender, comorbidity, pull test, and trichoscopic findings according to the use of FVP, it was clear that most of the FVP users were women (p=0.027). Among those who did not use FVP, positive pull test scores were significantly higher (p=0.026). The fact that the pull test was significantly lower in patients in our study using FVP may suggest that FVP has no effect on TE's development.

Conclusion: We found no studies on the effect of FVP on alopecia and TE. We believe that the use of FVP reduces the positivity of the pull test, therefore, its effect on hair loss may be related to non-TE alopecia. We believe that our study is also important in this regard.

Keywords: Favipiravir, Telogen effluvium, COVID-19

Öz

Amaç: Favipiravir (FVP), viral RNA'ya bağımlı RNA polimerazın yarışmalı bir inhibitörüdür ve aynı zamanda bir pürin nükleozid analoğudur. SARS-CoV-2 virüsüne karşı antiviral aktivite üretir ve COVID-19'u tedavi etmek için kullanılmıştır. Telogen effluvium (TE), telogen faz sırasında saçın erken gelişimine bağlı olarak yaygın bir dökülmedir. En yaygın nedenler; ilaçlar, fizyolojik ve duygusal stres, ameliyat, yüksek ateş, kronik enfeksiyonlar, diyet, demir eksikliği ve sigaradır. Bu çalışmada son 1 yıl içinde COVID-19 tanısı almış olup, FVP tedavisi alan ve almayan hastaları sorgulayarak TE açısından anlamlı bir fark olup olmadığını araştırdık.

Gereç ve Yöntem: Bu çalışmaya Karaman Eğitim ve Araştırma Hastanesi Deri ve Zührevi Hastalıklar polikliniğine saç dökülmesi şikayeti ile başvuran ve son bir yıl içinde COVID-19 tanısı konan 18-65 yaş arası hastalar dahil edildi. Pull testi pozitif olan hastalarda trikoskopi kullanarak TE tanısını doğruladık. FVP tedavisi alan ve almayan hastalar arasında TE ve diğer saç dökülme tipleri açısından fark olup olmadığını araştırdık. Çalışma için Karamanoğlu Mehmet Bey Üniversitesi etik kurul onayı alındı (29 Haziran 2022).

Bulgular: Hastaların cinsiyet, komorbidite, pull testi ve trikoskopik bulgularının FVP kullanımına göre karşılaştırılması sonucunda FVP kullananların çoğunun kadın olduğu görüldü (p=0.027). FVP kullanmayanlar arasında pozitif pull testi oranı anlamlı olarak daha yüksekti (p=0.026). Çalışmamızda FVP kullanan hastalarda pull testinin anlamlı olarak daha düşük olması, FVP'nin TE gelişimi üzerinde etkisinin olmadığını düşündürebilir.

Sonuç: FVP'nin alopesi ve TE üzerine etkisi ile ilgili herhangi bir çalışmaya rastlamadık.FVP kullanımının pull testi pozitifliğini azalttığını bu nedenle saç dökülmesi üzerine etkisinin TE dışı alopesilerle ilişki olabileceğini düşünüyoruz. Çalışmamızın bu açıdan da önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Favipiravir, Telogen effluvium, COVID-19

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INTRODUCTION

The causative pathogen of COVID-19, which has resulted in the current worldwide pandemic beginning in December 2019, is SARS-CoV-2.[1] Favipiravir (FVP) is a competitive inhibitor of viral RNA-dependent RNA polymerase and is also a purine nucleoside analogue. It produces antiviral activity against the SARS-CoV-2 virus and has been used to treat COVID-19.[2] Cutaneous side effects associated with FVP are rare and include pruritus, rash, and eczema in <0.5% of patients.[3] Telogen effluvium (TE) is a widespread, non-scarring shedding due to the early entry of hair during the telogen phase. Kligman first described it in 1961.[4] The most prevalent causes are drugs, physiological and emotional stress, surgery, high fever, chronic infections, diet, iron deficiency, and smoking. Classic TE, which develops approximately 3-4 months after a triggering condition and is self-limiting, lasts less than 6 months. Forms exceeding 6 months have been reported as chronic TE.[4] In this study, we investigated whether there was a significant difference in terms of TE by questioning the patients who had coronavirus in the last 1 year, and who received and did not receive FVP treatment.

MATERIAL AND METHOD

18-65 years old patients are included in this study who applied to the Karaman Training and Research Hospital, Dermatology, and Venereal Diseases outpatient clinic complaining of hair loss and having had COVID-19 in the last year. Those who received and did not receive FVP treatment were determined and recorded. The patients involved in the study provided informed consent, and the pull test was performed from the places where hair loss was most active. In the pull test, about 50 strands of hair were pulled lightly without hurting and the presence of five (10%) or more hairs on the hand showed that telogen was active.[5-7] Trichoscopy is a noninvasive method in which the scalp is examined with a dermatoscope. Although it is recommended to use a video dermatoscope in trichoscopic examinations because of the high resolution—magnifying the image 20-1000 times—it is not always possible and practical to use the video dermatoscope because it is not portable. The hand dermatoscope, which provides ten times magnification, can magnify 30 times with the help of a digital camera. This pocketable device is much cheaper than a video dermatoscope and has proven to be as successful in diagnosing alopecia.[8-11] We also confirmed the diagnosis of TE by using trichoscopy on patients with a positive pull test. Routine laboratory tests, such as complete blood count, thyroid function tests, vitamin D levels, ferritin, B12, and folic acid were requested from patients with a confirmed diagnosis of hair loss, and the underlying secondary causes were recorded.[12,13] We investigated whether there was a difference in terms of TE and other types of hair loss between patients who received FVP treatment and those who did not. For the study Karamanoglu Mehmet Bey University ethics committee approval was obtained.

Statistical Analysis

The data were analyzed using the SPSS 25.0 package program. Continuous variables were given as mean±standard deviation, and categorical variables were given as numbers and percentages. Significance test of the difference between two means in comparison of independent group differences when parametric test assumptions are met; when parametric test assumptions were not met, the Mann-Whitney U test was used to compare the independent group differences. In dependent group comparisons, when the parametric test assumptions were met, a significance test was conducted of the difference between the two spouses. The Wilcoxon paired-sample test was used when parametric test assumptions were not met. In addition, the relationships between continuous variables were analyzed using Spearman or Pearson correlation analyses and the differences between categorical variables were analyzed using the Chi-square analysis.

RESULTS

The mean age of 100 patients was 32±10 years, and 62% were female. Nineteen percent of the participants had an additional chronic disease (six people with diabetes mellitus, three with hypertension, two with asthma, four with thyroid disease, one with a psychiatric disease, one with seborrheic dermatitis, one with ankylosing spondylitis, and one with PCOS). Fourteen percent regularly used medication. Ten percent had an additional dermatological disease (five with androgenic alopecia, two with maculopapular eruptions, one with herpes labialis, one with psoriasis, and one with urticaria). Forty-nine percent of the patients used FVP. As a result of comparing the patients' gender, comorbidity, pull test, and thyroscopic findings according to the use of FVP, it was clear that most of the FVP users were women (p=0.027). Among those who did not use FVP, positive pull test scores were significantly higher (p=0.026) (**Table 1**).

Table 1. Comparison of patients' gender, comorbidity, PULL test and trichoscopy findings according to FVP use

	FVP						p
	Not used		Used		Total		
	N	%	N	%	N	%	
Gender							0.027
Female	25	51.0	37	72.5	62	62	
Male	24	49.0	14	27.5	38	38	
Additional diagnosis							0.374
No	45	91.8	44	86.3	89	89	
Yes	4	8.2	7	13.7	11	11	
PULL							0.026
Negative	10	20.4	22	43.1	32	32	
Positive	39	79.6	29	56.9	68	68	
Trichoscopy							0.051
No finding	17	35.4	19	37.3	36	36	
Yellow dots	16	33.3	17	33.3	33	33	
Empty follicles.	15	31.3	15	29.4	30	30	

*Mann-Whitney U test FVP: Favipiravir

As a result of the comparison of the age and laboratory values of the patients according to the use of FVP, we did not find any difference in age and laboratory values between those who used and did not use FVP (**Table 2**).

Table 2. Comparison of the age and laboratory values of the cases according to the use of FVP

	FVP				Total		p*
	Not used		Used				
	Mean	SD	Mean	SD	Mean	SD	
Age	32	10	34	11	33	11	0.790
Hb	14	2	13	2	14	2	0.156
B12	422	138	433	166	427	152	0.761
Folic acid	14.2	8.5	17.9	29.5	16.1	22.0	0.955
Iron	67	33	75	38	71	36	0.240
TSH	2	1	2	1	2	1	0.750
Ferritin	34	36	27	27	31	32	0.213
D vit	25	19	22	9	24	15	0.702

SD:Standart Deviation * Mann-Whitney U test Hb:Hemoglobin TSH: Thyroid stimulating hormone FVP: Favipiravir

In addition, comparing laboratory values within normal limits and outside of normal limits according to FVP use showed no significant difference (**Table 3**).

Table 3. Comparison of the laboratory parameters of the cases according to the use of FVP

		FVP				P**
		Not Used		Used		
		N	%	N	%	
Hb	Normal	32	65.3	39	76.5	0.313
	Not Normal	17	34.7	12	23.5	
B12	Normal	47	95.9	51	100.0	0.238
	Not Normal	2	4.1	0	0.0	
Ferritin	Normal	46	93.9	45	88.2	0.264
	Not Normal	3	6.1	6	11.8	
TSH	Normal	49	100.0	51	100.0	NA*
	Not Normal	0	0.0	0	0.0	
Folik asit	Normal	38	77.6	44	86.3	0.191
	Not Normal	11	22.4	7	13.7	
D vit	Normal	26	53.1	33	64.7	0.327
	Not Normal	23	46.9	18	35.3	
Iron	Normal	25	51.0	28	54.9	0.851
	Not Normal	24	49.0	23	45.1	

* no appreciable ** Wilcoxon paired-sample test, Hb: Hemoglobin TSH: Thyroid stimulating hormone FVP: Favipiravir

DISCUSSION

This study investigated whether there was a significant difference in terms of TE by questioning the patients who had COVID-19 in the last year and who had received or not received FVP treatment. In addition, patients were also asked about their diagnosis of chronic dermatological diseases, and it was determined whether there was exacerbation or remission of the lesions after using FVP. Dominguez-Santás et al.[14] has been the first to report the development of acute TE after COVID-19. They described a case of TE occurring 3 months after contracting SARS-CoV-2. Other studies supporting these findings have since been conducted.[15,16] The effects that COVID-19 and FVP—which was widely used in treating COVID-19 had on various dermatological diagnoses, especially TE, were examined. There were significantly more women included in this study than men. This may be related to the fact that TE, which is the most common cause of diffuse hair loss, is more common in women.[17] Iron is an important cofactor in cell DNA, and its deficiency facilitates the development of TE by reducing the proliferation capacity in the hair matrix.[18] Çadırcı et al.[19] reported that 54% of the TE patients in their study had ferritin deficiency, 42% had iron deficiency, and 1% had B12 deficiency. In our study, iron deficiency was detected in 45% of patients using FVP and 49% of patients not using FVP. Hypothyroidism delays the onset of a new anagen phase by inducing the catagen phase. In this way, TE can develop. The mechanism of hair loss in hyperthyroidism is not clear.[20] In our study, these values were similar between patients who used FVP and those who did not. There is no clear consensus on the role of vitamin D in TE. Rasheed et al.[21] reported that serum 25 hydroxyvitamin D levels were significantly lower in female patients with a diagnosis of chronic TE when compared to healthy controls. On the other hand, there are also studies stating that the development of TE and vitamin D levels are unrelated.[22] In this study, vitamin D levels were similar between patients who used FVP and those who did not. The results suggest that more studies are needed in order to examine the role of vitamin D levels in both acute and chronic TE. A study conducted in Thailand reported that cutaneous side effects developed in five patients who had COVID-19 and received FVP treatment, two of which were diagnosed with maculopapular eruption, two with urticaria, and one with Stevens-Johnson syndrome. They stated that the time between FVP treatment and the onset of rash was 7 days. The mean duration of the rash was 5 days.[23] In another study, acute generalized exanthematous pustulosis was reported in a patient treated with FVP.[24] Çeviker et al.[25] reported that urticaria and angioedema developed on the 3rd day of FVP treatment in a 55-year-old female patient who was followed-up with for COVID-19 pneumonia. Maculopapular eruption developed after FVP use in three patients included in our study, and a 61-year-old male patient developed an urticaria attack that developed on the 4th day of FVP use and required a change in treatment. This may be a rare side effect of FVP or a cutaneous marker of COVID-19, and this distinction is not clear.Although TE is not a specific trichoscopic finding, decrease in hair density, empty follicles, and yellow spots are visible drums. There is an increase in the number of follicular units containing a single hair. Newly growing hair has a pointed, hard, and pigmented body.[8,10,11] In our patients, yellow spots and empty follicles were found among trichoscopic findings. Trichoscopic findings did not differ significantly between patients using and not using FVP. It is important to remember that androgenic alopecia and TE may coexist in many female patients. In our study, androgenic

alopecia was present in four female patients. Rossi et al.[26] examined TE cases that developed after the patient had COVID-19. This study emphasized that treatments for COVID-19 and stress are not important triggers in developing acute TE, and the most important factor in its development is the SARS-CoV-2 infection itself. The fact that the pull test was significantly lower in patients in our study using FVP may suggest that FVP has no effect on TE's development. Studies on the cutaneous side effects of the drug were examined, and we did not find any study on its effect on alopecia and TE. We think that our study is also important in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study, dated 29.06.2022 and numbered 06-2022/09, was obtained from the clinical research ethics committee of Karamanoğlu Mehmet Bey University, Faculty of Medicine.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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