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Effects of Various Direct-acting Antivirals in the Quality of Life of Patients with Chronic Hepatitis C

Hepatit C Hastalarında Direkt Etkili Antiviral Tedavilerin Yaşam Kalitesine Etkisinin Karşılaştırılması

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Abstract

Introduction: Chronic hepatitis C is an infectious disease known to affect people worldwide. The disease is characterized by both hepatic and extrahepatic manifestations that impair the patient's overall quality of life (QoL). Potent and easy-to-use direct-acting antivirals (DAAs) have been recently introduced to treat chronic hepatitis C virus (HCV) infection. This study aimed to assess the QoL of patients with chronic HCV before and after DAAs treatment.

Materials and Methods: The Liver Disease Symptom Index 2.0, Short Form-36 (SF-36), and Beck-Anxiety Inventory scale were administered before and at the end of the treatment to evaluate the QoL in patients who were initiated with sofosbuvir and ledipasvir (SOF/LED)±ribavirin (RBV) or ombitasvir, paritaprevir, ritonavir, and dasabuvir (PROD). In addition, another questionnaire was used to evaluate the treatment waiting period effects on the patients' psychology.

Results: A total of 46 patients receiving DAAs were included in the study, 22 of which received SOF/LED (group 1), four received SOF/LED+RBV (group 2), and 20 received PROD (group 3). At the end of the treatment, a significant improvement was observed in The Liver Disease Symptom Index 2.0 items including daytime sleepiness, effect of sleepiness on daily life, presence of depression, effect of depression on daily life, and fear of developing liver disease complication ($p=0.002$, $p=0.035$, $p<0.001$, $p=0.039$, and $p=0.013$, respectively). Among SF-36 parameters, a significant improvement was observed in physical functioning, physical role limitations, body pain, and vitality in groups 1 and 3 at the end of the treatment ($p<0.001$, $p<0.001$, $p=0.001$, and $p<0.001$). Direct-acting antivirals treatment has improved the Beck-Anxiety Inventory; however, when the RBV was added to the treatment, patients' anxiety increased ($p=0.0026$). The effect of the waiting period for receiving HCV treatment on patients caused anxiety about disease progression and fear of developing cirrhosis.

Conclusion: We conclude that DAAs contribute to improvement of the QoL of patients during and after HCV infection treatment.

Keywords: Hepatitis C, direct-acting antiviral, SF-36, Beck-Anxiety Inventory, quality of life

Öz

Giriş: Dünya genelinde yaygın olarak görülen hepatik ve ekstrahepatik tutulumlara neden olan Hepatit C virüs (HCV) enfeksiyonu, hastaların yaşam kalitesini (YK) de bozmaktadır. Kronik HCV tedavisinde yakın zamanda kullanıma girmiş olan direkt etkili antiviraller (DEA) potent ve kullanımı kolay ajanlardır. Çalışmamızda DEA tedavi verilen kronik HCV, hastalarında, tedavi öncesinde ve tedavi sonunda YK değerlendirmeyi ve tedavilerin YK'ya etkisini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Sofosbuvir/ledipasvir (SOF/LED)±ribavirin (RBV) veya ombitasvir/pariteprevir/ritonavir/dasabuvir (PROD) başlanan hastalara YK değerlendirmek için tedavi öncesi ve tedavi sonunda Kısa Form-36 (SF-36), Kronik Karaciğer Hastalığı Yaşam Kalitesi Ölçeği 2.0 ve Beck-Anksiyete Ölçeği uygulanmıştır. Ayrıca tedavi bekleme süresinin hastaların psikolojilerine etkisini değerlendirilmek amaçlı farklı bir anket daha uygulanmıştır.

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Bulgular: DEA alan 46 hasta çalışmaya alınmış olup 22 hasta SOF/LED (grup 1), dört hasta SOF/LED+RBV (grup 2), 20 hasta PROD (grup 3) almıştır. Tedavi sonuda Kronik Karaciğer Hastalığı Yaşam Kalitesi Ölçeği 2.0'ın gün boyu uykulu olma hali ve uyku halinin günlük yaşama etkisi, depresyon varlığı, depresyonun günlük yaşama etkisi ve karaciğer hastalığı komplikasyonu gelişme korkusu parametrelerinde anlamlı iyileşme saptanmıştır (p=0,002, p=0,035, p<0,001, p=0,039, p=0,013) grup 1 ve 3'te SF-36 parametrelerinden tedavi sonunda fiziksel işlev, fiziksel rol kısıtlamaları, vücut ağrısı ve canlılıkta anlamlı iyileşme gözlendi (p<0,001, p<0,001, p=0,001, p<0,001). Beck-Anksiyete Ölçeği'ne göre ise RBV verilmeyen gruplarda tedavi sonunda anksiyete düzeyinde anlamlı düzelme saptanırken, tedaviye RBV eklenildiğinde ise hastaların aksiyetesinin arttığı izlenilmiştir (p=0,0026). HCV tedavisi bekleme sürecinin hastalar üzerine etkisi değerlendirildiğinde ise en çok hastalığının ilerleme endişesi ve siroz olma korkusu olduğu görülmüştür.
Sonuç: HCV tedavisinde kullanılan DEA'lar tedavi sürecinde ve sonrasında hastaların YK iyileşmesine katkıda bulunmaktadır.
Anahtar Kelimeler: Hepatit C, direkt etkili antiviraller, SF-36, Beck-Anksiyete Ölçeği, yaşam kalitesi

Introduction

Hepatitis C virus (HCV) infection is a major health concern worldwide with a high rate of developing into a chronic condition. Approximately, 71 million people suffer from chronic HCV infection worldwide[1]. Chronic infection is characterized by both hepatic and extrahepatic manifestations. Complication development advanced stages of chronic HCV, such as ascites, encephalopathy, anxiety, depression, fatigue, and muscle cramps substantially impairs the health-related quality of life (QoL) in patients. Moreover, factors such as low socio-economic level, intravenous drug use, medical or psychiatric comorbidities, concurrent medications, increased disease severity, and feeling of being stigmatized with HCV infection also impair the QoL[2].

Previous studies showed that achieving a sustained virologic response in chronic HCV infection can significantly improve the QoL of patients[3,4].

Until recently, pegylated-interferon (PEG-IFN) and ribavirin (RBV) served as the primary therapy for patients with HCV. However, these medications are difficult to use and have numerous side effects, low treatment response levels, and high possibility of relapse. Recently, direct-acting antivirals (DAAs) are gaining importance as an alternative treatment owing to their easy-to-use nature and low side effects. Studies showing the effect of these medications on the QoL are limited; however, no QoL impairment was shown during this treatment[4,5]. The present study assessed the effect of sofosbuvir (SOF) and ledipasvir±RBV and ombitasvir, paritaprevir, ritonavir, and dasabuvir (PROD)±RBV as DAAs on the QoL of patients with chronic HCV. Direct-acting antivirals have been in use for treating HCV infection in several parts of the world; however, these were introduced in Turkey in 2016 and reimbursed by the Social Security Institution (SSI), and continuously used thereafter. Therefore, the effect on the patients' psychology of time that elapsed before these treatments had started to be reimbursed in Turkey was also studied. This study aimed to elucidate to countries that still do not have DAAs under social security and have limited access to these drugs.

Materials and Methods

Study Design and Participants

The present prospective study included patients older than 18 years, female or male, treatment-naive or treatment-experienced, cirrhotic or non-cirrhotic, and who started to receive any type of DAA (SOF±RBV or PROD) for the treatment of chronic HCV at the local university infectious disease and clinical microbiology clinic between July 2016 and July 2017. Patients under 18 years of age, and patients negative for HCV ribonucleic acid were excluded from the study. A comprehensive medical history was taken before the treatment, and the information about patients age, sex, educational status, smoking status, HCV genotype, cirrhosis status, treatment experience, and possible routes of transmission was recorded.

Ethical Consideration

Ethics Committee approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee for the study with the decision numbered 2016/282. All participants were informed about the contents and objectives of this study; they all provided the written consent.

QoL Questionnaire Used in the Study

To determine the effect of treatment on the QoL, Short-Form 36 (SF-36) QoL questionnaire[6], The Liver Disease Symptom Index 2.0[7], and Beck-Anxiety Inventory[8] were used in the beginning and at the end (at week 12 or 24) of the treatment. Changes in these scales were compared between treatment groups. Moreover, another 13-item questionnaire was used to evaluate the effect on the patients' psychology of time that lapsed until reimbursement of DAAs started in Turkey (Appendix 1).

SF-36

Short-Form 36 consists of a total of 36 items that cover eight domains: physical functioning (10 items), physical role limitations (four items), body pain (two items), general health (six items), vitality (four items), social functioning (two items), emotional role limitations (three items), and mental health (five

items). Each sub-scale is evaluated with a score from 0 to 100. A higher score reflects better health status. Short-Form 36 is a well-validated and widely used scoring system and has been especially used in studying patients with chronic hepatitis[6].

The Liver Disease Symptom Index 2.0

Consisting two domains, the questionnaire comprises a total of 24 sub-questions. The validity and safety of this questionnaire in the Turkish population were assessed by Eraydın et al.[9]. Each option in the questionnaire is scored between a minimum of "0" and a maximum of "4"; "0" reflects the lowest score and "4" the highest. Higher scores show poorer QoL.

Beck-Anxiety Inventory

It is used to determine the effect of emotions, such as worry, anxiety, and extended fear. Results of this 21-item test are as follows: a total score of 0-7 shows no anxiety, 8-15 shows mild anxiety, 16-25 shows moderate anxiety, and 26-63 shows severe anxiety[8].

Statistical Analysis

Clinico demographic parameters and baseline QoL scores were compared between three treatment regimen groups (SOF±RBV, PROD). At the end of the treatment, changes in QoL scores (decrements or improvements) from baseline were calculated for each patient.

Data were analyzed using the Statistical Package for the Social Sciences version 23 (Armonk, NY: IBM Corp). Shapiro-Wilk test was used to determine if data were normally distributed. Kruskal-Wallis and Wilcoxon tests were used to compare non-normally distributed quantitative data. Chi-square, McNemar, and two sample ratio tests were used to compare qualitative data. Qualitative data were presented as frequency (percentage), whereas quantitative data were presented as median (minimum-maximum). A p value of <0.05 was considered statistically significant.

Results

A total of 46 patients receiving DAAs were included in the present study. 76% of patients experienced previous treatment. Of which, 22 patients received SOF (group 1), four received SOF+RBV (group 2), and 20 received PROD (group 3). The median age was 57 (25-81) years and 25 (54%) of patients were female. No significant difference was found between treatment groups in terms of age and sex. All patients had HCV genotype 1, with 41 patients (89%) having genotype 1b and one (2%) having genotype 1a. Four (9%) patients had genotype 1 but subtype analysis was unknown. A total of 32 (69%) patients were non-cirrhotic, whereas 14 had compensated cirrhosis. Comorbidities were present in 67% of the patients (n=31; Table 1).

Table 1. Comparison of demographic data by treatment regimens

	Total (n=46) (%)	Group 1 (SOF/LDV) (n=22) (%)	Group 2 (SOF/LDV+RBV) (n=4) (%)	Group 3 (PROD) (n=20) (%)	p
Age (minimum-maximum)	57 (25-81)	56.5 (41-81)	56 (25-57)	60 (46-80)	0.406
≥70	7 (16%)	3 (42%)	-	4 (58%)	
Sex					
Male	21 (46%)	9 (43%)	1 (5%)	11 (52%)	0.383
Female	25 (54%)	13 (52%)	3 (12%)	9 (36%)	
Genotype					
1b	41 (89%)	17 (77%)	4 (100%)	20 (100%)	
1a	1 (2%)	1 (5%)	-	-	
1*	4 (9%)	4 (18%)	-	-	
Cirrhosis status					
Compensated	16 (35%)	8 (36%)	2 (50%)	6 (30%)	
Non-cirrhotic	30 (65%)	14 (64%)	2 (50%)	14 (70%)	
Treatment experience					
Yes	35 (76%)	21 (95%)	3 (75%)	11 (55%)	
No	11 (24%)	1 (5%)	1 (25%)	9 (45%)	
Smoking					
No	40 (87%)	18 (82%)	4 (100%)	18 (90%)	
Yes	6 (13%)	4 (18%)	-	2 (10%)	
Comorbidities					
No	15 (33%)	6 (27%)	3 (75%)	6 (30%)	
Yes	31 (67%)	16 (73%)	1 (25%)	14 (70%)	

*Subgenotype is unknown.
SOF/LED: Sofosbuvir/ledipasvir, SOF/LED+RBV: Sofosbuvir/ledipasvir+ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir/dasabuvir

Assessment by SF-36 QoL Questionnaire

Among SF-36 parameters, significant improvement was observed in physical functioning, physical role limitations, body pain, and vitality in groups 1 and 3 at the end of the treatment (p<0.001, p<0.001, p=0.001, and p<0.001, respectively).

Improvement in groups 1 and 3 at the end of the treatment concerning changes in general health parameters were observed. This improvement was significant for group 3 (p=0.01) but not for group 1. The general health parameter declined in group 2 at the end of treatment (Table 2). A significant improvement was observed in social functioning, emotional role limitations, and mental health parameters in all patients at the end of the treatment (p=0.024, p=0.002, and p=0.001, respectively). When the distribution of changes in these parameters was evaluated by treatment groups, a significant change was observed only in group 1. None of the SF-36 parameters showed a notable change in group 2 before and after the treatment (Figure 1).

Assessment by The Liver Disease Symptom Index 2.0

In The Liver Disease Symptom Index 2.0, questions on "the presence of jaundice" and "the effect of jaundice on daily life" were most frequently answered as "never" before and after the treatment (pre-treatment: 91.3% and 95.6%, respectively; post-treatment: 93.4% and 95.6%, respectively).

Questions on depression (14.6%) and lack of sexual drive (14.6%) were most frequently answered as "always" before the treatment.

The question of lack of sexual drive (13%) was most frequently answered as "always" after the treatment. In total, 6th (anorexia) and 12th (financial distruption) questions were not answered by any of patients as "always" before and after the treatment, respectively. At the end of the treatment, usually, >50% of patients answered "never" to questions. Only questions on depression, forgetfulness, and lack of sexual drive and activity were answered as "never" by <50% of patients.

Table 2. Distribution of pre-and post-treatment Short Form-36 scores by treatment groups

		Total	Group 1 (SOF/LDV) n=22	Group 2 (SOF/LDV+RBV) n=4	Group 3 (PROD) n=20	p
Physical functioning	Before	65 (25-100)	60 (25-100)	87.5 (25-100)	65 (30-100)	0.382
	After	80 (25-100)	80 (40-100)	90 (50-95)	75 (25-100)	0.482
	p	**<0.001**	**0.004**	0.414	**0.036**	
Physical role limitations	Before	75 (0-100)	62.5 (0-100)	100 (0-100)	75 (0-100)	0.398
	After	75 (0-100)	100 (50-100)	87.5 (0-100)	75 (0-100)	0.571
	p	**<0.001**	**0.003**	0.317	**0.015**	
Bodily pain	Before	64 (0-100)	71 (32-100)	87 (41-100)	52 (0-100)	0.260
	After	74 (20-100)	79 (20-100)	79 (52-84)	74 (22-100)	0.830
	p	**0.001**	**0.048**	0.276	**0.002**	
General health	Before	56 (5-100)	60 (35-100)	49.5 (10-100)	56 (5-100)	0.585
	After	65 (25-100)	67 (35-100)	46 (35-100)	65 (25-86)	0.456
	p	**0.004**	0.078	0.655	**0.010**	
Vitality	Before	55 (0-100)	47.5 (15-90)	65 (20-95)	55 (0-100)	0.573
	After	70 (15-100)	75 (40-95)	45 (20-95)	65 (15-100)	0.225
	p	**<0.001**	**<0.001**	0.317	**0.034**	
Social functioning	Before	75 (0-100)	75 (0-100)	81 (37-100)	75 (12-100)	0.951
	After	87 (0-100)	87 (50-100)	56 (0-100)	75 (12-100)	0.151
	p	0.024	0.003	0.655	0.507	
Emotional role limitations	Before	66 (0-100)	66 (0-100)	100 (66-100)	66 (0-100)	0.303
	After	100 (0-100)	100 (66-100)	100 (66-100)	100 (0-100)	0.994
	p	**0.002**	**0.008**	1.000	0.057	
Mental health	Before	72 (4-100)	72 (20-92)	72 (40-100)	72 (4-100)	0.935
	After	84 (28-100)	84 (60-96)	70 (44-96)	74 (28-100)	0.359
	p	**0.001**	**0.002**	0.785	0.097	

SOF/LED: Sofosbuvir/ledipasvir, SOF/LED+RBV: Sofosbuvir/ledipasvir+ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir/dasabuvir

Figure 1. Distribution of the pre-and post-treatment Short Form-36 parameters by treatment groups

SOF/LED: Sofosbuvir/ledipasvir, SOF/LED+RBV: Sofosbuvir/ledipasvir+ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir/dasabuvir

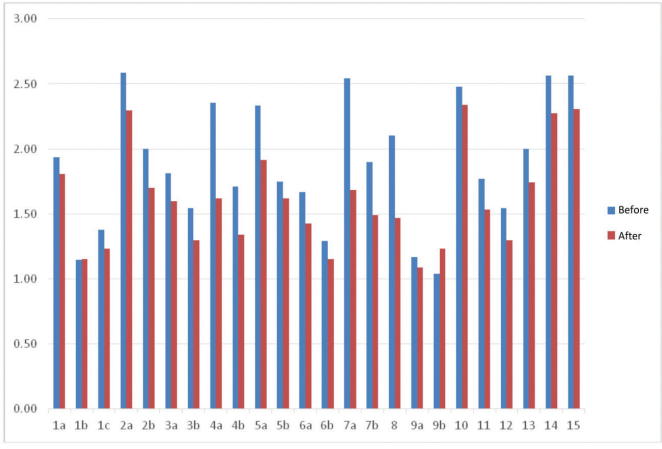

Figure 2. Comparison of answers given to questions in The Liver Disease Symptom Index 2.0 before and after the treatment

1a. Presence of itching,1b. Presence of itching hampering daily activities,1c. Presence of itching interrupting sleep, 2a. Presence of arthralgia, 2b. Presence of arthralgia blocking daily activities, 3a. Right upper abdominal quadrant pain, 3b. Right upper abdominal quadrant pain blocking daily activities, 4a. Daytime sleepiness, 4b. Daytime sleepiness blocking daily activities, 5a. Anxiety in family life due to liver disease, 5b. The effect of anxiety due to liver disease on daily activities, 6a. Decreased appetite, 6b. The effect of decreased appetite, 7a. The presence of depression, 7b. The presence of depression blocking daily activities and social relations, 8. The fear of complications, 9a. The presence of jaundice, 9b. The presence of jaundice hampering daily activities and social relations, 10. Forgetfulness, 11. Personality change, 12. Liver disease hampering financial affairs, 13. Liver disease affecting time use, 14. Reduced sexual drive, 15. Reduced sexual activity.

When the pre-and post-treatment scores in The Liver Disease Symptom Index were compared, post-treatment scores were found to decrease in the majority of questions, indicating improved patient complaints. The answer to question 7a related to the presence of depression was 2.54 before the treatment; however, it regressed to 1.68 after the treatment (Figure 2).

We observed a significant improvement in items, including daytime sleepiness, effect of sleepiness on daily life, presence of depression, effect of depression on daily life, and fear of developing liver disease complication, after the treatment (p values=0.002, 0.035, <0.001, 0.039, and 0.013, respectively).

Beck-Anxiety Inventory Scores

Of our patients, 27% had a history of psychiatric examination. Mean Beck-Anxiety Inventory score showed mild anxiety in patients before the treatment and 90% of patients had moderate to severe anxiety. While the median pre-treatment Beck-Anxiety Inventory score was 10, it was 5.5 after the treatment, and the decrease observed at the end of the treatment was statistically significant (p=0.001). Median post-treatment values also differed by treatment groups. A decrease was observed in the Beck-Anxiety Inventory score in groups that received SOF/LDV (group 1) and PROD (group 3), the group receiving SOF/LDV+RBV (group 2) reported an increase. It was observed that when RBV was added in the SOF/LDV treatment, the median anxiety score increased significantly (p=0.0026; Table 3).

Effect of the Waiting Period for DAAs on Patients

The median waiting period for DAAs for treating chronic HCV was four years (1-15 years) for patients included in the study. Among patients waiting for treatment, 58.3% of the patients had planned to obtain these drugs with a fee if the prices were not too expensive. The waiting period caused worrying for disease progression (56%) and fear of developing cirrhosis (48%) During the waiting period, 21% of the patients had used herbal remedies, and 6.3% had sought help from non-medical individuals and institutions. The majority of the patients (81%) started being treated hoped to be cured by these treatments.

Discussion

Health-related QoL assessments are used to determine the patient's perspective on the burden of a disease and its treatments. Substantial impairment in the QoL of patients with chronic liver disease has been reported[10]. Previous treatments used for chronic HCV included IFN and RBV that are considered to be very intense treatments that significantly impair the QoL of patients during treatment. A significant improvement in the QoL of patients has been reported when a sustained virologic response was achieved[11]. Our study is the first of its kind to investigate the QoL of patients receiving DAAs with HCV in Turkey

Table 3. The distribution of the pre- and post-treatment Beck-Anxiety Inventory scores by treatment groups

	Total (n=46)	Group 1 (SOF/LDV) (n=22)	Group 2 (SOF/LDV+RBV) (n=4)	Group 3 (PROD) (n=20)	p
Comparison of Beck-Anxiety Inventory scores					
Pre-treatment	10 (1-35)	9 (1-28)	6.5 (4-23)	11 (1-35)	0.762
Post-treatment	5.5 (0-40)	4 (0-25)[a]	16 (7-21)[b]	8 (0-40)[ab]	**0.026**
Difference	4 (-30–23)	5 (-4–23)	-4 (-15–3)	4 (-30–20)	0.062
p	0.001				

[ab]: There is no difference between the groups with the same letter.
SOF/LED: Sofosbuvir/ledipasvir, SOF/LED+RBV: Sofosbuvir/ledipasvir+ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir/dasabuvir

and the first study in the literature evaluating the psychological status of patients waiting to reach the drug. Short-Form 36 has been widely used by several studies to evaluate the effect of HCV treatment on the QoL. For example, in 2015, Stahmeyer reported a significant decrease in the SF-36 score during and after the treatment of 2,223 patients with PEG-IFN+RBV, and a substantial increase in the mean QoL scores 24 weeks after the treatment as compared to baseline scores[12].

Studies investigating the effect of DAAs on the QoL were mostly performed using SOF/LDV and showed that the treatment regimens that did not contain IFN substantially improved the QoL[4,13]. Moreover, literature cites no large study on the PROD regimen, and limited studies have shown a minimal decrease in the SF-36 score[5].

Younossi et al.[4] reported an improvement in the SF-36 parameters of patients who received SOF/LDV during and after the treatment. Moreover, this improvement was sustained at week 12 after the treatment. In another study by Younossi et al.[13] in 106 Asian patients who received SOF/LDV±RBV±IFN, improvement in social functioning, emotional role limitations, and mental health problems was only observed in the group that was given SOF/LDV at the end of the treatment. Improvement in the SF-36 at the end of the treatment in groups 1 and 3 were also observed. When changes in these parameters were evaluated by treatment groups, a significant improvement in physical functioning, physical role limitations, body pain, and vitality scores were observed in the group that received SOF/LDV and PROD. The change in general health was significant in the PROD group; however, it was not significant in the SOF/LDV arm (p=0.010 and p=0.078, respectively). In ION 1-2-3 studies, phase studies for SOF/LDV, the end-of-treatment SF-36 scores were evaluated in 582 patients who received SOF/LDV. A significant improvement has been reported in general health at the end of treatment[11]. The lack of a significant change in the SOF/LDV arm in our study could be attributed to a low number of patients.

Literature reports studies evaluating the individual effects of PROD and SOF/LDV on the QoL; however, our study is the first of its kind to compare the effects of these two treatment regimens on the QoL.

Concurrently, using The Liver Disease Symptom Index 2.0 and SF-36 questionnaire in our study provided a holistic approach for the evaluation of patients. According to The Liver Disease Symptom Index 2.0, the higher score was given to joint pain (2.58) before the treatment and to forgetfulness (2.34) after the treatment. However, the improvement was observed in both symptoms after the treatment. In a Dutch study performed by van der Plas et al.[7] in 1,175 patients, most common symptoms were found to be sleepiness (71%), joint pain (58%), and personality change (69.6%). In our study, >50% of patients had joint pain, daytime sleepiness, anxiety, depression, forgetfulness, and lack of sexual drive activity before the treatment, and these symptoms generally improved after treatment. Especially, symptoms such as depression, sleepiness, and the fear of developing complications showed significant improvement after the treatment.

HCV infection is one of the several infections that are known to be associated with psychiatric disorders[14]. Neuropsychiatric symptoms, such as depression and anxiety, are common in patients with HCV[15]. In their study on 500 patients having HCV infection, Navinés et al.[16] detected a psychiatric disorder in 23% of patients and overall anxiety in 7%, regardless of the severity of the liver disease. Similar to the literature, 27% of our patients had a history of examination for a psychiatric disorder and 23% had treatment history for psychiatric disorder. Depression and anxiety seen in patients with HCV infection affect the QoL. Successful treatment of HCV infection is known to improve the neuropsychiatric manifestations of the disease and QoL scores[17].

In our study, 19% of patients had moderate to severe anxiety according to the Beck-Anxiety Inventory before the treatment. Median Beck-Anxiety Inventory scores of patients significantly improved after the treatment. A decrease in the Beck-Anxiety Inventory score in groups that received SOF/LDV and PROD was observed, whereas an increase was observed in the group that received SOF/LDV+RBV. However, only four patients are included

in the SOF/LDV+RBV treatment arm, thus, scientific comments were not made on this issue. Further large scale studies are needed to evaluate the possible effects of this treatment arm.

In Turkey, DAAs were introduced into the market by the SSI two years after they became available worldwide. During the waiting period, several of our patients manifested worries for disease progression (56%) and fear of developing cirrhosis (48%). Moreover, our patients also had a fear of getting cancer, fear of death, and fear of transmitting the disease to their spouse, children, or friends. Under the effect of these fears, 21.2% of our patients used herbal remedies and 6.3% sought help from non-medical individuals and institutions during the waiting period. These data showed that patients waiting for treatment did not only suffer from HCV-related complications, but were also forced to try non-pharmacological and unproven treatments due to fear, worry, and anxiety linked with the disease. For all these reasons, patients who were waiting for the treatment were at more risk than thought.

One of the limitations of our study was the small number of patients as compared to large studies conducted on DAAs. Our patient population included only those with genotype 1 and more non-cirrhotic patients than cirrhotic patients. In our study, questionnaires were usually filled using self-administration technique. However, questionnaires were filled using a face-to-face interview technique in patients who did not meet ideal conditions to fill the forms owing to advanced age and poor educational level. While this might cause discrepancy, it also made the participants understand the questions better and answer them carefully.

Conclusion

In conclusion, data collected from SF-36, The Liver Disease Symptom Index 2.0, and Beck-Anxiety Inventory questionnaires showed that SOF/LDV or PROD treatment regimen for chronic HCV improved the QoL and reduced the anxiety and depression of patients at the end of the treatment. The delay in reimbursing the medications by the SSI caused significant worry and anxiety among patients for disease progression and fear of developing cirrhosis, thereby compelling patients to switch to non-pharmacological or unproven treatment methods.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee for the study with the decision numbered KAEK: 2016/282.

Informed Consent: All participants were informed about the contents and objectives of this study; they all provided the written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.Ö., M.Ç., T.Ö., Concept: Ş.E., E.T., Design: Ş.E., E.T., Data Collection or Processing: B.A.Ö., M.Ç., T.Ö., Analysis or Interpretation: İ.B., Literature Search: H.Ö.Ç., İ.B., Writing: H.Ö.Ç.

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Appendix 1. Questionnaire to evaluate the effect of the waiting period for hepatitis C treatment on patients

1. How many years have you been waiting for new medications for hepatitis C?

2. Did you consider paying for these medications out of pocket?

1. No
2. Yes, I did; however, the medications were costly.

3. What was the effect of the waiting period for new treatments on you? (You can choose more than one option).

1. Worry
2. Fear of developing cirrhosis
3. Fear of getting cancer
4. Fear of death
5. Fear of transmitting hepatitis C to my spouse
6. Fear of transmitting hepatitis C to my children
7. Fear of transmitting hepatitis C to my friends
8. It did not have any effect on me
9. Other

4. What are your expectations from the new treatments?

1. I can be cured
2. There might be a possibility of recurrence
3. The disease may not be cured completely
4. Other

5. Did you use any herbal remedies during the waiting period?

1. Yes
2. No (If no, please move on to question 11)

6. Which herbal remedies did you use?

7. Where did you learn about the herbal remedy that you have used?

1. Friend
2. Internet
3. TV
4. Herbalist
5. Another hepatitis patient
6. Physician
7. Other

8. Did you have any complaint during the herbal treatment?

1. Yes
2. No

9. If yes, what were your complaints?

10. Did you see any changes in your laboratory tests about hepatitis C?

1. Impaired liver function tests (AST, ALT, GGT, ALP, INR, and aPTT)
2. Increased HCV-RNA
3. Impaired renal function
4. Electrolyte imbalance
5. Other

11. Did you seek help for the treatment from a non-medical individual or institution during the waiting period?

1. Yes
2. No

12. Were you examined for a psychiatric disorder (depression or anxiety) in the past?

1. Yes
2. No

13. Did you get treatment for a psychiatric disorder (depression or anxiety) in the past?

1. Yes
2. No