Research Article

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Long-Term Outcomes of Patients with Chronic Hepatitis C Treated with Direct-Acting Antivirals in Turkey

Türkiye'de Direkt Etkili Antivirallerle Tedavi Edilen Kronik Hepatit C Hastalarının Uzun Dönem Sonuçları

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ABSTRACT

Objectives: Direct-acting antivirals (DAA) improve clinical outcomes in chronic hepatitis C (CHC). Data about the long-term outcomes of patients with CHC treated with DAAs in Turkey. We aimed to analyze the characteristics and outcomes of patients with CHC who attended the 3-year follow-up visit after completing DAA therapy and to present their implications for clinical management and public health.

Materials and Methods: This single-center, single-arm, retrospective study included adult CHC patients treated with DAA ± ribavirin and attended the year 3 follow-up visit after completing treatment. Data on patient characteristics, laboratory parameters, recurrent/relapsing hepatitis C virus (HCV) infection, cirrhosis, and hepatocellular carcinoma (HCC) were collected from the hospital medical records and descriptively analyzed.

Results: Sixty-eight patients (55.9% women), including 15 patients (22.1%) of foreign origin, were included in the study. Forty-six patients (67.6%) had a known route of HCV transmission, and 27 (58.7%) were infected through blood transfusion and/or surgical intervention. Most participants (57.4%) were infected with HCV genotype (GT) 1b: all patients of European origin with GT1b, two-thirds of Syrian participants with GT4, and half of Asians with GT3. Three patients had cirrhosis (4.4%; all compensated) at baseline. No patient developed relapse, reinfection, cirrhosis, decompensation, or HCC.

Conclusion: Sustained virologic response, absence of new cases of cirrhosis, decompensation, or HCC during follow-up support the

ÖZ

Amaç: Direkt etkili antiviraller (DAA), kronik hepatit C (KHC) tedavi sonuçları iyileştirmiştir. Türkiye'de DAA'larla tedavi edilen KHC hastalarının uzun dönem takibine ilişkin veriler sınırlıdır. DAA tedavisini tamamladıktan sonra 3. yıl takibine gelen KHC hastalarının özelliklerini ve sonuçlarını analiz etmeyi ve bunların tedavi yönetimine ve halk sağlığına etkilerini sunmayı amaçladık.

Gereç ve Yöntemler: Bu tek merkezli, tek kollu, retrospektif çalışmaya DAA ± ribavirin ile tedavi edilen ve tedavi tamamlandıktan sonra 3. yıl takibine gelen yetişkin KHC hastaları dahil edildi. Hastaların özellikleri, laboratuvar parametreleri, nüks veya yeni gelişen hepatit C virüsü (HCV) enfeksiyonu, siroz ve hepatoselüler karsinom (HCC) gelişimi verileri hastane tıbbi kayıtlarından toplanmış ve tanımlayıcı olarak analiz edilmiştir.

Bulgular: Çalışmaya 15'i (%22,1) yabancı kökenli olmak üzere 68 hasta (%55,9'u kadın) dahil edildi. Kırk altı hastada (%67,6) HCV'nin bulaşma yolu biliniyordu ve bunların 27'si (%58,7) kan transfüzyonu ve/veya cerrahi müdahale yoluyla enfekte olmuştu. Katılımcıların çoğu (%57,4) HCV genotip (GT) 1b ile enfekteydi: Avrupa kökenli hastaların tümü GT 1b, Suriyeli katılımcıların üçte ikisi GT 4 ve Asyalıların yarısı GT 3 ile enfekteydi. Başlangıçta üç hastada siroz vardı (%4,4; hepsi kompanse sirozdu). Hiçbir hastada nüks, yeniden enfeksiyon, siroz, dekompansasyon veya HCC gelişmedi.

Sonuç: Kalıcı virolojik yanıt, takip sırasında yeni siroz, dekompansasyon veya HCC vakalarının görülmemesi DAA'ların uzun vadeli klinik etkinliğini desteklemektedir. Hepatit C önleme

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long-term clinical effectiveness of DAAs. Hepatitis C Prevention and Control strategies should include post-treatment follow-up of patients at high risk of progression, HCC, recurrence, and relapse, and individuals who could potentially spread the infection.
Keywords: Hepatitis C, hepatocellular carcinoma, cirrhosis, death, sustained virologic response

ve kontrol stratejileri, ilerleme, HCC, nüks ve yeniden enfeksiyon riski yüksek olan hastaların ve enfeksiyonu yayma potansiyeli olan kişilerin tedavi sonrası takibini içermelidir.
Anahtar Kelimeler: Hepatit C, hepatoselüler karsinom, siroz, ölüm, kalıcı virolojik yanıt

Introduction

Chronic hepatitis C (CHC) affects millions of people worldwide and predisposes individuals to clinical conditions with significant morbidity and mortality, such as liver cirrhosis and hepatocellular carcinoma (HCC) (1).

To eliminate hepatitis C as a public health threat by 2030, the World Health Organization (WHO) aims to reduce new hepatitis C infections by 75% (from 20 to 5 per 100,000) and associated deaths by 60% (from 5 to 2 per 100,000) between 2020 and 2030 (2). Given that there is not yet an effective hepatitis C virus (HCV) vaccine and acute hepatitis C silently progresses to chronicity in 70% of cases, it is crucial to identify and effectively treat patients with CHC to achieve these targets (1,2).

The introduction of direct-acting antivirals (DAAs) in the 2010s marked a major milestone in the treatment of CHC (3). The oral route of administration, short duration of treatment (8-12 weeks in most cases), specific mechanisms of action targeting proteins essential for HCV replication, availability of pangenotypic regimens, achievement of better clinical outcomes with an acceptable safety and tolerability profile are the key advantages of DAAs over pegylated interferon-ribavirin therapy, which was the standard of care for hepatitis C in the 2000s (3,4).

Sustained virological response (SVR) rates exceed 95% with current DAA regimens and are above 85% even in challenging clinical conditions such as decompensated cirrhosis and HCC (5,6,7,8,9,10). The achievement of SVR is considered cure in patients with non-cirrhosis (5,6) and independently predicts reduced mortality, decompensation, HCC occurrence, and recurrence in CHC (11).

The European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver Diseases: The Infectious Diseases Society of America recommends regular post-treatment follow-up, even if SVR is achieved, for individuals with liver cirrhosis or predisposition to liver disease (obesity, diabetes mellitus and excessive alcohol intake) and those with ongoing risk behaviors for HCV reinfection and transmission, such as people who inject drugs (PWIDs) and men who have sex with men (MSMs) (5,6).

To eliminate hepatitis C, the 5-year National Viral Hepatitis Prevention and Control Program was created by the Turkish Ministry of Health in 2018, and in the same year, a road map for hepatitis C was developed in cooperation with the Viral Hepatitis Society and the Turkish Association for the Study of the Liver (12,13,14).

In Turkey, the first DAA therapy for CHC was approved in 2015, and DAAs have been reimbursed by the Social Security Institution since June 2016 (15). Real-life studies from Turkey have reported SVR12/24 rates of 85% to 100% with various DAA regimens in CHC, but data on long-term follow-up are limited (16,17,18,19,20, 21,22,23,24,25).

This article presents a descriptive analysis of the characteristics and clinical outcomes of patients with CHC who were followed-up for 3 years after completing DAA therapy and their implications for clinical management and public health.

Materials and Methods

This real-world study was based on a retrospective review of hospital medical records of patients treated for chronic HCV infection at the Infectious Diseases Clinic of the Haseki Training and Research Hospital between June 1, 2016 and January 31, 2020. The inclusion criteria were age ≥18 years, treatment with DAA ± ribavirin, adherence to the treatment regimen, and attendance at the follow-up visit 3 years after the completion of DAA treatment.

Information on patients' demographics [age, sex, body mass index (BMI), country of origin], comorbidities (diabetes mellitus, hypertension, heart disease, chronic renal failure, thyroid disease, cirrhosis, and co-infection with [hepatitis B virus (HBV)/human immunodeficiency virus (HIV)], HCV genotypes (GT), hepatitis activity index (HAI), and fibrosis (F) score before DAA treatment (if a liver biopsy was made), route of HCV transmission, and DAA regimens were recorded. In addition, data on HCV-RNA, blood counts [leukocytes, erythrocytes and platelets (PLT)], coagulation, prothrombin time, international normalized ratio, and blood biochemistry [urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total protein, albumin, total bilirubin, alpha-fetoprotein (AFP)] at the onset of DAA therapy and at post-treatment weeks 12 and years 3 were collected.

The study was approved by the Ethics Committee of Clinical Research Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences Turkey (decision no: 105-2021, date: 27.10.2021) and conducted in accordance with The Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means and standard deviations, categorical variables as numbers and percentages, and non-normally distributed variables as median (minimum-maximum) values. The normality of the data was checked using the Kolmogorov-Smirnov or Shapiro-Wilk tests. The Friedman and Wilcoxon tests were used to compare continuous variables. Results were assessed on a bilateral basis at a 95% confidence level, with a significance level of <0.05.

Results

At the time of analysis, 77 out of the 143 patients treated with DAAs for CHC had at least 3 years since treatment completion. The study included 68 (55.9% women) patients who attended year 3 visits after the end of DAA therapy. The remaining nine patients died: two due to a heart attack and the third due to postoperative bleeding. The exact causes of death were not available for six patients, but none of these patients had cirrhosis or HCC at the last follow-up, and the deaths were not related to CHC complications. Table 1 presents the key demographic and clinical characteristics of the study population.

Table 1. Patients' characteristics

Characteristics (n=68)		**n (%)* or mean ± SD**
Sex	Female	38 (55.9)
	Male	30 (44.1)
Age, years		52±15
Country of origin	Türkiye	53 (77.9)
	Others**	15 (22.1)
BMI, kg/m²		26.9±5.1
	Obese (>30 kg/m²)	20 (29.4)
HBV	Inactive carrier	2 (2.9)
	Chronic hepatitis	2 (2.9)
	Immune (natural infection)	11 (16.2)
Anti-HIV (+)		2 (2.9)
HCV genotype	1	54 (79.4)
	Subtype 1a	12 (17.6)
	Subtype 1b	39 (57.4)
	Subtype not determined	3 (4.4)
	3	8 (11.8)
	4	5 (7.4)
	5	1 (1.5)
Cirrhosis	Compensated (Child-Pugh A)	3 (4.4)
Liver biopsy		43 (63.2)
	Hepatic activity index	6.2±2.2
	Fibrosis score	1.7±1.0
Route of transmission	Transfusion	11 (16.2)
	Surgery	8 (11.8)
	Surgery + transfusion	8 (11.8)
	IV drug use	6 (8.8)
	Other medical intervention	4 (5.9)
	Intrafamilial Dental procedure	4 (5.9) 3 (4.4)
	Sexual relation***	2 (2.9)
	Not known	22 (32.4)
Comorbidities	Hypertension	16 (23.5)
	Diabetes mellitus	12 (17.6)
	Renal disease****	6 (8.8)
	Cardiac disease	6 (8.8)
	Thyroid disease	6 (8.8)

*presented as % in the total study population
**Syria (n=6), Turkmenistan (n=2), Afghanistan (n=1), Azerbaijan (n=1), China (n=1), Uzbekistan (n=1), Ukraine (n=1), Moldova (n=1), Romania (n=1)
***includes 1 man having sex with men
****5 patients on hemodialysis
BMI: Body mass index, HBV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, IV: Intravenous, SD: Standard deviation

HCV GT1 was detected in 79.4% (n=54) of patients, the majority of whom (n=39; accounting for 57.4% of the whole study population) were infected with subtype 1b. The study population included 15 foreign nationals (22.1%), six from Syria and Asia, and three from Eastern Europe. Four out of six patients from Syria (66.7%) were infected with GT4, and the other two patients (33.3%) were infected with GT1a. Asian patients were equally infected with GT1b and GT3. All patients from Europe were infected with GT1b.

Two-thirds of the patients (67.6%; n=46) had a known route of HCV transmission, and 27 (58.7%) were infected through blood transfusion and/or surgical intervention. Seven foreign nationals (46.7%) and two Turkish patients (3.8%) reported HCV transmission through surgery or transfusion outside Turkey: Ukraine (n=1), Bulgaria (n=1), Uzbekistan (n=1), Turkmenistan (n=1), and Syria (n=5).

IV drug users (n=6) were equally infected with HCV GT1 and GT3. There were four patients (5.9%) co-infected with HBV (inactive carrier/chronic), two of whom were already on treatment at the time of onset of DAA therapy.

A liver biopsy was performed in 63.2% (n=43) of the study participants before starting DAAs. The mean HAI and F score in these patients were 6.2±2.2 and 1.7±1.0, respectively. Three patients (4.4%) had cirrhosis (all Child-Pugh A); none of them progressed during follow-up.

Overall, 39 patients (57.4%) had at least one comorbid condition. Hypertension was the most common comorbidity (23.5%; n=16) followed by diabetes mellitus (17.6%; n=12).

Table 2 summarizes the key treatment characteristics of the study. Overall, 23.5% (n=16) of patients were treatment-experienced, and relapse was the main reason for switching to DAAs in these patients (93.8%; n=15). The antiviral regimen used before DAAs in all patients except one was pegylated interferon plus ribavirin. Paritaprevir/ritonavir/ombitasvir-dasabuvir was the most frequently used (44.1%) DAA regimen.

The median serum viral load was 4500000 (31.880-41.100.000) IU/mL at baseline, which was significantly reduced and became undetectable at the first month of DAA treatment. All patients achieved SVR12, and the response was maintained at post-DAA year 3. The results of serial laboratory assessments at baseline and post-treatment assessment time-points are shown in Table 3. Liver function tests improved significantly compared with baseline at both 12 weeks and 3 years after treatment. There were no clinically significant changes in other laboratory parameters.

Discussion

In this retrospective study evaluating the clinical outcomes of patients with CHC over a 3-year period after completing

DAA therapy, virologic response was maintained in all patients, regardless of GT and treatment regimen. No new cirrhosis cases occurred during follow-up, and no patient developed relapse, reinfection, decompensated cirrhosis, or HCC.

The long-term maintenance of a 100% virologic response rate in the current study confirmed the suitability of SVR12 as a marker for predicting cure in CHC. Most studies have shown that SVR12/24 rates are lower in patients with decompensated cirrhosis or HCC (5,6,7,8,9,10). The achievement and maintenance of virologic response in all patients in the current study may be explained by the low proportion of patients with cirrhosis (4.4%; all compensated) and the absence of patients with HCC in our patient population. In a recent retrospective study in which all patients without cirrhosis achieved SVR12, Ebik et al. (23) found a 94.1% SVR rate in patients with cirrhosis, 53% of whom were classified as Child-Pugh B and C. In contrast, there are real-life studies from Turkey that reported that baseline cirrhotic status did not have a significant impact on achieving SVR with DAA treatment despite the inclusion of higher percentages of patients with cirrhosis compared with our study (34% and 58%; 42% of whom were decompensated in both studies) (18,19,20,21,22). Several factors, including study population characteristics and treatment regimens, are likely to play a role in the inconsistency of results on the cirrhosis-SVR relationship in real-life studies.

Decompensation and HCC are important clinical outcomes that determine prognosis in patients with CHC and cirrhosis. A systematic review and meta-analysis of 39 studies evaluating the impact of various DAA combinations on disease progression revealed that the risks of decompensation, HCC occurrence, and recurrence were significantly lower in patients with CHC who achieved SVR than in those who did not (11). Furthermore, estimates in another meta-analysis showed that despite achieving SVR with IFN-free DAA regimens, the incidence of HCC was approximately four-fold higher in patients with cirrhosis than in those with F3 fibrosis (26). To date, few studies have investigated the development of HCC in DAA users in Turkey

Table 2. Treatment characteristics

Characteristics (n=68)		**n (%)***
Prior treatment for HCV		16 (23.5)
	Peg – IFN + RBV	15 (22.1)
	TVR + Peg – IFN + RBV	1 (1.5)
Reason for switching to DAA	Relapse	15 (93.8)
	Non-response	1 (6.3)
DAA regimen	PRoD	30 (44.1)
	LDV/SOF	16 (23.5)
	PRoD + RBV	9 (13.2)
	SOF + RBV	5 (7.4)
	GLE/PIB	3 (4.4)
	LDV/SOF + RBV	3 (4.4)
	OMV/PTR/r + RBV	1 (1.5)
	SOF	1 (1.5)
Duration of DAA therapy (weeks), mean ± SD		13.4±4.9

*All patients were reported as n (%) unless otherwise specified
HCV: Hepatitis C virus, DAA: Direct acting antiviral, GLE: Glecaprevir, LDV: Ledipasvir, OMV: Ombitasvir, PIB: Pibrentasvir, PRoD: Paritaprevir/ritonavir/ombitasvir-dasabuvir, PTR: Paritaprevir, r: Ritonavir, RBV: Ribavirin, SD: Standard deviation, SOF: Sofosbuvir, TVR: Telaprevir

Table 3. Laboratory assessments throughout the observation period*

Laboratory parameters	**Before starting DAA therapy**	**12 weeks after completing DAA therapy**	**3 years after completing DAA therapy**	**p**	**p1**	**p2**	**p3**
HCV-RNA (IU/mL)	450000 (31880-41100000)	0	0	<0.001	<0.001	11	<0.001
AST (U/L)	37 (11-190)	19 (7-194)	18 (9-102)	<0.001	<0.001	0.002	<0.001
ALT (U/L)	37 (10-374)	14 (4-138)	14 (5-63)	<0.001	<0.001	0.373	<0.001
GGT (U/L)	35 (6-3023)	18 (7-1388)	19 (6-1021)	<0.001	<0.001	0.127	<0.001
Total bilirubin (mg/dL)	0.7 (0.2-1.8)	0.6 (0.2-1.6)	0.5 (0.2-1.9)	<0.001	0.113	0.003	<0.001
ALP (IU/L)	79 (44-286)	72 (45-157)	70 (32-238)	0.010	0.397	0.016	0.001
Albumin (g/dL)	4.2 (2.8-5.0)	4.2 (3.3- 4.8)	4.4 (3.3- 5.1)	<0.001	0.496	<0.001	0.004
AFP (ng/mL)	3.7 (1.1-24)	2.8 (1.1-9)	2.7 (0.9-7.8)	<0.001	<0.001	0.004	<0.001
Urea (mg/dL)	30 (10-171)	30 (11-210)	30 (9-195)	0.238	0.338	0.871	0.351
Creatinine (mg/dL)	0.6 (0.3-8.6)	0.6 (0.4-7.1)	0.7 (0.48-9.6)	<0.001	0.911	<0.001	0.002
HCT (%)	41.0 (11.6-52.7)	40.8 (14.2- 50.0)	41.0 (27.0- 50.0)	0.169	0.117	0.730	0.128
WBC (x10^3/mL)	6.96 (2.91-14.00)	6.78 (3.88-13.61)	6.80 (1.30-13.50)	<0.001	0.844	<0.001	<0.001
PLT (x10^3/mL)	226 (79-541)	246 (74- 483)	255 (88-1710)	0.087	0.135	0.708	0.013
PT (sec)	11.8 (10.5-46.7)	11.6 (9.8-17.1)	12 (8.5-33.4)	0.030	0.016	0.004	0.120
INR	0.9 (0.7-3.8)	0.9 (0.8-1.3)	1 (0.7-2.8)	<0.001	0.412	<0.001	<0.001

*Values are presented as median (minimum-maximum)
p: Across the 3 time-points, p1: Before starting DAA therapy vs 12 weeks after completing DAA therapy, p2: 12 weeks after completing DAA therapy vs 3 years after completing DAA therapy, p3: Before starting DAA therapy vs 3 years after completing DAA therapy
AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, HCT: Hematocrit, HCV-RNA: Hepatitis C virus ribonucleic acid, INR: International normalized ratio, PLT: Platelet, PT: Prothrombin time, WBC: White blood cell

(23,27). In a study evaluating the incidence of HCC in patients who achieved SVR with DAAs, HCC occurred in 5.7% of patients during a median follow-up of 29 months (6-66 months). In that study, only Child-Pugh B and C patients developed HCC (>six-fold more frequent in Child-Pugh C), and 40% of these cases were recurrences (23). Similarly, HCC occurred in 5.6% of patients during a median follow-up of 43±16.2 months (all in patients with cirrhosis; information on decompensation not reported) in a study investigating the biochemical determinants of HCC development in CHC patients who achieved SVR24 with DAAs. The authors reported that serum AFP and albumin levels before, at the end of, and 24 weeks after treatment, and the PLT count at 24 weeks after treatment were predictors of HCC development (27). The low percentage of patients with cirrhosis compared with those studies (4.4% vs 47.6% and 33.5%) and the absence of patients classified as Child-Pugh B or C may explain why we did not observe any HCC cases in our study population. The mean fibrosis score of 43 patients (63.2%) who underwent biopsy at baseline was 1.7±1.0. Since HCV-RNA levels became undetectable after the first month of DAA treatment and subsequent clinical, laboratory, and ultrasound evaluations did not indicate progression, decompensation, or HCC, no patient underwent liver biopsy during follow-up. Three patients with compensated cirrhosis at baseline remained clinically stable throughout the study period.

The findings on HCV GT distribution and transmission routes in the present study are noteworthy as they may have implications for the prevention and effective management of HCV infections in Turkey. Consistent with global HCV data (28), the most common HCV GT in our study population was GT1 (79.4%; 57.4% GT1b), followed by GT3 (11.8%) and GT4 (7.4%). In a recent large-scale study involving centers from different geographical regions of Turkey, GT3 was the second most frequently encountered HCV GT (3.6%) after GT1, while GT4 ranked fourth (1.3%) (29). GT3 is the leading GT in South Asia and the second most common GT in Central Asia, while GT4 is an "endemic" GT predominant in Africa, accounting for 65% of HCV cases in North Africa and the Middle East and 83% of those in Central Sub-Saharan Africa (28). Consistent with our findings, real-life studies in Turkey have shown that GT3 and GT4 have become more prevalent in Turkey in recent years (17,22,29,30,31,32,33). This can be explained, at least in part, by increased migration to Turkey from countries where these HCV subtypes are predominant (17,30,31), as shown by the latest available national migration statistics (34). In the current study, both GT3 (11.8%) and GT4 (7.4%) were more frequent than recently reported data (29,30,31,32,33) except for a study from southern Turkey, which reported a frequency of 28.6% for GT3 (17). Patients of foreign nationality accounted for >20% of the study population and were from Asia, the Middle East, and Central and Eastern Europe. Syria was the most common foreign country (40%) and two-thirds of Syrian patients were infected with GT4. Similarly, in a recent large-scale study conducted in Southern Turkey, GT4 was the most common GT among Syrian refugees (48.8%), who made up 7.8% of the study population (17). Some groups of foreign origin, such as irregular migrants and asylum seekers, experience problems in accessing treatment services. Hepatitis C poses a significant threat to the prevention and control of infection (35). In addition, there are barriers to treatment for those who have acquired the infection in their home country. Overcoming these problems is expected to contribute to reducing the prevalence of hepatitis C in Turkey by improving treatment and follow-up rates.

PWIDs, a group with a high probability of being infected with GT3 (17,36,37), accounted for 8.8% of our study population, and half of them were infected with GT3. Consistent with our findings, several studies reported GT3 as the most common GT among PWIDs (17,36,37). Sarıgül Yıldırım et al. (36) reported that GT3 was almost 9 times more prevalent in PWIDs than in non-PWIDs. In another large-scale study conducted in Turkey, GT3 was detected in 61.5% of GT PWIDs (17). Consistently, GT3 was the most frequently detected GT among PWIDs receiving substance abuse treatment in specialized centers in Turkey (37). The clinical significance of GT3 is based on its association with poorer prognosis due to high rates of hepatosteatosis, rapid progression to cirrhosis, high rates of HCC (38), and increased risk of treatment failure due to the inherent presence of resistance-associated substitutions (RAS) to non-structural protein 5A (NS5A) inhibitors (39). According to official data, injected drug use in Turkey has increased in recent years (40). This may further increase the prevalence of HCV GT3 infected people in the coming years.

The high-risk of re-infection in PWIDs and MSMs due to ongoing high-risk behavior should also be considered in the follow-up of patients who have cleared HCV. To reduce the risk of relapse, recurrence, or transmission to healthy individuals, these individuals should be carefully monitored even if SVR is achieved (5,6). In our practice, we comprehensively inform PWIDs about harm reduction and behavior change through constructive communication from the start of treatment. After achieving SVR12, annual follow-ups with HCV RNA testing are performed to ensure prompt and effective management of the infection, if necessary, and to prevent further spread of the virus.

Consistent with the findings of a national study investigating the risk factors for HCV transmission (30), we observed that surgical and other medical interventions, including blood transfusions and dental procedures, were the main routes of HCV transmission. Many patients in the present study had a history of potential exposure to the virus before 1996 when HCV screening became mandatory prior to blood donation and medical/surgical interventions in Turkey. In addition, two-thirds of the migrant patients reported HCV transmission through surgery and/or blood transfusion before migrating to Turkey. These findings emphasize the importance of taking measures to eliminate the risks associated with unsafe medical practices. This is of particular concern for patients with limited or no health insurance. It is of great importance for individuals and public health to identify these vulnerable individuals and ensure that they are appropriately treated and followed up.

In this study, 24 patients (35.3%) had at least one condition requiring post-treatment surveillance according to the EASL guideline recommendations. The two most common conditions were obesity and diabetes mellitus. In recent real-life studies in Turkey, diabetes was reported in 19-40% of HCV-infected patients (19,27). Referral of patients to relevant healthcare professionals for effective diabetes management, including diet and exercise

recommendations, is important and should not be ignored during and after antiviral therapy to prevent future liver damage.

Study Limitations

The major limitations of this study are the small sample size and retrospective design. The study population characteristics did not allow a comparison between patients with and without cirrhosis. Furthermore, the study was conducted at a single center, which may have affected the generalizability of the findings. However, our findings are valuable because, to our knowledge, this is the first study in Turkey to report long-term follow-up outcomes in patients who completed DAA therapy for CHC.

Conclusion

This study, examining the 3-year follow-up results after the end of antiviral therapy, demonstrated the long-term benefit of DAA therapy in terms of maintaining virological response and preventing adverse outcomes in CHC. The follow-up strategy should consider the sociodemographic and clinical characteristics of patients. To achieve the WHO's target of eliminating HCV as a public health priority by 2030, it would be useful to expand the scope of the National Viral Hepatitis Prevention and Control Program and the HCV roadmap to include post-treatment follow-up of patients at risk of progressive liver damage, HCC, relapse, and recurrent infection.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Clinical Research Ethics Committee of Haseki Training and Research Hospital, University of Health Sciences Turkey (decision no: 105-2021, date: 27.10.2021) and conducted in accordance with The Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.Z., Design: E.Z., Data Collection or Processing: E.Z., M.B., İ.Y.N., Analysis or Interpretation: E.Z., M.B., İ.Y.N., Literature Search: E.Z., M.B., İ.Y.N., F.P., Writing: E.Z., F.P.

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