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Evaluation of Direct-acting Antiviral Agents and Clinical Responses in Chronic Hepatitis C Patients

Kronik Hepatit C Hastalarında Doğrudan Etkili Antiviral Ajanların ve Klinik Yanıtların Değerlendirilmesi

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ABSTRACT

Objectives: Direct-acting antiviral (DAA) agents have made a breakthrough for treating chronic hepatitis C virus (HCV) with their high efficacy and tolerability. In this study, the end of treatment response of DAA treatment regimens was analyzed with respect to epidemiological data.

Materials and Methods: A total of 143 patients, over 18 years of age, who were treated with the diagnosis of HCV infection were analyzed retrospectively. The comorbid diseases, co-infection status (hepatitis B virus and human immunodeficiency virus-co-infection), genotype distribution and transmission routes were noted. The changes in the laboratory parameters were evaluated before treatment, at the first month and at the end of treatment and after treatment at the 12th week.

Results: When the genotype distributions of the patients were examined, it was found that 75.5% of the patients (n=108) were genotype-1, 4.2% (n=6) were genotype-2, 12.6% (n=18) were genotype-3, 4.9% (n=7) were genotype-4, and 1.4% (n=2) were genotype-5. The treatment regimens of the patients were; paritaprevir + ritonavir + ombitasvir + dasabuvir in 54 (37.8%) patients, ledipasvir + sofosbuvir in 28 (19.6%) patients, glecaprevir + pibrentasvir in 23 (16.1%) patients, and paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin (RBV) in 15 (10.5%) patients. Dose reduction was implemented in 31 patients who received RBV treatment. Adverse events were observed in 49.7% (n=71) n of the study population. The rate of sustained viral response-12 (SVR12) was 100% in all treatment regimens.

Conclusion: Achieving a SVR12 in chronic HCV decreased all-cause mortality, whether liver-related or unrelated. Second-generation DAAs have been a beacon of hope for humanity in this regard.

Keywords: Sustained viral response, direct-acting agents, HCV, genotype, adverse events

ÖZ

Amaç: Direkt etkili antiviraller (DAA), yüksek etkinlikleri ve tolere edilebilirlikleri ile kronik hepatit C virüs (HCV) tedavisinde çığır açmıştır. Bu çalışmada, DAA tedavisi alan hastaların epidemiyolojik verileri ve tedavi sonu yanıtları analiz edilmiştir.

Gereç ve Yöntemler: HCV enfeksiyonu tanısı ile tedavi edilen 18 yaş üstü toplam 143 hasta retrospektif olarak incelendi. Komorbid hastalıklar, ko-enfeksiyon durumu (hepatit B virüsü ve insan bağışıklık yetmezlik virüsü-ko-enfeksiyonu), genotip dağılımı ve bulaşma yolları not edildi. Laboratuvar parametrelerindeki değişiklikler tedavi öncesi, tedavinin ilk ayı ve sonunda ve tedavi sonrası 12. haftada değerlendirildi.

Bulgular: Hastaların genotip dağılımları incelendiğinde hastaların %75,5'inin (n=108) genotip-1, %4,2'sinin (n=6) genotip-2, %12,6'sının (n=18) olduğu bulundu. Genotip-3, %4,9 (n=7) genotip-4 ve %1,4 (n=2) genotip-5 idi. Hastaların tedavi rejimleri; 54 hastada (%37,8) paritaprevir + ritonavir + ombitasvir + dasabuvir, 28 hastada (%19,6) ledipasvir + sofosbuvir, 23 hastada (%16,1) paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin (RBV) (%10,5) idi. RBV tedavisi alan 31 hastada doz azaltımı uygulandı. Yan etki çalışma popülasyonunun %49,7'sinde (n=71) gözlenmiştir. Tüm tedavi rejimlerinde kalıcı virolojik yanıt-12 (SVR12) oranı %100 idi.

Sonuç: Kronik HCV'de SVR12'nin elde edilmesi, karaciğerle ilişkili veya ilişkisiz tüm nedenlere bağlı ölümleri azaltmıştır. İkinci nesil DAA'lar bu konuda insanlık için bir umut ışığı olmuştur.

Anahtar Kelimeler: Kalıcı virolojik yanıt, direkt etkili antiviraller, HCV, genotip, yan etki

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Introduction

The prevalence of chronic hepatitis C virus (HCV) infection over the globe is between 1.2-1.7%. The prevalence of HCV in Turkey has been reported as 1-2%. The lack of an effective vaccine and serious consequences such as cirrhosis and hepatocellular cancer still poses an important research area worldwide (1,2).

While standard alpha interferon was used in the treatment of chronic HCV infection in the previous years, then the combination of pegylated interferons and ribavirin (RBV) has been used. These treatment options achieved 40-50% sustained viral response (SVR) (3,4). However interferon treatments have always caused compliance problems for patients since they were administered in the form of injections. In addition, flu-like symptoms, hemolytic anaemia and adverse psychiatric effects were other common side effects (4). This situation revealed the expectations of oral therapy in terms of better SVR rates, shorter duration of treatment and ease of use both in patients and clinicians.

The American Association for Liver Diseases Research and the American Infectious Diseases Society have stated in their HCV guidelines that direct-acting antiviral (DAAs) can be used in all chronic HCV patients who are likely to live longer than 12 months (5,6). The possibility of developing potential drug-related undesirable effects is also important for the sustainability of the treatment continuation. New treatment regimens (DAAs) present improved efficacy and a better safety profile (7).

Grade of liver fibrosis, decompensated cirrhosis, accompanying conditions (such as cryoglobulinemia, lymphoma) or special patient groups [human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection, hemodialysis, diabetes, pregnancy, drug addiction, liver transplant patients, etc.] are other factors that should be considered in the treatment process (3).

In this study, we aimed to present the epidemiological data and treatment outcomes of 143 patients who received DAAs.

Materials and Methods

A total of 143 patients, over 18 years of age, who were treated with the diagnosis of chronic HCV in the Infectious Diseases Outpatient Clinic of University of Health Sciences Turkey, Haseki Training and Research Hospital between 1 July 2016 and 1 September 2020, and who were admitted to their follow-up visits in the 12th week after the end of the treatment were analyzed retrospectively.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all participants. The study was approved by Ethics Committee University of Health Sciences Turkey, Haseki Training and research Hospital (approval number: 2020-180; date: 23.09.2020).

The comorbid diseases of all individuals (diabetes mellitus, hypertension, heart disease, chronic renal failure, thyroid disease, cirrhosis) have been examined. Additionaly, co-infection status (HBV and HIV co-infection) and transmission routes were noted. HCV genotype analyzes were conducted.

HCV-RNA, hemogram and biochemical parameters [urea, creatinine, aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase, total protein, albumin, total bilirubin, alpha-fetoprotein, prothrombin time, international normalized ratio) measured before treatment, at 4th week, end of treatment and 12th week after the end of treatment. The changes in the laboratory parameters of the patients as a result of the selected treatment were evaluated.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM SPSS for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data, mean and standard deviation for continuous data were given as descriptive values.

For comparisons between groups, "Independent sample t-test" was used for two groups, and the "Pearson chi-square test" was used for the comparison of categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

Results

A total of 143 patients have been enrolled in this retrospective analysis. The most prevalent HCV genotype was genotype 1 detected in 77.5% of the patients. The distribution of demographic and clinical findings of the patients was denoted in Table 1.

Patients with HBV co-infection consisted of 4.2% (n=6) of the individuals and 3 of these subjects were chronic HBV patients and 3 of them were inactive carriers. Additionally, 28 patients were (19.6%) anti-hepatitis B surface antigen (anti-HBs) (+) and were anti-hepatitis B core antigen (anti-HBc) immunoglobulin G (+). Three of our patients has been initiated chronic HBV treatment as they met the criteria and their medication still continued. Three of our patients did not receive any medication although they were HBsAg (+) and no reactivation developed after the end of treatment. HBV-DNA was negative in one patient at the end of treatment but became >2000 IU/mL in the follow-up however, AST and ALT values did not increase.

There were 4 patients (2.8%) with HIV co-infection. Treatment was changed in 2 patients due to drug interactions. As a treatment, 2 of our patients were taking tenofovir disoproxil fumarate + emtricitabine + dolutegravir, and one patient was taking tenofovir disoproxil fumarate + emtricitabine + lopinavir/ritonavir, and one patient was taking abacavir + lamivudine + dolutegravir. As hepatitis C treatment, 2 patients received sofosbuvir/ledipasvir (SOF/LDV), and one patient received glecaprevir/pibrentasvir (GLE/PIB), and one patient received SOF/velpatasvir treatment.

Cirrhosis has been observed in 5.6% (n=8) patients and all cases were compensated (Child-Pugh A).

Four patients with chronic renal failure who did not need dialysis, 1 received paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) + RBV and 3 received GLE/PIB. There was no deterioration in urea-creatinine values during the treatment and they did not need dialysis.

Table 1. Distribution of demographic and clinical findings of the patients

Characteristics (n=143)	n (%) or median ± SD
Gender	
Female	82 (57.3)
Male	61 (42.7)
Age	53±15
Height	165.8±10.1
Weight	75.1±13.9
BMI	27.4±5.2
HBV coinfection	6 (4.2)
Inactive carrier	3 (50.0)
Chronic HBV	3 (50.0)
Anti-HBs (+), anti-HBc IgG (+)	28 (19.6)
Anti-HIV (+)	4 (2.8)
Cirrhosis	8 (5.6)
Compensated (Child-Pugh A)	8 (100.0)
Genotype	
1	108 (75.5)
1b + 4	2 (1.4)
2	6 (4.2)
3	18 (12.6)
4	7 (4.9)
5	2 (1.4)
Genotype-1 subgroup	
1a	18 (16.7)
1b	88 (81.5)
Not determined	2 (1.8)
Biopsy	75 (52.4)
Biopsy HAI	6.2±2.4
Biopsy fibrosis score	1.8±1.1
Known transmission cause	83 (58.0)
Transmission cause	
Surgery	19 (22.9)
Transfusion	17 (20.5)
Surgery + transfusion	10 (12)
Intravenous substance use	14 (16.9)
Medical intervention	10 (12)
Dental operation	6 (7.2)
Family spread	5 (6.0)
Sexual intercourse	2 (2.4)
Comorbidities	
Renal disease	13 (9.1)
Cardiac disease	18 (12.6)
Hypertension	37 (25.9)
Thyroid disease	13 (9.1)
Diabates mellitus	23 (16.1)

SD: Standard deviation, BMI: Body mass index, HBV: Hepatitis B virus, HBs: Hepatitis B surface antigen, IgG: Immunoglobulin G, HIV: Human immunodeficiency virus, HAI: Histological activity index

The distribution of laboratory parameters collected during and at the end of 12th week treatment period has been elaborated in Table 2.

The most common regimen used in treatment was PROD. The distribution of the treatment process was given in Table 3.

The rate of SVR12 was 100% in all treatment regimens.

Adverse effects were observed in 49.7% (n=71) of the 143 patients included in the evaluation. A total of 96 side effects were detected in 71 patients. A wide variety of these side effects were dermatologic (hair loss), gastrointestinal (diarrhoea, abdominal pain, distension) and muscle joint pain. Side effect distribution was shown in Table 4. Since the drug use was not the same in every patient the occurrence of side effects was also different. There was no statistically significant difference between the drugs in terms of side effects. A majority of our patients have been given PrOD and SOF/LDV treatment, side effects were mostly observed in these two groups.

Discussion

Viral hepatitis is an important public health problem all over the globe. HCV and chronic alcohol consumption are the most common causes of chronic liver disease in Western society while it is chronic viral hepatitis due to HBV and HCV in our country. Viral hepatitis viruses lead to increased morbidity and mortality by causing acute-chronic viral hepatitis, cirrhosis, liver failure and liver cancer (2).

PegIFN and RBV which were previously used in the treatment of HCV had low efficacy and high side effect profile. However, new treatment regimens (DAAs) present improved efficacy and a better safety profile (7). SVR rates have been reported to be over 90% in chronic HCV patients receiving DAA treatment (8). The rate of SVR12 was 100% in all treatment regimens and no recurrence was observed in our study.

In patients with chronic HCV genotype-1 and 4, Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± RBV have been found to be well tolerated and highly effective in clinical trials (9,10). In a study conducted in chronic HCV genotype 1b treatment-naive and unresponsive non-cirrhotic patients in with PrOD SVR12 rates were 95.2% and 90%, respectively. In the same study, treatment-naive and treatment-experienced patients with cirrhosis SVR12 rates were 97.9% and 96.2%, respectively (9). In our study, we have achieved 100% SVR with ombitasvir/paritaprevir/ritonavir ± dasabuvir ± RBV.

In a study from Turkey, the overall SVR rate in genotype-1 patients was 96.4%, and the treatment SVR rate 98.2% in treatment with PrOD ± RBV while it was 96% in treatment with SOF + LDV ± RBV (11). Çakır (12) published that the rate of SVR24 was determined as 100% in HCV genotype-1a and genotype-4 patients who we were treated with PrOD ± RBV for 12 weeks. Ioannou et al. (13) found the rate of viral response as 92.8% in 13,974 patients with genotype-1 who were administered SOF/LDV or PrOD treatments. In this study, no significant difference was found between the treatment regimens. We have achieved 100% SVR with both PrOD ± RBV and SOF/LDV ± RBV in genotype 1 patients.

Table 2. Distribution of patients' laboratory values

Laboratory parameteters	Baseline (median ± SD)	First month (median ± SD)	Treatment end (median ± SD)	SVR12 (median ± SD)
HCV-RNA	7609577.6±12263951	0±0	0±0	0±0
AST	47.4±33.4	21.8±8	20.4±8.2	21.1±15.7
ALT	56.9±54	18.1±11.3	15.4±8.2	15.3±12.5
Albumin	4.2±0.4	4.2±0.4	4.2±0.4	4.2±0.3
Total bilirubin	0.7±0.4	0.9±0.6	0.7±0.5	0.8±1.8
INR	0.9±0.3	0.9±0.2	1±0.9	1±0.9
AFP	5±4.4	3.9±2.7	3.5±2.8	3.9±7.3
ALP	91.9±47.6	95.2±44.6	104.4±115.7	85.2±34.7
GGT	76.1±258.2	58.1±284.8	27.3±66.7	32±115.7
Urea	35.7±24.6	36.3±26.1	35.4±21.9	36.5±30.1
Creatinine	1.1±1.5	1.1±1.6	1.1±1.4	1.1±1.5
WBC	7.2±2.0	7.6±2.1	7.5±2.2	7.3±1.9
HCT	40.6±5.8	39.8±4.7	39.4±5.1	40.4±7.4
PLT	227.1±66.9	241.6±78.4	246.5±80.0	238.2±62.9
PT	12.1±3.1	11.8±2	11.8±1.1	11.9±1

SD: Standard deviation, HCV: Hepatitis C virus, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio, AFP: Alpha-fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamil transferase, WBC: White blood cell, HCT: Hematocrit, PLT: Platelet, PT: Prothrombin time, SVR12: Sustained viral response-12

Table 3. Distribution of treatment and treatment processes

Characteristics (n=143)	n (%) or median ± SD
Previous treatment	22 (15.4)
Recurrence	13 (59.1)
Not responding to treatment	9 (40.9)
Previous treatment regimens	
PR	20 (90.9)
Telaprevir + PR	1 (4.5)
Sofosbuvir + ribavirin	1 (4.5)
Final treatment	
Paritaprevir + ritonavir + ombitasvir + dasabuvir	54 (37.8)
Ledipasvir + sofosbuvir	28 (19.6)
Glekaprevir + pibrentasvir	23 (16.1)
Paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin	15 (10.5)
Sofosbuvir + ribavirin	8 (5.6)
Ledipasvir + sofosbuvir + ribavirin	7 (4.9)
Sofosbuvir + daclatasvir	3 (2.1)
Sofosbuvir + velpatasvir	3 (2.1)
Paritaprevir + ritonavir + ombitasvir + ribavirin	1 (0.7)
Sofosbuvir	1 (0.7)
Ribavirin dose reduction	3 (9.7)
Ribavirin early discontinuation	3 (9.7)
Study duration (12 weeks)	12.9±4.8
Side effects	71 (49.7)

SD: Standard deviation, PR: Pegylated interferon + ribavirin

In clinical trials the SVR12 was 95% with GLE/PIB, regardless of RBV coadministration, and was not affected by the previous treatment regimen or the presence of baseline resistance-associated substitutions. SVR12 rates of 100% and 94% have been achieved with no virological relapses. The GLE/PIB treatment is safe and well tolerated, regardless of treatment duration (12 or 16 weeks), and there were no adverse effects that led to study drug discontinuation (14). In our study, we have achieved 100% SVR with GLE/PIB.

Many studies have shown that IFN-free treatment regimens in HCV in chronic renal failure are effective and safe, regardless of Genotype, viral load, cirrhosis status, and whether RBV is used (15,16). Elbasvir-grazoprevir and PrOD are among the DAA treatment regimens that can be used in patients with advanced chronic renal failure (17). In a multicenter study evaluating the treatment of PrOD in patients with chronic renal failure, 90% of SVR-12 was achieved with 12 weeks of treatment in genotype-1, non-cirrhotic chronic HCV patients. The researchers did not observe any significant side effects during the treatment and concluded that PrOD treatment can be utilized safely in patients with stage 4 and 5 chronic renal failure without requiring dose adjustment (15). In our study CRF patients have been treated via PrOD or GLE/PIB and 100% SVR12 has been achieved and no significant side effects were observed during treatment.

Patients with HIV co-infection should also be emphasized in terms of the treatment they receive. Drug interactions should be kept in mind when using DAA as interactions with potential drugs may affect adherence to treatment. In our study, we had to implement amendments in the treatment regimens of patients with HIV co-infection due to drug interactions.

Tenofovir nephrotoxicity can develop in the use of SOF/LDV (5). In our study nephrotoxicity did not develop in 3 patients

Table 4. The side effects exposed during treatment

	Side effects n (%)	Details of side effect
1. Gastrointestinal	**36 (37.5)**	-
Change in appetite	6 (6.25)	-
Distension	6 (6.25)	-
Nausea	6 (6.25)	-
Diarrhoea	5 (5.2)	-
Abdominal pain	4 (4.16)	-
Constipation	2 (2.08)	-
Other	7 (7.2)	Belching (1), sternal burning/reflux (1), weight loss (2), reflux (1), diarrhea (1), weight gain (1)
2. Dermatological	**17 (17.7)**	-
Itching	7 (7.2)	-
Other	10 (10.4)	Hair loss (2), gingival itching (1), folliculitis (1), acne (3), dry skin (1), eczema (2)
3. Muscle-joint pain	**13 (13.5)**	-
4. CNS side effect	**7 (7.2)**	Changes in sleep patterns (3), dizziness (2), balance problem (1), forgetfulness (1)
5. Depression	**5 (7.2)**	-
6. Get Angry Quickly	**4 (4.1)**	-
7. Shortness of breath	**3 (3.1)**	-
8. Other	**11 (11.4)**	Palpitation (2), menstrual irregularity (1), increased need for suboxone (1), increased spontaneous bleeding (1), cough (2), sweating (2), urine redness (1), chills in the arm with fistula (1)
Total	**96**	-

with HBV-HCV co-infection who were treated with tenofovir disoproxil fumarate and 2 patients with HIV-HCV co-infection who were treated with tenofovir disoproxil fumarate + emtricitabine combination.

According to EASL chronic HCV Guideline (2018) it was stated as "Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post-anti-HCV therapy and be monitored monthly if HBV treatment is stopped (B1). In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly to detect possible reactivation (B1) (18). In our study, three of our patients did not receive any medication although they were HBsAg (+) and no reactivation developed after the end of treatment.

In a study from Turkey, the most common adverse events were pruritus (22.2%), fatigue (17%) and headache (19.8%) (11). In our study, the most common adverse events with a rate of 37% were gastrointestinal side effects (diarrhoea, abdominal pain, distension). We did not detect severe side effects and none of these had deteriorated the quality of life of the patients due to treatment. No hospitalisation occurred due to adverse events. We have observed laboratory parameter deviations in subjects using PrOD treatment however, the variables were statistically insignificant.

Study Limitations

The main limitation of this study could be attributed to its retrospective nature. Secondly, we had a relatively small sample size. The strength of this article lies beneath the fact that it merged epidemiological, biochemical and treatment-related parameters of a certain period.

Conclusion

Achieving a SVR in chronic HCV decreased all-cause mortality whether liver-related or unrelated. Second-generation DAAs have been a beacon of hope for humanity in this regard. DAAs have made a breakthrough in the treatment of chronic HCV with their high efficacy and tolerability. Time will elaborate on whether there will be a relapse after the follow-ups.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee University of Health Sciences Turkey, Haseki Training and research Hospital (approval number: 2020-180; date: 23.09.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.Z., Design: E.Z., Supervision: E.Z., Materials: E.Z., İ.Y.N., Data Collection or Processing: E.Z., İ.Y.N., Analysis or Interpretation: E.Z., İ.Y.N., Literature Search: E.Z., İ.Y.N., F.P., Writing: E.Z., F.P., Critical Review: E.Z., F.P.

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