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The real-world efficacy and safety of direct-acting oral antiviral treatment in chronic Hepatitis C Genotype 1 patients in Turkey

Türkiye'de kronik Hepatit C Genotip 1 hastalarında direkt-etkili oral antiviral tedavinin gerçek yaşamda etkinliği ve güvenliği

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SUMMARY

Objective: The aim of this study was to investigate the real-world efficacy and safety in Turkey of the paritaprevir/ritonavir, ombitasvir, dasabuvir (PrOD) ± ribavirin (RBV) and ledipasvir/sofosbuvir (LDV/SOF) ± RBV combination regimens used for chronic hepatits C virus (HCV) genotype 1 patients, which is the most common form of this disease seen both in Turkey and worldwide.

Method: The study included a total of 81 HCV genotype 1 patients receiving PrOD ± RBV or LDV/SOF ± RBV treatment regimens between June 2016 and October 2017. The patients were evaluated in respect of demographic, clinical and virological data, sustained virologic response (SVR) and detailed adverse events (AE).

Results: The 81 HCV patients comprised 35 (43.2%) males and 46 (56.8%) females with a mean age of 62 years. All the patients were genotype 1, which is the most commonly seen genotype in Turkey, and the sub-genotypes were HCV genotype 1a in 12.3% and genotype 1b in 87.7%. The SVR12 rate of all the chronic HCV genotype 1 patients was 79 (96.4%), 98.2% in the PrOD ± RBV patients and 96% in SOF/LDV ± RBV. AEs were reported in 46 (56.8%) of the total patient group. The most common AEs were pruritus in 18 (22.2%) patients, fatigue in 17 (21%) and headache in 16 (19.8%).

Conclusions: According to the real-world data obtained in this study from a single centre in our region, a high rate of SVR12 response was obtained direct-acting oral viral treatment regimens in patients with chronic HCV genotype 1 and there was seen to be excellent tolerability.

Keywords: Antiviral agents, Hepatitis C chronic, safety, sustained virologic response.

ÖZET

Amaç: Bu çalışmanın amacı, Türkiye'de ve dünyada kronik hepatit C virüsünün (HCV) en yaygın şekli olan genotip 1 hastalarında kullanılan paritaprevir / ritonavir, ombitasvir, dasabuvir (PrOD) ± ribavirin (RBV) ve ledipasvir / sofosbuvir (LDV / SOF) ± RBV kombinasyon rejimlerinin gerçek yaşamda etkinliğini ve güvenirliğini araştırmakdı.

Yöntem: Haziran 2016 ile Ekim 2017 yılları arasında, PrOD ± RBV veya LDV / SOF ± RBV tedavi rejimleri alan toplam 81 HCV genotipi 1 hasta dahil edildi. Hastalar demografik, klinik ve virolojik verileri, kalıcı virolojik yanıt (KVY) ve ayrıntılı yan etkiler değerlendirildi.

Bulgular: 81 HCV hastası, 35 (% 43.2) erkek, 46 (% 56.8) kadın olup ortalama yaş 62 idi. Hastalar Türkiye'de en sık görülen genotip olan genotip 1 ve alt genotipler % 12.3 genotip 1a ve % 87.7 genotip 1b idi. Kronik HCV genotip 1 hastalarının KVY oranı 79 (% 96.4), PrOD ± RBV hastalarında % 98.2 ve SOF / LDV ± RBV'de % 96 idi. Ayrıntılı yan etki 46 (% 56.8) hastada bildirildi. Hastalarda en sık görülen yan etkiler; 18 (% 22.2) kaşıntı, 17 yorgunluk (% 21) ve 16 (% 19.8) baş ağrısı idi.

Sonuç: Bu çalışmada bölgemizdeki tek bir merkezden elde edilen gerçek yaşam verilerine göre, kronik HCV genotip 1 hastalarında direkt etkili oral viral tedavi rejimleri ile yüksek KVY 12 yanıtı elde edildi ve mükemmel tolere edildiği görüldü.

Anahtar sözcükler: Antiviral ajanlar, Hepatitis C kronik, güvenlik, kalıcı viral yanıt.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection causes progressive liver disease including cirrhosis and hepatocellular carcinoma and is a primary indication for liver transplantation [1]. In the study of the World Health Organization (WHO), it was estimated that 1.1% of the global population and approximately 80 million individuals have viremic HCV infection. The prevalence of this infection shows geographical differences and very few people are aware of the disease [2]. In Turkey, it is estimated that the prevalence of chronic HCV infection is 1% and approximately 800,000 individuals have the virus [3]. Both worldwide and in Turkey, the most common HCV genotype is genotype 1 with a prevalence of 91.8% [4, 5].

Successful eradication of HCV infection reduces complications which develop associated with HCV, liver transplantation and the mortality risk [6]. With interferon (IFN)-based treatment in chronic HCV genotype 1 patients, the sustained virologic response (SVR) rate is 40%-50%, there are greater side-effects related to the treatment and the treatment-dependence rate is extremely low [7, 8]. In recent years, with the use of second-generation direct-acting antiviral agents (DAA) without interferon, SVR12 rates in genotype 1 patients have been reported to be >90% and treatment-dependence rates have increased [8]. One of these new combined regimens is formed of paritaprevir/ritonavir, ombitasvir, dasabuvir (PrOD); paritaprevir (NS3/4A protease inhibitor), ritonavir (cytochrome P450 inhibitor), ombitasvir (NS5A inhibitor) and dasabuvir (NS5B polymerase inhibitor). In real-world data, this combined regimen of PrOD, with or without ribavirin (RBV) has been reported to obtain SVR12 rates of 94%-100% in treatment-naive and treatment-experienced genotype 1 patients with and without cirrhosis [9]. Another regimen of ledipasvir (NS5A inhibitor) and sofosbuvir (NS5B polymerase inhibitor) (LDV/SOF) has been reported to obtain SVR12 rates of 94.2% [10].

Real world data are necessary to support clinical research results and to confirm treatment choices. This is because the patient populations in clinical studies are highly selectively determined and may not be heterogenous. The aim of this study was to present the real-world data which evaluated the clinical efficacy and reliability of PrOD ± RBV and LDV/SOF ± RBV treatment regimens in an HCV genotype 1 patient group living in our region.

MATERIAL AND METHODS

Study population

This study was an observational cohort study which evaluated antiviral treatment in HCV-infected patients in routine clinical practice. The study recorded the data of consecutive HCV genotype 1a and 1b patients aged >18 years who were treated with PrOD ± RBV or LDV/SOF ± RBV in the single-center study of the Gastroenterology Clinic of Cumhuriyet University between June 2016 and October 2017. Exclusion criteria were acute HCV infection or co-infection of hepatitis A, B, D or human immunodeficiency virus (HIV). Approval for the study was approved by the local ethical committee (Cumhuriyet University 2017-10/23).

Data collection

A record was made of demographic and clinical data of the patients, adverse events (AEs), and pre and post-treatment laboratory test results and virological data. Liver cirrhosis diagnosis of the patients was based on clinical findings, ultrasound findings consistent with cirrhosis, and histological findings (METAVIR F4). The liver decompensation sign was defined as Child-Pugh score B or C, ascites, encephalopathy and esophageal varices. HCV RNA levels were tested using the real-time polymerase chain reaction assay (COBAS AmpliPrep/ COBAS TaqMan system; Roche Molecular Systems Inc., Branchburg, NJ, USA). Measurements were taken at baseline, at 4, 12, and 24 weeks of treatment and at 12 weeks post-treatment (SVR12). The lower limit of determination for HCV RNA was 15 IU/Ml. Virologic response was defined as HCV RNA not determined at 4 weeks (rapid viral response; RVR), at end of treatment (EOT) and at 12 weeks post-treatment (SVR12). Virologic failure was defined as HCV RNA determined at any time throughout treatment or the follow-up period, up to 12 weeks post-treatment. AEs which occurred from the first administration of treatment up to 12 weeks post-treatment were recorded in detail. Anemia was defined as hemoglobin level <10 g/dL.

Treatment

The treatment regimens (including RBV use) and durations were selected according to the preference of the insurance company of the patient and the approval of the researchers. When determining the treatment regimen, particular attention was paid to drug interactions. The treatment regimens of PrOD (ombitasvir: 25 mg, paritaprevir: 150 mg, ritonavir: 100 mg once per day and dasabuvir: 250 mg twice per day) and LDV/SOF (ledipasvir: 90 mg and sofosbuvir: 400 mg once per day) were administered orally at standard doses. The RBV dose was 1200mg for patients with bodyweight ≥ 75 kg and 1000 mg for those <75 kg and each dose was split as 2 doses per day. With the approval of the researchers, PrOD + RBV was given to HCV genotype 1a treatment-naive, non-cirrhotic patients for 12 weeks and PrOD was given to genotype 1b treatment-naive, non-cirrhotic patients for 12 weeks. HCV genotype 1a, treatment-naive Child-Pugh Class A cirrhotic patients received PrOD + RBV for 24 weeks and genotype 1b treatment-naive Child-Pugh Class A cirrhotic patients received PrOD for 12 weeks, or HCV genotype 1a and 1b, treatment-naive, cirrhotic patients received LDV/SOF +RBV for 12 weeks or HCV genotype 1a and 1b, treatment-naive, cirrhotic patients received LDV/SOF for 24 weeks.

HCV genotype 1a, treatment-experienced (Pegile-interferon [PEG-IFN] + RBV ± telaprevir [TVR] / boceprevir[BOC]) non-cirrhotic patients received PrOD + RBV for 12 weeks and those with genotype 1b received PrOD for 12 weeks. HCV genotype 1a, and 1b, treatment-experienced, non-cirrhotic patients received LDV/SOF +RBV for 12 weeks or LDV/SOF for 24 weeks. HCV genotype 1a, treatment-experienced, Child-Pugh Class A cirrhotic patients received PrOD + RBV for 24 weeks and genotype 1b, treatment-experienced, Child-Pugh Class A cirrhotic patients received PrOD for 12 weeks, or all genotype 1a and 1b, treatment-experienced, cirrhotic patients received LDV/SOF + RBV for 12 weeks or all genotype 1a and 1b, treatment-experienced, cirrhotic patients received LDV/SOF for 24 weeks.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 software (Statistical Package for the Social Sciences, Chicago, Illinois, USA). In the evaluation of the data, the Chi-square test was used in 2 x 2 sets and multi-cell sets. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Patient population

The demographic and clinical characteristics of the 81 HCV patients in the study are shown in Table 1. The 81 HCV patients comprised 35 (43.2%) males and 46 (56.8%) females with a mean age of 62 years. A total of 41 (50.6%) patients were aged ≥65 years with BMI ≥ 28kg/m^2. Similar to the HCV genotype seen in Turkey, the majority of the patients in the study were genotype 1b, with 12.3% determined as genotype 1a and 87.7% as genotype 1b. Of the total 81 patients in the study, 43 (53.1%) were treatment-experienced and of those, the majority (n:41, 95.3%) had received PEG-IFN + RBV. The other 2 (4.7%) patients had used first-generation protease inhibitors (PI) combinations. Pre-treatment, 54 (67.7%) patients were non-cirrhotic, 18 (22.2%) were compensated cirrhotic and 9 (11.1%) were decompensated cirrhotic.

Table 1. Baseline patient demographics and characteristics

Variables	n=81
Sex, male, n (%)	35 (43.2%)
Age, (years, mean ± SD)	62.4 ± 12.2
BMI, (kg/m^2, mean ± SD)	28 ± 5
Comorbidities, n (%)	
Diabetes	22 (27.2%)
Hypertension	19 (23.5%)
Coronary artery disease	16 (19.8%)
Chronic renal disease	5 (6.2%)
HCV genotype, n (%)	
1a	10 (12.3%)
1b	71 (87.7%)
Treatment history, n (%)	
Naive	38 (46.9%)
Experienced	43(53.1%)
Treatment-experienced, n (%)	
PEG-IFN 2a+RBV	25 (58.1%)
PEG-IFN 2b+RBV	16 (37.2%)
TVR/BOC-INF+RBV	2 (4.7%)
HCV antiviral treatment history, n (%)	
Null-responders	6 (14%)
Partial responders	3 (3.7%)
Relapsers	32 (74.4%)
Discontinued due to side effects	2 (2,5)
Disease severity, n (%)	
No cirrhosis	54 (66.7%)
Cirrhosis	18 (22.2%)
Decompensated cirrhosis	9 (11.1%)
Therapeutic regimen, n (%)	
PrOD	50 (61.7%)
PrOD + RBV	6 (7.4%)
SOF/LDV	10 (12.4%)
SOF/LDV + RBV	15 (18.5%)
SVR12, n (%)	
Yes	79 (96.4%)
No	1 (1.2%)
Relaps	1 (1.2%)
Treatment duration, n (%)	
12 weeks	74 (91.4%)
24 weeks	7 (8.6%)

BMI - body mass index; HCV - hepatitis C virus; PEG-INF - Pegile-interferon; RBV - ribavirin; TVP/BOC - telaprevir/boceprevir; PrOD - paritaprevir, ritonavir, ombitasvir, dasabuvir; SOF/LDV - sofosbuvir, ledipasvir; SVR - sustained virologic response.

Clinical effectiveness

Of the total 81 patients, 50 (61.7%) received PrOD, 6 (7.4%) PrOD + RBV, 10 (12.4%) SOF/LDV and 15 (18.5%) SOF/LDV + RBV treatment regimens. The duration of treatment was 12 weeks in 74 (91.4%) patients and 24 weeks in 7 (8.6%). SVR12 response was obtained in 79 (96.4%) patients and could not be obtained in 2 (2.4%). In respect of the different treatment regimens, SVR12 response was obtained in 55 (98.2%) of the patients receiving PrOD ± RBV and in 24 (96%) of those receiving SOF/LDV ± RBV. No statistically significant difference was determined between the treatment regimens in respect of SVR12 response (p=0.273). SVR12 was obtained in all the treatment-naive patients, irrespective of whether they were cirrhotic or non-cirrhotic. Of the 2 HCV genotype 1 patients who did not reach SVR12, virologic failure was

observed in one and virologic relapse in the other. The patient with virologic failure was genotype 1b, treatment-experienced (PEG-IFN + RBV) and was later non-cirrhotic with relapse. The treatment regimen of PrOD was given for 12 weeks but SVR12 could not be obtained. The other patient with virologic relapse was genotype 1b, treatment-experienced (PEG-IFN + RBV) and was null-responder to treatment and decompensated cirrhotic. For 12 weeks the LDV/SOF + RBV treatment regimen was administered, but following treatment virologic relapse was observed in the 3rd week. The laboratory test values are shown in Table 2. The mean HCV RNA level was 1.61 log IU/mL. Of the laboratory tests, the mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined to be elevated and all other values were within the normal ranges.

Table 2. Baseline laboratory values.

Variables	n=81
HCV RNA (log IU/mL)	1.61 ± 1.99
White cell count, (x 10^9/L)	3.9 ± 1.7
Hemoglobin, g/dL	13.6 ± 2.1
Platelets, (x 10^9/L)	172.3 ± 79.7
ALT, U/L	52.4 ± 41.7
AST, U/L	53.3 ± 40.2
Total biluribin, mg/dL	0.96 ± 0.5
Albumin, g/dL	3.8 ± 0.6
Creatinine, mg/dL	1.1 ± 0.7
INR	1.1 ± 0.2

Data expressed as mean ± SD. HVC RNA, hepatitis C virus RNA; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

Safety

AEs were reported in 46 (56.8%) of the patients in this study (Table 3). Treatment was not stopped because of side-effects in any case and all the patients completed the treatments. The most common of the side-effects reported in ≥5 patients were pruritus, fatigue, headache, nausea, insomnia, myalgia and anemia. No statistically significant difference was determined between the PrOD ± RBV and LDV/SOF ± RBV regimens in respect of AEs (p=0.174). The most common AEs were pruritus in 18 (22.2%) patients, fatigue in 17 (21%) and headache in 16 (19.8%). When evaluated according to the treatment regimen, the AEs reported in those receiving PrOD were headache in 13 (23.2%), pruritus in 12 (21.4%), and fatigue in 12 (21.4%) and in those receiving LDV/SOF treatment, the most common AEs were pruritus in 6 (24%) and fatigue in 5 (20%). Anemia was observed in 6 (28.6%) of the 21 patients using RBV and it did not cause termination of treatment in any case.

Table 3. Adverse events of patients

	All patients (n=81)		PrOD ± RBV (n=56)		LDV/SOF ± RBV (n=25)		p Values
	n	%	n	%	n	%	
Advers reactions	46	56.8%	29	51.8%	17	68%	0.174
Pruritis	18	22.2%	12	21.4%	6	24%	0.797
Fatigue	17	21%	12	21.4%	5	20%	0.805
Headache	16	19.8%	13	23.2%	3	12%	0.242
Nausea	12	14.8%	9	16.1%	3	12%	0.634
İnsomnia	11	13.6%	8	14.3%	3	12%	0.781
Myalgia	7	8.6%	4	7.1%	3	12%	0.472
Anemia	7	8.6 %	3	5,3%	3	12%	0.427
Rash	3	3.7%	2	3.6%	1	4%	0.925

PrOD, paritaprevir, ritonavir, ombitasvir, dasabuvir; RBV, ribavirin; SOF/LDV, sofosbuvir, ledipasvir.

DISCUSSION

As patient selection is applied according to various criteria in Phase III studies that have been conducted on second-generation direct-acting antivirals (DAAs) in chronic hepatitis C patients, the efficacy and safety of the drugs has been lower than real-world data [11]. The aim of this real-world cohort study was to evaluate in a single-center study the efficacy and safety of the second-generation DAA treatment regimens of PrOD ± RBV and SOF/LDV ± RBV, which have started to be used in clinical practice, on chronic HCV genotype 1 patients living in our region.

Both in Turkey and throughout the world, the most common genotype is 1, and the dominant subtype of this is genotype 1b. In an extensive prevalence study in Turkey, genotype 1 was found to be the most common in patients with HCV infection and the majority (92.1%) were sub-genotype 1b [12]. Similar to this reported prevalence in Turkey, the patients in the current study were all genotype 1 and the majority (87.7%) were sub-genotype 1b. Most of the patients were treatment-experienced and were patients with relapse following PEG-IFN treatment. SVR12 reponse was obtained at the rate of 96.4% from the HCV genotype 1 patients in this study, including those with cirrhosis or previous treatment failure. When the patients were evaluated according to the treatment regimen, SVR12 was obtained at the rate of 98.2% in those receiving PrOD ± RBV and at 96% in SOF/LDV ± RBV. No statistically significant difference was determined between the treatment regimens in respect of SVR12 rates and both were observed to have reached a high rate.

Clinical studies made of drugs which have newly come into use include selected patients and they are followed up closely. Real-world data are obtained from heterogenous patient groups in clinical practice. To confirm the findings of clinical research, evaluate the efficacy and safety of drugs and guide treatment decisions, real-world data are necessary.

The discovery of second-generation DAAs was made with several Phase III studies. Of these, the PEARL -III and PEARL-IV studies were conducted on HCV genotype 1a and genotype 1b infected patients treated with PrOD ± RBV, and SVR12 response was obtained in 90.2%-99.5%. There was no significant difference between genotypes 1a and 1b in respect of SVR12 response although virologic failure was determined at a higher rate in the genotype 1a group without RBV compared to the group with RBV [13]. In the TURQUOISE-II study, SVR12 response was obtained at the rate of 86.7%-100% in HCV genotype 1a and 1b infected cirrhotic patients treated with PrOD ± RBV. However, the SVR12 rate was determined to be slightly lower in the HCV genotype 1a, null-responder cirrhotic patients with 12 weeks treatment of PrOD + RBV [14]. In the ION 1 and 2 studies, the SVR12 rates were reported as 99% and 94%, respectively in treatment-naive and treatment-experienced HCV genotype 1 patients treated with SOF/LDV±RBV [15, 16]. As seen in many Phase III studies of second-generation DAAs, high SVR12 rates have been obtained at similar rates for both PrOD ± RBV and SOF/LDV ± RBV. In the current study, SVR12 responses were obtained at high rates similar to those of Phase III studies.

In many regions of the world, real-world data has started to be presented related to the second-generation DAA treatment regimens of PrOD ± RBV and SOF/LDV ± RBV. A study in Germany conducted with real-world data obtained SVR12 responses at the rate of 96%-97% for HCV genotype 1 patients treated with PrOD ± RBV [17]. Chan et al [18] reported an SVR12 response rate of 95.1% in Hong Kong HCV genotype 1b patients treated with PrOD ± RBV. According to the real-world data of Shin et al, SVR12 response of 92.2% was obtained with treatment of SOF/LDV in HCV genotype 1 patients [19]. In the real-world data of heterogenous patient groups of a study by Backus et al, SVR12 responses were obtained of 90%-91.4% with SOF/LDV ± RBV, and 85.8%-95.1% with PrOD ± RBV [20]. According to the real-world data of a study in Spain, SVR12 responses in HCV genotype 1 infections were 96.8% with PrOD ± RBV and 95.8% with SOF/LDV ± RBV [21]. In a study by Ionnou et al of elderly (≥ 65 years) HCV genotype 1 infection patients, SVR12 response was reported as 92.2%-94.2% in patients treated with PrOD and SOF/LDV [22]. In the current study of real-world data in a Turkish population, high rates of SVR12 response were obtained of 96%-98.2% in HCV genotype 1 infected patients, and these results were seen to be consistent with the real-world data from different geographic regions.

The rate of second-generation DAA virologic failure in the current study was low, which was similar to the results of Phase III studies and real-world data [21, 22]. SVR12 was not obtained in 1.8%-4% of the HCV infected genotype 1 patients of the current study. This was due to virologic failure in 1 patient and virologic relapse in 1 patient. The patient with virologic failure was non-cirrhotic, genotype 1b, PEG-IFN + RBV treatment-experienced and received 12 weeks of PrOD treatment.

The other patient with virologic relapse was decompensated cirrhotic, genotype 1b, null-responder to PEG-IFN +RBV treatment and received LDV/SOF + RBV treatment for 12 weeks. Relapse developed in this patient in the 3rd week after treatment. However, SVR12 response was obtained in all treatment-naive patients, irrespective of whether they were cirrhotic or non-cirrhotic. Therefore, care is necessary in treatment-experienced patients in respect of the choice of treatment and duration.

Hepatitis C infection is now a treatable infection for many cases, unlike HBV and HIV, but requires the use of multiple agents as resistance can develop against a single agent. A high rate of replication and virus heterogeneity cause DAA resistance in patients. The treatment regimen, baseline viral load, host genetic factors and treatment duration are important in resistance to DAA used in HCV infection. However, despite the high rates of SVR12 with DAA treatment, in some patients it cannot be obtained. Baseline resistance-associated substitutions (RASs) in NS5A, NS5B and NS3 have a minimal effect on patient response to PrOD and SOF/LDV therapy. The most common RASs in HCV infection are K24R, L31M, Q30H/R, and Y93 H/N in genotype 1a, and Y93 H/N, L31M and K24R in genotype 1b. As resistance tests were not examined in our laboratory, the resistant mutant strains could not be determined in the 2 patients where SVR12 could not be obtained [23, 24].

Although the current study group was heterogenous, safety and tolerability was found to be excellent in both groups. AEs were reported in 56.8% of the current study patients. The most common AEs in both regimens were pruritus, fatigue and headache. In patients receiving PrOD ± RBV, the most frequent AEs were headache, pruritus and fatigue and in those receiving LDV/SOF ± RBV, pruritus and fatigue. No statistically significant difference was determined between PrOD ± RBV and LDV/SOF ± RBV in respect of AEs. Previous studies have reported treatment termination at a rate of 12.7%-13% in HCV genotype 1 patients who used PEG-IFN alpha 2a and 2b before second-generation DAA [25]. The compatibility with patients of this new second-generation DAA is extremely high and the rate of early cessation of treatment is very low at 0.3%-1% [26, 27]. In the current study, treatment was not terminated early because of side effects in any case. The compatibility of this treatment with the patients was excellent.

In a previous Phase III study of HCV genotype 1 infected cirrhotic patients treated with PrOD ± RBV, side-effects were reported in 91.8%, the most common being fatigue, headache, nausea and pruritus. Treatment could not be completed by 2.1% of the patients because of the development of side-effects [26]. The AEs seen in previous extensive Phase III studies have been at an extremely high rate. In these studies, side-effects were reported at 73.4%-87.5% in HCV genotype 1 infected patients treated with PrOD ± RBV, most commonly fatigue, headache and nausea. In those studies, treatment could not be completed by 0.6% of the patients because of the development of side-effects [26]. In the ION 3 study, AEs in genotype 1 patients treated with SOF/LDV ± RBV were 74%-88%. In this study the most common AEs were fatigue, headache and nausea [27]. Fewer AEs have been reported in real-world data than in Phase III studies and there are slightly lower rates of terminating treatment. According to real-world data in a study in Latin America, the incidence of side-effects associated with PrOD ± RBV treatment of HCV genotype 1 patients was 62% and the most frequently seen side-effects were fatigue and pruritus [28]. In a study by Terrault et al [29] of genotype 1 patients, AEs were reported at 63% in those treated with PrOD ± RBV, and at 85% in those treated with SOF/LDV ± RBV. The most common side-effects were reported to be fatigue, headache and nausea. In both Phase III studies and real-world data, headache, pruritus and fatigue are the most commonly seen AEs with the use of both treatment regimens. However, the rates of AEs in Phase III studies are higher than those of real-world data. In the current study, the rate of AEs was similar to that of previous real-world data and lower than findings in Phase III studies.

However in patients whose HCV-RNA is negative three months after tretament; follow-up HCV RNAs should also be requested at 24th and 48th weeks after treatment.

Limitations of this study can be said to be that the total numbers of patients and the treatment groups were low and heterogenous. Nevertheless, the real-world data obtained with close monitoring of the patients and recording of the data increased the efficacy and reliability of the study.

In conclusion, a high rate of SVR12 response was obtained and excellent tolerability was seen in the real-world data of chronic HCV infected genotype 1 patients in our region, which were similar results to the findings of Phase III studies. Moreover, AEs were determined at a lower rate than in Phase III studies. With the use of second-generation DAA, higher rates of tolerability and SVR12 response were obtained in the HCV infected genotype 1

patients of this study, compared to patients previously applied with a PEG-IFN-based regimen. The efficacy and tolerability of second-generation DAA regimens for genotype 1 patients were determined to be extremely high in the real world.

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