Research Article

Doi: 10.4274/vhd.galenos.2019.2019.0042
Viral Hepatitis Journal 2020;26(1):22-27

The Long-term (10.6 years) Outcome of Hepatitis C patients with Sustained Virologic Response Following Treatment with Pegylated Interferon + Ribavirin

Pegile Interferon + Ribavirin ile Tedavisi ile Kalıcı Virolojik Yanıt Elde Edilen Hepatit C Hastalarının Uzun Dönemli (10,6 yıl) Sonuçları

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ABSTRACT

Objectives: Directly-acting anti-viral agents for the treatment of hepatitis C have been revolutionised. In the meantime, hepatitis C patients with sustained virologic response (SVR) achieved with previous treatments have been forgotten. Hepatitis C patients with SVR achived by pegylated interferon + ribavirin (INF + RIB) treatment are followed and it is investigated whether cirrhosis, hepatocellular carcinoma (HCC) and/or decompensation developed or not in these patients.

Materials and Methods: One hundred thirty-five patients with hepatitis C virus who achieved SVR with pegylated INF alpha + RIB treatment between 2006 and 2010 are included in the study. At least twice a year, these patients were followed-up with ultrasonography, alpha fetoprotein and routine laboratory tests.

Results: Out of the patients, 97.8% were genotype 1 and 95% were evaluated with biopsy before the treatment. One hundred twenty non-cirrhotic patients and 15 patients with compensated cirrhosis were followed for a period of 10.6 years (distribution: 9-13 years). None of the non-cirrhotic patients developed cirrhosis or HCC. HCC was developed in one of 15 cirrhotic patients (6 years after the treatment), resulting in the death of the patient. There were no decompensation case.

Conclusion: It is evaluated that non-cirrhotic hepatitis C patients who achieved SVR with pegylated INF can be followed in a wider range of time. There should be a strict follow-up of cirrhotic patients, especially for HCC development.

Keywords: Hepatitis C, sustained virologic response, pegylated INF, cirrhosis, hepatocellular carcinoma

ÖZ

Amaç: Hepatit C'nin tedavisi için doğrudan etkili anti-viral ajanlar devrim yaratmıştır. Zamanla, önceki tedavilerle elde edilen kalıcı virolojik yanıtı (SVR) olan hepatit C hastaları unutulmuştur. Bu çalışmada Pegile interferon + ribavirin (INF + RIB) tedavisi ile SVR elde edilen hepatit C hastaları takip edilmiş ve bu hastalarda siroz, hepatoselüler karsinom (HCC) ve/veya dekompansasyon gelişip gelişmediği araştırılmıştır.

Gereç ve Yöntemler: Çalışmada, 2006-2010 yılları arasında pegile INF alfa + RIB tedavisi ile SVR elde edilen 135 HCV hasta incelenmiştir. Bu hastalar yılda en az iki kez ultrasonografi, alfa fetoprotein ve rutin laboratuvar testleri ile takip edilmiştir.

Bulgular: Hastalarımızın %97,8'i genotip 1 olup, %95'i tedavi öncesi biyopsi ile değerlendirilmiştir. Siroz olmayan 120 hasta ve kompanse sirozlu 15 hasta ortalama 10,6 yıl (dağılım: 9-13 yıl) takip edilmiştir. Siroz olmayan hastaların hiçbirinde siroz veya HCC gelişmemiştir. Sirozlu 15 hastanın 1'inde (tedaviden 6 yıl sonra) HCC gelişmiş ve bu hasta kaybedilmiştir. Dekompansasyon olgusu görülmemiştir.

Sonuç: Pegile INF ile SVR elde edilen, siroz olmayan hepatit C hastalarının daha geniş zaman aralıklarında izlenebileceği değerlendirilmiştir. SVR'li sirotik hastalarının ise, özellikle HCC gelişimi açısından sıkı takibi yapılmalıdır.

Anahtar Kelimeler: Hepatit C, kalıcı virolojik cevap, pegile interferon, siroz, hepatoselüler karsinom

Özdoğan O, Yaraş S. The Long-term (Over Ten Years) Outcome of Hepatitis C patients with Sustained Virologic Response Following Treatment with Pegylated Interferon + Ribavirin. Viral Hepat J. 2020;26:22-27.

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Introduction

The hepatitis C virus (HCV), commonly seen across the globe, is one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC) (1). Interferon (INF)-based treatments have been used in HCV treatment for many years. INF treatments have a low success rate (40%-45%), especially in genotype-1 patients (2). Patients who did not respond to INF treatment either terminated with death by their liver-related complications over time, or eradicated HCV virus with new treatments. There have always been questions relating to the outcomes of patients who achieved sustained virologic response (SVR) using INF therapy. Previous studies have shown that in hepatitis C patients with SVR following treatment with INFs, the risk of cirrhosis and HCC is significantly reduced; inflammation and fibrosis are improved (3,4,5,6).

The main priority in hepatitis C patients is to eradicate the virus and achieve SVR (7). SVR is generally accepted as being the result of a negative HCV-RNA at 24 months after treatment. The next objective is to identify, prevent and treat liver complications that affect morbidity and mortality in patients with SVR. The fundamental issues here are progression to cirrhosis and development of HCC in non-cirrhotic patients with SVR. Another issue is decompensation and HCC develop risk in compensated cirrhotic patients with SVR? There have been previous studies seeking out answers to these questions. However, in most of these studies (4,8,9,10,11), the follow-up period was short and retrospective, and the number of prospective studies with long-term follow-up and only patients receiving pegylated-INF was very small (12,13).

Materials and Methods

Three hundred and sixty-nine HCV-RNA positive patients admitted between 2006 and 2010 were included in the study. Biopsy was performed in 95% of these patients. Biopsy was not performed in patients who showed apparent decompensated or compensated liver cirrhosis as detected during physical examination, laboratory tests, imaging examination and endoscopically. Liver biopsy was carried out in our clinic using a 16-gauge hepafix needle under ultrasound guidance. Histopathological examinations were evaluated by two experienced pathologists from the pathology department of our hospital. The Ishak scoring system was applied for histopathological evaluation (14). A haemogram, biochemical markers and other tests were investigated in the laboratory of our hospital. Hepatitis B and HIV were also investigated. HCV-RNA levels were measured in real time using the "polymerase chain reaction (PCR) technique with COBAS TaqMan 48 (Roche Diagnostic, USA)". HCV genotype was determined using the AMPLIQUALITY HCV-TS (AB Analitica, Italy) kit. The patient's age was accepted as the age at which he received treatment. Body mass index (BMI) and homeostatic model assessment for insulin resistance (HOMA-IR) were calculated with the following formulas before treatment: BMI=weight (kg) / height (m^2); HOMA-IR= fasting plasma insulin (µU/mL) X fasting plasma glucose (mg/dL) /405.

Treatment was given subcutaneously with Pegile INF alpha (α) 2a 180 µg weekly (Pegasys®) or Pegile IFN-α 2b (Pegintron®) at 1.5 µg/kg per week. Additionally, ribavirin was given at 800, 1000 or 1200 mg daily (depending on patient weight and genotype). Genotypes 1 and 4 received 48 weeks of treatment and genotypes 2 and 3 received 24 weeks of treatment.

The following patients were excluded from the study (Figure 1): 84 patients who showed no primary response to treatment; 63 patients who developed a relapse after treatment; 15 patients who could not tolerate treatment or became decompensated during treatment; 17 patients who could not be treated due to decompensated liver cirrhosis; 12 patients who were on a hemodialysis program; and 43 patients who were not followed-up regularly. 24 weeks after the end of treatment, patients with negative HCV-RNA values were considered as SVR. We proceded with the study with 120 non-sirotic and 15 compensated cirrhotic patients meeting these conditions (Figure 1).

In addition to routine laboratory tests, screening with ultrasound and alpha fetoprotein (AFP) levels is recommended in individuals at risk for HCC (1). magnetic resonance imaging (MRI) and/or computed tomography (CT) for the diagnosis of HCC in suspected patients and acceptance as HCC for those with typical imaging findings are recommended in the guidelines (15,16). After the treatment, we evaluated our patients at least twice a year and looked at AFP levels and ultrasonography (USG) in addition to routine laboratory tests. While HCV-RNA levels were measured at 3, 6, 12, 18, and 24 months over the first 2 years after treatment, it was evaluated just once per year after the first 2-year follow-up. MRI and/or CT scans and endoscopy were performed in suspicious patients. When at least one of variceal bleeding, ascites, or encephalopathy was present, decompensated cirrhosis were accepted as being present.

The study protocol was prepared in accordance with the Helsinki Declaration. This study was approved by the Local Ethics Committee Mersin University (approval number: B.30.2. MEU.0.01.00/1871). Written and oral consent was obtained from the patients.

Statistical Analysis

Categorical variables were recorded in percentage, and continuous variables as mean (± standard deviation) or as median. Shapiro Wilk-W test was used to evaluate the normal distribution of the variables. While the Student's t-test used for continuous variables with normal distribution, and Mann-Whitney test was

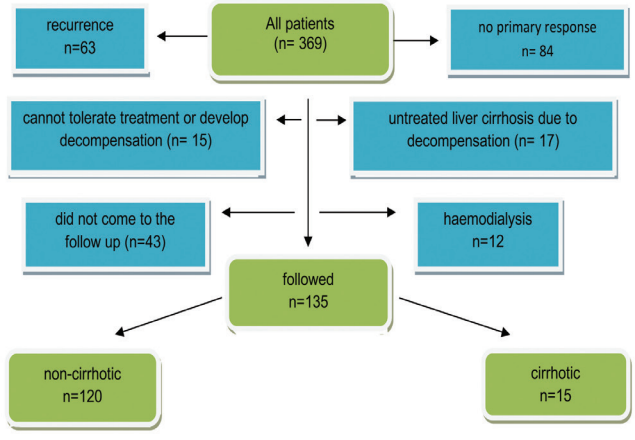

Figure 1. Flow chart

used for continous variables without normal distribution; chi-square test was used for categorical variables. The data were analysed using SPSS version 21.0.0 for Windows (IBM Corp™, Armonk, NY).

Results

The mean age was 49.3±9.82 years (22-67 years). Eighty patients were female and 55 patients were male. The mean follow-up was 10.6 years (9-13 years). With the exception of 3 patients (in the cirrhotic group: one patient, of genotype 2; in the non-cirrhotic group: one patient each for genotypes 2 and 4), all remaining patients (97.8%) were genotype 1. While 114 of the genotype1 patients were genotype 1b, 4 of them were genotype 1a; no subgroup could be detected in 14 patients. 82 patients received Pegile INF alpha (α) + 2a + Ribavirin (RIB) and 53 patients received Pegile INF-α 2b + RIB. A total of 14 patients were using alcohol and were social drinkers (one to two times a month, one to two glasses). Of these 14 patients, 10 were non-cirrhotic and 4 were cirrhotic. None of our patients were alcohol-dependent. Hepatitis B was present in one of our non-cirrhotic patients. HIV was not detected in any of our patients. 11.7% (14/120) of our non-cirrhotic patients had diabetes mellitus (DM); 3.4% (n=4) had hypothyroidism; and 0.8% (n=1) had hyperthyroidism. 40% (6/15) of the cirrhotic patients had DM; and 13.3% (n=2) had hypothyroidism. Demographic data and results from laboratory testing of the patients before treatment are shown in Table 1.

It seemed that while alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and AFP values were higher in the cirrhotic group, the number of platelets, leukocytes and erythrocytes was higher in the non-cirrhotic group (Table 1). However, due to the difference between the number of patients in these two groups, these was not suitable for any beneficial statistical evaluation.

Liver biopsy was not carried out in 7 of 15 patients with cirrhosis due to obvious cirrhosis in the pre-treatment evaluation. A fibrosis score of 6 was determined in 3 of 8 patients diagnosed with cirrhosis (Ishak fibrosis 5-6) by biopsy. Histological activity index (HAI) scores for these patients ranged from 5 to 13. All non-

Table 1. Demographic and laboratory data of patients

	Total group (n=135)	Non-cirrhotic group (n=120)	Cirrhotic group (n=15)
Age (year)	49.3±9.82	48.39±9.86	56.6±5.43
Sex (female)	80 (59.3)	71 (59.2%)	9 (60%)
BMI	26.9±4.34	26.52±4.12	30.47±4.76
Duration of follow-up (years)	10.6±1.03	10.49±0.87	11.47±1.63
peg-IFN 2α + RBV	82 (61%)	76 (63%)	6 (40%)
peg-IFN 2β + RBV	53 (39%)	44 (37%)	9 (60%)
HCV-RNA (x103 IU/mL)	1310±2648	1276±2464	1612±3933
Genotip 1	132 (97.8%)	118 (98.3%)	14 (93.3%)
Plt (x103/μL)	203.4±68.5	211.9±66.1	135.5±46.2
Htc (%)	40.62±4.22	40.37±4.2	37.2±4.86
Wbc (μL)	6786±1942	6949±1883	5483±1908
AFP (IU/mL)	4.09±2.17	3.79±1.86	6.48±2.89
ALT (U/L)	76.94±64.34	73.18±64.24	107±56.86
AST (U/L)	58.36±39.33	54.75±37.99	97.67±46.7
GGT (U/L)	47.5±44.8	43.58±42.97	78.93±46.75
ALP (U/L)	87.76±35.9	86.03±34.77	101.67±41.41
Bilirubin (mg/dL)	1.34±0.56	1.12±0.42	3.12±1.67
INR	1.12±0.08	1.08±0.07	1.42±0.15
FBG (mg/dL)	105.39±37.73	101.48±29.35	136.67±69.42
INSULIN (μU/mL)	12.55±7.41	12.43±7.36	13.47±7.75
HOMA-IR	3.45±3.03	3.27±2.8	4.88±4.15
TC (mg/dL)	175.8±40.77	176.77±41.06	168.07±37.46
LDL (mg/dL)	100.05±34.11	100.84±34.5	93.73±30.12
HDL (mg/dL)	48.31±12.97	48.59±13.13	46.07±11.4
TG (mg/dL)	137.21±67.36	136.69 65.25	141.33 82.16
TSH (μIU/mL)	2.23±1.78	2.22±1.66	2.72±2.59

AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, FBG: Fasting blood glucose, GGT: Gamma glutamyl transpeptidase, HDL: High-density lipoprotein, Htc: Hematocrit, LDL: Low-density lipoprotein, peg-IFN 2α: Pegylated interferon-2α, peg-IFN 2β: Pegylated interferon-2β, Plt: Platelet, RBV: Ribavirin, TB: Total bilirubin, TC: Total cholesterol, TG: Triglycerides, TSH: Thyroid stimulating hormone, Wbc: Leukocyte

cirrhotic patients underwent biopsy before treatment. 80% had mild fibrosis (0-2). Significant inflammation (HAI: 8-12) was present in 10.8%. 20% had moderate to severe steatosis. Fibrosis, HAI scores and steatosis rates of non-cirrhotic patients are shown in Table 2.

During the treatment, HCV-RNA levels were negative in 92% (124/135) of the patients after 3 months. The remaining 11 patients were determined to be below 10.000 IU/mL; all of these were negative after 6 months of treatment. No recurrence was observed in any patient who was followed up for a mean of 10.6 years after treatment.

In the follow-up of cirrhotic patients, one patient developed HCC. The AFP level of the patient was 7.09 IU/mL before treatment, increasing to 654 IU/mL in 7 years. Abdominal USG showed localised hypoechoic areas in the liver. MRI was performed and infiltrative HCC invading the portal vein was detected. This patient died 9 months after diagnosis. In addition, another cirrhotic patient with diabetes died of coronary artery disease at 4 years after treatment. With the exception of these, 13 cirrhotic patients had stable follow-up. Decompensation did not develop. It was found that the most recent AST, ALT, GGT, AFP levels of these patients were improved as compared to pre-treatment values (Table 3).

In the follow-up of 120 Hepatitis C patients with SVR, cirrhosis and HCC were not detected in any of the patients. Four of these patients died due to extra-hepatic causes.

Discussion

Directly-acting antiviral drugs for the treatment of chronic hepatitis C have been revolutionized. Treatment success rates are over 95% (17,18,19). High success has also been achieved in HCV-induced decompensated liver patients who were not able to receive interferon therapy (20). In addition, these drugs are used safely in patients who have not been able to obtain SVR in interferon treatments previously, and almost complete success is achieved (21). It seems that eradication of HCV is not an issue anymore. Subsequently, the real question has been: "should we monitor HCV patients with SVR in terms of whether cirrhosis, HCC, relapse or decompensation develops". These questions have also begun to be asked in direct acting-oral antiviral drugs, and can be seen in studies in this direction (22,23). Previously, there have been studies in this direction, but the number of long-term studies is limited.

In this study, with a mean follow-up period of 10.6 years in 135 hepatitis C patients (15 of whom presented with compensated-cirrhosis), no recurrence was detected in any of the patients. Some previous studies (mean follow-up of 2-5 years) support our results (5,24,25,26). Even though there are publications indicating that late relapse may occur, the probability of this is reported to be around 1% in most cases (8,11,27,28). After treatment, we regularly checked the HCV-RNA level at least once per year using a sensitive method up to 50 IU/mL.

Table 2. Histopathological evaluation of non-cirrhotic patients

Ishak fibrosis	Number of patients	Ishak HAI	Number of patients	Steatosis	Number of patients
0	15	0-4	36	NO (0%)	55
1	43	5-8	71	Mild (1-33%)	41
2	38	8-12	13	Moderate (34-66%)	17
3	16	12-18	0	High (67-100%)	7
4	8	-	-	-	-
5	-	-	-	-	-
6	-	-	-	-	-

HAI: Histological activity index

Table 3. Cirrhotic patients' final values compared with pre-treatment values*

	Cirrhotic patient (n=13)		
	Pre-teatment value	Last value	p
ALT (U/L)	107.2±60.9	31.3±15.6	0.0001
AST (U/L)	95.6±48.7	33.2±13.8	0.0001
GGT (U/L)	64.8±31.9	50.2±34.4	0.0105
Albumin (g/dL)	3.58±0.42	4±0.49	0.0011
AFP (IU/mL)	6.29±3.01	2.74±1.19	0.0063
Plt (x10^3/µL)	139±43.6	149.6±69.3	0.0261
Htc (%)	37.5±5.3	37.1±4.41	0.3068
Wbc (µL)	5495±1782	5536±1689	0.3026

AFP: Alpha fetoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transpeptidase, Htc: Hematocrit, Plt: Platelet, Wbc: Leukocyte, *: Two patients who died were excluded from the evaluation

None of our non-cirrhotic patients developed cirrhosis or HCC. In a study of 137 non-cirrhotic hepatitis C patients who achieved SVR with interferon-based treatments, no HCC or cirrhosis was detected after approximately 8.6 years (range: 2-19.9 years) (12). In another study including 150 patients with SVR (pretreatment and 5 years later, biopsy was performed), it was determined that in more than 90%, improvements in fibrosis scores or inflammation were found (5). In this study too, the development of HCC or cirrhosis was not detected in non-cirrhotic patients. Although some studies have reported cirrhosis, the rate of this is low (>5%) (9,29). Only one of our patients had concomitant hepatitis B, but no additional liver disease. Diseases of comorbidity such as DM and hypothyroidism were limited in number, and most importantly, there were no alcohol-dependent patients. We believe that cirrhosis does not develop due to these factors in our study.

The 5-year decompensation rate in non-SVR compensated cirrhotic patients ranges between 18%-25% (30,31). In cirrhotic patients with acquired SVR, the decompensation rate decreases significantly (32). In our study, no decompensation occurred in cirrhotic patients. In a study of 103 patients with SVR (two patients were cirrhotic) with a 23-year follow-up period, no decompensation was found (13). In a joint study of 5 hepatology units in Europe and Canada, they found 30% (142/479) SVRs after interferon-based treatment in patients with cirrhosis or advanced fibrosis (Isaac fibrosis score 4-6). The mean follow-up period for these patients was 2.1 years (0.8 to 4.9 years), and no patients developed decompensation (4). In another study involving 8 centers from Europe, the 5-year decompensation rate was found to be 1% [95% confidence interval (CI), 0.0% 32.3%] (33). In our patients, we believe that the most important factor behind the lack of development of decompensation, as we mentioned above, was that there were no alcohol-dependent patients or patients suffering from further hepatic diseases.

HCC is one of the most common complications and causes of death in patients with cirrhosis due to hepatitis C (34). This risk is reduced by HCV eradication. In our study, none of the non-cirrhotic patients developed HCC, while only one (6.7%) of 15 compensated cirrhotic patients developed HCC. In a study involving cirrhotic hepatitis C patients, with an average follow-up of 32 months, it was determined that 3% of cirrhotic patients with SVR and 17% of non-SVR patients developed HCC (35). In a study with an average follow-up of 46.7 months, HCC developed in 1% of hepatitis C patients with SVR, while HCC developed in 5.5% of patients with non-SVR (9). In this study, a proportional decrease was observed in non-cirrhotic patients. Some studies with different follow-up times have shown that the risk of HCC development is less than 10% in cirrhotic patients (5,12,13). In a meta-analysis covering those obtained from IFN-based SVR, the annual risk of HCC formation was calculated as 1.14% (95% CI 0.86-1.52) (36).

In our study, one of the limitations was the low rate of cirrhosis patients. This low rate may cause limitations in generalizing the results to the population.

Conclusion

Although there are many studies following hepatitis C patients who had previously taken interferon therapy and achieved SVR, our study shows some different features. Our study offers some advantages, such as: 95% of our patients being diagnosed by biopsy; 97.8% of patients being genotype 1 (greater than 90% of them were genotype 1b); patients received only pegileinterferon+ribavirin treatment; no cases of HIV, HBV (except one patient) or alcohol dependence; long-term follow-up period (10.6 years); and the fact the study was conducted at a single center.

None of the non-cirrhotic patients that we followed up had cirrhosis or HCC. Although no decompensation was observed in the cirrhotic patients, 6.7% developed HCC. In the light of previous studies, we believe that non-cirrhotic hepatitis C patients with interferon therapy may be followed up less frequently than those with cirrhotic patients, and that cirrhotic patients should be followed closely especially in terms of HCC.

Acknowledgements

The authors are grateful to Dr. Orhan Sezgin, Dr. Engin Altıntaş, Dr. Fehmi Ateş, and Dr. Enver Üçbilek for their contributions, which have helped to improve the paper.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee Mersin University (approval number: B.30.2. MEU.0.01.00/1871)

Informed Consent: Verbal and written informed consent received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: O.Ö., S.Y., Design: O.Ö., S.Y., Data Collection or Processing: O.Ö., S.Y., Analysis: O.Ö., S.Y., Literature Search: O.Ö., Writing: O.Ö., S.Y.

Conflict of Interest: All authors declare to have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018 69:461-511.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335-1374.
3. Yu ML, Lin SM, Chuang WL, Dai CY, Wang JH, Lu SN, Sheen IS, Chang WY, Lee CM, Liaw YF. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: A nationwide, multicentre study in Taiwan. Antivir Ther. 2006;11:985-994.
4. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147:677-684.
5. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology. 2009;49:729-738.
6. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano E, Fujiyama S, Yamada G, Yokosuka O, Shiratori Y, Omata M. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology. 2002;123:483-491.
7. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol. 2014;60:392-420.

8. Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, Abergel A, Pessôa MG, Lin A, Tietz A. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010;139:1593-1601.
9. Moon C, Jung KS, Kim DY, Baatarkhuu O, Park JY, Kim BK, Kim SU, Ahn SH, Han KH. Lower incidence of hepatocellular carcinoma and cirrhosis in hepatitis C patients with sustained virological response by pegylated interferon and ribavirin. Dig Dis Sci. 2015;60:573-581.
10. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, Kuroki T, Nishiguchi S, Sata M, Yamada G, Fujiyama S, Yoshida H, Omata M. Histologic improvement of fibrosis in patients with Hepatitis C who have sustained response to interferon therapy. Ann Int Med. 2000;132:517-524
11. Desmond CP, Roberts SK, Dudley F, Mitchell J, Day C, Nguyen S, Pianko S. Sustained virological response rates and durability of the response to interferon-based therapies in hepatitis C patients treated in the clinical setting. J Viral Hepat. 2006;13:311-315.
12. Morisco F, Granata R, Stroffolini T, Guarino M, Donnarumma L, Gaeta L, Loperto I, Gentile I, Auriemma F, Caporaso N. Sustained virological response: a milestone in the treatment of chronic hepatitis C. World J Gastroenterol. 2013;19:2793-2798.
13. Koh C, Heller T, Haynes-Williams V, Hara K, Hao X, Feld JJ, Kleiner DE, Rotman Y, Ghany MG, Liang TJ, Hoofnagle JH. Long Term Outcome of Chronic Hepatitis C after Sustained Virological Response to Interferon-Based Therapy. Aliment Pharmacol Ther. 2013;37:887-894.
14. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22:696-699.
15. Bruix J, Sherman M. Management of hepatocellular carcinoma (AASLD Practice Guideline). Hepatology. 2005;42:1208-1236.
16. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421-430.
17. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisc P, Foster GR, Bräu N, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889-1898.
18. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari ZB, Zhao Y, Brown DD, Wan S, DiNubile MJ, Nguyen BY, Robertson MN, Wahl J, Barr E, Butterton JR. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163:1-13.
19. T. Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, Colombo M, Calinas F, Aguilar H, de Ledinghen V, Mantry PS, Hezode C, Marinho RT, Agarwal K, Nevens F, Elkhashab M, Kort J, Liu R, Ng TI, Krishnan P, WeiLin C, Mensa FJ. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16:417-426.
20. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F, Hughes EA, Noviello S, Swenson ES. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatolog. 2016;63:1493-1505.
21. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014;147:359-365.
22. Cardoso H, Vale AM, Rodrigues S, Gonçalves R, Albuquerque A, Pereira P, Lopes S, Silva M, Andrade P, Morais R, Coelho R, Macedo G. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. J Hepatol. 2016;65:1070-1071.
23. Lashen SA, Shamseya MM, Madkour MA. Hepatocellular Carcinoma Occurrence/Recurrence after Direct-Acting Antivirals for Hepatitis C in Egyptian Cohort: Single-Center Experience. Dig Dis. 2019;37:488-497.
24. Maylin S, Martinot-Peignoux M, Moucari R, Boyer N, Ripault MP, Cazals-Hatem D, Giuily N, Castelnau C, Cardoso AC, Asselah T, Féray C, Nicolas-Chanoine MH, Bedossa P, Marcellin P. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology. 2008;135:821-829.
25. Formann E, Steindl-Munda P, Hofer H, Jessner W, Bergholz U, Gurguta C, Ferenci P. Long-term follow-up of chronic hepatitis C patients with sustained virological response to various forms of interferon-based anti-viral therapy. Aliment Pharmacol Ther. 2006;23:507-511.
26. Chavalitdhamrong D, Tanwandee T. Long-term outcomes of chronic hepatitis C patients with sustained virological response at 6 months after the end of treatment. World J Gastroenterol. 2006;12:5532-5535.
27. Reichard O, Glaumann H, Fryden A, Norkrans G, Wejstal R, Weiland O. Long-term follow-up of chronic hepatitis C patients with sustained virological response to alpha-interferon. J of Hepatology. 1999;30:783-787.
28. Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, Kilani A, Areias J, Auperin A, Benhamou JP, Degott C, Erlinger S. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Int Med. 1997;127:875-881.
29. Pradat P, Tillmann HL, Sauleda S, Braconier JH, Saracco G, Thursz M, Goldin R, Winkler R, Alberti A, Esteban JI, Hadziyannis S, Rizzetto M, Thomas H, Manns MP, Trepo C, HENCORE Group. Long-term follow-up of the hepatitis C HENCORE cohort: response to therapy and occurrence of liver-related complications. J Viral Hepat. 2007;14:556-563.
30. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis. 2011;52:889-900.
31. Lawson A, Hagan S, Rye K, Taguri N, Ratib S, Zaitoun AM, Neal KR, Ryder SD, Irving WL. The natural history of hepatitis C with severe hepatic fibrosis. J Hepatol. 2007;47:37-45.
32. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010;8:280-288.
33. Veldt BJ, Saracco G, Boyer N, Cammà C, Bellobuono A, Hopf U, Castillo I, Weiland O, Nevens F, Hansen BE, Schalm SW. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. Gut. 2004;53:1504-1512.
34. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, Del Ninno E, Morabito A, Colombo M. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology. 2006;43:1303-1310.
35. Cheinquer N, Cheinquer H, Wolff FH, Coelho-Borges S. Effect of sustained virologic response on the incidence of hepatocellular carcinoma in patients with HCV cirrhosis. Braz J Infect Dis. 2010;14:457-461.
36. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, George J, Dore GJ. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol. 2017;67:1204-1212.