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ORIGINAL ARTICLE

The markers predicting response to Hepatitis C virus treatment and evaluation of treatment responses

Özgür Günal[1], Hüseyin Şener Barut[1], Ünal Erkorkmaz[2]

[1] *MD, Department of Infectious Diseases and Clinical Microbiology, Gaziosmanpasa University, Tokat, Turkey*

[2] *PhD, Department of Biostatistics, Gaziosmanpasa University, Tokat, Turkey*

ABSTRACT

Objectives: Currently pegylated interferon alpha (peg-IFN) and ribavirin treatment is recommended for chronic hepatitis C treatment. The aim of treatment is to provide sustained viral response (SVR).

Material and methods: A total of 125 patients, who have been treated for chronic hepatitis C diagnosis and are followed up until 6 months after treatment, were enrolled into the study. Markers, which have indicated treatment response against hepatitis C virus treatment, treatment responses according to peg-IFNα type used, and experienced side effects in patients have been compared.

Results: Of patients, 103 were (82.4%) female and 22 were (17.6%) male and mean of age was 54.74±7.93 years. Markers indicating SVR in our study were calculated as rapid viral response (RVR) ($p<0.001$); early viral response (EVR) ($p<0.001$); high baseline thrombocyte ($x10^3$ / µl) value (240,93 ± 75,61) ($p<0.004$); baseline total bilirubin level (0.55±0.19) ($p<0.001$) and hepatic fibrosis stage (according to Knodell or modified ISHAK staging >2) ($p<0.034$). Predictive parameters for EVR in our study were defined as absence of diabetes in patients, high baseline lymphocyte numbers (2024.74±625.93) and high baseline cholesterol level (in EVR positive patients 180.47±32.77 mg/dl; in EVR negatives 152.00±24.56). There was no statistical difference between peg-IFN type in patients and RVR, EVR and SVR. Also there was no statistical difference in hematological side effects (neutropenia, anemia, and thrombocytopenia) in both treatment groups.

Conclusions: As the efficacy of treatment against HCV is defined, predictive markers for the treatment response are becoming more significant. Therefore, it is concluded that these factors should also be considered in patient treatment plans. *J Microbiol Infect Dis 2012; 2(3): 100-108*

Key words: Treatment of Hepatitis C, Sustained Viral Response, Markers of Treatment

Hepatit C virüs tedavi yanıtını önceden gösteren belirteçler ve tedavi yanıtlarının değerlendirilmesi

ÖZET

Amaç: Kronik hepatit C tedavisi için günümüzde pegile interferon alfa (peg-IFN) ve ribavirin tedavisi önerilmektedir. Tedavide amaç kalıcı viral yanıt (KVY) elde etmektir.

Gereç ve yöntem: Bu çalışmaya Kronik hepatit C tanısıyla tedavi verilen ve tedavi bitiminden 6 ay sonrasına kadar izlenen 125 hasta dahil edildi. Hastalarımızda Hepatit C virüsüne tedavi yanıtını önceden gösteren belirteçler ve tedavide kullanılan peg-IFNα türüne göre tedavi yanıtları ve oluşan yan etkiler karşılaştırıldı.

Bulgular: Hastaları 103 kadın (%82,4), 22'si erkek (%17,6)'di ve yaş ortalaması 54,74±7,93 idi. Çalışmamızda KVY'yi önceden gösteren belirteçler olarak; Hızlı viral yanıt (HVY) ($p<0.001$), Erken viral yanıt (EVY) ($p<0.001$), başlangıç PLT (x103 / µl) değerinin yüksek olması (240, 93 ± 75, 61) ($p<0.004$), başlangıç total bilürubin düzeyi (0,55±0,19) ($p<0.001$) ve karaciğer fibrozis evresi (Knodell veya modifiye ISHAK evrelemesine göre >2) ($p<0.034$) olarak saptanmıştır. Çalışmamızda EVY'i önceden tahmin ettiren parametreler olarak; hastalarda DM olmaması, başlangıç lenfosit düzeyinin yüksekliği (2024,74±625,93) ve başlangıç kolesterol düzeyi yüksekliği (EVY pozitiflerde 180,47 ± 32,77 mg/dl iken negatiflerde 152,00 ± 24,56) olarak saptanmıştır. Hastalarda kullanılan peg-IFNα türüne göre HVY, EVY ve KVY açısından istatistiksel bir fark saptanmadı. Yine her iki tedavi grubunda da hematolojik yan etkiler açısında (nötropeni, anemi, trombositopeni) istatistiksel bir fark saptanmamıştır.

Sonuç: HCV'ye karşı uygulanan tedavinin etkinliğinin gösterilmesi ile bu tedaviye verilen yanıtları öngörmeyi sağlayan belirteçleri kavramamız giderek daha önemli hale gelmektedir. Bu nedenle hastaların tedavi planlarında bu faktörlerinde göz önünde bulundurulması gerektiği sonucuna varılmıştır.

Anahtar kelimeler: Hepatit C tedavisi, kalıcı viral yanıt, tedavi belirteçleri

Correspondence: Özgür Günal,
Gaziosmanpaşa Üniv. Tıp Fak., İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD. Tokat, Türkiye Email: ozgurgop@yahoo.com
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INTRODUCTION

One of the prominent causes of chronic hepatic disease in the world is Hepatitis C virus (HCV) infection. Throughout the world, approximately 130-210 million people are infected by HCV.[1] HCV can cause a wide range of severe hepatic disease from hepatitis to cirrhosis and hepatocellular carcinoma.[2] There are six genotypes, from 1 to 6, and many subtypes of HCV.[3] Genotype 1 is the most common genotype in the world and subtype 1b is most commonly encountered in Europe.[4] While the genotype 1 responses weakly to treatment, genotype 2 and 3 respond to the treatment better.[5]

Pegylated interferon (peg-IFN)-α - ribavirin combination is a reliable and accepted treatment method in chronic Hepatitis C treatment.[6] Currently, two peg-IFNs (α2a and α2b), whose pharmacokinetics is different from each other, are being employed.[7] Recently, phase III studies about peg-IFN-α and ribavirin in combination with protease inhibitors, telaprevir and boceprevir, in genotype 1 patients have been published.[8] The aim of chronic Hepatitis C treatment is to reach sustained viral response (SVR), which is known as undetected serum HCV-RNA levels at 6-months after the treatment is discontinued. It is demonstrated in studies that once SVR is reached, virological relapse possibility is low. Moreover, morbidity and mortality rates due to chronic HCV infection are decreased by antiviral treatment.[5]

Some predictors, which have been detected before initiation of treatment, have been reported to be useful in estimating patient SVR beforehand.[6] In this study, we have investigated predictors of treatment response and the treatment response rates, themselves, in 125 chronic hepatitis patients, who have completed the treatment.

MATERIAL AND METHODS

A total of 125 patients, who have applied outpatient clinic of Infectious Diseases and Clinical Microbiology at the School of Medicine in Gaziosmanpasa University between dates June 2006 and June 2011; have been treated for chronic hepatitis C diagnosis and were followed up until 6 months after treatment, were enrolled into the study. Patient data have been recorded retrospectively by medical record review in the files and analyses have been performed according to the obtained results. Predictive markers for treatment response in patients with hepatitis C virus have been investigated. Therefore, age, gender, presence of diabetes mellitus (DM), HCV RNA levels, fibrosis stage in hepatic biopsy, IFN type used, baseline weights before treatment, platelet (PLT) count, baseline lymphocyte count, alanine amino transferase (ALT), hemoglobin (Hb) levels, blood cholesterol level, blood Triglyceride level, albumin level, total bilirubin level, rapid virologic response (RVR) and early virologic response (EVR) have been compared in patients with positive and negative SVRs. Also SVR rates and hematological side effects (neutropenia, anemia, thrombocytopenia) have been compared according to IFN type used in patients.

Treatments in line with national and international guidelines have been initiated and continued. Combination of peg-IFN alpha 2a (180 mg) or 2b (at the dose of 1.5 μg/kg) with adjusted dose of ribavirin according to body weight (1200 mg in patients with body weight >75 kg; 1000 mg/day in patients with body weight <75 kg) have been given to patients. Majority of patients have received the treatment for 48 weeks. Appropriate dose adjustments have been performed in patients, who developed anemia and cytopenia. Quantitative RNA is studied in patient serums at months 1, 3, 6 and at the end of treatment and 6 months after the treatment has ended. If HCV RNA was negative at the first month of treatment, it was accepted as RVR; if there was more than 2 log decrease compared with baseline values, it was accepted as EVR; and if it was at undetectable levels at 6 months after treatment has ended, it was accepted as SVR. HCV RNA values, which did not decrease more than 2 logs at the third month or which were not negative at the 6th month of treatment were accepted as unresponsive. Unresponsive patients or relapsed patients made up the SVR negative group.

Statistical Analysis

Pearson's chi-square test was used to compare the categorical variables between groups. Categorical variables were presented as count and percentages. Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables were normal. Accordingly, it was seen that all variables displayed a normal distribution. Therefore, two independent sample t test was used to compare the continuous variables

between groups. Repeated measures one way ANOVA test was used to compare the haematological parameters among control periods. Repeated measures two way ANOVA test was used to compare the changes of hematological parameters between inf 2a and 2b groups. Continuous variables were presented as mean and standard deviation. A p values <0.05 were considered as statistically significant. Analyses were performed using commercially software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY)

Ethics statement

The study protocol was approved by the institutional review board of Gaziosmanpasa University, Tokat, Turkey (IRB No:12-BADK-027).

RESULTS

A total of 125 patients were enrolled into the study, and 103 patients (82.4%) were female whereas 22 (17.6%) were male; mean of age was 54.74±7.93 years. Of patients 72.8% was in 40-59 year age group. Among 51 patients, whose genotyping was performed, 50 was infected by genotype 1 and only 1 patient had genotype 2 infection.

Of enrolled patients, 18-months follow up data were reached in 121 patients; 78 were positive for SVR (64.4%) and 43 (35.5%) were SVR negative. Predictive markers for SVR in the study were defined as RVR positivity (p<0.001), EVR positivity (p<0.001), baseline high PLT value (240.93 ± 75.61) (p<0.004), baseline total bilirubin level (0.55 ± 0.19) (p<0.001) and high fibrosis stage (according to Knodell or modified ISHAK staging; >2 (p<0.034)) in hepatic biopsy (Table 1).

In our study, it was investigated if there were predictive markers for RVRs and EVRs (according to gender, age, weight, hepatic fibrosis, HCV RNA level, ALT and PLT counts, Total cholesterol level and IFN types). No predictive parameter was detected for RVR (Table 2). Predictive parameters for EVR were defined as absence of DM, high baseline lymphocyte count (2024.74 ± 625.93) and high baseline cholesterol level (EVR positives=180.47 ± 32.77 mg/dl; EVR negatives= 152.00±24.56 mg/dl) (Table 3).

While 76 patients received peg-IFNα2b treatment, 45 had peg-IFNα2a treatment; there was no statistical difference in RVR, EVR and SVR between these two groups (Table 4). And also there was no statistical difference in hematological side effects (neutropenia, anemia, thrombocytopenia) between the two therapy groups (Table 5).

DISCUSSION

In HCV treatment, HCV RNA negativity (<50 IU/ml) at the 4th week of treatment is defined as rapid virological response (RVR); decrease >2 log or negativity of HCV RNA at the 12th week of treatment is defined as early virological response (EV), and HCV RNA negativity 6 months after the treatment discontinuation is defined as SVR.[5]

Predictors for estimation of SVR are investigated in the previous studies, and as a result of these studies two major predictors have been defined for SVR. These are viral genotype and viral load before the treatment.[9] Hadziyannis et al. reported that SVR rates were higher in patients, who were infected by genotypes other than genotype 1 (mainly genotype 2 and 3) and had viral load of <600,000 IU/ml.[10] Zeuzem et al. indicated that treatment responses of genotype 1 infected patients with lower viral loads (<400,000 IU/ml) were higher than those with high viral loads.[11]

Although the threshold has not been defined absolutely in European Association of Study of the Liver (EASL) guideline, treatment responses of genotype 1 infected patients with viral loads 400,000 – 800,000 IU/ml were better.[12] In our study, approximately all of the patients were infected by genotype 1. Therefore, no comparison between genotypes could be performed. Pretreatment viral load was not defined as a significant marker for SVR detection in our patients (p=0.552). It has been thought that this was because of few numbers of patients and they were followed up by different PCR methods during the 5-6years' monitorization period.

It has been reported that RVR was highly predictive for SVR independently from treatment regimens and genotypes.[13] Approximately,15% of HCV genotype 1 infected patients have reached RVR. In retrospective analyses of large scale clinical studies, genotype 1 infected patients, who developed RVR, would develop SVR at a rate of 90%.[13,14] RVR in our patients was 34%. In our study, SVRs in cases with positive RVRs were statistically significantly higher than those in the negative ones (p <0.001).

Table 1. Comparisons of baseline characteristics between sustained viral response (SVR) negative and positive groups

		SVR – (n=43)	SVR + (n=78)	p
Age, year		56. 1 ± 8. 5	53. 4 ± 7. 4	0.071
Gender, n (%)	Female	9 (20. 9)	11 (14. 1)	0.476
	Male	34 (79. 1)	67 (85. 9)	
Weight, kg		72.7 ± 14,0 (n=37)	76. 5 ± 15. 6 (n=70)	0.223
Weight, n (%)	≥75 kg,	18 (48. 6)	31 (44. 3)	0.821
	<75 kg,	19 (51. 4)	39 (55. 7)	
Diabetes Mellitus, n (%)	Yes	9 (20. 9)	12 (15. 4)	0.603
	No	34 (79. 1)	66 (84. 6)	
RNA, n (%)	≥600,000	17 (53. 1)	27 (44. 3)	0.552
	<600,000	15 (46. 9)	34 (55. 7)	
Lymphocyte, / µl		1862,86 ± 510,72 (n=42)	1999,36 ± 671,75	0.253
Platelets (x10^3 / µl)		201,28 ± 62,26	240,93±75,61 (n=76)	0.004
PLT, n (%)	≥150000	33 (76. 7)	70 (92.1)	0.038
	<150000	10 (23. 3)	6 (7. 9)	
Hemoglobin (gr/dl)		14,07 ± 1,11	13,93 ± 1,23 (n=77)	0.556
ALT (U/L)		86. 5 ± 54. 9	71. 1 ± 43. 1 (n=76)	0.093
ALT, n (%)	≤40	8 (18. 6)	19 (25. 0)	
	41-80	18 (41. 9)	37 (48. 7)	
	81-120	10 (23. 3)	10 (13. 2)	0.542
	>120	7 (16. 3)	10 (13. 2)	
Total Bilirubin (mg/dl)		0,77±0,38 (n=42)	0,55±0,19 (n=73)	<0.001
Albumin (mg/dl)		4,31±0,46 (n=38)	4,32±0,36 (n=69)	0.907
Cholesterol (mg/dl)		174,65±37,17 (n=34)	178,21±32,06 (n=66)	0.619
Cholestero(mg/dl)l , n(%)	≥130	32 (94. 1)	63 (95. 5)	0.771
	<130	2 (5. 9)	3 (4. 5)	
Triglycerides (mg/dl)		107,78 ± 45,97 (n=36)	116,09 ± 0,92 (n=67)	0.349
Fibrozis stage, n (%)	≥3	21 (60.0)	24 (35. 8)	0.034
	<3	14 (40. 0)	43 (64. 2)	
RVR, n(%)	Yes	3 (9. 4)	28 (49. 1)	<0.001
	No	29 (90. 6)	29 (50. 9)	
EVR, n(%)	Yes	23 (59. 0)	70 (100.0)	<0.001
	No	16 (41. 0)	0	

Data were presented as mean ± standard deviation and count (percentage). SVR -: ***. SVR +: ***.

Table 2. Comparisons of baseline characteristics between rapid viral response (RVR) negative and positive groups

		RVR – (n=61)	RVR + (n=32)	p
Age, year		54,62±7,43	54,63±8,17	0.999
Gender, n (%)	Female	51 (83. 6)	26 (81. 3)	0.775
	Male	10 (16. 4)	6 (18. 7)	
Weight, kg		73,60±15,27 (n=59)	74,80±16,34 (n=30)	0.733
Weightn (%)	<75 kg,	33 (55. 9)	19 (63. 3)	0.658
	≥75 kg,	26 (44. 1)	11 (36. 7)	
Diabetes Mellitus, n (%)	Yes	11 (18. 0)	5 (15. 6)	0.998
	No	50 (82)	27 (84. 4)	
RNA, n(%)	≥600000	29 (51. 8)	15 (50. 0)	0.875
	<600000	27 (48. 2)	15 (50. 0)	
Lymphocyte / µl		1856,39±567,96	2018,75±731,14	0.240
Platelets (x10^3 / µl)		235,57±61,48	213,48±71,76 (n=31)	0.127
PLT≥150000, n (%)		57 (93. 4)	27 (87. 1)	0.435
		4 (6. 6)	4 (12. 9)	
Hemoglobin (gr/dl)		13,96±1,13	13,92±1,30 (n=31)	0.861
ALT (U/L)		65,62±47,56 (n=60)	77,94±42,68 (n=31)	0.229
ALT, n(%)	≤40	21 (35. 0)	6 (19. 4)	
	41-80	26 (43. 3)	13 (41. 9)	
	81-120	7 (11. 7)	6 (19. 4)	0.273
	>120	6 (10. 0)	6 (19. 4)	
Total Bilirubin (mg/dl)		0,60±0,29 (n=57)	0,58±0,22 (n=30)	0.689
Albumin (mg/dl)		4,43±0,37 (n=55)	4,32±0,37 (n=26)	0.248
Cholesterol (mg/dl)		181,92±35,39 (n=49)	178,00±34,23 (n=24)	0.655
Cholesterol(mg/dl) , n(%)	≥130	48 (98. 0)	23 (95. 8)	1.000
	<130	1 (2. 0)	1 (4. 2)	
Triglycerides (mg/dl)		110,80 ± 42,34 (n=51)	122,88 ± 51,89 (n=25)	0.282
Fibrozis stage, n (%)	≥3	22 (44. 9)	12 (48.0)	0.995
	<3	27 (55. 1)	13 (52.0)	

Data were presented as mean ± standard deviation and count (percentage). RVR -: ***. RVR +: ***.

Table 3. Comparisons of baseline characteristics between early viral response (EVR) negative and positive groups

		EVR – (n=16)	EVR +(n=97)	p
Age, year		54,38±7,86	54,24±7,85	0.948
Gender, n (%)	Female	12 (75.0)	82 (84. 5)	0.468
	Male	4 (25.0)	15 (15. 5)	
Weight, kg		70,71±14,82 (n=14)	75,58±15,32 (n=88)	0.270
Weightn (%)	≥75 kg,	5 (35. 7)	41 (46. 6)	0.638
	<75 kg,	9 (64. 3)	47 (53. 4)	
Diabetes Mellitus, n (%)	Yes	6 (37. 5)	13 (13. 4)	0.028
	No	10 (62. 5)	84 (16. 6)	
RNA, n(%)	≥600000	7 (53. 8)	39 (50.0)	0.797
	<600000	6 (46. 2)	39 (50.0)	
Lymphocyte / µl		1588,13±459,50	2024,74±625,93	0.009
Platelets (x10^3 / µl)		203,81±51,08	234,19±68,00 (n=96)	0.091
PLT, n (%)	≥150000	13 (81. 3)	88 (91. 7)	0.192
	<150000	3 (18. 7)	8 (8. 3)	
Hemoglobin (gr/dl)		14,25±0,92	13,97±1,19 (n=96)	0.372
ALT (U/L)		91,31±63,14	72,75±45,89 (n=95)	0.161
ALT, n (%)	≤40	3 (18. 8)	25 (26. 3)	
	41-80	7 (43. 8)	41 (43. 2)	
	81-120	3 (18. 8)	15 (15. 8)	0.939
	>120	3 (18. 8)	13 (13. 7)	
Total Bilirubin (mg/dl)		0,64±0,35 (n=15)	0,61±0,27 (n=92)	0.758
Albumin (mg/dl)		4,26±0,51 (n=12)	4,37±0,35 (n=88)	0.326
Cholesterol (mg/dl)		152,00±24,56 (n=9)	180,47±32,77 (n=83)	0.013
Cholesterol, n(%)	≥130	8 (88. 9)	80 (96. 4)	0.342
	<130	1 (11. 1)	3 (3. 7)	
Triglycerides (mg/dl)		123,18±58,62 (n=11)	113,50±41,37 (n=84)	0.490
Fibrozis stage, n(%)	≥3	8 (66. 7)	33 (40. 7)	0.169
	<3	4 (33. 3)	48 (59. 3)	

Data were presented as mean ±standard deviation and count (percentage). EVR -: ***. EVR +: ***.

Table 4. Comparisons of treatment response between Inf 2a and 2b using groups

		Inf 2a	Inf 2b	p
RVR, n (%)	No	21 (55. 3)	39 (72. 2)	0.111
	Yes	17 (44. 7)	14 (27. 8)	
EVR, n (%)	No	6 (14. 6)	10 (14. 5)	0.984
	Yes	35 (85. 4)	59 (85. 5)	
SVR, n (%)	No	17 (31. 5)	26 (35. 1)	0.854
	Yes	37 (68. 5)	48 (64. 9)	

RVR -: ***. RVR +: ***. Data were presented as mean ±standard deviation and count (percentage)

Table 5. Comparisons of changing of haematologic parameters between Inf 2a and 2b using groups.

			Inf 2a		Inf 2b		
		n	Mean ±SD	n	Mean ±SD	* p	** p
	Baseline	45	3153.11 ± 962.35	76	3525.13±1216.76	0.082	
	2nd weeks	39	1820.51±682.27	63	2119,19±982,89	0.100	
	1st month	43	1620.93±660.74	74	2004.32±1134.86	0.023	
Neutrophils / µl	2nd months	41	1571.46±589.93	64	1969.53±1103.21	0.018	0.330
	3rd months	46	1734.78±1253.22	74	1841.04±993.77	0.608	
	6th months	43	1724.42±944.36	72	1734.44±640.62	0.946	
	12th months	37	2103.03±1506.50	62	1953.24±945.62	0.544	
	[3] p		<0.001		<0.001		
	Baseline	45	13.86±1.06	76	14.04±1.26	0.439	
	2nd weeks	40	13.12±1.19	66	12.91±1.24	0.396	
	1st month	43	12.00±1,24	74	11.94±1.12	0.768	
Hemoglobin (gr/dl)	2nd months	40	11.41±1.57	67	11.30±1.22	0.672	0.254
	3rd months	45	11.24±1.54	74	11.10±1.15	0.587	
	6th months	42	10.60±1.42	71	10.71±1.23	0.677	
	12th months	33	10.65±1.21	59	10.82±1.43	0.564	
	[3] p		<0.001		<0.001		
	Baseline	44	221.27±69.95	76	228.53±72.85	0.595	
	2nd weeks	40	169.93±57.72	67	189.12±67.42	0.136	
	1st month	42	166.17±51.63	74	195.15±72.78	0.014	
Platelets (x10^3 / µl)	2nd months	41	155.76±51.28	67	180.25±66.44	0.046	0.157
	3rd months	45	161,27±54,54	74	184.20±73.87	0.076	
	6th months	43	151.44±56.51	72	185.43±74.63	0.007	
	12th months	33	170.63±80.31	59	194.56±74.18	0.153	
	*** p		<0.001		<0.001		

Data were presented as mean ±standard deviation and count (percentage)

* results of the comparison between inf 2a and 2b goups.

**: results of the comparison between two groups, according to alterations of heamotological parameters.

***: results of the comparison among seven treatment periods.

Hwang et al. defined predictive markers for RVR in their study as basal mass index, AST/ALT rate, ferritin, platelet, LDL, DM and peg-IFN type.[15] In our study, no predictive marker was defined for RVR.

EVR occurs in approximately 80% of HCV genotype 1 infected patient.[13] It has been emphasized in the conducted studies that there was a significant rate of correlation between development of no EVR and unresponsiveness to treatment in genotype 1 infected patients.[16,17] In our study, EVR rate was 85.8%, and the possibility of SVR positivity in EVR positive patients were significantly higher than the possibility in EVR negative ones (p <0.001). None of patients has developed SVR in EVR negative patients.

Huang CF et al. investigated predictors for EVR in their study and defined two independent risk factors; HCV viral load of < 104 IU/mL after the 4th week of treatment and treatment with high ribavirin dose during the first 12 weeks.[18] In our study, absence of DM, high baseline lymphocyte count (2024.74 ± 625.93) and high baseline cholesterol levels (in EVR positive patients= 180.47 ± 32.77 mg/dl and in the negatives= 152.00 ± 24.56) were defined as the predictive parameters for EVR.

While SVR would not develop in patients without EVR, treatment is suggested to be stopped, it is suggested that the treatment is elongated for 48 weeks in genotype 1 infected patients with EVR development.[17]

It has been reported that if HCV RNA negativity is developed between 4-12 weeks in genotype 1 infected patient, then SVR rate would be around at 66%, whereas if it is developed between 12-24 weeks, the SVR rate would be around 45%. The statement of “slow responder(s)” is used for patients, whose HCV RNA becomes negative at the 12-24 weeks of treatment, and treatment elongation to 72 weeks is reported to decrease the relapse rate in these patients at a great extend.[19,20] In a similar studies, pegylated interferon dose (1.5 µg/kg/week, sequentially 0.5 µg/kg/week), ribavirin dose (>10.6 mg/kg), female gender, non-African American ethnic background, high ALT (3 folds higher than the upper normal limit), low body weight (<75 kg), absence of insulin resistance, absence of bridging fibrosis and cirrhosis in hepatic biopsy were reported to be positive predictors for SVR.6 In this present study, predictive markers for SVR were defined as RVR positivity (p<0.001), EVR positivity (p<0.001), high baseline PLT value (p<0.038), high baseline total bilirubin level (p<0.001) and low fibrosis stage in hepatic biopsy (≤ 2) (p<0.034). Few numbers of cases in our study has been evaluated as a limitation. In some of the recent studies, it has been reported that peg-IFNα2a use in the treatment has increased SVR rate more significantly than peg-IFNα2b use.[21,22] According to IDEAL study, there was no significant difference on SVR rate between the two peg-IFN molecules.[7] In our study, although there were few patients receiving peg-IFNα2a, there was no statistically significant difference in SVR development rate between the two patient groups.

In recent publications, IL28B gene region polymorphism is underlined as the strongest pretreatment predictor in viral response, relapse and SVR rates in HCV.[23]

In the conducted studies it is reported that SVR rates in genotype 1 and 4 infected patients have been detected as 40-60% after 48-week treatment. In line with the mentioned results, SVR rate of our patients was 64.4%.

Peg-IFN/ribavirin combination can cause some negative effects in HCV treatment. The most important ones among these negative effects are flu-like symptoms, psychiatric disorders, autoimmune reactions and hematological toxicities. These negative effects can be successfully managed in many patients; peg-IFN or ribavirin dose should be decreased or stopped temporarily in approximately 20-40% of cases. Moreover, drug treatment should be totally withdrawn in 10-14% of patients due to sere side effects.[9,17] In a meta-analysis, which has compared side effects that would prevent continuation of the treatment between two peg-IFN groups, it has been reported that there was no difference between the groups.[24] In line with these studies, there was no statistical difference in hematological side effects between two peg-IFN groups in our study.

Conclusion

It is getting more important to demonstrate the efficacy of anti-HCV treatment and to comprehend predictive markers for the treatment response. As SVR rates differ among patients according to genotypes, the rates differ due to other significant SVR predictors. SVR rates in patients are

affected by other factors including RVR and EVR. Therefore, it is obvious that these factors should be considered to a great extend in the treatment plans.

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