Doi: 10.4274/Vhd.77486

Evaluation of 219 Patients with Chronic Hepatitis C Receiving Pegylated Interferon + Ribavirin Treatment

Pegile interferon + Ribavirin Tedavisi Alan Kronik Hepatit C'li 219 Olgunun Değerlendirilmesi

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ABSTRACT

Objective: In chronic hepatitis C (CHC) treatment, consensus guidelines recommend the use of either pegylated interferon (PEG-IFN) alfa 2a(40 KD), or PEG-IFN alfa 2b(12 KD) both plus ribavirin for treatment of chronic hepatitis C virus (HCV) infection. The aim of this study was to evaluate treatments of CHC in our patients retrospectively.

Materials and Methods: A total of 219 treatment naïve or relapser (n=8), HCV RNA positive patients with CHC were assigned to once-weekly peginterferon 2a (180 µg, group PEG-A, n=115) or peginterferon 2b (1.5 µg/kg, group PEG-B, n=104) plus ribavirin (RBV) (800-1200 mg/day) for 48 weeks. End of treatment response (ETR) and sustained virological response (SVR) were defined, respectively, as a negative qualitative HCV RNA level at the end of the treatment and after 24 weeks of untreated follow up.

Results: End-of-treatment response (ETR) was obtained in 103 patients (92%) in PEG A group and 87 patients (86.1%) in group PEG B (p=0.171). SVR was 73.7% (n=157) in all of patients. This rate was 76.8 % (86/115) in group PEG A, and 70.3% (71/104) in group PEG B (p=0.283). SVR rates were not significantly different between two PEG IFN groups. Patients in groups PEG A discontinued treatment 4 (4.3%) and 8 (7.7%) in group PEG B respectively. There was no stastically difference in treatment discontinuation rate between groups (p=0.296). SVR was decreased with advanced age in both groups.

Conclusion: Ribavirin plus peginterferon alpha-2a or peginterferon alpha-2b were comparable outcomes in patients with CHC. *(Viral Hepatitis Journal 2013; 19(2): 71-5)*

Key words: Chronic hepatitis C, pegylated interferon alfa-2a, pegylated interferon alfa-2b, ribavirin, sustained virological response

ÖZET

Amaç: Kronik hepatit C (KHC)tedavisinde standart protokol pegile interferon (PEG-IFN) alfa 2a(40 KD), veya PEG-IFN alfa 2b(12 KD) ve ribavirin kombinasyonudur. Çalışmamızda kronik hepatit C'li hastalarımızın tedaviye yanıtlarının retrospektif olarak değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: 48 hafta süresince haftada bir kez peginterferon 2a (180 µg, grup PEG- A, n:115) veya peginterferon 2b (1,5 µg/kg ,grup PEG-B, n:104) ve ribavirin (800-1200 mg/gün) kombinasyon tedavisi uygulanan naiv veya relapser (n:8) toplam 219 HCV RNA pozitif KHC'li hasta değerlendirildi. Erken virolojik yanıt (tedavinin 12. haftasında serum HCV-RNA'nın negatif olması veya >2 log düşüş), Tedavi sonu yanıt (tedavi sonunda HCV_RNA'nın negatif olması),Kalıcı virolojik yanıt (tedavi sonlanmasını takiben 24. haftada HCV_RNA'nın negatif olması) oranları değerlendirildi.

Bulgular: Tedavi sonu yanıt oranı PEG A grubunda %92 (n:103), PEG B grubunda ise %86,1(n: 87) idi. (p=0,171). Kalıcı virolojik yanıt tüm hastalarda %73,7 (n=157) ; PEG A grubunda %76,8 (86/115) , PEG B grubunda ise % 70,3 (71/104) olarak tespit edildi. Her iki PEG IFN grubu arasında kalıcı virolojik yanıt oranları açısından anlamlı fark yoktu (p=0,283). PEG A grubundan 4 (% 4,3) PEG B grubundan ise 8 (%7,7) hastada tedavinin kesilmesi gerekti.Ancak tedavinin kesilmesi açısından her iki grup arasında istatistiki anlamlı fark yoktu. (p=0,296)

Sonuç: KHC hastalarında ribavirin ile kombine olarak kullanılan peginterferon alfa-2a ve peginterferon alfa-2b tedaviye yanıt açısından kıyaslanabilir bulunmuştur. *(Viral Hepatit Dergisi 2013; 19(2): 71-5)*

Anahtar Kelimeler: Kronik hepatit C, Pegile interferon alfa -2a, Pegile interferon alfa -2b, ribavirin, kalıcı virolojik yanıt

Introduction

According to World Health Organization (WHO) assumptions, hepatitis C virus (HCV) infection is an important health problem, which is encountered at 3% of the world's population. (1). There is no vaccine for prevention from HCV infection, yet. Approximately 20% of patients infected by HCV develop cirrhosis in about 20 years and every year 5% of them develop hepatocellular carcinoma (HCC). Current epidemiologic models suggest that the incidence of HCC and of the mortality associated with chronic HCV infection will continue to increase (2,3).

Peginterferon plus ribavirin combination therapy is a standard protocol in treatment guidelines of CHC (4-6). With combination therapy SVR rate was 41-63% in treatment naive CHC patients who sufficiently complied with the treatment schedule (7-9).

Two pegylated interferon (peginterferon)-α molecules are commercially available for the treatment of chronic hepatitis C, These two drugs have different pharmacological characteristics and are administered at different doses. Peginterferon-α-2a at 180 µg s.c./once a week dose and ribavirin adjusted per kg (1000 mg / day in patients <75 kg; 1200 mg/day in patients >75 kg p.o. divided

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Table 1. Comparisons of groups in demographic and laboratory characteristics

	Group PEG A (n=115)	Group PEG B (n=104)	p
Age (mean±SD, median)	52.1±9.3 (52)	50.8±11.0 (53)	0.352
Gender (n,%)			0.816
Female	78 (67.8)	69 (66.3)	
Male	37 (32.2)	35 (33.7)	
AST (mean±SD, median)	59.6±46.9 (46)	49.3±29.1 (41)	0.062
ALT (mean±SD, median)	67.9±48.5 (50)	62.1±44.2 (47)	0.432
HCV RNA (cpy/mL)(log) (mean±SD, median)	5.5±0.9 (5.6)	5.6±0.9 (5.7)	0.527
HCV RNA groups			
$0\text{-}10^5$	19 (16.5)	18 (17.3)	0.518
$10^5\text{-}10^6$	46 (40.0)	34 (32.7)	
$>10^6$	50 (43.5)	52 (50.0)	
Fibrosis (mean±SD, median)*	1.9±0.9 (2)	2.1±1.2 (2)	0.832
Fibrosis (mean±SD, median)**	1.6±1.1 (1)	1.8±1.0 (1)	0.216

* Mean of fibrosis (with Ishak scoring); ** Mean of fibrosis (with Knodell scoring).

Table 2. Treatment response rates of the groups

	Group PEG A (n=115) N	%	GroupPEGB (n=104) N	%	p
EVR	112	97.4	101	97.1	1.000
ETR	103	92.0	87	86.1	0.171
SVR	86	76.8	71	70.3	0.283

in to two doses) and Peginterferon-α-2b at 1.5 µg/kg s.c./once a week dose and ribavirin adjusted per kg (40-64 kg: 800 mg, 65-85 kg: 1000 mg, >85 kg: 1200 mg p.o. divided into two doses (9,10).

Treatment regimens for chronic hepatitis C have evolved over the last years, resulting in improved SVR rates. Despite these advances, the current gold standard therapy with peginterferon alfa-2a or alfa-2b and ribavirin is successful in only one-half of treated patients. Various clinical and virologic factors are well established as predictors of a reduced response to interferon-based therapy, including genotype 1, high baseline serum HCV RNA level, obesity, African American ethnicity, older age, and presence of advanced fibrosis or cirrhosis. Therefore, a significant proportion of treated patients, particularly those infected with HCV genotype 1, will have persistent or recurrent viremia in spite of therapy and are potential candidates for retreatment (7-9,11,12).

In this study, we investigated response to treatment and effects of clinical features on virologic response in CHC patients.

Material and Methods

Patients, who were diagnosed and treated for CHC at the Infectious Diseases Clinic at the Eskisehir Yunus Emre State Hospital between dates January 2003 and December 2008, and whose medical data were obtained, were retrospectively evaluated. A total of 219 naive or relapser (n:8) patients, who had positive Anti-HCV; were determined to have quantitative HCV RNA by real-time polymerase chain reaction; with normal or high ALT values; and received PEG-IFN plus ribavirin combination therapy, were eligible for study. Histopathological evaluation of 155 patients was performed. Patients were evaluated in two groups (PEG A and PEG B) according to presence of peginterferon 2a or peginterferon 2b in treatment combination. Drug choice was performed without depending on any protocol by physician.

Patients with HIV co-infection, decompensated hepatic disease, hepatocellular carcinoma or other malignancies, severe cardiac and pulmonary diseases, psychosis and uncontrolled depression history, hemoglobin values of <13 g/dL for males and <12 g/dL for females, neutrophil count <1500/mm3 and creatinine >1.5 mg/dL were not enrolled in the study.

Serum HCV RNA was evaluated with a qualitative TagMan real-time technology (Roboscreen kit and an ABI Prism 7700 Perkin Elmer; limit of detection $10\text{-}10^8$ copy/ml) between 2003-2004. The Real time polymerase chain reaction (RT-PCR) kits (Qiagen, Hamburg and Gorbett-Research 6000, Australia); limit of detection $10\text{-}10^9$ IU/ml) was performed from 2005 to 2008.

EVR was defined as qualitative HCV RNA negative or a reduction from baseline HCV RNA level of >2 log10 IU/mL at week 12. End-of-treatment response (ETR) and SVR were defined, respectively, as a negative qualitative HCV RNA level at the end of treatment and after 24 weeks of untreated follow-up. Virological relapse was defined as reversion to HCV RNA–positive status in patient who had an undetectable HCV RNA level at the end of treatment. Peginterferon treatment was discontinued if the neutrophil count was $<0.50 \times 10^9$/L or the platelet count was $<25 \times 10^9$/L. Ribavirin treatment was discontinued if hemoglobin level decreased to <8.5 g/dL.

Statistical analysis was performed with SPSS 15.0 for Windows software program. In descriptive analyses, continuous variables

were defined as means, standard deviations, medians; whereas intermittent variables were defined as numbers and percentages. When normal distribution assumption was provided in comparison between groups student's t test was employed, whereas it was not provided then Mann-Whitney U test was employed. Categorical variables between groups were compared by chi-square test. Risk factors were determined by logistic regression analysis. Statistical significance level was accepted as $p<0.05$.

Results

211(96.4%) patients were defined treatment naive and 8 (3.6%) patients were defined relapser (who had previously received interferon alfa and serum HCV RNA was detectable at 24 weeks after treatment). There were 115 patients in group PEG A and 104 patients in group PEG B. Mean age was 52.1±9.3 years in group PEG A; and 50.8±11.0 years in group PEG B. Liver biopsy was performed in 155 patients. Fibrosis stages in liver specimens were evaluated by Ishak scoring methods in 133 patients, whereas fibrosis evaluated by Knodell scoring methods in 22 patients. Comparisons of groups in demographic characteristics and laboratory results are given in Table 1.

Overall, an EVR, as reported in Table 2, was obtained in 112/115 patients (97.4) in group PEG- A and 101/ 104 (%97.1) in group PEG-B. The majority of patients obtained EVR with no difference between in group PEG- A and group PEG- B. An ETR was obtained in 103 patients (92%) in group PEG- A, 87 patients (86.1%) in group PEG-B (p=0.171). SVR was 73.7% (n=157) in all of patients. SVR was achieved by 86/103 patients (76.8%) in group PEG A, and 71/87 patients (70.3%) in group PEG B (p=0.283). SVR was not achieved by 17/103 patients (23.2%) in group PEG A, and 16/87 patients (29.7%) in group PEG B. EVR, ETR and SVR rates did not differ significantly between the two treatment groups. A negative qualitative HCV RNA level at the end of the treatment and after 48 weeks of untreated follow up were 71.4% in group PEG A and 69.3% in group PEG B (p=0.735) (Figure 1).

Drug discontinuation rate due to side effects was 8.7% (n=9) in PEGB and 2.6% (n=3) in PEG A groups (p=0.05). There was no statistically significant difference between groups in treatment discontinuation [PEG B 7.7%, (n=8); PEG A 4.3%, (n=5); p=0.296]. (Table 2).

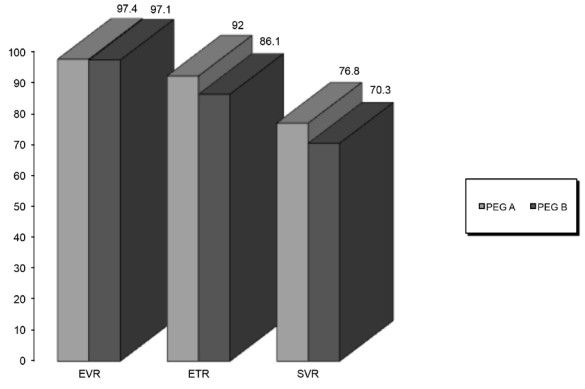

Figure 1. Comparisons of treatment responses.

When we compared the characteristics of patients in SVR (+) and SVR (-) groups, means of ages were statistically significantly higher in SVR (-) group (Table 3).

Discussion

Standard treatment for CHC patients is peginterferon plus ribavirin combination. (14). After standard combination treatment, SVR rate was higher than in patients infected with genotype 1 (42-56%) than genotype 2 and 3 (76% and 82%, respectively) (13). SVR was unsuccessfully achieved in majority of patients infected with genotype 1. Although new investigations for the treatment of chronic hepatitis C have been continued, combination of peginterferon plus ribavirin seems to be standard part of treatment even further (15).

McHutchison et al. (17) reported (The study included a totally of 3070 patients with genotype 1 HCV infection), that SVR rates for standard doses of peginterferon alpha-2b and peginterferon alpha-2a were 39.8% and 40.9%, respectively. They also reported no difference in the safety profile between two groups. A total of 126 treatment-naive patients who received peginterferon alpha-2a + ribavirin or peginterferon alpha-2b + ribavirin; Lee et al. (18) reported that viral and biochemical response rates at end of the treatment and SVR rates were similar (84.8 vs. 89.4%; 70.9 vs. 72.3%; and 70.9 vs. 74.5%) respectively. Lee et al. showed no significant difference in response to the treatment both in patients with HCV genotype 1 and other genotypes respectively.

In the study conducted on 320 treatment naive patients by Ascione et al. (18) it was detected that more patients in

Table 3. Patient characteristics between SVR (-) and SVR (+) patients

	SVR (-)	SVR(+)	p
Age	55.7±9.7 (57)	50.1±10.1 (51)	<0.001
Gender			0.912
Female	37 (66.1)	105 (66.9)	
Male	19 (33.9)	52 (33.1)	
AST	63.9±53.0 (49)	50.8±33.2 (42)	0.067
Increased AST	36 (64.3)	86 (54.8)	0.217
ALT	73.2±56.7 (49)	61.6±42.2 (48)	0.397
Increased ALT	37 (66.1)	101 (64.3)	0.815
HCV RNA cpy/ml(log)	5.6±1.0 (5.7)	5.5±0.9 (5.6)	0.488
HCV RNA groups			
$0\text{-}10^5$	13 (23.2)	24 (15.3)	0.242
$10^5\text{-}10^6$	22 (39.3)	56 (35.7)	
$>10^6$	21 (37.5)	77 (49.0)	
Fibrosis*	2.3±0.9 (3)	1.9±0.9 (2)	0.125
Fibrosis**	1.8±1.2 (1)	1.6±1.0 (1)	0.805

Values are given as mean±SD (median) OR n (%).
* Fibrosis mean (with Ishak scoring)** Fibrosis mean (with Knodell scoring)

peginterferon alpha-2a group reached SVR at higher rates than that of in the peginterferon alpha-2b group (68.8% vs. 54.4%, respectively). Awad et al. (20) reported SVR rates in peginterferon alpha-2a patients were significantly higher than in peginterferon alpha-2b patients (47% vs. 41%, respectively) in their meta-analysis. In Turkey; Akhan et al. (21) reported SVR rates 61.7% with peginterferon alpha-2a + ribavirin, Ceylan et al. (22) reported 59% with peginterferon alpha (2a or 2b) + ribavirin; Senturk et al. (23) reported 39% with peginterferon alpha-2b + ribavirin; Yenice et al. (24) 48.6% with peginterferon alpha-2a + ribavirin and 35.1% with peginterferon alpha-2b + ribavirin.

In our study, SVR rates in both treatment groups were generally higher than literature. Inclusion criteria might cause differences in the study population, so they could affect the results. In some studies only patients with genotype 1 or treatment naive patients were included, whereas in some studies special groups (like hemodialysis patients) were evaluated.

Studies showed that a variety of factors affect treatment response (HCV genotype and disease severity; treatment-related factors such as sufficiently complied with the treatment schedule and history of prior treatment; and several patient-related factors (i.e. age, ethnicity, and comorbidity presence).

ETR and SVR rate are increased with compliance to the treatment (25). In our clinic HCV patients were controlled for treatment compliance and monitored for adverse effects strictly. During the treatment white blood cell count, absolute neutrophil count, hemoglobin, platelet count, ALT levels recruited weekly in the first month, two visits were performed in the second month, and visit was performed once in a month later, so treatment compliance and adverse effects have been observed, and examinations have been performed immediately. When adverse effects occured (i.e. anemia, rash, depression, thyroid function disorder, diabetes etc.); consultation with other clinicians were performed and their treatment options was taken for them. So that compliance level to our medical schedule was the highest. We believe that the treatment compliance had increased with our approach. Moreover, absence of patients with comorbidities, such as alcohol or substance abuse, could be an advantage for the treatment compliance.

In recent years, it has been reported that SVR rates in Asian patients were higher than the European patients. In 154 treatment naïve, genotype 1 patients Liu et al. (26) reported EVR rate was 97%; ETR was 91%; and SVR was 76% at the 48-weeks with peginterferon alpha-2a + ribavirin combination therapy. A study performed with peginterferon + ribavirin combination; SVR achieved 67.2% (n= 58) of 106 patients with genotype 1b patients in Korea; similar with our results. In the study; higher SVR rate was reported because of difference in IL28B genetic variation from the European patients (high prevalence of rs12979860 CC-genotype) (27).

Patients infected with genotype 1 were reported 84-97.4% of all the CHC patients in Turkey (28-31). Although one of the limitations in our study was absence of HCV genotype; the studies originated from our country genotype 1 is the most common genotype.

The efficacy of combination therapy of peg-interferon plus ribavirin for CHC infection in elderly patient has not been fully clarified. In several studies it has been reported that SVR rates were lowest in elderly patients than non elderly patients (32). In our study, advanced age was determinated as a factor which was decreasing the response rate in both treatment groups.

In conclusion, it seems that combination of peginterferon alpha-2a with ribavirin has been more advantageous, because treatment discontinuation rate was lower. However, at the end of treatment, treatment response was not statistically significant between the two pegile-interferon groups. The treatment response rate decreased with advanced age in both treatment groups. Ribavirin plus peginterferon alpha-2a or peginterferon alpha-2b were comparable outcomes in patients with CHC.

Conflict of interest: None declared.

References

1. World Health Organization. HepatitisC.2010 http://www.who.int/csr/disease/hepatitis/ whocdscsrlyo2003/en/index.html. Arrival date, .
2. Mallet V, Vallet-Pichard A, Pol S. New trends in hepatitis C management. Presse Med. 2010; 39(4): 446-51.
3. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
4. Ersöz G.Treatment of Hepatitis C. Turkiye Klinikleri J Gastroenterohepatol-Special Topics. 2010; 3(1): 96-102.
5. Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, The Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, Ministry of Health, Labour and Welfare of Japan. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. Hepatol Res. 2010; 40(1): 8-13.
6. Sherman M, Shafran S, Burak K, Doucette K, Wong W, Girgrah N, Yoshida E, Renner E, Wong P, Deschênes M. Management of chronic hepatitis C: consensus guidelines. Can J Gastroenterol. 2007; (Suppl): 25-34.
7. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R,et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 22; 358(9286):958-65.
8. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr,et at. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347(13): 975-82.
9. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P,et al. PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004; 140(5): 346-55.
10. Foster GR. Pegylated interferons for the treatment of chronic hepatitis C: pharmacological and clinical differences between peginterferon-alpha-2a and peginterferon-alpha-2b. Drugs. 2010; 70(2): 147-65.

11. Gonzalez SA, Keeffe EB. Management of chronic hepatitis C treatment failures: role of consensus interferon. Biologics. 2009; 3: 141-50.
12. Muir AJ, Bornstein JD, Killenberg PG; Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med. 2004; 350(22): 2265-71.
13. Garg G, Kar P. Management of HCV infection: current issues and future options. Trop Gastroenterol. 2009; 30(1): 11-8.
14. Mendoza J, Trapero-Marugán M, González-Moreno L, Jones EA, Gómez-Domínguez E, Moreno-Otero R. Hepatic fibrosis in patients with chronic hepatitis C assessed by transient elastography: implications for determining the efficacy of antiviral therapy. Rev Esp Enferm Dig. 2010; 102(7): 426-34.
15. Shiffman ML. Treatment of hepatitis C in 2011: what can we expect? Curr Gastroenterol Rep. 2010; 12(1): 70-5.
16. Sharma SD. Hepatitis C virus: molecular biology & current therapeutic options. Indian J Med Res. 2010; 131: 17-34.
17. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J,et al. IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009; 361(6): 580-93.
18. Lee S, Kim IH, Kim SH, Kim SW, Lee SO, Lee ST,et al. Efficacy and tolerability of pegylated interferon-alpha2a plus ribavirin versus pegylated interferon-alpha2b plus ribavirin in treatment-naive chronic hepatitis C patients. Intervirology. 2010; 53(3): 146-53.
19. Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Costanzo GG, Lanza AG, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology. 2010; 138(1): 116-22.
20. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. Hepatology. 2010; 51(4): 1176-84.
21. Akhan SC, Kalender B, Ruzgar M. The response to pegylated interferon alpha 2a in haemodialysis patients with hepatitis C virus infection. Infection. 2008; 36(4): 341-4.
22. Ceylan B, Fincancı M, Müderrisoğlu C, Eren G, Soysal F. Variables predicting virologic response to pegylated interferon and ribavirin treatment in patients with chronic hepatitis C. Turkish Journal of Infection. 2009; 23: 185-92.
23. Senturk H, Ersoz G, Ozaras R, Kaymakoglu S, Bozkaya H, Akdogan M. Interferon-alpha2b induction treatment with or without ribavirin in chronic hepatitis C: a multicenter, randomized, controlled trial. Dig Dis Sci. 2003; 48(6): 1124-9.
24. Yenice N, Mehtap O, Gümrah M, Arican N. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006; 17(2): 94-8.25. Xin Sun, Carrie D, Clara Williams, Caitlyn A. Senger, Tanya J. Kapka, Evelyn P. Whitlock, Interventions To Improve Patient Adherence toHepatitis C Treatment: Comparative Effectiveness) Research Review – Final. 2012; 20.
26. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS,et al. Pegylated interferon-alpha plus ribavirin for treatment naive Asian patient with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. 2008; 47(10): 1260-9.
27. Jung YK, Kim JH, Ahn SM at al. Role of Interleukin 28B-related Gene Polymorphisms in Chronic Hepatitis C and the Response to Antiviral Therapy in Koreans. J Clin Gastroenterol. 2013; 24.
28. Aktaş E, Ogedey ED, Külah C, Beğendik Cömert F. [Hepatitis C virus genotypes in a province of western Black-Sea region, Turkey]. Mikrobiyol Bul. 2010; 44(4): 647-50.
29. Altuglu I, Soyler I, Ozacar T, Erensoy S. Distribution of hepatitis C virus genotypes in patients with chronic hepatitis C infection in Western Turkey. Int J Infect Dis. 2008; 12(3): 239-44.
30. Bozdayi AM, Aslan N, Bozdayi G, Türkyilmaz AR, Sengezer T, Wend U,et al. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. Arch Virol. 2004; 149(11): 2115-29.
31. Sanlidağ T, Akçali S, Ozbakkaloğlu B, Ertekin D, Akduman E. [Distribution of hepatitis C virus genotypes in Manisa region, Turkey]. Mikrobiyol Bul. 2009; 43(4): 613-8.
32. Zheng YY, Fan XH, Wang LF, Tian D, Huo N, Lu HY,et al. Efficacy of pegylated interferon-alpha-2a plus ribavirin for patients aged at least 60 years with chronic hepatitis C. Chin Med J (Engl). 2012; 125(11): 1852-6.