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RESEARCH ARTICLE

Pegylated Interferon/Ribavirin dual therapy in patients with chronic Hepatitis C: results of 323 cases

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ABSTRACT

Objective: The combination of pegylated interferon-α (PEG-IFN) and ribavirin has become a mainstay in the treatment of chronic hepatitis C (CHC). We aimed to evaluate the efficacy of this treatment in patients with CHC, while considering new approaches.

Methods: A total of 323 patients with CHC underwent PEG-IFN and ribavirin combination treatment from the 3 centers (2 in Ordu and 1 in Samsun provinces) in Middle Black Sea region between the years of 2003-2013.

Results: Of the patients, 208 (67%) were female and had a mean age 54 ± 10 years (median: 54; 19-70). Genotyping was performed in 163 patients, and 161 patients (98.8%) revealed genotype 1. Sustained virologic response (SVR) and the end of treatment response rates were 58.3% and 75.6%, respectively. In patients with rapid virological response, the SVR rate was 85.1%, whereas in patients with a HCV RNA level less than 800,000 IU/ml, the SVR rate was 71.2%. The SVR rates were found to be higher in patients who developed hypothyroidism, which was statistically significant (p = 0.03). The most frequent side effect was anemia, followed by thrombocytopenia, fatigue, and loss of appetite.

Conclusion: Presently, PEG-IFN/ribavirin is still an option in the treatment of certain patient populations even after the consideration of newer treatment methods. *J Microbiol Infect Dis 2015;5(4): 151-155*

Key words: Pegylated interferon, ribavirin, therapy, hepatitis C

Kronik Hepatit C'li hastalarda pegylated ınterferon/ribavirin ikili tedavisi: 323 hastanın sonuçları

ÖZET

Amaç: Pegile interferon-α (PEG-IFN) ve ribavirin kombinasyonu Kronik Hepatit C (KHC) tedavisinde standarttır. Bu tedavinin yeni yaklaşımlar eşliğinde KHC'li hastalarda etkinliğinin araştırılması amaçlandı.

Yöntemler: Orta Karadeniz Bölgesinde 2003-2013 yılları arasında toplam 3 merkezden (2'si Ordu ve 1'i Samsun'dan) KHC'li 323 hasta PEG-IFN ve ribavirin kombinasyon tedavisi alan hasta çalışmaya dahil edildi.

Bulgular: Hastaların 208'i (% 64,4) kadındı, ortalama yaş 54 ± 10 yıl (medyan: 54, 19-70 yıl arası). Genotip 163 hastada araştırıldı, 161 hasta (% 98,8) genotype 1 bulundu. Kalıcı virolojik yanıt (KVY) ve tedavi sonu yanıt sırasıyla % 58,3 ve % 75,6 idi. Hızlı virolojik yanıtlı hastalarda KVY oranı %85,1 iken, HCV RNA <800 000 IU/ml olan hastalarda KVY oranı %71,2 idi. İstatistiksel olarak anlamlı şekilde (p=0,03) KVY oranları hipotiroidizm gelişen hastalarda daha yüksek bulundu. En sık yan etki anemi idi, onu trombositopeni, yorgunluk ve iştah kaybı izledi.

Sonuç: Yeni tedavi yöntemlerinin ortaya çıktığı günümüzde PEG-IFN ve ribavirin kombinasyonu belli bazı hastalarda halen tedavide bir seçenektir.

Anahtar kelimeler: Pegile interferon, ribavirin, tedavi, hepatit C

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INTRODUCTION

Despite the great success achieved in the fields of virology and diagnostics, several difficulties affect improvements in hepatitis C virus (HCV) infection control and eradication in this new era. With a global prevalence of infection estimated at 2%-3%, it has been calculated that 130-170 million people are infected with HCV.[1] Compared to the global prevalence, Turkey has low rates of HCV infection, which have been estimated to be around 1.0%. The majority of chronic infections are genotype 1b, which range between 75% and 90%.[2] Approximately 75%-85% of people infected with HCV will develop chronic hepatitis, 60%-70% will develop hepatic steatosis or fibrosis, 5%-20% will develop cirrhosis, and in 1%-5% disease will progress to life-threatening complications and hepatocellular carcinoma within 20 years from acute infection.[1]

The combination of pegylated interferon-α (PEG-IFN) and ribavirin has been a standard of care for the management of chronic hepatitis C (CHC) and this regimen has significantly contributed to the improvement of long-term clinical outcomes for treated patients. Nevertheless, the rate of treatment success defined by sustained virologic response (SVR) is just 38% to 41% in the genotype 1 infection.[3] We aimed to evaluate the efficacy of double drug treatment with the combination of PEG-IFN and ribavirin in patients with CHC, which is a new era of treatment.

METHODS

This study included a total of 323 patients diagnosed as CHC from the 3 centers (2 in Ordu and 1 in Samsun provinces) in Middle Black Sea region between the years of 2003-2013. Requirements for these patients included PEG-IFN and ribavirin combination treatment and at least 6 months of regular follow-up after therapy. Exclusion criteria included patients who were younger than 18 years old, patients who failed routine follow-up, co-infected with human immunodeficiency virus (HIV), and those with autoimmune hepatitis, decompensated cirrhosis, and pregnancy. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamiltransferase, urea, creatinine, bilirubins, albumin, thrombocytes, prothrombin time, activated partial thromboplastin time, and autoantibodies analyses were obtained in all patients prior to the treatment. HBsAg, anti-HCV, anti-HIV tests were studied by Advia Centaur XP device (SIEMENS) with chemilluminesence method. Polymerase chain reaction (PCR) detectable HCV ribonucleic acid (RNA) isolation was performed using “real time” PCR “COBAS AMPLICOR HCV Monitor2.0” (Roche Diagnostics, USA). A total of 237 patients underwent percutaneous liver biopsy and the specimens were evaluated according to Knodell and Ishak scoring systems.

In patients with genotype 1, once-weekly injections of 180 µg of PEG-IFN-2a plus ribavirin were given orally for 48 weeks at a dose of: (i) 1000 mg per day for patients weighing 75 kg or less and (ii) 1200 mg per day for those weighing more than 75 kg. PEG-IFN-2b at a standard dose of 1.5 µg per kilogram of body weight per week, plus oral ribavirin were administered at a dose according to body weight < 65 kg, 800 mg per day; >65 to 85 kg, 1000 mg per day; >85 kg, 1200 mg per day. Anemia was regarded as 2 g/dL decrease from initial level. The ribavirin dose was reduced if hemoglobin (Hb) decreased to <10 g/dL and stopped if Hb decreased to <8.5 g/dL.

After therapy initiated, HCV RNA levels were measured at 4, 12, 24, and 48 weeks. Rapid Virological Response (RVR) was defined as non-detectable for HCV RNA level at 4 weeks. Early Virological Response (EVR) was defined as non-detectable for HCV RNA level or reduction of HCV RNA levels by 2 log or more at 12 weeks of treatment. The end of treatment response (ETR) was defined as continuing non-detectable HCV RNA level at 48 weeks. Patients with an insufficient virologic response at 12 weeks (a detectable HCV RNA level and a decrease of <2 log10 IU from the baseline level) or at 24 weeks (a detectable HCV RNA level) were considered to have treatment failure, and therapy was discontinued. After completion of therapy, HCV RNA levels were obtained at 3, 6, and 12 months. SVR was considered as HCV RNA negativity at the 6th month. Ethical consent was obtained from EPK (Council for Planning of Training and Coordination).

Statistical Analysis

Data were analyzed using SPSS 17.0 program (Chicago, IL, USA) and given as numerical (%), mean ± standard deviation and median (min-max). Chi-square test was used in comparison of cathegorical variables. Mann-Whitney U test was used to compare both groups with data that not represent normal distribution. Student t-test was used in evaluating data with normal distribution. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Of the 323 patients, 208 (67%) were female with a mean age 54 ± 10 years (median: 54, 19-70). A total of 283 patients were naive, and 40 patients were given treatment previously. PEG-IFN-2a plus ribavirin combination treatment was started in 162 patients (50.1%), whereas 161 patients (49.9%) received PEG-IFN-2b plus ribavirin. On follow-up, treatment completely stopped in 12 (3.7%) patients due to either side effects or intolerance. Therapy was completed fully in 311 patients. A total of 6 (2%) patients revealed alcohol intake. Genotyping was searched in 163 patients, while 161 patients (98.8%) revealed genotype 1 (genotype 1b 96.3%, genotype 1a 1.2%, and genotype 1c 2.5%), while only 1(0.6%) patient revealed genotype 3, and the other 1 patient (0.6%) genotype 4. Percutaneous liver biopsies were obtained in 237 patients. Biopsy scores were as follows: Knodell score mean 10 ± 3 (median: 10, 4-18), Ishak histologic activity index (HAI) mean 7.8 ± 2.8 (median: 7, 4-18). Of all patients tested, 80% revealed Ishak fibrosis stages below 4.

Fourty-two percent of patients had some aggravating factors leading to increased morbidity like diabetes mellitus, hypertension, heart failure, and chronic obstructive pulmonary disease. However, no statistical differences were noted between SVRs in patients with and without aggravating factors ($p > 0.05$).

Prior to treatment, ALT and AST levels were median 54 U/L (8-454) and 42 U/L (15-247), respectively. The HCV RNA level had a median of 13×105 IU/ml (983-29×107). The SVR and ETR rates were 58.3% and 75.6%, respectively. In patients with RVR, the SVR rate was 85.1%; whereas in patients with a HCV RNA levels less than 800,000 IU/ml, the SVR rate was 71.2%. The SVR rate did not differ significantly in patients treated with PEG-IFN-2a and 2b ($p > 0.05$). However, thrombocytopenia was much more detectable in patients receiving PEG-IFN-2a ($p < 0.01$). Table 1 shows the characteristics of patients with SVR (+) and SVR (-).

Table 1. Data of patients with sustained virologic response (+) and sustained virologic response (-)

Variables	Total	SVR(+)	SVR(-)	p value
Sex (Male/Female)	103/208	61/120	42/88	> 0.05
HAI ≤9, n (%)	134(57)	86(64)	48(36)	0.01
Knodell score, mean ± SD	10 ± 3	9 ± 3	11 ± 3	0.01
Fibrosis ≤ 2, Stage ≤ 3, n (%)	190 (83)	114 (60)	76 (40)	> 0.05
HCV-RNA ≤ 800,000 IU/ml	125 (40.6)	89 (71.2)	36 (28.8)	< 0.001
HCV-RNA Log_{10} value (IU/ml)	6 ± 0.8	5.8 ± 0.8	6.2 ± 0.7	< 0.001
Type of interferon used, n (%)				
Pegylated interferon α2a	154 (49.5)	90 (58.4)	64 (41.6)	> 0.05
Pegylated interferon α2b	157 (50.5)	91 (58)	66 (42)	> 0.05
Rapid virologic response, n (%)	27 (25.7)	23 (85.2)	4(14.8)	< 0.001
Early virologic response, n (%)	260 (90.6)	165 (63.5)	95 (36.5)	< 0.001
Hypothyroidism, n (%)	18 (5.8)	15 (4.9)	3 (1)	0.03
Age (year), mean ± SD	54 ± 10	53 ± 11	56 ± 9	< 0.01
Weight (kg), mean ± SD	73 ± 14	74 ± 14	73 ± 13	> 0.05
Albumin (g/dL), mean ± SD	4.2 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	0.05
ALT (U/L) Median (Min-Max)	54 (8-454)	51 (8-454)	51 (13-360)	> 0.05
AST (U/L) Median (Min-Max)	42 (15-247)	38 (15-247)	45 (20-234)	0.03

ALT: alanine aminotransferase, AST: aspartateaminotransferase, HCV RNA: riboneucleic acid of hepatitis C virus, SD, standard deviation, HAI: Ishak histologic activity index

PEG-IFN-2a or PEG-IFN 2 b and ribavirin were well tolerated. The most frequent side effect was anemia, followed by thrombocytopenia, fatigue, and loss of appetite. Table 2 presents various side effects encountered. Ribavirin dose reduction was needed in 66 (20%) patients due to anemia and ribavirin treatment was discontinued in 31 (9%) without the need to give erythropoietin and blood

transfusion. Dose reduction in interferon treatment was needed in 17 (5%) patients as a result of mostly neutropenia (1%) and thrombocytopenia (1%). The SVR rates were found to be higher in patients who developed hypothyroidism, which was statistically significant (p = 0.03).

Table 2. Common side effects

Side effect	N (%)
Anemia	235 (76)
Neutropenia	36 (12)
Thrombocytopenia	96 (31)
Hyperthyroidism	19 (6)
Hypothyroidism	18 (6)
Pyrexia	17 (5)
Loss of appetite	57 (18)
Alopecia	9 (3)
Nausea	32 (10)
Weight loss	51 (16)
Pruritus	22 (7)
Fatigue	163 (50)
Depression	31 (10)

DISCUSSION

In the pivotal clinical trials for registration of PEG-IFN and ribavirin therapy, SVR was achieved in 46% and 40% of patients infected with HCV genotype 1 treated with PEG-IFN-2a or PEG-IFN-2b and ribavirin, respectively.[4-6] Various factors have been identified that influence response rates, including HCV genotype, body mass index, and co-existent liver disease. Ethnicity was recently noted to impact the treatment responses. Studies conducted in African Americans suggest that these individuals have lower SVR rates when compared to Caucasians, even after adjusting for confounders that could potentially influence treatment response rates.[7,8] We found the SVR rate to be 58.3%, which was higher than those in the United States. One possible explanation for this may be ethnicity as well as the lower rates of advanced fibrosis and alcohol consumption in our patients. In a study searching the role of ethnicity on treatment responses in Asians and Caucasians with CHC infection, Yan et al. found that Asians infected with HCV genotype 1 achieved a higher SVR rate when compared to a cohort of matched Caucasians.[9]

The strongest predictors of SVR are the recently identified genetic polymorphisms located in chromosome 19, which is close to the region coding for IL28B, the HCV genotype, and the stage of fibrosis. Other predictors of response besides the above mentioned, include baseline HCV RNA levels, the dose and duration of therapy, host factors, such as age, insulin resistance, and the stage of fibrosis or co-infection with another hepatotropic virus or with HIV.[10] In patients with favorable predictors for SVR (low baseline HCV RNA, IL28CC, no advanced fibrosis), dual therapy with PEG-IFN/Ribavirin may still be an option. In those patients, a lead-in of 4 weeks PEG-IFN/Ribavirin can identify patients with RVR who can achieve high SVR without adding a protease inhibitor. Patients with low viral load at baseline who achieve an RVR have demonstrated 78-100% SVR with 24 weeks PEG-IFN/Ribavirin dual therapy alone.[11-13] Similarly, we detected the SVR rate as 85.1% in patients with RVR, whereas the SVR rate was 71.2% in patients with HCV RNA levels less than 800,000 IU/ml. As a favorable predictor, we found the SVR rate at 60% in cases with Ishak fibrosis stage that remained below 4.

In the IDEAL (Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy) trial that compared two approved treatment regimens in the United States, which were 41% with PEG-IFN-2a (180 µg/week plus weight-based ribavirin, 1000-1200 mg/day) and 40% with PEG-IFN-2b (1.5 µg/kg/week plus weight-based ribavirin 800-1400 mg/day for 48 weeks) found no significant differences.[3] Similarly, we detected no differences between PEG-IFN-2a and 2b considering SVR.

The most common adverse events are influenza-like symptoms, depression, and the hematologic events of anemia and neutropenia.[3] Several side effects including fatigue and flu-like symptoms in about 60% of patients and depression in 20%-30% may develop. Laboratory abnormalities such as neutropenia, anemia, and thrombocytopenia were the most frequent indicators for dose reduction. Thus, approximately 25% of patients required at least one dose reduction for laboratory abnormalities during therapy.[14] The main side effect of ribavirin is hemolytic anemia as this complication may frequently result in ribavirin dose reduction or even discontinuation, which may significantly affect the overall SVR, especially in patients with HCV genotype 1.[10] Anemia was detected in 75% in our patients, being the most frequent side effect; however, 20% of patients needed dose reduction. On follow-up, treatment was discontinued in 31 (9%) patients due to anemia. It is an interesting finding

that patients with considerably higher rates (75%) of anemia represented somewhat lower rates (9%) of treatment discontinuation compared other studies.[10] In general, other side effects were detected in similar rates. Because the dose arrangement might be needed, potential side effects must be monitored closely during therapy.

Interferon (IFN) has immuno-modulatory properties, and treatment can induce autoimmune phenomena. The most frequent problem is the development of autoimmune thyroiditis. In most cases, thyroiditis starts with hyperthyroidism that later becomes hypothyroidism. Autoimmune thyroiditis has been reported in up to 20% of patients under or after IFN based therapies.[10] We found autoimmune thyroiditis in 12% of patients, and SVR rates to be higher in patients who developed hypothyroidism. This may be due to strong immune response making SVR rates higher and destroying thyroid gland. Mauss et al. revealed thyroid dysfunction that is triggered during PEG IFN-2b plus ribavirin treatment was an independent predictor to indicate higher SVR rates in CHC patients infected with genotype 1.[15]

In conclusion, dual therapy with PEG-IFN/ribavirin is still an option in treating CHC infection, especially when considering the costs and side effects as well as patients therapy toleration. On the other hand, the shortcomings of PEG-IFN/ribavirin therapy for HCV eradication is hardly expected in patients with high baseline viral loads, older age, and advanced fibrosis. Treatment regimens including protease inhibitor or newer treatment modalities should be administered.

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