***Case Report* / Olgu Sunumu**

Short-Term Treatment and Sustained Virologic Response in Two Chronic Hepatitis C Cases

Kronik Hepatit C Enfeksiyonlu İki Olguda Kısa Süreli Tedavi ve Kalıcı Virolojik Yanıt

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The standard treatment for chronic hepatitis C infection is the combination of pegylated interferon-alpha (Peg-IFN-α) and ribavirin for 48 weeks in patients infected with genotype-1. In genotype-2 or -3 infections, treatment by either conventional IFN-α and ribavirin or Peg-IFN-α with or without ribavirin for 24 weeks is recommended. We hereby report two cases of chronic hepatitis C infection whose genotypes are not specified, with sustained virological response despite early discontinuation of antiviral treatment.

Key words: Chronic hepatitis C; infection; short-term treatment.

Kronik hepatit C infeksiyonunda standart tedavi genotip 1 ile enfekte hastalarda pegile interferon-alfa (Peg-IFN-α) ve ribavirin kombinasyonunun 48 hafta uygulanmasıdır. Genotip 2 ve 3 enfeksiyonlarında 24 haftalık konvansiyonel interferon ve ribavirin kombinasyonu ya da ribavirinle birlikte veya tek başına uygulanan Peg-IFN-α tedavisi önerilmektedir. Biz burada antiviral tedavinin önerilen süreden daha erken sonlandırılmasına rağmen kalıcı viral yanıt elde edilmiş, genotipi bilinmeyen iki kronik hepatit C olgusunu sunduk.

Anahtar sözcükler: Kronik hepatit C; enfeksiyon; kısa süreli tedavi.

The standard treatment for chronic hepatitis C infection is the combination of pegylated interferon-alpha (Peg-IFN-α) and ribavirin for 48 weeks in patients infected with genotype-1. In patients who achieve a rapid virological response (RVR) at week 4, treatment can be discontinued after 24 weeks. In chronic HCV genotype-2 or -3 infections, treatment by either conventional IFN-a and ribavirin or Peg-IFN-α with or without ribavirin for 24 weeks is recommended.[1,2] A number of authors also suggest a 24-week therapy in patients with genotype-1 and low viral load.[3,4] It is unclear if shorter treatment duration is possible for patients showing a RVR without compromising the sustained virological response (SVR).

In this report, we present two cases of chronic hepatitis C infection with SVR, whose antiviral treatments were ceased for intolerance.

CASE REPORT

Case 1

A 50-year-old woman was admitted to our clinic with weakness, fatigue, generalized arthralgia and myalgia in June 2005. Her medical history revealed hepatitis C virus (HCV) infection diagnosed one week before. On admission, physical examination revealed hepatomegaly. Laboratory findings were as follows; white blood cell count: 8800/mm^3, hemoglobin: 13.4 g/dL, platelet

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count: 215 000/mm^3, alanine aminotransferase (ALT): 10 IU/L, aspartate aminotransferase (AST): 26 IU/L, and albumin: 4.14 mg/dL. Anti-HCV was positive. Viral load (HCV-RNA) was 300 000 IU/L, measured by real-time polymerase chain reaction (RT-PCR), (Cobas TaqMan HCV 48, Roche Diagnostics, detection limit 15 IU/ml). Hepatitis B surface-antigen (HBsAg), antibody to HB core antigen (anti-HBc), anti-nuclear antibody, antimicrosomal antibody, and anti-thyroglobulin antibody were all negative. No risk factor for HCV infection was detected. During a 5-month follow-up period, her ALT levels fluctuated from normal to 153 IU/L. The patient refused liver biopsy. A treatment with Peg-IFN-α2a (180 μg standard dose) per week and ribavirin 1000 mg/day was initiated in December 2005. During the third month of therapy, the patient developed thyroid dysfunction, which manifests early transient hyperthyroidism (Free T3: 13.2 pg/mL, Free T4: 6 ng/dL, TSH: 0.007 uIU/mL) followed by hypothyroidism (Free T3: 2.29 pg/mL, Free T4: 0.42 ng/dL, TSH:16.45 uIU/mL). Thyroid anti-thyroglobulin and anti-microsomal antibodies were positive, HCV-RNA was negative, and aminotransferases were normal during this period. Phropylthiouracil 150 mg/day was initiated in the early period and switched to levothyroxine 0.1 mg/day in the hypothyroidic period. Treatment was discontinued after the 12th dose of Peg-IFN-α2a due to endocrinology department's recommendation. At this time, serum HCV-RNA was undetectable by PCR. After discontinuation of treatment, thyroid functions and aminotransferase levels were monitored at 3-month intervals and HCV-RNA at 6-month intervals. In 18 months of follow-up period, the patient became euthyroidic with the levothyroxine maintenance treatment, aminotransferase levels were within normal range, and HCV-RNA remained negative.

Case 2

A 50-year-old man was admitted to our hospital with a diagnosis of chronic hepatitis C infection in September 2005. His medical history revealed chronic obstructive pulmonary disease (COPD) and diabetes mellitus diagnosed six years before. His HCV infection had been diagnosed 20 days before during hospitalization for an acute exacerbation of COPD. Physical examination was normal on admission except for dyspnea, adventitious rhonchi and wheezing. Laboratory results were as follows: white blood cell count: 14500/mm^3, hemoglobin: 15.8 g/dL, platelet count: 237700/mm^3, ALT: 32 IU/L, AST: 25 IU/L, anti-HCV antibody positive, HCV-RNA: 370 000 IU/L (Cobas TaqMan HCV 48, Roche Diagnostics, detection limit 15 IU/ml). HBsAg, anti-HBc, anti-nuclear antibody, antimicrosomal antibody, and anti-thyroglobulin antibody were all negative. Abdominal ultrasonography was normal. In October 2005, he underwent a liver biopsy confirming a histopathologic diagnosis of chronic viral hepatitis. Liver biopsy indicated moderate inflammation (Knodell score 7) and stage 1 fibrosis. A treatment with Peg-IFN-α2a (180 μg standard dose) per week and ribavirin 1000 mg/day was initiated in October 2005. ALT level was normal and HCV-RNA was negative at the 8th week of the treatment. By the end of the 20th week, the treatment was discontinued due to severe depression and multiple side effects. Serum HCV-RNA measured at this week was undetectable by PCR. During the subsequent 18 months of follow-up period, ALT levels were monitored at 3-month intervals and HCV-RNA at 6-month intervals. ALT activity remained normal; HCV-RNA levels were all undetectable, and the patient achieved SVR.

DISCUSSION

Although chronic hepatitis C infection can be cured in up to 40% of the patients, current treatment is not ideal and is associated with a wide spectrum of side effects, leading to a relatively small number of patients being offered therapy. Additionally, half of the patients who receive therapy fail to respond while approximately 15-20% discontinue due to adverse events.[5] Adverse events make completion of treatment exceedingly difficult, and also increase its duration.[6,7] Furthermore, longer regimens create unnecessary cost burdens.

Previous studies suggest that early clearance of virus during treatment period predicts sustained response, which is defined as both a biochemical and virological response six months after stopping therapy, in chronic hepatitis C infection.[3,7-10] Some studies also imply that patients with low pre-treatment viral load can be successfully treated by shorter regimens. Zeuzem et al.[3] tested the hypothesis that patients infected with HCV genotype-1 with low pre-treatment HCV-RNA (≤600 000 IU/ml at baseline) can receive Peg-IFN-α2b 1.5 μg/kg weekly plus weight-based ribavirin for 24 weeks and obtain the same SVR rate as those treated for 48 weeks. A recent study showed that patients infected with HCV genotype-2 or 3 that were treated with Peg-IFN-α2b and weight-based ribavirin for 12 or 24 weeks presented similar SVR rates if they had a RVR.[7]

In 2005, we were not performing routine genotyping of HCV in the cases reported here, therefore, HCV genotypes are not specified. However, according to previous studies, the prevalent HCV genotype (91% to 100%) in Turkey is genotype-1.[11-14]

In our first case, antiviral treatment was discontinued sooner than standard recommended durations for all genotypes, and in the second case, sooner than recommended duration for genotype-1. However, both patients achieved SVR. These two cases presenting SVR without relapsing suggest that treatment duration might further be shortened. There have been few isolated reports of patients who had SVR with therapy withdrawal after only 4 to 12 weeks.[15-17] Most of these reports include patients with non-genotype-1 infections.

In a few cases with genotype1, SVR despite early discontinuation have been reported.[15,17] Almost all of these cases have low pre-treatment viral load, and have HCV-RNA negativity at week 4. Similarly, our cases also had low pre-treatment viral load. However, although we did not analyze their viral loads at the 4th treatment week, the HCV-RNA was negative at week 12 in both cases.

In conclusion, the cases here reported imply that patients with low pre-treatment viral load and clear virus at week 12 may not require a full 24- or 48-week treatment. We believe that our cases will add an additional contribution to the literature that describes favorable results of early-discontinued therapy or shorter treatment regimens. Nevertheless, additional trials are required in order to optimize treatment duration in HCV infection with either genotype-1 or other genotypes and low viral load.

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