Research Article

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Evaluation of Chronic Hepatitis C Patients from Different Aspects Before the Use of Direct Acting Antivirals

Direkt Etkili Antiviraller Dönemi Öncesi Farklı Yönlerden Kronik Hepatit C Hastalarının Değerlendirilmesi

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ABSTRACT

Objective: Chronic hepatitis C (CHC) virus infection is one of the leading causes of chronic liver disease in all over the world. The prevalence of CHC is almost 0.5-1% in Turkey. Until recently, pegylated-interferon (PEG IFN) alpha in combination with ribavirin was the main treatment of CHC. The aim of the study was to evaluate the real life data of CHC patients.

Materials and Methods: We retrospectively evaluated the demographical data and treatment responses of patients with CHC who were followed and treated in our clinic between January 2008 and December 2015.

Results: A total of 117 patients (67 female and 50 male) with a mean age of 48 (15-65) were included in the study. 105 patients were genotype 1, 3 were genotype 2 and 9 were with genotype 3. The patients were treated with PEG IFN alpha-2a (81/117) or alpha-2b (36/117) combined with ribavirin. We observed sustained virologic response (SVR) in 68% of all genotype 1 patients. While relapse was observed in only 1 patient among those with genotype 2 and 3, SVR was achieved in 11. The rate of SVR was only 42% among patients older than 60 years of age, whereas SVR was achieved in all young patients (range: 15-30). The overall SVR rate was 70%.

Conclusion: As CHC can result in long-term complications (cirrhosis, terminal liver failure and hepatocellular carcinoma), patients without therapy remain at risk of developing progressive liver disease. Since advanced fibrosis is a predictor for poor prognosis and insufficient therapy outcome, early treatment is required to efficiently cope with this health problem, Although the rates of SVR with direct acting antivirals are very high, starting treatment in early stage could reduce the complications of CHC and transmission of the disease.

Keywords: Chronic hepatitis C, pegylated-interferon, ribavirin, sustained virologic response

ÖZ

Amaç: Kronik hepatit C (KHC) virüsü enfeksiyonu, tüm dünyada kronik karaciğer hastalığının önemli bir nedenidir. Türkiye'de hastalığın prevalansı %0,5-1 arasındadır. Yakın zamana kadar, KHC hastalarının standart tedavisinde pegile-interferon (PEG IFN) ve ribavirin kombinasyonu kullanılmaktaydı. Bu çalışmada amacımız KHC hastalarının gerçek yaşam verilerini değerlendirmektir.

Gereç ve Yöntemler: Ocak 2008-Aralık 2015 tarihleri arasında kliniğimizde takip edilen ve tedavisi tamamlanan naif KHC tanılı hastaların dosyaları retrospektif olarak incelendi; hastaların demografik verileri ve tedavi yanıtları değerlendirildi.

Bulgular: Çalışmamızda değerlendirmeye alınan toplam 117 hastanın 67'si kadın olup ortanca yaş 48 (15-65) idi. Hastaların 105'inde genotip 1, 3'ünde genotip 2, 9'unda genotip 3 saptandı. Hastalara PEG IFN alfa-2a (81/117) veya alfa-2b (36/117) ve ribavirin kombine tedavisi başlandı. Genotip 1 hastalarının %68'inde kalıcı virolojik yanıt (KVY) saptandı. Genotip 2 ve 3 hastalarından sadece bir kişide relaps gözlenirken, 11 hastada KVY sağlandı.15-30 yaş grubunda tüm hastalarda KVY sağlanırken, 60 yaş üstünde KVY oranı %42 bulunmuştur. Tüm hastalar değerlendirildiğinde ise, olguların %70'inde KVY saptanmıştır.

Sonuç: KHC uzun dönemde bir çok komplikasyona (siroz, terminal karaciğer yetmezliği ve Hepatoselüler karsinom) neden olabildiğinden, tedavisiz kalan hastalar progresif karaciğer hastalıkları açısından risk altındadır. Bu sağlık sorunuyla etkili bir şekilde başa çıkabilmek için erken tedavi gereklidir, çünkü ileri fibroz kötü prognoz ve başarısız tedavinin önemli bir göstergesidir. Direkt etkili ajanlarla KVY oranları oldukça yüksek olmakla beraber, yine de tedaviye erken başlanması KHC'nin komplikasyonlarından korunmak ve bulaş zincirinin kırılması açısından önemlidir.

Anahtar Kelimeler: Kronik hepatit C, pegile-interferon, ribavirin, kalıcı virolojik yanıt

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Introduction

Chronic hepatitis C (CHC) virus infection is one of the leading causes of chronic liver disease. The estimated global prevalence of hepatitis C virus (HCV) infection is about 3% (1,2,3). According to the guideline prepared by the Turkish Viral Hepatitis Society, the prevalence of CHC is about 0.5-1% in Turkey (1,4,5,6). Patients might develop chronic disease (60-80%), cirrhosis (30%) and hepatocellular carcinoma (1-4%) over the years (3,7). Currently, direct acting antivirals (DAAs), such as sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, simeprevir and daclatasvir have been licensed for the treatment of CHC. In Turkey, these DAAs have been used since July 2016. Before DAAs, pegylated-interferon alpha (PEG-IFNa plus ribavirin (RBV) was standard treatment of CHC (2). Sustained virologic response (SVR) rate is 40-50% for genotype 1 that widely seen in Turkey, and 80% for genotype 2 and 3 (2).

In this study, especially before the new treatments, we evaluated overall demographical, clinical and laboratory characteristics of patients who were followed in our clinic between January 2008 and December 2015 and treatment responses to CHC.

Materials and Methods

A total of 117 patients were included in this study. We retrospectively evaluated the data on demographic characteristics and treatment responses of patients with CHC virus infection who were followed in our clinic between January 2008 and December 2015. These data were collected from the patient files. In the same period, we could not administer treatment in about 90 patients because of various reasons, including older age, underlying disease and intolerance to the drugs.

The treatments were PEG-IFNa-2a (180 µg/week) or PEG-IFNa-2b (1.5 µg/week) combined with RBV (800-1200 mg/day). We monitored HCV RNA levels at 0 (baseline), 4 [rapid virologic response (RVR)], 12 [early virologic response (EVR)] weeks of therapy, end of the therapy (end-of-treatment response) and 24 weeks after the therapy (SVR or relapse).

The planned duration of treatment was 24 weeks for genotype 2 and 3, and 48 weeks for genotype 1. The treatment was stopped at 24 weeks for some genotype 1 patients with RVR.

Statistical Analysis

Data analysis was performed by using the SPSS 20.0 program. The laboratory values of patients were compared with univariate analysis. Afterwards, chi-square test and Mann-Whitney U test were used for categorical variables and continuous variables, respectively. A p value of less than 0.05 ($p \leq 0.05$) was regarded as statistically significant.

Results

A total of 117 patients (67 female, 50 male) were included in the study. The mean age of the patients was 48 (15-65) years. 105 patients were genotype 1, three were genotype 2 and nine were genotype 3 (Table 1).

While all young patients (15-30 years) had SVR, this rate was only 42% among patients older than 60. As the patients got older, hepatic fibrosis stage increased and treatment response decreased (Table 2).

Initial high alanine aminotransferase (ALT) levels (>40 IU/L) and high viral load (>800.000 IU/L) were detected in 81 and 75 patients, respectively. The initial ALT and viral load were statistically unremarkable in terms of SVR. The cut-off value for high viral load is >6.000.000 IU/mL in recent guidelines. According to this data, the SVR rates were found to be 42% and 76% in patients with high and low viral load, respectively. Significant differences were observed compared to 800.000 IU/mL reference value.

Table 1. The baseline characteristics of patients

	Number	Percent (%)
Sex		
Female	67	56
Male	50	44
Genotype		
1	105	90
2	3	2.5
3	9	7.5
HCV RNA		
<800.000 IU/mL	42	36
>800.000 IU/mL	75	64
<6.000.000 IU/mL	98	84
>6.000.000 IU/mL	19	16
ALT		
<40 IU/mL	36	31
>40 IU/mL	81	69
Fibrosis score		
F0-2	25	30
F3-6	58	70
Treatment (RBV+)		
PEG-IFN alpha-2a	81	69
PEG-IFN alpha-2b	36	31

PEG-IFN: Pegylated-interfon, RBV: Ribavirin

Table 2. The rate of treatment response according to age groups

Age	No. of patients N	Genotype 1 N	Genotype 2-3 N	Patients with high viral load n/N (%)	Patients with high ALT level n/N (%)	Patients with advanced hepatic fibrosis n/N (%)	Patients with SVR n/N (%)	Non-responders n/N (%)	Relapse n/N (%)
15-30	15	12	3	4/11 (36)	7/15 (46)	0/11 (0)	15/15 (100)	0/15 (0)	0/15 (0)
31-40	22	19	3	11/22 (50)	17/22 (77)	4/15 (26)	16/22 (72)	3/22 (13)	3/22 (13)
41-50	34	31	3	22/34 (64)	27/34 (79)	5/24 (20)	26/34 (76)	4/34 (11)	4/34 (11)
51-60	33	31	2	23/33 (69)	25/33 (75)	11/25 (44)	20/33 (60)	7/33 (21)	6/33 (18)
61-70	13	12	1	7/13 (53)	8/13 (61)	5/8 (62)	6/13 (46)	4/13 (30)	3/13 (23)

SVR: Sustained virologic response, ALT: Alanine aminotransferase, n: Number of patients of positive for related parameter, N: Number of patients of screening for related parameter

Eighty three patients underwent liver biopsy. Twenty five patients (30%) had moderate-to-advanced fibrosis (F3 and higher according to the Knodell Histological Activity Index) with 44% SVR rate. The rate of SVR in patients with low-to-moderate fibrosis was 86% (p<0.001).

In 29 patients evaluated for RVR, 10 patients (34%) had undetectable HCV-RNA level at the end of 1 month. The treatments of 5 patients with RVR were stopped at the 24th week. At the end of the 12th week, while we detected EVR in 86 (84%) of 102 patients who were evaluated for HCV-RNA level, 1 patient had more than 2-log decline at the 12th week but detectable HCV-RNA at the end of the 24th week. Eighteen patients were considered as non-responders at the 24th week. 80% of genotype 1 patients who were treated for 48 weeks achieved SVR (Table 3). We detected SVR in all 10 patients with RVR.

In our study, while 1 of the 16 relapse cases was genotype 3, the rest of them were genotype 1. Of the 15 genotype 1 patients with relapse, 6 were male (40%). Thirteen patients (86%) had high ALT levels and high HCV-RNA was detected in 9. Four of ten patients who underwent biopsy had moderate-to-advanced hepatic fibrosis. In 12 cases, we had to stop the treatments early due to adverse effects. Only one patient achieved SVR among these patients.

We observed SVR in 68% of all genotype 1 patients. While relapse was observed in only 1 patient among genotype 2 and 3 patients, SVR was achieved in 11. Overall, 70% of the cases achieved SVR.

Discussion

HCV is currently the leading cause of chronic hepatitis (1). Initially, its treatment was IFN-α. The addition of a polyethylene-glycol molecule to standard interferon produces a biologically active molecule with a longer half-life (1,6,8,9). Use of this molecule with RBV has shown to increase SVR rates. Afterwards, combinations with specifically targeted antiviral therapy have been developed (10). Clinical trials have suggested that protease inhibitors (telaprevir or boceprevir) combined with PEG-IFNα+RBV could produce increase of SVR rates but discontinuation of treatment because of adverse events was more frequent (10). Nowadays, DAAs were licensed in the treatment of CHC with or without RBV. The IFN-free regimens are well tolerated than ever before and achieved SVR >90-100%.

PEG-IFNa+RBV treatment is the individualized treatment, a response-guided therapy, which is based on host- and HCV-related factors. Strong predictors of SVR are HCV genotype and the initial virologic response to treatment (10). A number of pre-treatment factors, such as older age, presence of cirrhosis or advanced fibrosis, African-American race, overweight, genotype, viral load, low level of ALT, and low platelet count are known to reduce the SVR rate (10,11).

In Turkey, the most common genotype is 1b (75-97%). 89% of our patients had genotype 1. In genotype 1 group, SVR can be achieved in 40-50% and 91% in genotype 2 and 3 (8). In our study; 68% of genotype 1 and 11 of 12 patients with genotype 2 and 3 achieved SVR.

Male gender and older age have been reported to associate with poor outcome of therapy (8,10,11). We found no difference in SVR rate between genders. In our young patient group (15-30 years of age), all subjects had SVR without relapse.

When comparing the SVR rate between the groups with elevated and normal ALT levels (66% and 80%, respectively), or between subjects with initial high and low viral load, there was no statistically significant difference (70% and 71%, respectively). Unlike our study, it has been reported that high ALT and initial viral load reduced the SVR rate (8,10,12,13,14).

In 83 patients, who underwent biopsy, SVR was achieved in 44% of subjects with moderate to severe stage and in 86% of patients with mild-to-moderate stage (p=0.001). It is well known that low stage is a good prognostic factor for high SVR rate (9,10,15,16).

A higher proportion of patients with advanced age had more severe fibrosis in our study (Table 2). This is probably due to the duration of HCV infection because chronic liver failure and HCV-associated complications may develop many years after infection (1,17).

Patients with RVR have a better likelihood of achieving SVR. We had 10 patients with RVR (m/f: 5/5). Six patients stopped the therapy at the 6th month, 1 patient interrupted the therapy at the 9th month because of severe side effects and, the duration of

Table 3. The characteristics of the patients according to treatment response

	Patients with ETR n/N (%)	Patients with SVR n/N (%)	Non-responders n/N (%)	Relapsers n/N (%)
Male	43/50 (86)	36/50 (72)	7/50 (14)	7/50 (14)
Female	56/67 (83)	47/67 (70)	11/67 (16)	9/67 (13)
Genotype 1	87/105 (82)	72/105 (68)	18/105 (17)	15/105 (14)
Genotype 2-3	12/12 (100)	11/12 (91)	0/12 (0)	1/12 (8)
Patients with HCV RNA <800.000 IU/mL	36/42 (85)	30/42 (71)	6/42 (14)	6/42 (14)
Patients with HCV RNA >800.000 IU/mL	63/75 (84)	53/75 (70)	12/75 (16)	10/75 (13)
Patients with normal ALT level	31/36 (86)	29/36 (80)	5/36 (13)	2/36 (5)
Patients with high ALT level	68/81 (84)	54/81 (66)	13/81 (16)	14/81 (17)
Patients with low hepatic fibrosis	56/58 (96)*	50/58 (86)*	2/58 (3)*	6/58 (10)
Patients with advanced hepatic fibrosis	16/25 (64)*	11/25 (44)*	9/25 (36)*	5/25 (20)

*p<0.05
ETR: End-of-treatment response, SVR: Sustained virologic response, ALT: Alanine aminotransferase, HCV: Hepatitis C virus, n: Number of patients of positive for related parameter, N: Number of patients of screening for related parameter

the therapy was 12 months in 3 patients. In all patients, SVR was achieved. Seven of eight patients with liver biopsy had mild stage.

Only 1 of 16 patients with relapse had genotype 3. This subject had a high viral load (6.450.000 IU/mL) and advanced stage (stage: 3/6). Among the patients with genotype 2 or 3, only this subject had advanced fibrosis and relapse. Fourteen patients (87%) had elevated ALT levels and 11 patients (68%) had high viral load. Five of the 11 patients with liver biopsy had advanced fibrosis. We found statistically significant positive correlation between advanced stage fibrosis and relapse.

All of the 11 patients with RVR and 75 of 87 patients (86%) with EVR had SVR, and the SVR rate in subjects who completed the 48-week therapy was 83%. HCV-RNA decrease, RVR and EVR are supposed to be strong independent on-therapy predictors.

Conclusion

As CHC can result in long-term complications (cirrhosis, terminal liver failure and hepatocellular carcinoma), patients without therapy remain at risk of developing progressive liver disease. To efficiently cope with this health problem, early treatment is required, because advanced fibrosis is a predictor for poor prognosis and insufficient therapy outcome. Although the rates of SVR with DAAs are very high, starting treatment in early stage could reduce the complication of CHC and transmission of the disease.

Etichs

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Authorship Contributions

Surgical and Medical Practices: S.Y.K., B.M., Concept: Ö.F.T., Design: İ.İ.B., B.M., Data Collection or Processing: S.Y.K., A.K., Analysis or Interpretation: Ö.F.T., N.S., Literature Search: S.Y.K., Writing: S.Y.K., A.K.

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