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Comparison of Patient Adherence and Treatment Response in Patients with Chronic Viral Hepatitis: Results of a 48-Week Observational Study

Kronik Viral Hepatit Hastalarında Hasta Uyumu ve Tedavi Yanıtının Karşılaştırılması: 48 Hafta Gözlemsel Çalışma Sonucu

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ABSTRACT

Objectives: Viral hepatitis is one of the significant health problems in the world. The main purpose of treatment is virological eradication. There are many factors that determine treatment response. The most important factor that can be affected is treatment adherence. In our study, we aimed to compare compliance with treatment response, which is one of the factors that can be affected in chronic viral hepatitis patients. We highlight that this element should be considered in treatment failures, especially in chronic diseases that require long-term treatment.

Materials and Methods: Chronic hepatitis patients over 18 years of age and under 65 years of age, who were neither co-infected with Human immunodeficiency virusnor pregnant, were prospectively analyzed after receiving ethics committee approval. Treatment adherence was defined as taking the prescribed medication in the required number of doses and for the required duration. Drug count and questionnaires were used in the compliance assessment. Patients' compliance and patients' 12, 24, 36, and 48th-week virological responses were compared.

Results: Seventy-six patients were included in the study. Sixty point five percent of patients had chronic hepatitis B, and 39.5% had chronic hepatitis C. According to the drug count data, it was determined that 83.9% of the patients did not take their treatment during at least one visit. At the end of the treatment (48th-week follow-up), 89.4% of all chronic hepatitis patients were compliant and 92.6% of the compliant patients responded to the treatment. Five out of eight non-compliant patients, accounting for 62.5%, were able to respond to the treatment. Response rates of

ÖZ

Amaç: Viral hepatitler dünyadaki önemli sağlık sorunlarından biridir. Hepatit tedavisinde ana amaç virüs eradikasyonun sağlanmasıdır. Bu hedefe ulaşmada tedavi yanıtın etkileyen pek çok faktor mevcuttur. Etkilenebilen en önemli faktör ise hastaların tedaviye uyumlarıdır. Çalışmamızda kronik viral hepatit hastalarında etkilenebilen faktörlerden olan uyum ile tedavi yanıtı karşılaştırılarak özellikle uzun dönem tedavi gerektiren kronik hastalıklarda tedavi başarısızlıklarında bu öğenin de akılda tutulması gerektiğine dikkat çekmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamıza 18 yaş üstü ve 65 yaş altı yeni tedavi başlanması planlanan kronik hepatit B ve hepatit C hastaları alındı. İnsan bağışıklık yetmezliği virüsü ile ko-enfekte ve gebe hastalar çalışma dışı bırakıldı. Çalışma öncesi etik kurul onayı alınarak hastalar 48 hafta prospektif olarak izlendi. Tedaviye uyum, reçete edilen ilacı reçete edildiği gibi uygun doz ve sürede almış olmak olarak tanımlandı. Uyum belirlenirken ilaç sayımı ve anket yöntem kullanıldı. Hastaların uyum ile 12., 24., 36. ve 48. hafta virolojik yanıtları karşılaştırıldı.

Bulgular: Çalışmaya 76 hasta dahil edildi. Hastaların %60,5 kronik hepatit B, %39,5'i kronik hepatit C hastası idi. İlaç sayım verilerine göre hastaların %83,9'unun en az bir vizitte ilaçlarını almayı unuttuğu tespit edildi. Kırk sekiz haftalık izlem sonunda hastaların %89,4'ünde uyum tespit edildi. Uyumlu hastaların ise %92,6'sında tedaviye cevap mevcut idi. Uyumsuz tespit edilen hastaların ise %62,5'inde tedaviye cevap alındı. Tedaviye uyumlu ve tedaviye uyumsuz hastaların tedavi cevap oranları istatistiksel olarak anlamlı bulundu.

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compliant and non-compliant patients to treatment were found to be statistically significant.
Conclusion: Non-adherence to treatment in chronic viral hepatitis is infrequent. Given the increased risk of virological failure in poorly adherent patients, clinicians should keep in mind adherence issues in every patient treated for viral hepatitis.
Keywords: Adherence, hepatitis B, hepatitis C

Sonuç: Kronik viral hepatit hastalarında tedavi uyumsuzluk çok sık görülen bir durum olmamasına rağmen, düşük uyumlu hastalarda virolojik cevabın yetersizliği riski yüksek olmasından dolayı hekimler tüm tedavi alan kronik hepatit hastalarında tedaviye uyum faktörünü aklında bulundurmalıdır.
Anahtar Kelimeler: Uyum, hepatit B, hepatit C

Introduction

Viral hepatitis is one of the common health problems all over the world. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are viruses that can cause an infection progressing from acute to cirrhosis and hepatocellular carcinoma. Achieving virological eradication and slowing this progression are among the goals of treatment. Today, there are many therapeutic agents used in the treatment of viral hepatitis. There are many factors that canbe changed in treatment response. Viral load, genotype, and race of the patient are traits that can affect the sustained response but cannot be changed. The most important factor that can be changed is the patient's adherence to treatment. Adherence to treatment can be defined under two subheadings, and for a successful treatment, both should be:

Compliance: Compliance to patient's appointments, medical recommendations such as medication and regulation of living conditions as required by the disease and treatment,

Cooperation (Adherence): Taking prescribed medication as required (in number and at appropriate time) and attending the health institution appointments without interruption (1).

Compliance becomes more important in patients with chronic diseases, which are costly and require long-term treatment. This study aimed to investigate the effect of treatment compliance on a virological response in hepatitis, a chronic disease that requires long-term treatment.

Materials and Methods

Our study was conducted in an infectious disease's out patient clinic in Trabzon from July 2012 to July 2014. Chronic hepatitis patients, who were over 18 years of age and under 65 years, who weren't co-infected with Human immunodeficiency virus and not pregnant, were prospectively analyzed after receiving ethics committee approval. A follow-up form was created and virological, biochemical and serological responses were evaluated at the 12th, 24th, 36th and 48th weeks from the beginning of treatment. Fourth-week response was also evaluated in chronic hepatitis C (CHC) patients. This study approval was received from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 74, dated: 12.02.2013). A patient informed consent form was obtained. Publication approval has been given.

Hepatitis B medication regimens were defined as pegylated-interferon (PEG-IFN) α2a or -α2b, the nucleos(t)ide analogues including lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate and telbivudine (2).

Medication regimens for hepatitis C were defined as combination therapy, including PEG-IFN α2a or -α2b combined with ribavirin and triple therapy with protease inhibitors boceprevir and telaprevir (3,4).

Patient adherence was assessed by the monthly number of prescribed antiviral drugs and compliance questionnaire, The questionnaire comprised two sections designed to understand treatment behaviors. Section 1 consists of 6 questions with yes or no answers adapted from Turkish modified Morisky questions, whose validity and reliability were confirmed by Vural et al. (5). Second section includes questions focusing on treatment regimen, doses and patient perceptions.The survey results were given as percentages.

Treatment response in CHC was defined as normal liver function tests, HCV-RNA becoming negative in the 4th week of treatment (rapid virological response), HCV-RNA becoming negative or a 2-log decrease in the 12th week of treatment (early virological response), and RNA becoming negative end of treatment and thereafter (6). Treatment response in chronic hepatitis B (CHB) patients was defined as the normalization of liver function tests, the decline of HBV-DNA to an undetectable level, and the maintenance of these levels (7).

Full compliance is defined as not having a forgotten dose; moderate compliance is forgetting 1 dose in the last 4 days or on the weekend; incompatibility is defined as forgetting more than one dose in the last 4 days or more than one dose on the weekend (8). Compliance percentage is obtained by subtracting the forgotten amount from the amount of medication prescribed to the patient and dividing the result by the amount of medication that should be taken daily multiplied by the duration. And multiplying it by 100 (9).

Statistical Analysis

IBM SPSS Statistics for Windows. Version 22.0 (Statistical Package for the Social Sciences, IBM Corp. Armonk, NY, USA) was used for data analysis. For categorical variables, descriptive statistics include numbers(n) and percentages (%); for numerical variables, descriptive statistics include mean and standart deviations. Risk factors affecting adherence were identified by univariate analysis, the chi-square test was used for qualitative data. Analysis results were presented as p-value estimated relative risk (odds ratio) and 95% confidence interval. Statistical significance level was accepted as $p<0.05$. Variables found to be statistical significant in univariate analysis were subjected to further detailed multivariate analysis using the logistic regression technique.

Results

Seventy-six patients were included in the study. Sixty point five percent (n=46) of patients were CHB patients, and 39.5% (n=30) were CHC patients. Forty-two point one percent of the patients were women. The mean age of the patients was 45.18±13.2 years. Thirty-nine point five percent of the patients had comorbid diseases, and 26.3% of these patients used an additional drug.

According to the survey, all CHB patients received oral treatment. No patient received interferon. Ninety-three percent

of CHB patients disrupted their treatment for at least one visit. Thirty-two percent stated that they forgot to take their medication on weekends. The most common reason for non-adherence was "forgetfulness". Twenty-two percent of them had difficulty remembering to take medications because they were using multiple medications. Twenty-five percent of them used the telephone setting methods to remember medication. Twenty percent of them considered stopping treatment because they thought that their disease was stable.

Twenty percent of CHC patients were given triple treatment. Six point six percent of patients disrupted their treatment for at least one visit. The most common reason for this was drug side effects. It was observed that 12% of CHC patients had difficulty remembering medications. The telephone setting method was the most common recall method. All our patients stated that they take their treatment with them when they travel. According to drug count data, at the end of the 48-week treatment follow-up, 89.4% of all chronic hepatitis patients had compliance and 92.6% of compatible patients responded to the treatment. Sixty-two point five percent of the eight incompatible patients were able to respond to treatment. Response rates of compliant and incompatible patients to treatment were statistically significant (p=0.034).

The average compliance percentage of CHB patients at 48-week follow-up was 90.9%. At the 4th week follow-up, 28.2% (n=13) of patients were fully compliant, while 56.5% (n=26) were moderately compliant and 15.2% (n=7) of patients were incompatible. At the 12th week, 19.5% (n=9) of patients were fully compliant, 65.2% (n=30) were moderately compliant, and 15.2% (n=7) of patients were incompatible. Sixty-six point six percent (n=6) of fully compliant, 53.3% (n=16) of moderately compliant patients, and 28.6% (n=2) of incompatible patients responded to treatment.

At 24th week, 36.9% (n=17) of patients were fully, 43.4% (n=20) were moderately compliant and 19.5% (n=9) of patients were incompatible. Response was achieved in 70.6% (n=12) of fully compliant, 60% (n=12) of moderately, and 22.2% (n=2) of incompatible patients.

At the end of a 48-week follow-up after treatment, 13 CHB patients were fully adherent, 25 CHB patients were moderately adherent, and 8 were non-adherent. The viral load became negative in 92.1% of compliant patients and 62.5% of non-compliant patients. This rate was statistically significant (p=0.048). The average compliance rate of CHC patients was 95% at 48-week follow-up. At the 4th week, 63.3% (n=19) of CHC patients were fully compliant, and 36.6% (n=11) were moderately compliant. We had no incompatible patients. Rapid virological response occurred in 94.7% (n=18) of fully compliant patients and 45.5% (n=5) of moderately compliant patients. This rate was statistically significant (p=0.004). At the 12th week, 70% (n=21) of the patients were fully compliant, 26.6% (n=8) were moderately compliant, and one patient was non-compliant. Virological response was observed in 95.2% (n=20) of fully compliant patients and 75% (n=6) of moderately compliant patients.

Virological response could not be achieved in one non-responsive patient. At the 24th week, while 80% of patients were fully compliant, treatment response rates were 95.8% (n=23). Success was achieved in 80% of five moderate patients and the single patient with incompliance. At the end of the 48-week follow-up after treatment, full compliance was observed in 2 patients, and moderate compliance was observed in 28 patients with CHC.

We did not have any incompatible patients. While no response was obtained in 2 patients with compatibility, 28 patients with moderate compatibility showed a 100% response. This rate was statistically significant (p=0.002).

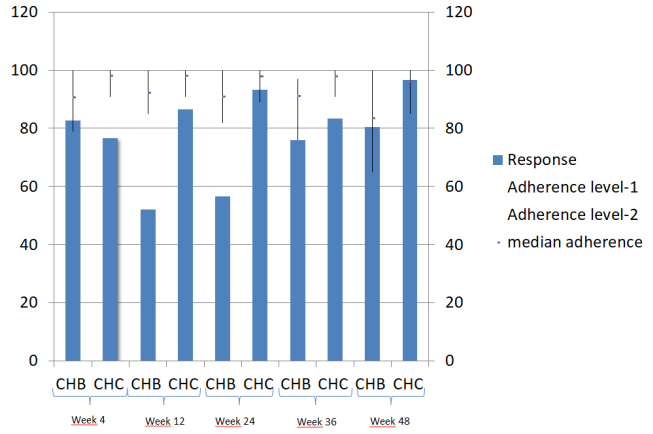
Compliance and response charts according to treatment follow-up weeks, in chronic hepatitis B and hepatitis C patients are given in Table 1.

Graphs of compliance and treatment response by week in CHB and CHC patients are presented in Graph 1.

Table 1. Compliance and response charts in chronic hepatitis B and hepatitis C patients

	Full adherence/ response (%)	Moderate adherence/ response (%)	Incompliance/ response (%)	p-value
CHB				
Week 0-4	28.2 (n=13)/92.3 (n=12)	56.5 (n=26)/84.7 (n=22)	15.2 (n=7)/57.1 (n=4)	
Week 5-12	19.5 (n=9)/66.6 (n=6)	65.2 (n=30)/53.3 (n=16)	15.2 (n=7)/28.6 (n=2)	
Week 13-24	36.9 (n=17)/70.6 (n=12)	43.4 (n=20)/60 (n=12)	19.5 (n=9)/22.2 (n=2)	
Week 25-36	34.7 (n=16)/100 (n=16)	52.1 (n=24)/79.2 (n=19)	13.04 (n=6)/0 (n=0)	
Week 37-48	43.7 (n=20)/90 (n=18)	39.1 (n=18)/83 (n=15)	17.3 (n=8)/50 (n=4)	
Median	28.2 (n=13)/100 (n=13)	54.3 (n=25)/88 (n=22)		
Median	82.6 (n=38)/92.1 (n=35)		17.3 (n=8)/62.5 (n=5)	0.048
CHC				
Week 0-4	63.3 (n=19)/94.7 (n=18)	36.6 (n=11)/45.5 (n=5)	0	0.004
Week 5-12	70 (n=21)/95.2 (n=20)	26.6 (n=8)/75 (n=6)	3.3 (n=1)/0 (n=0)	
Week 13-24	80 (n=24)/95.8 (n=23)	16.6 (n=5)/80 (n=4)	3.3 (n=1)/100 (n=1)	
Week 25-36	73.3 (n=22)/90.9 (n=20)	23.3 (n=7)/57.1 (n=4)	3.3 (n=1)/100 (n=1)	
Week 37-48	73.3 (n=22)/100 (n=22)	23.3 (n=7)/85.7 (n=6)	3.3 (n=1)/100 (n=1)	
Median	6.6 (n=2)/0 (n=0)	93.3 (n=28)/100 (n=28)	0	0.002

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C



Graphic 1. Compliance and treatment response graphs by weeks in hepatitis patients

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C

Discussion

Nowadays, reliable and effective treatments are used to prevent unwanted complications of hepatitis, such as cirrhosis, liver failure, and hepatocellular carcinoma, which is one of the important health problems in the world.Besides drug performance, compliance with treatment is also an important factor in chronic diseases like hepatitis (1-10).

Chronic hepatitis patients are generally asymptomatic, so long-term compliance rates may be suboptimal. Due to the difficulty of measuring adherence, many methods have been developed. Pharmacy filling data, reports provided by patients and doctors, patient compliance questionnaires, and medication count are methods used to measure compliance. In many studies patient reports was used to calculate compliance. However, compliance measurements that were made based on patient statements can yield results higher than the actual compliance rate. Assessing compliance through drug count gives more objective results than other methods. In our study, toevaluate compliance, we used drug counting and adherence questionnaires. In recent studies on CHB and compliance, the compliance range has been reported to be 81-99% (10). We found a 90% compliance rate in CHB patients, consistent with the literature. It is estimated that the single daily dose used in the treatment, good tolerance and minimal side effects are reasons for this high rate of compliance in CHB (12).

The average compliance rates vary between 54.1% and 95% in CHC patients in recent studies. In our study, we found the average compliance is over 95% in CHC patients. Wide range of compliance rates is attributed to many factors such as changing methods in calculating compliance, duration of follow-up, socio-cultural status, economic characteristics, and the different side effects of drugs in each patient. In addition to these reasons, in our study, reasons such as close following up and knowing patients that they would bring their medications boxes with them may have caused these high average compliance percentage. Tolerance to CHC treatment may vary among individuals. Sometimes serious side effects may occur. These side effects are the main reason for dose reduction and disruption in the treatment of CHC. Dose reduction or treatment interruptions due to side effects, in CHC treatment may be confused with patient-induced noncompliance. Dose reduction or skipping by the doctor should not be considered unresponsiveness to treatment. Joint evaluation of dose reduction by doctor and patient in CHC can be another reason for the wide range of compliance observed among CHC patients (13). When the compliance in CHB treatment is compared with the compliance in CHC treatment, the compliance of CHC patients to treatment is higher. The reasons for this may be closer follow-up due to side effects, providing motivation after frequent patient-doctor communication (10-14). Additionally, the long treatment of CHB leads to a decrease in patient compliance due to decreased interest in medication and the patient's motivation (12).

In a few studies on CHB, although the virological testing varies, the effect of compliance on virological response is variable. Some studies have found that compliance is not a predictor for HBV-DNA negativity (14). In our study, compliance and response rates were variable, too, which support this view.

Adherence of >85% to treatment in CHC patients was associated with increased early virological outcomes (15). In our study, good treatment responses were obtained with high compliance rates in first 12 weeks of treatment. At week 24, high compliance and high response rates were also correlated in our patients, consistent with the literature (16). The fact that our incompatible patients also responded to treatment suggests that other factors, such as the structure of the virus can be effective in the response to treatment. In practice, medication side effects are seen as a major cause of non-compliance (19). According to compliance survey questions, while we found similar results in CHC patients (18), the most common reason for non-compliance in CHB patients was "forgetfulness" in line with the literature (17). The reason for this may be that drug side effects are rare in CHB patients (12). Furthermore, "Feel better already and do not think it is necessary to continue," and "Multiple medications are taken daily," were other reasons that impact regular medication use in patients, unlike the findings of Giang et al. (12).The main drawback of this study was that adherence was assessed by patients' self-reports, although medication enumeration was also performed. Although self-reported adherence is the most appropriate method for evaluating adherence to a medication, it is subject to overestimation (20). Additionally, due to the small sample size, these findings are not generalizable. Nevertheless, these results could help in understanding patients' treatment behaviors and highlight areas to improve adherence. In addition, the success of treatment in hepatitis patients who was considered incompatible in our study indicates that the definitions of compatible and incompatible in drug counting should be reconsidered in further studies. In the future, more objective results will be obtained in compliance evaluations with current and new treatment approaches by contacting patients one-on-one, such as through home health services using technology.

Conclusion

In conclusion, while compliance is important in chronic diseases that require long-term treatment, this situation has become even

more important with the newly developed oral antiviral agents in hepatitis. In CHB patients, as in CHC patients, shortening the treatment period with newly developed drugs can lead to higher treatment success by increasing the compliance rate.

Ethics

Ethics Committee Approval: This study approval was received from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 74, dated: 12.02.2013).

Informed Consent: A patient informed consent form was obtained.

Footnotes

Authorship Contributions

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

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