Evaluation of depression, anxiety and quality of life in hepatitis C patients who treated with direct acting antiviral agents

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ABSTRACT

Background/Aims: Hepatitis C virus (HCV) infection is known to impair the quality of life (QoL). Increased levels of anxiety and depression have been found in HCV infection with a prevalence of 28% and 33%, respectively. Our aim was to investigate depression, anxiety, and QoL of chronic hepatitis C (CHC) patients before and after treatment with a direct-acting antiviral agent (DAAA).

Materials and Methods: In this study, enrolled CHC patients who had undergone DAAA treatment in our out-patient clinic. We administered the Hospital Anxiety and Depression (HAD) questionnaire to measure the severity of the anxiety and depression symptoms and the Short Form-36 (SF-36) questionnaire to measure the QoL at the beginning and at the end of the treatment.

Results: Pretreatment anxiety and depression scores showed a statistically significant difference from the post treatment scores (p=0.000 and p=0.029 respectively). When we compared the SF-36 subitems before and after the treatment, a statistical significance was found in physical functioning (p=0.026), physical role limitation (p=0.009), bodily pain (p=0.011), general health (p=0.017), social functioning (p=0.006), and emotional role limitation (p=0.007). Also, an improvement was seen in the vitality (p=0.488) and mental health (p=0.714), which was not statistically significant.

Conclusion: Depression got minimally worse in the male group despite an improvement in CHC. Anxiety scores were improved with treatment in the cirrhotic and non-cirrhotic groups significantly. A decrease in anticipatory anxiety may be related to the high treatment success with DAAA. Nearly all the subitems of the QoL scores were improved after treatment and these were more common in the female group. Elimination of HCV may itself decrease the number of patients who need psychiatric treatment.

Keywords: Anxiety, depression, direct acting antiviral agent, hepatitis C, quality of life

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the most common reasons of chronic hepatitis and may cause acute or chronic hepatitis, cirrhosis, or hepatocellular carcinoma (1,2). Liver structure and prognosis directly affected from the treatment of HCV and measuring these parameters objectively are possible. Besides this, there is also a change in subjective parameters, such as the quality of life (QoL), which can be measured with some questionnaires as a patient-related outcome (3).

HCV infection may also impair the QoL with or without the presence of an advanced liver disease. Impaired socialization because of social isolation, anxiety, and psychological stress were seen in patients who were aware of the disease progression to cirrhosis or cancer (4). Also, fatigue and some other extrahepatic symptoms play a role in the decreased QoL (5).

Anxiety and depression levels have been found to be higher in HCV with a prevalence of 28% and 33%, respectively (6). This comorbidity was associated with side effects of interferon (IFN) (e.g., substance use, direct manifestation of virus, and indirect effect of disease including self-stigmatization, social isolation etc.)

IFN based regimens were first used in HCV treatment, but these drugs did not achieve satisfying and sustained rates of virologic response (SVR). After IFN based regimens, direct-acting antiviral agents (DAAA) came onto

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use, and increased SVR rates were seen with these drugs. However, a worsened QoL was seen with IFN based regimens, contrary to treatment regimens involving DAAAs (7). This effect may arise due to the side effects of IFN treatment such as anemia or depression (8).

In this study, our aim was to investigate depression, anxiety, and QoL of chronic hepatitis C (CHC) patients before and after the DAAA treatment.

MATERIALS AND METHODS

We evaluated the patients with CHC in our gastroenterology and hepatology out-patient clinic and enrolled only those patients who had been treated with DAAA. The study was approved by the local ethics committee and was conducted according to the ideal clinical practice guidelines. A total of 80 patients signed the informed consent form and registered as participants in our study.

The inclusion criteria were: patient age of more than 18 years, having HCV-RNA positivity and being treatment naïve, or having HCV-RNA positivity and being previously treated for CHC. The exclusion criteria were: CHC patients with hepatic encephalopathy, active variceal bleeding, been previously treated for major depression or having had suicidal tendencies, DAAA treatment-contraindicated patients, or those who rejected to provide their informed consent.

We evaluated all patients by taking a detailed medical history and by performing a physical examination. We recorded the participants' gender, age, height, weight, education status (years), marital status, employment, monthly income, psychiatric treatment history, alcohol and tobacco use, CHC diagnosis date, child and MELD scores, blood samples, and liver biopsy results. The HCV-RNA results were checked before treatment, at the 1st and 3rd months of treatment, and at the 6th month (those who had undergone 6 months of DAAA therapy), and in the 3rd month after completing the therapy (9 months after the start of DAAA therapy).

We administered the Hospital Anxiety and Depression (HAD) questionnaire to measure the severity of the anxiety and depression symptoms and the Short Form-36 (SF-36) questionnaire to measure the QoL at the beginning (1 month before the initiation of the treatment) and at the end of the treatment (1 month after the completion of the treatment). The HAD questionnaire is a self-reported screening tool that includes 14 multiple-choice questions. The validity and reliability study of HAD was performed in a Turkish clinical sample; we used the cutoff scores for anxiety as 10 and for depression as 7, in accordance with the previous validity and reliability study (9,10). SF-36 is a multiple-choice, self-reported Likert questionnaire. Increased scores on the SF-36 are related to a better quality of life. SF-36 evaluates 8 categories of health (physical functioning, physical role limitation, social functioning, mental health, vitality, bodily pain, emotional role limitation, and general health perception) with 36 questions (11,12).

Statistical analysis

Continuous data were calculated as mean and standard deviation. We compared the continuous demographic and psychiatric data with the t-test. The categorical data were compared with the Chi-square test. A p-value of below 0.05 was accepted as significant.

RESULTS

We enrolled 80 patients in the study; 7 of whom refused to fulfill the questionnaires at the end of the treatment and were automatically excluded from the study. Out of the total of 80 patients, 45 (61.6%) were female. The mean patient age was 58.90 ± 10.51 years. A total of 18 patients were treatment naïve, 55 had been treated previ-

Table 1. Clinic and demographic data of CHC patients.

Mean Age (years)	58.90±10.51
Gender (n)	
Male	28 (38.4%)
Female	45 (61.6%)
Liver Transplantation (n)	5 (6.8%)
Kidney Transplantation (n)	1 (1.4%)
Previous HCV Treatment (n)	
Treatment Naïve	18 (24.7%)
IFN-α+Rbv	47 (64.4%)
IFN-α+Rbv+Teleprevir/Boceprevir	8 (11.0%)
Genotype (n)	
1a	3 (3.8%)
1b	73 (91.3%)
3	3 (3.8%)
4	1 (1.3%)
Cirrhosis (n)	
Non-cirrhotic	46 (63.0%)
Child A	19 (26.0%)
Child B	8 (11.0%)
Mean Disease Duration (years)	8.00±5.29

Table 2. Comparement of anxiety and depression scores before and after the DAAA treatment.

	Before Treatment (mean±SD)	After Treatment (mean±SD)	p
All Patients (n=73)			
Anxiety (n=73)	7.56±5.05	5.34±3.76	<0.001*
Depression (n=73)	6.84±4.52	5.73±3.93	0.029*
Physical Functioning (n=73)	58.62±32.99	65.89±28.77	0.026*
Physical Role Limitation (n=73)	44.06±43.43	58.56±43.34	0.009*
Bodily Pain (n=73)	61.72±22.90	69.34±19.08	0.011*
General Health (n=73)	45.97±18.93	51.91±21.41	0.017*
Vitality (n=73)	56.12±20.09	58.08±20.21	0.488
Social Functioning (n=73)	65.78±25.75	75.34±21.54	0.006*
Emotional Role Limitation (n=73)	43.33±43.86	60.27±42.54	0.007*
Mental Health (n=73)	61.85±18.62	63.34±16.94	0.714
Female Patients (n=45)			
Anxiety (n=45)	9.28±5.28	6.06±4.28	<0.001*
Depression (n=45)	8.13±4.85	6.15±4.31	0.001*
Physical Functioning (n=45)	51.66±32.59	56.77±28.18	0.266
Physical Role Limitation (n=45)	33.33±40.94	50.55±42.80	0.026*
Bodily Pain (n=45)	56.86±24.40	65.95±20.90	0.024*
General Health (n=45)	43.40±21.22	48.64±21.76	0.113
Vitality (n=45)	51.66±20.56	52.33±20.18	0.846
Social Functioning (n=45)	58.05±27.97	70.83±20.64	0.004*
Emotional Role Limitation (n=45)	43.70±43.12	54.81±42.13	0.145
Mental Health (n=45)	59.20±17.77	60.53±18.57	0.631
Male Patients (n=28)			
Anxiety (n=28)	4.78±3.13	4.17±2.38	0.251
Depression (n=28)	4.78±3.03	5.07±3.17	0.739
Physical Functioning (n=28)	66.96±32.35	80.53±23.50	0.038*
Physical Role Limitation (n=28)	55.35±43.75	71.42±41.78	0.156
Bodily Pain (n=28)	69.32±20.69	74.78±14.47	0.246
General Health (n=28)	49.03±16.61	57.17±20.10	0.073
Vitality (n=28)	63.57±18.40	67.32±16.80	0.387
Social Functioning (n=28)	78.57±18.89	82.58±21.33	0.462
Emotional Role Limitation (n=28)	42.85±47.01	69.04±42.48	0.016*
Mental Health (n=28)	67.85±18.87	67.85±12.99	1.000
Non-cirrhotic Patients (n=46)			
Anxiety (n=46)	7.91±5.70	5.50±4.24	<0.001*
Depression (n=46)	6.86±5.13	6.06±4.10	0.254
Physical Functioning (n=46)	56.95±34.52	67.28±29.28	0.051
Physical Role Limitation (n=46)	45.10±43.65	61.95±43.05	0.033*
Bodily Pain (n=46)	59.95±26.09	70.89±18.44	0.007*
General Health (n=46)	46.71±19.62	50.73±21.87	0.213
Vitality (n=46)	56.30±21.43	56.63±20.76	0.918

Table 2. Comparement of anxiety and depression scores before and after the DAAA treatment. (Continued)

	Before Treatment (mean±SD)	After Treatment (mean±SD)	p
Social Functioning (n=46)	65.48±27.02	76.63±20.85	0.006*
Emotional Role Limitation (n=46)	49.27±45.40	61.59±42.14	0.097
Mental Health (n=46)	59.04±19.52	61.56±18.40	0.427
Cirrhotic Patients (n=27)			
Anxiety (n=27)	6.96±3.73	5.07±2.82	0.015*
Depression (n=27)	6.81±3.35	5.18±3.61	0.017*
Physical Functioning (n=27)	58.51±31.25	63.51±28.27	0.297
Physical Role Limitation (n=27)	36.11±42.36	52.77±44.03	0.133
Bodily Pain (n=27)	64.51±19.06	66.70±20.21	0.627
General Health (n=27)	43.59±19.92	53.92±20.84	0.027*
Vitality (n=27)	56.11±19.13	60.55±19.38	0.363
Social Functioning (n=27)	66.66±26.62	73.14±22.91	0.303
Emotional Role Limitation (n=27)	33.33±41.36	58.02±43.94	0.03*
Mental Health (n=27)	68.44±15.38	66.37±13.91	0.463

*p<0.05 accepted as statistically significant.

Table 3. Patients anxiety and depression scores above and below the cut-off point.

	Before Treatment (n)	After Treatment (n)	p
Depression score above cut-off point	26	26	0.075
Depression score below cut-off point	47	47	
Anxiety score above cut-off point	18	10	0.0001*
Anxiety score below cut-off point	55	63	

*p<0.05 accepted as statistically significant.

ously for CHC, 47 had been treated with interferon-α and ribavirin, and 8 had been treated with telaprevir- or boceprevir-based regimens. Sixty-eight patients (93.2%) had a genotype 1b, 3 (4.1%) had a genotype 1a, 1 (1.4%) had a genotype 3, and 1 (1.4%) had a genotype 4. Forty-six patients (63.0%) were non-cirrhotic, 19 (26.0%) had child A cirrhosis, and 8 (11.0%) had child B cirrhosis. Liver transplantation had been previously performed in 5 patients (6.8%). Hepatocellular carcinoma (HCC) was present in 2 patients (2.7%). Three patients (4.1%) were enrolled in a hemodialysis program and 1 patient (1.4%) had undergone renal transplantation before the treatment (Table 1).

HCV-RNA positivity was found only in 2 patients after the DAAA treatment, both of whom were treated with Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir (OBV/PTV/r+DSV).

All participants completed the HAD and SF-36 questionnaires at the beginning of the treatment and 73 patients fulfilled both questionnaires after completing the treatment. The mean anxiety score was 7.56±5.05 and the depression score was 6.84±4.52 before the treatment, while after the treatment, the mean anxiety score was 5.34±3.76 (n=73) and the mean depression score was 5.73±3.93 (n=73). The pretreatment anxiety and depression scores showed statistically significant differences from the posttreatment scores (p=0.000 and p=0.029, respectively) (Table 2).

We found 18 (24.7%) patients' anxiety score above the cutoff and 26 (35.6%) patients' depression score above the cutoff before treatment. However, 10 (12.5%) patients' anxiety score and 26 (32.5%) patients' depression score was above the cutoff point even after the DAAA treatment. Therefore, this difference was statistically significant for anxiety (p=0.0001) but not for depression (p=0.075) (Table 3).

When we compared the SF-36 subitem results before and after the treatment; a statistical significance was found in the physical functioning (PF) (p=0.026), physical role limitation (PRL) (p=0.009), bodily pain (BP) (p=0.011), general health (GH) (p=0.017), social functioning (SF) (p=0.006), and emotional role limitation (ERL) (p=0.007)

items. Also, an improvement was seen in the vitality (Vt) (p=0.488) and mental health (MH) (p=0.714) items, but it was not statistically significant (Table 2).

The anxiety and depression scores were improved with treatment in the female patients (p=0.0001 and p=0.001 respectively), however, in the male patients, the anxiety score was improved but it was not statistically significant (p=0.251). Interestingly, the depression score got minimally worse after the treatment. All SF-36 sub-scores were improved in the female patients but this was only statistically significant in PRL, BP, and SF (p=0.026, p=0.024, and p=0.004, respectively). In the male patients, the MH sub-score stayed the same after treatment and all the other sub-scores were improved. Improvement in PF and ERL were significant (p=0.038 and 0.016, respectively) (Table 2).

The anxiety and depression scores were improved with treatment in non-cirrhotic patients and this was significant for anxiety scores (p=0.0001). In cirrhotic patients, a significant improvement in anxiety and depression was observed (p=0.015 and p=0.017, respectively). All SF-36 subs-cores were improved in the non-cirrhotic group and this was significant in PRL, BP, and SF (p=0.033, p=0.007, and p=0.006, respectively). Improvement in GH and ERL was also significant in the cirrhotic group (p=0.027 and p=0.030, respectively). However, in the cirrhotic group, the MH sub-score got minimally worse after treatment (Table 2).

DISCUSSION

The anxiety and depression scores were higher in female patients as compared to male patients before treatment, and these scores were significantly decreased after treatment in the female group. Depression, anxiety, and related disorders were more common in females in the general population, and our results were similar to the previous findings (13). Neuroendocrine, sociocultural, and individual factors may affect these scores. An interesting finding of our study was that, contrary to the anxiety score, the depression score got minimally worse in the male group despite improvement in CHC. This alteration may be due to the small size of the male group in our study and low anxiety and depression scores before treatment. Sex differences and psychiatric conditions in the HCV infection-affected population may be an important issue and specific variations should be evaluated in future studies.

The anxiety score significantly improved with treatment in both cirrhotic and non-cirrhotic groups. Anxiety seems to be more sensitive for treatment response in the HCV population. A decrease in anticipatory anxiety may be related to the high treatment success with DAAA. Treatment with DAAA may permanently remove the etiological factor of HCV. Unpredictable complications, difficulty in administering treatment, and intolerance of uncertainty are highly related to anticipatory anxiety (14). Also, according to previous studies, the OBV/PTV/r+DSV regimen is well-tolerated and has strong adherence with a very small burden of psychiatric side effects (15).

Depression is common in patients with HCV who were treated with IFN (8, 16, 17), and in such cases antidepressant drugs are known to cause an improvement in depressive symptoms. To the best of our knowledge, DAAA treatment is superior to IFN with regards to preventing the onset of depression (17). In our study, we used DAAA and not IFN for our patients, thus eliminating a major described risk factor for depression. Intravenous (IV) drug use is a serious risk factor for hepatitis C transmission and it is accompanied by personality problems, high-risk behaviors, mood disorders, and *vice versa* (18). In our study population, there was no IV drug user, which eliminated this confounding factor for psychiatric disorders. However, depression has also been defined as a risk factor for patients with HCV regardless of interferon treatment and substance and alcohol abuse. This correlation was related to the extrahepatic manifestations of HCV in the central nervous system (19, 20). Therefore, the decrease in depression could be due to the elimination of HCV in this study.

The HAD questionnaire is a screening tool for anxiety and depression disorders. According to the previous study, 95.71% of patients, whose HAD score was above the cutoff points, were diagnosed as having a psychiatric disorder and were in need of psychiatric treatment (21). Psychiatric disturbances and emotional distress are common in HCV-infected patients. Elimination of HCV itself may decrease the number of patients who need psychiatric treatment, because in our study, patients with scores above the cutoff point for anxiety showed decreased scores after the treatment (Table 3). Treatment with DAAA resulted in a decrease in both depression and anxiety levels, and also reduced the number of patients who were in need of psychiatric treatment. This alteration might be related to the increased level of physical health after the treatment of HCV with DAAA.

Nearly all the sub-items of the QoL scores were improved after the treatment and these were more common in the

female group. Our results were similar to the previous findings in terms of QoL scores (18). QoL scores may be affected by both mental and physical health, according to bio-psycho-social model. Fatigue, lassitude, impaired concentration, and memory are related to impaired QoL, and these signs and symptoms are commonly observed in patients with chronic HCV infection (16). Thus, the treatment of chronic HCV infection may lead to increased QoL scores due to a direct effect of the treatment. Moreover, higher anxiety and depression scores in the HCV population were related to decreased QoL scores. Improvement in depression and anxiety scores secondary to HCV treatment may have an additive effect on QoL scores in MH parameters of QoL, especially in females.

One of the limitations of this study was the small size of the study population. Further, the psychiatric assessment was based on questionnaires without an interview by a psychiatric specialist. The follow-up duration was short; longer follow-up durations may provide us with better knowledge about psychiatric disorders.

In conclusion; the patients' anxiety, depression, and QoL improved after treatment with DAAA. According to previous studies, this treatment is superior to IFN based regimens in terms of the psychologic perspective. Contrary to female patients, the depression score in male patients was minimally increased, which may be due to the small size of the male group and low anxiety and depression scores before treatment. According to our study, the DAAA treatment improves the depression and anxiety symptoms and also QoL, in addition to improving the state of CHC.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Marmara University School of Medicine.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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REFERENCES

1. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis 2000; 20: 17-35. [CrossRef]
2. Liver EAfSo. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015; 63: 199. [CrossRef]
3. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology 2005; 41: 790-800. [CrossRef]
4. Cho HJ, Park E. Quality of Life of Chronic Hepatitis C Patients and Its Associated Factors. Osong Public Health Res Perspect 2017; 8: 124-9. [CrossRef]
5. Blasiole JA, Shinkunas L, Labrecque DR, Arnold RM, Zickmund SL. Mental and physical symptoms associated with lower social support for patients with hepatitis C. World J Gastroenterol 2006; 12: 4665-72. [CrossRef]
6. Patterson AL, Morasco BJ, Fuller BE, Indest DW, Loftis JM, Hauser P. Screening for depression in patients with hepatitis C using the Beck Depression Inventory-II: do somatic symptoms compromise validity? Gen Hosp Psychiatry 2011; 33: 354-62. [CrossRef]
7. McHutchison JG, Ware JE, Jr., Bayliss MS, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. J Hepatol 2001; 34: 140-7. [CrossRef]
8. Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. Digest Liver Dis 2014; 46: S186-S96. [CrossRef]
9. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-70. [CrossRef]
10. Aydemir Ö, Guvenir T, Kuey L, Kultur S. Validity and reliability of Turkish version of Hospital Anxiety and Depression Scale. Turk Psikiyatri Derg 1997; 8: 280-7.
11. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992; 30: 473-83. [CrossRef]
12. Kocyigit H, Aydemir O, Fisek G, Olmez N, Memis A. Validity and reliability of Turkish version of Short form 36: A study of a patients with romatoid disorder. Turk J Drugs Therap 1999; 12: 102-6.
13. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013; 34: 119-38. [CrossRef]
14. Pagoto S. Psychological co-morbidities of physical illness: a behavioral medicine perspective. New York: Springer; 2011. [CrossRef]
15. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. New Eng J Med 2014; 370: 1983-92. [CrossRef]
16. Monaco S, Mariotto S, Ferrari S, et al. Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. World J Gastroenterol 2015; 21: 11974-83. [CrossRef]
17. Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C. Psychosomatics 2003; 44: 104-12. [CrossRef]
18. Rifai MA, Gleason OC, Sabouni D. Psychiatric care of the patient with hepatitis C: a review of the literature. Prim Care Companion J Clin Psychiatry 2010; 12: PCC.09r00877. [CrossRef]
19. Carta MG, Hardoy MC, Garofalo A, et al. Association of chronic hepatitis C with major depressive disorders: irrespective of interferon-alpha therapy. Clin Pract Epidemiol Ment Health 2007; 3: 22. [CrossRef]
20. Carta MG, Angst J, Moro MF, et al. Association of chronic hepatitis C with recurrent brief depression. J Affect Disord 2012; 141: 361-6. [CrossRef]
21. Yanartas O, Kani HT, Bicakci E, et al. The effects of psychiatric treatment on depression, anxiety, quality of life, and sexual dysfunction in patients with inflammatory bowel disease. Neuropsychiatr Dis Treat 2016; 12: 673-83. [CrossRef]