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Major drivers influencing adherence and quality of life during antiviral triple therapy in patients with chronic hepatitis C

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ABSTRACT
Background & Aims. Triple therapy with Peg-IFNs, Ribavirin and protease inhibitors raise the treatment success for hepatitis C up to 83%, but also bring together with the significantly higher rates of sustained virologic response (SVR) more side effects, interfering with patient's quality of life (QoL) and work productivity. We aimed to analyze the factors influencing the adherence and the QoL during triple therapy using Peg-IFNs, Ribavirin and protease inhibitors in 50 patients diagnosed with chronic hepatitis C with first line therapy failure. Multivariate Cox proportional hazards regression was used to analyze determinants of retreatment initiation and treatment compliance, according to patient features. Results: We identified as major drivers of retreatment initiation the younger age, the female gender, the urban provenience, the high income, and the psychiatric and alcohol or drugs abuse history. The adherence and the QoL during retreatment therapy were similar, despite the regimen used, and obvious lower in patients with history of previous abandon, drugs and alcohol abuse or hematologic/ psychiatric decompensation. A lower capacity to work and a temporary withdrawal from job necessary to continue the therapy were seen similar in patients taking Boceprevir/Telaprevir. Abandon of therapy without a known reason was more frequent in males, with alcohol and drugs intake history, from rural region, with low income, and with psychiatric disturbances in personal history. Conclusion. Physicians should focus to develop medical strategies or drugs to increase the adherence and to provide a better QoL for patients with chronic hepatitis C making antiviral therapy.

Keywords: adherence, quality of life, triple therapy.

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Introduction

Chronic hepatitis C affects 170 mil people and represents a major therapeutic worldwide priority [1]. As the number of available treatments for hepatitis C has increased, so has the chance of patients suffering of this disease to be cured. Still, not all patients who undergo treatment will have success in this direction. Some patients will not respond to current treatment options and will need a new approach to obtain a viral sustained response. These patients are called non-responders or relapsers according to the moment of the viral load decline during or after first line treatment, and triple therapy with Peg-IFNs, Ribavirin and protease inhibitors raise the treatment success up to 75%-83%, and the rate of sustained response with approximately 30-40% [2-5].

The main problem for these patients in front of a new treatment challenge remains the low adherence, the new combination regimens bringing together

with the significantly higher rates of sustained viral response (SVR) more side effects interfering with patient's quality of life (QoL) and work productivity, this being the reason for a secondary low adherence.

The first failure to treatment, the big number of side effects and the medical rules that should be respected during the treatment make understanding the necessity of a new line treatment sometimes difficult. The decision to start a new therapy is hard, and how patients approach it, will have a significant effect upon its success.

Aim

This study aimed to analyze the major drivers influencing the adherence and the quality of life during triple therapy using Peg-IFNs, Ribavirin and protease inhibitors (Telaprevir vs. Boceprevir) in patients diagnosed with chronic hepatitis C or compensate liver cirrhosis, with failure to first line therapy, in correlation with different features: the first line regimen used, the type of response to previous treatment – relapse or non-response, duration of treatment, side effects including severe ones, who imposed treatment dose reduction or discontinuation, socio-demographic data, co-morbidities, personal habits who interfered with the overall adherence to treatment. Our goal was to establish if an expensive and hard to manage therapy should be introduced into the national guideline for treatment in chronic hepatitis C, knowing that new, more potent and less aggressive antiviral therapies are on their way to become gold-standard treatments in whole the world.

Patients and methods

The study was conducted in Gastroenterology Department of Emergency Hospital of Constanta County. Patients enrolled came from several counties from Western, Eastern and South-Eastern Romania.

50 adult patients with chronic hepatitis C or liver compensate cirrhosis with relapse or failure to first line double antiviral therapy were enrolled in the study in order to detect the factors influencing the adherence to a new line therapy. The study enrolment period begun in July 2010 and finished in December 2012. The small number of patients enrolled was caused by the fact that the triple therapy in Romania is not reimbursed completely by the government and all financial resources for treatment with protease inhibitors were private. Multivariate Cox proportional hazards regression was used to analyse determinants of retreatment initiation and treatment compliance, according to patient features.

Eligible patients were males or females with chronic hepatitis C or compensated liver cirrhosis (Child–Pugh score $\leq$7), aged over 18 years, with documentation of a confirmed diagnosis, and of the first line therapy with Peg-IFNs and Ribavirin. Patients were enrolled in the study before treatment initiation or during triple therapy.

We used a paper case report form to extract information from patient charts at the baseline visit. Information recorded was composed of: age, sex, socio-demographic data (type of professional activity, social status and income), disease characteristics, treatment history, current treatment, changes in disease characteristics and changes in hepatitis management, co-morbidities, physical features and activity. Written informed consent was obtained from all participants.

Patients were grouped by baseline treatment status: patients who were under retreatment at the baseline visit – group A (26 patients), and those who were naive to retreatment at the baseline visit – group B (24 patients), and who had begun the triple therapy during the study period.

The two groups of patients were further subdivided according to: type of previous treatment, response to previous treatment (relapsers or non-responders), duration of treatment, side effects during first therapy, severe side effects who required dose reduction or discontinuation, co-morbidities

who required dose modification or discontinuation, non-compliancy to visits or dosage schedules, withdrawal of treatment for unknown reasons. Whatever membership patients were, all of them received detailed explanations about the advantages of a new therapeutic challenge. We noted the decision to initiate a new line treatment with three drugs and the refusal to go through a new antiviral therapy. Patients from group A, in whom retreatment was already initiated at baseline, were followed-up for the compliance to visits schedule, dosages and duration of triple therapy. Were also noted severe side effects that imposed to stop the treatment and the decision of patients to withdrawal the triple therapy due to bad QoL.

We made comparison between the compliances according to treatment regimens, Peg-IFN alfa 2a + Ribavirin +Telaprevir or Peg-IFN alfa 2b + Ribavirin + Boceprevir.

Patients from group B, naive to triple therapy at baseline visit, after a thoroughly analyze of adherence to the first line treatment as we noted before, were questioned about the understanding of retreatment benefits and the desire to follow it. We noted the time duration and number of visits to physician till taking the decision to follow-up the retreatment.

Statistical analyses

Determinants for treatment adherence during the study period were explored by means of a multivariate Cox proportional hazards model. Baseline covariates of patients were: age, sex, socio-demographic data, disease characteristics (chronic hepatitis or compensate liver cirrhosis, co-morbidities who required dose modification or discontinuation, non-compliancy to visits or dosage schedules, withdrawal of treatment for unknown reasons). Baseline covariates of previous treatment were: regimen used, response to previous treatment (relapse or non-response), duration of treatment, side effects during first therapy, severe side effects who required dose reduction or discontinuation. Hazard ratios (HRs), 95% confidence intervals (95%CIs), and associated p-values are reported for each covariate retained in the sample size-adjusted model. All statistical analyses were performed using GraphPadInState and GraphPadStateMate softs.

Results

Baseline demographics and disease characteristics were generally comparable between the two groups (table I). Patients were predominantly females, with a median age of 40 years. The dominant ethnicity was Caucasian (23/26, respectively 22/24). The provenience of patients was more frequently urban (18/26, respectively 17/22). The educational degree of patients was, in general, homogeneous. According to the personal habits, 1/3rd of patients related alcohol intake history, 6% confirmed history of drugs dependency, and 34% confirmed tobacco use (table I).

Table I Demographic data and disease characteristics at baseline:

Patients	**Group A** n=26	**Group B** n=24
Median age (yrs, interval)	39 (19–65)	40 (18–65)
Male (n/%)	12/26 (47.16)	10 (41.66)
Ethnicity (n/%)		
Asian	3/26 (11.53)	2/24 (8.33)
Caucasian	23/26 (88.46)	22/24 (91.66)
Provenience (n/%)		
Urban	18/26 (69.23)	17/22 (77.27)
Rural	8/26 (30/76)	5 (22.72)
Education degree (n/%)		
Primary school	4/26	3/24
High school	11/26	11/24
College	11/26	10/24
Social status and income (n)		
Low (1.000 RON/month)	9/26	8/24
Medium (1.000-3.000 RON/month)	7/26	8/24
High (>3000 RON/month)	10/26	8/24
Personal habits (n/%)		
Alcohol intake	7/26 (26.92)	7/24 (29.16)
Drugs	2/26 (7.69)	1/24 (4.16)
Smoking	10 (38.46)	7/24 (29.16)
Disease characteristics (n/%)		
Chronic hepatitis	24/26 (92.30)	23/24 (95.83)

The combination therapies used were: Peg-IFN alfa 2a + Ribavirin in 29 (58%) of patients and Peg-IFN alfa 2b + Ribavirin in 19 (42%) of patients. According to the response to first line therapy, there were more patients retreated with relapse then patients

with non-response, in both groups studied (p=0.0467, respectively p=0.044). According to the regimen used, more patients treated with Peg-IFN alfa 2a + Ribavirin had failure to treatment (p=0.0291; CI95%, 5-49). The side effects altering the QoL were present in 66% of treated patients, whatever regimen used. Severe side effects requiring reduction of doses or withdrawal were present in 12% of cases. The alcohol and drug intake were more frequent correlated with patients who were unreasonable unable to finish the treatment, demonstrating that history of alcohol or drugs can be a reason of non-adherence to antiviral therapy (p=0.0283; CI95%, 12-45; respectively, p=0.0117; CI95%, 1-38). Smoking was not a significant risk factor associated with decrease of adherence (p=0.721). Non-compliancy to visits or dosage schedules was more frequent in patients with poor social state (low income, and low degree of education – p=0.0231; CI95%, 2-33) and also in patients with alcohol or drug intake and history of psychiatric disorders (p=0.0231; CI95%, 1-48). Most frequently recorded co-morbidities who interfered with treatment completion were: cardiovascular diseases, especially arterial hypertension in 14 patients (28%), depression in 8 patients (16%) and haemolytic anaemia in 6 patients (12%).(Table II).

Boceprevir or Telaprevir plus Ribavirin (RBV) and Pegylated Interferon-α (Peg-IFN-α) is the new standard of care therapy for patients who are chronically infected with genotype 1 hepatitis C virus (HCV) already treated by double therapy or naïve to treatment [6].

The addition of protease inhibitors to the RBV/ Peg-IFN-α combination regimen has significantly improved rates of sustained viral response (SVR). Our observational study followed two types of patients, according to initiation moment of therapy, prior or after baseline visit, this split being utile, on one hand, to follow more patients, inclusively patients who already started therapy, and, on the other hand, to detect features who interfere with the decision to initiate a new antiviral therapy and features who interfere with the quality of life during treatment (Table II).

Table II. Patients first line therapy characteristics:

Patients	**Group A** (n=26)	**Group B** (n=24)
Type of response to first therapy (n/%)		
Relapse	18 (69.23)	17 (70.83)
Non-response	8 (30.76)	7 (29.16)
Type of previous treatment (n/%)		
Peg-IFN alfa 2a+Ribavirin	16/26 (61.53)	13/24 (53.16)
Peg-IFN alfa 2b+Ribavirin	10/26 (38.46)	11/24 (45.83)
Duration of treatment	7 mo±18 dy	8 mo±8 dy
Side effects during first therapy altering the QoL (n/%)	18/26 (69.23)	15 (62.50)
Severe side effects that required dose reduction or discontinuation (n/%)	3/26 (11.53)	3/24 (12.50)
Non-compliancy to visits or dosage schedules (n/%)	7/26 (26.92)	4/24 (16.66)
Withdrawal of treatment for unknown reasons (n/%)	3/26 (11.53)	5/24 (20.83)
Co-morbidities that required dose modification or discontinuation (n/%)		
Cardiac	7/26 (26.92)	7/24 (29.16)
Respiratory	1/26 (3.84)	0/24 (0.00)
Psychiatric (depression)	5/26 (19.23)	3/24 (12.5)
Diabetes mellitus	2/26 (7.69)	1/24 (4.16)
Neurologic	1/26 (3.84)	2/24 (8.33)
Hematologic	5/26 (19.23)	4/24 (16.66)
Other	2/26 (7.69)	1/24 (4.16)

Patients from group B, in whom the triple therapy was proposed at baseline, was the group who raised our interest in studying the first impact in front of a new therapeutic challenge. The age over 40 years old was a major factor that significantly postponed or influenced the patient's decision to retreat. The time spent to provide information about treatment and to take decision to initiate retreatment was longer than in younger patients (4-8 medical visits vs. 2-3 visits, p=0.031; respectively, 3months ± 7days vs. 2 weeks ± 3days, p=0.030). The gender influenced also the decision to retreat. More females than males were interested to retreat their liver disease (28 vs. 22). The treatment initiation was done in more patients without any history of alcohol abuse or drug intake (p=0.0351; CI95%, 11.98-44.51). According to provenience and income status, more patients from urban, with medium and high income agreed to initiate the retreatment sooner, probably due to more

possibilities of information about the retreatment options (p=0.0337; 95%CI, 4.66-44.56).

Patients that finished the retreatment during the study period were monitored according to compliance to visit schedule and dosages. Adherence and full compliance to treatment were more frequent in patients without history of alcohol or drugs abuse and with high degree of education or income (p=0.0266; 95%CI, 0.26-44.19). More patients with low adherence to first line therapy fail to accomplish the treatment schedule or to finish the therapy (p=0.0228; 95%CI, 2.47-39.01). Decompensation of psychiatric diseases during first line therapy was also present during second line therapy and was an important reason for low compliance to retreatment (p=0.0334; CI95%, 6.78-49.00) (table II).

According to the second antiviral regimen used, the addition of Telaprevir to the standard double therapy increased the number of most common adverse events including fatigue (n=9, 56.25%), rash (n=10, 63%), pruritus (n=8, 50%), anemia (n=9, 32%), diarrhea (n=3, 20%), and nausea (n=5, 31.25%). The most common adverse event in the Telaprevir group was rash (overall, occurring in 63% of patients, with severe rash in 8%) [2]. As an inhibitor of cyp3a4 and of p-glycoprotein, Telaprevir was responsible for drug interactions [7]. In patients taking anticonvulsivants (phenytoin, carbamazepin), benzodiazepine (midazolam, alprazolam), antihypertensive drugs (lecarnidipine), or PPIs (Omeprazole, Esomeprasole, Lansoprasole) were noted more frequent discontinuations or withdrawal of therapy, due to decompensation of co-morbidities (p=0.0311; 95%CI, 1.22-46.34).

On the other hand, Boceprevir based regimen, a protease inhibitor that binds to the nonstructural 3 active site of the virus, was responsible for more gastrointestinal side effects including nausea (n=15, 44.11%), dysgeusia (n=18, 52.94%), diarrhea (n=8, 23.52%), vomiting (n=7, 20.58%), general side effects such as fatigue (n=20, 58.82%), chills (n=11, 32.35%), and altered general status (n=22, 64.70%). More important in Boceprevir group were hematologic side effects: anemia (n=13, 39%), neutropenia (n=20, 55.82%), and thrombocytopenia (n=3, 7%). Frequent psychiatric side effects altering the QoL were insomnia (n=11, 32.35%), irritability (n=7, 20.58%), and decompensation of depression (n=8, 23.52%). Were also noted respiratory side effects: dyspnea (n=4, 11.76%), and respiratory infections, some of them responsible for temporary discontinuation of antiviral therapy (pneumonia, n=2, 6.8%) (table III).

Table III. Comparison of adherence and side effects altering the QoL during the second line therapy, according to regimen used:

Regimen used	**4 weeks PEG-IFN-α + RBV lead-in + 44 weeks BOC + PEG-IFN-α + RBV (n=34/%)**	**12 weeks TPV + PEG-IFN-α + RBV + 36 weeks PEG-IFN-α + RBV (n=16/%)**
Compliance to triple therapy (n/%)		
Visits schedule	27/34 (79.41)	11/16 (68.75)
Dosages	30/34 (88.23)	11/16 (68.75)
General side effects occurred during triple therapy altering the QoL (n/%)		
Disgeusia	18/24 (52.94)	7/16 (43.75)
Rash	4/24 (11.76)	10/16 (62.50)
Altered general status	24/24 (70.58)	11/16 (68.75)
Flulike symptoms	26/24 (76.47)	12/16 (75.00)
Digestive symptoms	28/24 (82.35)	12/16 (75.00)
Weight loss	19/24 (54.28)	10/16 (62.50)
Other	8/24 (23.52)	6/16 (37.50)
Hematologic severe side effects who required dose reduction, discontinuation or GM-CSF (n/%)		
Leucopenia	7/24 (20.58)	3/16 (18.75)
Anemia	5/24 (15.00)	2/16 (12.25)
Severe thrombocytopenia	1/24 (2.94)	1/16 (6.25)

Overall, withdrawal of therapy because of severe adverse events was more frequent in the Telaprevir group than in Boceprevir group (n=2, 12.50% vs. n=3, 8.82%). Half of the patients (n=8, 50%) receiving Telaprevir experienced a serious adverse event compared to 1/3rd of those treated with Boceprevir (n=11, 32.35%). Hematologic side effects and subsidiary symptoms were the most common side effects that imposed discontinuation or withdrawal of triple therapy. Moderate anemia (8.0-10.0 g/dl) occurred in 20% of patients (n=4) treated

by Telaprevir and 24% of patients (n=8) receiving Boceprevir (p>0.05, ns). Severe anemia (<8.0 g/dl) was observed in 12% (n=2) of those taking Telaprevir, and 15% (n=5) of patients treated with Boceprevir (p>0.05, ns). Erythrocytes growth factor was used for anemia correction in 37.5% (n=6) of Telaprevir patients, and 38.23% (n=13) of Boceprevir treated patients (p>0.05, ns). Severe thrombocytopenia (<50,000/mm3) required blood transfusions in 6.25% (n=1) of Telaprevir treated patients, and in 3% (n=1) in patients treated with Boceprevir regimen. Moderate neutropenia (<1.000/mm3) was observed in 31.25% (n=5) of Telaprevir and 38.23% (n=13) of Boceprevir treated patients (p=0.0344; 95%CI, 13.25-44.34). Severe neutropenia (<500/mm3) requiring stimulation of bone marrow with granulocyte/macrophage-colony stimulating factors (GM-CSF) was present in 18.75% (n=3) of Telaprevir group, and 20.58% (n=7) of Boceprevir group (p<0.05, ns). 6.25% (n=1) of Telaprevir treated patients and 11.76% (n=4) of Boceprevir group were temporary discontinued from therapy due to neutropenia (p=0.0447; 95%CI, 9.66-34.86) (table III).

A bad QoL and the secondary implication on work capacity were the most common reasons for therapy withdrawal. Severe rash and pruritus in Telaprevir treated patients, and disgeusia in Boceprevir treated patients were the most common side effects who were responsible for therapy withdrawal (p=0.0369; 95%CI, 22.22-48.22; respectively, p=0.0229; CI95%, 11.91-36.72). On the other hand, the capacity of work was influenced by the antiviral medication. 12.5% of patients (n=2) taking Telaprevir, and 8.82% of patients (n=3) taking Boceprevir temporarily dropped the work to continue the therapy.

Therapy abandon without an apparent reason was seen more frequently in patients with history of alcohol and drugs abuse (p=0.0221), male gender (p=0.0345), rural provenience (p=0.0119), low income (p=0.0371), decreased education status (p=0.0334), and psychiatric diseases (p=0.0290), despite the therapeutic regimen used (p>0.05, ns) (Table III).

Discussions

Improvements in adherence to treatment require sometimes lot of medical interventions and social support. The difficult posology, the big number of side effects accompanying the triple therapy in chronic hepatitis C and the successive bad quality of life during therapy are the major drivers that influence the adherence to retreatment. One of the most important elements in this equation that influence the adherence behaviour is determined by the complicated administration of medication. The big number of tablets that patients should take can reach 18 per day in Boceprevir regimen, for example. Simplifying the dosage regimen can be one of technical solutions for retreated patients with chronic hepatitis C to increase the compliance to therapy. Most reviewers who studied the adherence to treatment in a variety of medical disorders and pathologies arrived at the same conclusion that a less frequent dosage results in better adherence [8, 9-13]. The only one exception to this rule is depression; the number of anti-depressant drugs does not seem to be related to the number of drop-outs [13, 14]. On a meta-analysis on adherence of 56 primary studies who explored the adherence related to number of tablets taken per day, Buring et al. showed that adherence rates were higher with regimens containing three or fewer doses a day, compared to four to six doses a day ($p = 0.001$), seven to eleven ($p = 0.009$) or 12 or more ($p < 0.0001$) [9, 14]. Adherence appears to decline as the number of daily doses increase. Claxton et al. [8] showed that adherence to one dose is 79%, two doses 69%, three doses 65% and four doses 51%. There is strong evidence showing that simplifying medication dosage schedules we can improve adherence [15]. Long releasing or combined formulations of two or more drugs in one package or tablet can be one solution to improve the hardness of taking many tablets per day.

Our study results and literature information relate the low adherence to therapy in hepatitis C re-treated patients less with the complicated administration of treatment, but especially with the big number of side effects and the subsequent low

quality of life during therapy. Side effects alter the capacity to work properly. A meta-analysis of 122 studies conducted by DiMatteo demonstrated that practical social support of patients during any type of treatment can improve the adherence [16]. In the particular case of patients retreated for hepatitis C, the incapacity to conduct their professional and social activity due to side effects requires familial support and special social measures.

Regarding the social and professional implication of retreatment, patients should be supported by appropriate authorities to reduce the number of work hours or to temporary quit the job without any consequence. In our study, 12.5% of patients (n=2) taking Telaprevir, and 8.82% of patients (n=3) taking Boceprevir temporarily dropped the work to continue the therapy. On the other hand, the bad QoL and the secondary implication on work capacity were the most common reasons for therapy withdrawal. Severe rash and pruritus in Telaprevir treated patients, disgeusia and hematologic disturbances in Boceprevir treated patients were the most common side effects who were responsible for therapy withdrawal ($p=0.0369$; 95%CI, 22.22-48.22; respectively, $p=0.0229$; CI95%, 11.91-36.72).

In terms of medical care, supportive medication decreasing the intensity of side effects such as leucopenia with GM-CSF, anemia with erythrocytes growth factors, the medical advice and the collaborative care can improve the adherence to retreatment by raising the patient's QoL [17]. Our study results showed that severe neutropenia (<500/mm3) requiring stimulation of bone marrow with granulocyte/macrophage-colony stimulating factors (GM-CSF) was present in 18.75% (n=3) of Telaprevir group, and 20.58% (n=7) of Boceprevir group ($p<0.05$, ns). Also, erythrocytes growth factor was used for anemia correction in 37.5% (n=6) of Telaprevir patients, and 38.23% (n=13) of Boceprevir treated patients ($p>0.05$, ns). Severe thrombocytopenia (<50,000/mm3) required blood transfusions in 6.25% (n=1) of Telaprevir treated patients, and in 3% (n=1) in patients treated with Boceprevir regimen. All these disturbances should be guided and managed by care providers, in order to improve, as good as possible, the QoL during the complicated and side effects producing therapy.

Collaborative care, defined as an approach improving patient education through health suppliers, such as nurses in primary care, can play an active role in adherence to retreatment [14, 17]. In our study, the therapy abandon without an apparent reason was seen more frequently in patients with history of alcohol and drugs abuse ($p=0.0221$), male gender ($p=0.0345$), rural provenience ($p=0.0119$), low income ($p=0.0371$), decreased education status ($p=0.0334$), and psychiatric diseases ($p=0.0290$), despite the therapeutic regimen used ($p>0.05$, ns). Health professionals or other care providers can increase the patient's acknowledgments about the life style rules during treatment.

Still, all the above measures to improve the adherence and the QoL of hepatitis C patients treated with triple therapy using Pegylated Interferons, Ribavirin and first generation of protease inhibitors require lots of medical efforts and consistent financial support. The spectacular results already communicated in the recent liver meetings change our directions to interferon-free therapies in hepatitis C management. The patient's QoL and the subsequent adherence to treatment could be improved by the new therapeutic challenge.

Conclusions.

This observational study identified as major drivers of retreatment initiation in patients with chronic infection with C virus younger age, female gender, urban provenience, high income, psychiatric history, and alcohol or drugs abuse. The adherence during treatment and the quality life during the retreatment were similar despite the regimen used and obvious lower in patients with history of previous abandon, drugs and alcohol abuse, hematologic and psychiatric decompensation, presence of side effects altering the QoL and capacity to work. Abandon of therapy without any known reason was more frequent in males, with alcohol and drugs intake history, from rural region, with low income or with psychiatric

history. Our study results, next to similar literature information, should focus researchers and physicians to develop medical strategies and new guidelines in order to provide a better quality of life and to increase adherence to antiviral therapy in chronic hepatitis C patients.

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