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Evaluation of health status in patients with hepatitis c treated with and without interferon

R. Ragusa^{1*} , G. Bertino², A. Bruno³, E. Frazzetto⁴, F. Cicciu⁵, G. Giorgianni⁵ and L. Lupo⁶

Abstract

Background: The evolution of technology in healthcare has increased the health care's costs and, the universal healthcare systems, in developed countries, need to ensure proper allocation of resources. Thus, the major issue is assessing the effectiveness of new medical technologies. The evaluation of quality of life in response to new treatments has become a key indicator in chronic conditions for which medical interventions are evaluated not only in terms of increasing the number of expected life years but also in terms of increasing quality of life. The aim of this observational study was to verify whether a simple instrument (EQ-5D-5 L) can capture variations in health-related quality of life (HRQoL) and allow us to evaluate the impact of different drug treatment protocols in patients with hepatitis C virus (HCV) on daily activities.

Methods: Sixty six patients with HCV were consecutively enrolled in the Hepatology Unit at the University Hospital of Catania "G. Rodolico". Sixteen patients received new direct-acting-antiviral agents (DAAs) plus pegylated alpha interferon (Peg- α -IFN) protocol (Group A) and 50 DAAs IFN free protocol (Group B). The EQ-5D-5 L[®] questionnaire and visual analog scale (VAS) were given to both groups to calculate coefficient's utility. We used the EQ-5D-5 L Crosswalk Index Value Calculator to obtain the utility EQIndex and both parametric and non parametric tests for the statistical analysis.

Results: The biopsy taken at the beginning of treatment showed comparable cell damage in both groups. The difference in the VAS results was negative for patients who received protocols containing IFN (indicating decreased quality of life), whereas it was positive in patients treated with IFN-free protocols. The baseline EQIndex did not reveal any differences between the two treatment groups. The post-treatment EQIndex was statistically better in the groups that received IFN-free therapy.

Conclusions: When innovative treatments are introduced into clinical practice, assessing quality of life is mandatory to determine their benefits. The instruments used in the present study are effective in detecting the areas in which improvement has occurred. These instruments can be easily managed by general practitioners for follow up of progression of the disease and referred to the specialist.

Keywords: Direct-acting antiviral agents (DAAs), Quality of life (QoL), Interferon (IFN), Hepatitis C, EQ-5D-5 L, EQIndex, Visual analog scale, Questionnaire

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Background

The evolution of technology has increased the health care's costs and the universal healthcare systems need to ensure proper allocation of resources. Thus, the major issue is assessing the effectiveness of new medical technologies [1, 2]. Benefits must be measured by criteria other than survival (efficacy) alone. In particular, in chronic conditions improvement in quality of life (QoL) has become a valuable indicator for determining the costs and benefits of new treatments [3–6]. Health-related QoL (HRQoL) is considered to represent the set of qualitative aspects of an individual's life that are related to the domains of health and disease and therefore modifiable by medicine [7].

The EQ-5D is a standardized measure of health status that provides a simple measure of health for clinical and economical appraisal [8–12]. It is composed of a questionnaire and a visual analog scale (VAS), which are used to calculate utility coefficients (EQ index). The 5D-5 L is the latest version used in cost-utility analyses and is better than the previously used EQ-3D-3 L or EQ-5D-3 L [13, 14]. Quality-adjusted life years (QALYs) can be determined by the EQ index for one-year intervals. A QALY of 1 corresponds to a life expectancy of one year in good health; a value of 0 corresponds to death.

The EQ index can also represent HRQoL, which includes multidimensional functional, subjective, emotional and overall well-being indicators of an individual's overall health status. The latter has become an important outcome measure in the evaluation of chronic disease management over the past 20 years [15–18].

The aim of this work was to assess the effect of two different drug treatment protocols (new direct-acting antiviral agents) with and without interferon (IFN) on QoL in patients with hepatitis C through EQ index calculations. We intend to evaluate the ability of this simple but non-specific instrument to detect the differences in clinical criteria that are due to the different treatments and the feasibility of utilizing this tool in clinical practice.

Methods

Subjects and setting

Sixty six patients who were diagnosed HCV disease eligible for treatment, by regional referral center at the Hepatology Unit of the University Hospital "G. Rodolico" in Catania, were consecutively enrolled from May 2014 to January 2016.

Sixteen of them were treated with DAAs plus Peg- α -IFN (Group A) and 50 received DAAs IFN free protocol (Group B). Both groups were administered EQ-5D-5 L questionnaire before (subgroup1) and at the end of the treatment (subgroup 2).

Informed consent was previously obtained by each patient.

For inclusion in this study, patients had to be adults over 18 years old with a history of viral chronic liver disease (CLD) due to HCV and with no history of any of the clinical features of encephalopathy. All patients had chronic fibrosis (level III-IV) at biopsy.

Patients with mental disorders or dementia were excluded. Individuals with concomitant comorbidities such as heart failure, chronic renal failure, chronic obstructive pulmonary disease, malignancy and inflammatory bowel disease (ulcerative colitis and Crohn's disease) were also excluded.

Patients followed two different protocols of treatment with direct-acting antiviral agents due to the different timing of marketed products. Until October 2015, patients were consecutively treated with direct-acting agents plus IFN. Afterward, new IFN-free direct-acting drugs became available in Italy. Sixteen patients (group A) were treated with Boceprevir or Telepravir plus Peg- α -IFN and ribavirin. Fifty patients (group B) were treated with the new IFN-free direct-acting antiviral agent (DAAs) protocols (Sofosbuvir, Simeprevir, Ombitasvir/ Paritaprevir/ Ritonavir + Dasabuvir, Daclatasvir) for 12 weeks. Seven patients in group A received IFN + Boceprevir and 9 received IFN + Telaprevir. Ten patients in group B received Sovaldi (Sofosbuvir + Ribavirin; 31 received Olisyo (Simeprevir + Sofosbuvir), 5 received Viekirax + Exviera) and 4 received Daklinza (Daclatasvir).

We administered the EQ-5D-5 L questionnaire and VAS to both groups during a face-to-face interview, before and three months after the end of treatment. The EQ-5D-5 L questionnaire was administered by two different referrals in a waiting room inside the clinic and was administered in the patient's native language.

Instruments

EQ-5D is a standardized instrument developed by EuroQol Group that is used to measure a patient's health status as a single index value [19]. The EQ-5D-5 L version consists of 2 pages: the EQ-5D descriptive system and the EQ-VAS.

The EQ-5D-5 L descriptive system is a self-administered standardized questionnaire that includes five dimensions, each with 5 levels (Fig. 1). The EQ-5D-5 L is an indirect method for measuring a patient's health status. The EQ-5D-5 L descriptive system comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has the following 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The respondent is asked to indicate his/her health status by ticking (or placing a cross in) the box next to the most appropriate statement in each of the 5 dimensions. In the EQ-5D-5 L, as each dimension has five levels [1 to 5], scores range from 1-11-1-1 (best health) to 5-55-5-5 (worst health).

Under each heading, please tick the ONE box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about

I have slight problems in walking about

I have moderate problems in walking about

I have severe problems in walking about

I am unable to walk about

SELF-CARE

I have no problems washing or dressing myself

I have slight problems washing or dressing myself

I have moderate problems washing or dressing myself

I have severe problems washing or dressing myself

I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

PAIN/DISCOMFORT

I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

ANXIETY/DEPRESSION

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

Fig. 1 EQ-5D-5 L Questionnaire (UK sample version)

The EQ-VAS (Fig. 2) is also an integral part of the EQ-5D-5 L. The VAS is a continuous scale on which a cross along the line is directly marked by the patient according to his/her perceived health status. The VAS is a thermograph-like 20-cm linear scale rated from 0 (the worst imaginable health) to 1 (the best imaginable health). Subjects are asked to mark the scale according to their current health status, and the fraction to unity is reported. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

Both instruments (the Eq-5D-5 L descriptive system and EQ-VAS) are combined to obtain the utility EQ index for each subject using the crosswalk link function [20].

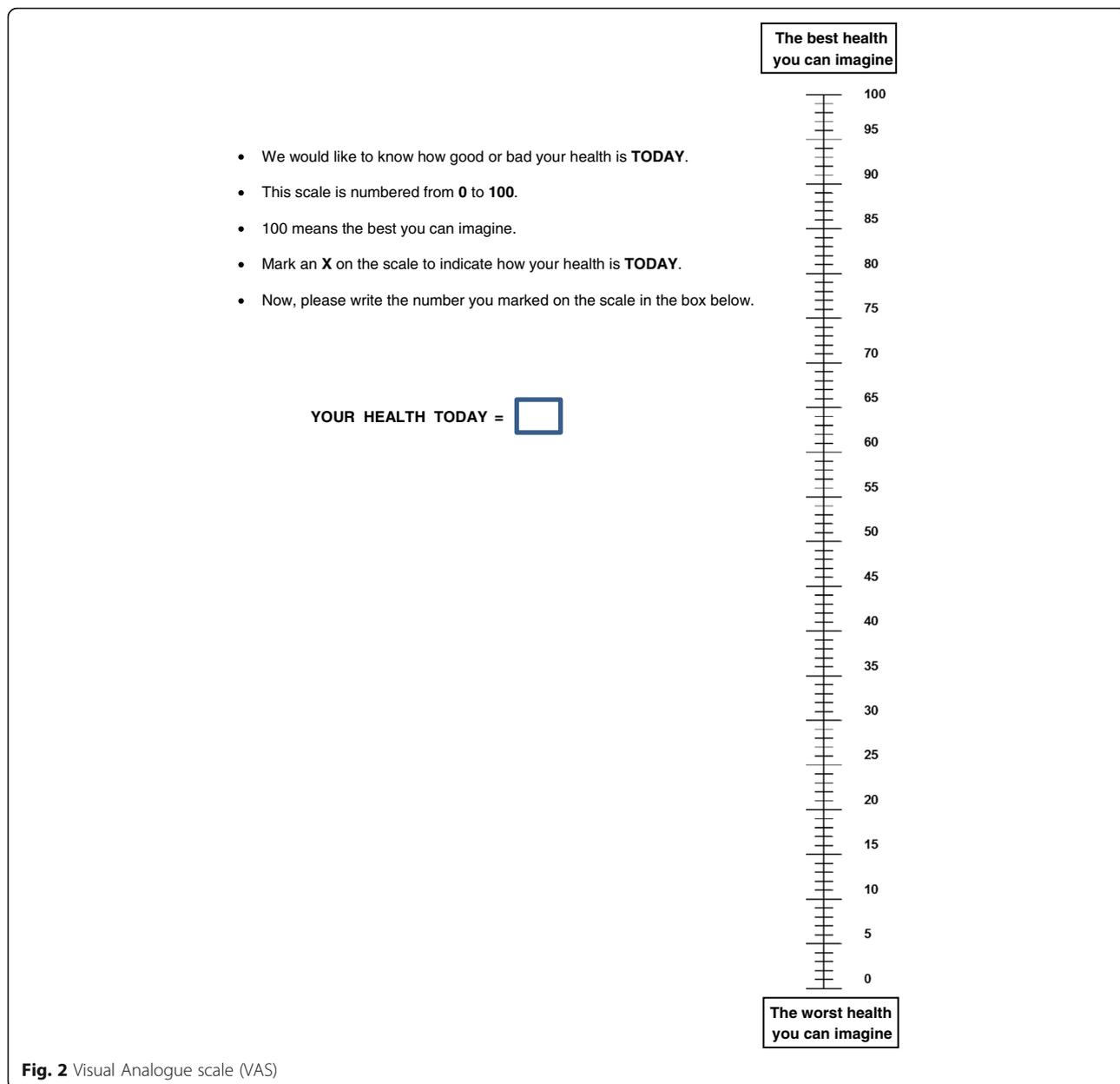
Analysis

There are country-specific combinations of either EQ-5D-5 L datasets or reported VAS values into a single

index value (EQ index). Since no specific Italian combination data sets exist, we decided to adopt the Spanish dataset, which was the closest available dataset. However, because we wanted to examine the differences within each subject before and after treatment, no bias can be attributed to the use of the Spanish dataset.

Using the crosswalk link function and the individual responses to the EQ-5D-5 L descriptive system, index values for the EQ-5D-5 L were calculated. Documents containing information on the crosswalk project, tables of values for all 3125 health statuses and the ‘EQ-5D-5 L Crosswalk Index Value Calculator’ can be downloaded from the EuroQol website [21].

The mean values and standard deviations (SDs) of the differences in the VAS and EQ indexes of the two different treatment groups were calculated.



We used a paired Student’s t-test to compare the pre- and post-treatment paired VAS data between the two subgroups of group A (IFN treatment) and the two subgroups of group B (IFN-free treatment) using a 5% two-sided significance level.

An unpaired Student’s t-test was used to compare the EQIndex values obtained in the two groups at the end of treatment.

Results

A total of 128 questionnaires were administered. The complete results refer to 16 patients from group A and

46 patients from group B. Four patients from group B did not complete the second questionnaire. In group A, 68% of the patients were males and 32% were females, whereas in Group B 58% were males and 42% were females. The average age of patients was 59 years in both groups Table 1 shows the homogeneous distribution of the patients by age and group.

The average time taken to administer the test was 7 min. All of the patients understood the questions and quickly indicated an answer, suggesting that reporting the perceived health status as shown in the graph was simple and intuitive.

Table 1 Distribution patients by age and group

Age (years)	31–40	percent	41–50	percent	51–60	percent	61–70	percent	> 71	percent
Group A	0	/	3	19%	5	31%	6	37%	2	13%
Group B	3	6%	8	16%	16	33%	12	25%	11	22%

The data were later input into the program 'EQ-5D-5 L Crosswalk Index Value Calculator,' which had previously been downloaded from the EuroQol website.

Table 2 shows the replies for the 5 dimensions of the questionnaire in the two groups of patients who underwent the different therapies. The table shows the percentage of patients with NO problems (level 1) and the percentage of patients with no problems for each of the 5 dimensions of the questionnaire. The comparisons are made within each treatment and between the groups. The data are reported as the percentage of the total.

The percentage of patients with NO problems decreased in three of the dimensions (self-care, pain/discomfort, and anxiety/depression) in group A, whereas the percentage of patients with NO problems increased in four of the dimensions (mobility, self-care, usual activity and pain/discomfort) in group B. The percentage of patients receiving IFN-free therapy (group B) who reported anxiety/depression remained unchanged, whereas the percentage of patients reporting anxiety/depression more than doubled in group A.

Table 3 and Table 4 show the frequencies of the five dimensions in the different groups.

The descriptive statistics, including the means, standard deviations and ranges of the EQ-VAS analyses in the two groups pre- and post-treatment are presented in Table 5. We used a paired Student's t-test to compare the pre- and post-treatment paired VAS data between the two subgroups of group A (IFN treatment) and the two subgroups of group B (IFN-free treatment). By

comparing the mean of the differences before and after treatment in group A, we found no significant difference (t_{n-1} 1,64). By comparing the mean of the differences before and after treatment in group B, we found a significant difference (t_{n-1} 3816) ($P < 0.01$).

A non parametric sign test was also performed in order to evaluate the direction of the differences in the VAS score of each patient before and after treatment both in Group A and Group B.

While there was no significant differences between those who gave a better answer in VAS score after treatment in group A, we found highly significant difference in those who reached a higher VAS score (45.6%) after treatment in Group B, while only 6.5% signed a worse score.

The EQ Index for each patient in both groups before and after treatment and the averages, standard deviations, medians, and 25th and 75th percentiles in the various groups were calculated. The descriptive statistics for the EQ Index analysis in the two groups pre- and post-treatment are shown in Table 6.

The average EQ Index before treatment was 0.82 in group A and 0.81 in group B. There was no significant difference. We used an unpaired Student's t-test to compare the post-treatment EQIndex values between groups A and B, and the t_{n-2} value obtained was 2.40 ($P < 0.02$).

The difference between the means of the EQ INDEX values before and after treatment in Group A was -0.111; the difference between the means of the EQ INDEX values before and after treatment in Group B

Table 2 Frequency of reporting of problems in both group of treatment

		Group A				Group B			
		PRE	(%)	POST	(%)	PRE	(%)	POST ^a	(%)
MOBILITY	NO Problem	10	62	10	62	29	58%	33	72%
	Problem	6	38	6	38	21	42%	13	28%
SELFCARE	NO Problem	13	81	11	69	46	92%	42	91%
	Problem	3	19	5	31	4	8%	4	9%
USUAL ACTIVITY	NO Problem	8	50	8	50	34	68%	37	80%
	Problem	8	50	8	50	16	32%	9	20%
PAIN/DISCOMFORT	NO Problem	7	44	6	37	27	54%	32	70%
	Problem	9	56	10	63	23	46%	14	30%
ANXIETY/DEPRESSION	NO Problem	7	44	2	12	35	70%	35	76%
	Problem	9	56	14	88	15	30%	11	24%

^aFour patients did not complete the second questionnaire

Table 3 Frequencies of the five levels for each dimension in the Group A pre and post treatment

EQ-5D DIMENSION	LEVEL 1 (%)		LEVEL 2 (%)		LEVEL 3 (%)		LEVEL 4 (%)		LEVEL 5 (%)		PRE n.16
MOBILITY	10	62	4	25	2	13	0	/	0	/	
SELFCARE	13	81	3	19	0	/	0	/	0	/	
USUAL ACTIVITY	8	50	7	44	1	6	0	/	0	/	
PAIN/DISCOMFORT	7	44	4	31	5	25	0	/	0	/	
ANXIETY/DEPRESSION	7	44	6	37	3	19	0	/	0	/	
EQ-5D DIMENSION											
MOBILITY	10	62	4	25	2	13	0	/	0	/	POST n.16
SELFCARE	11	69	5	31	0	/	0	/	0	/	
USUAL ACTIVITY	8	50	5	31	3	19	0	/	0	/	
PAIN/DISCOMFORT	6	37	3	19	3	19	4	25	0	/	
ANXIETY/DEPRESSION	2	13	8	50	5	31	0	/	1	6	

was 0.062. The averages of the differences obtained in the group A and the group B showed a statistically significant difference ($P < 0.0001$).

Discussion

The availability of DAAs enables highly efficacious treatment of chronic HCV infection [22]; however, whenever a new drug is approved, particularly if it is a high-impact therapy, an economic assessments should be performed to determine whether the medication will produce real health benefits for patients and cost savings for the healthcare system [23–26].

Previous studies on the HRQoL of patients treated for HCV infection have used specific questionnaires [27–30]. We wanted to determine whether a non-specific questionnaire could provide QoL data in patients with the same disease who are treated with different regimens.

In patients with liver damage caused by HCV, once the viral infection is eradicated, the mode and duration of patient monitoring are determined by the degree of impairment of the liver before treatment. Thus, if the patient was cirrhotic, he or she should continue the

treatment protocol and be monitored for complications of liver cirrhosis for approximately 2 years, after which the HCV surveillance protocol will end.

The patients included in our study completed the questionnaire before beginning treatment and three months after the end of treatment to investigate decrements in everyday functional health status and general health perception.

In the group B (IFN-free treatment), the increase in the EQ-VAS after treatments with DAAs was statistically significant. The perceived QoL decreased in the patients treated with IFN while improved in patients treated with IFN-free therapy.

The EQ Index was comparable between the two groups of patients before treatment: the two treatment groups included patients with the same disease characteristics. There was no difference between the EQ index in the subjects who received Telaprevir and Boceprevir. In addition, there was no difference between the EQ index in the subjects who received Sofosbuvir and Simeprevir.

We compared the post-treatment values, and the values for the patients who received IFN treatment were

Table 4 Frequencies of the five levels for each dimension in the Group B pre and post treatment

EQ-5D DIMENSION	LEVEL 1 (%)		LEVEL 2 (%)		LEVEL 3 (%)		LEVEL 4 (%)		LEVEL 5 (%)		PRE n.50
MOBILITY	29	58%	12	24%	5	10%	3	6%	1	2%	
SELFCARE	46	92%	1	2%	2	4%	0	0%	1	2%	
USUAL ACTIVITY	34	68%	10	20%	4	8%	1	2%	1	2%	
PAIN/DISCOMFORT	27	54%	17	34%	2	4%	3	6%	1	2%	
ANXIETY/DEPRESSION	35	70%	11	22%	1	2%	3	6%	0	0%	
EQ-5D DIMENSION											
MOBILITY	33	72%	5	11%	7	15%	0	0%	1	2%	POST n.46
SELFCARE	42	91%	2	5%	1	2%	0	0%	1	2%	
USUAL ACTIVITY	37	80%	4	9%	3	7%	1	2%	1	2%	
PAIN/DISCOMFORT	32	70%	7	15%	6	13%	1	2%	0	0%	
ANXIETY/DEPRESSION	35	76%	8	18%	2	4%	1	2%	0	0%	

Table 5 Values of EQ-VAS analysis in the two groups pre and post treatment

EQ VAS	Group A		Group B	
	PRE	POST	PRE	POST
Mean	66.6	62.2	74.1	80.1
SD	15	12.8	19.9	17
Median	67.5	60	80	80
25th	50	50	60	71.25
75th	76.25	72.5	90	90
t test	$(P > 0.05)$		$(P < 0.001)$	
sign test	$(P > 0.05)$		$(P > 0.001)$	

significantly lower than those for the patients who received IFN-free treatment.

Therefore, the EQ Index in the group that received IFN-free treatment was significantly higher than that of the group that received IFN treatment.

IFN-free treatment guarantees a better QoL instead of the baseline condition. Compared with IFN treatment, IFN-free treatment significantly improves the EQIndex.

This combined approach (EQ-VAS plus EuroQol 5D) could be a useful tool for monitoring the health of patients. The instrument, although generic, has been shown in our study to be simple, fast and capable of determining changes in the health of patients. This instrument can also be easily managed by general practitioners for follow up of progression of the disease and referred to specialist.

The Italian Association for the Study of the Liver (AISF) published a joint document with general practitioners for the appropriate management of patients with HCV, in which the term “management” includes the identification of risk factors and risk behaviors, as well as the clinical circumstances in which the diagnosis of HCV should be suspected [31].

Table 6 Analysis of EQ INDEX in both groups pre and post treatment

EQ INDEX	Group A		Group B	
	PRE	POST	PRE	POST
Cases	16	16	46	46
Mean	0.82	0.71	0.81	0.88
SD	0.13	0.22	0.29	0.25
Median	0.85	0.72	0.91	0.97
25th	0.73	0.56	0.79	0.86
75th	0.9	0.89	1	1
EQ Index Post treatment				
T _{n-2}	2.40 ($P < 0,02$)			

Patients without access to new DAAs therapies should be monitored for the progression of the disease by both the specialist and doctor.

The role of the general practitioner remains important, even after the eradication of the infection [32, 33]. In addition to the first few months post-therapy, during which the patient will remain under the supervision of the specialist, it is important that the physician ensures the subsequent monitoring of the disease, particularly for patients with advanced disease who remain at risk of developing liver disease complications despite undergoing treatment for HCV [34–37].

Even monitoring changes in any of the dimensions of EQ INDEX may reveal impairment of health status and subsequent progression of the disease to be referred to hepatologist.

Conclusions

There was no difference in the average EQ Index between the two groups before treatment. The post-treatment EQ Index was statistically better in the group that received IFN-free therapy (group B). There was none evidence of a significant difference between the two treatment groups; the only difference was highlighted by the presence of IFN.

This type of combined approach (EQ-VAS plus EuroQol 5D) could be a useful tool for monitoring the health of patients. This tool has proven to be simple, fast and capable of detecting changes in the health of patients. The EQ-5D-5 L has also shown some sensitivity for detecting small variations, which, if systematically collected and thoroughly analyzed by the program [20] can be useful to monitor the effects of different treatments.

The EQ-5D-5 L can be even filled by patient himself and sent to the general practitioner or hepatologist, allowing a proper follow-up of the patient without the necessity of having the patient visit the reference center. The instrument is a particularly useful tool to follow-up patients who can not be treated immediately and is a useful surveillance tool for specialists.

The data in this study suggest that the main cause of the reduction in the VAS score and EQIndex in our patients was IFN therapy. Follow up of their values along with deterioration of the items in the EQ-5D-5 L can be predictive of relapse.

Abbreviations

AISF: Italian Association for the Study of the Liver; CLD: Chronic liver disease; DAAs: Direct-acting antiviral agents; EQ-5D-5 L: EuroQol standard questionnaire with five dimensions, each with 5 levels; HCV: Hepatitis C virus; HRQoL: Health-related quality of life; IFN: Interferon; NHS: National Health System; Peg- α -IFN: Pegylated alpha interferon; QALY: Quality adjusted life year; QoL: Quality of life; SD: Standard deviation; VAS: Visual analog scale

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Ragusa R has designed, coordinated and worked out the paper. Bertino G is the hepatologist who performed the clinical treatment of patients in the two groups analyzed. Bruno A uploaded data on EuroQol and processed EqIndex. Ciccio F, Frazzetto E administered the questionnaire to the patients. Giorgianni G provided for the graphics processing of the results obtained. Lupo L provided statistical data analysis and the final correction of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by Health Technology Committee ethic section. All patients gave signed consent to participate.

Consent for publication

Not applicable for this section.

Competing interests

The authors declare that they have no competing interests.

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References

- Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med*. 2015;162(6):397–406. <https://doi.org/10.7326/M14-1336>.
- Najafzadeh M, Andersson K, Shrank WH, Krumme AA, Matlin OS, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Ann Intern Med*. 2015;162(6):407–19. <https://doi.org/10.7326/M14-1152>.
- Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(11):1–205. iii
- Cortesi PA, Scalone L, Mantovani LG. Cost-effectiveness Analysis of new drugs for chronic hepatitis C: the importance of updating utility values. *Hepatology*. 2015;61(3):1096–7.
- Croce D, Bonfanti M, Restelli U. Financial and feasibility implications of the treatment of hepatitis C virus in Italy: scenarios and perspectives. *Clinicoecon Outcomes Res*. 2016;8:377–85. <https://doi.org/10.2147/CEOR.S106769>.
- Brettschneider C, Lühmann D, Raspe H. Informative value of patient reported outcomes (PRO) in health technology assessment (HTA). *GMS Health Technol Assess*. 2011; 7:Doc01. doi: <https://doi.org/10.3205/hta000092>. PMID:21468289.
- Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development Of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*. 1999;45(2):295–300.
- Devlin NJ, PFM K. The development of new research methods for the valuation of EQ-5D-5L. *Eur J Health Econ*. 2013;14(Suppl 1):1–3. <https://doi.org/10.1007/s10198-013-0502-3>.
- The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
- Brooks R. EuroQol: The current state of play. *Health Policy*. 1996;37(1):53–72.
- Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–36. <https://doi.org/10.1007/s11136-011-9903-x>.
- Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717–27. <https://doi.org/10.1007/s11136-012-0322-4>.
- Jia YX, Cui FQ, Li L, Zhang DL, Zhang GM, et al. Comparison between the EQ-5D-5L and the EQ-5D-3L in patients with hepatitis B. *Qual Life Res*. 2014; 23(8):2355–63.
- Scalone L, Ciampichini R, Fagioli S, Gardini I, Fusco F, et al. Comparing the performance of the standard EQ-5D 3L with the new version EQ-5D-5L in patients with chronic hepatic diseases. *Qual Life Res*. 2013;22(7):1707–16.
- Revicki DA, Lenderking WR. Methods and issues associated with use of quality-adjusted life-years. *Expert Rev Pharmacoecon Outcomes Res*. 2012; 12(1):105–14.
- Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *J Hepatol*. 2014;60(4):741–7. <https://doi.org/10.1016/j.jhep.2013.12.006>.
- Younossi ZM, Stepanova M, Nader F, Lam B, Hunt S. The patient's journey with chronic hepatitis C from interferon plus ribavirin to interferon- and ribavirin-free regimens: a study of health-related quality of life. *Aliment Pharmacol Ther*. 2015;42(3):286–95. <https://doi.org/10.1111/apt.13269>.
- Carrieri MP, Protopopescu C, Younossi Z, Vilotitch A, Fontaine H. Health-Related Quality Of life in chronic HCV-infected patients switching to Pegylated-interferon-free regimens (ANRS CO20 CUPIC cohort study and SIRIUS trial). *Patient*. 2017; <https://doi.org/10.1007/s40271-017-0232-1>.
- Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. Published by Springer Netherlands. ISBN 978-94-007-7596-1 (eBook). DOI <https://doi.org/10.1007/978-94-007-7596-1>.
- Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–15.
- EuroQol Group. User Guide EQ-5D-5L. <http://www.euroqol.org/about-eq-5d/publications/user-guide.html>.
- Bertino G, Arditi A, Proiti M, Rigano G, Frazzetto E, et al. Chronic hepatitis C: this and the new era of treatment. *World J Hepatol*. 2016;8(2):92–106.
- Ciaccio A, Cortesi PA, Bellelli G, Rota M, Conti S, Okolicsanyi S, Rota M, Cesana G, Mantovani LG, Annoni G, Strazzabosco M. Direct-acting antivirals combination for elderly patients with chronic hepatitis C: a cost-effectiveness analysis. *Liver Int*. 2017;37(7):982–94. <https://doi.org/10.1111/liv.13339>.
- Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. *Hepatology*. 2014; Jul;60(1):37–45. <https://doi.org/10.1002/hep.27151>.
- Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol*. 2014;60(3):530–7. <https://doi.org/10.1016/j.jhep.2013.11.009>.
- Wong WW, Lee KM, Singh S, Wells G, Feld JJ, et al. Drug therapies for chronic hepatitis C infection: a cost-effectiveness analysis. *CMAJ Open*. 2017; 5(1):E97–E108. <https://doi.org/10.9778/cmajo.20160161>.
- Hartwell D, Cooper K, Frampton GK, Baxter L, Loveman E. The clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people: a systematic review and economic evaluation. *Health Technol Assess*. 2014; 18(65):i-xxii, 1–202. <https://doi.org/10.3310/hta18650>.
- Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, et al. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res Jan*. 1998;7(1):39–55.
- Casanovas Taltavull T, Chandía Frías A, Vilallonga Vilarmau JS, Peña-Cala MC, de la Iglesia Vicario I, et al. (2016) prospective validation of the Spanish

- version of the short form-liver disease quality of life. *Gastroenterol Hepatol.* 2015;39(4):243–54. <https://doi.org/10.1016/j.gastrohep.2015.08.001>.
30. Casanovas T, Herdman M, Chandia A, Peña MC, Fabregat J, et al. Identifying improved and non-improved aspects of health-related quality of life after liver transplantation based on the assessment of the specific questionnaire liver disease quality of life. *Transplant Proc.* 2016;48(1):132–7. <https://doi.org/10.1016/j.transproceed.2015.11.009>.
 31. Armstrong AR, Herrmann SE, Chassany O, Lalanne C, Da Silva MH, et al. The international development of PROQOL-HCV: an instrument to assess the health-related quality of life of patients treated for hepatitis C virus. *BMC Infect Dis.* 2016;16(1):443. <https://doi.org/10.1186/s12879-016-1771-0>.
 32. Marzioni M, Rendina M, Senzolo M, Grattagliano I, Rossi A, Ubaldi E. Associazione Italiana per lo Studio del Fegato (AISF) e Società Italiana di Medicina Generale (SIMG). Indicazioni pratiche per un modello di gestione condivisa tra Medico di Medicina Generale e Specialista Epatologo del paziente con cirrosi epatica. <http://www.webaisf.org/> 15 maggio 2015.
 33. Van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol Oct.* 2016;65(1 Suppl):S95–S108. <https://doi.org/10.1016/j.jhep.2016.07.039>.
 34. Kwok RM, Tran TT. Management of cirrhotic patients after successful HCV eradication. *Curr Treat Options Gastroenterol.* 2017;15(2):305–15. <https://doi.org/10.1007/s11938-017-0134-2>.
 35. Kleinman L, Mannix S, Yuan Y, Kummer S, L'Italien G, Revicki D. Review of patient-reported outcome measures in chronic hepatitis C. *Health Qual Life Outcomes.* 2012;10:92. <https://doi.org/10.1186/1477-7525-10-92>.
 36. Zevin B. Managing chronic hepatitis C in primary-care settings: more than antiviral therapy. *Public Health Rep.* 2007;122(Suppl 2):78–82.
 37. Brew IF, Butt C, Wright N. Can antiviral treatment for hepatitis C be safely and effectively delivered in primary care?: a narrative systematic review of the evidence base. *Br J Gen Pract.* 2013;63(617):e842–51.

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