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Current practice of hepatitis C treatment in Southern Italy

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ABSTRACT

Background: Only a small proportion of subjects referring to hospitals for hepatitis C virus (HCV) positivity receives antiviral therapy.
Aim: To evaluate the rate of antiviral treatment and the causes for no treatment in HCV-RNA positive subjects seen in hospital settings.
Patients and methods: A prospective study enrolling over a 6-month period (February–July 2009) all consecutive anti-HCV positive subjects initially referred (naïve patients) to 12 liver units in Southern Italy for HCV treatment.
Results: Out of 608 subjects evaluated, 74 (12.2%) had no detectable HCV-RNA in the serum and thus were excluded. Of the remaining 534 HCV-RNA positive subjects, 357 (66.9%) were not treated for the following reasons: 49.9% were older than 65 years of age (75% of them >70 years), 14.3% had normal liver enzymes, 13.2% had compensated/decompensated cirrhosis, 10.4% refused treatment, 9.8% had ongoing substance or alcohol abuse. Multivariate analysis showed that females (O.R. 2.27; C.I. 95% 1.05–4.90) and subjects with low educational level (O.R. 4.38; C.I. 95% 1.27–15.11) were more likely to decline therapy.
Conclusions: The majority of patients with HCV infection does not receive antiviral treatment. The effectiveness of the current standard therapy for HCV infection is low despite its good efficacy.

1. Introduction

The current standard treatment for chronic hepatitis C virus (HCV) infection, i.e. pegylated interferon (PEG-IFN) plus ribavirin, can achieve viral clearance in the majority of treated patients. The proportion of subjects who obtain a sustained virological response (i.e. serum HCV-RNA negativity 6 months after the end of scheduled therapy) may be >50% in those infected by HCV genotype 1, and more than 80% in those infected by genotype 2 or 3 [1].

Unfortunately, only a small proportion of subjects referred to hospitals for HCV positivity receives treatment. In the U.S.A., from 28% [2] to 35% [3] of HCV-RNA positive subjects are treated. In Italy, a study conducted in a single referral centre showed that only 26% of evaluated HCV positive subjects were treated [4]. In a recent survey evaluating the effectiveness of antiviral treatment in the general anti-HCV positive population, only 8 (9.5%) out of 84 HCV-RNA positive subjects detected by a random screening from the

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Table 1
Comparison of baseline features according to antiviral treatment in 534 serum HCV-RNA positive patients.

	All patients (n = 534)	Treated patients[a] (n = 177) (33.1%)	Untreated patients[a] (n = 357) (66.9%)	p-Value
Age, years (mean ± S.D.)	60.7 ± 14.4	51.7 ± 12.2	65.1 ± 12.3	<0.001
Gender				
Male	288 (53.9%)	100 (56.5%)	188 (52.7%)	0.3
Female	246 (46.1%)	77 (43.5%)	169 (47.3%)	
B.M.I., kg/m^2 (mean ± S.D.)	26.1 ± 3.7	25.8 ± 3.6	26.2 ± 3.8	0.2
ALT, IU/ml (mean ± S.D.)	84 ± 75	104 ± 90	74 ± 65	<0.001
Years of schooling[a]				
<6	140 (28.6%)	28 (17.7%)	112 (33.8%)	<0.001
6–13	249 (50.9%)	82 (51.9%)	167 (50.5%)	
>13	100 (20.4%)	48 (30.4%)	52 (15.7%)	
HCV genotype				
1a/1b	251 (65.2%)	98 (60.9%)	153 (68.3%)	0.014
2a/2c	99 (25.7%)	41 (25.5%)	58 (25.9%)	
3a	26 (6.8%)	14 (8.6%)	12 (5.4%)	
4	9 (2.3%)	8 (5.0%)	1 (0.4%)	
Missing	149 (27.9%)			
Diagnosis				
PNALT carrier	64 (12.0%)	4 (2.3%)	60 (16.8%)	<0.001
Chronic hepatitis	389 (72.8%)	161 (91.0%)	228 (63.9%)	
Cirrhosis	84 (15.2%)	12 (6.7%)	69 (19.3%)	
Liver biopsy				
Yes	130 (24.3%)	85 (48.0%)	45 (12.6%)	<0.001
No	404 (75.7%)	92 (52.0%)	312 (87.4%)	
Referral pattern[a]				
Self-referral	62 (12.0%)	21 (12.4%)	41 (11.7%)	0.5
General practitioner	293 (56.6%)	101 (59.8%)	192 (55.0%)	
Other	163 (31.4%)	47 (27.8%)	116 (33.3%)	

[a] Some data are missing. PNALT: persistently normal alanine aminotransferase.

general population received treatment [5]. However, because the two Italian studies were both performed in a single Hepatology unit, results may have been affected by a potential bias due to centre effect.

We performed a prospective study to assess the treatment rate and the causes for non-treatment in HCV-RNA positive subjects referred to various liver units in Southern Italy.

2. Methods

2.1. Study population

During a 6-month period (February–July 2009) all consecutive anti-HCV positive subjects initially referred (naïve patients) to 12 liver units located in two Southern Italian Regions (Calabria and Sicily) were recruited. Patients were eligible for the study if they were older than 18 years of age, had a positive anti-HCV test by ELISA and were under consideration for HCV treatment with PEG-IFN plus ribavirin. Patients were excluded from the study if they had undetectable HCV-RNA by PCR.

2.2. Study design

At the time of enrolment, all patients received comprehensive counselling by a treating physician, including natural history and prognosis of chronic HCV infection and treatment options. The treating clinician at each centre was a gastroenterologist, hepatologist, or infectious diseases specialist who was experienced in the management of patients with chronic HCV infection. Patients were evaluated for HCV therapies by the clinician using standardized criteria based on current international treatment guidelines. Demographic information and results of laboratory testing were recorded on standardized data collection sheets.

2.3. Laboratory assay

The presence of HCV-RNA was determined using PCR. The lower limit of detection was 15 IU/ml. HCV genotyping was performed using the INNO-LIPA HCV II assay (Innogenetics, Gent, Belgium). The virological assays were performed in the laboratories of the different hospitals participating to the study.

2.4. Statistical analysis

Differences in proportions and means were evaluated by a chi-squared test or a Student's t-test, respectively. A p value <0.05 was considered to be significant. Univariate analysis was used to identify the crude Odds Ratios (O.R.) for the association of different variables with declining therapy in subjects eligible for treatment. Subsequently, multivariate regression analysis was performed to identify the independent predictors and their 95% Confidence Intervals (C.I.) of declining therapy.

3. Results

Of the 608 subjects who were evaluated after testing positive for HCV antibody, 74 (12.2%) had no detectable HCV-RNA and thus were excluded from the survey. Of the remaining 534 HCV-infected subjects, 357 (66.9%) were not treated. Compared to the 177 subjects receiving treatment, these 357 untreated patients were more likely older (mean age 65.1 vs. 51.7 years; $p < 0.01$), with lower mean ALT values (74 vs. 104 IU/ml; $p < 0.01$), with lowest number of years of schooling (33.8% vs. 17.7%; $p < 0.01$) (Table 1).

Non-mutually exclusive causes of non-treatment are reported in Table 2. Nearly half of cases (49.3%) was not treated because of age >65 years (75% were older than 70 years of age). Normal ALT and cirrhosis represented 14.3% and 13.2%, respectively of untreated cases. The proportion of refusals was 10.4%.

Table 2
Reasons for withholding antiviral treatment in 357 anti-HCV positive patients. *Note*: more than one item in the same patient.

	Number of subjects	%
Age >65 years	176[a]	49.3
Normal ALT	51	14.3
Compensated/decompensated cirrhosis	47	13.2
Psychiatric disease	37	10.4
Patient's refusal	37	10.4
Drug addiction/alcohol abuse	35	9.8
Decompensated diabetes	26	7.3
Heart disease	18	5.0
Mild necro-inflammation	17	4.8
Thyroiditis	17	4.8
Non-hepatic neoplasia	16	4.5
Obesity	15	4.2
Autoimmunity	5	1.4
HBV co-infection	3	0.8
Anemia/thrombocytopenia	3	0.8

[a] 75% older than 70 years of age.

Comparison of the features of the subjects older than ≥65 years of age according to treatment received is shown in Table 3. Untreated subjects were more likely older (mean age 73.4 years vs. 68.9 years; $p \leq 0.01$), with lower mean ALT values (70 IU/ml vs. 102 IU/ml; $p \leq 0.01$) and had a higher proportion of subjects with persistently normal alanine aminotransferase values (13.9% vs. 0).

The analysis of baseline characteristics of 37 subjects who refused antiviral therapy shows a preponderance of females (64.9%), a very low proportion (8.6%) of subjects with the highest educational level, and a prevalence of HCV genotype 1a/1b (65.4%) (Table 4).

We performed a multivariate analysis to identify variables independently associated with refusal of therapy. After adjusting for the confounding effect of all considered variables, we found that female gender (O.R. 2.27; 95% C.I. 1.05–4.90), and, to a major extent, a lower education level (O.R. 4.48; 95% C.I. 1.27–15.11), both were independent predictors of the likelihood of declining therapy. HCV genotype 1a/1b did not show an association (Table 5).

Table 3
Comparison of baseline features of anti-HCV positive patients older than 65 years of age according to antiviral therapy.

Variable	Treated ($n=21$)	Untreated ($n=218$)	p
Age, years (mean ± S.D.)	68.9 ± 2.6	73.4 ± 5.0	<0.001
Gender			
Male	13 (61.9%)	115 (52.8%)	0.4
Female	8 (38.1%)	103 (47.2%)	
B.M.I., kg/m^2 (mean ± S.D.)	25.9 ± 3.1	26.6 ± 4.0	0.4
ALT, IU/ml (mean ± S.D.)	102 ± 53	70 ± 52	0.008
Years of schooling[a]			
<6	10 (52.6%)	89 (44.5%)	0.5
6–12	6 (31.6%)	89 (44.5%)	
≥13	3 (15.8%)	22 (11.0%)	
HCV genotype[a]			
1a/1b	13 (68.4%)	92 (71.3%)	0.8
2a/2c	6 (31.6%)	37 (28.7%)	
3a/4	0	0	
Diagnosis			
PNALT carrier	0	30 (13.9%)	0.01
Chronic hepatitis	20 (95.2%)	136 (63.0%)	
Cirrhosis	1 (4.8%)	50 (23.1%)	
Referral pattern[a]			
Self-referral	2 (10.5%)	18 (8.5%)	0.3
General practitioner	14 (73.7%)	123 (58.0%)	
Other	3 (15.8%)	71 (33.5%)	

[a] Some data are missing. PNALT: persistently normal alanine aminotransferase.

Table 4
Baseline features of 37 anti-HCV positive patients who refused antiviral therapy.

Variable	
Age, years (mean ± S.D.) (range)	57.9 ± 12.8 (26–80)
Age class	
<40 years	4 (10.8%)
40–65 years	23 (62.2%)
>65 years	10 (27.0%)
Gender	
Male	13 (35.1%)
Female	24 (64.9%)
B.M.I., kg/m^2 (mean ± S.D.)	26.5 ± 2.4
ALT, IU/ml (mean ± S.D.)	87 ± 101
Years of scholarship[a]	
<6	12 (34.3%)
6–12	20 (57.1%)
≥13	3 (8.6%)
HCV genotype[a]	
1a/1b	17 (65.4%)
2a/2c	7 (26.9%)
3a/4	2 (7.7%)
Diagnosis	
PNALT carrier	7 (18.9%)
Chronic hepatitis	28 (75.7%)
Cirrhosis	2 (5.4%)
Referral pattern	
Self-referral	3 (8.1%)
General practitioner	22 (59.5%)
Other	12 (32.4%)

[a] Some data are missing. PNALT: persistently normal alanine aminotransferase.

4. Discussion

In this large multicenter prospective cohort study nearly two thirds of HCV-RNA positive subjects resulted not eligible for the current standard of antiviral therapy (i.e. PEG-IFN plus ribavirin). These findings from the real world are very different from those reported in international randomized clinical trials, where only 22.2–33.9% of screened patients resulted not eligible for PEG-IFN plus ribavirin therapy [6,7]. In contrast, the present findings are in agreement with previous reports performed in real world settings. A retrospective study of 293 HCV-infected patients attending a referral liver unit in Cleveland, Ohio, and a prospective multicenter study of 4084 veterans referred for HCV treatment over a one year period at 24 Veterans Affairs (VA) Medical Centers showed that only 28.3% and 32.2% patients, respectively, were considered eligible for antiviral treatment [2,3]. Only 8 (9.5%) out of the 84 unselected HCV-RNA positive subjects detected by screening of the general population in a small Southern Italian town, seen in a single liver unit, received treatment [5].

A previous Italian study [4] has shown that the rate of eligibility to antiviral therapy was lower than we found in our survey (26% vs. 33%), but this divergence could be related to different treatment guidelines in 2004 with respect to current recommendations (possibility to treat patients over 65 years of age, and those with persistently normal alanine aminotransferase).

Overall, these data add more evidence of a lack of applicability of trial results in real world patients and the limited effectiveness of the current standard therapy for HCV infection, despite its good efficacy [8,9].

In the USA ongoing substance abuse (alcohol and/or illicit drugs) is the strongest predictor (O.R. = 17.68; 95% C.I. 12.24–25.53) of not being a treatment candidate [3]. In our experience the majority (nearly half of cases) of untreated patients were older that 65 years of age, with 75% over 70 years and thus likely not suitable for treatment. This is a serious treatment barrier to overcome even

Table 5
Variables associated with treatment refusal in anti-HCV positive patients. Crude and adjusted Odds Ratios (O.R.) derived by multiple logistic regression analysis.

Variable	Untreated ($n = 37$)	Treated ($n = 177$)	Crude O.R. (95% C.I.)	Adjusted O.R. (95% C.I.)	p
Age (years)					
≤50	8 (21.6%)	77 (43.5%)	1	1	
>50	29 (78.4%)	100 (56.5%)	2.79 (1.21–6.45)	1.84 (0.75–4.55)	0.2
Gender					
Male	13 (35.1%)	101 (57.1%)	1	1	
Female	24 (64.9%)	76 (42.9%)	2.46 (1.18–5.15)	2.27 (1.05–4.90)	0.036
Years of schooling[a]					
≥13	3 (8.6%)	48 (30.4%)	1	1	
<13	32 (91.4%)	110 (69.6%)	4.66 (1.36–15.94)	4.38 (1.27–15.11)	0.019
HCV genotype[a]					
2–3	8 (30.8%)	55 (34.2%)	1		
1–4	18 (69.2%)	106 (65.8%)	1.17 (0.48–2.86)		

[a] Some data are missing.

at a national level, because it reflects the epidemiological pattern of HCV infection common in all Italian areas as shown by several population-based surveys [10–13]. However, it should be considered that we are treating the patient and not the virus, in order to prevent HCV-related morbidity and mortality. Older patients with mild forms of chronic hepatitis and possibly with competitive causes of death are unlikely to have their life expectancy reduced by HCV infection. Therefore, although theoretically eligible, they do not require treatment, which could eradicate the virus but not change the expected natural history of their disease.

Decompensated cirrhosis represents a major contraindication to treatment, but patients with compensated cirrhosis, although less likely to respond, are susceptible to liver decompensation (preventable by HCV eradication) in their near future and strongly justify treatment.

Refusals represent a subgroup of untreated patients deserving special attention. A previous study has focused on the reasons for declining therapy, showing that concerns regarding potential side effects of therapies was one of the most important reason affecting therapy acceptance [3]. In this paper we evaluated the characteristics of the refusals: females and, to a major extent, subjects with low educational level were 2.3-fold and 4.4-fold, respectively, more likely to decline treatment among subjects who were therapy candidates. Appropriate counselling should be addressed to these subjects in order to improve the rate of acceptance of antiviral treatment.

The strengths of the present survey comprise the inclusion of patients from several units (thus avoiding the single centre effect) and the prospective study design. However, the present study may have overestimated the proportion of subjects who are eligible fro treatment because of referral bias. In fact, the evaluation concerned subjects referred for HCV therapy and general practitioners may have only referred those that they perceived as good candidates.

In conclusion, these findings confirm previous reports that only a small proportion of candidates for HCV treatment results suitable for therapy. Despite the good efficacy of current HCV therapy, its effectiveness needs to be improved.

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