Limited Fibrosis Progression but Significant Mortality in Patients Ineligible for Interferon-Based Hepatitis C Therapy

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Background: Individuals ineligible for interferon-based hepatitis C therapy may have a worse prognosis than patients who have failed or not received treatment. **Aims:** To provide information about the limitations of medical treatment of hepatitis C in real-world patients. **Methods:** We studied 969 treatment-ineligible patients and 403 treated patients enrolled between 1/1/01 and 6/30/06; data were collected until 3/31/13. Treatment barriers were grouped into five categories and classified as health-related or health-unrelated. Fibrosis stage was assessed initially and at the end of follow-up. Mortality was determined by search of the Social Security database. Death certificates of treatment-ineligible patients were reviewed. **Results:** Initially, 288 individuals had advanced fibrosis and compensated disease; 87 untreated patients developed advanced fibrosis during follow-up. Health-related treatment barriers were more commonly associated with fibrosis progression and worse survival. During follow-up, 247 untreated patients died: 47% of liver-related and 53% of liver-unrelated causes. Patients with significant comorbid illness had the worst five-year (70%) and ten-year (50.5%) survival. Despite high mortality (47%) in persons with decompensated liver disease, no treatment barrier was associated with a greater incidence of liver-related death. Only significant comorbid medical illness was an independent predictor of disease progression; however, it was not associated with a greater incidence of liver-related death. Furthermore, treated patients had better 10-year survival than untreated patients on Kaplan–Meier analysis (80.3% vs. 74.5%, $P = 0.005$). **Conclusion:** Many patients with hepatitis C will die of non-liver-related causes and may not be helped by anti-viral treatment. (J CLIN EXP HEPATOL 2016;6:100–108)

Approximately 3.9 million Americans are chronically infected with hepatitis C virus (HCV) [<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6218a4.htm>. Data as of August 17, 2014]. According to published data, 5–20% of patients with chronic hepatitis C will have cirrhosis after 20–25 years of infection and 3–8% of the latter individuals will develop hepatocellular carcinoma (HCC) annually.¹ End-stage liver disease secondary to HCV infection is the most common indication for orthotopic liver transplantation in the United States.² Individuals who successfully complete hepatitis C therapy have significantly slower disease progression to cirrhosis and HCC and improved quality of life as compared to untreated control patients.^{3,4} Additionally, patients with

hepatitis C and significant fibrosis who have a sustained virological response (SVR) to interferon-based therapy have lower all-cause mortality than treated patients who fail to have an SVR.⁵

Many, if not most patients, however, are not candidates to receive interferon-based HCV treatment; only 15% of patients referred to our urban center for evaluation of hepatitis C were eligible for interferon-based antiviral therapy.⁶ Comorbid medical illness, lack of insurance, psychiatric illness, and active substance abuse have been identified as common barriers to initiation of treatment.^{7–9} We hypothesize that individuals with treatment barriers of this type may not be medically equivalent to, and may have a worse prognosis than, treatment-eligible control or unsuccessfully treated patients in published studies proving the benefits of SVR in persons who had hepatitis C.

The decision to prescribe any anti-HCV regimen requires an assessment of treatment barriers and the balance of potential risks and benefits as well as the likelihood of success of therapy. Critical variables in this calculation are estimates of the effects of treating or not treating on morbidity and mortality. With respect to this analysis, it may not be the case that all patients will derive the benefits of therapy reported in studies comparing individuals who

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Abbreviations: AA: African-American; APRI: aspartate-aminotransferase-to-platelet ratio index; DTB: dominant treatment barrier; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; SVR: sustained virologic response
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had an SVR to treatment-eligible control patients. In particular, individuals with barriers to therapy might experience more morbidity and have higher mortality rates when given medication than they may have if left untreated. There is evidence suggesting that this is true in reports of the outcomes of triple therapy with regimens including interferon, ribavirin, and a first-generation protease inhibitor.^{10,11} Conversely, untreated patients may die of causes unrelated to hepatitis C before they can be expected to experience any benefit of successful therapy. In balance, based on reports of adverse events related to treatment and those documenting slow stage-specific progression of fibrosis secondary to HCV infection and gradual development of hepatic decompensation in many persons with HCV cirrhosis, it is possible that some patients with barriers to HCV treatment might have better or the same outcomes without anti-viral therapy.^{12–14}

Published studies have compared morbidity and mortality from liver disease in patients successfully treated for hepatitis C to that in individuals who are treatment candidates but who have not yet started treatment, have refused treatment, or have failed to have an SVR to interferon-based therapy. In this single-center study, we address potential long-term consequences of not treating patients with hepatitis C who have barriers to therapy: medical, social, and psychiatric problems that make interferon-based HCV treatment impossible or undesirable. The purpose of this study is to improve the objectivity of hepatitis C treatment decisions by uncovering and clarifying potential relationships between treatment barriers and survival without anti-viral therapy of any type. We hypothesize that while persons who were ineligible to begin medications might die of complications of liver disease, many might die of causes other than liver disease during the observation period. These data are hoped to provide information about the limitations of medical treatment of hepatitis C in real-world patients of the type treated in our urban practice setting.

PATIENTS AND METHODS

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approvals by the appropriate institutional review committees: the Institutional Review Boards of the New York City Department of Health, and the Montefiore Medical Center and the Albert Einstein College of Medicine. Patients' consent was not needed for this study given that it involved only retrospective data collection.

We reviewed the medical records of all adult patients evaluated between January 1, 2001 and June 30, 2006 in the hepatology Faculty Practice of the Albert Einstein College of Medicine and the attending-supervised Liver Clinic at Montefiore Medical Center, Bronx, New York to identify persons with hepatitis C who were considered ineligible for interferon-based therapy. Patient evaluations were done or

supervised by one full-time clinical hepatologist (JFR). Eligibility for interferon-based hepatitis C treatment was decided in accordance with the general requirements and under conditions of everyday clinical practice. Adequately complete medical records of 969 treatment-naïve, HIV-antibody negative, and hepatitis-B surface-antigen negative patients ineligible for hepatitis C therapy were culled and used to collect a pre-defined data set. In addition, we identified 403 patients evaluated for hepatitis C during this period who were prescribed interferon-based therapy under the direction of the supervising physician in accordance with the general requirements for treatment. Clinical data pertaining to treatment eligibility and data concerning complications of liver disease and fibrosis stage were recorded. Demographic data also were recorded; ethnicity was defined by patient self-reporting. Analysis is based on data collected from January 1, 2001 to the end of the follow-up period, March 31, 2013.

Treatment Ineligibility

Reasons for treatment ineligibility (treatment barriers) were classified into five categories (Table 1). These barriers were assigned a hierarchical rank to determine the dominant treatment barrier (DTB) in patients who had multiple reasons for treatment ineligibility. Patients with category-1 and category-2 DTBs (Table 1) were classified as having health-related (medical) contraindications to treatment while patients with other DTBs were classified as having health-unrelated (non medical) treatment barriers.

Disease Stage and Progression

Modified Ishak fibrosis stage was recorded for patients who had liver biopsies. Advanced fibrosis on liver biopsy was defined as stage-5 or stage-6 disease. The aspartate-aminotransferase-to-platelet ratio index (APRI) at the times of initial evaluation and the last blood test during the follow-up period also were recorded. Advanced fibrosis was defined as an APRI greater than 1.5. CT and MR findings suggestive of significant fibrosis and cirrhosis, including the presence of liver nodularity, ascites, splenomegaly, and varices were recorded. Individuals were considered to have advanced fibrosis if they had any of the latter findings on cross-sectional imaging. Patients who had initial but no paired follow-up biopsy, blood test (APRI), or cross-sectional abdominal imaging were omitted from the disease-progression analysis. Initial evaluation for fibrosis was done within six months of the patient's presentation.

Mortality

All-cause mortality incidence as of March 31, 2013 in both treatment-eligible and treatment-ineligible patients was determined by search of the US Social Security database. Additionally, the death certificates of deceased treatment-ineligible patients were obtained from the New York

Table 1 Classification of Treatment Barriers and Included Diagnoses.

	Included diagnoses or conditions
Medical treatment barriers (n = 358)	
(1) Comorbid medical illness (n = 200)	Decompensated cirrhosis Severe cardiopulmonary disease Chronic kidney disease Stroke Active malignant disease Hematologic disorder Autoimmune disease
(2) Recent active substance abuse (n = 158)	Intranasal or parenteral drugs Alcohol
Non-medical treatment barriers (n = 611)	
(3) No expected treatment benefit (n = 168)	Advanced age Low-stage liver disease Treatment likely ineffective
(4) Psychosocial obstacles (n = 124)	Uncontrolled psychiatric disease Lack of insurance Inadequate housing
(5) Lack of cooperation (n = 319)	Treatment refusal Failure to return for follow-up Failure to take prescribed medications

Department of Health and the principal cause of death and associated conditions were recorded. Liver-related mortality was defined as any death in a person who had liver disease listed as the principal cause of death or an associated condition.

Outcomes

The primary study outcome is all-cause mortality in treatment-ineligible patients. Mortality in treatment-ineligible patients was compared to mortality in treated patients. The secondary study outcome is liver-disease progression in treatment-ineligible patients as determined by worsening in biopsy, abdominal imaging, or APRI results.

Statistical Analysis

Data were collected prospectively and analyzed retrospectively. Categorical variables were expressed as valid percentages and compared using the Chi-Squared test. Continuous variables were expressed as the mean $\pm$ standard deviation and compared using the Student's *t*-test. Survival time was expressed as the median $\pm$ standard error of the mean. Patient survival was calculated using the Kaplan-Meier method and compared using the Log-Rank Test. Variables with prognostic significance on univariate analysis ($P < 0.05$) were entered into multivariate logistic regression or Cox's Proportional Hazards Model to determine whether or not they had independent predictive value; P values < 0.05 were

considered significant. Analysis was done using SPSS 18.0 (SPSS, Chicago, IL).

RESULTS

Of 969 treatment-ineligible patients, 555 were males and 414 females with a mean age of 44 years (SD 10.8); 38 patients were 65 years or older (Table 2). Median follow-up was 110.9 months (0.12–146.9).

Treatment Barriers

DTBs were lack of cooperation with healthcare providers, 33%; significant comorbid medical illness, 20.6%; no expectation of treatment benefit, 17.3%; active or recent substance abuse, 16.3%; and psychosocial obstacles to completion of therapy, 12.8% (Table 1). Forty-five patients with significant comorbid medical illness as a DTB had decompensated liver disease.

Significant comorbid medical illness was the DTB in 24.2% of females vs. 18% of males (OR 1.4; 95% CI 1.06–1.9, $P = 0.02$). No expectation of treatment benefit was the DTB in 22.9% of females vs. 13.2% of males (OR 1.9; 95% CI 1.4–2.7, $P = 0.01$). Active or recent substance abuse was the DTB in 21.6% of males vs. 9.2% of females (OR 2.3; 95% CI 1.6–3.3, $P = 0.001$). Recent or active substance abuse as a DTB was observed in 23.2% of Hispanics, 12.4% of AAs and 14.5% of whites ($P = 0.01$). No expectation of treatment

Table 2 Patient Characteristics; Ethnicity is Self-Reported.

Patient characteristics (n = 969)	n	%
Gender		
Male	555	57.3
Female	414	42.7
Ethnicity		
African-American	346	35.7
Hispanic	168	17.3
White	131	13.5
Other	324	33.5
Age		
≥65 years	38	4
<65 years	931	96

benefit as a DTB was seen in 21.4% of AAs, 8.3% of Hispanics and 19.8% of whites ($P = 0.003$). No difference based on gender or ethnicity was noted between medical (54.3%) and non-medical DTBs.

Liver-Disease Progression

Liver-disease progression data were available for 847 patients (87.4%); progression was assessed by comparison

of biopsy results in 39, imaging in 288, and APRI in 520. Disease progression occurred during follow-up in 236 of the assessed patients (27.8%) (Table 3). At initial evaluation, 288 patients had advanced fibrosis without decompensated liver disease (biopsy 24; imaging 142; APRI 122); an additional 87 patients developed advanced fibrosis during follow-up (biopsy 0; imaging 42; APRI 45). On multivariate logistic regression analysis, only significant comorbid medical illness was an independent predictor of fibrosis progression (HR 2.3; 95% CI 1.6–3.3, $P < 0.001$). Medical DTBs were more commonly associated with fibrosis progression than non-medical DTBs (HR 1.4, 95% CI 1.04–1.8, $P = 0.02$). Disease progression was not affected by the number of treatment barriers.

Mortality

During the 146 months between evaluation of the first patient and the end of follow-up (median 110.9 months), 247 patients died (25.5%); 185 had identifiable causes of death (New York State death certificates), of whom 87 (47%) died of liver-related and 98 (53%) of liver-unrelated causes. The ten-year Kaplan–Meier survival of patients ineligible for anti-viral therapy was 74.5%; survival of patients with multiple treatment barriers (409) was no different than that of patients with a single treatment barrier (560) (71.6% vs. 75.5%, respectively, $P = 0.15$).

Table 3 Factors Associated with Liver Disease Progression.

	Disease progression (%)	Univariate P value	Multivariate P value	HR	95% CI
Ethnicity (n)		0.006			
African-American (308)	65 (21.1)		0.1		
Hispanic (130)	43 (33.0)		0.4		
White (113)	31 (27.4)		Reference		
Other (296)	97 (32.8)		0.2		
Gender		0.062			
Male (477)	91 (19.1)				
Female (370)	145 (39.2)				
Treatment barrier					
Co-morbid illness ^a (189)	80 (42.3)	<0.001	<0.001	2.3	1.6–3.3
Substance abuse ^a (125)	33 (26.4)	0.6			
No expected benefit ^b (156)	32 (20.5)	0.02	0.4		
Psychosocial ^b (112)	27 (24.1)	0.2			
Uncooperative ^b (265)	64 (24.2)	0.06			
Barrier type ^c		0.03	0.02	1.4	1.04–1.8
Medical (470)	145 (30.9)				
Non-medical (377)	91 (24.1)				

^aMedical barrier.

^bNon-medical barrier.

^cSeparate multivariate analysis done for barrier type.

Table 4 Kaplan–Meier Ten-Year Survival of Patients and Associated Factors.

	Treatment-ineligible patients (n = 969)				
	Survival (died/total)	Univariate P value	Multivariate P value	HR	95% CI
Ethnicity		<0.001			
African American	75.7% (84/346)		0.8		
Hispanic	60.7% (66/168)		0.002	2.1	1.3–3.2
Caucasian	74.8% (33/131)		Reference		
Other	80.2% (64/324)		0.06		
Total	74.5% (247/969)				
Gender		0.7			
Male	75.3% (137/555)				
Female	73.4% (110/414)				
Treatment barrier					
Comorbid illness ^a	50.5% (99/200)	<0.001	<0.001	2.6	1.8–3.6
Substance abuse ^a	76.5% (37/158)	0.3			
No expected benefit ^b	78.5% (36/168)	0.1			
Psychosocial ^b	83% (21/124)	0.02	0.6		
Uncooperative ^b	83% (54/319)	<0.001	0.4		
Barrier type	<0.001	<0.001			
Medical	67.3% (172/526)			1.8	1.3–2.4
Non-medical	83% (75/443)				
Disease progression		<0.001	<0.001		
Yes	58.4% (98/236)			2.4	1.8–3.1
No	79.8% (123/611)				
Age		<0.001	0.004		
<65 years	75.4% (229/931)			2.1	1.2–3.5
≥65 years	52.6% (18/38)				
	Treatment-eligible patients (n = 403)				
	Survival (died/total)	Univariate P value	Multivariate P value	HR	95% CI
Ethnicity		0.08			
African-American	83.1% (17/101)				
Hispanic	76.6% (48/206)				
White	79.1% (10/48)				
Other	91.6% (4/48)				
Total	80.3% (79/403)				
Gender		0.007	0.007		
Male	76% (57/238)			1.97	1.2–3.2
Female	86.6% (22/165)				
SVR		0.004	0.006		
Yes	92.6% (5/68)			3.5	1.4–8.6
No or lost-to-follow-up	77.9% (74/335)				

^aMedical barrier.^bNon-medical barrier.

Figure 1 Kaplan-Meier survival curves: (A) treated patients with SVR; (B) patients with non-medical barriers to treatment; (C) patients who failed therapy; (D) patients with medical barriers to treatment; (E) patients with comorbid illness as DTB.

Survival of patients with treatment barriers also was no different than that of patients who failed therapy (74.5% vs. 77.9%, respectively, $P = 0.09$). Patients who were ineligible for treatment because of comorbid medical illness, however, had significantly worse survival than patients who failed therapy (50.5% vs. 77.9%, respectively, $P < 0.001$), as did patients with any medical barrier to treatment (67.3% vs. 77.9%, respectively, $P < 0.001$). Overall, medical treatment barriers were associated with worse ten-year survival than non-medical barriers (67.3% vs. 83%, respectively, $P < 0.001$); survival in patients with non-medical treatment barriers was comparable to that of persons who failed therapy 83.0% vs. 77.9%, respectively, $P = 0.1$) (Table 4) (Figure 1a).

Patients with significant comorbid medical illness as the DTB had the worst five- (70%) and ten-year (50.5%) survival

($P < 0.001$) (Table 5). This group included 10 patients with decompensated liver disease as the only treatment barrier and an additional 35 patients with decompensated liver disease as well as other treatment barriers. Of these 45 individuals, 21 died of liver-related, 18 of liver-unrelated, and six of unknown causes. Sixty percent of deaths in patients with comorbid medical illness as the DTB occurred within five years; 89% of deaths in patients with other DTBs occurred during this same time interval (Table 5).

Medical barriers to treatment, Hispanic race, progression of liver disease, and age greater than 65 years also were associated with decreased ten-year survival by Cox-regression analysis (Table 4). Among patients with an identifiable cause of death, there was no statistical difference in the incidence of liver-related death based on ethnicity, gender or even DTB despite the significant mortality in persons with decompensated liver disease (47%).

The mean age of the 403 treated patients was 48.2 years (SD 8.4). The median follow-up of these individuals was 123.7 (3–146.9) months. The ten-year Kaplan-Meier survival of treated patients was better than that of treatment-ineligible patients (80.3% vs. 74.5%, $P = 0.005$) (Figure 1b). Sixty-eight treated patients (16.9%) had a SVR; their ten-year survival was 92.6% whereas the ten-year survival of patients who did not have an SVR was 77.9% ($P = 0.004$) (Table 4).

DISCUSSION

Patients successfully treated for hepatitis C with interferon-based therapy were reported by Backus et al. to have less all-cause mortality than treated patients who did not have an SVR during a median follow-up of approximately 45 months.¹⁵ Our data also indicate that successfully treated patients who were followed for a median of 123.7 months have significantly improved survival as compared to patients who were treated but failed to have an SVR. Overall, survival of our patients who were ineligible for treatment was the same as that of patients who failed therapy, as was that of our patients with non-medical treatment barriers. These observations are consistent with those of Lee et al. who

Table 5 Five- and Ten-Year Survival by Barrier to Treatment.

Treatment barrier	5-year survival	10-year survival	Univariate <i>P</i> value	Multivariate <i>P</i> value
Comorbid medical illness ^a	70% (60/200)	50.5% (99/200)	<0.001	<0.001
Recent active substance abuse ^a	78.4% (34/158)	76.5% (37/158)	0.3	
No expected benefit ^b	80.9% (32/168)	78.5% (36/168)	0.1	
Psychosocial ^b	83% (21/124)	83% (21/124)	0.02	0.6
Lack of cooperation ^b	85.8% (45/319)	83% (54/319)	<0.001	0.4

^aMedical barrier.

^bNon-medical barrier.

concluded that HCV infection is a major determinant of mortality.¹⁶ All of these findings, however, obscure the fact supported by our data that survival of patients with medical barriers to interferon-based therapy, especially comorbid medical illness, is significantly worse than that of individuals who fail to have an SVR to treatment. Thus, patients who have medical barriers to interferon-based treatment are not the same as the treatment-eligible control patients in previously published studies.

The observed excess mortality in our untreated patients suggests that these individuals died from causes in some way related to HCV infection, in particular from complications of worsening fibrosis and development of end-stage liver disease. The effect of therapy on disease progression has been addressed indirectly by several authors^{16–18} who have shown that disease-directed therapy with SVR in patients who have advanced fibrosis and cirrhosis at initiation of treatment reduces liver-related mortality. As expected, disease progression in our study was associated with significantly decreased 10-year Kaplan–Meier survival. The only factor associated with fibrosis progression on multivariate logistic regression was significant comorbid medical illness, again implying, with respect to worsening fibrosis, that patients who are ineligible for interferon-based treatment for medical reasons are not the same as treatment-eligible patients who fail to have an SVR. Surprisingly, however, despite high mortality in persons with decompensated liver disease (47%) as a contraindication to therapy, no treatment barrier, including comorbid medical illness, was associated with a greater incidence of liver-related death. While patients with medical obstacles to treatment were more likely to have progression of fibrosis and had worse ten-year survival, and while patients with significant comorbid medical illness as the DTB had the worst ten-year survival, patients with comorbid medical illness were not more likely to die of liver disease. Furthermore, while a significant number of untreated patients (47%) died of liver-related causes during follow-up, a slightly larger number (53%) died from causes unrelated to liver disease. A limitation of this analysis is that, because the cause of death could not be determined for 68 patients, it is possible that the majority of these people died of liver-related causes, something that could have affected the outcome. On the other hand, we used a broad definition of liver-related death in our review of death certificates: any patient whose death certificate mentioned liver disease as an associated cause of death was considered to have died of liver disease. Therefore, we also may have overestimated total liver-related mortality. In balance, it must be acknowledged that death certificates have limitations as data sources. Inaccuracies introduced by their unreliability hopefully were balanced by the number of cases reviewed.

Many of our patients had several commonly accepted contraindications to interferon-based therapy. We

classified similar contraindications into groups (Table 1) and created a hierarchical rank of groups to establish a DTB for purposes of statistical comparison with the intention of uncovering and clarifying potential relationships between treatment barriers and survival.

There are problems inherent to this approach. First, although the assignment of barriers to groups superficially seems straightforward, the prognostic implications of barriers in the same group may be qualitatively different. For example, the three category-3 barriers each logically might justify the conclusion that treatment will not be beneficial; however, the potential clinical outcomes in patients with low-stage disease and in those with a combination of race and infection genotype associated with a low probability of SVR clearly may be very different. This may have undermined the utility of these categories as predictors of who will benefit from therapy.

The validity of our classification system, moreover, may depend on the chosen rank order of DTBs. While the appropriate order of DTB precedence can be questioned, defined barrier dominance ultimately was not predictive of disease progression or survival. Instead, it served as an epidemiological descriptor: for example, the prevalence of DTBs in our patient population was associated with gender and race. While a different order of dominance might have produced different results, we found no indication that this was the case.

The most meaningful classification of DTBs was characterization of some and not others as medical. We called any health-related problem that was a contraindication to interferon-based therapy or was expected to be independently associated with morbidity and mortality as medical; other problems were called non-medical. As a result, we considered any irreversible clinical problem that was a contraindication to interferon therapy to be the primary DTB and health-related.

Irremediable drug and alcohol addiction were chosen as the second most DTB and were classified as health-related obstacles to therapy because addiction is recognized to be a major cause of medical morbidity and mortality in the United States.¹⁹ As such, inclusion of substance use as a health-related treatment barrier may explain to some extent the fact that patients with medical treatment barriers had the worst ten-year survival of those in any group. Alcohol-addiction and hepatitis C are synergistic causes of liver-disease progression²⁰ and therefore classification of alcohol addiction as a medical DTB might have biased the results by increasing the apparent incidence of hepatitis C liver-related mortality in these patients, but we found no difference in the incidence of liver-related death among treatment-barrier groups.

Patients classified as having no expectation of treatment benefit as a DTB were otherwise medically eligible for interferon-based therapy and, as such, were considered not to have a health-related treatment barrier. No

expectation of treatment benefit as a DTB was given precedence over the remaining obstacles to therapy. It is interesting to note that patients who were ineligible for therapy because there was no expectation of benefit were less likely to have fibrosis progression.

The toxicity of interferon-based therapy and consequent inability of many, and in our experience most, patients to tolerate treatment created a unique opportunity to study factors that might influence the decision to treat individuals affected by a chronic disease with significant potential for adverse outcomes. As reported by others, our successfully treated patients had the best 10-year survival and better 10-year survival than persons who were eligible for interferon-based treatment but failed to have an SVR. Significantly, patients who were ineligible for interferon-based therapy had the worst 10-year survival of all (25.5%, median 110.9 months). On multivariate logistic regression analysis, comorbid medical illness, advanced age, and liver disease progression were independent predictors of high mortality. Furthermore, significant comorbid medical illness was the only independent predictor of disease progression; however, it was not associated with a greater incidence of liver-related death.

While previous studies of the effects of therapy on morbidity, mortality, and disease progression might suggest that every patient with hepatitis C will benefit from treatment, this may not be the case. In the new era of highly effective and easily tolerated, but very costly, treatments, it is tempting to assume that every patient with hepatitis C is a treatment candidate. Our data show that hepatitis C treatment might not be beneficial for some of these patients who may die from significant medical comorbidities before experiencing treatment benefit. Although our study describes patients' experience with an old anti-hepatitis C regimen, its lessons can be applicable to patients undergoing treatment with the new regimens given that having a significant comorbid medical illness and its impact on survival is a constant problem in our patients regardless of the type of treatment used. Alternatively, it may be shown by future studies that successful non-toxic treatment of hepatitis C in persons with significant comorbid medical illness will reduce mortality from causes other than liver disease and confer a survival benefit on most or every affected individual. While this has been implied by the results of previous work,^{5,16} it has not been addressed directly by controlled trials including patients with hepatitis C as well as significant comorbid medical illness. We conclude that many patients with hepatitis C may die of non-liver-related causes and may not be helped by antiviral treatment. For now, it is reasonable to first treat patients with hepatitis C who have liver fibrosis and who do not have other medical problems that are known to have a significant effect on life expectancy. We await results of controlled studies that demonstrate a benefit of treatment in other patient populations.

CONFLICTS OF INTEREST

The authors have none to declare.

AUTHOR'S CONTRIBUTIONS

Manhal Izzy: concept and design; acquisition of data; interpretation of data; drafting of manuscript; study supervision. Ghalib Jibara: analysis and interpretation of data; statistical analysis. Aws Aljanabi, Mustafa Alani, Emily Giannattasio, Hina Zaidi, Zaid Said: acquisition of data. Paul Gaglio and Allan Wolkoff: critical revision of the manuscript for important intellectual content. John F. Reinus: study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of manuscript for important intellectual content; administrative; study supervision.

REFERENCES

1. Seeff LB, Hoofnagle JH. Management of hepatitis C: 2002. *Hepatology*. 2002;36:S1–S2.
2. Ghobrial RM, Farmer DG, Baquerizo A, et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Ann Surg*. 1999;229:824–831.
3. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med*. 2005;142:105–114.
4. Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. *Aliment Pharmacol Ther*. 2006;23:777–785.
5. Van der Meer A, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308:2584–2593.
6. Feuerstadt P, Bunim AL, Garcia H, et al. Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. *Hepatology*. 2010;51:1137–1143.
7. Rousseau CM, Ioannou GN, Todd-Stenberg JA, et al. Racial differences in the evaluation and treatment of hepatitis C among veterans: a retrospective cohort study. *Am J Public Health*. 2008;98:846–852.
8. Bini EJ, Bräu N, Currie S, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. *Am J Gastroenterol*. 2005;100:1772–1779.
9. Melia MT, Muir AJ, McCone J, et al. Racial differences in hepatitis C treatment eligibility. *Hepatology*. 2011;54:70–78.
10. Hézode C, Foontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicenter cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890. *J Hepatol*. 2013;59:434–441.
11. Bicoupan K, Schwartz JM, Martel-Laferrere V, et al. Effect of fibrosis on adverse events in patients with hepatitis C treated with telaprevir. *Aliment Pharmacol Ther*. 2013;39:209–216.
12. Terrault NA, Im K, Boylan R, et al. Fibrosis progression in African Americans and Caucasian Americans with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2008;6:1403–1411.

13. Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology*. 2008;48:418–431.
14. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112:463–472.
15. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol*. 2011;9:509–516.
16. Lee M-H, Yang H-I, Lu S-N, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis*. 2012;206:469–477.
17. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon- α is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology*. 2007;45:579–587.
18. Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology*. 2010;52:833–844.
19. McGinnis JM, Foege WH. Mortality and morbidity attributable to use of addictive substances in the United States. *Proc Assoc Am Physicians*. 1999;111:109–118.
20. Ostapowicz G, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus. *Hepatology*. 1998;27:1730–1735.