

Surprisingly Small Effect of Antiviral Treatment in Patients with Hepatitis C

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Background: The effect and applicability of interferon-based antiviral therapies in the general population of persons with hepatitis C virus (HCV) infection are unknown.

Objective: To determine the applicability and usefulness of antiviral therapy in a metropolitan clinic population.

Design: Retrospective case series of consecutively referred patients.

Setting: A teaching county hospital in Cleveland, Ohio.

Patients: 327 patients referred to a liver clinic after a positive result for antibody against HCV on enzyme-linked immunosorbent assay (ELISA).

Measurements: Treatment rates; reasons for nontreatment.

Results: 34 patients had no detectable HCV RNA. Of the remaining 293 patients, 72% were not treated for the following reasons: 37% did not adhere to evaluation procedures, 34% had medical or psychiatric contraindications, 13% had ongoing substance or alcohol abuse, 11% preferred no treatment, and 5% had normal liver enzyme levels. Only 83 patients (28%) were treated; 13% had a sustained viral response.

Conclusion: Most patients with HCV infection are not candidates for interferon-based therapies; alternative interventions should be sought for these patients.

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Hepatitis C virus (HCV) infection is a major health problem. In the United States, approximately 4 million persons are infected with HCV, and 8000 to 10 000 persons die of HCV-related liver disease annually (1). The U.S. Centers for Disease Control and Prevention estimate that deaths from HCV infection will increase substantially and surpass those from HIV infection in 8 to 10 years (2). Currently, the recommended therapeutic strategy is to eradicate HCV infection by using interferon-based therapies, thereby potentially reducing HCV-related morbidity and mortality from the development of cirrhosis (3).

The average rate of sustained viral response with the combination therapy of interferon- α plus ribavirin (4, 5) and with pegylated interferon (6) range from 30% to 40%. However, these results may not represent the experience of the entire HCV-infected population because most studies have used highly selected patient groups, have been performed in referral centers, and have not reported screening sample size.

A trial in the United States (4), for example, excluded 404 of the 1337 screened patients, mostly because of selection criteria similar to those in the current study. Moreover, a large international trial (5) did not report screening data. Reports of treatment trials often do not clarify whether all patients or only potentially

suitable study candidates were screened. Data are limited for important patient subgroups that do not fit the standard profile—for example, patients with active alcohol or substance abuse, children, homeless and incarcerated patients, elderly patients, and patients with comorbid conditions such as psychiatric disorders or autoimmune disease (7–10). Finally, cultural and educational characteristics may impede patient acceptance of treatment (11). Therefore, the extent to which the results of clinical trials in HCV-infected patients apply to the entire HCV-infected population is unknown. Several factors also may prevent use of antiviral treatment regimens. Side effects of interferon-based therapy are significant (10) and are similar with both standard and pegylated interferons (6).

We hypothesized that a substantial proportion of HCV-infected patients may not be candidates for currently available antiviral treatment. Therefore, we investigated the overall antiviral treatment rate and the reasons for nontreatment in a general population of HCV-infected patients in a metropolitan liver clinic.

METHODS

We reviewed the charts of new consecutive patients referred to the liver clinic at MetroHealth Medical Cen-

ter in Cleveland, Ohio, because they had tested positive for HCV antibody on enzyme-linked immunosorbent assay (ELISA) during a 23-month period from January 1998 to November 1999. All patients were evaluated by one of two hepatologists who decided on treatment or nontreatment on the basis of previously agreed upon criteria. A specially trained nurse gave all patients a standardized comprehensive education program during their first office visit. Follow-up office appointments were scheduled for all appointments, and reminders were mailed for any missed office visits.

The criteria for treatment were a positive test result for HCV RNA and elevated levels of alanine aminotransferase or aspartate aminotransferase on two occasions during the preceding 6 months. The exclusion criteria were decompensated cirrhosis, other types of liver disease, active alcohol or drug use, nonadherence (missing >2 visits before treatment during the education process), poorly controlled psychiatric or seizure disorders, autoimmune disease, symptomatic cardiac disease, neutrophil count less than 1.5×10^9 cells/L and platelet count less than 0.75×10^9 cells/L, retinopathy, or cancer.

RESULTS

Of the 327 patients who were evaluated after testing positive for HCV antibody, 34 patients (10%) had no detectable HCV RNA and therefore were not considered for treatment. Of the remaining 293 HCV-infected patients, 72% were not treated for the following reasons (Figure):

1. Nonadherence to evaluation and education—37%: These patients did not follow recommendations for evaluation; for example, they did not have blood drawn or attend the appointment for liver biopsy, or they missed more than two office appointments. Other complicating factors included homelessness or incarceration (the county prison system has had no established treatment protocol for persons with HCV infection).

2. Medical contraindication—34%: The most frequent contraindications were psychiatric disease, including poorly controlled severe depression, bipolar disease, and previous suicide attempt or specific ideation; decompensated cirrhosis; pregnancy; refusal to practice contraception; autoimmune disease; poorly controlled diabetes mellitus; or cytopenias.

Context

Hepatitis C virus is the most common cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the United States.

Trials show that about 50% of patients with chronic hepatitis C virus infection respond to prolonged treatment with antiviral drugs, such as pegylated interferon and ribavirin. Physicians are selective about whom to treat because antiviral therapy is expensive and difficult to take and has many side effects.

Contribution

This study shows that 72% of patients with hepatitis C virus infection who attended an urban county clinic did not receive antiviral therapy because of failure to show up for appointments or tests, severe comorbid medical or psychiatric illness, ongoing alcohol or drug abuse, or preferences against treatment.

Implications

Most patients with chronic hepatitis C virus infection may not be good candidates for antiviral therapy.

—The Editors

3. Substance abuse—13%: Ongoing drug or alcohol use prevented these patients from receiving antiviral treatment.

4. Patient preference—11%: These patients chose not to be treated after considering possible side effects, treatment duration, family planning issues, or difficulties with injecting interferon after recovery from intravenous drug use. One patient declined treatment because of fear of high laboratory bills, despite free medications.

5. Normal alanine aminotransferase levels—5%: These patients were not treated, as per established treatment guidelines of the U.S. National Institutes of Health (12).

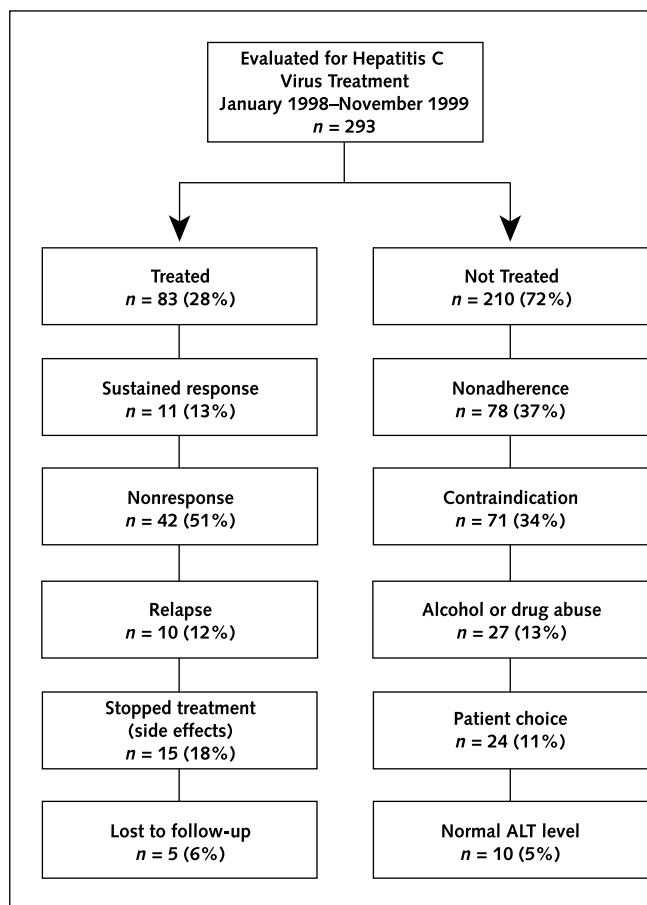
As shown in the Figure, only 83 of the 293 patients (28%) received interferon-based antiviral therapy, which consisted of interferon alone or interferon combined with ribavirin. Eleven patients (13%) had a sustained viral response, defined as an undetectable HCV RNA level 6 months after completing treatment. Thus, in the

entire group of 293 patients who had tested positive for HCV RNA, the rate of sustained viral response was only 4%. Even if the sustained viral response rate were 40% (which is the mean rate reported for the more recent treatment regimens), only 11% of our total sample would have reached this end point.

In 52 (63%) of the 83 treated patients, viral eradication was not successful because of nonresponse (42 patients) or relapse (10 patients). Fifteen patients (18%) stopped treatment because of side effects, and 5 patients (6%) were lost to follow-up.

The treated and untreated groups did not differ significantly for age, sex, ethnicity/race, or risk factors. Although 72% of our patients were uninsured or were insured through Medicaid, financial status prevented treatment in only 1 patient. Liver biopsy was performed

Figure. Reasons for nontreatment with interferon in patients with hepatitis C virus infection.



ALT = alanine aminotransferase.

Table. Comparative Demographic Information on Patient Groups*

Variable	Study Group	NHANES Study†	MetroHealth Medical Center‡
All participants, n	327	386	909 805
Sex, %			
Male	63	65	36
Female	37	35	64
Mean age, y§	50	–	–
Ethnicity/race, %			
White	54	61	51
African American	35	20	35
Mexican or Hispanic	10	7	10
Other	1	12	4
Risk factors, %			
Injection drug use	66	–	–
Noninjection drug use	4	42	–
Blood transfusion	12	–	–
Other	7	–	–
None	22	–	–
Insurance status, %			
Medicaid	41	–	33
Medicare	6	–	14
Private insurance	22	–	32
No insurance	31	–	21

* NHANES = National Health and Nutrition Examination Survey.
 † The NHANES study (1) only obtained data on marijuana and cocaine use as drug use–related risk factors for hepatitis C virus infection. Because data on other drug use, specifically intravenous drug use, were not obtained, total drug use in this sample is probably underestimated.
 ‡ The entire patient population at the MetroHealth Medical Center during the study period.
 § Ninety percent of patients in the current study were between 30 and 59 years of age. The NHANES study reported no data on this subject that would yield a meaningful comparison with the present study group.
 || The percentage of all MetroHealth Medical Center patients with risk factors for hepatitis C virus infection is unknown.

in 88% of treated patients and in 17% of untreated patients. Mild or moderate inflammation (Ishak stage 1 or 2) occurred more frequently in the untreated group (92% vs. 78%; $P < 0.05$); however, the proportion of patients with mild versus moderate fibrosis (Ishak stage 1 or 2) did not differ significantly (78% vs. 72%, respectively).

The Table shows the characteristics of our HCV study group, the patients with HCV infection in the National Health and Nutrition Examination Survey (NHANES) (1), and the overall patient population at our medical center during the study period. There was no significant difference in sex between the two HCV groups, but the proportion of men in each of these groups was higher than in the overall population at our medical center. The NHANES group had a lower proportion of African-American patients and a higher proportion of patients classified in the “other” category for

ethnicity/race. The NHANES study only obtained data on marijuana and cocaine use as risk factors. Because history of intravenous drug use was not obtained, total drug use in the NHANES population is probably underestimated compared with our study group. Compared with the entire MetroHealth Center population, our study group of patients with HCV infection had more uninsured persons and Medicaid recipients and had a smaller proportion of persons with private insurance or Medicare coverage.

DISCUSSION

As compared with previously reported treatment results from clinical trials (4–6), interferon-based therapies for HCV infection may be less useful in diverse HCV-infected populations. Most of the patients with HCV seen at our liver clinic, whose characteristics were similar to those of the HCV-infected patients in the general population described in NHANES (1), did not receive interferon-based treatment for the reasons shown in the **Figure**.

Preliminary data from a study in a clinic setting agree with our results (13). These researchers found that 41% of HCV-infected patients were untreated, primarily because patients declined to undergo therapy or had medical contraindications. Another preliminary study (14) found that receiving antiviral therapy depended on the type of medical facility at which the patient was seen: Only 34% of HCV-infected patients seen by community-based gastroenterologists received antiviral therapy compared with 64% at a tertiary referral center and 81% at a military medical center. The reasons for non-treatment in that study were similar to those in our study.

Because injection drug use and low socioeconomic status are currently the factors most strongly associated with HCV infection (15), our HCV-infected population—in whom the prevalence of intravenous drug use was 66% and the prevalence of low socioeconomic status was 72%—had risk factors that represent those of the general HCV-infected population. In fact, our data may overestimate the proportion of HCV-infected patients who receive treatment, because our study included few incarcerated persons; yet, approximately 31% to 50% of the 5 million incarcerated persons in the United

States have HCV infection, and these cases of HCV infection go largely untreated (16).

In summary, these combined data indicate that a large proportion—perhaps the majority—of U.S. patients with chronic HCV infection are not candidates for interferon-based therapy. This information emphasizes the need to develop better-tolerated and more effective antiviral drugs (17), socioeconomically and culturally targeted screening programs (2, 11, 13), interventional strategies for substance abuse (18), and educational interventions to improve adherence to treatment and to decrease comorbid conditions, which increase the risk for progressive liver injury (19, 20).

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