TREATMENT OF ACUTE HEPATITIS C WITH INTERFERON ALFA-2b

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ABSTRACT

Background In people who are infected with the hepatitis C virus (HCV), chronic infection often develops and is difficult to eradicate. We sought to determine whether treatment during the acute phase could prevent the development of chronic infection.

Methods Between 1998 and 2001, we identified 44 patients throughout Germany who had acute hepatitis C. Patients received 5 million U of interferon alfa-2b subcutaneously daily for 4 weeks and then three times per week for another 20 weeks. Serum HCV RNA levels were measured before and during therapy and 24 weeks after the end of therapy.

Results The mean age of the 44 patients was 36 years; 25 were women. Nine became infected with HCV through intravenous drug use, 14 through a needle-stick injury, 7 through medical procedures, and 10 through sexual contact; the mode of infection could not be determined in 4. The average time from infection to the first signs or symptoms of hepatitis was 54 days, and the average time from infection until the start of therapy was 89 days. At the end of both therapy and follow-up, 43 patients (98 percent) had undetectable levels of HCV RNA in serum and normal serum alanine aminotransferase levels. Levels of HCV RNA became undetectable after an average of 3.2 weeks of treatment. Therapy was well tolerated in all but one patient, who stopped therapy after 12 weeks because of side effects.

Conclusions Treatment of acute hepatitis C with interferon alfa-2b prevents chronic infection. (N Engl J Med 2001;345:1452-7.)

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to a polymerase chain-reaction (PCR) assay, and had elevated serum alanine aminotransferase levels. Acute HCV infection was considered to be present if at least one of the following criteria was met: known or suspected exposure to HCV within the preceding four months, documented seroconversion to positivity for antibodies against HCV, or a serum alanine aminotransferase level of more than 350 U per liter (20 times the upper limit of the normal range), with a documented normal level during the year before the infection (normal range, 0 to 17 U per liter for women and 0 to 22 U per liter for men). The high cutoff value for alanine aminotransferase was chosen to prevent the inclusion of patients with chronic hepatitis among patients who did not fulfill the first or second criterion. In the case of patients who had elevated serum alanine aminotransferase levels and positive tests for HCV RNA, but who had no clear exposure to the virus, toxic hepatitis or superinfection with other hepatitis viruses was ruled out. Patients were excluded if they had uncompensated liver disease, liver diseases unrelated to HCV infection, anemia (defined by a hemoglobin level of less than 12 g per deciliter in women and of less than 13 g per deciliter in men), leukopenia (defined as a leukocyte count of less than 3000 per cubic millimeter), thrombocytopenia (defined as a platelet count of less than 100,000 per cubic millimeter), decompensated renal disease (defined by a serum creatinine level of more than 1.5 mg per deciliter [130 μmol per liter]), decompensated thyroid disease, infection with HIV or hepatitis B virus, psychiatric conditions such as severe depression, a history of seizures, poorly controlled autoimmune diseases, a history of organ transplantation, or ongoing abuse of intravenous drugs or alcohol.

Study Design

In order to recruit a sufficient number of patients with acute hepatitis infection, we distributed more than 7000 brochures about the study to hospitals, outpatient clinics, private practices, patient-advocacy groups, and the Berufsverband der deutschen Ärzte (the Central Registry of Work-Related Accidents), which receives data on all work-related accidents in Germany, including needle-stick injuries, even if they do not result in the transmission of any diseases. The brochures also contained detailed recommendations for screening for HCV infection after exposure. Employees of Essex-Pharma (Munich, Germany) helped deliver the brochures to hospitals and private practices, and the study was supported in part by an unrestricted research grant from Essex-Pharma. The study was approved by the ethics committee of the University of Hannover, the Berufsverband der deutschen Ärzte und Wohlfahrtspflege, and the German Association for the Study of the Liver. All patients provided written informed consent.

The patients received 5 million U of interferon alfa-2b (Intron A, Essex-Pharma) subcutaneously daily for the first 4 weeks, followed by a dose of 5 million U three times a week for another 20 weeks. All patients were evaluated as outpatients before therapy (week 0); at weeks 2, 4, 12, and 24 of therapy; and 24 weeks after the end of therapy. Biochemical and hematologic testing was performed by the laboratory at each participating center. Serum levels of HCV RNA were determined centrally, at the Hannover Medical School, before treatment and after each visit (weeks 0, 2, 4, 12, 24, and 48) with use of a reverse-transcription–PCR assay (Cobas AmpliCord HCV C monitor, version 2.0, Roche Diagnostics, Mannheim, Germany) that has a lower limit of detection of 600 copies of HCV RNA per milliliter. Viral genotypes were also determined centrally with use of a second-generation assay (INNO-LIPA HCV II Kit, Innogenetics, Heiden, Germany).

Assessment of Efficacy

The primary end point was a sustained virologic response, defined by the absence of detectable levels of HCV RNA in serum 24 weeks after the end of treatment. Secondary end points were the absence of detectable levels of HCV RNA in serum at the end of therapy and the normalization of serum alanine aminotransferase levels.

Statistical Analysis

We used Student's t-test for paired samples to calculate P values related to blood tests. The comparison was with values before the start of therapy. A P value of less than 0.05 was considered to indicate statistical significance. All P values were two-tailed.

RESULTS

Base-Line Characteristics of the Patients

Forty-four patients fulfilled the inclusion criteria and were treated at a total of 24 centers from March 1998 until March 2001 (1 center treated 15 patients, another center 4 patients, 3 centers treated 2 patients each, and the remaining centers treated a single patient each). All 44 patients were treated, and 43 completed therapy according to the protocol; the remaining patient stopped therapy after 12 weeks because of hair loss and influenza-like symptoms. All patients have completed follow-up. Thirty patients (68 percent) met the first criterion of known or suspected exposure to HCV during the preceding four months (Table 1); 17 of these patients also had documented seroconversion. An additional six patients had documented seroconversion but did not have a documented exposure (four of whom had HCV-positive partners and two for whom the mode of transmission was unclear). Eight patients met only the third criterion, since they had serum alanine aminotransferase levels ranging from 635 to 1500 U per liter with no prior signs of liver disease (six of whom had HCV-positive partners and two for whom the mode of transmission was unclear).

### Table 1. Base-Line Characteristics of the 44 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>36±11</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>25 (57)</td>
</tr>
<tr>
<td>Icterus — no. (%)</td>
<td>30 (68)</td>
</tr>
<tr>
<td>Mode of infection — no. (%)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Intrahepatic drug use</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Needle-stick injury</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Medical procedure</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Sexual contact with HCV-positive partners</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Unclear</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Viral load — copies of HCV RNA ×10⁶/ml</td>
<td>0.42±0.93</td>
</tr>
<tr>
<td>Alamine transaminase — U/liter</td>
<td>885±554</td>
</tr>
<tr>
<td>HCV genotype — no. (%)</td>
<td>27 (61)</td>
</tr>
<tr>
<td>1</td>
<td>12 (27)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>0</td>
</tr>
<tr>
<td>Unclear</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD.*

[The medical procedures consisted of dental surgery, aortic-valve replacement, gynecologic laparoscopy, transrectal biopsy, resection of sigmoid colon, skin surgery, and varicocelectomy surgery.]

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All 44 patients had hepatitis as defined by elevated serum alanine aminotransferase levels (lowest level, 140 U per liter) (Table 1). Serocconversion was documented in 52 percent. The most frequent sources of infection were a needle-stick injury (in 32 percent of patients), sexual contact with HCV-positive partners (in 23 percent), intravenous drug use (in 20 percent), and medical procedures (in 16 percent). All seven medical procedures were surgical in nature. The average time from infection to the first signs or symptoms of disease was 54 days (range, 15 to 105), and the average time from infection until the start of therapy was 89 days (range, 30 to 112).

**Efficacy**

In all 44 patients, serum levels of HCV RNA became undetectable during therapy (Fig. 1). The average time for levels of HCV RNA to become undetectable after the beginning of treatment was 3.2 weeks (range, 2 to 12). After 24 weeks of follow-up, 43 patients (98 percent) had undetectable levels of HCV RNA.

Serum levels of alanine aminotransferase fell rapidly during therapy and normalized within 10.4 weeks after the initiation of treatment (range, 2 to 48). At the end of the 24 weeks of therapy, 80 percent of the patients had a normal serum alanine aminotransferase level. The remaining 20 percent of patients had only a mild elevation in alanine aminotransferase, with levels not more than twice the upper limit of the normal range. All 9 of these patients had normal liver-enzyme values after the end of therapy, and the 42 patients who had undetectable levels of HCV RNA after 24 weeks of follow-up also had normal serum alanine aminotransferase levels by the end of follow-up.

One patient, who stopped therapy after 12 weeks, had a self-limited flare of hepatitis with HCV viremia at week 20 and subsequently had undetectable levels of HCV RNA in serum. The patient had persistently normal levels of aminotransferases and had no detectable serum levels of HCV RNA during a further follow-up of 12 months after the relapse of hepatitis.

Another patient, who had stable multiple sclerosis, received a short course of pulsed corticosteroids at week 17 for neurologic symptoms while continuing to receive interferon alfa-2b. Although the neurologic symptoms improved, the patient's serum alanine aminotransferase levels increased 15 days after the end of interferon therapy. She had a positive HCV RNA assay 35 days after therapy ended. Because of the persistently elevated alanine aminotransferase levels and the rising levels of HCV RNA, the patient received combination therapy with interferon alfa-2a (6 million U subcutaneously three times a week) and ribavirin (400 mg twice a day) starting 89 days after therapy ended. She had undetectable serum levels of HCV RNA and normal serum levels of alanine aminotransferase after three weeks of combination therapy. These findings
were still present at the time of her most recent fol-
low-up (week 37 of combination therapy), and no fur-
ther neurologic deterioration was noted.

Safety

Therapy was well tolerated in all patients except
the one who discontinued treatment. The spectrum
of side effects was similar to that reported in previous
trials of monotherapy with interferon alfa-2b.27,28

There were no serious adverse effects during therapy.
The incidence of adverse effects was not higher dur-
ing the initial 4 weeks of daily dosing than during the
subsequent 20 weeks. None of the 43 patients who
completed treatment required a dose modification. No
signs of decreased liver function (as measured clini-
cally and on the basis of coagulation activity and se-
rum albumin levels) were noted during acute HCV
infection, interferon therapy, or the hepatitis flares
in the two patients who had relapses. In all patients,
thrombocytopenia (mean ±SD) platelet count at
week 4, 161,000±43,000 per cubic millimeter, as
compared with 250,000±66,000 per cubic milli-
meter before therapy; P<0.001) and leukopenia (mean
leukocyte count at week 4, 3900±1100 per cubic mil-
limeter, as compared with 6600±1500 per cubic mil-
limeter before therapy; P<0.01) developed during
therapy and resolved after the end of therapy.

We enrolled a large number of patients in a short
period by conducting a nationwide study that includ-
ed a suggested protocol for screening after suspected
exposure to HCV. Although it is possible that our
findings apply only to a subgroup of seriously ill pa-
ients, we believe that our methods of enrollment
minimized the likelihood of a referral bias.

We did not include a placebo group. However,
when our results are compared with those among pa-
ients who did not receive therapy after acute HCV
infection, the beneficial effect of early treatment is
clear. A group of 40 untreated patients who were
seen and prospectively followed during a similar ob-
servation period (1995 to 2000) at the clinic of in-
fectious diseases of the University of Bari in Italy3
had base-line characteristics (mean age, 40 years; 42
percent were women, and 50 percent had icterus)
and a distribution of HCV genotypes (53 percent had
genotype 1, 35 percent had genotype 2 or 3, and
5 percent had genotype 4) that were similar to those
of our patients. Chronic HCV infection developed
in 70 percent of these untreated patients. This rate is
similar to the rate of chronic infection in other stud-
ies.4,44 Although rates of conversion to chronic HCV
infection of 50 to 55 percent have been found in some
groups of children45 and young women,211 most stud-
ies have reported rates of 70 to 84 percent, even af-
ter the exclusion of patients with transfusion-associ-
ated HCV.3,6,8,14,41,44,46

It is likely that about 30 percent of our patients
would have had self-limited disease, regardless of
whether they received interferon alfa-2b. So far, there
are no means to identify such patients at presenta-
tion.42 Since the current treatment for chronic HCV
infection eliminates the virus in only about half of
cases,12,13,38 we suggest that all patients with acute
hepatitis C should be treated. The value of other treat-
ments, such as peginterferon alfa should also be stud-
ied. Since all our patients had hepatitis, as defined by
an elevated serum alanine aminotransferase level, our
findings may not apply to patients with HCV RNA
in serum and normal serum liver-enzyme levels after
acute infection. However, we did not identify any
such patients during our national study.

In summary, early treatment of acute hepatitis C
with interferon alfa-2b alone prevents the develop-
ment of chronic HCV infection in almost all pa-
tients. The response to interferon alfa-2b was not
influenced by the viral genotype, the patients' sex, or
the mode of transmission. The use of interferon alone
rather than in combination with ribavirin — the stan-
dard therapy for chronic HCV infection — results in
fewer side effects and lower costs. Furthermore, a 24-
week course of treatment was sufficient to prevent
chronic infection. The suggested course of treatment
is 48 weeks in patients with chronic infections with
HCV genotype la or lb.27,28 Even shorter periods of
treatment might be sufficient in patients in whom
serum levels of HCV RNA quickly become unde-
tectable.

There is no standard therapy for acute HCV in-
fec tion.29 Several studies have evaluated the efficacy
of interferon therapy for acute HCV infection,6,8,30-41
and all but one8 reported a beneficial effect of treat-
ment. However, these studies had substantial limita-
tions. Some included primarily patients with trans-
fusion-associated HCV infection,28-30 some were very
small,29,33,35,37,39-41 and others used interferon beta34,35
or treated patients for only a short period.8,30,32,34,36,40
Not all studies measured outcome on the basis of se-
rum levels of HCV RNA.35,36,38 A larger prospective
trial with a more representative group of patients was
therefore needed.3,42

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APPENDIX

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