Peginterferon Alfa-2a in Patients with Chronic Hepatitis C and Cirrhosis

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PEGINTERFeron ALFA-2a IN PATIENTS WITH CHRONIC HEPATITIS C AND CIRRHOSIS

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ABSTRACT

Background Chronic hepatitis C virus (HCV) infection in patients with cirrhosis is difficult to treat. In patients with chronic hepatitis C but without cirrhosis, once-weekly administration of interferon modified by the attachment of a 40-kd branched-chain polyethylene glycol moiety (peginterferon alfa-2a) is more efficacious than a regimen of unmodified interferon. We examined the efficacy and safety of peg-interferon alfa-2a in patients with HCV-related cirrhosis or bridging fibrosis.

Methods We randomly assigned 271 patients with cirrhosis or bridging fibrosis to receive subcutaneous treatment with 3 million units of interferon alfa-2a three times weekly (88 patients), 90 µg of peginterferon alfa-2a once weekly (96), or 180 µg of peginterferon alfa-2a once weekly (87). Treatment lasted 48 weeks and was followed by a 24-week follow-up period. We assessed efficacy by measuring HCV RNA and alanine aminotransferase and by evaluating liver-biopsy specimens. A histologic response was defined as a decrease of at least 2 points on the 22-point Histological Activity Index.

Results In an intention-to-treat analysis, HCV RNA was undetectable at week 72 in 8 percent, 15 percent, and 30 percent of the patients treated with interferon alfa-2a and with 90 µg and 180 µg of peginterferon alfa-2a, respectively (P = 0.001 for the comparison between 180 µg of peginterferon alfa-2a and interferon alfa-2a). At week 72, alanine aminotransferase concentrations had normalized in 15 percent, 20 percent, and 34 percent of patients, respectively (P = 0.004 for the comparison between 180 µg of peginterferon alfa-2a and interferon alfa-2a). In the subgroup of 184 patients with paired liver-biopsy specimens, the rates of histologic response at week 72 were 31 percent, 44 percent, and 54 percent, respectively (P = 0.02 for the comparison between 180 µg of peginterferon alfa-2a and interferon alfa-2a). All three treatments were similarly tolerated.

Conclusions In patients with chronic hepatitis C and cirrhosis or bridging fibrosis, 180 µg of peginterferon alfa-2a administered once weekly is significantly more effective than 3 million units of standard interferon alfa-2a administered three times weekly.

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I NTERFERON has had a fundamental role in the treatment of patients with chronic hepatitis C virus (HCV) infection. In patients with cirrhosis, interferon, either alone or in combination with ribavirin, has been used cautiously, largely because it may exacerbate the patients’ neutropenia and thrombocytopenia.1 In large trials of interferon-based therapies, the proportion of patients with HCV-related advanced liver disease has been small,2 6 and we are aware of only two studies that have focused exclusively on such treatment in patients with HCV-related cirrhosis.7 8

To overcome some of the drawbacks of interferon, a modified form of the drug, called peginterferon alfa-2a, was developed by attaching a 40-kd branched-chain polyethylene glycol moiety to interferon alfa-2a.9 11 Recent data12 suggest that the sustained virologic response achieved with peginterferon alfa-2a is similar to that observed for interferon alfa-2a in combination with ribavirin in patients with hepatitis C.13 In addition, the tolerability of peginterferon is similar to that of the unmodified drug.12 We compared the efficacy and safety of two doses of peg-interferon alfa-2a, each given once weekly, with the efficacy and safety of a standard regimen of unmodified interferon alfa-2a in patients with hepatitis C cirrhosis or bridging fibrosis.

METHODS

Patients

Patients who had chronic HCV infection and biopsy-proved liver cirrhosis or bridging fibrosis and who had not previously been treated with interferon were eligible for the study if the following two conditions were met: the serum alanine aminotrans-
treatment assignments. HCV genotyping was performed by se-
at week 72 by pathologists who were unaware of the patients’
subsequently coded and evaluated in parallel with those obtained

Study Design

This open-label, randomized, parallel-dose study was conduct-
ed by the Pegasys International Study Group at 30 centers in the
United States, Canada, Australia, and the United Kingdom between
September 1997 and October 1999. The study was approved by
the ethics committees at each center, and all the patients provided
written informed consent. The trial was designed by F Hoffmann–
LaRoche and by expert hepatologists in conjunction with the health
authorities in each country. F. Hoffmann–LaRoche was respon-
sible for monitoring adherence to the International Conference on
Harmonization guidelines
and for monitoring the analysis of
data collected by the investigators.

Patients who met the criteria for entry were randomly assigned
to receive, in a 1:1 ratio, interferon alfa-2a (Roferon-A, F Hoff-
mann–LaRoche, Basel, Switzerland) at a dose of 3 million units
given subcutaneously three times weekly or peginterferon alfa-2a
(Pegasys, F Hoffmann–LaRoche) at a dose of 90 µg or 180 µg
given subcutaneously once weekly. Randomization was performed
according to center, in blocks of six patients, and random assign-
ments were made according to a computer-generated scheme man-
aged by Applied Logistic Associates (Houston). Patients adminis-
tered the study drug subcutaneously on an outpatient basis for 48
weeks and then were followed for the next 24 weeks.

Laboratory tests, including assessments of plasma HCV RNA
levels and serum alanine aminotransferase concentrations, viral
genotyping, and histologic evaluation of biopsy specimens, were
performed at central laboratories. Pretreatment biopsy specimens
were examined withoutblinding before randomization and were
subsequently coded and evaluated in parallel with those obtained
at week 72 by pathologists who were unaware of the patients’
treatment assignments. HCV genotyping was performed by se-
quence analysis of a portion of the 5’ untranslated region of the
viral genome at the end of the study.

Safety was assessed by an-
alyzing the occurrence of adverse events, changes in vital signs, and
the results of laboratory tests recorded at weeks 1, 2, 4, 6, and 8
of the study and then every 4 weeks for the remainder of the 72-
week study period.

The protocol guidelines allowed dose modification (a 25%, 50,
or 75% reduction in the assigned dose) for patients who had
important adverse events or important abnormalities in laboratory
values. If a patient received more than three consecutive reduced
doses or more than a total of six reduced doses, the dose could
not subsequently be increased. Patients were withdrawn from the
study if they missed four consecutive weeks of treatment or if an
investigator was concerned about their safety.

Assessment of Efficacy

The primary end points were sustained virologic and biochem-
ical responses. A sustained virologic response was defined as un-
detectable levels of HCV RNA (<100 copies per milliliter) on
analysis (Cobas Amplicor HCV Test version 2.0, Roche Diag-
nostics, Branchburg, N.J.) at the end of the follow-up period. A
sustained biochemical response was defined as an alanine amin-
transferase value below the upper limit of the normal range at
the end of the follow-up period. Other end points included virologic
and biochemical responses at the end of the 48-week treatment
period. Liver-biopsy specimens were evaluated for changes from
values at the beginning of treatment (base line) in the score on the
22-point Histological Activity Index, where inflammation is graded
from 0 (none) to 18 (severe) and fibrosis is graded from 0 (none)
to 4 (cirrhosis). A histologic response at week 72 was defined as
a decrease of at least 2 points in the total score on this index (fibrosis
and inflammation scores combined, with a fibrosis score of 3 in-
dicating bridging fibrosis).

Statistical Analysis

In comparisons of the peginterferon groups with the interferon
group, all categorical variables were analyzed with use of the Coch-
ran–Mantel–Haenszel test, with stratification according to center.
To control the overall probability of a type I error (5 percent),
a two-sided significance level of 0.025 was used for the two pair-
wise treatment comparisons (peginterferon alfa-2a at each of two
doses vs. interferon alfa-2a). All end points (except for changes
from base-line histologic findings) were evaluated by intention-
to-treat analysis. The analysis of histologic response included only
patients who underwent both a pretreatment biopsy and a biopsy
at week 72. The analysis of safety included all the patients who
received at least one dose of study medication and who under-
went at least one assessment of safety during the study.

RESULTS

Characteristics of the Patients

Of the 397 patients screened, 271 met the criteria
for entry and underwent randomization. The main
reasons for exclusion from the study were histologic
features that did not suggest cirrhosis or bridging fi-
brosis (67 patients), a low platelet count (12), and a
normal alanine aminotransferase concentration (10); 37
patients were excluded for other reasons. Two pa-
tients assigned to interferon alfa-2a did not receive
treatment, and one assigned to 180 µg of peginter-
feron alfa-2a elected alternative therapy; all three
were included in the intention-to-treat analysis of ef-
ficacy. Characteristics of the patients at base line
were similar among the three groups.

Of the 271 eligible patients, 88 were randomly as-
signed to treatment with 3 million units of interfer-
onalfa-2a, and 96 and 87 were randomly assigned
to treatment with 90 µg and 180 µg of peginter-
feron alfa-2a, respectively. Treatment was completed
by 64, 78, and 67 patients, respectively, and follow-up
was completed by 68, 79, and 74 patients. Patients
who discontinued drug therapy were encouraged to
remain in the study for assessments through week
72. The main reasons for withdrawal were adverse
events, failure to return or refusal of treatment, in-
sufficient therapeutic effects, or laboratory abnormal-
ities (Table 2).

Virologic Response

The rates of sustained virologic response (the re-
response at week 72) were 8 percent, 15 percent, and
30 percent in patients assigned to unmodified inter-
feron alfa-2a, 90 µg of peginterferon alfa-2a, and 180
µg of peginterferon alfa-2a, respectively (P=0.001
for the comparison between 180 µg of peginterfer-
onalfa-2a and interferon alfa-2a [Table 3]). A response
to therapy at week 12 predicted a sustained response;
at week 12, all of the 26 patients who had a sustained
response to 180 µg of peginterferon alfa-2a had had a decrease in viral load by a factor of at least 100 as compared with base line, and 23 of them had had undetectable HCV RNA.

Peginterferon alfa-2a was also associated with a higher rate of virologic response at the end of treatment (week 48) (Table 3). HCV RNA was undetectable at week 48 in 14 percent of the patients assigned to receive interferon alfa-2a, as compared with 42 percent of the patients assigned to receive peginterferon alfa-2a at a dose of 90 µg and 44 percent of the patients assigned to receive it at a dose of 180 µg (P=0.001 for the comparison between each dose of peginterferon alfa-2a and interferon alfa-2a). Although the virologic rate of response at the end of treatment was similar with the two doses of peginterferon alfa-2a, the response was more likely to be sustained with the 180-µg dose.

### Biochemical Response

A biochemical response was more likely to be sustained with the higher dose of peginterferon alfa-2a (Table 3). The rates of biochemical response at week 72 were 15 percent, 20 percent, and 34 percent in patients assigned to receive interferon alfa-2a, 90 µg of peginterferon alfa-2a, and 180 µg of peginterferon alfa-2a.
The percentages of patients who had both a biochemical and a virologic response at week 72 were identical to the percentages who had a virologic response at that time (Table 3).

**Histologic Response**

Most of the 271 patients enrolled had cirrhosis at baseline (Table 1). As is common with other trials in patients with liver disease,\textsuperscript{2,3} nearly one third of the patients did not return for second biopsies. Among the 184 patients with paired liver biopsies, the proportion who had a histologic response was lower among the patients assigned to receive unmodified interferon (31 percent) than among those assigned to 90 µg of peginterferon alfa-2a (44 percent [P=0.22]) and those assigned to 180 µg (54 percent [P=0.02]).

### Table 2. Rates of Discontinuation of Treatment and Dose Modification.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERFERON ALFA-2a (N=88)</th>
<th>PEGINTERFERON ALFA-2a 90 µg (N=96)</th>
<th>PEGINTERFERON ALFA-2a 180 µg (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to adverse events</td>
<td>7 (8)</td>
<td>7 (7)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Due to laboratory abnormality</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Due to insufficient therapeutic response</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other reasons†</td>
<td>10 (11)</td>
<td>5 (5)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Dose modification‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to neutropenia</td>
<td>12 (14)</td>
<td>9 (9)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Due to thrombocytopenia</td>
<td>5 (6)</td>
<td>17 (18)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Due to adverse event</td>
<td>12 (14)</td>
<td>2 (2)</td>
<td>12 (14)</td>
</tr>
</tbody>
</table>

*Dose modification was defined as the reduction or omission of one or more doses.

†Other reasons included administrative factors, refusal of treatment, failure to return for additional treatment, and protocol violation.

‡One or more doses were modified or were not given.

### Table 3. Virologic, Biochemical, and Histologic Responses.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERFERON ALFA-2a (N=88)</th>
<th>PEGINTERFERON ALFA-2a 90 µg (N=96)</th>
<th>PEGINTERFERON ALFA-2a 180 µg (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>12 (14)</td>
<td>40 (42)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Week 72</td>
<td>7 (8)</td>
<td>14 (15)</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Biochemical response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>19 (22)</td>
<td>34 (35)</td>
<td>34 (39)</td>
</tr>
<tr>
<td>Week 72</td>
<td>13 (15)</td>
<td>19 (20)</td>
<td>30 (34)</td>
</tr>
<tr>
<td>Combined virologic and biochemical response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>9 (10)</td>
<td>30 (31)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Week 72</td>
<td>7 (8)</td>
<td>14 (15)</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Histologic response†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 72</td>
<td>17/55 (31)</td>
<td>27/61 (44)</td>
<td>37/68 (54)</td>
</tr>
</tbody>
</table>

*The assessments of efficacy were carried out by intention-to-treat analysis and included all enrolled patients, regardless of whether they withdrew from the study prematurely or discontinued treatment. A virologic response was defined as an undetectable level of HCV RNA (<100 copies per milliliter). A biochemical response was defined as an alanine aminotransferase value below the upper limit of normal. A histologic response was defined as a decrease of at least 2 points in the total score on the Histological Activity Index (on which a score of 3 indicates bridging fibrosis, and a score of 4 cirrhosis).

†Values are the numbers of patients with a histologic response divided by the total number with paired biopsy specimens.
A histologic response correlated with a sustained virologic response; among the patients with a virologic response at week 72, 80 percent of those assigned to receive interferon alfa-2a also had a histologic response, as did 100 percent of those assigned to 90 µg of peginterferon alfa-2a and 88 percent of those assigned to the 180-µg dose. The virologic response was similar among patients with bridging fibrosis or cirrhosis. A histologic response was seen in 26 percent, 33 percent, and 35 percent, respectively, of patients who did not have a sustained virologic response. The histologic response also correlated with the biochemical response at week 72: 40 percent, 79 percent, and 82 percent of the patients who had a biochemical response to interferon alfa-2a or peginterferon alfa-2a at 90 µg or 180 µg, respectively, also had a histologic response.

Correlation of Base-Line Characteristics with Virologic Response

The rates of sustained virologic response with respect to pretreatment variables are presented in Table 4. Treatment with peginterferon alfa-2a was consistently associated with higher rates of sustained viro-

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**Table 4. Rates of Virologic Response at Week 72 as a Function of Base-Line Prognostic Variables.***

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERFERON ALFA-2a (N=88)†</th>
<th>PEGINTERFERON ALFA-2a (N=96)</th>
<th>PEGINTERFERON ALFA-2a (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>90 µg</td>
<td>180 µg</td>
</tr>
<tr>
<td>Alanine aminotransferase quotient‡</td>
<td>2/48 (4)</td>
<td>8/52 (15)</td>
<td>7/28 (25)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5/40 (12)</td>
<td>6/44 (14)</td>
<td>19/59 (32)</td>
</tr>
<tr>
<td>HCV RNA level (copies/ml)</td>
<td>2/41 (5)</td>
<td>10/45 (22)</td>
<td>16/43 (37)</td>
</tr>
<tr>
<td>&lt;2,000,000</td>
<td>4/45 (9)</td>
<td>4/51 (8)</td>
<td>10/44 (23)</td>
</tr>
<tr>
<td>&gt;2,000,000</td>
<td>1/47 (2)</td>
<td>3/58 (5)</td>
<td>6/48 (12)</td>
</tr>
<tr>
<td>HCV genotype 1</td>
<td>0/28</td>
<td>1/27 (4)</td>
<td>3/33 (9)</td>
</tr>
<tr>
<td>1a</td>
<td>1/19 (5)§</td>
<td>2/31 (6)</td>
<td>3/15 (20)</td>
</tr>
<tr>
<td>1b</td>
<td>6/41 (15)</td>
<td>11/38 (29)</td>
<td>20/39 (51)</td>
</tr>
<tr>
<td>Other than 1 or unknown</td>
<td>0/5</td>
<td>1/13 (8)</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>Total Histological Activity Index score¶</td>
<td>7/83 (8)</td>
<td>13/83 (16)</td>
<td>24/82 (29)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>5/67 (7)</td>
<td>11/76 (14)</td>
<td>22/69 (32)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2/21 (10)</td>
<td>3/19 (16)</td>
<td>4/18 (22)</td>
</tr>
<tr>
<td>Histologic diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5/67 (7)</td>
<td>11/76 (14)</td>
<td>22/69 (32)</td>
</tr>
<tr>
<td>Bridging fibrosis</td>
<td>2/21 (10)</td>
<td>3/19 (16)</td>
<td>4/18 (22)</td>
</tr>
<tr>
<td>HCV genotype in relation to RNA level 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2,000,000</td>
<td>0/21</td>
<td>3/26 (12)</td>
<td>3/19 (16)</td>
</tr>
<tr>
<td>&gt;2,000,000</td>
<td>1/25 (4)§</td>
<td>0/22</td>
<td>3/29 (10)</td>
</tr>
<tr>
<td>Other than 1</td>
<td>2/20 (10)</td>
<td>6/18 (33)</td>
<td>12/22 (55)</td>
</tr>
<tr>
<td>&lt;2,000,000</td>
<td>4/20 (20)</td>
<td>4/18 (22)</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/2 (100)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>&gt;2,000,000</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Values are the numbers of patients with a virologic response at week 72 divided by the numbers with the given base-line variable. A virologic response was defined as an undetectable level of HCV RNA (<100 copies per milliliter).

†HCV RNA levels were not measured in the two patients in this group who did not receive treatment.

‡The alanine aminotransferase quotient is the average of the alanine aminotransferase values before treatment divided by the upper limit of normal.

§This patient elected to continue treatment with an alternative regimen of interferon alfa-2a at the end of follow-up and was receiving interferon alfa-2a at the time of the assessment at week 72.

¶The total Histological Activity Index score is the sum of two scores, one for inflammation (0 [none] to 18 [severe]) and one for fibrosis (0 [none] to 4 [cirrhosis]); a fibrosis score of 3 indicates bridging fibrosis.

| Unknown | 1/2 (100) | 1/2 (50) | 1/2 (50) |
| >2,000,000 | 0/1 | 0/1 | 0/1 |
logic response among subgroups of patients defined by factors such as genotype and pretreatment viral load. Among patients with cirrhosis, the rate of sustained virologic response associated with the dose of 180 µg of peginterferon alfa-2a was more than four times that associated with the dose of interferon alfa-2a (32 percent vs. 7 percent). Among patients infected with HCV genotype 1, the rates of sustained virologic response were 2 percent, 5 percent, and 13 percent, respectively, in those assigned to interferon alfa-2a and peginterferon alfa-2a at 90 µg and 180 µg. Treatment with 180 µg of peginterferon alfa-2a was more efficacious in treating infection with genotype 1b than infection with genotype 1a (rates of virologic response at week 72, 20 percent and 9 percent). Among patients with HCV genotypes other than 1 (or with no data on genotype), the rates of sustained virologic response were 15 percent, 29 percent, and 51 percent, respectively, in patients assigned to interferon and peginterferon alfa-2a at 90 µg and 180 µg. Among patients with a combination of poor prognostic factors (infection with genotype 1 and a high viral load at baseline (>2,000,000 copies per milliliter)), 10 percent of those assigned to 180 µg of peginterferon alfa-2a and none of those assigned to 90 µg had a sustained virologic response.

Safety

Information about discontinuation of treatment and dose modifications is shown in Table 2. In patients with cirrhosis, exacerbation of cirrhosis-related neutropenia and thrombocytopenia is a risk associated with the use of interferon. In this study, the mean (±SD) neutrophil counts at baseline were 3400±2100, 3400±1200, and 3100±1100 per cubic millimeter, respectively, in patients assigned to receive unmodified interferon alfa-2a, 90 µg of peginterferon alfa-2a, and 180 µg of peginterferon alfa-2a. These values decreased shortly after the initiation of treatment but stabilized during treatment and then rapidly returned to baseline values after the end of treatment. The proportion of patients with a neutrophil count below 500 per cubic millimeter at any time during treatment was similar in the three groups (3 percent with interferon alfa-2a, and 3 percent and 1 percent with 90 µg and 180 µg of peginterferon alfa-2a, respectively). In none of the patients did a serious infection or sepsis associated with neutropenia develop. Dose modification (defined as reduction or omission of one or more doses of study medication) because of neutropenia was deemed necessary in 14 percent of the patients assigned to interferon alfa-2a and 9 percent and 11 percent of those assigned to 90 µg and 180 µg of peginterferon alfa-2a, respectively. Only rarely (in two patients receiving peginterferon alfa-2a at 180 µg) was permanent dose modification necessary, and no patient discontinued treatment because of neutropenia.

In most of the patients the total platelet count decreased to some extent during treatment. At base line, the mean platelet counts were 153,000±51,300, 162,000±54,100, and 166,000±50,600 per cubic millimeter in the patients assigned to interferon alfa-2a, 90 µg of peginterferon alfa-2a, and 180 µg of peginterferon alfa-2a. These values reached a nadir of 128,000±47,600, 110,000±42,300, and 108,000±50,100 per cubic millimeter, respectively, by week 8. The platelet count decreased to a level below the entry criterion of 75,000 per cubic millimeter in 27 percent, 48 percent, and 46 percent of patients, respectively. The proportion of patients with a platelet count below 50,000 per cubic millimeter at any time during treatment was significantly lower among those assigned to interferon alfa-2a (7 percent) than among those assigned to peginterferon alfa-2a at 90 µg (26 percent, P<0.001) or 180 µg (19 percent, P=0.04). None of the patients had clinically significant bleeding associated with thrombocytopenia. Dose modification was deemed necessary because of thrombocytopenia in 6 percent, 18 percent, and 19 percent of the patients receiving interferon and 90 µg and 180 µg of peginterferon alfa-2a, respectively; permanent dose modification was necessary in 4 percent, 8 percent, and 13 percent. Discontinuation of therapy because of thrombocytopenia was infrequent (it was required in 2 percent, 4 percent, and 2 percent of patients, respectively).

In all three treatment groups, the adverse events were typical of those produced by unmodified interferon alfa. Table 5 summarizes the adverse events that were reported during treatment or within eight weeks after the end of treatment. The incidence of most of the adverse events was similar in the three treatment groups; the most commonly reported events were fatigue, headache, myalgia, rigors, and pyrexia. A higher proportion of the patients assigned to receive peginterferon alfa-2a at a dose of 180 µg had myalgia and inflammation at the injection site than of patients in the other two groups. Dose modification was necessary because of adverse events in 14 percent of the patients assigned to interferon alfa-2a and in 2 percent and 14 percent of those assigned to peginterferon alfa-2a at 90 µg and 180 µg, respectively. Treatment was discontinued because of adverse events in 8 percent, 7 percent, and 13 percent of patients, respectively (Table 2).

Four deaths were reported, one in a patient assigned to receive 90 µg of peginterferon alfa-2a and three in patients assigned to receive 180 µg. Two patients died of hepatic failure; 420 and 179 days after the end of treatment; one patient died of hepatic neoplasm, 219 days after the end of treatment; and one patient who had received 180 µg of peginterferon alfa-2a died of a cerebral hemorrhage after a suspected methadone overdose, 24 days after the end of treatment. In the latter patient, the platelet count was 64,000 per cu-
The use of a combination of peginterferon alfa-2a and ribavirin will require evaluation by direct comparison with a combination of standard interferon and ribavirin. Although a phase 2 study of peginterferon alfa-2a and ribavirin has been conducted, full results are not yet available.

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DISCUSSION

Patients with chronic HCV infection and advanced liver disease usually have poor responses to treatment with interferons. Our study found that peginterferon alfa-2a produces higher rates of virologic, biochemical, and histologic responses than unmodified interferon alfa-2a among patients with chronic HCV infection and related compensated cirrhosis or bridging fibrosis. In most patients who had a virologic response at week 72, this sustained response could be predicted by measurement of HCV RNA at week 12. Our results are similar to those obtained in a large trial involving patients with chronic HCV infection who were treated with the same formula-

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>INTERFERON ALFA-2a (N=86)</th>
<th>PEGINTERFERON ALFA-2a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 µg (N=96)</td>
<td>180 µg (N=86)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52 (60)</td>
<td>51 (53)</td>
</tr>
<tr>
<td>Headache</td>
<td>46 (53)</td>
<td>52 (54)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>33 (38)</td>
<td>35 (36)</td>
</tr>
<tr>
<td>Rigors</td>
<td>39 (45)</td>
<td>36 (38)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31 (36)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (34)</td>
<td>29 (30)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>21 (24)</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Depression</td>
<td>18 (21)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (19)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Inflammation at injection site</td>
<td>12 (14)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19 (22)</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19 (22)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (16)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (8)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (15)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (7)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (5)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>6 (7)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12 (14)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Pain</td>
<td>10 (12)</td>
<td>10 (10)</td>
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<tr>
<td>Sinusitis</td>
<td>6 (7)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>10 (12)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Pain in limb</td>
<td>4 (5)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (7)</td>
<td>11 (11)</td>
</tr>
</tbody>
</table>

*The adverse events listed are those that occurred in at least 10 percent of the patients. Values are based on the patients who received at least one dose of study medication.
Dr. Heathcote is a member of an advisory board for F. Hoffmann-LaRoche. Dr. Shiffman is a speaker for Schering-Plough, Amgen, and E. Hoffmann-LaRoche and is on the advisory boards for Roche Molecular Systems and F. Hoffmann-LaRoche. Dr. DuShaw has served as a consultant to Schering-Plough, F. Hoffmann-LaRoche, and Zanatelli and Amgen. Dr. Lee is a consultant to and participates in speakers’ bureaus for SmithKline Beecham, Glaxo Wellcome, and F. Hoffmann-LaRoche. Dr. Reindollar is a speaker for Schering-Plough and F. Hoffmann-LaRoche. Dr. Reddy is a speaker for Schering-Plough, Amgen, and E. Hoffmann-LaRoche and is on advisory boards for Roche Molecular Systems and F. Hoffmann-LaRoche. Dr. Wright is a speaker for and is on an advisory board for F. Hoffmann-LaRoche.

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APPENDIX

In addition to the authors, members of the study group who participated in this study were: V. Bain, University of Alberta, Edmonton, Canada; M.F. Bassendine, Freeman Hospital, Newcastle upon Tyne, United Kingdom; C.L. Berg, University of Virginia Health System, Charlottesville, Va.; D.T. Boy-er, Emory University School of Medicine, Atlanta; M. DeMicco, Associated Gastroenterology Medical Group Clinical Research, Anaheim, Calif.; P. Desmond, St. Vincent’s Hospital, Melbourne, Victoria, Australia; G. Farrall, Westmead Hospital, Westmead, Australia; M. Fried, University of North Carolina, Chapel Hill; K. Lindsay, Ambulatory Health Center, University of Southern California, Los Angeles; P.K. Maley, University of Texas Southwestern Medical Center, Dallas; P. Martín, UCLA School of Medicine, Los Angeles; G.Y. Minuk, Health Sciences Centre, Winnipeg, Man., Canada; D.K. Moonka, Henry Ford Hospital, Detroit; N.V. Naoumov, University College London Medical School, London; J. O’Grady, King’s College School of Medicine and Dentistry, London; S. Fedder and B.P. Rae, Hoffmann-LaRoche, Nutley, N.J.; P.I. Pockros, Scripps Clinic, La Jolla, Calif.; W. Rosenberg, University of Southampton School of Medicine, Southampton, United Kingdom; S. Ryder, Queen’s Medical Center, Nottingham, United Kingdom; M. Sherman, Toronto General Hospital, Toronto, C. Smith, Minnesota Clinical Research Center, St. Paul; H.C. Thomas, St. Mary’s Hospital, London; and S. Whalley, Royal Free Hospital, London. Members of the Safety Review Board were: C. Ghent, St. Thomas’s Hospital, London; S. Whalley, Royal Free Hospital, London; and S. Whalley, Royal Free Hospital, London.

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