# Histologic Outcomes in Hepatitis C–Infected Patients with Varying Degrees of Virologic Response to Interferon-Based Treatments

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**Patients with chronic hepatitis C with partial virologic response or nonresponse to interferon-based therapies can experience treatment-related improvements in liver histology. This retrospective analysis assessed the histologic response to treatment in patients with varying degrees of virologic response (sustained virologic response [SVR], breakthrough, relapse, or nonresponse), time to hepatitis C virus (HCV) RNA undetectability, and duration of viral suppression. Patients (HCV genotypes 1-6) with baseline and follow-up liver biopsies from eight phase 2 to phase 4 interferon-based trials were analyzed. Blinded biopsies were evaluated by a single pathologist. Improvements or worsening of METAVIR necroinflammatory activity and fibrosis were defined as increase or decrease of $\geq$1 grading category from baseline to 24 weeks after end of treatment. A majority of the 1571 patients with paired biopsy data were white, male, with HCV genotype 1/4, baseline HCV RNA levels >800,000 IU/mL, and baseline alanine aminotransferase levels $\leq$3 × upper limit of the normal range; mean baseline activity and fibrosis scores were 1.8 and 1.7, respectively. Overall, 80% of patients received peginterferon alfa-2a monotherapy or peginterferon alfa-2a/ribavirin combination therapy. Mean treatment duration was 46 weeks. There was a positive correlation between the degree of virologic response and improvements in METAVIR activity and fibrosis, and an inverse correlation with worsening activity and fibrosis (all comparisons, $P < 0.0001$). Patients with SVR had the greatest histologic benefit. As a combined group, relapsers and patients with breakthrough had significantly greater benefits than nonresponders (activity, $P = 0.0001$; fibrosis, $P = 0.003$). Consistent with these results, a better histologic response was correlated with a shorter time to undetectable HCV RNA and a longer duration of viral suppression (all comparisons, $P < 0.0001$). *Conclusion:* In patients with chronic hepatitis C who were treated with interferon-based therapies, histologic benefits may be observed even in the absence of an SVR. (HEPATOLOGY 2010;52:1193-1200)**

Although viral clearance is the primary goal of hepatitis C virus (HCV) treatment, improvements in liver histology, characterized by decreases in inflammatory and fibrosis scores, have also been documented in numerous clinical trials. In the majority of these trials, histologic response has been

*Abbreviations: APRICOT, AIDS Pegasys Ribavirin International Coinfection Trial; cEVR, complete early virologic response; CHC, chronic hepatitis C; HALT-C, Hepatitis C Antiviral Long-term Treatment Against Cirrhosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NIF, necroinflammatory; RVR, rapid viral response; SD, standard deviation; SVR, sustained virologic response.*

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closely linked to normalization of alanine aminotransferase levels, sustained clearance of HCV RNA, or both.[1-7] Many of these trials showed only a reduction in inflammation with no change in fibrosis, and most evaluated histology within 6 months of the last dose of therapy. However, long-term histologic improvement, including improvement in fibrosis and loss of detectable intrahepatic HCV RNA, has been demonstrated in patients with chronic hepatitis C (CHC) who have had a sustained virologic response (SVR) to interferon alfa therapy.[5] Although histologic response is correlated with SVR, improvements in liver histology have been observed in non-SVR treatment-naïve HCV-monoinfected patients.[8-11] Histologic response has also been observed in non-SVR patients who are coinfected with HCV/human immunodeficiency virus (HIV),[1,4,6,7] patients with advanced fibrosis or compensated cirrhosis,[2,3] and hemodialyzed patients with CHC.[12] Some of these studies also suggested that histologic improvements occurred in patients who became HCV RNA detectable following initial viral clearance (patients with relapse and breakthrough).[2,4] However, the number of patients with paired-biopsies in these individual studies was small. It is also important to note that there were no improvements in fibrosis stage or progression after long-term maintenance therapy with pegylated interferons or in posttransplant patients who failed to achieve SVR with HCV therapy.[13,14]

The objective of this analysis was to assess the histologic response to interferon-based therapies, based on changes in the METAVIR necroinflammatory (NIF) activity and fibrosis scores in a large group of patients with varying degrees of virologic response, time to HCV RNA undetectability, and duration of viral suppression.

## Patients and Methods

***Patients.*** Patients (HCV genotypes 1-6) who had both baseline and follow-up liver biopsies from eight phase 2 to phase 4 interferon-based clinical trials were pooled and included in the analysis.[15-22] Four of the eight studies were open-label, randomized, multicenter, phase 2/3 studies comparing different dose regimens of peginterferon alfa-2a monotherapy with interferon alfa-2a monotherapy in interferon-naïve patients with CHC.[15-17,20] Two of the studies were phase 4 trials of peginterferon alfa-2a/ribavirin combination therapy, which evaluated patients with adverse prognostic factors, including African Americans and Latinos.[18,22] The remaining two studies were randomized, multicenter, phase 3 studies of interferon-naïve patients; the first study compared peginterferon alfa-2a monotherapy, peginterferon alfa-2a/ribavirin combination therapy, and interferon alfa-2b/ribavirin combination therapy. The second study compared the efficacy of a 24-week versus 48-week regimen of peginterferon alfa-2a plus a low or standard dose of ribavirin.[19,22] All patients participating in the eight clinical trials signed appropriate consent forms and all studies were approved by the institutions' Human Subjects Committees.

In this analysis, patients with HCV genotypes 1-6 who were assigned 48 weeks of interferon alfa-2a monotherapy, peginterferon alfa-2a monotherapy, or peginterferon alfa-2a/ribavirin combination therapy, and had baseline and posttreatment (i.e., week 72) biopsies, were included.

***Virologic Response Categories.*** The impact on histologic response was evaluated by three categories of virologic response: (1) degree of virologic response: SVR, relapsers, patients with breakthrough, and nonresponders; (2) time to HCV RNA undetectability: rapid viral response (RVR; weeks 0-4), complete early virologic response (cEVR; weeks 5-12), 24-week undetectable (weeks 13-24), and never undetectable; and (3) duration of viral suppression: none, $<$24 weeks, 24 to 48 weeks, and 48 weeks. Because HCV RNA was assessed only at certain time points (i.e., baseline, weeks 4, 12, 24, 48, 60, and 72), a precise measure of the duration of viral suppression could not be obtained. For this reason, patients were grouped to the duration of viral suppression categories based on the midpoints of the minimum and maximum duration of suppression according to the assessment schedule.

The virologic response categories were defined as follows: SVR (undetectable HCV RNA at 24-weeks after end of treatment); relapsers (undetectable HCV RNA at end of treatment but detectable at 24 weeks after end of treatment); breakthroughs (initially undetectable HCV RNA but later detectable while on treatment); and nonresponders (HCV RNA detectable throughout treatment; never became undetectable). Missing HCV RNA test results at the end of treatment or 24 weeks after the end of treatment were counted as HCV RNA detectable. Because the analysis included only patients with both baseline and posttreatment biopsies, very few patients had missing HCV RNA test results.

***Histologic Outcome.*** Histologic outcome was determined on the basis of changes in the METAVIR NIF activity and fibrosis scores from baseline to 24 weeks after the end of treatment. Patients were classified with respect to the activity grade and fibrosis stage as either: improved (decrease of $\geq$1 categories from baseline to

**Table 1. Patient Demographic and Baseline Characteristics by Virologic Response Category**

| Characteristic | Virologic Response Category | | | | |
|---|---|---|---|---|---|
| | SVR (n = 614) | Relapsers (n = 338) | Breakthroughs (n = 127) | Nonresponders (n = 492) | Total (n = 1571) |
| Male, n (%) | 406 (66.1) | 233 (68.9) | 85 (66.9) | 352 (71.5) | 1076 (68.5) |
| Age, years | | | | | |
| Mean ± SD | 42.5 ± 9.4 | 44.7 ± 8.5 | 45.1 ± 8.4 | 44.9 ± 8.7 | 43.9 ± 9.0 |
| Range | 18-69 | 19-66 | 29-72 | 19-70 | 18-72 |
| BMI | | | | | |
| Mean ± SD, kg/m$^2$ | 27.0 ± 5.3 | 27.1 ± 4.9 | 27.4 ± 4.7 | 28.3 ± 4.8 | 27.4 ± 5.0 |
| ≤30 kg/m$^2$, n (%) | 467 (76.4) | 264 (78.8) | 92 (73.6) | 338 (68.8) | 1161 (74.3) |
| >30 kg/m$^2$, n (%) | 144 (23.6) | 71 (21.2) | 33 (26.4) | 153 (31.2) | 401 (25.7) |
| Race, n (%) | | | | | |
| Black | 25 (4.1) | 10 (3.0) | 8 (6.3) | 57 (11.6) | 100 (6.4) |
| Hispanic | 72 (11.7) | 41 (12.1) | 11 (8.7) | 40 (8.1) | 164 (10.4) |
| White | 469 (76.4) | 259 (76.6) | 104 (81.9) | 378 (76.8) | 1210 (77.0) |
| Others | 48 (7.8) | 28 (8.3) | 4 (3.1) | 17 (3.5) | 97 (6.2) |
| HCV genotype, n (%) | | | | | |
| 1 | 399 (65.2) | 251 (74.9) | 94 (74.0) | 422 (85.9) | 1166 (74.5) |
| 2 | 87 (14.2) | 27 (8.1) | 14 (11.0) | 21 (4.3) | 149 (9.5) |
| 3 | 112 (18.3) | 48 (14.3) | 18 (14.2) | 36 (7.3) | 214 (13.7) |
| 4 | 11 (1.8) | 5 (1.5) | 1 (0.8) | 10 (0.2) | 27 (1.7) |
| 5 | 1 (0.2) | 2 (0.6) | - | 2 (0.4) | 5 (0.3) |
| 6 | 2 (0.3) | 2 (0.6) | - | - | 4 (0.3) |
| Missing | 2 | 3 | - | 1 | 6 |
| ALT quotient, n (%) | | | | | |
| ≤3 × ULN | 381 (62.1) | 235 (69.5) | 78 (61.4) | 344 (69.9) | 1038 (66.1) |
| >3 × ULN | 233 (37.9) | 103 (30.5) | 49 (38.6) | 148 (30.1) | 533 (33.9) |
| HCV RNA titer | | | | | |
| Mean ± SD, $\log_{10}$ IU/mL | 5.9 ± 0.9 | 6.3 ± 0.6 | 6.0 ± 0.7 | 6.1 ± 0.7 | 6.0 ± 0.8 |
| ≤400,000 IU/mL, n (%) | 242 (39.4) | 63 (18.6) | 43 (33.9) | 166 (33.7) | 514 (32.7) |
| ≤800,000 IU/mL, n (%) | 283 (46.1) | 85 (25.1) | 53 (41.7) | 187 (38.0) | 608 (38.7) |
| METAVIR activity score, mean ± SD | 1.8 ± 0.6 | 1.8 ± 0.5 | 1.9 ± 0.5 | 1.8 ± 0.5 | 1.8 ± 0.5 |
| METAVIR fibrosis score, mean ± SD | 1.5 ± 0.9 | 1.7 ± 1.0 | 1.9 ± 1.2 | 2.0 ± 1.3 | 1.7 ± 1.1 |
| Advanced fibrosis or cirrhosis, n (%) | 84 (13.7) | 73 (21.6) | 39 (30.7) | 163 (33.1) | 359 (22.9) |
| Duration of treatment in weeks, mean ± SD | 47.5 ± 2.5 | 47.4 ± 1.6 | 42.4 ± 10.1 | 43.8 ± 9.0 | 45.9 ± 6.4 |

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; SD, standard deviation; SVR, sustained virologic response; ULN, upper limit of normal.

follow-up); stable (no change in category from baseline to follow-up); or worsened (increase of ≥1 categories from baseline to follow-up). Biopsies from all patients in the eight clinical trials were evaluated in a blinded fashion by a single pathologist. All liver biopsies were required to be a minimum of 1 cm in size. All biopsy samples had a minimum of four portal tracts. Biopsies that were <1 cm in size or had less than four portal tracts were considered inadequate and were excluded.

***Statistical Analysis.*** Statistical testing was performed based on Cochran-Mantel-Haenszel statistics to assess the overall correlation between viral response and histologic outcomes.[23] All four viral response categories and the three histologic outcomes (improved, stable, and worsened METAVIR activity and fibrosis scores) were considered to be ordinal categories. In addition to the overall Cochran-Mantel-Haenszel correlation test, the correlation between viral response and histologic response was assessed further and more stringently by two independent trend tests, one for the proportion of improved and the other for the proportion of worsened activity or fibrosis. Because equal space between levels for viral response categories or histologic outcomes could not be assumed, modified ridit scores were used.

## Results

***Patient Demographic and Baseline Characteristics.*** A total of 1571 patients were included in the pooled analysis. The demographic and baseline characteristics of the patients by virologic response category are summarized in Table 1. The majority of the patients were white, male, infected with HCV genotype 1, and had a body mass index ≤30 kg/m$^2$. Most patients had baseline HCV RNA levels >800,000 IU/mL (61%), baseline alanine aminotransferase levels ≤3 × upper limit of normal (66%), and minimal hepatic inflammation and scarring at baseline (mean ± standard deviation [SD] METAVIR activity and fibrosis scores were 1.8 ± 0.5, and 1.7 ± 1.1, respectively). Approximately 80% of the patients received either peginterferon alfa-2a monotherapy or peginterferon

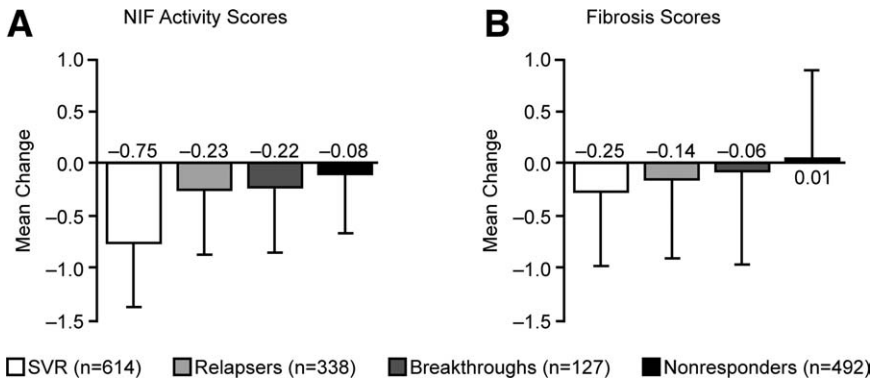


Fig. 1. Mean change from baseline in METAVIR (A) necroinflammatory (NIF) activity and (B) fibrosis scores. Error bars indicate standard deviations.

alfa-2a/ribavirin combination therapy. The demographic and baseline characteristics were generally similar between the patients with paired biopsy data that were included in the analysis (n = 1571) and the patients who were excluded from the analysis (n = 2158). The mean ± SD duration of treatment, however, was shorter for the excluded patients compared with the paired biopsy cohort (39 ± 14 weeks versus 46 ± 6 weeks).

***Virologic Response Status and Histologic Outcomes.*** The changes from baseline to 24 weeks after end of treatment in METAVIR activity scores by virologic response category are shown in Fig. 1A. There was a correlation between the degree of virologic response and mean change in activity scores from baseline to 24 weeks after end of treatment, with patients with SVR experiencing the greatest decrease in activity scores, followed by relapsers and patients with breakthrough. Table 2 shows the proportion of patients with improved, stable, or worsened activity grade by virologic response category. Overall, approximately half of the patients (51%) had a stable METAVIR activity grade and considerably more patients had an improved activity grade (42%) than worsened activity grade (7%). There was a significant correlation between the degree of virologic response and the net changes in the activity grade ($P < 0.0001$). The trend tests for the correlation between virologic response and NIF activity improvements and between virologic response and NIF activity worsening were also significant ($P < 0.0001$ for both). Patients with SVR experienced the greatest net benefits in activity scores (Table 2). The net changes in activity scores were not significantly different between patients with breakthrough and nonresponders ($P = 0.18$), or between patients with breakthrough and relapsers ($P = 0.10$). As a combined group, relapsers and patients with breakthrough experienced greater net benefits in activity scores than nonresponders (22% versus 8%; $P = 0.0001$) (data not shown).

A correlation was also observed between the degree of virologic response and mean change in METAVIR

**Table 2. Virologic Response Category and Change in METAVIR Activity and Fibrosis Scores**

| Virologic Response Category | n | Improvement | Stable | Worsening | Net Effect* | *P* Value† |
|---|---|---|---|---|---|---|
| Change from Baseline in NIF Activity Scores, n (%) | | | | | | |
| SVR | 614 | 411 (66.9) | 198 (32.2) | 5 (0.8) | 66.1‡ | <0.0001 |
| Relapsers | 338 | 107 (31.7) | 199 (58.9) | 32 (9.5) | 22.2 | <0.0001 |
| Breakthroughs | 127 | 40 (31.5) | 74 (58.3) | 13 (10.2) | 21.3 | 0.0002 |
| Nonresponders | 492 | 100 (20.3) | 333 (67.7) | 59 (12.0) | 8.3§ | 0.0011 |
| *P* value | | <0.0001§ | | <0.0001‖ | <0.0001¶ | |
| Change from Baseline in Fibrosis Scores, n (%) | | | | | | |
| SVR | 614 | 163 (26.5) | 411 (66.9) | 40 (6.5) | 20.0‡ | <0.0001 |
| Relapsers | 338 | 69 (20.4) | 239 (70.7) | 30 (8.9) | 11.5 | <0.0001 |
| Breakthroughs | 127 | 29 (22.8) | 75 (59.1) | 23 (18.1) | 4.7 | 0.4054 |
| Nonresponders | 492 | 91 (18.5) | 312 (63.4) | 89 (18.1) | 0.4§ | 0.8815 |
| *P* value | | <0.0001§ | | <0.0001‖ | <0.0001¶ | |

*Net Effect = % improvement – % worsening.

†McNemar's test for whether the net effect equals zero.

‡$P < 0.0001$ versus relapsers.

§$P < 0.001$ versus relapsers for activity; $P = 0.0003$ versus relapsers for fibrosis.

‖Cochran-Mantel-Haenszel mean score test comparing dichotomized histologic responses (e.g., improved versus not improved, or worsened versus not worsened).

¶Cochran-Mantel-Haenszel test on ordered 4 × 3 table for overall correlation between virologic and histologic responses.

All tests used modified ridit scores and adjusted for baseline activity score and treatment.

**Table 3. Time to HCV RNA Undetectability and Change in METAVIR Activity and Fibrosis Scores**

| Time to Undetectability | n | Improvement | Stable | Worsening | Net Effect* | *P* Value† |
|---|---|---|---|---|---|---|
| Change from Baseline in NIF Activity Scores, n (%) | | | | | | |
| RVR | 311 | 205 (65.9) | 99 (31.8) | 7 (2.3) | 63.7 | <0.0001 |
| cEVR | 516 | 250 (48.4) | 246 (47.7) | 20 (3.9) | 44.6 | <0.0001 |
| 24-week undetectable | 252 | 103 (40.9) | 126 (50.0) | 23 (9.1) | 31.7 | <0.0001 |
| Never undetectable | 492 | 100 (20.3) | 333 (67.7) | 59 (12.0) | 8.3 | 0.0011 |
| *P* value | | <0.0001‡ | | <0.0001‡ | <0.0001§ | |
| Change from Baseline in Fibrosis Scores, n (%) | | | | | | |
| RVR | 311 | 79 (25.4) | 212 (68.2) | 20 (6.4) | 19.0 | <0.0001 |
| cEVR | 516 | 125 (24.2) | 345 (66.9) | 46 (8.9) | 15.3 | <0.0001 |
| 24-week undetectable | 252 | 57 (22.6) | 168 (66.7) | 27 (10.7) | 11.9 | 0.0011 |
| Never undetectable | 492 | 91 (18.5) | 312 (63.4) | 89 (18.1) | 0.4 | 0.8815 |
| *P* value | | <0.0001‡ | | <0.0001‡ | <0.0001§ | |

*Net Effect = % improvement – % worsening.

†McNemar's test for whether the net effect equals zero.

‡Cochran-Mantel-Haenszel mean score test comparing dichotomized histologic responses (e.g., improved versus not improved, or worsened versus not worsened).

§Cochran-Mantel-Haenszel test on ordered 4 × 3 table for overall correlation between virologic and histologic responses.

All tests used modified ridit scores and adjusted for baseline METAVIR score and treatment.

fibrosis scores from baseline to 24 weeks after end of treatment, with patients with SVR experiencing the greatest decrease in fibrosis score, followed by relapsers and patients with breakthrough (Fig. 1B). Most patients had a stable METAVIR fibrosis stage (60%-70%) regardless of the virologic response category (Table 2), with overall more patients having improved fibrosis stage (22%) than worsened fibrosis stage (12%). A significant positive correlation was observed between the degree of virologic response and net changes in fibrosis status ($P < 0.0001$). Trend tests for the correlation between virologic response and fibrosis improvements and between virologic response and fibrosis worsening were also significant ($P < 0.0001$ for both). As with the NIF activity scores, the greatest net benefits in fibrosis scores were seen in patients with SVR, whereas net changes were not significantly different between patients with breakthrough and nonresponders ($P = 0.61$) or between patients with breakthrough and relapsers ($P = 0.06$). As a combined group, relapsers and patients with breakthrough had significantly greater net benefits in fibrosis scores compared with nonresponders (10% versus 0.4%; $P = 0.0032$) (data not shown).

The correlation between the degree of virologic response and histologic benefits observed in the overall population was also consistent across the subgroups of patients who received peginterferon alfa-2a monotherapy and peginterferon alfa-2a/ribavirin combination therapy (data not shown).

***Time to HCV RNA Undetectability and Change in METAVIR Scores.*** The earlier patients became HCV RNA undetectable, the more likely they were to have a better histologic outcome. This correlation was significant for both overall changes in METAVIR activity ($P < 0.0001$) and fibrosis scores ($P < 0.0001$; Table 3). The greatest net benefits in activity and fibrosis scores were seen in patients with undetectable HCV RNA levels by week 4 (RVR), followed by patients with undetectable HCV RNA by week 12 (cEVR) and patients with undetectable HCV RNA at week 24.

***Duration of Viral Suppression and Change in METAVIR Scores.*** The relationship between the duration of viral suppression and histologic outcomes was consistent with the results seen with the other two virologic response categories; there was a significant positive correlation between the duration of viral suppression and overall changes in the activity and fibrosis scores ($P < 0.0001$ for both) (Table 4). The longer the period of viral suppression, the more likely the patients were to have a better histologic outcome. The greatest histologic benefits were seen in patients with undetectable HCV RNA levels for 48 weeks.

## Discussion

Although the primary goal of treatment with current HCV therapy is virologic cure, only approximately half of all treated patients in the United States achieve SVR with currently approved agents.[15,16] The greatest rates of histologic response have been seen in patients who achieve SVR; however, improvements in liver histology have also been seen in virologic nonresponders.[8-11] In an earlier study of treatment-naïve CHC patients receiving either interferon monotherapy or interferon plus ribavirin combination therapy,

**Table 4. Duration of Viral Suppression and Change in METAVIR Activity and Fibrosis Scores**

| Duration of Viral Suppression | n | Improvement | Stable | Worsening | Net Effect* | *P* Value† |
|---|---|---|---|---|---|---|
| Change from Baseline in NIF Activity Scores, n (%) | | | | | | |
| 48 weeks | 654 | 427 (65.3) | 220 (33.6) | 7 (1.1) | 64.2 | <0.0001 |
| 24-48 weeks | 332 | 104 (31.3) | 196 (59.0) | 32 (9.6) | 21.7 | <0.0001 |
| <24 weeks | 93 | 27 (29.0) | 55 (59.1) | 11 (11.8) | 17.2 | 0.0094 |
| None | 492 | 100 (20.3) | 333 (67.7) | 59 (12.0) | 8.3 | 0.0011 |
| *P* value | | <0.0001‡ | | <0.0001‡ | <0.0001§ | |
| Change from Baseline in Fibrosis Scores, n (%) | | | | | | |
| 48 weeks | 654 | 169 (25.8) | 440 (67.3) | 45 (6.9) | 18.9 | <0.0001 |
| 24-48 weeks | 332 | 73 (22.0) | 231 (69.6) | 28 (8.4) | 13.6 | <0.0001 |
| <24 weeks | 93 | 19 (20.4) | 54 (58.1) | 20 (21.5) | −1.1 | 0.8728 |
| None | 492 | 91 (18.5) | 312 (63.4) | 89 (18.1) | 0.4 | 0.8815 |
| *P* value | | <0.0001‡ | | <0.0001‡ | <0.0001§ | |

*Net Effect = % improvement – % worsening.

†McNemar's test for whether the net effect equals zero.

‡Cochran-Mantel-Haenszel mean score test comparing dichotomized histologic responses (e.g., improved versus not improved, or worsened versus not worsened).

§Cochran-Mantel-Haenszel test on ordered 4 × 3 table for overall correlation between virologic and histologic responses.

All tests used modified ridit scores and adjusted for baseline METAVIR score and treatment.

decreases in inflammatory scores were seen in 86% of patients with SVR and 39% of patients without SVR.[8] Similar improvements in hepatic inflammation were observed in a study of CHC patients receiving interferon alfa 2-b monotherapy as well. In this study, the reduction in hepatic inflammation was shown to correlate with a reduction in HCV RNA levels, especially in patients who did not achieve SVR.[9] No significant changes in fibrosis scores were reported in either of these studies. Improvements in fibrosis progression following interferon-based therapy are generally less remarkable than improvements in hepatic inflammation; however, some studies have also reported modest decreases in fibrosis progression following treatment. Poynard et al. conducted a pooled analysis of more than 3000 treatment-naïve patients with CHC from four different trials of interferon alfa-2b or peginterferon alfa-2b administered alone or in combination with ribavirin; 73% of all patients had F1 fibrosis and 5% had cirrhosis at baseline. Following treatment, fibrosis progression remained stable in 65% of patients; however improvements in fibrosis progression rates were seen in 25% of patients with SVR, 16% of relapsers, and 17% of nonresponders.[11]

Consistent with the results from these trials, improvements in liver histology were observed regardless of the virologic response to interferon-based therapy in our analysis of patients pooled from eight HCV clinical trials. Of the 1571 patients with paired biopsies, improvement in the METAVIR activity grade was observed in 42% of patients overall whereas worsening was seen in only 7%, resulting in a net beneficial effect of 35% (percent improved minus percent worsened). As expected, the histologic improvements were closely correlated to the virologic response status, time to HCV RNA undetectability, and duration of viral suppression, with the greatest improvements observed in patients with an early and sustained virologic response to therapy. However, modest improvements in METAVIR activity and fibrosis were also observed in a large proportion of patients who failed to achieve a SVR (patients with breakthrough and relapse combined: 32% with activity improvements and 10% with activity worsening resulting in a net benefit of 22%; 21% with fibrosis improvements and 11% with fibrosis worsening resulting in a net benefit of 10%). It is important to note that many patients in this analysis had characteristics that are associated with reduced rates of SVR. Adverse prognostic factors for virologic response can include black or Latino race, obesity, genotype 1 or 4 infection, advanced fibrosis, or insulin resistance.[15,16,18,21,24] In this analysis, more than 16% of patients were black or Hispanic, 76% had genotype 1 or 4 infection, 26% had a body mass index exceeding 30 kg/m$^2$, and 61% had HCV RNA levels exceeding 800,000 IU/mL, yet as the results demonstrate, even in patients with poor prognostic factors, some degree of histologic response may be observed in the absence of a virologic cure.

Our data clearly show that the sooner a patient becomes HCV RNA undetectable, and the longer they remain HCV RNA undetectable, the greater the histologic benefit they experience with treatment. The markers of early HCV RNA undetectability (RVR and cEVR) and the duration of undetectability are now accepted predictors of SVR[25,26] and should also be

considered measures of histologic improvement in patients with viral breakthrough, relapse, and SVR. In patients who were nonresponders, this benefit was seen only in inflammation and not fibrosis. The mechanisms by which interferon therapy might produce histologic improvements in the absence of complete viral eradication remain unclear; however, it is likely that by suppressing the virus temporarily, or by interacting more directly with the immune system, interferon may ameliorate some of the histologic activity. Although histologic benefits have been observed in patients with a partial virologic response, it is important to note that there is no evidence to suggest that this response is durable in the absence of complete and persistent virus suppression.

Maintenance therapy with peginterferon with the goal of delaying or preventing progression to cirrhosis and/or hepatic decompensation has been assessed in two ongoing trials and one completed randomized trial in the United States and Europe.[13,27-29] The results of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial in the United States were recently published.[13] The primary endpoint of this trial was the progression of liver disease (as indicated by death, hepatocellular carcinoma, hepatic decompensation, or for patients with bridging fibrosis at baseline, an increase in the Ishak fibrosis score of $\geq$2 points) within 3.8 years after randomization to low-dose peginterferon alfa-2a therapy or no treatment. For patients with noncirrhotic fibrosis, the rate of progression to cirrhosis was similar in the treated and untreated groups. In both groups, the mean Ishak fibrosis score increased by study end despite a significant mean reduction in the average NIF score in the treated versus untreated group (difference = $-1.00$; 95% confidence interval, $-1.46$, $-0.55$; $P < 0.001$). No significant difference in the primary outcome rate was observed between the treated and untreated groups.[13]

Recent data from the HALT-C trial, which have been presented but are unpublished, indicate that patients with HCV with advanced liver disease who achieved a SVR had an 80% to 90% reduction in liver-related clinical outcomes.[30] Importantly, patients with transient suppression of HCV RNA had a 50% reduction in liver-related clinical outcomes. Although our retrospective analysis did not involve patients on maintenance therapy, these results from the HALT-C trial support our findings. One should note that there were a number of differences between the HALT-C trial and our current analysis: the HALT-C study only enrolled genotype 1 patients who failed to respond to peginterferon/ribavirin therapy; all of the patients in the HALT-C cohort had advanced fibrosis (in contrast to only 23% of the patients in this analysis having advanced fibrosis); the dosing of peginterferon alfa-2a in the HALT-C trial was 50% of full dose (90 $\mu$g weekly) as opposed to 95% of full dose in this analysis, and more black patients were enrolled in the HALT-C trial resulting in lower SVR rates compared with this analysis.[24] Lastly, the measurement of improvement in fibrosis score in patients with cirrhosis is far more difficult than in patients without cirrhosis because of the marked increase in total collagen content in the livers of patients with cirrhosis.[31]

In conclusion, this retrospective analysis is one of the largest analyses examining the association between histologic response and various categories of virologic response in patients with paired biopsy data from multiple interferon-based studies. In this analysis we observed a direct correlation between mean changes in the METAVIR activity and fibrosis scores and virologic response as measured by the degree of viral response, time to HCV RNA undetectability, and the duration of viral suppression. Patients with SVR had the greatest histologic benefits; however, improvements in liver histology were also observed in patients who experienced an initial virologic response but later became HCV RNA detectable. As a combined group, patients with breakthrough and relapsers had significantly greater responses in both activity and fibrosis scores than virologic nonresponders. This analysis demonstrates that modest histologic improvement may occur with HCV therapy even in the absence of SVR. These findings might be considered when evaluating the need for treatment in patients with HCV who are less likely to achieve a virologic cure.

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