

Brief Communication: The Relationship of Regression of Cirrhosis to Outcome in Chronic Hepatitis C

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Background: The effect of regression of cirrhosis in chronic hepatitis C is unknown.

Objective: To evaluate the relation between regression of cirrhosis and clinical outcome in patients with chronic hepatitis C after antiviral therapy.

Design: A cohort of patients with cirrhosis treated between 1988 and 2001.

Setting: Hepatology unit of a tertiary care center in France.

Patients: 96 patients with chronic hepatitis C and biopsy-proven cirrhosis (METAVIR score F4) who were treated with an interferon-based regimen and had at least 1 posttreatment liver biopsy. Patients were followed until November 2006.

Measurements: Occurrence of a combined end point of liver-related events (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatocellular carcinoma, or liver transplantation) and death in patients with regression of cirrhosis (defined as a decrease from 4 to ≤ 2 METAVIR units on post-therapy liver biopsy).

Results: The median follow-up was 118 months (interquartile range, 86 to 138 months). Eighteen patients had regression of cirrhosis. The incidence of the combined end point per 100 patient-years was 0 in patients with regression of cirrhosis and 4 in patients without regression of cirrhosis ($P = 0.002$, log-rank test). The transplantation-free survival rate at 10 years was 100% in patients with regression of cirrhosis and 74.2% in patients without regression of cirrhosis ($P = 0.025$).

Limitations: Selection of patients was retrospective; selection and survival biases may have influenced the estimates of the overall rate of regression of cirrhosis. The low number of patients who experienced regression of cirrhosis precludes analysis of factors that could predict regression of cirrhosis.

Conclusion: Regression of cirrhosis occurs after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival.

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Single or multifactorial damage to the liver ultimately leads to cirrhosis and its complications, especially hepatocellular carcinoma (1–3). Different types of evidence—histologic; morphologic (as assessed by abdominal ultrasonography or digestive endoscopy); and biochemical (as assessed by measurement of hyaluronate, procollagen III peptide, prothrombin time, and platelets), including analyses of native livers—support the idea that cirrhosis can be reversed, provided that the underlying disease is controlled (5–8). Nevertheless, whether cirrhosis regresses is still debated (9, 10). To provide definitive support for this concept, we evaluated the relation between histologic regression of cirrhosis and clinical outcome in patients treated for chronic hepatitis C.

METHODS

Study Design

We established a cohort of 143 patients with biopsy-proven cirrhosis (METAVIR F4) who received specific treatment between 1988 and 2001 at a single hepatology unit in a tertiary care center in France and who underwent a second liver biopsy to assess the effect of treatment on cirrhosis (Appendix Figure, available at www.annals.org) (6, 8, 11). All patients in this cohort currently undergo prospective follow-up and are seen by a senior hepatologist at least every 6 months. The institutional review board of

our hospital approved the past and present studies, and all patients gave informed consent.

We included patients who met the following criteria: Child–Pugh class A cirrhosis related to chronic hepatitis C; absence of hepatitis B co-infection; absence of immunosuppression (HIV-associated infection, long-term hemodialysis, organ transplantation, immunosuppressive therapy); and treatment with conventional α -interferon or pegylated interferon, with or without ribavirin. The exclusion criteria were age older than 70 years at the time of diagnosis of cirrhosis and previous liver-related complications.

Sustained virologic response was defined as undetectable hepatitis C virus RNA on the latest available assaying technique and normal alanine aminotransferase level 24 weeks after the end of treatment and during follow-up. Patients who did not fulfill these criteria were classified as nonresponders and did not receive long-term treatment.

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Context

Few studies have documented histologic regression of cirrhosis.

Contribution

This study describes 96 patients with chronic hepatitis C and biopsy-proven cirrhosis who were treated with an interferon-based regimen and who had at least 1 post-treatment liver biopsy. Eighteen patients had biopsy-proven regression of cirrhosis. Patients with regression had better 10-year survival rates than did patients without regression (100% vs. 74%).

Implication

Cirrhosis may be reversible in some patients with chronic hepatitis C.

—The Editors

Liver disease was staged and graded according to the METAVIR score (12), which combines an activity stage from 0 to 3 and a fibrosis grade from 0 to 4 (4 corresponds to cirrhosis). Regression of cirrhosis was defined as a decrease in the score from 4 to 2 or fewer METAVIR fibrosis units to avoid the 15% rate of false-negative results in patients with F3 disease (13, 14).

Patients underwent clinical and biological evaluation, including measurement of aminotransferase, bilirubin, albumin, prothrombin time, platelet, and hepatitis C viral load at each visit. All patients were screened for hepatocellular carcinoma with ultrasonography and had α -fetoprotein measured every 6 months. The diagnosis of hepatocellular carcinoma followed the guidelines of the European Association for the Study of the Liver (15). Hepatic encephalopathy was defined clinically (16). Ascites was diagnosed by clinical examination and ultrasonography. The source of gastroesophageal bleeding was confirmed by endoscopy.

Outcome Measures

Our main goal was to evaluate the effect of regression of cirrhosis on a composite end point of liver-related complications (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatocellular carcinoma, liver transplantation) and death from liver-related causes. For patients with more than 1 event, only the first event was analyzed. The incidence of liver-related deaths or transplantation was analyzed as a secondary end point.

Statistical Analysis

Total duration of follow-up was calculated from the date of the first liver biopsy until death, last consultation, or liver transplantation until November 2006. Eight patients (8%) were not followed in our unit as of this date after a median follow-up of 96 months (range, 36 to 127 months). These patients were censored at the time of the last visit. The time from diagnosis of cirrhosis (time of the index biopsy) to liver-related complications or to the date when the data were cen-

sored was plotted according to groups by using Kaplan–Meier estimates, and *P* values were computed with the log-rank test. All *P* values are 2-sided, and the type I error was set at 5%. Continuous values are presented as medians and interquartile ranges and categorical variables as counts and proportions. The differences between groups were assessed with the Fisher exact test and the Mann–Whitney U test. All statistical analyses were performed by using SPSS software, version 16 (SPSS, Chicago, Illinois).

Role of the Funding Source

The study did not receive funding.

RESULTS**Sample**

Ninety-six patients fulfilled the inclusion criteria (Table 1). All had Child–Pugh class A biopsy-proven cirrhosis at enrollment and thereafter received specific therapy. The median interval between the first liver biopsy and treatment was 2 months (interquartile range, 0 to 6 months). Sixty-one patients (64%) received interferon monotherapy, 34 (35%) received interferon and ribavirin, and 1 (1%) received pegylated interferon and ribavirin. Eighty-two patients (85%) did not respond to the first treatment course; of these, 47 (49%) received at least 1 more treatment course. Thirty-nine patients (41%) achieved a sustained virologic response, and 57 (59%) did not.

Histologic Outcome

The median interval between the end of treatment and the second liver biopsy was 17 months. The median length of the liver biopsy samples was 15 mm (interquartile range, 10 to 20 mm) both before and after treatment (*P* = 0.86, Wilcoxon signed-rank test). In terms of fibrosis scores, 69 liver biopsies (71.9%) showed persistent cirrhosis (METAVIR fibrosis stage 4), 9 (9.4%) showed extensive fibrosis (stage 3), 10 (10.4%) showed intermediate fibrosis (stage 2), 7 (7.3%) showed moderate fibrosis (stage 1), and 1 (1%) showed no fibrosis (stage 0).

Of the 18 patients with regression of cirrhosis on the second liver biopsy (METAVIR fibrosis stage 0, 1, or 2), 17 (94.4%) had long-term response to therapy and 1 had biochemical response (normal liver function tests and no detectable activity on liver biopsy but persistent viremia) to anti-hepatitis C therapy.

Clinical Outcome

The median follow-up was 118 months (interquartile range, 86 to 138 months), and total follow-up was 900 patient-years. The time from achievement of sustained virologic response to the end of follow-up was similar between patients with and those without regression of cirrhosis (*P* = 0.38). During follow-up, 27 (35%) patients with persistent cirrhosis developed at least 1 cirrhosis-related complication (Table 2). The incidence of liver-related complications, including hepatocellular carcinoma, was lower in patients with a sustained virologic response (Figure, top). Nevertheless, 4 patients with hepatitis C–related

Table 1. Patient Characteristics at Baseline

Characteristic	Patients			P Value
	Total (n = 96)	Without Regression of Cirrhosis (n = 78 [81%])	With Regression of Cirrhosis (n = 18 [19%])*	
Median age (IQR), y	45 (36–56)	50 (39–58)	43 (33–53)	0.197
Men, n (%)	58 (60)	47 (60)	11 (61)	1.0
Ethanol intake >40 g/d, n (%)	34 (35)	30 (38)	4 (22)	0.28
Median BMI (IQR), kg/m ²	24.7 (21.9–27.6)	25.2 (22.3–27.6)	23.2 (21.3–27.5)	0.091
Positive for anti-HBcAg, n (%)†	38 (40)	30 (38)	8 (44)	1.0
Genotype 1, n (%)†	51 (53)	44 (56)	7 (39)	0.21
Median METAVIR activity score (IQR)‡	2 (1–3)	2 (1–3)	1 (1–2)	0.065
Steatosis >30%, n (%)	32 (33)	27 (35)	5 (28)	0.78
Median ALT level (IQR), U/L	106 (73–159)	107 (78–171)	105 (73–148)	0.21
Median AST level (IQR), U/L	81 (54–119)	85 (59–120)	49 (41–86)	0.002
Median bilirubin level (IQR) μmol/L	12 (8–18)	13 (8–18)	10 (8–13)	0.185
mg/dL	0.7 (0.47–1.05)	0.76 (0.47–1.05)	0.58 (0.47–0.76)	
Median platelet count (IQR), × 10 ⁹ cells/L	150 (118–183)	137 (111–179)	148 (155–205)	0.049
Median prothrombin time (IQR), % of normal	88 (77–98)	84 (76–96)	96 (87–100)	0.006
Median albumin level (IQR), g/L	42 (39–45)	42 (39–45)	44 (41–47)	0.032
Median total interferon received (IQR), million U	432 (306–648)	432 (225–704)	432 (432–486)	0.73
Sustained virologic response, n (%)§	35 (36)	18 (23)	17 (94)	<0.001
Median length of posttherapeutic liver biopsy sample (IQR), mm	15 (10–20)	12 (10–15)	20 (9–22)	0.169
Median time between pre- and posttherapeutic liver biopsy (IQR), mo	38 (23–69)	35 (23–67)	48 (29–72)	0.122
Median follow-up (IQR), mo	118 (86–138)	117 (86–138)	123 (86–137)	0.66

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HBcAg = hepatitis B virus core antigen; IQR = interquartile range.

* Regression of cirrhosis was defined as a decrease in the fibrosis score from 4 to ≤2 METAVIR units on paired liver biopsies.

† Genotype could not be assessed in 6 patients, and screening for anti-HBcAg antibodies was missing in 14 patients.

‡ The METAVIR activity score (range, 0 to 3) measures the degree of necroinflammation in liver biopsy specimens.

§ "Sustained virologic response" was defined as persistent undetectable hepatitis C virus RNA (<12 U/L by real-time polymerase chain reaction) and normal ALT level during follow-up. Patients who did not fulfill these criteria were classified as nonresponders.

cirrhosis developed a liver-related event, including variceal bleeding (1 patient) and hepatocellular carcinoma (3 patients); all had anti-hepatitis B core antigen antibodies. In contrast, patients with regression of cirrhosis had no complications (Figure, bottom). The incidence of cirrhosis-related complications per 100 patient-years was 1.14 in patients with sustained virologic response and 4.63 in those without sustained virologic response ($P = 0.009$);

respective values in patients with and those without regression of cirrhosis were 0 and 4 ($P = 0.002$).

During follow-up, 22 patients (23%) without regression died ($n = 16$ [17%]) or underwent a liver transplantation ($n = 6$ [6%]), whereas neither of these events occurred in the 18 patients with regression ($P = 0.010$). The incidence of liver-related death or liver transplantation per 100 patient-years was 0.85 in patients with sustained viro-

Table 2. Clinical Outcomes, by Virologic and Histologic Response

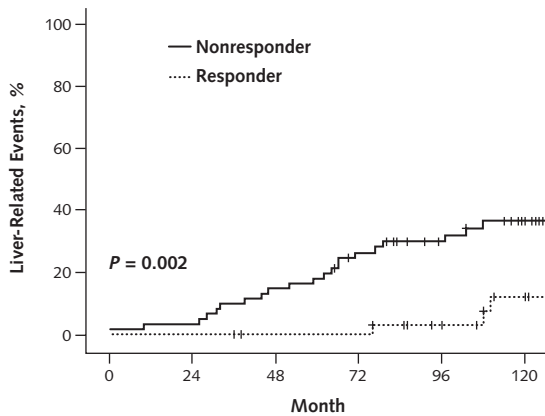
Outcome	Events, n (%)		P Value	Events, n (%)		P Value
	Patients without Sustained Virologic Response (n = 57)	Patients with Sustained Virologic Response (n = 39)		Patients without Regression of Cirrhosis (n = 78)	Patients with Regression of Cirrhosis (n = 18)	
Overall deaths	17 (27.9)	4 (11.4)	0.075	20 (25.6)	1 (5.6)*	0.110
Liver-related death or liver transplantation†	19 (31.1)	3 (8.6)	0.012	22 (28.2)	0 (0)	0.010
Liver-related event‡	23 (37.7)	4 (11.4)	0.009	27 (34.6)	0 (0)	0.002
Hepatocellular carcinoma	14 (23.3)	3 (8.6)	0.097	17 (22.1)	0 (0)	0.036
Variceal bleeding	6 (9.8)	1 (2.9)	0.42	7 (9)	0 (0)	0.34
Ascites	10 (23.3)	0 (0)	0.004	10 (16.9)	0 (0)	0.197
Spontaneous bacterial peritonitis	2 (4.8)	0 (0)	0.50	2 (3.4)	0 (0)	1.0
Hepatic encephalopathy	7 (16.7)	0 (0)	0.018	7 (12.1)	0 (0)	0.33

* The patient died of myocardial infarction.

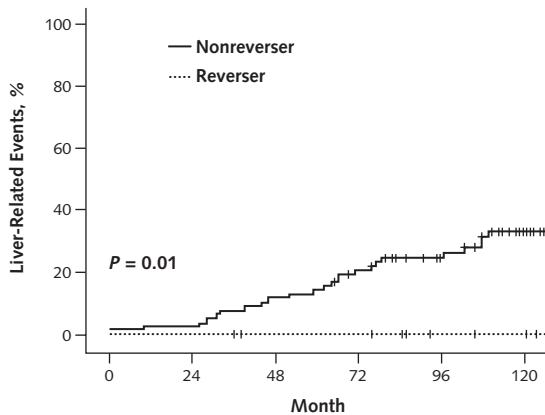
† Includes 16 deaths and 6 patients who had liver transplantation. Patients with liver transplantation are included in "Liver-related death" but not in "Overall death," unless a patient died after liver transplantation (as occurred in 1 patient).

‡ Includes 8 patients with >1 liver-related event.

Figure. Kaplan–Meier estimates of time to a liver-related event and death in patients with or without a sustained virologic response (*top*) and in patients with or without regression of cirrhosis (*bottom*).



Number at risk	0	24	48	72	96	120
Nonresponders	61	59	52	43	32	22
Responders	35	35	33	33	27	18



Number at risk	0	24	48	72	96	120
Nonreversers	78	76	69	60	47	30
Reversers	18	18	16	16	12	10

“Liver-related events” were hepatocellular carcinoma, hepatic encephalopathy, variceal bleeding, ascites, spontaneous bacterial peritonitis, and liver transplantation.

logic response and 3.43 in those without sustained virologic response ($P = 0.004$, log-rank test); respective values in patients with and those without cirrhosis were 0 and 2.96 ($P = 0.025$, log-rank test). Among the 6 patients who had liver transplantation, 5 survived and 1 died during the perioperative period. Four patients died of non-liver-related causes. One patient with regression of cirrhosis died of myocardial infarction.

DISCUSSION

During more than 10 years of follow-up in 96 patients with treated hepatitis C–related cirrhosis, 18 patients

achieved histologically proven regression. The absence of liver-related morbidity and mortality in these patients supports the concept of cirrhosis reversal. Persistence of cirrhosis carries a risk for hepatocellular carcinoma, which warrants regular screening.

Regression of hepatitis C–related cirrhosis after treatment ranges from 10% to 49% (19% in our cohort) and correlates closely with viral suppression (6, 23). In our series, inactivation of the underlying viral disease was a sufficient but not a necessary condition to allow regression of cirrhosis. Indeed, 1 patient had both cirrhosis regression and long-term protection against liver-related events despite viral persistence during a total follow-up of 124 months, including 95 months after confirmation of regression on the paired liver biopsy. This patient was considered a long-term biochemical responder (persistent normal aminotransferase levels despite detectable viremia after antiviral treatment and no detectable necroinflammatory activity on the second liver biopsy). This suggests that control of the necroinflammatory activity of the liver disease, more so than viral clearance, is of paramount importance to allow remodeling and regression of cirrhosis, at least in chronic hepatitis C.

Sustained virologic response was associated with a strong reduction in morbidity and mortality in our patients but did not prevent the onset of primary liver cancer in 3 of 35 patients (9%). This observation is in agreement with former studies reporting a statistically significant decrease in but persistent risk for primary liver cancer in patients with sustained treatment response who had hepatitis C–related cirrhosis (25–31). None of these studies focused on liver histology after viral eradication (26, 30). In our series, primary liver cancer and absence of remodeling were closely related. The 3 patients who developed primary liver cancer despite viral eradication had persistent cirrhosis on the follow-up biopsy and indirect signs of advanced cirrhosis (low platelet count and a dysmorphic liver at the time of diagnosis or on follow-up). Of note, all had anti–hepatitis B core antigen antibodies.

Our study has several limitations. First, the retrospective selection of patients does not allow estimation of the overall rate of regression of cirrhosis in chronic hepatitis C. Second, the low number of patients with regression of cirrhosis precluded the analysis of the independent factors associated with regression.

In conclusion, in hepatitis C–related cirrhosis, sustained suppression of necroinflammation may result in regression, defined as a posttreatment fibrosis score of 2 or fewer METAVIR units as established by liver biopsy. In our series, reversibility was associated with absence of cirrhosis-related complication. The absence of cirrhosis complications at 10 years after therapy and improvement of survival are the strongest evidence for the reversibility of cirrhosis. Patients with sustained virologic response to treatment but persistent cirrhosis are at lower risk for complications than those who do not

respond to therapy, but they still must comply with recommended follow-up.

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Appendix Figure. Study flow diagram.

