

# Correlation Between Beta-Lipoprotein Levels and Outcome of Hepatitis C Treatment

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**The low-density lipoprotein receptor (LDLR) has been proposed as a candidate receptor for the hepatitis C virus (HCV). Competitive inhibition of HCV binding to the LDLR by low-density lipoprotein (LDL) has been shown *in vitro*. If similar inhibition occurs *in vivo*, an elevated serum concentration of beta-lipoproteins may reduce the efficiency of infecting hepatocytes with HCV by competitively inhibiting HCV viral receptor binding. We investigated the role of baseline lipid values in influencing the outcome of HCV treatment. We conducted a retrospective chart review of patients treated with an interferon-based regimen at our liver and gastroenterology clinics between 1998 and 2004. Of 99 patients enrolled in the study, 49 (49.5%) had HCV genotype 1 (LDL  $100.2 \pm 30.2$  mg/dL [mean  $\pm$  SD]), and 50 patients (50.5%) had genotype 2 or 3 (LDL  $110.1 \pm 40$  mg/dL) infection. Early viral response (EVR), end-of-treatment response (ETR), and sustained viral response (SVR) were documented in 99, 88, and 77 patients, respectively. LDL and cholesterol levels prior to treatment were found to be higher in patients with positive EVR, ETR, and SVR. This difference remained significant independent of age. Multivariate analysis controlling for genotype and age showed that the higher the cholesterol and LDL levels prior to treatment, the greater the odds of responding to treatment. **In conclusion**, having higher serum LDL and cholesterol levels before treatment may be significant prognostic indicators for treatment outcome of those with chronic hepatitis C infection, particularly in genotypes 1 and 2. (HEPATOLOGY 2006;44:335-340.)**

**H**epatitis C viral infection is a common cause of chronic liver disease, with a worldwide prevalence of 3%. About 140 million people worldwide and 4 million in the United States are infected with HCV. An estimated 65% to 80% of the individuals infected with HCV develop persistent infection. As many as 20% to 50% of these individuals develop cirrhosis and 5% develop hepatocellular carcinoma.<sup>1,2</sup> The rate of disease progression varies widely, and unknown factors other than alcohol use, obesity, and age may influence the long-term clinical outcome of the disease. In recent years many

efforts have been made to identify receptors involved in viral entry into host cells. Two molecules are proposed to function as HCV receptors, namely, the low-density lipoprotein receptor (LDLR) and CD81.<sup>3-5</sup> Experiments *in vitro* showed competitive inhibition of binding between HCV and LDLR by purified LDL.<sup>3</sup> If similar inhibition occurs *in vivo*, the serum concentration of beta-lipoproteins may influence HCV proliferation because cell infection is required for replication of the virus.<sup>6</sup> Serum HCVAg levels negatively correlated with serum beta-lipoproteins, supporting the concept that LDLR is the HCV receptor and that beta-lipoproteins competitively inhibit infection of hepatocytes with HCV.<sup>6</sup> Additional *in vivo* evidence has been reported by *in situ* hybridization studies on keratinocytes obtained from vasculitic lesions of patients with type II cryoglobulinemia.<sup>3</sup> These keratinocytes with upregulation of LDL receptors were found to have the positive HCV RNA strand compared to keratinocytes obtained from normal skin of the same person with low levels of LDL receptors. In those with chronic HCV infection, polymorphisms of the LDLR can influence the severity of fibrosis (single-nucleotide polymorphism [SNP] in exon 8), clearance of virus (SNP in exon 10),

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Abbreviations: LDLR, low-density lipoprotein receptor; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; EVR, early viral response; ETR, end-of-treatment response.

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and response to treatment (SNP in 3'UTR).<sup>7</sup> Polymorphisms in LDLR are associated with the pathogenesis of familial hypercholesterolemia, obesity, and atherosclerosis, suggesting a genetic component may control HCV treatment outcome via the LDLR.<sup>7</sup> Interferon (IFN) may exert its effects in part by down-regulation of LDL receptors. IFN- $\alpha$  is known to induce the interleukin-1 (IL-1) receptor antagonist, which blocks IL-1-receptor-mediated stimulation by IL-1. Because IL-1 is known to increase LDL receptor activity, IFN- $\alpha$  would indirectly cause downregulation of LDL receptor activity.<sup>3</sup> The relation between lipid profile prior to treatment and response to HCV treatment was mentioned in two published letters.<sup>8,9</sup> Our aim in the present study was to investigate the influence of pretreatment LDL and cholesterol levels on the outcome of HCV treatment with a combination of interferon and ribavirin.

## Patients and Methods

We retrospectively reviewed the charts of 462 consecutive patients with chronic HCV infection who received interferon-based treatment. Patients were at least 18 years of age and had been seen in the gastroenterology or liver clinics of Beth Israel Medical Center in New York City from January 1998 to December 2004. Patients with HIV, HBV, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, or nonalcoholic steatohepatitis, without pretreatment lipid profiles, or who had been using lipid-modifying drugs were excluded from the study. Because LDL level is a derived value and is not reliable when triglycerides (TG) levels are high, patients with TG levels over 400 mg/dL were also excluded from the study. All patient evaluations by gastroenterology fellows were done under the direct supervision of attending hepatologists. Decisions on whether to treat were based on standard criteria.<sup>10</sup>

Charts were reviewed for the following characteristics: age; gender; HCV genotype; type of treatment; values of total cholesterol, LDL, very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL), TG, and ALT prior to treatment; baseline viral load; stage of fibrosis at liver biopsy<sup>11</sup>; early viral response (EVR); end-of-treatment response (ETR); sustained viral response (SVR); and treatment complications. EVR was defined as a drop of log 2 or loss of HCV RNA 12 weeks into therapy.<sup>10</sup> ETR and SVR were defined as undetectable serum HCV RNA by qualitative analysis at completion of treatment and 24 weeks after completion of treatment, respectively.<sup>10</sup> Patients who do not achieve EVR have no more than a 3% chance of ultimately achieving a sustained viral response.<sup>12</sup> Therefore, treatment was stopped earlier, spar-

**Table 1. Categorization of Serum LDL and Cholesterol Levels\***

Lipid Profile	Medium (Between 33rd and 67th Percentiles)		
	Low (Below 33rd Percentile)	Medium (Between 33rd and 67th Percentiles)	High (Above 67th Percentile)
LDL (mg/dL)	<87	88-119	120
Cholesterol (mg/dL)	<150	150-200	>200

\*To carry a typical regression analysis, the subjects were split into three groups as low, medium, or high LDL/cholesterol.

ing patients infected with HCV genotype 1 up to 36 weeks of ineffective therapy.

A two-sided independent-sample Student *t* test, ANOVA, and Fisher's exact test were used to analyze statistically significant differences between responders and nonresponders in pretreatment LDL, total cholesterol, TG, VLDL, and HDL levels. Multivariate analysis using exact logistic regression accounting for age and genotype was performed to compare the relationship between pretreatment LDL and total cholesterol levels and response to treatment in patients with chronic hepatitis C. During the logistic regression analysis, which was based on the LDL levels, we categorized subjects into low, medium, and high LDL groups and analyzed the groups in relation to treatment response. Because there was no theoretical basis for selecting such cutoff points, we trisected the distribution of LDL scores by placing patients with LDL levels below the 33rd percentile in the low LDL category, those between the 33rd and 67th percentiles in the medium LDL category, and those above the 67th percentile in the high LDL category (Table 1). A similar approach was taken for cholesterol (Table 1). Not included in the multivariate analysis were the variables ethnicity, because there was not complete data from a sufficient number of subjects, and type of treatment, because the proportion of patients receiving combined pegylated interferon and ribavirin therapy was disproportionately high.

## Results

A total of 99 chronic HCV-infected patients receiving treatment were identified. Demographic and laboratory values at the time of initial evaluation are shown in Table 2. Sixty-seven patients (67.6%) were male, and mean age ( $\pm$  SD) of the patients at time of treatment was 48.9 ( $\pm$  10.1) years. Forty-nine patients (49.5%) had HCV genotype 1, and 50 patients (50.5%) had genotype 2/3. Baseline characteristics by HCV genotype are given in Table 3. Eighty-five patients (86%) had had a liver biopsy performed, 39 of whom (46%) had stage 3 or 4 fibrosis. Before treatment mean HCV RNA viral load and ALT level ( $\pm$  SD) were 3,527,882 ( $\pm$  7,712,014) copies/mL

**Table 2. Pretreatment Characteristics of Patient Population**

Variable	Value
Number of patients	99
Mean ( $\pm$ SD) age at treatment (yr)	48.9 ( $\pm$ 10.1)
Number of males (%)	67 (67.6)
Patients with HCV genotype 1 (%)	49 (49.5)
Patients with HCV genotype 2/3 (%)	50 (50.5)
Mean ( $\pm$ SD) HCV RNA (copies/mL)	3,527,882 ( $\pm$ 7,712,014)
Mean ALT (U/L $\pm$ SD)	89.8 ( $\pm$ 59.9)
Fibrosis stage 3 or 4 (%)	39 (39.4)
Mean ( $\pm$ SD) total cholesterol (mg/dL)	179.4 ( $\pm$ 42.7)
Mean ( $\pm$ SD) LDL (mg/dL)	105.4 ( $\pm$ 35.8)
Mean ( $\pm$ SD) HDL (mg/dL)	53.8 ( $\pm$ 17.8)
Mean ( $\pm$ SD) triglycerides (mg/dL)	114.4 ( $\pm$ 66.4)

and 89.8 ( $\pm$  59.9) IU/L, respectively. Pretreatment lipid values were: LDL, 105.4 ( $\pm$  35.8) mg/dL ( $n = 76$ ); total cholesterol, 179.4 ( $\pm$  42.7) mg/dL ( $n = 99$ ); HDL, 53.8 ( $\pm$  17.8) mg/dL ( $n = 78$ ); and triglycerides, 114.4 ( $\pm$  66.4) mg/dL ( $n = 81$ ).

Overall, the rates of EVR, ETR, and SVR were 80%, 71%, and 58%, respectively. The EVR, ETR, and SVR for genotypes 1 and 2/3 were 69.3%, 55%, and 39.3% and 90%, 83.6%, and 73.3%, respectively. For all patients LDL level was statistically significantly different between responders and nonresponders for EVR, ETR, and SVR ( $P = 0.0253$ ,  $P = .0091$ ,  $P = .0071$ , respectively; Fig. 1). Similarly, total cholesterol level differed significantly between responders and nonresponders for EVR, ETR, and SVR for all patients ( $P = .0009$ ,  $P = .0008$ ,  $P = .0004$ , respectively; Fig. 2). A significant difference between responders and nonresponders in pretreatment HDL was also observed for EVR, but not for ETR or SVR. Pretreatment HDL level was significantly different between responders and nonresponders who achieved EVR, 54.7 ( $\pm$  19.2) and 49.8 ( $\pm$  7.1) mg/dL, respectively ( $P = .0106$ ), but there was no significant difference in later treatment results (ETR or SVR). The differences between responders and nonresponders in pretreatment VLDL and triglycerides levels were not sig-

**Table 3. Comparison of Pretreatment Characteristics by HCV Genotype**

Variable	Genotype 1	Genotype 2/3
Number of patients (%)	49/99 (49.5)	50/99 (50.5)
LDL (mg/dL), mean ( $\pm$ SD)	100.2 ( $\pm$ 30.2)	110.1 ( $\pm$ 40)
Total cholesterol (mg/dL), mean ( $\pm$ SD)	171.8 ( $\pm$ 36.2)	186.9 ( $\pm$ 47.5)
Triglycerides (mg/dL), mean ( $\pm$ SD)	134.4 ( $\pm$ 83.2)	96.6 ( $\pm$ 40.1)
HDL (mg/dL), mean ( $\pm$ SD)	52.1 ( $\pm$ 14.4)	55.5 ( $\pm$ 20.5)
Fibrosis stage 3 or 4/total (%)	21/44 (47.7)	18/41 (43.9)
Diabetes mellitus/total (%)	3/47 (6.4)	5/46 (10.9)
ALT (U/L), mean ( $\pm$ SD)	90.1 ( $\pm$ 52.3)	89.5 ( $\pm$ 67)
Sex (number of males/total; %)	37/49 (75.5)	30/50 (60)
Age at treatment (yr), mean ( $\pm$ SD)	48.7 ( $\pm$ 11.8)	49.2 ( $\pm$ 8.3)

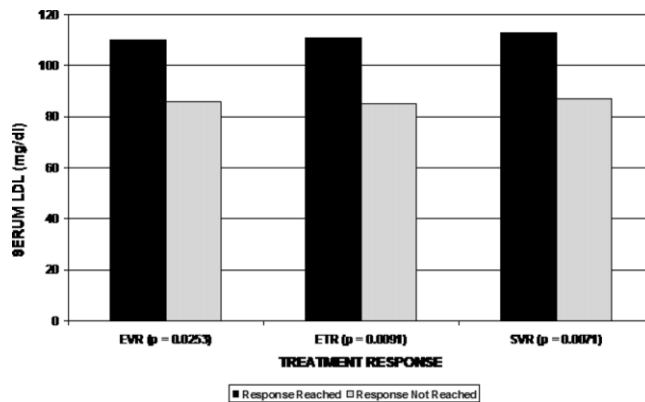


Fig. 1. Correlation between serum LDL levels and outcome of hepatitis C treatment.  $P$  values were calculated using ANOVA and Student  $t$ -test univariate analyses.

nificant. Univariate analysis comparing pretreatment LDL level with pretreatment viral load also did not show a significant correlation.

The prevalence of steatosis was higher in patients infected with HCV genotype 3 (9 of 18, 50%) than in patients infected with HCV genotype 1 or 2 (13 of 43, 30%; and 7 of 22, 32%, respectively). However, the sample size was too small to analyze the effect of steatosis on treatment outcome in patients with HCV genotype 3. Mean pretreatment LDL levels of patients with genotypes 1, 2, and 3 were 100.1 ( $\pm$  30.1), 122.7 ( $\pm$  35.3), and 91.1 ( $\pm$  39.8) mg/dL, respectively. Similarly, pretreatment cholesterol levels of patients with genotype 1, 2, and 3 were 171.7 ( $\pm$  36.2), 202.4 ( $\pm$  44.1), and 165.3 ( $\pm$  44.3) mg/dL, respectively.

Univariate analysis using age, gender, fibrosis stage, viral load, ethnicity, and steatosis as variables showed only age and genotype to have a significant relationship with treatment outcome. Multivariate exact logistic regression analysis evaluated the effect of pretreatment LDL and

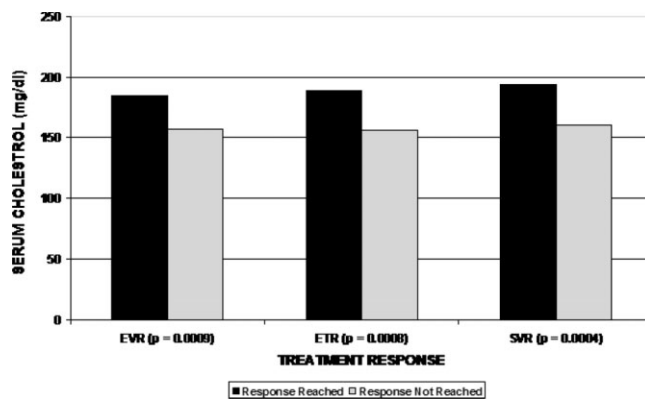


Fig. 2. Relationship between serum cholesterol levels and outcome of hepatitis C treatment.  $P$  values were calculated using ANOVA and Student  $t$  test univariate analyses.

**Table 4A. Rates of EVR, ETR, and SVR According to Pretreatment LDL and Cholesterol Levels**

Treatment Response	Low LDL (<88 mg/dL) n = 27	Medium LDL (88-119 mg/dL) n = 23	High LDL (>119 mg/dL) n = 26	Low Cholesterol (<150 mg/dL) n = 33	Medium Cholesterol (150-200 mg/dL) n = 33	High Cholesterol (>200 mg/dL) n = 33
EVR %	70 (19/27)	83 (19/23)	92 (24/26)	69 (23/33)	76 (25/33)	94 (31/33)
ETR %	52 (14/27)	69 (16/23)	73 (19/26)	45 (15/33)	67 (22/33)	76 (25/33)
SVR %	37 (10/27)	43 (10/23)	58 (15/26)	33 (11/33)	39 (13/33)	64 (21/33)

cholesterol levels on treatment response after controlling for age and genotype. The rates of EVR, ETR, and SVR among patients with low, medium, and high LDL/cholesterol levels are shown in Table 4A. The statistical significance of differences between responders and nonresponders in LDL and total cholesterol levels remained after controlling for these confounding variables (Table 4B). When we observed the effect of pretreatment LDL level, controlling for age and genotype, we found the odds of patients in the medium LDL group achieving EVR was 2.43 times that of patients in the low LDL group. Similarly, the odds of patients in the high LDL group achieving EVR was 2.43 times that of the patients in the medium LDL group. Likewise, looking at the effect of pretreatment cholesterol level while controlling for genotype and age showed the odds of patients in the medium cholesterol group achieving EVR was 1.93 times that of patients in the low cholesterol group, and similarly, the odds of patients in the high cholesterol group achieving EVR was 1.93 times greater than patients in the medium cholesterol group. The odds ratio of LDL predicting a treatment response was higher than that of total cholesterol. Pretreatment LDL and total cholesterol levels in relation to antiviral response are given in Table 5.

Most of our patients, 81 (86%), had not experienced any previous course of antiviral treatment. Previous treatment history of 5 patients was unknown. Only 1 of the 13 (14%) previously treated patients had been treated with a course of pegylated interferon. Seventy-six (77%) of the

study patients were treated with a combination of pegylated interferon and ribavirin, 22 (22%) with standard interferon and ribavirin, and 1 (1%) with interferon alone.

## Discussion

The current standard of HCV therapy is a combination of pegylated interferon and ribavirin. Successful treatment outcome is defined as sustained absence of the virus in the blood for at least 6 months after completion of treatment. Nearly half of all individuals undergoing treatment either fail to achieve eradication of HCV from serum (nonresponders) or relapse once treatment is stopped (relapsers). Molecular studies of HCV replication and infection have shown entry of the virus into the cell may occur via LDL and CD 81 receptors.<sup>3-5</sup> Binding and endocytosis of the virus is limited by LDL particles via competitive inhibition *in vitro*.<sup>3</sup> We evaluated the possibility of such inhibition *in vivo* and examined the influence of LDL level on treatment outcome.

Patients infected with HCV genotype 1 have low rates of SVR compared to patients with non-genotype 1 HCV infection.<sup>13</sup> In our study population, the SVR rate was 39% and 72% in patients with genotype 1 and with genotype 2 or 3, respectively. These results were similar to those obtained in the pivotal trials of pegylated interferon and ribavirin therapy.<sup>12,13</sup> Among the variables considered to affect treatment outcome, including genotype, stage of fibrosis, steatosis, age, gender, and viral load, only genotype and age were associated with SVR. It may well have been that no association was found between treatment response and fibrosis, steatosis, gender, or viral load because of a combination of a relatively small sample size and about half the study population having non-genotype 1 HCV infection. Multivariate analysis of serum LDL level and SVR, after accounting for age and viral genotype, showed patients with higher LDL levels had significantly higher odds of achieving EVR, ETR, and SVR. Similarly, higher pretreatment serum cholesterol level was associated with higher odds of having EVR, ETR, and SVR. Because cholesterol and LDL bind to the same receptor, cholesterol level might affect both the entry of HCV into cells and treatment outcome via the same

**Table 4B. Multivariate Analysis—Odds Ratios for Rate of Treatment Response According to Total Cholesterol and LDL Levels\***

Variable	Treatment Outcome	Odds Ratio	P value
LDL groups			
Low (<88)	EVR	2.429	.0282
Medium (88-119)	ETR	2.568	.0217
High group (>119)	SVR	2.598	.0092
Cholesterol groups			
Low (<150)	EVR	1.934	.0447
Medium: (150-200)	ETR	2.258	.0147
High (>200)	SVR	2.074	.0242

\*Multivariate analysis controlling for age and genotype. Odds ratios are for an increase in levels from one total cholesterol or LDL range to the next. Analysis run using exact logistic regression.

**Table 5. Differences Between Respondents and Nonresponders in Pretreatment LDL and Cholesterol**

Treatment Response	Mean ( $\pm$ SD)			Mean ( $\pm$ SD)		
	Pretreatment Cholesterol (mg/dL)	n	P Value	Pretreatment LDL (mg/dL)	n	P Value
EVR(+)	185.1 ( $\pm$ 44.1)	79	.0009	109.7 ( $\pm$ 36.1)	62	.0253
EVR(-)	156.8 ( $\pm$ 27.8)	20		86.2 ( $\pm$ 28.4)	14	
ETR(+)	189.2 ( $\pm$ 43.4)	62	.0008	111.2 ( $\pm$ 35.8)	49	.0091
ETR(-)	156.3 ( $\pm$ 32.3)	26		85.8 ( $\pm$ 29.8)	18	
SVR(+)	194.2 ( $\pm$ 44.3)	45	.0004	113.4 ( $\pm$ 37.2)	35	.0071
SVR(-)	159.5 ( $\pm$ 35.2)	32		87.3 ( $\pm$ 30.8)	23	

mechanisms proposed for LDL. In our study pretreatment HDL level was not associated with SVR. HDL does not bind to the LDLR and thus is not expected to exert an inhibitory effect on HCV endocytosis. Even after controlling for age and viral genotype, an increase in pretreatment LDL and cholesterol levels significantly increased the chances of achieving a positive EVR, ETR, and SVR. Although the differences between responders and nonresponders in pretreatment LDL and cholesterol levels (Table 5) were statistically significant, they were numerically small. However, studies have shown a significant decrease in mortality with the reduction of LDL level from 100 to 70 mg/dL in patients at very high risk of coronary artery disease.<sup>14</sup> Atorvastatin at a dosage of 80 mg reduced LDL level by 33 mg/dL more than pravastatin at a dosage of 40 mg, thereby reducing the hazard ratio for death or a major cardiovascular event by 16%.<sup>15</sup> The relative risk for a major coronary artery disease event is reduced by approximately 1% for every 1% reduction in LDL level, indicating that small changes in LDL level can bear biological importance.<sup>14-18</sup> Thus, the relatively small differences between responders and nonresponders in LDL and cholesterol levels in our study might similarly have a significant impact on outcome of HCV treatment.

The presence of severe fibrosis was shown to be an independent predictor of SVR in IFN-based therapy for patients with chronic hepatitis C.<sup>19</sup> There is a decrease in serum cholesterol and LDL levels as the severity of liver disease increases.<sup>20</sup> Thus, the inability of patients with low LDL levels to achieve SVR could be secondary to advanced liver fibrosis. However, this effect is unlikely to completely explain the observed association because the effect on cholesterol is generally seen only in very advanced disease. Patients with HCV genotype 2 or 3, most of whom achieve SVR and are thus treated empirically, accounted for about half our study population. Thus, unlike patients with genotype 1, liver biopsy is often not performed in patients infected with non-genotype 1 HCV. A chi-square test with available data for stage of fibrosis and SVR, however, did not show any significant correlation. Therefore, fibrosis stage was not included as a covariate in the multivariate analysis. Among those pa-

tients with genotype 2, LDL level remained a significant prognostic indicator for SVR.

We found a higher prevalence of steatosis in patients with genotype 3 than in patients with genotypes 1 or 2. The sample sizes in this study were too small to analyze the effect of steatosis on treatment outcome in patients with only HCV genotype 3. The mean pretreatment LDL levels for genotypes 1, 2, and 3 were 100.1, 122.7, and 91.1 mg/dL, respectively, and a similar pattern of results was found for total cholesterol level. This is consistent with previous studies that showed a high prevalence of hypobetalipoproteinemia and steatosis in genotype 3-infected patients.<sup>21-23</sup> The rates of SVR in patients with genotypes 1, 2, and 3 were 39%, 85%, and 53%, respectively, in our study. Thus, having higher LDL or cholesterol levels prior to treatment might indicate a good outcome only for patients with genotype 1 or 2, not for patients infected with genotype 3. This could be a result of alteration in beta-lipoprotein metabolism induced by genotype 3a by interfering with the synthesis of cholesterol in hepatocytes.<sup>21</sup> Although the pretreatment LDL and cholesterol levels were low in patients with genotype 3, those who achieved sustained viral response seemed to have comparatively higher LDL and cholesterol levels than those who did not. The same analysis could not be done for EVR and ETR as our data were biased toward responders, and an analysis with a larger cohort of genotype 3 patients would be needed to further evaluate this in future studies.

A better understanding of the mechanisms underlying HCV infection and efficacy of interferon treatment will suggest advances to improve the outcome of therapy. The potential involvement of the LDL receptor in HCV infection provides a new approach to therapy in the future. Such advances may include the use of LDL receptor-blocking analogues that may slow viral replication and progression of the disease, prevent reinfection of a transplanted liver, or improve the rate of sustained viral response. Because the number of patients analyzed for antiviral response in our retrospective study was relatively small, the results may be considered preliminary findings. Furthermore, although there was an insufficient number

of relapsers for comparison with responders and nonresponders, our findings would have been reinforced with the finding of a trend between LDL/total cholesterol levels and antiviral response from a comparison of responders, relapsers, and nonresponders. Thus, a prospective study investigating the association between serum lipid level, HCV viral load, liver histology, and response to pegylated interferon and ribavirin treatment in patients with chronic hepatitis C is in progress.

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