Factors Affecting Serum Concentrations of Hepatitis C Virus (HCV) RNA in HCV Genotype 1-Infected Patients with Chronic Hepatitis

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The serum concentration of hepatitis C virus (HCV) RNA is usually stable (4 to 8 log10 IU/ml) in untreated patients with chronic hepatitis C. While this baseline HCV RNA concentration ([HCV RNA]BL) is predictive of a sustained virologic response to treatment, its determinants are only partially identified. We therefore analyzed the baseline characteristics of 2,472 HCV genotype 1-infected patients to identify correlations with gender, age, race, weight, body mass index (BMI), HCV acquisition mode, HCV subtype, alanine aminotransferase concentration, or histopathologic changes in the liver. After separation of the data according to four [HCV RNA]BL groups (<5.0, >5.0 to 5.6, >5.6 to 5.9, and >5.9 log10 IU/ml), we determined that increasing [HCV RNA]BL correlated (P < 0.05) with increasing proportions of patients who were male, >40 years of age, or heavier (a weight of >85 kg or a BMI of >27 kg/m2). Histologic activity index (HAI) data were available for 1,304 of these patients: increasing [HCV RNA]BL correlated with higher fibrosis and necrosis-inflammation scores. As a continuous variable, [HCV RNA]BL correlated with age, gender, weight (continuous or ≥85 kg or a BMI of >27 kg/m2), subtype, fibrosis score, and necrosis-inflammation score; however, multiple-regression analysis yielded P values of <0.1 only for age, gender, BMI (≥27 versus >27 kg/m2), and fibrosis score. While our findings are suggestive of a role for these factors in maintenance of the pretreatment state of HCV infection, the multiple-regression model accounted for only ≤4.6% of the [HCV RNA]BL differences between individuals (R2 = 0.046 for 1,304 patients with HAI scores; 0.043 for all 2,472 patients).

The serum levels of hepatitis C virus (HCV) RNA represent the abundance of HCV production versus clearance and are usually stable in humans with untreated chronic hepatitis C (CHC) (1, 9, 12, 18, 22, 34, 39, 44, 49, 63). Between individuals, however, these baseline HCV RNA concentrations ([HCV RNA]BL) vary by 3 to 4 log10 IU/ml and the factors that explain these differences are poorly understood.

To identify the determinants of interpersonal [HCV RNA] variability, one study examined [HCV RNA] among 969 individuals who acquired HCV through injection drug use (63). Human immunodeficiency virus type 1 (HIV-1)-coinfected individuals had higher [HCV RNA] than those who were infected only with HCV; and among the latter group, a lower [HCV RNA] was independently associated with younger age, ongoing hepatitis B virus infection, and the absence of needle sharing. However, these factors explained only 8.5% of the person-to-person variability in [HCV RNA]. Similar results were observed in cohorts of 676 female injection drug users and 313 current and former drug users (59, 65). These results may have been affected by HIV-1 coinfection, HCV reinfection, the biologic and analytic effects from the various HCV genotypes that infected these individuals, interassay variability of the assays used to quantify HCV RNA, or the absence of data for certain key factors or for very low [HCV RNA] (21, 59, 63, 65).

In studies of alpha interferon-based therapy for CHC, [HCV RNA]BL have been predictive of a sustained virologic response (SVR) (16, 20, 24, 29, 36, 37, 41, 51, 72). Another viral characteristic, the HCV genotype, has also been predictive of an SVR: genotype 1 (gt1), the most prevalent HCV type in the United States, was independently associated with a lower likelihood of achieving an SVR (9, 15, 16, 24, 37, 72). Subsequently, patients with >2 × 106 copies/ml of HCV gt1 RNA, which corresponds to 5.9 log10 IU/ml, have been regarded to be less likely to achieve an SVR than those with lower baseline concentrations of HCV gt1 RNA or those with >5.9 log10 IU/ml of gt2 or gt3 (16, 20, 24, 29, 36, 37, 41, 46–48, 51, 54, 72). We recently identified 5.6 log10 IU/ml as the [HCV RNA]BL that best discriminated a high (70%) from a low (43%) SVR: genotype 1 (gt1), the most prevalent HCV type in the United States, was independently associated with a lower likelihood of achieving an SVR (9, 15, 16, 24, 37, 72). Subsequently, patients with >2 × 106 copies/ml of HCV gt1 RNA, which corresponds to 5.9 log10 IU/ml, have been regarded to be less likely to achieve an SVR than those with lower baseline concentrations of HCV gt1 RNA or those with >5.9 log10 IU/ml of gt2 or gt3 (16, 20, 24, 29, 36, 37, 41, 46–48, 51, 54, 72). We recently identified 5.6 log10 IU/ml as the [HCV RNA]BL that best discriminated a high (70%) from a low (43%) SVR for 568 gt1-infected patients who were treated for 48 weeks with 180 μg/week of peginterferon α-2a and 1,000 to 1,200 mg/day of ribavirin (unpublished data). Another recent study associated baseline HCV quasispecies diversity and lymphoproliferative responses to HCV antigens with a lower SVR rate among patients with advanced fibrosis (42). While these studies underscore the clinical importance of HCV RNA attributes, they also provide opportunities to identify correlations between [HCV RNA]BL and other baseline characteristics among the...
types of patients who are treated for CHC. Such correlations could be directly or indirectly predictive of an SVR.

Six recent clinical trials enrolled 3,985 HCV-infected patients to determine the safety and efficacy of peginterferon α-2a, with or without ribavirin, for CHC (16, 20, 24, 48, 54, 72). Combined data from these studies, which had a wide range of [HCV RNA]_{int} and a high proportion of patients with g1t infections, enabled us to study the interpersonal variability of [HCV RNA] among a large number of highly characterized patients who were infected with a prevalent and relatively treatment-resistant genotype. We therefore analyzed data from 2,472 g1t-infected patients to determine if there were any correlations between [HCV RNA]_{int} and a variety of demographic, clinical, and other baseline characteristics.

**MATERIALS AND METHODS**

**Patients.** We retrospectively analyzed data from 2,472 g1t-infected patients in six clinical trials of peginterferon α-2a, with or without ribavirin, for the treatment of CHC (16, 20, 24, 48, 54, 72). These multicenter trials were conducted in Australia, Canada, Europe (including France, Germany, Greece, Spain, and Switzerland), Mexico, New Zealand, South America, Taiwan, and the United States. Each trial was approved by the ethics committee or review board for the institutions at which it was conducted. The patients' dates of HCV acquisition and CHC diagnosis were not known. When baseline data were collected, these patients had compensated CHC, without evidence of other chronic liver disease or infection with HIV-1, hepatitis A virus, or hepatitis B virus. They also had serum concentrations of alanine aminotransferase ([ALT]) higher than the upper limit of the reference range (ULRR) in the laboratory where testing was performed. Other inclusion and exclusion criteria are described in the trials' reports.

**HCV RNA data.** As reported previously (16, 20, 24, 48, 54, 72), [HCV RNA] were determined as the numbers of copies/mL by use of the COBAS Amplipcr HCV Monitor test (version 2.0; Roche Diagnostics, Branchburg, NJ). These studies determined the genotype and the subtype by phylogenetically analyzing the nucleotide sequence (6, 16, 24, 48, 54, 72) or the restriction fragment length polymorphism (17, 20) from amplified cDNA representing part of the HCV 5' nontranslated region. We converted HCV RNA concentrations to IU/mL by using the manufacturer-recommended factor of 2.7 copies/IU (46) and then logarithmically transformed these values before performing the analyses.

**Baseline characteristics evaluated for correlations with [HCV RNA]_{int}**

For all 2,472 patients, we evaluated gender, race (Caucasian or other), age, weight, mode of HCV acquisition (injection drug use or other), g1t subtype (g1t1 or g1t2), and [ALT]. Because the 121 patients of African descent represented a small portion of the total (4.9%) and preliminary analyses did not identify any racially associated trends, we grouped these patients into the “other” category. We categorized a patient as cirrhotic if local histopathologic assessment indicated cirrhosis or a transition to cirrhosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of patients with characteristic (n = 2,472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>58 (n = 219) 64 (n = 264) 67 (n = 226) 73 (n = 1,465)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>84 (n = 27) 87 (n = 33) 87 (n = 9) 86 (n = 1)</td>
</tr>
<tr>
<td>Age, &gt;40 yr</td>
<td>49 (n = 20) 55 (n = 27) 67 (n = 33) 66 (n = 1)</td>
</tr>
<tr>
<td>BMI, &gt;85 kg</td>
<td>25 (n = 20) 32 (n = 27) 36 (n = 33) 36 (n = 1)</td>
</tr>
<tr>
<td>Injection drug use mode of HCV acquisition</td>
<td>31 (n = 20) 35 (n = 27) 35 (n = 33) 33 (n = 1)</td>
</tr>
<tr>
<td>HCV subtype 1b infection</td>
<td>49 (n = 20) 42 (n = 27) 44 (n = 33) 49 (n = 1)</td>
</tr>
<tr>
<td>Mean [ALT], &gt;3× ULRR</td>
<td>31 (n = 20) 33 (n = 27) 31 (n = 33) 32 (n = 1)</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>19 (n = 20) 23 (n = 27) 18 (n = 33) 24 (n = 1)</td>
</tr>
</tbody>
</table>

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* For all 2,472 patients, the [HCV RNA]_{int} range was 2.6 to 7.4 log_{10} IU/mL.
* Among patients who acquired HCV by modes other than injection drug use, 12% had transfusion-associated HCV infections; the percentage of transfusion-acquired infections did not correlate with the [HCV RNA]_{int} group.
* Determined from phylogenetic or restriction fragment analysis of amplified cDNA representing part of the 5' nontranslated region of the HCV genome.
* Defined as cirrhotic if local histopathologic assessment indicated cirrhosis or a transition to cirrhosis.
equal to 0, after adjustment for other characteristics in the model. All statistical analyses were performed with SAS software (SAS Institute, Cary, NC).

RESULTS

Overall ranges and proportions of baseline characteristics. Among all 2,472 patients, [HCV RNA]BL were between 2.6 and 7.4 log10 IU/ml. While the majority (55.1%) of these HCV RNA values were >6 log10 IU/ml, 80.9% were between 5.25 and 7 log10 IU/ml, and only 2.5% were >7 log10 IU/ml (Fig. 1). These patients were predominantly male, Caucasian, and more than 40 years old (for overall percentages, see the right-hand column of Table 1 and the bottom row of Table 2; for ranges, see Table 3). While 33.8% weighed more than 85 kg, 42.4% had BMIs of greater than 27 kg/m2. More than 45% were infected by parenteral exposure, and the numbers infected with HCV subtypes 1a and 1b, as determined from analysis of the 5’ nontranslated region of cDNA, were nearly equal. Noting that elevated [ALT] was an inclusion criterion for the trials in which these patients were enrolled, 68.2% of the mean baseline [ALT] were more than threefold higher than the upper limit of the testing laboratory’s reference range.

Correlations between [HCV RNA]BL and other baseline characteristics. To enable visual assessment of the spread in our data, we plotted [HCV RNA]BL versus the continuous-variable characteristics BMI (Fig. 2), weight (data not shown), and age (data not shown). These scatter plots were suggestive of an upper [HCV RNA]BL boundary that is a well-known feature of chronic HCV infections: none of the 2,472 points represented >7.5 log10 IU/ml of HCV RNA. A minority of points, in the lower portion of each plot and predominantly corresponding to [HCV RNA]BL of <5.2 log10 IU/ml, appeared to show evidence of an upward slope (14.3% of the patients had <5.2 log10 IU/ml). Patients with BMIs of >38 kg/m2 or weights of >110 kg did not have [HCV RNA]BL of >7.0 log10 IU/ml, so the right-hand portion of the BMI and weight plots appeared to indicate a decreasing slope, but the proportions of such patients were small.

The distribution of points in Fig. 2 also had a gap corresponding to 5.6 < [HCV RNA]BL < 6.0 log10 IU/ml, in which there were relatively few points, especially for patients with BMIs of <23 or >32 kg/m2. Plots of [HCV RNA]BL versus weight and versus age had similar gaps for the same range of

TABLE 2. Baseline HAI scores of hepatic histopathologic changes for a 1,304-patient subset according to groups that represent ranges of [HCV RNA]BL.

<table>
<thead>
<tr>
<th>Group, designated by [HCV RNA]BL (log10 IU/ml) range</th>
<th>No. of patients in group</th>
<th>Fibrosis score of 3 or 4a</th>
<th>Necrosis-inflammation score b</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HCV RNA]BL ≤5.0</td>
<td>116</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>&gt;5.0 to 5.6</td>
<td>382</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>&gt;5.6 to 5.9</td>
<td>71</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>&gt;5.9</td>
<td>735</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>2.8 to 7.4 (all HAI-scored patients)</td>
<td>1,304</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

a The HAI scores (33) were determined at a central laboratory for 1,304 patients, who represented 53% of all 2,472 patients. Within this 1,304-patient subset, the [HCV RNA]BL range was 2.8 to 7.4 log10 IU/ml and the numbers of patients in the first four listed [HCV RNA]BL groups respectively represent 53%, 68%, 31%, and 50% of the [HCV RNA]BL groups in Table 1.

b HAI score component, IV. P value is the probability, as determined by the Cochran-Armitage linear trend test for proportions, that chance alone accounted for an observed linear trend among the four [HCV RNA]BL groups in the percentage of patients who had an HAI fibrosis score of 3 or 4.

c Sum of HAI score components, I, II, and III. P value is the probability, from regression analysis, that chance alone accounted for an observed linear trend in mean scores among the four [HCV RNA]BL groups.
[HCV RNA], with especially few points representing patients who weighed <61 kg or >86 kg and were <29 or >59 years old, respectively. These distributions are somewhat analogous to the two bars in Fig. 1 that indicate relatively low percentages of patients with [HCV RNA]BL of between 5.51 and 6.0 log10 IU/ml (7.7% and 9.3%, respectively) versus those for patients with [HCV RNA]BL of 5.26 to 5.5 log10 IU/ml (11.3%) and 6.01 to 6.25 log10 IU/ml (13.3%).

The vast majority of patients were represented by ranges of intermediate values for [HCV RNA] (5.2 to 6.9 log10 IU/ml) and BMI (23 to 30 kg/m2), weight (63 to 95 kg), or age (30 to 55 yr), in which many points overlapped. Within these intermediate-value ranges, any relationship between [HCV RNA]BL and the other characteristic was not apparent.

Analyses of [HCV RNA]BL groups. We therefore divided our data into [HCV RNA]BL groups, each with a range of ≈0.3 log10 IU/ml, to identify any trends among the proportions of patients with other baseline characteristics. For the example shown in Tables 1 and 2, we identified correlations with P values of <0.05 between increasing [HCV RNA]BL and higher percentages of patients who (i) were male, >40 years old, >85 kg in weight, or >27 kg/m2 in BMI (Table 1) or (ii) had higher HAI scores for fibrosis or necrosis-inflammation (Table 2). We identified similar trends (data not shown) when we analyzed [HCV RNA]BL as a continuous variable, we identified correlations with P values >0.05 between [HCV RNA]BL and BMI among either age group, those with [HCV RNA]BL of <5.2 log10 IU/ml, or those with [HCV RNA]BL of >5.2 log10 IU/ml (Table 3). The strength of each correlation was low; however, no individual factor explained more than 2.4% (R2 = 0.024) of the person-to-person differences in [HCV RNA]BL.

For certain subpopulations, linear regression analysis yielded correlations that were consistent with the observations pertaining to Fig. 2 (see above) and like those shown in Table 3 for all 2,472 patients, but with somewhat higher coefficients. Among 353 patients with [HCV RNA]BL of <5.2 log10 IU/ml, we identified correlations with P values >0.05 between [HCV RNA]BL and BMI as a continuous or categorical (>27 kg/m2) variable, with higher R2 values (0.018 and 0.028, respectively) than those for BMI in Table 3 (0.0027 and 0.0053, respectively). Among 838 patients younger than 40 years of age, [HCV RNA]BL correlated again with continuously or categorically variable BMI, but with R2 values of 0.0058 and 0.0062, respectively. We did not identify linear associations with P values <0.05 between [HCV RNA]BL and (i) BMI among patients ≥40 years old or those with [HCV RNA]BL of ≥5.2 log10 IU/ml; (ii) HAI fibrosis score among patients in either age group (<40 or ≥40 years) or (iii) mean [ALT] (≤3× ULRR) among either age group, those with [HCV RNA]BL of <5.2 log10 IU/ml, or those with [HCV RNA]BL of ≥5.2 log10 IU/ml.

We also constructed a multiple-regression model that com-
prised each baseline characteristic in Table 3. That model yielded gender, age, BMI (>27 kg/m²), and HAI fibrosis score as independent predictors \( (P < 0.1) \) of \([HCV RNA]_{\text{Int}}\). Even this model, however, explained less than 5% of the person-to-person variability in \([HCV RNA]_{\text{Int}}\); \( R^2 = 0.046 \) for 1,304 patients (the model that included available HAI scores) and \( R^2 = 0.043 \) for all patients (without the inclusion of HAI scores).

None of our various analyses revealed correlations between \([HCV RNA]_{\text{Int}}\) and race, BMIs of 25 to 27 kg/m², or a higher HAI score for fibrosis or cirrhosis (Tables 1 to 3 and data not shown).

### DISCUSSION

While the implications of \([HCV RNA]_{\text{Int}}\) for the treatment of CHC are well recognized, the reasons for differences between relatively stable \([HCV RNA]\) among individuals with chronic HCV infection have remained obscure. We therefore analyzed the baseline data from 2,472 HCV gt1-infected patients in six trials of peginterferon \( \alpha-2a \), with or without ribavirin (16, 20, 24, 48, 54, 72). We limited this study to HCV gt1 because it (i) infected 62% of the six trials’ patients; (ii) is the most prevalent genotype in Australia, Europe, Japan, and the Western Hemisphere; and (iii) is relatively resistant to treatment (7, 9, 41, 71). To our knowledge, our report also represents the largest number of patients who have been evaluated for determining the relationships between \([HCV RNA]_{\text{Int}}\) and other baseline characteristics.

By analyzing such characteristics according to \([HCV RNA]_{\text{Int}}\) groups, we identified correlations between increasing \([HCV RNA]_{\text{Int}}\) and male gender, age >40 years, a weight of >85 kg, a BMI of >27 kg/m², or a higher HAI score for fibrosis or necrosis-inflammation. We obtained similar results, including those with \( P \) values of <0.05 for \( R \) not equal to 0, with HCV subtype 1b when we analyzed \([HCV RNA]_{\text{Int}}\) as a continuous variable. Multiple-regression analysis identified gender, age, BMI, and the fibrosis score as independent predictors of higher \([HCV RNA]_{\text{Int}}\). Several of our findings are consistent with those presented in previous reports, e.g., higher \([HCV RNA]\) among older persons (21, 63, 65). Others determined that BMI and histopathologic changes were independent predictors of the response to interferon-based therapy (2). While reports pertaining to correlations between \([HCV RNA]\) and the extent of liver disease have been inconsistent (13, 14, 19, 23, 43, 49, 53, 64, 70), at least one of our \([HCV RNA]_{\text{Int}}\)–HAI score associations appeared to be sample size dependent; i.e., regression of the \([HCV RNA]_{\text{Int}}\) and the fibrosis score yielded a \( P \) value of 0.0029 for 1,304 patients of all ages (Table 3) and a \( P \) value of 0.16 for 425 patients younger than 40 years of age, while the \( R^2 \) values (0.011 and 0.012, respectively) were nearly identical. Interestingly, Wilson et al. (68) recently correlated higher \([HCV RNA]\) with the subsequent progression of fibrosis among injection drug users.

The most remarkable conclusion from these studies is that we do not understand a great deal about the determinants of \([HCV RNA]\). In our study, less than 5% of the interpersonal differences in the baseline HCV gt1 RNA concentration could be explained by the sociodemographic, HCV subtype, biochemical, and histopathologic characteristics that we analyzed. Other studies, which included HIV-1-coinfected individuals and characteristics such as the durations of HCV infection and drug use, explained <10% of the interpersonal variability in \([HCV RNA]\) (21, 63, 65). These results indicate that as yet unidentified biologic or analytic factors explain most of the person-to-person differences in \([HCV RNA]\).

Several factors may have contributed to our low multiple-regression \( R^2 \) values of 0.043 and 0.046. First, biologic variation and assay imprecision may have biased the \([HCV RNA]_{\text{Int}}\) that we analyzed. Imprecision may have been relatively high (due to the use of several testing laboratories, technologists, runs, and reagent lots), but the same well-characterized HCV RNA assay was used for all six trials. If these trials’ HCV RNA testing yielded within-patient variability of approximately \( \pm 0.5 \log_{10} \) IU/ml, as others have reported (1, 9, 12, 18, 22, 34, 39, 44, 49, 63), such “noise” in single \([HCV RNA]\) values would not have affected our analyses more than in earlier studies.

### TABLE 3. Associations between \([HCV RNA]_{\text{Int}}\) and other baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable evaluated</th>
<th>( R )</th>
<th>( R^2 )</th>
<th>( P (R &gt; 0) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ((n = 2,472))</td>
<td>Male vs female</td>
<td>0.11</td>
<td>0.011</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>Caucasian vs other</td>
<td>0.019</td>
<td>0.00036</td>
<td>0.65</td>
</tr>
<tr>
<td>Race</td>
<td>18 to 76 yr, continuous</td>
<td>0.16</td>
<td>0.024</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>40 to 184 kg, continuous</td>
<td>0.070</td>
<td>0.0048</td>
<td>0.0005</td>
</tr>
<tr>
<td>BMI</td>
<td>16 to 55 kg/m², continuous</td>
<td>0.052</td>
<td>0.0027</td>
<td>0.0094</td>
</tr>
<tr>
<td>BMI</td>
<td>( \leq 27 ) vs ( &gt;27 ) kg/m²</td>
<td>0.073</td>
<td>0.0053</td>
<td>0.0003</td>
</tr>
<tr>
<td>HCV acquisition mode</td>
<td>Transfusion vs injection drug vs other</td>
<td>0.020</td>
<td>0.0004</td>
<td>0.62</td>
</tr>
<tr>
<td>HCV subtype (^b)</td>
<td>1a vs 1b</td>
<td>0.041</td>
<td>0.0017</td>
<td>0.041</td>
</tr>
<tr>
<td>Mean [ALT] (^c) component(s) ((n = 1,304))</td>
<td>( \leq 3 \times ) ULRR vs ( &gt;3 \times ) ULRR</td>
<td>0.0039</td>
<td>0.000015</td>
<td>0.85</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Noncirrhotic vs cirrhotic(^c)</td>
<td>0.031</td>
<td>0.00096</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\(^a\) For the continuous variables, \( R \) is the correlation coefficient from which \( R^2 \) was calculated. For the categorical variables, \( R^2 \) is the coefficient of determination from which \( R \) was calculated.

\(^b\) Determined from phylogenetic or restriction fragment analysis of amplified cDNA representing part of the 5' nontranslated region of the HCV genome.

\(^c\) Defined as cirrhotic if local histopathologic assessment indicated cirrhosis or a transition to cirrhosis.

\(^d\) The HAI scores (33) were determined for a subset of 1,304 patients at a central laboratory.
Regardless of any unexpected imprecision, it is unlikely that 2,472 HCV RNA values were unidirectionally biased. Second, [HCV RNA]_{in}–HCV subtype correlations may have been obscured because the six trials’ subtyping methods, which were based on characterization of part of the HCV 5’ nontranslated region (6, 16, 17, 20, 24, 48, 54, 72), are less accurate than phylogenetic analysis of the nucleotide sequence representing a segment of the HCV open reading frame (3–5, 35, 45, 58, 71). Third, if relationships between [HCV RNA]_{in} and other baseline characteristics were not linear, as our results indicated, more complex relationships may have been affected by undetermined factors that limit maximum the [HCV RNA]_{in}. Fourth, certain baseline characteristics may have had [HCV RNA]_{in}-independent interactions. For example, a review by Dufour et al. (8) cited five pre-1993 studies in which [ALT] had direct relationships with age, weight, and BMI. Recent reports correlated CHC patients’ [ALT] with metabolic syndrome and perhaps to the development of optimal therapy for CHC.

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REFERENCES


