A dynamic equilibrium between viral production and clearance characterizes untreated chronic hepatitis C viral infection. After initiating antiviral treatment, a typical multiphasic decay of viremia can be observed and analyzed using mathematical models. To elucidate the antiviral mechanism of ribavirin when used in combination with (pegylated) interferon alfa, we investigated kinetic parameters in patients with chronic hepatitis C treated with either peginterferon α-2a with or without ribavirin and standard interferon α-2b plus ribavirin for 48 weeks. Serum HCV RNA was measured frequently before, during, and at the end-of-treatment and the follow-up period. By using an appropriate model for viral dynamics, kinetic parameters were derived from nonlinear, least square fitting of serum HCV RNA quantifications. The first phase of viral decay (day 1) and the second phase of viral decay (days 2 to 21) were similar for all treatment groups. After about 7 to 28 days, a third phase of viral decay was seen in several patients, and this phase of decay was significantly faster in patients treated with peginterferon α-2a plus ribavirin compared with those treated with peginterferon α-2a alone. The decay of this third phase was associated with the virologic end-of-treatment response and sustained virologic response. In conclusion, the third-phase decay of initial viral kinetics, which may represent a treatment-enhanced degradation of infected cells, was more pronounced in patients treated with peginterferon α-2a plus ribavirin. This finding suggests that combination treatment leads to a better restoration of the patient’s immune response. (HEPATOLOGY 2003;37:1351-1358.)

See Editorial on Page 1257

Chronic infection with hepatitis C virus (HCV) is characterized by a dynamic equilibrium between virus production and clearance. A characteristic biphasic or multiphasic initial decline of serum HCV RNA is observed when this equilibrium is disturbed by interferon alfa and can be analyzed mathematically. Viral kinetic models estimated a very short half-life of free hepatitis C virions in vivo (<5 hours) and suggested that a rapid first phase (day 1) of viral decline relates to the decay of free viral particles, whereas the much slower second phase (days 2 to 14) of viral decline reflects the clearance of productively infected cells. Moreover, a typical biphasic decay could be explained if interferon has a single therapeutic effect of partially blocking viral production. Kinetic analyses were central to our current understanding of antiviral therapy and have influenced approaches toward treatment of patients with chronic hepatitis C. New results indicate that a third phase of viral decay can be present and may be due to suppression of the immune response during chronic HCV infection and a restoration of the cellular immune response that occurs when the serum viral load declines below an individual threshold.

Wide fluctuations in the plasma concentration of interferon are seen because of its short elimination half-life (4 to 10 hours) and render mathematical modeling of HCV kinetics more difficult. Furthermore, suboptimal interferon plasma concentrations may lead to intermittent increases of serum HCV RNA between interferon alfa injections. Covalent attachment of polyethylene glycol to interferon alfa results in a more sustained absorp-
tion from the subcutaneous injection site, decreased clearance, and increased serum half-life compared with interferon alfa itself. Once per week, application of pegylated (40 kD) interferon α-2a leads to almost constant serum levels with very small fluctuations in the peak-to-trough concentrations and conceptually sustained antiviral activity, which not only facilitates the modeling of HCV dynamics but could also improve the chance of achieving a sustained virologic response. Viral kinetics of patients treated with pegylated interferon also showed a typical interferon-like profile of viral decline.

The synthetic purine nucleoside ribavirin has no antiviral activity against HCV in monotherapy; however, in combination with interferon alfa, the end-of-treatment and sustained virologic response rates are substantially enhanced. The antiviral mechanisms of ribavirin in patients with chronic hepatitis C when used in combination with an alfa interferon are unknown, and both direct and indirect antiviral and immunologically mediated effects have been suggested. Mathematical modeling of viral kinetics can assist in elucidating the mechanism of action of ribavirin. Therefore, the effect of ribavirin on HCV dynamics was studied here in patients chronically infected with hepatitis C virus who were treated with long-acting peginterferon α-2a alone or in combination with ribavirin. Only patients infected with genotype HCV-1 were studied because viral kinetics are genotype dependent and because the synergistic antiviral effect of ribavirin is most pronounced in HCV-1-infected patients.

**Patients and Methods**

Male and female patients aged 18 or older with elevated serum alanine aminotransferase (ALT) levels, consistent detection of HCV RNA above 5,000 IU/mL, and compensated, histologically proven chronic HCV infection not previously treated with any form of interferon were eligible for enrollment. Patients were excluded if they were positive for hepatitis B surface antigen, IgM antibody to the hepatitis B virus core antigen, or antibody to the human immunodeficiency virus. The present kinetic study is an investigator lead part of 2, phase III, randomized, multicenter trials. At 2 centers (Frankfurt and Randwick), 34 patients infected with HCV genotype 1 met the criteria and were all enrolled both into the global trial and into the present kinetic study. The global trials and the kinetic study were approved by the Ethics Committee according to the Declaration of Helsinki. All patients gave written informed consent before enrollment.

Patients were randomly assigned to receive subcutaneously either 180 μg peginterferon α-2a (PEGASYS; Hoffmann-La Roche, Basel, Switzerland) once weekly for 48 weeks with \((n_1 = 10)\) or without ribavirin \((n_2 = 17)\) or 3 million units (MU) standard interferon α-2b 3 times per week plus ribavirin (Rebetron; Schering-Plough, Kenilworth, NJ) for 48 weeks \((n_3 = 7)\). Ribavirin was given orally twice a day for a total dose of 1,000 mg (body weight <75 kg) or 1,200 mg (body weight ≥75 kg) per day. All patients were evaluated twice before initiation of treatment and at day 1 (6 and 12 hours after the first dose) and days 2 to 5, 8, 11, 15, 22, 29, 43, and 57 and subsequently every 4 weeks during treatment and the 24-week follow-up period. The primary efficacy end point for the study was defined as undetectable serum HCV RNA levels 24 weeks after treatment. The concentration of HCV RNA in pretreatment serum samples and samples obtained during treatment was determined using a quantitative reverse-transcription polymerase chain reaction assay (Cobas Amplicor HCV Monitor 2.0; Roche Diagnostic Systems, Branchburg, NJ) and in 2 independent serum samples obtained at the end-of-treatment and the end of follow-up period by a qualitative detection assay (Amplicor HCV, Roche Diagnostic Systems). The lower detection limit of the quantitative and qualitative assay is 600 and 50 IU/mL, respectively. Patients with no detectable serum HCV RNA levels for both qualitative assays at the end-of-treatment (week 48) were classified as end-of-treatment responders (ETR). Patients with no detectable serum HCV RNA levels for both qualitative assays 24 weeks after discontinuation of treatment were classified as sustained responders (SR). HCV genotyping was performed by reverse hybridization assay (Inno LiPA HCV II; Innogenetics, Gent, Belgium).

Viral kinetic models use compartments of productively infected \((I)\) and uninfected \((T)\) hepatocytes and of the free viral load \((V)\). They assume rates for clearance of free virus \((c)\), infected cell loss \((β)\), virus production \((p)\), and de novo infection \((β)\). Antiviral effects during the initial phases were modeled by efficiency factors \(ε\) and \(η\) on virus production and on de novo infection, respectively, and were assumed to start after a short delay time \(t_0\). Here, a possible further immunologic effect was modeled by an inflation factor \(M ≥ 1\) on the infected cell loss, which started at some delayed time point \(t_1 > t_0\) (Fig. 1). A simple linear model for the compartment of uninfected cells was included, which leads to a stabilization of the total number of hepatocytes and, therefore, reflects the rate for liver regeneration. The resulting model during therapy is expressed by the differential equations:

\[
V'(t) = (1 - ε) \cdot p \cdot I(t) - c \cdot V(t)
\]

\[
I'(t) = (1 - η) \cdot β \cdot T(t) \cdot V(t) - δ \cdot I(t)
\]

\[
T'(t) = γ (T(0) + I(0) - T(t) - I(t))
\]
for $t_0 \leq t \leq t_1$. For $t \geq t_1$, the infected cell loss changes to $M\delta$ and, therefore, the second equation becomes

$$I'(t) = (1-\eta) \beta T(t) V(t) - M \delta I(t)$$

whereas the other equations remain unchanged. The distinction between pretreatment infection rate $\beta$ and viral production rate $p$ and the possibly treatment-related infection rate $(1-\eta) \beta$ and viral production rate $(1-\epsilon) p$ during treatment is necessary because we used conditions from the pretreatment steady-state assumption before therapy was initiated to eliminate the parameters $p$ and $\beta$ as previously described.$^{2,6,7,18}$ The model function of the viral load compartment $V$ could be approximated during the first few weeks quite well by a biphasic exponential function in which the first-phase decline is given by $c$, the second-phase decline is mainly determined by $\delta$, and the relative dose-dependent decay during the first phase is given by $1-\epsilon$. Such a nearly biphasic decay results from a single effect on viral production, which may or may not be accompanied by an effect on de novo infection.$^{2,23}$ Here, we assume that the infected cell loss may increase after a further delay time $t_1$. This change in the infected cell loss will be reflected by a change of the exponential decay. Therefore, a third phase of viral decay may be starting at $t_1$ with an exponential decline rate of approximately $M\delta$.

We used these approximations to define the starting parameters for a nonlinear least squares approach of the logarithmic viral load to derive estimates for $c$, $\delta M\delta$, $\epsilon$, the delay time $t_1$, and the viremia levels $V_0 = V(t_0)$ and $V_1 = V(t_1)$. All these parameters were estimated simultaneously with a general multivariate minimization procedure. The parameters $\eta$, $\gamma$ [day$^{-1}$], and $T(0)/I(0)$ had only minor influence on the resulting curve. The minor influence of the efficacy factor $\eta$ on de novo infection for the initial viral kinetics was also observed by others.$^{18}$ Here, $\eta$ was fixed to 0.5. The parameter $\gamma$ can be explained as a rate constant describing the velocity of liver regeneration. Extreme situations can be modeled by $\gamma = 0$ (compartment of uninfected cells remains constant) and $\gamma$ as infinity (compartment of uninfected cells always equals a fixed number of hepatocytes minus the infected ones). Here, it was fixed to $0.07$ [day$^{-1}$].$^{23}$ Furthermore, we assumed that 50% of all liver cells are infected and, therefore, set $T(0)/I(0) = 1$. To avoid bias effects on the first phase of viral kinetics, we fixed the first delay $t_0$ to 8 hours. To include data below the detection limit, the Tobit approach was used as previously described.$^7$ Numerical minimization and solution of the differential equations was performed using Matlab software (MathWorks Inc., Natick, MA). As an alternative, we investigated an analogous model, which assumed 2 different viral compartments. This approach allows an increased production of much less infectious or noninfectious virus in the presence of treatment.$^{16}$ Nevertheless, even this simplified model is very complex and can only serve as a rough diagnostic test for the base model without further data on quasispecies kinetics.

Results

We randomized 34 patients infected with chronic hepatitis C genotype 1 virus to receive either peginterferon $\alpha$-2a with ($n_1 = 10$) or without ribavirin ($n_2 = 17$) or combination treatment of standard interferon plus ribavirin ($n_3 = 7$) with similar baseline characteristics between the groups (Table 1). Already 14 days after initiating treatment, transaminase levels in patients from both combination regimens were significantly lower than

![Diagram](image.png)

**Fig. 1.** Kinetic compartment model after the second delay time $t_1$. $c$ describes the clearance rate of free virus, $M\delta$ describes the possibly enhanced infected cell loss, $(1-\eta) \beta$ describes the possibly reduced de novo infection rate, and $(1-\epsilon) p$ describes the possibly reduced viral production rate.

<table>
<thead>
<tr>
<th>Table 1. Patient Baseline Characteristics and Virologic Response</th>
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<tbody>
<tr>
<td><strong>PEG-IFN + RBV</strong> ($n_1 = 10$)</td>
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<tr>
<td>Age (yr, mean ± SD)</td>
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<tr>
<td>Sex (male/female)</td>
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<td>Body weight (kg, mean ± SD)</td>
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<td>Mean pretreatment ALT (× upper limit of normal, mean ± SD)</td>
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<td>HCV genotype (1a/1b)</td>
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<td>Mean ± SD HAI score</td>
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<td>Sex (male/female)</td>
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<tr>
<td>Virologic response End-of-treatment (%)</td>
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<td>End of follow-up (%)</td>
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Abbreviations: HAI, histological activity score.
those seen in patients treated with peginterferon α-2a alone (**P = .026 for ALT, **P = .006 for AST, Table 2). A similar but less obvious and more delayed trend was observed for viremia. Especially in patients treated with peginterferon α-2a plus ribavirin, serum HCV RNA levels were significantly lower than those seen in patients treated with peginterferon α-2a alone (**P = .048 at week 8 after initiating treatment). Serum viral load for the treatment groups of peginterferon α-2a alone and standard interferon α-2b plus ribavirin were comparable with a trend to be more favorable for peginterferon α-2a alone between weeks 2 and 4 and less favorable for peginterferon α-2a alone at week 8 (Table 2).

A more detailed look at the individual viral kinetics revealed that 1 of 10 and 1 of 17 patients treated with peginterferon α-2a plus ribavirin and peginterferon α-2a alone, respectively, showed a very fast decay with undetectable HCV RNA 10 days after starting treatment and later on. In 8 of 9 patients treated with peginterferon α-2a alone and 4 of 7 patients treated with standard interferon α-2b plus ribavirin, a pronounced third phase
of viral decay (Table 2, Fig. 2A-D) was observed. Typically, the second phase was very flat, and, in 6 patients, viremia increased during the second phase before the third phase of viral decline started.

A general triphasic decline function was used to fit the data for all patients. We obtained estimates for the pretreatment viremia $V_0$, the efficiency factor $e$ on viral production, a rough estimate for the degradation rate of free virus $c$, which mainly determines the first-phase decay, the pretreatment infected cell loss $\delta$, which mainly determines the second-phase decay, and the infected cell loss $M\delta$, which determines the third-phase decay and may be treatment-enhanced after some further delay $t_1$. Some kinetic parameters including an efficiency factor $\eta$ on de novo infection were fixed to suitable values as described in the Patients and Methods section. The efficiency factor $e$ on viral production showed a trend to be stronger in patients treated with peginterferon $\alpha-2a$ plus ribavirin or peginterferon $\alpha-2a$ alone than in those treated with standard interferon $\alpha-2b$ plus ribavirin ($P = .06$). No significant differences between the 2 peginterferon $\alpha-2a$ treatment groups were seen in the estimated kinetic parameter $c$, which determines the first-phase decay, and in the estimated pretreatment infected cell loss $\delta$, which determines the second-phase decay (Table 2). Nevertheless, significant differences can be seen in the estimates of the treatment-enhanced infected cell loss rate $M\delta$, which determines the third-phase decay ($P = .02$ for comparison of the peginterferon $\alpha-2a$ groups and $P = .05$ for the comparison of all 3 groups). The inflation factor $M$ was larger than 5 in 7 of 9 patients (77.8%) treated with peginterferon $\alpha-2a$ plus ribavirin and in 11 of 16 patients (68.8%) treated with peginterferon $\alpha-2a$ alone. $M$ was even larger than 100 in 6 of 9 patients (66.7%) and in 7 of 11 patients (43.8%), respectively. For all treatment groups, the third phase of viral decline started about 7 to 28 days after initiating therapy at a similar level of viremia of $5 \pm 1 \log_{10} \text{IU/mL}$ (Table 2).

In the present study, the end-of-treatment virologic response (ETR; no detectable HCV RNA serum levels with a qualitative test at the end of treatment) and the sustained virologic response (SR; no detectable HCV RNA serum levels with a qualitative test 24 weeks after the end of treatment) were highest in patients treated with peginterferon $\alpha-2a$ plus ribavirin (100% and 50% for patients treated with peginterferon $\alpha-2a$ plus ribavirin, 71% and 12% for patients treated with peginterferon $\alpha-2a$ alone, and 29% and 14% for patients treated with standard interferon plus ribavirin, all for ETR and SR, respectively, Table 1). The differences between all 3 groups were significant for ETR ($P = .006$) and almost significant for SR ($P = .063$). When analyzing the predictive values of the kinetic parameters derived from the viral response during the first weeks of treatment, the most pronounced association with ETR and SR could be found for the increased infected cell loss $M\delta$ reflecting the third-phase decay ($P = .001$ for ETR, $P = .11$ for SR). All estimates of the following parameters, the efficiency factor $e$ on viral production, the degradation rate $c$ of free virus, the pretreatment infected cell loss $\delta$, and the second delay time $t_1$ were not significantly associated with virologic response. The viremia $V_1$ when the third phase started was significantly associated with ETR ($P = .01$) but not with SR ($P > .2$). All but 2 patients without ETR had estimates...
for $M\delta$ below 0.13 [day$^{-1}$], and all patients with SR had estimates for $M\delta$ above 0.25 [day$^{-1}$] (Fig. 2A-D).

Alternatively, a compartment model with 2 free viral compartments was used to describe the data of a representative patient treated with peginterferon $\alpha$-2a plus ribavirin. In this model, one viral compartment dominates during the steady-state situation before starting therapy, and the other viral compartment represents mutant virus with a 1,000-fold decreased infectivity. An increased mutagenesis was modeled to start 6 days after initiating therapy. Here, the second-phase decay is difficult to interpret, but the third phase of viral decline observed about 16 days after initiating therapy again reflects the infected cell loss during therapy (Fig. 2E).

**Discussion**

We randomized 34 patients infected with chronic hepatitis C genotype 1 virus to receive either peginterferon $\alpha$-2a with or without ribavirin or combination treatment of standard interferon plus ribavirin. Recent studies showed that treatment with pegylated interferon alfa considerably enhances the end-of-treatment and, less pronounced, the sustained virologic response rates compared with standard interferon alfa.19,27 Ribavirin, however, mainly affects the sustained virologic response rates by reducing relapse rates after the end-of-treatment.12-14 Here, 100%, 71%, and 29% in patients treated with peginterferon $\alpha$-2a plus ribavirin, peginterferon $\alpha$-2a alone, and standard interferon alfa plus ribavirin, respectively, showed an ETR. These rates differ in comparison with those from the whole study, in which 69%, 59%, and 36%, respectively, showed an ETR. These rates differ in comparison with those from the whole study, in which 69%, 59%, and 36%, respectively, showed an ETR. These rates differ in comparison with those from the whole study, in which 69%, 59%, and 36%, respectively, showed an ETR.

Here, 100%, 71%, and 29% in patients treated with peginterferon $\alpha$-2a plus ribavirin, peginterferon $\alpha$-2a alone, and standard interferon alfa plus ribavirin, respectively, showed an ETR. These rates differ in comparison with those from the whole study, in which 69%, 59%, and 36%, respectively, in patients of all genotypes showed an ETR (genotypic ETR rates were not reported). Besides the inclusion of all genotypes in the rates of the whole study, reasons for the improved rates for the peginterferon groups may be that we did not consider patients who dropped out here and that all patients were treated at very experienced centers. The sustained virologic response rates in the present study were 50%, 12%, and 14% in patients treated with peginterferon $\alpha$-2a plus ribavirin, peginterferon $\alpha$-2a alone, and standard interferon alfa plus ribavirin, respectively, and were more in accordance with sustained virologic response rates of 46%, 21%, and 36%, respectively, for genotype 1-infected patients in the whole study.

Differences in the ETR rates for the peginterferon $\alpha$-2a groups were mainly due to the fact that 7 of 10 patients and 12 of 17 patients for the peginterferon $\alpha$-2a plus ribavirin and for the peginterferon $\alpha$-2a alone group showed only a moderate decay during the first 48 hours and no further decay in the following week. Nevertheless, all of the patients from the peginterferon $\alpha$-2a plus ribavirin group but only 7 of 12 patients in the peginterferon $\alpha$-2a alone group showed an accelerated viral decay after 7 to 28 days.

To find possible explanations for these observations and to analyze the predictive value of the viral response during the first 6 weeks of treatment for SR, we used a mathematical compartment model of viral kinetics. Obviously, findings based on such a kinetic model have to be supported by future virologic and immunologic research. The kinetic model used here resulted in a multiphasic exponential decay function. The decay during the first phase, which takes about 24 to 48 hours, is mainly determined by the clearance rate of free virus $c$. In contrast to the pretreatment viremia, $c$ and $t_0$ are difficult to identify from our data set because there were only a few observations during the first-phase decay. Possible biases can occur and may explain the differences to the larger estimates of $c$ obtained in previous analyses.2,25,26 After 24 to 48 hours, the exponential decay is mainly determined by the loss of productively infected cells.2 Several patients showed a pronounced third-phase decay starting at 7 to 28 days after initiation of therapy. Our modeling confirmed that such a more rapid third phase of viral decay can be explained by a delayed treatment-induced inflation of infected cell loss $M\delta$. Thereby, we assumed a sudden change of the infected cell loss only for the sake of simplicity. The delay may be caused by the pharmacokinetics of interferon and/or ribavirin or further reasons discussed below. Interestingly, and in accordance with viremia levels at weeks 4 to 8 (Table 2), one can observe a significantly faster infected cell loss $M\delta$ in patients treated with peginterferon $\alpha$-2a plus ribavirin compared with those treated with peginterferon $\alpha$-2a alone ($P = .02$). Patients treated with standard interferon plus ribavirin had an intermediate third-phase decay. In contrast to the treatment-dependent third-phase decay basing on $M\delta$, the time and the level of viremia when this third phase of viral decay started was very homogenous for all 3 treatment groups (Table 2). Therefore, the improved virologic response rates in patients treated with peginterferon $\alpha$-2a plus ribavirin compared with patients treated with peginterferon $\alpha$-2a alone can be explained by a ribavirin-enhanced infected cell loss. The estimated infected cell loss $M\delta$ as part of the initial viral response can also serve as predictor for ETR and SR. All but 2 patients without ETR had estimates for $M\delta$ below 0.13 [day$^{-1}$], and all patients with SR had estimates for $M\delta$ above 0.25 [day$^{-1}$].

Recently, a third phase of viral decay was explained by the hypothesis that restoration of a previously suppressed immune response could be seen if viremia declines below an individual threshold.5 In this case, the delay time $t_1$
coincides with the time point when this individual threshold is reached. Such an interpretation of our results has to include not only individual but also treatment-dependent thresholds or immune responses to adapt at the observation of treatment specific third-phase decays. A problematic point for this hypothesis remains the fact that even a nearly constant or slightly increasing second phase can be followed by a rapid third phase of viral decline. Nevertheless, the data of the present study confirmed that the third-phase decay most likely reflects a treatment-enhanced infected cell loss and showed that this infected cell loss rate is influential in predicting end-of-treatment and end-of-follow-up outcomes, especially for combination treatment regimens.

Several possible mechanisms of action have been proposed for ribavirin when the drug is used in the treatment of viral diseases, including depletion of the intracellular guanosine triphosphate pools, synthesis of RNA with abnormal 5′ cap structures, inhibition of viral polymerase activity, immune responses with a shift from TH2 to TH1, and an increased mutagenesis.3,15-17 The first suggested mechanism has been disproved, and the second is not applicable because of cap-independent replication of the hepatitis C virus. Preliminary analyses of initial viral kinetics suggested some synergistic antiviral activity between ribavirin and interferon in patients treated with 3 MU interferon alfa28,29 but not in patients treated with 3 MU interferon alfa daily or 6 MU interferon alfa given 3 times per week.29-31 Combination treatment with ribavirin did not show adverse effects on the infected cell loss rate in spite of improved decreases of ALT and AST levels.

As an alternative explanation of a 3-phase viral kinetics and to model an increased mutagenesis possibly induced by ribavirin, a compartment model with 2 free viral compartments was used to describe the data of a representative patient treated with peginterferon α-2a plus ribavirin (Fig. 2E). In this model, one viral compartment dominated during the steady-state situation before starting therapy, and the other viral compartment represents mutant virus with a substantially decreased infectivity. Here, the second phase was difficult to interpret but, again, the third-phase decay reflected the infected cell loss. Therefore, to account for the treatment-dependent third-phase decay, the data of the present study are best explained by an immune-mediated mechanism of ribavirin, e.g., activation of cytotoxic T cells leading to a treatment-enhanced elimination of productively infected cells. With respect to the rapidly improved ALT and AST levels in patients treated with ribavirin, this enhanced infected cell loss has to be due to elimination processes with only slight effect on transaminase serum levels, e.g., by apoptosis or cure of infected cells.

Alternative explanations such as a further improved antiviral activity on viral production at a delayed time could be described with a different kinetic model that shows 4 phases of viral decay, of which the first and the third ones are relatively short and faster than the almost identical second and fourth ones. Similarly, inclusion of nonhomogenous viral compartments with different sensitivities to interferon and/or ribavirin would typically result in a multiphasic exponential decay function in which the decay rates slow down with time. Both approaches do not reflect our data situation here. Treatment enhanced mutagenesis instead could explain a delayed observation of a more rapid third phase of viral decline but lead to alternative interpretations of the second-phase decay. Indeed, our observation of comparable second-phase decays and treatment-specific, third-phase decays fits well with the assumption that ribavirin improves the immune response already after the first week of treatment but also enhances mutagenesis, leading to a delayed observation of the immune response effect.

The predictive value of the initial decline of serum HCV RNA is more significant than all known baseline parameters including HCV genotype and pretreatment viremia.28,32 The assessment of HCV kinetics within the first weeks after initiation of treatment is anticipated to offer the possibility of individualized therapy. The present study confirms that the third-phase decay provides major predictive information. However, because the third phase of decline starts as late as 4 weeks after initiating therapy in some patients, individualizing therapy in patients with chronic hepatitis C based on viral dynamics will require sampling and HCV RNA quantification for the initial 6 to 8 weeks of therapy.

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