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News and Commentary

Hepatitis C viral kinetic models

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Mathematical models have provided insight in the dynamics of hepatitis C viral kinetics and calculated high turnover rates of infected hepatocytes and free virus with half-life of a few days and a few hours, respectively, in patients chronically infected with hepatitis.[1,2] For untreated patients with chronic hepatitis C, HCV RNA levels in serum show only minor fluctuations whereas a characteristic multiphasic decline of viremia can be observed after initiating antiviral therapy. Mathematical compartment models of viral kinetics which have first been developed for modelling anti-retroviral therapeutic effects in human immunodeficiency virus infection (HIV) can also explain such multiphasic declines of serum HCV RNA during antiviral treatment in patients with chronic hepatitis C.

Let us have a more detailed look at a typical mathematical model for HCV kinetics[1–4] basing on models for HIV.[5–7] It uses compartments of productively infected (I) and uninfected (T) hepatocytes and of the free viral load (V). Further important assumptions are that of constant rates for clearance of free virus (c), infected cell death (δ), virus production (p), and *de novo* infection (β) and of a steady state situation before treatment starts (Figure 1A and C).

Antiviral effects during the initial phases after starting therapy may be explained by direct inhibition of virus production or *de novo* infection which can be modelled by slowing down the respective rates. Alternative explanations are immunologic effects as forcing the degradation of free virus and productively infected cells, respectively, which can be modelled by an inflation of the respective rates. All such effects alone or in combinations will lead to a one- or biphasic exponential decay of viral load in serum. As the degradation of free virus is assumed to be faster than that of productively infected hepatocytes, an inflating effect on the degradation rate of free virus or a blocking effect of viral production will lead to a rapid decay which will be biphasic if viral production is not completely stopped. On the other hand, an effect on *de novo* infection and on the degradation of infected hepatocytes will be less dramatic and results in a relatively smooth transition of the constant serum viral load function in a one-phasic exponential decay function.

Probably, the most important information from the work of Neumann *et al*.[2] was that a biphasic decay function which can be observed for many patients after initiating interferon-based therapy can be explained convincingly by an incomplete blocking effect on viral production modelled by an efficiency factor (1-ε) which may or may not be accompanied by a blocking effect on *de novo* infection. Blocking of *de novo* infection can even be complete[1] and is modelled by a factor (1-η) of the *de novo* infection rate β. The resulting kinetic system during therapy can then be described by the differential equation system

$$\dot{V}(t) = (1 \quad \varepsilon) pI(t) \quad cV(t)$$
$$\dot{I}(t) = (1 \quad \eta)\beta T(t)V(t) \quad \delta I(t),$$

which is reflected by the compartment model of Figure 1 (right panel). The compartment of non-infected cells can be set constant during the first few weeks of treatment. The amount of the relative decay during this first phase which is influenced not only by the decay itself but also by its duration depends on the efficacy, approaches (1-ε), and depends on the dose of the antiviral treatment. The first-phase decay itself will mainly reflect the degradation rate of free virus and will not depend on dose. The decay of the second phase will mainly reflect the dose-independent degradation rate of infected hepatocytes.

A problematic point is the assumption that the resulting rates will be constant during therapy which is more realistic for therapy with pegylated interferons than for standard interferon.[8] In general, such compartment models leading to multiphasic decay functions can explain changes from one phase to another by two different approaches. Differentiating between these approaches is important for correct understanding which effects are really modelled and might be confirmed by observation of real viral kinetics. On the one hand, the change of phases can be explained by a new effect on the included rates. An example is the change from the steady-state situation to the biphasic model in Figure 1. Such a change may also be interesting for modelling further delayed effects, for example from combination treatment. Then, a new biphasic model will start whose exponential decays will again mainly reflect the degradation rate of free virus and of infected hepatocytes. Nevertheless, only one of both new phases may be observable. Delayed effects on viral production, degradation of free virus, or *de novo* infection would result in a displaced bi-phasic decay with a slower phase similar to the second-phase decay before. Delayed effects on the degradation of infected cells will be observable, mainly, as a third-phase which is accelerated in comparison with the second-phase decay. Such an observation of a third-phase in HCV RNA kinetics possibly resulting from a restoration and hence acceleration of infected cell degradation has

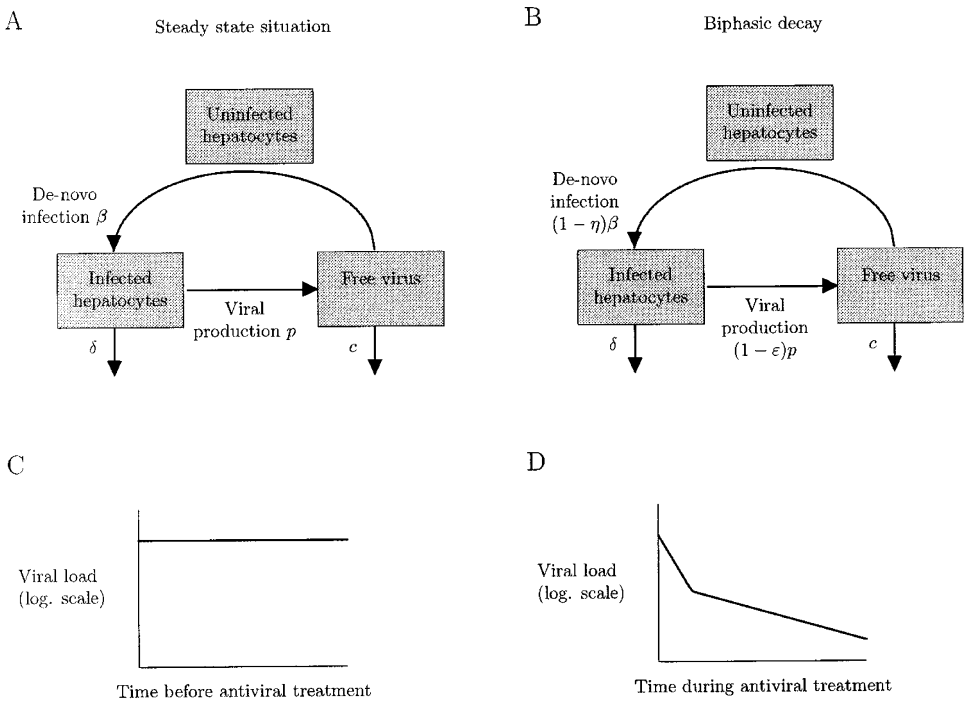

Figure 1 Compartment model (**A** and **B**) and a typical idealized serum viral load function (**C** and **D**) of the initial kinetics before (**A** and **C**) and during (**B** and **D**) interferon-based treatment for patients chronically infected with HCV

recently been described.[9] On the other hand, new phases can simply reflect the degradation rates of virus from different compartments, for example the compartment of free virus and the compartment of productively infected hepatocytes in the simple biphasic model (Figure 1B and D). Here, changes have to be from fast to slow. Such effects are important for HIV models including compartments of long-living latently infected cells.

In conclusion, mathematical modelling of viral kinetics have markedly improved the understanding of the mechanisms of antiviral therapy. Nevertheless, interpretation of and results from viral kinetics models still need to be verified. Possible approaches comprise comparisons with results from modelling related situations as post-transplantation viral kinetics[10] and the inclusion of the kinetics of transaminase levels or even interferon levels in serum. All these theoretical models have to be confirmed by direct immunologic and virologic analyses. Future applications of mathematical modelling will show if they can come up to the expectations in individualizing management of therapy.

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