Effect of Antibodies on HCV Infection

B. D. Aggarwala

Abstract — **We present a mathematical model which describes the development of HCV, and its resistant variants, in a patient. We assume that, apart from the variants that are already in the patient's blood stream, it requires only one more mutation at a specific nucleotide for an HCV virus to become resistant to the antiviral drug being administered, i.e. for u_0 (virus, together with all its variants, present when the treatment starts) to change into u_1 (virus which is resistant to the drug). We assume that, in the presence of drug pressure, it is easier for u_0 to change to u_1 than the other way around. The Model will say that there are exactly two outcomes of treatment: either the patient has a REBOUND of virus or SVR, sustained virologic response. The model will also outline the important role of a patient's immune system and say that if the immune system of the patient is strong enough, then HCV does not take hold.**

Index Terms — **Hepatitis C Virus, Immune System, Mathematical modeling, Sustained Virologic Response**

I. INTRODUCTION

ONE hundred and seventy million people are infected with HCV worldwide [1]. In the United States, more than five million people are supposed to be living with HCV [2]. Approximately 30,000 new cases are diagnosed each year. This situation is likely to get worse as the number of people infected with HCV from blood transfusions before 1990 come to be newly diagnosed. This is because, before 1990, there was no screening of blood against HCV, so that millions of patients must have been infected through blood transfusions. These cases are now coming to light.

Presently, there is no vaccine against HCV, and the standard treatment consists of weekly doses of peginterferon alpha and daily doses of ribavirin along with some protease inhibitor. In the beginning, cases of HCV were treated with ribavirin only but with very little success [3]. When peginterferon alpha was added, a sharp drop in virion was observed within a couple of days. However, even this treatment is unsuccessful in over half the patients, and many of these non responders go on to develop cirrhosis and then liver cancer. If the liver is transplanted in such patients, chances of their getting infected again are relatively high.

Like the Human Immunodeficiency virus (HIV), HCV can stay dormant for twenty years and more while attacking the liver all this time. This accounts for HCV cases transmitted through blood transfusions before 1990 now coming to light. HCV mutates easily which makes for a large number of mutant viruses. There are six known genotypes (numbered 1 through 6) and more than 50 subtypes (e.g., 1a, 1b, 2a...) [4]. Because HCV mutates easily, some mutated virus is observed in patients who have never been treated, so that HCV exists in infected patients as HCV quasi-species.

While HIV has received major attention from the medical community in recent years, HCV is just as serious. While it is true that HIV positivity was a death sentence before the discovery of HAART, and is a manageable illness now, HCV is still a death sentence for a large percentage of people that get infected. It has been suggested that, apart from the liver, which is the main target of the virus, HCV may also affect the nervous system [5]. The genotype 1 of HCV is responsible for most of the infections in North America.

We present a mathematical model which describes the development of HCV, and its resistant variants, in a patient. It is known that, in an HCV virus, some virus mutations are hundreds of times more effective against the drug being administered than others. As an example, it has been reported that the variant V36A/M confers ~3.5-fold resistance, whereas A156V/T confers ~466-fold resistance to telaprevir [6]. Ignoring the mild resistance, we assume that, apart from the variants that are already in the patient's blood stream, it requires one more mutation, **at a specific nucleotide**, for an HCV virus to become resistant to the antiviral drug being administered, i.e. for u_0 (virus, together with all its variants, present when the treatment starts) to change into u_1 (virus which is resistant to the drug being administered). We assume that, in the presence of drug pressure, it is easier for u_0 to change to u_1 than the other way around, so that we assume that the probability of u_1 changing to u_0 is much smaller than the one of u_0 changing to u_1. We also assume that u_0 changes to u_1 after **one specific mutation at a given nucleotide.** HCV has approximately 9600 nucleotides, and its copying mechanism is error prone at the rate of 1 in about 10,000. The virus lives for 2-3 hours outside a cell, so that new viruses are being produced inside the infected cells at about the same rate. On average, it replicates about ten times in a day. The probability of its mutating at any **given** site in 9 replication cycles comes out to be 9.37031×10^{-8} and 1.04109×10^{-7} in 10 such cycles. We take this probability to be 10^{-7} which is the value of Q_1 in our model.

We also consider the effect of antibodies in our model. The antibodies are produced in response to the presence of the virus and decay when they encounter a virus. We show that if the rate of production of antibodies is high enough, the virus does not develop a chronic state. This says that, if the (adaptive) antibody response of the host is strong enough, an HCV infection does not take hold. We speculate that this may be the reason why a significant number of HCV infected patients do not develop the chronic state of the disease.

Our model will also say that, depending upon the antibody response of the host, there is a chronic state of the

Manuscript received June 17, 2014; revised July 24, 2014.

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disease in an untreated patient. This state is an equilibrium state of our model in the absence of any treatment. However, there is also an (unstable) equilibrium state in a treated patient when the drugs have taken effect and reduced the virus count but the virus has not developed any resistance yet (so that $u_1 = 0$), and also an equilibrium state when all the virus has become resistant to the drugs being administered (i.e. when $u_0 = 0$ after a very long time). The former state (with $u_1 = 0$) is unstable in a patient under treatment, because the virus is slowly developing resistance, i.e., u_0 is slowly turning into u_1. As for the third state (the equilibrium state with $u_0 = 0$), if this state is stable, we have a rebound, otherwise we have SVR.

II. The Model

A. Set Up

We take one day as the unit of time and write

$$F_1(x_1,u_0,u_1,y_1) = A_1 - A_2x_1 - (1-e_1)x_1(A_3u_0 + A_6u_1) \quad (1)$$

$$F_2(x_1,u_0,u_1,y_1) = A_9A_4(1 - e_1e_2)[(1-Q_1)p_0x_1u_0 + Q_2p_1x_1u_1] - c_1u_0 - c_3y_1u_0] \quad (2)$$

$$F_3(x_1,u_0,u_1,y_1) = A_9A_4(1-e_1e_2)[Q_1p_ox_1u_0 + (1-Q_2)p_1x_1u_1] - c_1u_1 - c_3y_1u_1 \quad (3)$$

$$F_4(x_1,u_0,u_1,y_1) = A_{10}(u_0+u_1) - c_2(u_0+u_1)y_1 \quad (4)$$

with $x_1' = F_1$, $u_0' = F_2$, $u_1' = F_3$ and $y_1' = F_4$;

In these equations, the quantity x_1 stands for the number of susceptible cells in one unit of volume, which cells are attacked by the viruses u_0 and u_1 at the rates A_3 and A_6 respectively. Generally $A_3 > A_6$ because of the higher fitness of the 'wildtype' virus u_0. Since HCV is not (or is only mildly) cytopathic, we have not included a separate equation for the infected cells as is done in most models of HIV where the virus is highly cytopathic. It should be noted that half-life of infected cells is not very different from those of susceptible cells and they may also multiply like the susceptible cells. The life cycle of infected cells is, therefore, very much like that of susceptible cells. The infected cells produce both wild type and resistant virions at the rates p_0 and p_1 respectively. Since, eventually, most of the virions produced will be of the resistant type, we assume that $p_1 > p_0$. The antibodies y_1 are produced in response to the presence of both u_0 and u_1 at the rate A_{10} (u_0+u_1) and are neutralized at the rate $c_2(u_0+u_1)y_1$ as and when they encounter a virus. The parameter $A_4 < A_3$ accounts for a protease inhibitor.

The value of A_1, the rate at which the susceptible cells are being created, has been estimated at anywhere from one to 180,000/mL in the literature while the value of A_1/A_2, the equilibrium value of total number of cells, has been estimated to be anywhere from 4 million to 13 million cells/mL [7]. We take this value to be one million in an (appropriate) one unit of volume, and look at the effect of taking different values of A_1 in the model.

B. Equilibrium Points

We begin to analyze our system by taking an example. We take the equilibrium value of y_1 as (obviously) A_{10}/c_2. We assume that

$A_1 = 10$; $A_2 = A_1/1{,}000{,}000$; $A_3 = 0.00000001$; $A_4 = A_3$; $A_5 = 0.005$; $A_6 = 0.5A_3$; $A_9 = 1000$; $A_{10} = 0.1$; $Q_1 = 0.0000001$; $Q_2 = Q_1{*}Q_1$; $p_0 = 0.9$; $p_1 = 0.99$; $e_1 = 0.1$; $e_2 = 0.9$; $c_1 = 8$; $c_2 = 0.0000001$; $c_3 = 0.0000001$; and solve our system numerically (on Mathematica 8.0). The result is the three points $\{(x_1, u_0, u_1) = (1{,}000{,}000, 0, 0), (989{,}011, 12.3456, 0), (899{,}101, 0, 249.383)\}$

Apart from the disease free solution, there are two other solutions. Notice that $u_0 = 0$ in one solution and $u_1 = 0$ in the other solution. What is happening? To see this, we solve the same system with the same values of parameters as above, but with $e_1 = e_2 = Q_1 = Q_2 = 0$, i.e. without any treatment. The result is the three points $\{(x_1, u_0, u_1) = (1{,}000{,}000, 0, 0), (900{,}000.0, 111.111, 0), (818181.8, 0, 444.444)\}$.

The relevant solution without any treatment is the one with $u_1 = 0$, which has $x_1 = 900{,}000$; and $u_0 = 111.111$. This is the so called chronic equilibrium point. It is intuitively clear that as the treatment starts, the number of virions should come down, and the body may reach another (unstable) equilibrium point where the treatment has reduced the virus count but no resistance has developed yet. Later on resistance may develop, which will result in a rebound. This is exactly what happens in our model. As the treatment starts, the number of healthy cells goes up and the system (i.e. the body) reaches another equilibrium point when the number of healthy cells has gone up (as expected, from 900,000 to 989,011), and the number of virions has come down (as expected, from 111.111 to 12.3456), but no resistance has developed yet. As the treatment continues, the resistance slowly develops, and we reach the next equilibrium point, where the number of healthy cells has gone down (as expected, from 989011 to 899101), all the virions have changed to the resistant type (as expected), and the number of resistant virions has gone up (as expected, to 249.383).

Alternatively, we may calculate the two equilibrium points (one with $u_0 = 0$ and the other with u_1=0) by **assuming** that $u_0 = 0$ for one point and that $u_1 = 0$ for the other point. For $u_1 = 0$, the result is

$$\{(x_1,u_0) = \left(\frac{A_1}{A_2},0\right), \left(\frac{c_1c_2 + A_{10}c_3}{A_4A_9c_2(e_1e_2-1)p_2(Q_1-1)}, \frac{A_2(c_1c_2+A_{10}c_3) - A_1A_4A_9c_2(e_1e_2-1)p_0(Q_1-1)}{A_3(c_1c_2+A_{10}c_3)(e_1-1)}\right)\} \quad (5)$$

and for $u_0 = 0$, the result is

$$\{(x_1,u_1) = \left(\frac{A_1}{A_2},0\right), \left(\frac{c_1c_2 + A_{10}c_3}{A_4A_9c_2(e_1e_2-1)p_1(Q_2-1)}, \frac{A_2(c_1c_2+A_{10}c_3) - A_1A_4A_9c_2(e_1e_2-1)p_1(Q_2-1)}{A_6(c_1c_2+A_{10}c_3)(e_1-1)}\right)\} \quad (6)$$

ISBN: 978-988-19253-7-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

The former equilibrium point (other than the disease free solution) with $u_1 = 0$ is seen to be unstable, if p_1 is sufficiently large compared to p_0.

For $e_1 = e_2 = Q_1 = Q_2 = 0$, (i.e. without any treatment), the value of u_0 (with u_1=0) turns out to be

$$u_0 = \frac{-A_2(c_1c_2 + A_{10}c_3) + A_1A_4A_9c_2p_0}{A_3(c_1c_2 + A_{10}c_3)}.$$

We write

$$R_0 = \frac{A_1A_4A_9c_2p_0}{A_2(c_1c_2 + A_{10}c_3)}.$$

If $R_0 < 1$, the corresponding value of u_0 is less than zero, and consequently, the chronic state will not develop. It follows that if

$$A_{10} > \frac{A_1A_4A_9c_2p_0 - A_2c_1c_2}{A_2c_3}, \qquad (7)$$

the chronic state will not develop and the infection does not take hold. We speculate that this is the reason why a large number of people do not proceed to a chronic state and self cure after being infected with HCV. Their adaptive immunity is just too strong. For the values of the parameters assumed above, we get the critical value of A_{10} as 1.0.

Noting that, with the values of the parameters as assumed above, (x_1, u_1) = (818,182, 444.444) which is what (7) gives and (x_1, u_0) = (900,000, 111.111) which is what (6) gives, we notice that these values coincide with those calculated directly (i.e. without the additional assumption that $u_0 = 0$ in one solution and $u_1 = 0$ in the other).

C. Positivity of the Solution

It is obvious that if a solution starts in $\{x_1, u_0, u_1, y_1\} > \{0, 0, 0, 0\}$, then it stays in that region. This is because at $x_1 = 0$, $x_1' > 0$. A similar argument applies to the other variables.

D. Boundedness of the Solution

The quantity x_1 is clearly positive and bounded by A_1/A_2. Also y_1 is positive and bounded by A_{10}/c_2. We have also assumed that $p_0 < p_1 < 1$. It follows that

$$\begin{aligned}(u_0 + u_1)' &= -c_1(u_0 + u_1) \\ &\quad + A_4A_9(1 - e_1e_2)(p_0u_0 \\ &\quad + p_1u_1)x_1 - c_3(u_0 + u_1)y_1 \qquad (8)\\ &< (u_0 + u_1)[A_4A_9(1 - e_1e_2)p_1x_1 \\ &\quad - c_1 - c_3y_1]\end{aligned}$$

For given values of u_0 and u_1, the equilibrium value of x_1 is

$$\frac{A_1}{A_2 + (1 - e_1)(A_3u_0 + A_6u_1)},$$

which value is clearly a maximum. Also, this value is less than (or equal to)

$$\frac{A_1}{A_2 + (1 - e_1)(u_0 + u_1)A_6},$$

so that we get

$$\begin{aligned}&(u_0 + u_1)' \\ &< \frac{(u_0 + u_1)A_1A_4A_9(1 - e_1e_2)p_1}{[A_2 + (1 - e_1)A_6(u_0 + u_1)] - c_1 - c_3y_1}. \qquad (9)\end{aligned}$$

It follows that, for large enough values of u_0+u_1, $(u_0$+$u_1)'$ is negative for arbitrarily small values of c_1 and c_3.

This proves the boundedness of the solutions of our system.

E. Treatment Outcomes

Since the equilibrium point with $u_1 = 0$ is unstable, there are only two possible outcomes of treatment. They are either the rebound, i.e. the solution with $u_0 = 0$ obtained above, or SVR, the disease free solution.

We write

$$R_3 = \frac{A_1A_4A_9c_2p_1(1 - e_1e_2)(1 - Q_2)}{A_2(c_1c_2 + A_{10}c_3)}.$$

If R_3 >1, we have REBOUND, otherwise we have SVR.

This says that if

$$A_{10} > \frac{c_2[-A_2c_1 + A_1A_4A_9p_1(1 - e_1e_2)(1 - Q_2)}{A_2c_3},$$

we will have an SVR. Notice that the right hand side may be made as small as we like depending upon the parameters that define the treatment, so that for a sufficiently strong treatment, we should have SVR. But of course, we must be mindful of the side effects of a strong treatment. We also recall that if statement (8) holds, then the chronic state will not develop. All these results are in line with what actually happens in a real situation.

F. Examples

We shall now give some examples to illustrate our model. We take $A_1 = 10$; $A_2 = A_1/1000000$; $A_3 = 0.00000001$; $A_4 = A_3$; $A_5 = 0.005$; $A_6 = 0.5A_3$; $A_9 = 1000$; $Q_1 = 0.0000001$; $Q_2 = Q_1*Q_1$; $p_0 = 0.9$; $p_1 = 0.99$; $c_1 = 8$; $e_1 = 0.1$; $e_2 = 0.9$; $c_2 = 0.0000001$; $c_3 = 0.0000001$; and solve our model on Mathematica 8.0 for several values of A_{10}. The results are given in Figs. 1 and 2 where the values of $\text{Log}_{10}[u_0(t)+u_1(t)]$ are indicated along the vertical axis against time (in days**).**

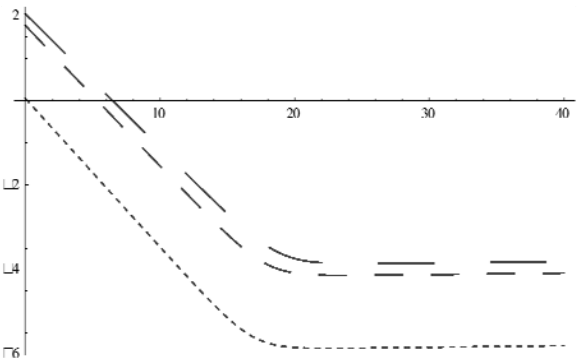

Fig. 1. The behavior of our model, showing drop in virus count with treatment, for several values of A_{10} for the first forty days (a) A_{10} = 0.1 (long dashes), (b) A_{10} = 0.5 median dashes (c) A_{10} = 0.99 (short dashes). Notice that higher values of A_{10}, the antibody production rate, result in lower values of u_0, the initial virus count at the chronic equilibrium point.

ISBN: 978-988-19253-7-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

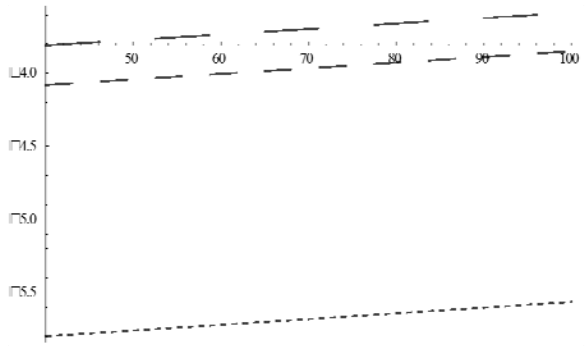

Fig. 2. The same case as in Fig. 1, showing the rebound of virus in each case during the next few weeks (from 40 to 100 days).

Decay of Virus:

It should be noted that in our examples, the virus decays in a bi-phasic manner over the first forty days. In actual studies, this decay of virus is noted to take place in tri-phasic ways, with virus coming down significantly during the first few days. A lot of attention has been paid in the literature to explain this tri-phasic delay. According to one opinion, "In such studies, the first phase is assumed to be an initial sharp decay related to the antiviral 'efficacy' of IFN in clearing of free virus by blocking viral production and secretion which occurred after a delay of about 8–9h from the beginning of therapy. The second decay phase showed a more gradual slope in HCV RNA levels, thus representing the rate of killing, clearance of virally infected cells while the third phase of viral decay may be attributed to the effect of RBV that may be related to restoration of a previously suppressed cellular immune response." [8]. According to another author, "the slope of the "shoulder phase" in patients with tri phasic viral decay represents the pre-treatment death rate of infected cells and the third-phase slope represents the treatment-enhanced death rate of infected cells due to the immune modulatory effect of RBV."[9]. The 'shoulder phase' refers to the second phase of tri-phasic decay. If the half life of infected cells is reasonably long, these explanations appear suspicious.

We argue that this tri-phasic decay may happen because of decay in the effectiveness of the drug during the first few days. We change the values of e_1 in our model with time, and show the results as $\text{Log}_{10}[u_0(t)+u_1(t)]$. Fig. 3 illustrates a situation where the effect of the drug is very high in the beginning and is maintained at a low level later on.

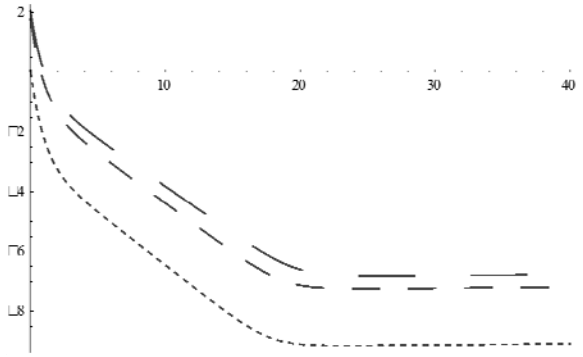

Fig. 3. Decay of virus when e_1 changes as $e_1(t) = 0.1 + 0.85e^{-t}$. All other parameters are the same as in Fig. 1. Tri-phasic decay of virus is clearly visible in all cases of A_{10} = 0.1(long dashes), 0.5 (median dashes), and 0.99(short dashes).

G. Number of Virions

It is to be noted that the number of virions in the chronic state in our model is of the order of a few hundreds. In actual cases, this number is in millions. We introduce an appropriate scaling factor A_{11} in our model and rewrite it as

$$F_1(x_1,u_0,u_1,y_1) = A_1 - A_2x_1 - A_{11}(1-e_1)x_1(A_3u_0 + A_6u_1) \quad (10)$$

$$F_2(x_1,u_0,u_1,y_1) = A_9A_4(1 - e_1e_2)[(1-Q_1)p_0x_1u_0 + Q_2p_1x_1u_1] - c_1u_0 - A_{11}c_3y_1u_0] \quad (11)$$

$$F_3(x_1,u_0,u_1,y_1) = A_9A_4(1-e_1e_2)[Q_1p_ox_1u_0 + (1-Q_2)p_1x_1u_1] - c_1u_1 - A_{11}c_3y_1u_1 \quad (12)$$

$$F_4(x_1,u_0,u_1,y_1) = A_{10}(u_0+u_1) - A_{11}c_2(u_0+u_1)y_1 \quad (13)$$

with $x_1' = F_1$, $u_0' = F_2$, $u_1' = F_3$ and $y_1' = F_4$;

The solution of this model for A_1 = 1000; A_2 = A_1/1,000,000; A_3 = 0.00000001; A_4 = 0.999A_3; A_5 = 0.005; A_6=0.5A_3; A_9 = 1000; Q_1 = 0.0000001; Q_2 = Q_1*Q_1; p_0=0.9; p_1 = 0.99; c_1 = 8; c_2 = 0.0000001; c_3 = 0.0000001; A_{10} = 0.1; $e_1(t) = 0.1 + 0.85e^{-t}$; e_2 = 0.9; A_{11} = 0.00001 is shown in the next figure, once again as $\text{Log}_{10}[u_0(t) + u_1(t)]$. The curve closely follows the actual readings of a patient reported by Reluga et al [7] over a span of 14 days.

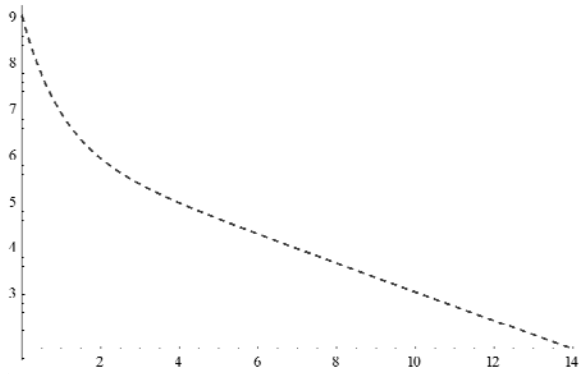

Fig. 4: Decay of virions in a particular case for the first 14 days. The curve closely follows the actual readings of a patient reported in the literature.

ACKNOWLEDGMENT

I wish to acknowledge the help of Dr. Rita Aggarwala in preparing this paper.

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ISBN: 978-988-19253-7-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)