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Optimal control of anti-HBV treatment based on combination of Traditional Chinese Medicine and Western Medicine

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ABSTRACT

In this paper, a Hepatitis B virus model with standard incidence rate and logistic proliferation of healthy and infected cells is presented. Based on this model, we study an optimal control problem about anti-HBV infection combination therapy of Traditional Chinese Medicine and Western Medicine, the optimal strategies of taking medicine are given by simulation. Two optimal strategies with or without the impact to the infection rate by treatment are compared, simulation shows the impact to the reduction of infection may be omitted when mathematical model is used to study the anti-HBV therapy which is consistent with some references. What is more, optimal control strategy with other constant control strategies are also compared, and the simulation shows the optimal control strategy is better than constant control strategies.

1. Introduction

Hepatitis B is one of the serious infectious diseases which threaten to global human health, and has become an important social and public health problems.

Most patients with chronic hepatitis B virus (HBV) infection require long-term therapy [1,2]. The effective treatment of chronic HBV patients aims to prevent progression of chronic hepatitis B (CHB) to cirrhosis, hepatocellular carcinoma and eventually death.

The most used Western Medicine (WM) to treat the HBV include interferon, nucleotide analogs (NA) and adenosine analogs (AA). The interferon, such as interferon alpha-2b, interferon alpha-2a, peginterferon alfa-2a is to kill the virus and activate the immune, the NA, for example, lamivudine, entecavir, telbivudine is to inhibit the activity of viral DNA polymerase and reverse transcriptase, and has the inhibited function to the virus DNA synthesis, when it comes to AA, such as adefovir dipivoxil and tenofovir disoproxil fumarate, its main function is to inhibit the replication of viral DNA [3].

Papers [4–7] showed that the combination therapy has a greater advantage over mono-therapy, both in terms of biochemical and virological response, paper [5] reported that combination therapy of lamivudine and adefovir can produce longer-lasting effects than mono-therapy in treating chronic hepatitis B virus infection patients.

Now, Traditional Chinese Medicines (TCM) therapy is also used in treating HBV [8–10], the most commonly used herbal ingredients, *Abrus cantoniensis*, *Ganoderma lucidum* and *Atractylodes macrocephala*, are not specifically anti-viral agents. These are herbs that have been used as to improve the immune function and maintain normal physiological activities of the internal organs [9]. Paper [11] studied the HBV combination treatment by TCM and acyclovir, and a better treatment effect was obtained. Paper [12] analyzed 30 years' data of hepatitis B liver cirrhosis by the combination therapy of TCM and WM, and the conclusion showed that the combination therapy is beneficial to reduce liver injury and improve liver function.

The use of mathematical models to interpret experimental and clinical results has made a significant contribution to the fields of (anti-)human immunodeficiency virus (HIV), HBV and hepatitis C virus (HCV) infections [13–16], paper [17] discussed an adefovir anti-HBV infection therapy immune model with ALT

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta x v}{x+y}, \\ \dot{y} = \dfrac{\beta x v}{x+y} - dy - \dfrac{pyz}{x+y}, \\ \dot{v} = (1-u)ky - \varepsilon v, \\ \dot{z} = (g + k_2 yz)(1 - z/z_{\max}) - \delta z, \\ \dot{w} = s + a_1 x + b_1 y + k_1 yz - d_1 w, \\ x(0) > 0, \quad y(0) \geq 0, \quad v(0) \geq 0, \quad z(0) \geq 0, \quad u(0) \geq 0. \end{cases} \tag{1}$$

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where x, y and v represent the numbers of uninfected (susceptible) cells, infected cells and free viruses, respectively. z represents the number of CTL, w represents the levels of alanine aminotransferase (ALT). u represents the efficacy of treatment.

Paper [18] pointed that the liver is an organ which can regenerate cells and any loss of infected hepatocytes would be compensated by the proliferation of hepatocytes, due to homeostatic mechanisms, and paper [18] gave the extended virus model:

$$\begin{cases} \dfrac{dx}{dt} = s + rx\left(1 - \dfrac{x+y}{X_{\max}}\right) - dx - \beta xv, \\ \dfrac{dy}{dt} = \beta xv + ry\left(1 - \dfrac{x+y}{X_{\max}}\right) - \delta y, \\ \dfrac{dv}{dt} = ky - \varepsilon v. \end{cases} \tag{2}$$

where x, y, v have the same meaning as those in model (1), the logistic function $rx(1-(x+y)/X_{\max})$ and $ry(1-(x+y)/X_{\max})$ represent the proliferation of healthy and infected cells respectively, where $X_{\max}$ is the maximum hepatocyte count in the liver.

On the other hand, optimal control theory has been applied extensively in case of virological models, especially in case of HIV models [19–26]. Joshi [25] built an optimal control model about HIV based on an ordinary differential equation. The optimal drug strategies are determined for various stages of treatment. Later, the HIV models become more and more complicated because more factors were considered, such as activated and resting CD4 + cells were contained [27]. Paper [28] presented a delay-differential equation model with optimal control that described the interactions between human immunodeficiency virus which is more closer to actual situation. Pachpute and Chakrabarty [29] considered an optimal therapy model for HCV with interferon and ribavirin.

$$\begin{cases} \dfrac{dT}{dt} = s + rT\left(1 - \dfrac{T+I}{T_{\max}}\right) - dT - \beta TV_I \\ \dfrac{dI}{dt} = \beta TV_I + rI\left(1 - \dfrac{T+I}{T_{\max}}\right) - \delta I \\ \dfrac{dV_I}{dt} = (1-\rho)(1-\varepsilon_p)pI - cV_I \\ \dfrac{dV_{NI}}{dt} = \rho(1-\varepsilon_p)pI - cV_{NI}. \end{cases} \tag{3}$$

where ε_p is the efficacy of interferon and ρ is the efficacy of ribavirin. T, I, V_I, V_{NI} represent the uninfected hepatocytes, infected hepatocytes, infectious virion and non-infectious virion, respectively. An objective functional is formulated to minimize the viral load, as well as the drug side-effects and the optimal system is solved numerically to determine optimal efficacies of the drugs. Obviously, the above model used the bilinear incidence rate βTV_I, but paper [30] has pointed that the standard incidence rate $\beta xv/x+y$ would be more reasonable than bilinear incidence rate when used for dynamics model about hepatitis virus infection. Based on the standard incidence rate $\beta xv/x+y$, Paper [31] and Paper [32] both discussed a HBV infection model and gave the stable analysis, but Paper [32] considered the return of the infected cells to uninfected cells by loss of all covalently closed circular DNA, and also based on the standard incidence rate, paper [33] investigated a five dimension model with CTL cells response and the antibody response, and gave the existence condition of five steady states and full analysis of such steady states' local stability.

On the other hand, seldom papers have been concerned with the HBV optimal control model, Hattaf and Rachik [34] proposed a three dimension optimal controls model, and the optimal control represented the efficiency of drug therapy in inhibiting viral production and preventing new infections. Besides, Mouofo [35] proposed an optimal control of a delayed system, but the incidence rate was also bilinear.

From what has been discussed above, in this paper, based on [17,29], we propose an anti-HBV treatment optimal model with two different WM (NA and AA) and TCM as follows:

$$\begin{cases} \dot{x} = \lambda - dx + rx\left(1 - \dfrac{x+y}{X_{\max}}\right) - (1-u_4)\dfrac{\beta xv}{x+y}, \\ \dot{y} = (1-u_4)\dfrac{\beta xv}{x+y} + ry\left(1 - \dfrac{x+y}{X_{\max}}\right) - \dfrac{pyz}{x+y}, \\ \dot{v} = (1-u_1)(1-u_2)ky - (1+\theta u_3)\varepsilon v, \\ \dot{z} = (1+u_3)(g + k_2yz)\left(1 - \dfrac{z}{z_{\max}}\right) - \delta z, \\ \dot{w} = s + a_1x + b_1y + k_1yz - d_1w. \end{cases} \tag{4}$$

where x, y, v, z, w have the same meaning as those in model (1), u_1 and u_2 stand for the influences of NA and AA respectively. $(1+u_3)$ represents the improvement of the cellular immune function by the TCM. Noting that humoral immunity and cellular immunity both have their own unique role, and can cooperate with each other. When viruses enter the body, it induces the humoral immune firstly, because T cells cannot identify the invading virus antigen, only when the viruses invade host cell, the small molecule protein antigens from virus would appear on the cell surface, and only after the combination with cell surface receptor into complex, T cells can recognize antigens and T-cell immune can be activated. Since humoral immunity and cellular immunity have the indivisible relation, when the cellular immunity is improved, the humoral immunity function should be reflected in our model, so we use $(1+\theta u_3)$ to embody the influence without using a single variable to stand for the humoral immunity.

Noting that, paper [36] pointed that nucleoside analogs may also interfere with de novo infection of hepatocytes by hindering the transformation of relaxed circular DNA into cccDNA. If this is the case, then treatment can reduce the rate of infection. And paper [36] used $(1-u_4)$ to reflect the reduction of infection rate. So when we omit the reduction of infection rate by treatment, we choose $u_4 = 0$. We will consider two cases: $u_4 = 0$ and $u_4 \neq 0$ to test how the reduction of infection rate by treatment can infect the treatment effect.

The organization of the paper is as follows. In Section 2, the control problem with $u_4 = 0$ is formulated. The necessary conditions for an optimal control and the corresponding states are derived using Pontryagin's Maximum Principle. In Section 3, the resulting optimality system about combination of Traditional Chinese Medicine and Western Medicine is numerically solved with $u_4 = 0$. The corresponding analysis and simulation with the case $u_4 \neq 0$ are given in Sections 4 and 5. Section 6 compares the results with other constant design strategies. Section 7 draws the conclusion.

2. Optimal control problem for combination of Traditional Chinese and Western Medicines with $u_4 = 0$

In this section, without considering the reduction of infection rate by treatment, that is $u_4 = 0$, we present an optimal control problem motivated by biomedical considerations. The control goal is not only to formulate an objective functional which lowers the levels of HBV and the infected hepatocytes during and at the end of therapy, but also to minimize the therapeutic side-effects and the cost of drugs, so the objective function is defined as:

$$J(u) = \frac{1}{2}(S_{22}y^2 + S_{33}v^2) + \frac{1}{2}\int_{t_0}^{t_f}(Q_{22}y^2 + Q_{33}v^2 + R_{11}u_1^2 + R_{22}u_2^2 + R_{33}u_3^2)dt, \tag{5}$$