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Combination anti-coronavirus therapies based on nonlinear mathematical models

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Abstract

Using nonlinear mathematical models and experimental data from laboratory and clinical studies, we have designed new combination therapies against COVID-19

1 Introduction

Emerging viral diseases have caused significant global devastating pandemics, epidemics, and outbreaks (Smallpox, HIV, Polio, 1918 influenza, SARS-CoV, MERS-CoV, Ebola, SARS-CoV-2).

Currently there are no approved treatments for any human coronavirus infection. Moreover, scientists do not know any treatment that would consistently cure COVID-19 patients.

The world is facing a general catastrophe as people see the reality of alarming rises in infections, a building economic crisis, a shortage of ventilators, the lack of coronavirus testing, and many other disasters.

The governments are desperate to find a solution. In some cases, they are even promoting unproven “remedies”. The novel coronavirus presents an unprecedented challenge for everybody, including the scientists: the speed at which the virus spreads means they must accelerate their research.

There is a wealth of literature dedicated to mathematical modeling of virus-immune-system interaction. See, for example [1].

This paper is an argument for combination therapies against COVID-19.

We need a treatment that is 95 % effective in order to safely open the countries and save the world from an economic catastrophe.

There are many treatments in development. However, most of them have drawbacks [2]. We have shown before that combination therapies can be better than monotherapies.

For instance, for some cancer tumors, the immunotherapies alone do not work at all.

We have proposed to use a combination of therapies that could eradicate the cancer completely [3, 4, 5].

In the present paper we will design new therapies based on antiviral agents in combination with other therapeutic approaches. These new therapies should improve patient outcomes.

2 Growth models

There are several famous equations that have been used to describe cell population growth: exponential, Gompertz, logistic, and power-law equations [6].

In reference [7], a biophysical justification for the Gompertz's equation was presented.

The deduction is based on the concept of entropy. The entropy definition used in Ref [7] is the well-known Boltzmann-Gibbs extensive entropy. Gonzalez et al have used the new non-extensive entropy [8, 9, 10] in the derivation of a new very general growth model [6].

The exponential, logistic, Gompertz, and power laws are particular cases of the new equation. The new model has the potential to describe all the known and future experimental data [6]. The non-extensive parameter q [8, 9, 10, 11] plays an important role in the new model. Suppose we are studying virus population dynamics.

Different types of viral diseases can possess different values of the non-extensive parameter q . The new generalized equation for population growth is the following

$$\frac{dX}{dt} = \frac{kX_\infty}{q-1} \left[1 - \left(\frac{X}{X_\infty} \right)^q - \left(1 - \frac{X}{X_\infty} \right)^q \right], \quad (1)$$

where $X(t)$ is the growing population, k is certain free parameter, and X_∞ is the asymptotic value of $X(t)$ when $t \rightarrow \infty$. We have already remarked that this is a very general model that contains most known growth models [6].

Now, we will show that the model is universal in the sense discussed in Ref. [12]. For early stages of the infection, (1) can be written in the following form

$$\frac{dX}{dt} = \alpha_q \left(\frac{X}{X_\infty(q)} \right)^q \left[1 - \left(\frac{X}{X_\infty(q)} \right)^{1-q} \right], \quad (1a)$$

where $\alpha_q = \frac{kqX_\infty(q)}{1-q}$, $X_\infty(q) = q^{\frac{1}{q-1}} X_\infty$.

An analytical solution to equation (1a) can be expressed as

$$\left(\frac{X}{X_\infty(q)} \right)^{1-q} = 1 - \left[1 - \left(\frac{X_0}{X_\infty(q)} \right)^{1-q} \right] e^{-qkt} \quad (1b)$$

where X_0 is the initial condition so that $X(t=0) = X_0$.

In order to get a system in dimensionless variables, we define $r = \left(\frac{X}{X_\infty(q)} \right)^{1-q}$ and $\tau = kt - \ln(1-r_0)^{1/q}$. Thus, we obtain

$$r(\tau) = 1 - e^{-q\tau}. \quad (1c)$$

This calculation shows that our model represents a universal growth law [12, 13]. So even this general class of growth laws are a particular case of equation (1).

3 The model

In the present paper, we will investigate the following dynamical system

$$\frac{dX}{dt} = \frac{kX_\infty}{q-1} \left[1 - \left(\frac{X}{X_\infty} \right)^q - \left(1 - \frac{X}{X_\infty} \right)^q \right] - bXY - c_1(t)X, \quad (2)$$

$$\frac{dY}{dt} = d(X - eX^2)Y - fY + V - c_2(t)Y, \quad (3)$$

where X denotes the virus population and Y denotes the population of lymphocytes. Equation (2) describes the reproduction of the virus. The virus is killed when it meets agents of the immune system (term $-bXY$).

The reproduction of the agents of the immune system is described by the term $d(X - eX^2)Y$, where initially the presence of the virus stimulates the reproduction of $Y(t)$. When virus load is very large, the person is so sick that the reproduction of $Y(t)$ is inhibited. The term $-fY$ corresponds the natural death of lymphocytes. The term V represents an external flow of lymphocytes.

The term $-c(t)X$ stands for virus-killing process due to different therapies. The term $-c_2(t)Y$ shows that therapies can also affect other normal cells (including the immune system).

The system (3) and (4) is inspired by models of the immune system developed in references [14] and [15]. However, instead of the exponential growth assumed in [14, 15], we are using our growth model given by Eq. (1).

4 Investigation of the model

First, we will consider the case where $q > 1$, $X_\infty e \gg 1$, $c(t) = 0$.

Let us define $a = \frac{2qk}{q-1}$. The dynamical system (2)-(3) can have, in principle, four fixed points

$$P_I = (X_1, Y_1) = \left(0, \frac{V}{f} \right) \quad (4)$$

$$P_{II} = (X_2, Y_2), \quad (5)$$

where $\frac{1}{2e} < X_2 < X_\infty$, $Y_2 = \frac{a}{b}$,

$$P_{III} = (X_3, Y_3), \quad (6)$$

where $0 < X_3 < \frac{1}{2e}$, $Y_3 = \frac{a}{b}$,

$$P_{IV} = (X_4, Y_4), \quad (7)$$

where $X_4 = X_\infty$,

The conditions for the existence of points P_{II} and P_{III} are the following inequalities

$$\frac{1}{4e^2} - h > 0, \quad (8)$$

$$h > 0, \quad (9)$$

where $h = \left(\frac{f a}{b} - V \right) \frac{b}{ead}$

The eigenvalues of the Jacobian matrix corresponding to the fixed point P_I are

$$\lambda_1^{(I)} = a - \frac{bV}{f}, \quad (10)$$

$$\lambda_2^{(I)} = -f. \quad (11)$$

If $af < Vb$, the fixed point P_I is a stable node and the fixed point P_{II} is a saddle. If $af > Vb$, and $h - \frac{1}{4e^2} < 0$, then the four fixed points exist and are non-negative. Both fixed points P_I and P_{II} are now saddles. Between these two points,

there is the point P_{III} , which is stable.

If $af > Vb$, and $h - \frac{1}{4e^2} > 0$, then there are only two fixed points: point P_I which is now unstable and point P_{IV} , which is stable. As a result, most trajectories tend to point P_{IV} . This is not a very favorable situation for the patient.

In the neighborhood of point P_{II} , the separatrix of the saddle can be approximated by the straight line

$$Y = - \left(\frac{\lambda_1^{(II)}}{bX_2} \right) x + \frac{a + \lambda_2^{II}}{b} \quad (12)$$

Any point corresponding to initial conditions of the Cauchy problem on the right of the separatrix leads to a dynamics where the trajectory approaches the point of maximum virus load (point P_{IV}).

On the other hand, if the initial conditions correspond to a point located on the left of the separatrix, the system will evolve to a stable fixed point.

Using (12), we can calculate the threshold or critical virus population that would lead to a dynamics approaching point P_{IV} :

$$X_{crit} = \left(1 + \frac{a}{\lambda_2^{(II)}} \right) X_2. \quad (13)$$

When X_∞ is small, the outcome can be very favorable.

For instance, when

$$X_\infty < \frac{11}{6e} + \frac{2f}{3d}, \quad (14)$$

all the phase trajectories tend to the fixed point $P_I(X = 0)$.

We can also apply the isocline method in order to further investigate the system. A careful analysis of the behavior of the phase trajectories allows us to conclude that the condition

$$d > 4ef, \quad (15)$$

is favorable for the patient. This is a sufficient condition to avoid an uncontrollable rise of the virus population leading to the point P_{IV} .

In many cases, it is convenient to re-write the system (2) -(3) as one equation where the only unknown is $X(t)$,

$$\frac{d^2x}{dt^2} + [f - d(x - ex^2)] \frac{dx}{dt} - \frac{1}{x} \left(\frac{dx}{dt} \right)^2 = - \frac{dU(x)}{dx} \quad (16)$$

In general, it is useful to discuss the dynamics of virus population as a general equation of the following type

$$\frac{d^2x}{dt^2} + F_{dis} \left(x, \frac{dx}{dt} \right) = - \frac{dU}{dx} \quad (17)$$

See Refs [16] for a simple explanation. Equation (17) is equivalent to a Newton's equation for a "fictitious" particle moving in the potential $U(x)$ under the action of nonlinear damping. The potential $U(x)$ can have minima and maxima. So we can conceive the situation where the "fictitious" particle is trapped inside a potential well. The particle needs to jump over a barrier for the virus population to continue increasing. Studying the relative heights of the barriers, we get the condition

$$9e(Vb - af) + 2ad > 0, \quad (18)$$

when this condition is satisfied, the "right" barrier of the potential well is higher than the "left" barrier. This case is more favorable for the patient.

A careful analysis shows that the condition

$$2d > 9ef, \quad (19)$$

is very favorable for the patient.

The general meaning of conditions (15), (18) and (19) is that the comparison between the values of d and the product ef can decide the outcome.

Let us analyze now the case $q \leq 1$. When

$$q \leq 1, \tag{20a}$$

the point P_I will be always unstable. This means that it is almost impossible to reduce the virus population to zero. This finding will play a very important part in the design of new therapies.

5 Monotherapies

When $q > 1$, the parameters of the system and the initial conditions play an important role in the outcome. The virus-host interaction is decisive. There are situations where the immune system by itself can reduce the virus population to zero. Under other circumstances, the virus population will increase to numbers that can threaten the patients survival. If we apply conventional antiviral therapies with $c(t) = c_0$ in the system (2) and (3) (where c_0 is a constant), for $q > 1$, the cure can be accelerated [6].

If $q \leq 1$, then for any value of c_0 , the virus population is never reduced to zero. The fixed point P_I is always unstable.

6 Combination therapies

Our analysis shows that for $q \leq 1$, the virus can develop resistance both against the attack of the immune system and all conventional monotherapies with constant doses of the medication. All this investigation leads to combination therapies. First, we have to use therapies that change the parameters in such a way that fixed point P_I becomes asymptotically stable (a stable node). Then we need to apply therapies that will help the phase trajectory to go to the point P_I . The condition $q > 1$ should be completed with the stability of fixed point P_I :

$$bV > \frac{2qkf}{q-1}, \tag{20b}$$

and complemented with condition (15).

This means that immuno-therapy is also very important for the development of antiviral therapies.

This work can guide physicians to rationally design new drugs or a combination of already existing drugs for the development of antiviral therapies.

Condition (20b) shows that the killing ability of the immune system and the external flow of lymphocytes should be stronger than the virus replication and the natural death of immune system agents.

Additionally, condition (15) says that the reproduction of the lymphocytes should be stronger than the inhibition of the immune system due to the general health weaknesses created by the disease.

The perfect strategy is to use a therapy that can change q so that the fixed P_I can be, in principle, stable. Of course, this does not guarantee that the point P_I is stable.

The condition $q > 1$ is a necessary condition for the stability of point P_I . However, it is not a sufficient condition.

Later we need another therapy that will change the other parameters (see section 3) so that the fixed point P_I is actually asymptotically stable. This step is probably satisfied with an immuno-therapy.

Finally, we need a treatment $c(t)$ that definitely kills the virus, leading the phase trajectory to the fixed point. The ideal candidate for the first task could be a gene-targeted therapy. On the other hand, we believe there are antivirals that can be utilized in order to accomplish this goal.

7 Real experiments and clinical studies

We will mention some anecdotal evidence together with published strong scientific evidence.

- (A) A Chinese woman infected with the novel coronavirus showed a dramatic improvement after she was treated with a combination of antivirals used to treat flu and HIV [17].
Thailand's doctor Kriengsak Attipornwanich used the combination.
Kriengsak said: "The lab result of positive on the coronavirus turned negative in 48 hours".
The combination was: anti-flu drug oseltamivir with lopinavir and ritonavir (antivirals used to treat HIV).
Singapore's health authorities have also been using lopinavir-ritonavir and have reported successes.
- (B) A Singapore start-up thinks cat leukemia drug could be COVID-19 cure. The drug, known as Retromad 1, has proven effective in treating feline infections with peritonitis virus, which is deadly to cats. It was designed to inhibit an enzyme Ebola, dengue, HIV and coronavirus use to infect their host. The drug has successfully treated coronavirus and leukemia in cats.
- (C) Bangkok and Hangzhou hospitals have put another combination of remedies to the test: Arbidol, an antiviral drug used for treating influenza in China and Russia, is combined with the anti-HIV drug Darunavir for treating coronavirus.
- (D) See some comments about the use of anti-HIV combinations against COVID-19 in Ref.[17].

There is some scientific evidence that the combination lopinavir/ritonavir + ribavirin could work. A paper published by Chu et al. [18] reported that this combination showed "substantial clinical benefit" when given to patients who had SARS, which is caused by a coronavirus very similar to SARS-CoV-2.

Ribavirin is an antiviral medication used to treat severe lung infections caused by respiratory syncytial virus (RSV), hepatitis C and some hemorrhagic fevers. For hepatitis C, it is used in combination with other medications such as simeprevir, sofosbuvir, peginterferon alfa-2b or peginterferon alfa 2-a.

Saudi Arabia has a carefully designed study underway in which patients with MERS receive the lopinavir/ritonavir combination plus interferon beta-1b, which boosts the immune response.

Sheahan et al [19] have published scientific evidence of the potential efficacy of remdesivir and combination of lopinavir, ritonavir, and interferon beta against MERS-CoV. Some doctors have reported anecdotal evidence that remdesivir has a good potential as an anti-COVID-19 medication [20].

Chloroquine can work. It can cripple the virus, but the doses needed are usually high and could cause severe toxicity. Chinese researchers have reported anecdotal evidence supporting the health benefits of chloroquine [2].

Didier Raoult has done a research work about the combination hydroxychloroquine + antibiotic azithromycin [20]. The results are encouraging.

Richardson [21] informs about an international poll of more than 6000 doctors in 30 countries, which found that the antimalarial drug hydroxychloroquine was the most highly rated treatment for COVID-19.

The so-called coalescent plasma therapy is now undergoing clinical trials in New York and elsewhere [23].

An experimental stem cell therapy derived from human placentas is being tested in patients with coronavirus. The treatment, being developed by the company Celularity (known as Cynk-001) involves using stem cells from the placenta, which are called "natural killer" cells [24].

Chloroquine and remdesivir were "highly effective in the control of SARS-CoV-2 infection in vitro" [25]. It has been suggested that chloroquine can change the acidity at the surface of the cell, thereby preventing the virus from infecting it. It is possible chloroquine helps activate the immune response [26].

People seriously ill with COVID-19 experienced striking improvement, according to several separate research teams [27, 28, 29, 30]. The teams extracted antibody-laden plasma from who had recovered from COVID-19.

Xiaoming Yang at the National Engineering Technology Research Center for Combined Vaccines in Wuhan and his colleagues gave the plasma to ten severely ill people. By the sixth day after treatment, the virus that causes COVID-19

was undetectable in seven of ten. The patients experienced no significant side effects [31]. A group led by Lei Liv at Shenzhen Third People’s Hospital in China gave survivor’s plasma to five critically ill people [32].

Symptoms dwindled in all five; within ten days of receiving the plasma, three recipients no longer needed ventilators.

Blood from COVID-19 survivors can save lives. New York city researchers hope antibody-rich plasma can keep people out of intensive care [29].

Therapeutic plasma can cure patients with fulminant COVID-19 [30].

A drug, called EIDD-2801, was shown to hinder the coronavirus behind COVID-19 as it attempted to replicate itself in human lung cells in test tubes [31, 32, 33].

The drug interferes with a key mechanism that allows the SARS-CoV-2 virus to reproduce in high numbers and cause infections. The same collaboration have found that experimental medicine remdesivir is effective in shutting down replication of the coronavirus that caused the original SARS and MERS epidemics.

The findings reported in Ref.[33] indicate that EIDD-2801 is possibly as successful as demdesivir in disrupting coronavirus replication.

While remdesivir brings SARS-CoV-2 replication process to a full stop, EIDD-2801 introduces mutations into the virus’s RNA as it makes copies so that the viral RNA becomes so damaged that it cannot infect cells. The drug EIDD-2801 could serve as a multipurpose antiviral because it is able to work against several RNA viruses.

Chinese scientists and physicians have been successful in containing the epidemic and recovering thousands of patients. They have been using the following treatments: Alpha-interferon nebulization; lopinavir/ritonavir; ribavirin/ritonavir combined with interferon; ribavirin combined with lopinavir/ritonavir; chloroquine phosphate; arbidol [34].

Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COVID-19 patients [35].

Gautret et al [35] study shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azitromycin.

Descriptions of the top 160 anti-COVID-19 treatments in development can be found in [36, 37].

Chinese researchers reported that both Chloroquine and Remdesivir where “highly effective in the control of SARS-CoV-2 infection in vitro” [38].

Holshue et al [39] present a positive case study about the administration of Remdesivir. Stem cell treatments can also be effective (see Ref.[40]) against COVID-19. Tuberculosis and COVID-19 are very different diseases. However a TB vaccine (The Bacillus Calmette-Guerin vaccine) is being studied in clinical trials around the world as a way to fight the novel coronavirus. It seems that BCG might help people build immune responses to different infections causing “off-target” effects [41].

It is believed that the vaccine can cause a nonspecific boost of the immune response. Angela Patri and Gabriella Fabbrocini have hypothesized that hydroxychloroquine and ivermectine could act in a consequential and synergistic manner [42].

8 Some biophysical analysis

Drug repurposing for SARS-CoV-2 is very important for our world. It can represent an effective drug discovery strategy from existing drugs. It could shorten the time and reduce the cost compared to de novo drug discovery [43].

Phylogenetic analysis of 15 HCoV whole genomes reveal that SARS-CoV-2 shares the highest nucleotide sequence identity with SARS-CoV [43].

A molecular docking study has been published by Abdo Elfiky [44].

The results show the effectiveness of Ribavirin, Remdesivir, Sofobuvir, Galidesivir, and Tenofovir as potent drugs against SARS-CoV-2 since they tightly bind to its RdRp. Additional findings suggest guanosine derivative (IDX-184), Sefosbuvir, and YAK as top seeds for antiviral treatments with high potential to fight SARS-CoV-2 strain specifically.

9 Important additional information for the development of new therapies

Grein et al have reported interesting information about the use of remdesivir against COVID-19 [45].

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown activity against SARS-CoV-2 [45]. In a cohort of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%).

Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.

The University of Chicago Medicine recruited 125 people with COVID-19 into Gilead’s two phase 3 clinical trials. Of those people, 113 had severe diseases. All the patients have been treated with daily doses of remdesivir [46].

Kathleen Mullane (from the University of Chicago) is overseeing the remdesivir study for the hospital. She said, “The best news is that most of our patients have already been discharged, which is great. We’ve only had two patients perish” [46]. She added: “Most of our patients are severe and most of them are leaving at six days, so that tells us duration of therapy does not have to be 10 days. We have very few that went out to 10 days, maybe three”.

The study lacks a control arm. Full trial data were not available April 16, the date of STAT publication of Feverstein and Herper [46].

STAT published an article April 23, 2020 that said: “New data on Gilead’s remdesivir, released by accident, show no benefit for coronavirus patients” [47].

According to this piece “The antiviral medicine remdesivir from Gilead Sciences failed to speed the improvement of patients with COVID-19 or prevent them from dying, according to results from a long-awaited clinical trial conducted in China”. A summary of the study results was inadvertently posted to the website of the World Health Organization. Later was removed

Andrew Hill, senior visiting researcher fellow at Liverpool University affirmed: “If there is no benefit to remdesivir in a study this size, this suggests that the overall benefit of remdesivir in this population with advanced infection is likely to be small in the larger Gilead trial.

Leon Caly et al [48] have observed that the FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. The authors have demonstrated that this drug actually “kills” the virus within 48 hours.

Ivermectin has also been shown to be effective against a broad range of viruses including HIV; Dengue, Influenza and Zika virus. Ivermectin is very widely used and seen as a safe drug.

Chunyan Wang et al have found a human monoclonal antibody (47D11) that neutralizes SARS-CoV-2 [49].

Leng et al. [50] describe clinical trials that suggest that Mesenchymal stem cells therapy is a very valuable treatment option for COVID-19. According to the mass cytometry streaming results, the virus infection caused a total function failure of the lymphocytes, even of the whole immune system. MSCs played a vital immune modulation role in restoring the lymphocyte subsets.

MSC therapy can inhibit the overactivation of the immune system and promote endogenous repair by improving the microenvironment. Ultimately, the patients with severe COVID-19 pneumonia survived the worst condition and entered

recovery. One of the reasons that the transplantation of MSCs improved the outcome of COVID-19 patients is that they regulated inflammatory response and promoted tissue repair and regeneration.

Natural killer cell therapy can elicit rapid and robust protective effects in defense against viral infections through direct cytotoxicity and immunomodulatory capability. Early data from a scientific work done by researchers in Hong Kong (using lopinavir/ritonavir, ribavirin and interferon beta 1b) shows that the triple antiviral therapy may be safe and effective in treating patients of COVID-19 according to a study published in Lancet by Fan-Ngai Hung et al. [51]. All three drugs are already approved by FDA to treat other illnesses.

Lopinavir/ritonavir is an anti-viral compound used to treat HIV, Ribavirin is commonly used to treat hepatitis C, and interferon beta 1b is a drug commonly used to treat multiple sclerosis. Interferon is an immune-system booster. The authors found that a typical patient given the three-drug-combo tested negative for the virus five days earlier than those who received just a single drug.

The triple therapy group had shorter hospital stays and said that their symptoms disappeared much faster than the control group. Early treatment is a success factor when physicians are using antivirals. None of the patients in the study died.

A new study showing that the experimental drug remdesivir might help COVID-19 patients recover more quickly is being discussed in the news [52].

Dr. Anthony Fauci (Director of NIAID) has said that this could become the “standard of care” for all infected patients. But beyond the initial optimism, the study also made clear that remdesivir is far from a cure for COVID-19. This is not a blockbuster treatment.

In fact, the limitations of remdesivir are quite clear in the study: the drug does not prevent death.

Dr. Andre Kalil said, “We have work to do. We are looking for other therapies. This trial is going to continue”. The study’s results show that the drug can have an impact on COVID-19.

Dr. Fauci has said, “it is a very important proof of concept: the drug can block the virus”. However there is little sign the drug can reduce deaths.

The government-funded study found that patients who took remdesivir recovered faster than patients who did not. It improved recovery time for coronavirus patients from 15 to 11 days.

Also, 8% of patients who took remdesivir died. People taking this drug still die. The study was run by the US NIAID.

Another study of remdesivir released recently shows the drug did not help people recover faster from coronavirus infections. We will discuss the details of this study below. The NIAID trial (which has not been peer reviewed yet) showed a 31% improvement in patients taking the drug compared with a placebo. The full study should be published in a scientific journal.

So a summary of this information is the following: Gilead reports early positive data in remdesivir study as COVID-19 drug, though Chinese trial sees no benefit [53].

The mentioned Chinese remdesivir study was published in The Lancet [53]. This was a double-blind, randomized, placebo controlled study.

The trial found that while safe and adequately tolerated, remdesivir did not provide significant benefits over placebo.

10 New combination therapies

The ideas discussed in the first 6 sections of the paper lead to the conclusion that we need a combination therapy that contains at least some the following features:

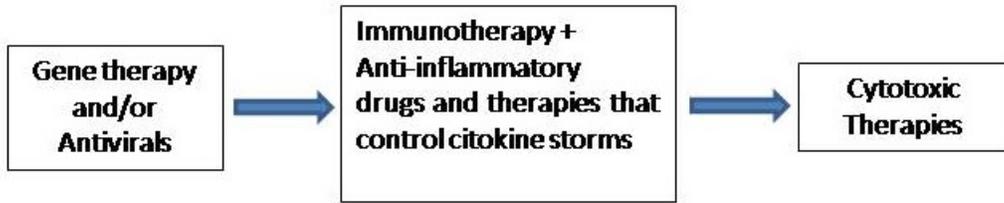


Figure 1: General Therapeutic Plan

- (A) A combination of drugs that impair somehow the biophysics of the virus replication, infection and/or treatment resistance.
- (B) A combination of drugs that enhance the immune system ability to provide enough agents and their capability to fight the virus + anti-inflammatory drugs.
- (C) A cell-killing therapy.

Our paper is not only about mathematical models. We have critically reviewed all the published data about possible medical treatments against COVID-19.

We have used a method that we have developed called Complex Systems Investigation to analyze the data.

Complex Systems Investigation contains ideas from Nonlinear Dynamical Systems, Inverse Problems, and Experimental Design Mathematics. Our results show that a successful treatment should be a combination of therapies as that shown in Fig. 1. This is just a useful therapeutic plan. We will see later that the role of a cytotoxic therapy sometimes can be played by an immunotherapy or an antiviral. Figure 1 shows a very general plan.

Now we will present several concrete combination therapies.

The simplest of our designed therapies is shown in Fig. 2. Figures 3-10 show different alternative treatments.



Figure 2: One of the simplest therapies: Remdesivir plus Immunotherapy plus Monoclonal antibodies



Figure 3: Anti-HIV cocktail plus Immunotherapy plus Ivermectin



Figure 4a: Antiviral combination plus Interferon beta plus Natural Killer Cell Therapy

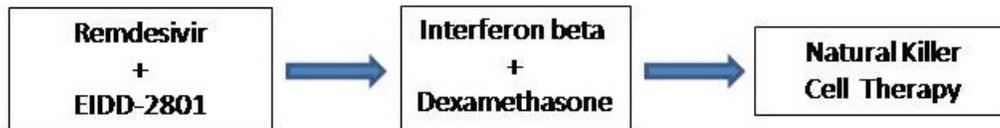


Figure 4b: Antiviral combination plus Interferon beta plus Natural Killer Cell Therapy plus Anti-inflammatory drug

Baricitinib is an important anti-inflammatory drug. It has also anti-viral effects [54].

A commonly used steroid, Dexamethasone, can control the cytokine storms and can reduce the risk of death.

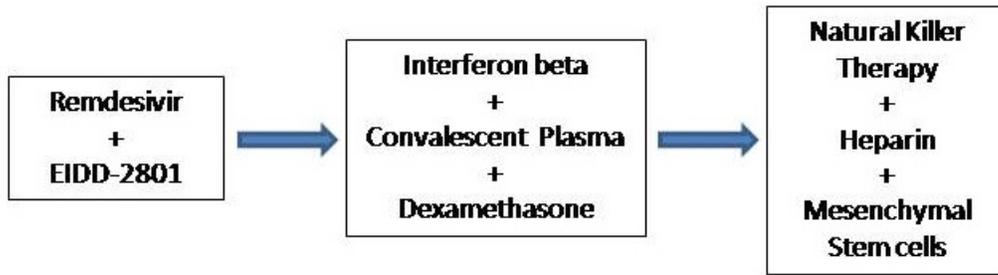


Figure 5: Powerful combination therapy that should kill the virus and save lives. The treatment includes a cocktail of antivirals: Remdesivir plus EIDD-2801, Immunotherapy, Natural Killer Cell therapy, Mesenchymal Stem Cells, a corticosteroid, and an anti-coagulant.

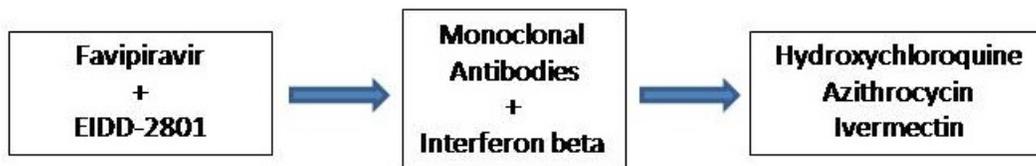


Figure 6: This is a combination of antivirals, an immune system booster, monoclonal antibodies, azithromycin, and the controversial hydroxychloroquine

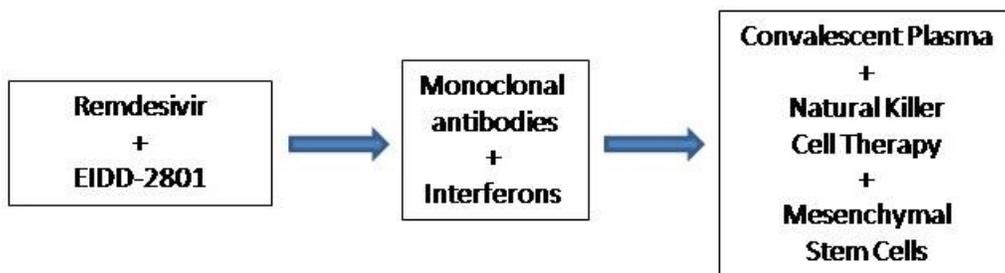


Figure 7: This therapy contains a combination of antivirals, monoclonal antibodies, an immune system booster, convalescent plasma, Natural Killer Cell Therapy, and an immune system modulator. This is a powerful combination.



Figure 8: This is a next-door therapy. Any hospital should be able to provide this treatment, which could save patients' lives.

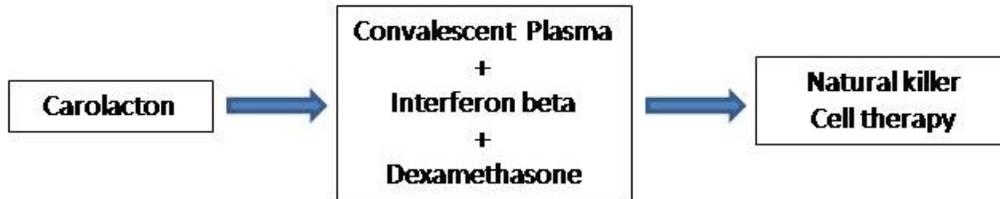


Figure 9: This could be a perfect realization of the General Therapeutic Plan (See Fig. 1): Gene therapy → Immunotherapy + an Anti-inflammatory drug → Cytotoxic therapy

Regeneron pharmaceuticals has developed monoclonal antibodies to treat MERS. This company is already working on similar antibodies that might work against SARS-CoV-2.

Lopinavir/ritonavir + arbidol improved pulmonary computed tomography images [54].

Interferons + Natural killer cells are promising. Interferons can enhance natural killer cells cytotoxicity. Mesenchymal stem cells will act against inflammatory factors (cytokine storms).

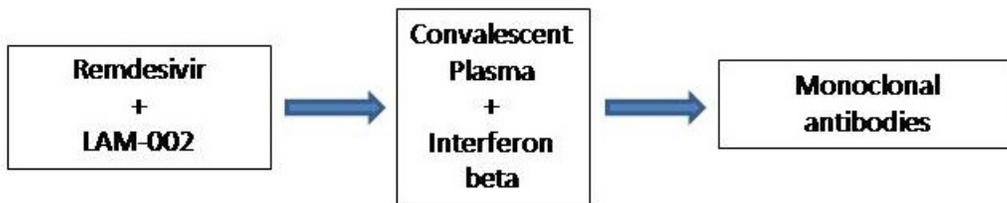


Figure 10: The combination Remdesivir plus LAM-002 should cripple the virus, the immunotherapies should kill the virus, and dexamethasone should relieve the inflammation and avoid the cytokine storms. The whole combination should control the immune system disorders, allergic reactions, and the breathing problems. This therapy should save lives and help patients recover faster.

MTHFV1 is a gene indispensable for viral replication in bat and human cells.

Carolacton is a MTHFV1 inhibitor. It is a natural bacteria-derived product [54].

This is a good candidate for the first round in the combination therapy (see Fig. 9). A candidate for natural killer cell therapy is CYNK-001 [36].

The most powerful therapy is shown in Fig. 5. Probably this therapy should be used in the most severe critical fulminant cases.

On the other hand, Fig. 8 shows the next-door therapy. In principle, all elements should be available right now in every American city.

11 Discussion

Remdesivir is considered the most promising drug for COVID-19 and MERS.

However, the clinical trials have produced conflicting results. Sometimes the results are encouraging, sometimes there are no significant benefits at all. Sometimes the people are still dying even taking remdesivir.

Our response to this paradox is that remdesivir will work as part of a combination therapy. Our result is that the idea of using remdesivir and some immunotherapies in combination would have profoundly excellent prospects. (see figures 1-10).

We have tried to construct the combinations using drugs that have shown proven efficacy in completed clinical trials and/or laboratory experiments [54].

Parameter q can be changed using drugs that change the nature of the virus.

Parameter q is related to the nature and structure of the virus.

For instance, the drug EIDD-2801 interferes with a key mechanism that allows the SARS-CoV-2 virus to reproduce in high numbers and cause infections.

EIDD-2801 is incorporated during RNA synthesis and then drives mutagenesis, thus inhibiting viral replication. So, this antiviral changes the nature of the virus.

Parameters q is related to the explosive reproduction of the virus and it is related to the difficulty to eradicate the virus.

The action of EIDD-2801 and Remdesivir is different. Remdesivir shuts down viral replication by inhibiting a key enzyme, the RNA polymerase.

Both Remdesivir and EIDD-2801 can change parameter q . Antivirals keep the virus from functioning and/or reproducing. If we combine them, we can increase the probability that they will do the job of changing the biophysics of the virus. Then we can add immunotherapies to eradicate the virus.

These two antivirals are much more potent if given early. In general, this is the case for most antivirals.

Some physicians can have concerns because, for them, it is not clear whether several combinations of medications and the high doses of the drugs in question could cause side effects.

Our research leads to the following solution to these problems: the addition of new drugs to the therapy and the total increase of doses can be administered using late-intensification schedules (e.g. logarithmic or power-law therapies [4, 5, 6]).

Our stable fixed point with a small but finite virus population explains the following mystery: why a lot of patients who recovered from Coronavirus have retested positive [7].

The existence of a finite minimum of the virus load in order to start an infection (Eq. (13)) explains that there is a threshold value for a person exposure to sick people so that the person becomes infected.

Some precedents. Therapy of HIV is complicated by the fact the HIV genome is incorporated into the host cell genome and can remain there in a dormant state for prolonged periods until it is reactivated. Some scientists believe that it is not possible to actually eradicate the virus completely.

Our research shows that this is a very striking example where $q \leq 1$. Following our ideas, it is possible that HIV can be completely eradicated. AZT was the first antiviral agent used for the treatment of HIV and was introduced in 1987. However, it became clear that mono therapy with AZT did not provide durable efficiency and hardly made any dent in the mortality rate.

Later, different studies showed that combination therapy with two nucleotide analogues were better than monotherapy with only one.

After several experimental breakthroughs, a combination therapy known as HAART (highly active antiretroviral therapy) using two or three agents became available. By combining drugs that are synergistic, non-cross-resistant and no overlapping toxicity, it may be possible to reduce toxicity, improve efficacy and prevent resistance from arising.

All the antiviral drugs and therapeutic methods now known were discovered by random search in the laboratory.

We believe that using mathematical biophysics it is possible to create a rational approach for the discovery of new antiviral compounds and the design of the optimal combination therapy.

12 Conclusions

J. H. Bergel et al [54] have published a paper in The New England Journal of Medicine with the information about the NIAID-supported study titled "Remdesivir for the treatment of COVID-19".

NIAID director had said that remdesivir will become the standard care of COVID-19.

The drug shortened the course of illness from an average of 15 days to about 11 days.

However, it is clear that the drug is not enough to help patients.

The medication is not a cure and it does not act quickly. There is high mortality despite the use of remdesivir. So, remdesivir is not sufficient to cure patients.

It seems that remdesivir does not cause an excess of side-effects.

Our take is that remdesivir alone is not enough. Many other treatments, given as monotherapies, have failed to provide the promised results.

Our conclusion is that we need new scientifically designed combination therapies.

Using mathematical models and experimental data from laboratory and clinical studies, we have been able to design new therapies, which, we expect, will cure the patients. (See figures 1-10).

The new therapies also should be validated in double-blind, placebo-controlled trials with a large number of patients.

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Competing interest: The authors declare no competing interests.

Figures



Figure 1

General Therapeutic Plan



Figure 2

One of the simplest therapies: Remdesivir plus Immunotherapy plus Monoclonal antibodies

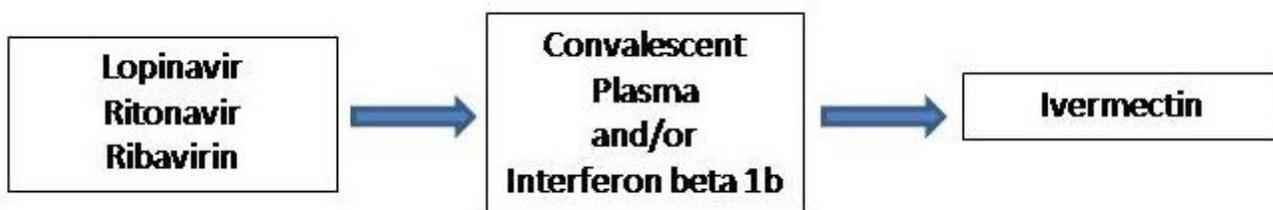


Figure 3

Anti-HIV cocktail plus Immunotherapy plus Ivermectin

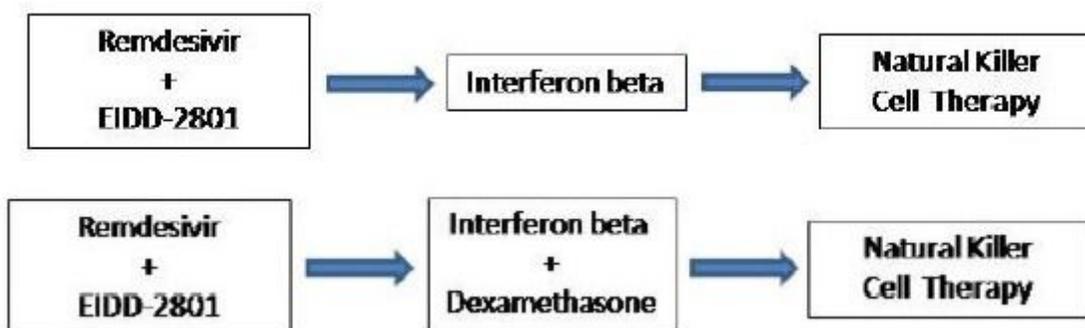


Figure 4

(Top) a: Antiviral combination plus Interferon beta plus Natural Killer Cell Therapy (Bottom) b: Antiviral combination plus Interferon beta plus Natural Killer Cell Therapy plus Anti-inflammatory drug

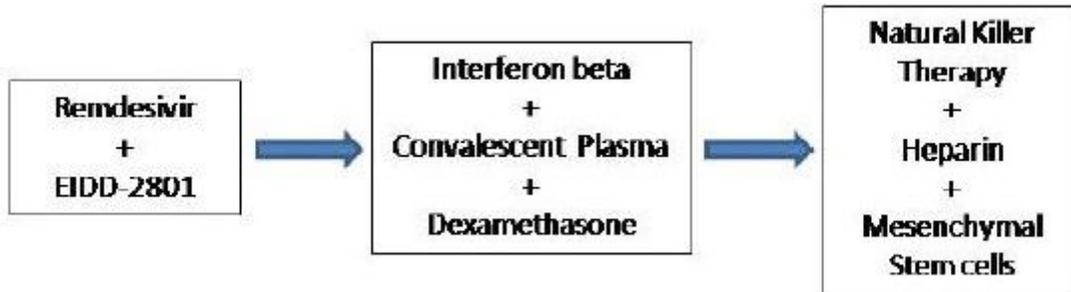


Figure 5

Powerful combination therapy that should kill the virus and save lives. The treatment includes a cocktail of antivirals: Remdesivir plus EIDD-2801, Immunotherapy, Natural Killer Cell therapy, Mesenchymal Stem Cells, a corticosteroid, and an anti-coagulant.

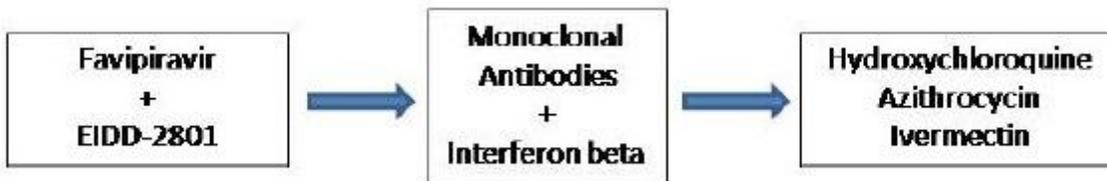


Figure 6

This is a combination of antivirals, an immune system booster, monoclonal antibodies, azithromycin, and the controversial hydroxychloroquine

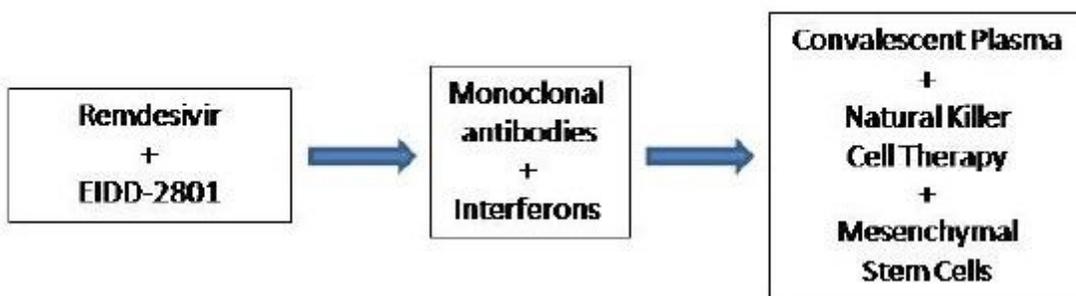


Figure 7

This therapy contains a combination of antivirals, monoclonal antibodies, an immune system booster, convalescent plasma, Natural Killer Cell Therapy, and an immune system modulator. This is a powerful

combination.



Figure 8

This is a next-door therapy. Any hospital should be able to provide this treatment, which could save patients' lives.

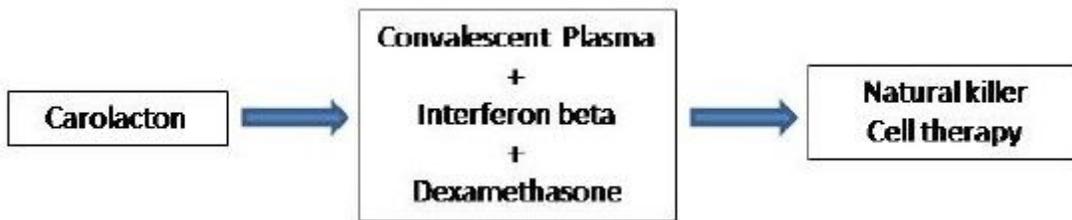


Figure 9

This could be a perfect realization of the General Therapeutic Plan (See Fig. 1): Gene therapy ! Immunotherapy + an Anti-inflammatory drug ! Cytotoxic therapy



Figure 10

The combination Remdesivir plus LAM-002 should cripple the virus, the immunotherapies should kill the virus, and dexamethasone should relieve the inflammation and avoid the cytokine storms. The whole combination should control the immune system disorders, allergic reactions, and the breathing problems. This therapy should save lives and help patients recover faster.