

## Case Report

# Twice-Daily Intravenous Injection of Interferon-Beta is a Promising Therapeutic Strategy for COVID-19

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## Abstract

Several in vitro and in vivo study have elucidated potent anti-SARS-CoV-2 activity of type 1 interferon (IFN). In particular, IFN-beta ( $\beta$ ) is increasingly recognized as a promising therapeutic agent. IFN- $\beta$  not only has antiviral activities, but also has immunomodulatory effects. NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is an important component of the innate immune system. Overactivity of NLRP3 inflammasome is one of the main causes of cytokine storm in COVID-19. There are many candidate compounds for inhibiting NLRP3 activity, however, IFN- $\beta$  is the sole agent that can inhibit both NLRP3 activity and viral replication simultaneously. In this review article, the author summarized the rationale for the use of IFN- $\beta$  against COVID-19. The author also sought the optimal regime of IFN- $\beta$  based on Gompertz function and dose density theory and proposed twice-daily intravenous injection of IFN- $\beta$  as best practice.

**Goals:** To elucidate the rationale of IFN- $\beta$  against COVID-19 and to present the best protocol.

**Results:** Twice daily intravenous injection of IFN- $\beta$  is the best practice.

**Keywords:** COVID-19; interferon beta; NLRP3; inflammasome; Gompertz curve

## Introduction

Intense efforts are under way to develop therapies for COVID-19. Type 1 interferon (IFN) is one of the promising agents [1,2]. It was observed that severe and critical patients had a highly impaired type 1 IFN response, associated with a persistent blood viral load and an exacerbated inflammatory response [3]. Inhibition of host's type 1 IFN has been acknowledged as an immune evasion mechanism employed by SARS-CoV-2 [4-6]. On the other hand, exogenous administration of IFN- $\beta$  dramatically reduces SARS-CoV-2 replication in vitro and in vivo. Type 1 IFN is widely known to possess not only antiviral activity, but also a pronounced immunomodulating effect [7]. Cytokine storm during SARS-CoV-2 infection is the main cause of multi-organ failure and mortality. In this perspective, the author shows the potential utility of IFN- $\beta$  as a promising therapeutic agent for COVID-19.

### Antiviral Activity In Vitro

Clementi et al. demonstrated that IFN- $\beta$ -1a is highly effective in inhibiting in vitro SARS-CoV-2 replication at clinically achievable concentration [8]. On Vero E6 cells, IFN- $\beta$ -1a inhibits SARS-CoV-2 replication in a dose-dependent manner. In vitro study on Calu-3 and Vero E6 cells revealed that SARS-CoV-2 is consistently more sensitive to IFNs than SARS-CoV-1 [9]. In comparison, IFN- $\beta$  has more potent anti-SARS-CoV-2 activity in cultured cells than IFN- $\alpha$  [1].

### Antiviral Activity In Vivo

Dastan, *et al.* reported a non-controlled prospective trial investigating the efficacy of subcutaneous administration of IFN- $\beta$ -1a for COVID-19 [10]. In the study, patients received IFN- $\beta$ -1a at a dose of 12 million units subcutaneously every other day up to 10 days. All patients received hydroxychloroquine and lopinavir/ritonavir, simultaneously. All patients had severe pneumonia. Eighteen out of 20 patients (90%) experienced virological clearance within 14 days. Most of their symptoms were also improved. No serious adverse events were observed. Although a dramatic improvement in clinical outcome was achieved, there was no control group. A randomized open-label trial using IFN- $\beta$  was conducted at 6 hospitals in Hong Kong [11]. Patients were randomly assigned to a 14-day combination of lopinavir, ritonavir, ribavirin, and three doses of 8 million units of interferon beta-1b on alternate days or to 14 days of lopinavir and ritonavir (control group). The clinical efficacy was evaluated with a national early warning score 2 (NEWS2) and a sequential organ failure assessment (SOFA) score. The addition of IFN- $\beta$  resulted in a significant shortening of the time to normalization of NEWS2 and SOFA score. Most patients treated with IFN- $\beta$  were RT-PCR negative by day 8. There was no serious adverse event. The authors stated that IFN- $\beta$  is a key component of their combination treatments.

## **Immunomodulating Effect**

Both in vitro and in vivo studies have shown potent anti-SARS-CoV-2 activity of IFN- $\beta$ . However, concern remains regarding the potential for amplification of cytokine storm. It is currently uncertain whether or not cytokine storm is exacerbated by IFN- $\beta$ . Here we speculate that IFN- $\beta$  may attenuate cytokine storm with its immunomodulatory effects.

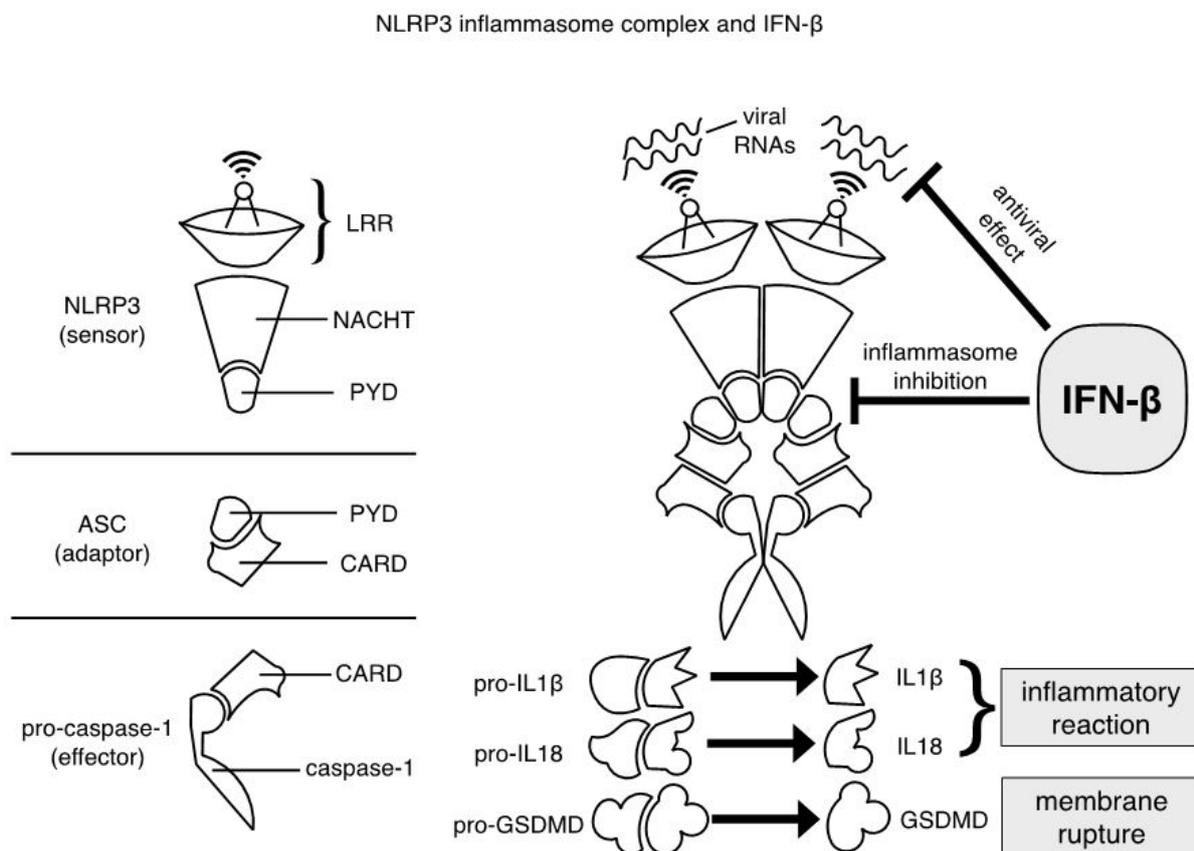
## **NLRP3 Inflammasome Activation in Cytokine Storm**

NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is an important component of the innate immune system [12]. The NLRP3 inflammasome consists of an NLRP3 as the cytosolic sensor, an adaptor protein apoptosis-associated speck-like protein containing a caspase activating recruitment domain (ASC), and a cysteine protease pro-caspase-1 as the effector. (Figure 1) NLRP3 is further divided into a C-terminal leucine-rich repeat (LRR), central NACHT domain, and an N-terminal pyrin-only domain (PYD). ASC is comprised of N-terminal PYD and a C-terminal caspase activation and recruitment domain (CARD). Pro-caspase-1 consists of CARD and caspase-1. When viral pathogens enter the host cell, LRR senses pathogen-associated molecular patterns, followed by NLRP3 activation. ASC and pro-caspase-1 are recruited by PYD-PYD and CARD-CARD homotypic interaction. Dimerized caspase-1 cleaves its natural substrates pro-gasdermin-D (GSDMD), pro-IL-1 $\beta$ , and pro-IL-18 into GSDMD, IL-1 $\beta$ , IL-18, respectively. GSDMD forms a pore in the plasma membrane that ultimately causes cell death (pyroptosis) [13]. IL-1 $\beta$  and IL-18 are major inflammatory mediators. The NLRP3 inflammasome plays a pivotal role in pathogen defense, however, an overactive response is detrimental to the host. Recent surveys have revealed that NLRP3 inflammasome plays a central role in cytokine storm in COVID-19 [14,15]. Ito et al. reported that NLRP3 inflammasome activation in lung vascular endothelial cells contributes to intestinal ischemia/ reperfusion-induced acute lung injury (ALI) [16]. In animal models with NLRP3 deficiency, ALI after reperfusion injury is prevented with decreasing permeability of lung alveolar cells. SARS-CoV-2 is known for its involvement in vascular endothelial injury. NLRP3 inflammasome plays a pivotal role in vascular endothelial damage in Kawasaki disease [17]. In vitro and in vivo experiments revealed anti-NLRP3 agents (eg. MCC950) markedly reduced coronary arterial damage in animal models for Kawasaki disease. Thus, NLRP3 inflammasome axis has emerged as promising therapeutic target for Kawasaki disease. Recent reports show that children with COVID-19 sometimes are followed by Kawasaki disease [18]. Further studies are required to clarify the involvement of NLRP3 inflammasome on Kawasaki-like lesions in COVID-19 patients.

## **IFN- $\beta$ and NLRP3 Inflammasome**

Several studies have documented that type 1 IFN inhibits NLRP3 inflammasome activity. (Figure 1) In particular, the relationship between IFN- $\beta$  and NLRP3 has been studied extensively in vitro and in vivo. IFN- $\beta$  inhibits NLRP3 inflammasome activation in a STAT1-dependent manner and suppresses IL-1-dependent inflammatory cell recruitment in vivo [19]. In clinical settings, IFN- $\beta$  is widely used as a first-line therapy

for multiple sclerosis (MS) [20]. The underlying mechanism for the therapeutic effects of IFN- $\beta$  is thought to be associated with its anti-inflammatory activity through inhibition of NLRP3. Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, is induced by the NLRP3. IFN- $\beta$  markedly attenuates EAE through suppression of IL-1 $\beta$ . EAE can be divided into two subsets based on NLRP3 dependency. NLRP3 dependent EAE is termed type A EAE, whereas NLRP3 independent EAE is termed type B EAE. NLRP3 independent type B EAE is resistant to IFN- $\beta$  treatment. Therefore, effect of IFN- $\beta$  on EAE is via inhibition of NLRP3 [21]. Mycobacterium tuberculosis is known for its ability to enhance IFN- $\beta$  activity in the host. Tuberculosis induced IFN- $\beta$  up-regulation results in reduced expression of NLRP3 inflammasome and IL-1 $\beta$ . This modulation takes advantage of the mycobacterial survival [22]. Zhang, *et al.* assessed the impact of Bacillus Calmette-Guerin (BCG) on IFN- $\beta$  production [23]. Pleural fluid mononuclear cells (PFMC) were treated with BCG. After stimulation, BCG significantly induced the production of IFN- $\beta$  in a dose-dependent manner.



**Figure 1:** (left) NLRP3 inflammasome consists of an NLRP3 (sensor), ASC (adaptor), and pro-caspase-1 (effector). NLRP3 is further divided into LRR, central NACHT, and PYD. ASC is comprised of PYD and CARD. Pro-caspase-1 consists of CARD and caspase-1. (right) LRR senses viral RNAs, followed by NLRP3 activation. ASC and pro-caspase-1 are recruited by PYD-PYD and CARD-CARD homotypic interaction. Dimerized caspase-1 cleaves pro-GSDMD, pro-IL-1 $\beta$ , and pro-IL-18 into GSDMD, IL-1 $\beta$ , IL-18. GSDMD forms a pore in the plasma membrane (pyroptosis). IFN- $\beta$  inhibits viral replication and inflammasome activity

## The optimal strategy for using type 1 IFN

### IFN- $\alpha$ vs. IFN- $\beta$

As stated above, IFN- $\beta$  has greater anti-SARS-CoV-2 activity in cultured cells than IFN- $\alpha$ . Aside from SARS-CoV-2, antiviral activity of IFN- $\beta$  generally is greater than IFN- $\alpha$ . We previously compared the effectiveness of IFN- $\alpha$  and IFN- $\beta$  on hepatitis C virus (HCV) [24]. Fourteen days administration of IFN- $\beta$  resulted in 60 times greater HCV reduction than pegylated-IFN- $\alpha$  and ribavirin.

### Subcutaneous vs. Intravenous injection

Jalkanen et al. stated that administration route of IFN- $\beta$  is of critical importance for optimizing therapeutic outcomes for COVID-19 [25]. Maximum serum concentrations and total exposure through serum concentrations are significantly higher after intravenous than subcutaneous injections, and the bioavailability via the subcutaneous route is about one third of that obtained by intravenous injection. As for HCV therapy, IFN- $\beta$  had been administered intravenously in Japan [26].

### Once-daily vs. Twice-daily

Asahina et al. compared once-daily injection of 6 million-unit (MU) IFN- $\beta$  and twice-daily injection of 3 MU IFN- $\beta$  for patients with chronic HCV infection (27). On day 14, twice-daily group achieved much greater reduction of HCV viral load (24 times) than once-daily group. Thereafter, many Japanese hepatologist had used twice-daily 3 MU IFN- $\beta$  as induction therapy for 2 weeks, followed by pegylated IFN- $\alpha$  and ribavirin. Nowadays, direct acting antivirals has replaced interferon therapy for chronic HCV infection.

## Material and Methods

### Sample and data

Data were retrieved from published article regarding IFN- $\beta$  therapy against chronic HCV infection by Asahina, *et. Al.* [27]. In Asahina's article, twice daily injection of 3 MU IFN- $\beta$  and once daily 6 MU IFN- $\beta$  were compared for 14 days. Twelve patients were included in each group, respectively.

### Measures of variables

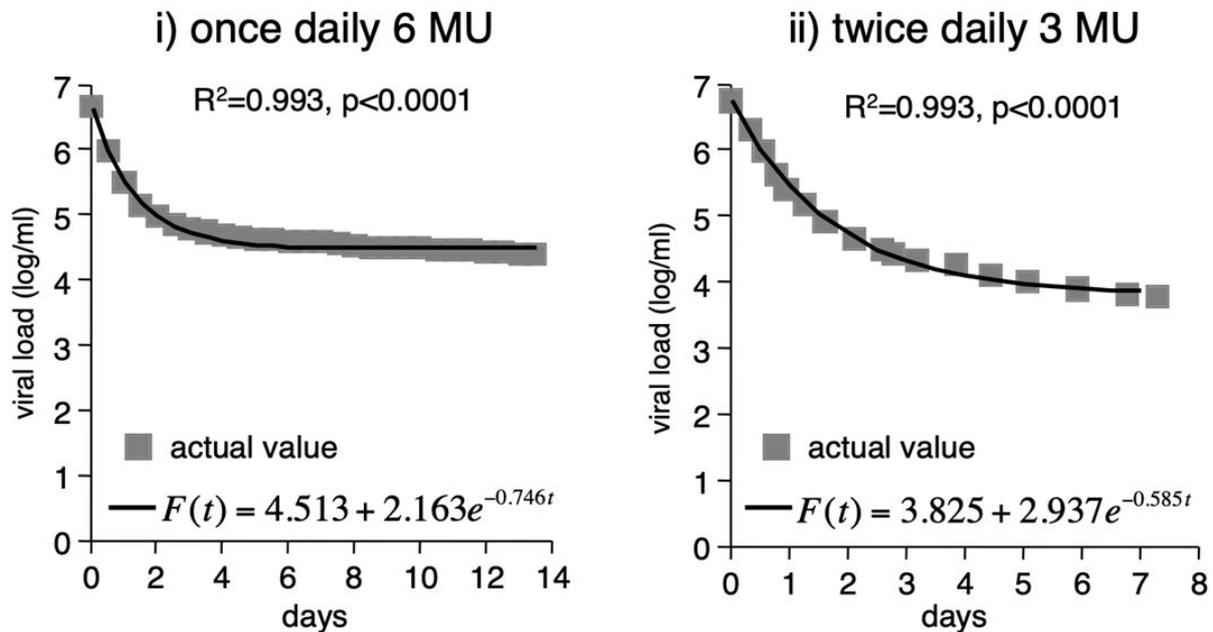
We scanned published data and estimated daily viral load in each group.

### Data analysis

Gompertz function was approximated to each data by using Gompertz-Matsui calculator, an iPhone application developed by Keiji Matsui (the author). Thereafter, change of viral load in each group was compared and analyzed in terms of dose-density theory.

## Results

Comparing once-daily injection of 6 MU IFN- $\beta$  and twice-daily injection of 3 MU IFN- $\beta$  for patients with chronic HCV infection, decrease curves are as follows (Figure 2);



**Figure 2:** Daily changes of HCV viral load. i) once daily 6 MU injection of IFN- $\beta$  ii) twice daily 3 MU injection of IFN- $\beta$ . Gray squares (\*) are actual values retrieved from Asahina's article. Solid lines (-) are calculated Gompertz function

i) once daily 6MU

$$\ln H(t) = 4.513 + 2.163e^{-0.746t}$$

initial decline slope ( $-D_0$ ) = -1.6, dumping coefficient ( $k$ ) = 0.746

ii) twice daily 3MU

$$\ln H(t) = 3.825 + 2.937e^{-0.585t}$$

initial decline slope ( $-D_0$ ) = -1.7, dumping coefficient ( $k$ ) = 0.585

Above equations denote that twice-daily injection keeps initial decline slope same as once-daily injection and has small dumping coefficient.

### Data analysis with Gompertz-Matsui model and dose density theory

We previously presented an assumption about HCV kinetics as follows; when HCV's growth obeys Gompertz model, an increase of HCV can be expressed as

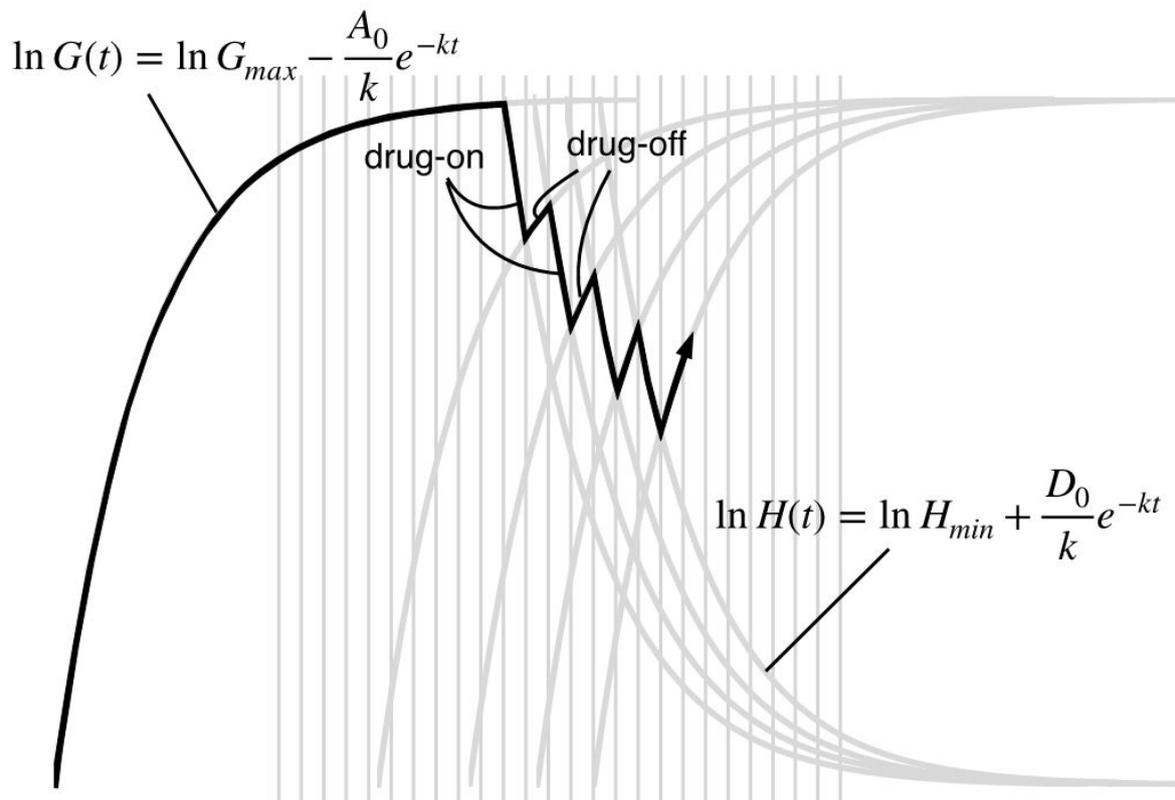
$$\ln G(t) = \ln G_{max} - \frac{A_0}{k} e^{-kt}$$

where  $\ln G(t)$  is a logarithm of HCV-viral load,  $\ln G_{max}$  is a logarithm of baseline viral load,  $A_0$  is an initial acceleration rate,  $k$  is a dumping constant of the acceleration rate, and  $t$  is time. When HCV's decay by IFN occurs in an exponential-decay manner, decrease of HCV can be expressed as

$$\ln H(t) = \ln G_{max} - \frac{D_0}{k} + \frac{D_0}{k} e^{-kt}$$

where  $\ln H(t)$  is a logarithm of HCV-viral load,  $D_0$  is an initial deceleration rate.

$\ln G_{max} - \frac{D_0}{k}$  is also expressed as  $\ln H_{min}$  (Figure 3) [24,28].



**Figure 3:** Intermittent administration of antiviral therapy results in two phases. Decrease curves and increase curves are horizontal transition of following formula,

$$\ln H(t) = \ln H_{min} + \frac{D_0}{k} e^{-kt} \text{ and } \ln G(t) = \ln G_{max} - \frac{A_0}{k} e^{-kt}.$$

## Dose-density theory

Intermittent administration of antiviral therapy results in two phases, alternating between increase and decrease of the viral load. Decrease curves and increase curves are horizontal transition of following formula,  $\ln H(t) = \ln H_{min} + \frac{D_0}{k} e^{-kt}$  and  $\ln G(t) = \ln G_{max} - \frac{A_0}{k} e^{-kt}$ , respectively. When host's immunity is ignored and the alternation persists, the viral load converges to certain equilibrium ( $\ln H_{eq}$ ), whose value varies with dose-density [29].

Slope of the decrease curve is;

$$\frac{d \ln H}{dt} = -k(\ln H_{eq} - \ln H_{min})$$

Slope of the increase curve is;

$$\frac{d \ln G}{dt} = k(\ln G_{max} - \ln H_{eq})$$

A) Drug-on : off = 1:1

When the duration of drug-on period is equal to that of drug-off, equilibrium is expressed as follows; (Fig. 4)

$$\begin{aligned} k\Delta t(\ln H_{eq} - \ln H_{min}) &= k\Delta t(\ln G_{max} - \ln H_{eq}) \\ \therefore \ln H_{eq} &= \frac{\ln G_{max} + \ln H_{min}}{2} \end{aligned}$$

$\ln H_{eq}$  is at the midpoint between  $\ln G_{max}$  and  $\ln H_{min}$ .

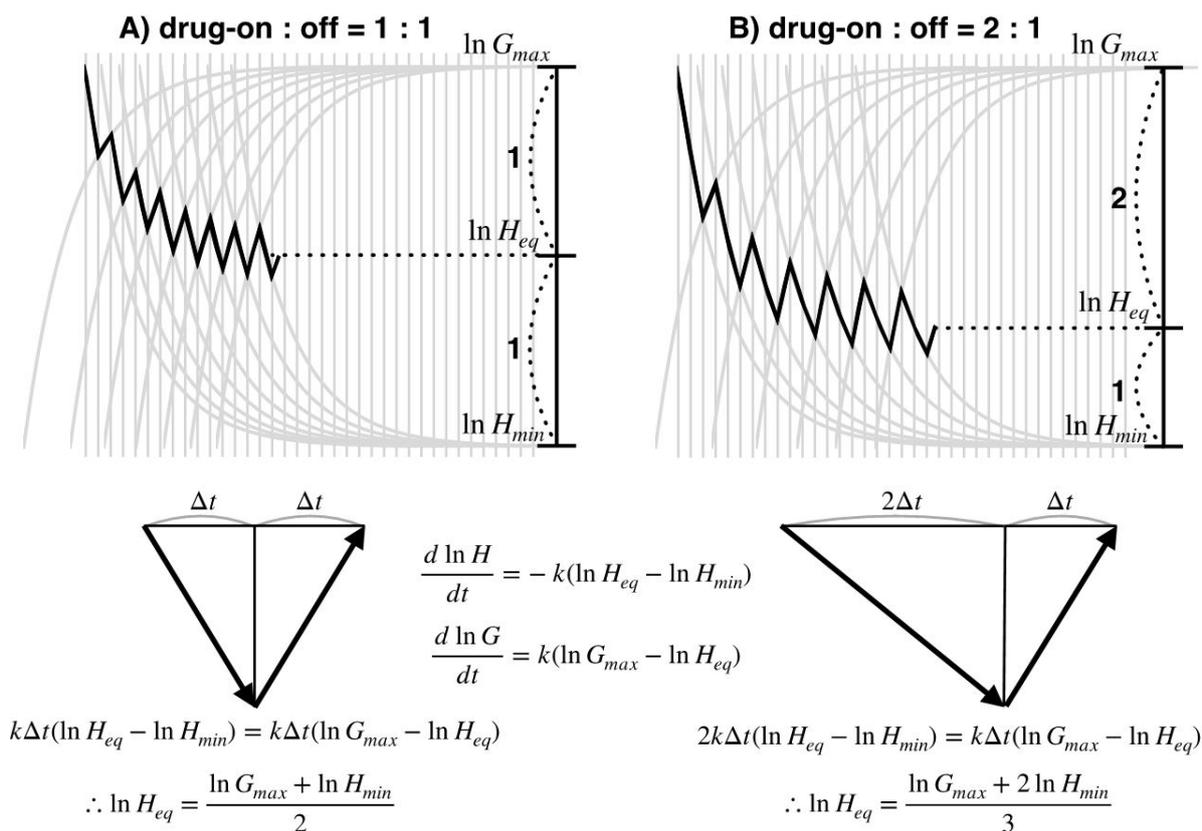
B) Drug on: off = 2:1

When the duration of drug-on period is twice as long as that of drug-off, equilibrium is expressed as follows; (Fig. 4)

$$\begin{aligned} 2k\Delta t(\ln H_{eq} - \ln H_{min}) &= k\Delta t(\ln G_{max} - \ln H_{eq}) \\ \therefore \ln H_{eq} &= \frac{\ln G_{max} + 2 \ln H_{min}}{3} \end{aligned}$$

$\ln H_{eq}$  is the point dividing  $\ln G_{max} - \ln H_{min}$  internally in the ratio of 2:1.

Thus, the difference in reduction of HCV-viral load between once-daily 6 MU injection and twice-daily 3MU injection of IFN- $\beta$  is explicable by dose-density theory.



**Figure 4:** Comparison between A) Drug-on: off = 1:1 and B) Drug on: off = 2:1

In case of drug-on: off = 1:1,  $\ln H_{eq}$  is at the midpoint between  $\ln G_{max}$  and  $\ln H_{min}$ . When drug on: off = 2:1,  $\ln H_{eq}$  is the point dividing  $\ln G_{max} - \ln H_{min}$  internally in the ratio of 2:1

## Discussion

### Limitations

The main limitation of this study is that this mathematical analysis is of IFN- $\beta$  for chronic HCV infection, not for acute SARS-CoV-2 infection. Thus, application of the results for SARS-CoV-2 is extrapolation.

### Optimal interferon strategy

Many Japanese hepatologists know that twice daily intravenous injection of IFN- $\beta$  is way better than any other interferon regimens, however, previous interferon regimens for SARS-CoV-2 were not optimal (e.g., intramuscular injection/ every other day injection). In this article, the author shows the rationale of twice daily intravenous injection of IFN- $\beta$  by literature reviews and dose density theory.

### Unfounded concern for IFN- $\beta$ administration

There is a concern for IFN- $\beta$  administration regarding exacerbation of cytokine storm. Practically, previous clinical studies have revealed excellent safety profiles of exogenous IFN- $\beta$  administration against COVID-19

even in severe patients. Theoretically, IFN- $\beta$  inhibits NLRP3 inflammasome, a pivotal player in cytokine storm.

### **Advantages of IFN- $\beta$ over other therapeutic agents**

The safety and efficacy profiles of IFN- $\beta$  offer significant advantages over other therapeutic agents. Clinicians have become familiar with IFN- $\beta$  due to decades of clinical use. In Japan, thousands of HCV patients had undergone twice-daily IFN- $\beta$  for 14 days as loading therapy prior to pegylated IFN- $\alpha$  and ribavirin [26]. Several clinical studies have revealed excellent safety profile of IFN- $\beta$  for COVID-19 even in severe cases [11,30]. IFN- $\beta$  offers advantages in terms of effectiveness over other therapeutic agents, namely, potent antiviral activity on SARS-CoV-2, and inflammasome inhibitory effect. There are several candidates for inhibiting NLRP3 inflammasome (i.e. MCC950, Canakinumab, Anakinra, and so on) [14], however, IFN- $\beta$  is the sole agent that can inhibit both NLRP3 activity and viral replication simultaneously.

### **Conclusion**

NLRP3 inflammasome is increasingly regarded as an important contributor to severe COVID-19 cases [14]. IFN- $\beta$ , a decades old remedy, may pave the way for combating SARS-CoV-2, emerged in late 2019. Twice-daily intravenous injection of IFN- $\beta$  had been utilized for chronic HCV infection in some Japanese institutions. Its rationale is based on Gompertz function and the dose-density theory. Further clinical trials are warranted to confirm this perspective.

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