

Editorial

Calmly and Scientifically

New Products

Remdesivir (trade name: Veklury)

Favipiravir (trade name: Avigan Tablet)

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Most probably no efficacy on COVID-19, and harmful

Calmly and Scientifically

Translated from the Editorial in Med Check (in Japanese) Jul 2020 ; 20 (90) : 75

Do you know the book, “The Shock Doctrine” by Naomi Klein? This book, published in 2007, sells well again in this corona-age. Shock doctrine can be defined as the execution of the disaster capitalism. When people are in a state of shock and lose their composure due to disasters, cruel market fundamentalism, which does not work in ordinary times, passes through. The reconstructions of New Orleans hit by Hurricane Katrina and Tohoku (north eastern region) in Japan hit by the Great East Japan Earthquake would be typical examples.

At present, another shock doctrine is progressing here in Japan: remdesivir is approved in Japan for the first time in the world and used clinically to treat COVID-19. Gilead Sciences, the manufacturer of this chemical, will make huge profits. The name of this company is mentioned in the chapter 15 in “The Shock Doctrine”. Donald Rumsfeld, US Defense Secretary for the Bush Junior administration(2001-2006), was once the chairman of Gilead Sciences which had the patent of Tamiflu. Since pandemic is a national security issue, the conflict of interest occurs for Defense Secretary. However, he never released his stocks of the company during his tenure. Gilead’s share price increased nine-fold due to the outbreak

risk of bird flu, bringing him huge profits. Likewise, many stockholders, including him, will gain huge profits by the Japanese approval of remdesivir. However, as evident in the article of this volume, the quality of ACTT-1 trial, which underpins the approval of remdesivir, is questionable. In addition, many of the ongoing clinical trials for favipiravir are largely observational studies with which efficacy cannot be determined.

In its editorial, BMJ (April 21, 2020) warned that we should not waste time for observational studies without control. Nature (May 13, 2020) also said in its editorial "remdesivir provides an example of the clinical chaos...clinical trials must be as robustly designed as possible. Some trials need to be small, initial explorations of potential treatments; but, after that, researchers must think big." Even the Japanese Medical Association’s Council of Experts for COVID-19, which has made a poor evaluation of the ACTT-1 trial, said that it is essential to have a high-quality RCT and the decision to disregard science is ultimately a disaster for the national health. A series of articles of Med Check and Med Check in English are effective measures against the Shock Doctrine.

New Products

Remdesivir (trade name: Veklury)

Most likely ineffective for COVID-19

Translated and revised from Med Check(in Japanese) Jul 2020 ; 20 (90):76-79

Med Check Editorial Team

Summary

- Remdesivir (trade name: Veklury) is an antiviral agent that was initially developed for Ebola virus infection, but was eventually proven ineffective. In Japan, it was officially approved for the treatment of COVID-19 for the first time in the world as a “special case” in which the approval was granted within 3 days after application.
- Three placebo-controlled randomized controlled trials (RCTs) have been conducted to examine the efficacy and safety of remdesivir on COVID-19. Of those, 2 were published as peer-reviewed papers for severe COVID-19.
- In the placebo controlled RCT conducted in China (Wuhan RCT), remdesivir did not reduce symptoms or death compared to placebo.
- In the RCT (ACTT-1) led by the US National Institutes of Allergy and Infectious Diseases (NIAID), remdesivir did not reduce severity of symptoms nor death in patients who had mild or moderate symptoms at the baseline. The same was true in patients who had very severe symptoms, including those on ventilator. It was effective only in patients with severe symptoms who required oxygen inhalation, but not ventilator. However, the symptom improvement and survival rate in these severe cases are unnaturally poor in the placebo group and unnaturally good in the remdesivir group. Therefore, it is highly likely that there was some bias in the study and the overall data is unreliable.
- In the SIMPLE trial comparing 5-day use and 10-day use, the number of cases that had recovered was significantly higher in the 5-day use group than in the 10-day use group. When a treatment is effective, longer-term use essentially yields better outcome. However, in this study, the opposite dose-response relationship was observed.
- In the special approval of remdesivir in Japan, the results of Wuhan RCT was excluded, and the opposite dose-response relationship in the SIMPLE trial was ignored. It was based only on the results of ACTT-1, which is likely to have bias in baseline characteristics.

Conclusion: The drug is most likely ineffective and should not be used.

Keywords:

RCT, ACTT1, SIMPLE, dose-response relationship, baseline characteristics, bias

Introduction

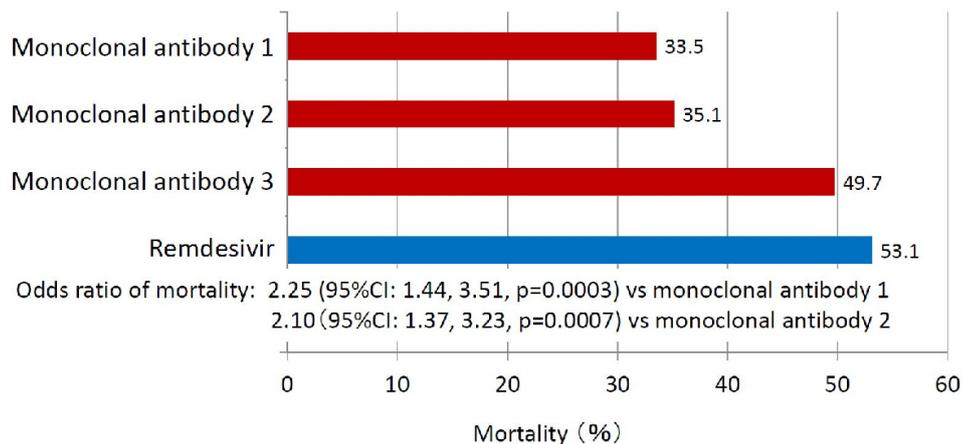
On May 7, 2020, remdesivir (product name Veklury) was approved as a “special case” only 3 days after the application was accepted [1]. This is because an emergency use authorization (EUA) [2] was issued in the U.S. on May 2, and the Japanese Ministry of Health, Labor and Welfare interpreted that it had been already approved abroad although EUA was not an official approval. On what basis the drug is claimed to be

effective? How about its safety? Let us verify them in this article.

Remdesivir is a synthetic inhibitor of viral RNA

Remdesivir is metabolized in the human body to a substance which acts as an analog of adenosine triphosphate (ATP), which is the source of the genetic information essential for viral and human cell replication in the cells of the human body. Therefore, it is said that

Figure 1: Remdesivir is not a remedy for Ebola virus infection



Compared with 2 kinds of monoclonal antibody, remdesivir increases mortality by double from Ebola virus infection: This indicates that remdesivir is not a remedy for Ebola virus infection.

an incomplete viral RNA chain is formed and replication is stopped in the middle, which inhibits viral RNA synthesis. For details, please refer to the package insert [3] and our article on favipiravir (trade name: Avigan).

It works only if used before the onset of symptoms?

In an experiment on monkeys inoculated with lethal viruses such as Ebola virus [4] and Nipah virus [5], administration of a sufficient amount of remdesivir before symptom onset of the infectious disease reduced mortality (Supplementary slides 2 and 3).

In addition, in monkeys infected with infectious diseases, such as MERS virus [6], SARS virus [7] or SARS-CoV-2 [8], timely administration of a sufficient amount of remdesivir before symptom onset reduced viral load as well as symptoms. (No comparison was reported in mortality. Supplementary slides 4-6).

However, what is important in treating infectious diseases in humans is whether or not a drug can be used to alleviate symptoms or reduce mortality after some symptoms have appeared and the condition is expected to deteriorate.

However, in the animal experiment of remdesivir, there is no report on an experiment in which the substance was administered after symptom onset. With such an experiment, it is impossible to predict whether it will work for humans or not. Rather, we suspect that there is no report because it does not work if it is used after symptom onset.

Not an "Ebola remedy"

Remdesivir is often wrongly labeled as an "Ebola remedy," and even some infectious disease experts describe it as such. However, as a result of a randomized controlled trial [9] comparing remdesivir with 3 types of monoclonal antibodies, which was conducted when the epidemic occurred in the Republic of Congo, the mortality rate in remdesivir group (53.1%) was higher than that in any types of monoclonal antibody (33.5%, 35.1% and 49.7%). The odds ratio was more than 2-fold higher (2.10 and 2.25) with remdesivir as compared with 2 of them (p<0.001) (Figure 1) (Supplementary slides 7,8).

It can be said that it is a substance that was developed for the treatment of Ebola but has failed.

Clinical studies of remdesivir for COVID-19

To date, 4 clinical studies of remdesivir on COVID-19 were published as peer-reviewed papers [10-13]: two placebo-controlled randomized controlled trials (RCTs) [10,11], a case-series report of compassionate use [12] and the SIMPLE trial [13] which compares the use of remdesivir for 5 days with 10-day use. The Japanese package insert [3] quoted one [11] of the 2 published placebo-controlled RCTs, the case-series report [12] and the SIMPLE trial [13]. We do not discuss the case series in this article as it does not offer any useful information on the efficacy and safety of remdesivir. Let's take a look at the 3 RCTs [10,11,13].

Results of RCT conducted in China (Wuhan RCT) [10] (Supplementary slides 10-17)

(1) No efficacy on symptom improvement and mortality reduction in remdesivir group

This RCT [10] is a placebo-controlled multicentre trial at 10 hospitals in Hubei (mainly Wuhan), China independent of the manufacturer Gilead Sciences (Gilead). Laboratory confirmed COVID-19 patients, who had radiologically confirmed pneumonia with oxygen saturation 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mmHg or less, were enrolled and were assigned in a 2:1 ratio to intravenous remdesivir and intravenous placebo infusion. The time from symptom onset to enrollment was 12 days or less. The study began on February 6, and patients who enrolled by March 12 were followed. The study ended on April 10. In this study, 158 patients and 78 patients were allocated to remdesivir group and placebo group, respectively (One patient did not use any medication, and was excluded). The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status as follows:

1. Discharged or having discharge criteria
2. Not requiring oxygen therapy
3. Requiring oxygen therapy
4. Requiring high-flow oxygen or noninvasive ventilation
5. Requiring invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation)
6. Death

The most important endpoint according to our standard, "all-cause mortality (at day 28)" was 13.9% in the remdesivir group and 12.8% in the placebo group (**Figure 2**). As one of the baseline characteristics, the proportion of patients whose time from onset was over 10 days was significantly higher in the remdesivir group (54%) than in the placebo group (40%) (p=0.037). Therefore, depending on whether time from onset was 10 days or less or over 10 days, various effect indicators were compared. Let's take a look at all-cause mortality by the time from onset to enrollment (≤ 10 days or >10 days).

All-cause mortality in the remdesivir vs. placebo group was 11% vs. 15% (p=0.56) in patients whose time from onset was 10 days or less. In patients whose time from onset was over 10 days, it was 14% vs 10% (P=0.51), and no significant difference was observed. (**Figure 2**) (Supplementary slides 12,13).

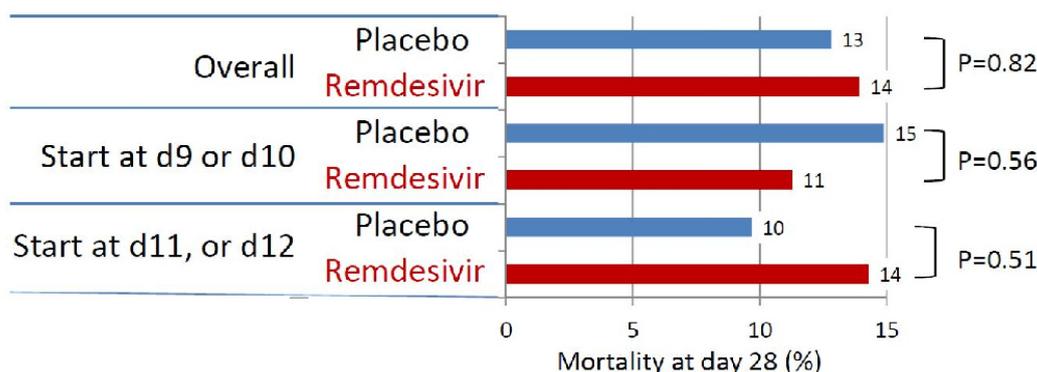
The primary endpoints "time to clinical improvement (2 levels or more improvement or live discharge) within 28 days after randomisation", was slightly shorter in remdesivir group, but difference was not significant (p=0.24). (Supplementary slides 14)

(2) Respiratory failure and rate of viral elimination contradict with tendency for symptom improvement

Remdesivir showed tendency to improve symptoms in both groups although the difference was not significant. However, it is not consistent with the rate of discontinuation due to severe respiratory adverse events and viral elimination.

Adverse events tended to occur more frequently in the remdesivir group with 11.6% than in the placebo group 5.1% in the placebo group (p=0.12). Especially, the number of patients who discontinued due to acute lung

Figure 2: All-cause mortality at day 28 by the time of commencement



injury/acute respiratory distress syndrome (ARDS) was higher in the remdesivir group (7 patients, 4.5%) than in the placebo group (1 patient, 1.3%) (p=0.20). Acute lung injury and ARDS are the most important conditions that indicate severe COVID-19. While symptoms, including respiratory symptoms, improved, more severe respiratory symptoms were observed as adverse events in the remdesivir group. We cannot explain such contradicting results. (Supplementary slides 15,16)

Moreover, since remdesivir is an antiviral agent, the virus should be eliminated faster in remdesivir group, but the opposite tendency was observed (though not a significant difference). In particular, the virus elimination rate in survivors was 80.4% in the remdesivir group, and 89.1% in the placebo group (8.7% higher) (p=0.16). This is another phenomenon which is difficult to explain. (Supplementary slides 17)

ACTT-1 study led by the National Institute of Allergy and Infectious Diseases (Supplementary slides 18-24)

(1) Information summarized in the package insert and abstract [11]

Results of the interim analysis of a placebo-controlled clinical trial (registration number: NCT04280705) led by the National Institute of Allergy and Infectious Diseases (NIAID) were published online in NEJM on [11]. The

outline of this study is summarized as follows [3,11]. (Supplementary slides 18)

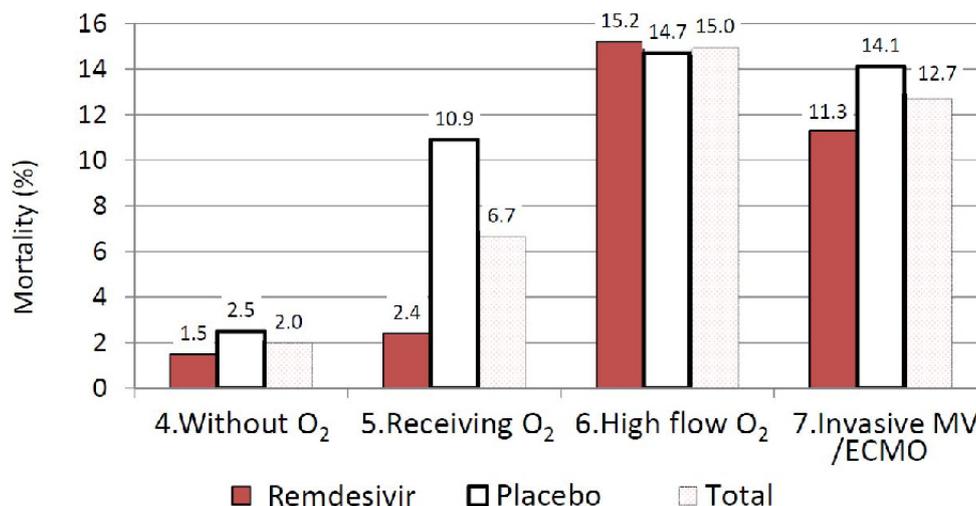
In a double-blind, randomised, placebo-controlled trial of in patients The primary was the time to recovery by day 28 post randomization. A preliminary analysis of the primary was performed when 1,063 patients were assigned to the remdesivir group (541) or the placebo group (522) at a ratio of 1:1 and 606 recovery cases were obtained. Total 538 patients in the remdesivir group and 521 in the placebo group were analyzed. As a result, the median time to recovery was 11 days in the remdesivir group and 15 days in the placebo group (rate ratio: 1.32, 95% confidence interval: 1.12-1.55, p<0.001). The death rate was 8.0% in the remdesivir-treated group and 11.6% in the placebo group (hazard ratio: 0.70, 95%CI:0.47-1.04, p=0.059).

(2) Critical appraisal of the interim analysis of the ACTT-1 study

The percentages of severity Level 7 (cases with invasive ventilator or ECMO) was 23% in the remdesivir group and 28% in the placebo group before the start of the study (p=0.059). The difference was nearly significant, but there was no other major difference in background factors. (Supplementary slides 19)

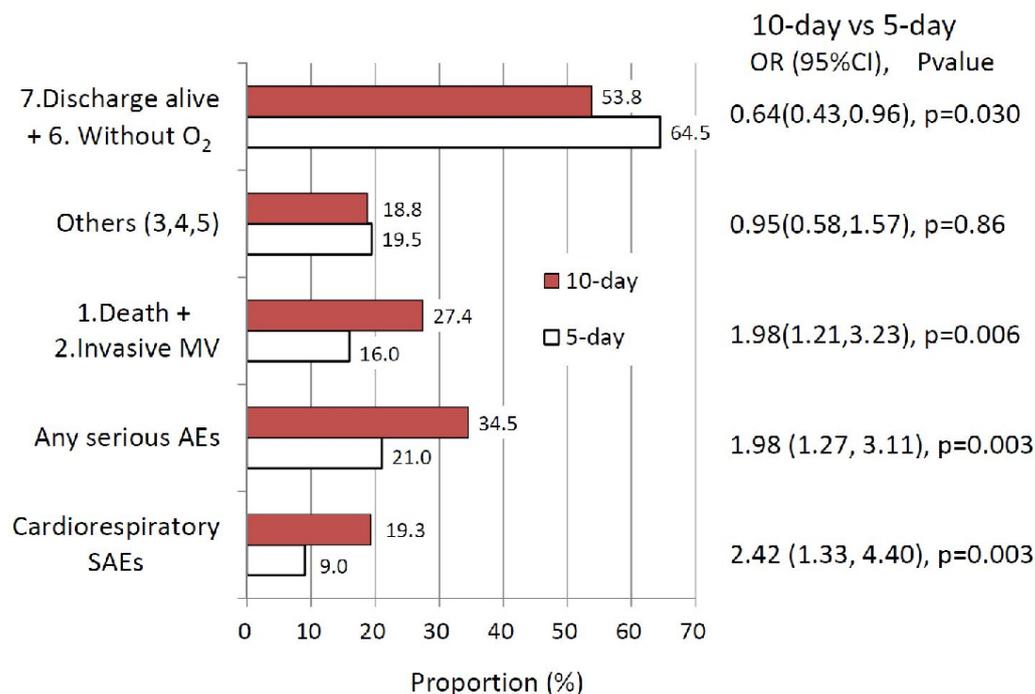
Comparing the improvement of clinical symptoms and

Figure 3: All-cause mortality at day 28 by the time of commencement



In all subgroups by baseline severity except level 5, mortality risk was not different between Remdesivir arm ■ and placebo group □. Only in the subgroup of level 5 (receiving O₂) mortality was extremely different. But in the subgroup of level 5, mortality of placebo group is unnaturally high (almost the same as those of the subgroups 6 or 7 with greater baseline severity) and mortality of remdesivir group is unnaturally low (almost the same as that of the subgroup 4). It is very hard to find appropriate reasons for that Remdesivir is effective only in the level 5.

Figure 4: Main results of SIMPLE trial



MV: mechanical ventilation or ECMO, AEs: Adverse events, SAE: Serious AEs. OR:odds ratio, 95% CI: 95% confidence interval
Cardiorespiratory SAEs include acute respiratory failure, respiratory failure, septic shock and acute respiratory distress syndrome.

overall survival rate by severity at the start of the study, no difference was observed in the subgroup of severity levels 4 (patients not receiving oxygen), 6 (receiving high flow oxygen or non-invasive mechanical ventilation) and 7 (receiving mechanical ventilation or ECMO). Only in level 5 (receiving oxygen), there was a difference (Figure 3). (Supplementary slides 20-23)

Mortality in Level 5 (2.4%) was almost similar to that of Level 4 (1.5%) in the remdesivir group, while mortality in Level 5 (10.9%) in the placebo group was similar to that of severer cases, Levels 6 (15.2%) and 7 (11.3%), and was extremely high (Figure 3). (Supplementary slides 21-23)

If remdesivir is effective in preventing aggravation of COVID-19, why was there a difference only in the mortality of Level 5 between the remdesivir group and placebo group? Why was the difference so marked only in the Level 5 subgroup? It is difficult to explain this phenomenon. However, as in cases of other severity levels, even if remdesivir is ineffective, this is possible when some kind of major bias is at work. The most likely bias we can think of is biased allocation of 421 Level 5 patients at the beginning within the Level 5 subgroup.

Unless details of baseline characteristics of the

Level 5 subgroup (222 patients in the remdesivir group and 199 patients in the placebo group) are available and it is confirmed that there is no difference in the baseline characteristics, the results of this study remains unreliable. The baseline characteristics include distribution of oxygen partial pressure or oxygen saturation, distribution of laboratory data related to severity, such as creatinine level and severity score such as APACHE II, MEDS, SAPS II or SOFA. (Supplementary slides 24)

APACHE II = Acute Physiology and Chronic Health Evaluation II

MEDS = Mortality in Emergency Department Sepsis Score

SAPS II = New Simplified Acute Physiology Score

SOFA = Sequential Organ Failure Assessment

SIMPLE Study: Five-day use is better than 10-day use (Supplementary slides 25-29)

The SIMPLE trial [13,14] only compares the use of remdesivir for 5 days (5-day group: 200 patients) with 10-day use (10-day group: 197 patients). The study does not include placebo or drug-free groups. In the peer-reviewed article [13], the authors reported "At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned

to the 5-day group ($P = 0.02$). By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group ($P = 0.14$). "

However, the total ratio of "death + invasive ventilator/ECMO" on day 14 was 16.0% vs. 27.4%, which is better in the 5-day group (unadjusted odds ratio 0.50, 95%CI: 0.31-0.82, $p=0.006$). The ratio of severely ill patients (high flow oxygen/ventilator/ECMO) at baseline was higher in the 10-day group (26.5% vs. 35.0%, odds ratio 0.67, $p=0.066$). Even if this is taken into consideration, we suspect that the conditions of patients in the 10-day group deteriorated. (Supplementary slides 27,28)

In addition, the ratio of mildly ill patients who were not on supplementary oxygen at the baseline was 17.0% vs. 10.7% ($p=0.07$), and not significant between the 2 groups. However, the ratio of patients who had recovered (survived and discharged or hospitalized without supplementary oxygen) was 70% vs. 58.9% (odds ratio 1.63, $p=0.02$), which was significantly lower in the 10-day group (Figure 4). (Supplementary slides 27,28)

It was reported in the NEJM that the adjusted risk of the median of time to recovery (probably hazard ratio) was 0.79 (95%CI: 0.61-1.01). P-value was not indicated, but the upper limit of 95% CI was 1.01, very close to 1.0, implying nearly significant difference.

Essentially, if a substance is effective, long-term use should yield better results than short-term use. However, in the SIMPLE study, the opposite dose-response relationship was confirmed.

Moreover, the number of serious adverse events in the 10-day group was about 2 times higher than in the 5-day group ($p=0.003$). Especially, the total number of serious adverse events related to respiratory failure (ARDS, acute respiratory failure, septic shock) was 2.4 times higher ($p=0.003$). (Figure 4) (Supplementary slides 28,29)

This result also contradicts with the results of the ACTT-1 study [11] and is consistent with the Wuhan RCT [10], which showed tendency that acute respiratory disorders occurred more frequently in the remdesivir group.

Wuhan RCT is not cited as a basis for approval

Despite that the approval was treated as a special case, examination for approval requires evidence. The approval was granted based on the 3 studies [11-13] cited in the above-mentioned package insert. The Wuhan RCT [10] was not included as an evidence for the examination.

In this regard, Yoshida, a chief of the Drug Administration Division, reportedly has commented as follows. "We are aware of the Lancet article [10], but the planned number of cases was not included (as the pandemic has ended) and the efficacy could not have been adequately assessed. It is also mentioned in the examination report (which is scheduled to be published)" [14].

The Wuhan RCT [10] is a placebo-controlled double-blind trial and is far more valuable than the other two trials [12, 13] cited in the package insert. Both Wuhan RCT and ACTT-1 [10,11] should be meta-analyzed, and based on the results of the analysis, the effectiveness should be assessed. However, if one of them is excluded, it is impossible to make fair assessment. We strongly suspect that the reviewers had already decided to "approve" before assessment, and used only the results that would support their decision.

Be careful of adverse reactions

As an adverse reaction, aggravation of renal dysfunction should be especially noted. It is stated in the package insert [3] that "renal dysfunction may be aggravated by the accumulation of additives in the renal tubules" and "non-clinical studies have shown that remdesivir has an effect on the renal tubules".

In addition to renal damage, liver damage, hypotension (lowered blood pressure), nausea, vomiting, sweating, tremor, various blood test values, blood chemistry test values, etc. are also listed. However, these can be the symptoms of COVID-19, and it is difficult to distinguish whether they are caused by aggravation of the disease or harm of remdesivir.

Conducting placebo-controlled trials would become increasingly difficult

An editorial of the British Medical Journal [15] states "A drug with potential—don't waste time on uncontrolled observations". Another British journal, the Nature [16]

also calls for "clinical trials must be as robustly designed as possible.... move quickly to larger, collaborative trials." They both emphasize the importance of placebo-controlled large-scale trials.

However, as explained at the beginning of this article, there is no animal experiment that showed reduction of mortality or symptom improvement if it were used by imitating the human clinical use: antivirals are commenced after the symptoms appeared. We suspect that appropriate animal studies have not been published because an experiment which had imitated human use may have shown the substance was ineffective. Moreover, in a large-scale trial which involved 6000 patients and was funded by the manufacturer (Gilead), there was no placebo group, or even a remdesivir-free control group. It is suspected that the manufacturer was afraid that if an appropriate trial was conducted, the substance would be proven ineffective.

Conclusion

Neither animal experiments with remdesivir-infected animals nor the clinical trials by the manufacturer were properly designed to prove efficacy and safety. Therefore, the possibility of demonstrating the efficacy and safety of the drug against COVID-19 seems extremely slim in the future.

Firstly, in an experiment with COVID-19 infected animals, in which remdesivir is administered after symptom onset, remdesivir must be proven to reduce death. Then, a placebo-controlled trial of appropriate scale should be conducted in humans under strict management to prove efficacy and safety. Unless these are realized, we should consider that remdesivir is ineffective, and thus it should not be used for the treatment of COVID-19.

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Favipiravir (trade name: Avigan Tablet)

Most probably no efficacy on COVID-19, and harmful

Translated and revised from Med Check(in Japanese) Jul 2020 ; 20 (90):80-82

Med Check Editorial Team

Summary

- Favipiravir (trade name: Avigan) was proven ineffective for treatment of seasonal influenza, but has been approved and stockpiled in Japan for almost unlikely novel influenza.
- Placebo-controlled trials of appropriate scale against novel coronavirus infection (COVID-19) have not been published in any country so far. In Japan, only an observational study has been conducted, with which efficacy cannot be evaluated. According to the very recent press release, no statistically significant improvement was observed in a Japanese small open trial comparing a favipiravir group with a standard care group for 6 days.
- In a Chinese open study which mainly involved non-severe cases and compared favipiravir with other drugs, the drug did not reduce the primary endpoint, "recovery at Day 7" nor mortality.
- The structure and action of favipiravir is very similar to those of an anticancer drug, 5-fluorouracil. In observational studies, the dose used in treating COVID-19 was 2 to 5 times higher than the no-observed-adverse-effect level (NOAEL) in animals, which is approximately half the toxic dose in mice or rats, or approximately the same dose in dogs when converted into blood exposure (Area under the curve). Moreover, for some people, it was estimated that blood level will reach lethal level in rats or dogs. Hence it is very dangerous.
- No experiments have been conducted on animals infected with SARS-CoV-2.

Conclusion: Most likely ineffective and harmful. Should not be used.

Keywords:

RCT, open label trial, lethal dose, toxic dose, NOAEL

Introduction

As of July 14, the Japanese government has not given approval for the use of favipiravir (trade name Avigan) in COVID-19, as the efficacy and safety have not been confirmed.

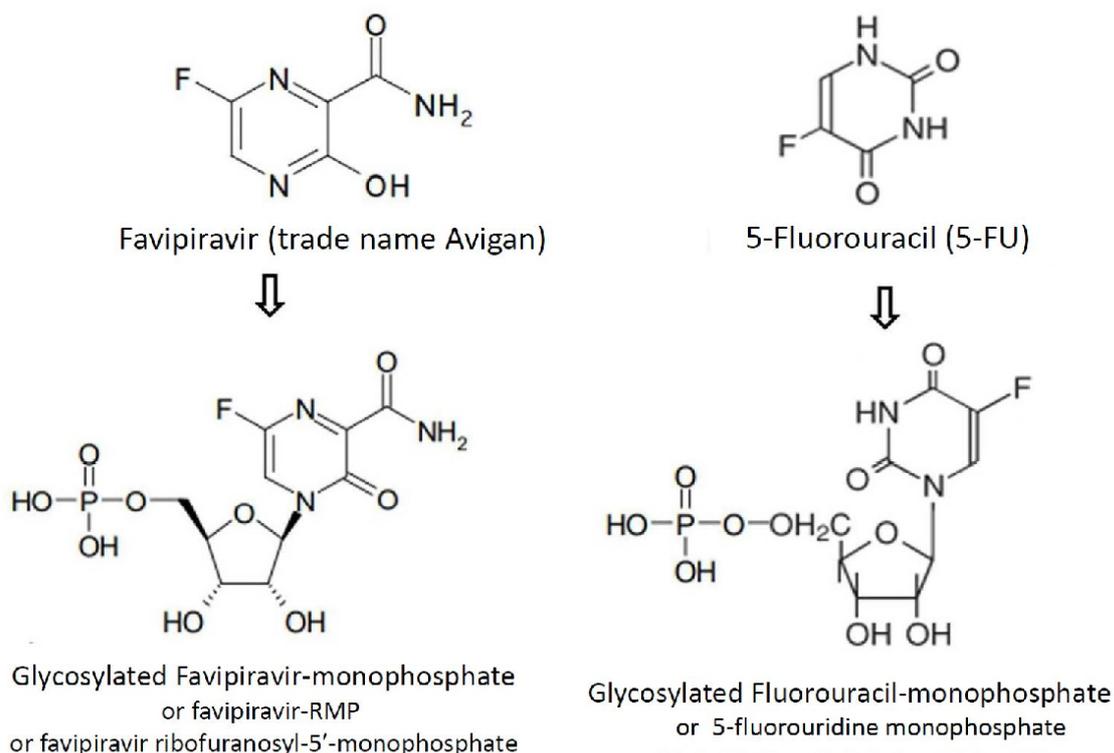
Avigan was developed for influenza, but was confirmed to be ineffective against seasonal influenza. However, it was approved only because it has a different mechanism of action from other anti-influenza virus agents [1]. Here we describe our analysis based on the data which we have as of now.

Avigan is an anticancer drug analog

The structure of Avigan is very similar to an anti-cancer drug, 5-fluorouracil (5-FU) (**Figure**), and its pharmacological action and toxicity are also similar. 5-FU is an analog of substances (uracil, adenine etc: generally termed as nucleobases) needed for the replication of RNA essential for protein synthesis and cell division, and is classified as an "antimetabolite".

Avigan and remdesivir (page 39) are called "RNA-dependent RNA polymerase inhibitors". They are also antimetabolites because they are analog of uracil, guanine (favipiravir) or adenine (remdesivir), which are the sources of RNA, and interfere with RNA synthesis

Figure : Similarity of favipiravir and anti-cancer agent 5-FU



(metabolism) just like 5-FU.

Influenza virus and coronavirus are viruses that have only RNA in their genes. Avigan and remdesivir interfere with the replication of viral RNA. Just like 5-FU inhibits not only RNA synthesis in cancer cells but also RNA replication in normal human cells, Avigan damages normal cells as well.

In addition, as these antiviral agents stop normal RNA replication in the middle, they could prevent viral load increase temporarily. However, it has no efficacy to eliminate the virus from infected cells. Therefore, it can be easily inferred that they have only limited therapeutic effect, such as that they are not effective at small dose.

Clinical dose is a toxic dose, which is lethal in some people

We examined the Summary Basis of Approval (SBA) of Avigan for the approval as an anti-influenza virus agent [2].

In a 1-month study in rats, 1 out of 15 males died at 200 mg/kg due to decreased bone marrow hematopoiesis and circulatory disorders such as, pulmonary edema (congestion and edema of the lung). Moreover, 80 mg/kg is the toxic dose that causes

decrease in hematopoietic ability, and the exposure (AUC_{0-t}) for Avigan at this dose was 1490 $\mu\text{g}\cdot\text{h/mL}$ (average of both sexes). When administered twice a day, AUC_{0-t} is roughly equivalent to AUC_{0-12} (half-day exposure). At the average dose in the observational study (3600 mg on the first day, 800 mg twice a day after the second day, used for 10.4 days in total) [3], the half-day exposure at Day 6 is estimated to be 739, almost half of the toxic exposure in rats. Decreased hematopoiesis is toxicity unique to anti-cancer drugs, and myelosuppression reduces the number of white blood cells, making infections more likely. The lethal exposure of 200 mg/kg in rats (male 3430 $\mu\text{g}\cdot\text{h/mL}$) is only 5 times higher than the clinical exposure.

In general, the blood concentration of a drug varies greatly from person to person, and it can be 5 to 10 times higher than the mean concentration in some people. This means that in some people, the clinical dose might reach the lethal dose of animals. In fact, in a patient with slow metabolism of Avigan, and extremely high blood concentration, after administration of 1600 mg on the first day and 400 mg twice a day after the second day, AUC_{0-12} reached 1743 $\mu\text{g}\cdot\text{h/mL}$. If this patient uses the dose for COVID-19, the AUC would reach 3486 $\mu\text{g}\cdot\text{h/mL}$ and be estimated to exceed the

Table 1 : Estimation of half-day human exposure (AUC₀₋₁₂) of unchanged Avigan when it is used for COVID-19 at day 6 when the level may be steady state.

Disease	Influenza			COVID-19		
	Dose (mg) /day	AUC _∞ (μg·h/mL) or AUC _τ (μg·h/mL) (measured)	AUC ₀₋₁₂ (measured)	Dose (mg) /day	AUC _∞ (μg·h/mL) or AUC _τ (μg·h/mL) (estimated)	AUC ₀₋₁₂ (estimated)
Day 1 AUC _∞ (μg · h/mL)	3200 *a	446.09 *a	446	3600 *b	502	1004
Day6 AUC _τ (μg · h/mL) *e	1200 *a	553.98 *a	554	1600 *b	738 .64 *c	739 *d
AUC ₀₋₁₂ (μg·h/mL) of extreme person (JP111) *f	D1 1200mg+400mg、D2-d5:400mg × 2/d	1743 *f (measured)		D1 1800mg × 2、D2-d9.4:800mg × 2/d		3486 *g (estimated)

*a: from the package insert of Avigan for influenza.

*b: Interim report of observational study of favipiravir for COVID-19

http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_0526.pdf

*c: 738.64=553.98 × 1600/1200, *d: 739 ≈ 738.64(*c)

*e: Note : τ = dosing interval . AUC τ ≈ AUC₀₋₁₂ as Avigan was given twice a day in animal toxicity tests.

*f: 1743 μg · h/mL is the measured data of a person among 6 healthy males in JP111 trial inSBA

*g: 3486=1743 × 800/400. If combined with the data of 8 healthy persons, these data show that one in 14 person reached extremely high concentration equivalent to the lethal dose for rats as shown in the Table 2.

Table 2 : Prediction of toxicity risk in humans from the toxicokinetic data of favipiravir

		Mice 2 weeks		Rats 1 month		Dogs 1 month		8 w-old dogs, 1M (2-11 y for humans)
		male	female	male	female	male	female	
Dose of favipiravir in animals mg/kg(HED:mg/kg) *a	NOAEL mg/kg, (HED)		100, (8)	32, (5.2)	32, (5.2)	10, (5.6)	10, (5.6)	30, (11)
	Toxic dose mg/kg, (HED)		300, (24)	80, (13)	80, (13)	30, (17)	30, (17)	60, (21)
	Lethal dose mg/kg, (HED)	1000, (81)	1000, (81)	200, (32)	200, (32)	150, (83)	150, (83)	60, (21)
Unmetabolized favipiravir Animals, AUC ₀₋₁₂ ÷ AUC ₁₂ (μg·h/mL)	NOAEL (μg·h/mL)		439	365	550	173	147	505
	Toxic dose (μg·h/mL)		1712	1190	1790	694	623	1285
	Lethal dose (μg·h/mL)	4654	9320	3430	4200	3836		1285
Unmetabolized favipiravir human AUC ₁₂ (μg·h/mL)	Dose for influenza	554	D1: 1600mg×2(53mg/kg)、d2~d5 600mg×2 (20mg/kg), AUC at d6 (measured)					
	Dose for COVID-19	739	D1: 1800mg×2(60mg/kg)、d2~d5 800mg×2(27mg/kg), AUC at d6 (estimated)					
	As above (extreme case)	3486	D1: 1800mg × 2(60mg/kg)、d2~d5 800mg × 2(27mg/kg), AUC at d6 (estimated)					
Ratio of AUC for COVID-19 to animal AUC *b	1. To NOAEL AUC		1.7	2.0	1.3	4.3	5.0	1.5
	2. To toxic dose AUC		0.4	0.6	0.4	1.1	1.2	0.6
	3. To lethal dose AUC	0.2	0.1	0.2	0.2	0.2	0.2	0.6
Ratio of AUC of extreme person to animal AUC *c	1. To NOAEL AUC		7.9	9.6	6.3	20.2	23.7	6.9
	2. To toxic dose AUC		2.0	2.9	1.9	5.0	5.6	2.7
	3. To lethal dose AUC	0.7	0.4	1.0	0.9	0.9	0.9	2.7

*a : HED: Human Equivalent dose. To convert animal dose (mg/kg) to HED for a person weighing 60 kg, divide the animal dose (mg/kg) by the conversion factors for mouse, rat and dog (12.3, 6.2 and 1.8) respectively.

*b*c: Ratio of the human half-day exposure (estimated value = 739*b, 3486*c) to the animal half-day exposure for NOAEL, toxic dose, and lethal dose of each animal. For example, ratio of exposure of extreme person was 1.0 times. It was calculated by 3486 (extreme person's AUC)/3430 (AUC of rats' lethal dose).

lethal AUC of the male rats (3430 μg · h/mL) (Table 1, 2).

In a 1-month dog study, some dogs in the 300 mg/kg group were moribund in one week, and the dose was reduced to 100 mg/kg, but later 2 out of 5 died (average 150 mg/kg, AUC = 3836 μg · h/mL). Pathologically, hemorrhagic necrosis of the lungs, inflammation, and

bacterial infection are observed. The lethal dose in dogs is almost the same as the AUC of some patients who tend to have extremely high blood concentration (AUC: 3486 μg · h/mL). At 30 mg/kg (AUC=659 μg · h/mL), which is below the clinical dose, signs of decreased hematopoiesis (reticulocyte count) was already observed.

In an experiment with juvenile dogs (8 weeks old, equivalent to 2-11 years old in humans), 9 out of 12 dogs died after administration of favipiravir at 60 mg/kg for one month. AUC was 1285 $\mu\text{g}\cdot\text{h}/\text{mL}$, which was 60% of the average exposure in humans and much lower than that of people with extremely high blood contraction. The causes of death are pneumonia, thrombosis in the lungs and liver, pulmonary infarction, and degeneration/necrosis of the cardiac papillary muscles.

It has been reported that COVID-19 causes not only pneumonia but also thrombosis in various parts of the body. If pneumonia and/or thrombosis occur while using Avigan, it would be impossible to distinguish whether they are caused by the virus or are adverse reactions to the drug.

In addition, 30 mg/kg is considered to be a non-toxic level in 8-week-old dogs, but when the dose is doubled to 60 mg/kg, most of the dogs died. This suggests that the drug is a dangerous substance with a very narrow safety margin. (See **Table 2** for details).

Teratogenic effect of Avigan is well known and is, of course, a serious harm. However, as mentioned above the fact that the toxic and lethal doses are used in treating COVID-19 in humans is more important point in considering whether it is appropriate to use the drug in humans. It should also be noted that no experiment has confirmed that Avigan improves the symptoms in animals infected with SARS-CoV-2.

No evidence of efficacy against COVID-19

Currently, 3 comparative trials of Avigan for COVID-19 have been published [4-6]. Two of them are non-blinded, and the remaining one is the only placebo-controlled blind trial, but is a small-scale trial with less than 10 patients in each group. Therefore, it is impossible to assess the efficacy and safety of Avigan with these 3 trials. On July 10 2020, researchers of a small open label trial on asymptomatic or mildly ill patients with COVID-19 [7] issued a press release on their results which did not show any significant efficacy [8].

(1) Report on comparison with an anti-HIV agent:

This is an open-label, nonrandomised, before-after controlled study comparing an anti-HIV agent (lopinavir/ritonavir, trade name Kaletra) which was given to 45 patients at first (before group) and favipiravir (Avigan)

which was then given to 35 patients (after group). The improvement rate at Day 14 showed remarkable difference: 62% in the Kaletra group and 91% in the Avigan group. However, the patients in the Avigan group was younger (43 years old vs. 49 years old), had less fever (63% vs. 82%, $p=0.11$) and had more lymphocyte counts (1.5 vs. $1.2 \times 10^9/\text{L}$, $p=0.06$), suggesting favorable background in the Avigan group. Therefore, it may be hard to conclude that the improvement observed was the effect of Avigan.

(2) Comparison with other antiviral agents [5]:

The second report is a published un-reviewed paper in medRxiv. It is a randomised controlled trial using anti-influenza virus drug (umifenovir: brand name Arbidol) as a control.

The primary endpoint, "improvement at Day 7" was 61% in the Avigan group compared with 52% in the control group, which was not a significant difference ($p=0.14$). This study reported that since the number of severely ill patients was higher in the Avigan group, if they are excluded and only moderately ill patients were compared, significantly higher rate of improvement was observed in the Avigan group. In addition, relief of fever and cough, which were secondary endpoints, were significantly faster in the Avigan group (both $p<0.0001$). There was no death in either group. The proportion of patients with elevated uric acid level was significantly higher in the Avigan group (14% vs. 2.5%, $p=0.001$).

If the above two trials were meta-analyzed, ignoring the background, there was no significant difference in the effect ($p=0.17$). Moreover, there were more young patients in the Avigan group, and the difference was nearly significant ($p=0.065$).

(3) Placebo-controlled small-scale study [6]:

The third is an open label trial without peer-review in which Avigan (9 patients) was compared with an anti-influenza virus agent baloxavir (Xofluza:10 patients) and placebo (10 patients). The percentages of patients who turned viral negative after 14-day treatment were 77%, 70%, and 100% in the favipiravir, baloxavir, and control group respectively. The effect on improving symptoms was not observed: the medians of time from randomization to clinical improvement was 14, 14 and 15 days, respectively.

(4) An open label comparative trial done in Japan [7]:

This is a multicenter, open-label, randomized trial of favipiravir in asymptomatic and minimally symptomatic patients infected with SARS-CoV-2 to evaluate viral load reduction. They compared immediate favipiravir arm with delayed arm. Favipiravir was commenced on day 1 for immediate arm (n=36) and on day 6 for delayed arm (n=33) [7]. According to the press release [8], the primary outcome, the percentages of patients who turned viral negative after 6 days (before the start of delayed arm) were 66.7% in immediate arm and 56.1 % in the delayed arm: adjusted odds ratio was 1.42 (95% CI:0.76-2.26, p=0.269). Even if efficacy of viral reduction in asymptomatic and minimally symptomatic patients infected with SARS-CoV-2 were proved, it cannot be said that favipiravir is useful for the treatment of COVID-19, because of the toxicity of favipiravir described in this article.

No placebo-controlled trials designed for COVID-19

In Japan, there is no plan to conduct a placebo-controlled trial aiming at full-scale approval as of July 2020. Only 2 observational studies in which Avigan is used for all patients and 2 trials with un-blinded treatment group as a control are designed were registered. One is a trial funded by a manufacturer (Fujifilm Toyama Chemical) (96 cases), and the other is the one described above.

Globally, there are 2 placebo-controlled Phase III trials (256 cases and 100 cases each) and 2 placebo-controlled Phase II trials are planned, but enrolment has not been carried out yet according to the Clinical trial.gov.

Conclusion

The clinical dose of Avigan is the dose at which toxicity, including death for some people, was observed in animals, and the toxic symptoms are similar to those of COVID-19. It is extremely difficult to distinguish whether they are symptoms of the disease or toxic signs of the drug. There is no experiment using Avigan on SARS-CoV-2 infected animals. In Japan, even the manufacturer has no plan to conduct a placebo-controlled trial.

It should be confirmed in an animal study that the drug reduces mortality in infected animals after symptom onset. Then, a placebo-controlled study of an appropriate scale should be conducted in humans under strict management to prove safety and efficacy. Until

then, it should be considered that Avigan is "ineffective" and should not be used.

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