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Mr. Katsunobu Kato, Minister of Health, Labour and Welfare

Opinion on Avigan (regarding COVID-19)

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Purpose of the request

We request that the following be done with caution: the use of Avigan (generic name: favipiravir) for the treatment of COVID-19 outside clinical trials (off-label use conducted as "observational studies") and the handling of applications for approval when submitted.

Reasons for the request

1 INTRODUCTION - EXCESSIVE EXPECTATIONS FOR AVIGAN, WHICH WAS APPROVED IN A HIGHLY UNUSUAL PROCEDURE

The Avigan Tablet 200mg (generic name: favipiravir) is an anti-influenza drug manufactured by Toyama Chemical Co., Ltd. (currently FUJIFILM Toyama Chemical Co., Ltd.). It was approved in March 2014[1].

However, this happened through highly unusual procedures as follows.

Avigan was submitted for the treatment of seasonal influenza. But not only did it fail to show non-inferiority compared to Tamiflu, it also failed to demonstrate robust

efficacy compared to a placebo[2].

Nevertheless, it was approved under the following very exceptional conditions of approval: “Avigan will be considered for administration to patients only in the event of an outbreak of a new or reemerging influenza virus infection for which other anti-influenza virus drugs are ineffective or insufficiently effective, and the government determines that it should be used to counter the influenza virus in question. Strict distribution control and adequate safety measures shall be implemented to prevent its use for the treatment of ordinary influenza virus infections[3].”

During deliberations by a health ministry advisory panel, the Pharmaceuticals and Medical Devices Agency (PMDA), which was in charge of the review, explained that Avigan was a "drug to prepare for the spread of highly pathogenic influenza virus infections that are resistant to existing anti-influenza virus drugs" such as Tamiflu. However, a number of panel members pointed out that it was unclear why the drug was effective against highly pathogenic influenza virus infections. The PMDA responded by saying, "The part you pointed out has not yet been clarified," so under normal circumstances, approval would not have been possible. However, the chairman of the panel pushed for approval by saying such things as, "I was thinking of suspending its approval, but I don't know how long I should suspend it for before the data come out" and "It is not for general distribution." [4]

Now, Avigan is being hyped as a potential treatment for COVID-19, and we are very concerned about this situation.

Our reasons are as follows.

2 EFFICACY

2.1 Clinical trials

To date, as far as we are aware, the only randomized controlled clinical trial that has investigated Avigan's efficacy against COVID-19, and whose results have been published, is a comparative study between Avigan and Arbidol (an anti-influenza drug used in China and Russia) at Wuhan University Hospital in China[6]. This was an open-label, randomized, controlled clinical trial (non-double blind). Though the secondary endpoint of duration of fever and cough was slightly reduced with a significant difference, the primary endpoint of clinical recovery rate on day seven was not significantly different.

Another non-randomized but comparative clinical trial that has been published is a study comparing Avigan with Lopinavir/Ritonavir (an anti-HIV drug) at the Third People's Hospital in Shenzhen, China[7]. However, this trial compared two groups whose timing of admission and administration differed. They were not randomized or double-blind trials.

On the other hand, comparative clinical trials for COVID-19 in Japan have just started and not yielded any results. Included are a single-blind, randomized, multicenter, comparative study (JapicCTI-205238, expected duration of study: March 31, 2020-June 30, 2020) by Fujifilm Toyama Chemical, the manufacturer and distributor of Avigan[8], to demonstrate that the treatment effects of adding Avigan to the standard treatment for pneumonia exceeds that without Avigan in patients with COVID-19 non-severe pneumonia, and an open-label, multicenter, randomized clinical trial (non double-blind trial) to evaluate viral load reduction in asymptomatic and minimally symptomatic patients. This trial was supported by the Japan Agency for Medical Research and Development (AMED) and led by Fujita Health University (CRB180003, specified clinical research, date of first enrollment March 20, 2020)[9].

At this point, Avigan's efficacy against COVID-19 remains unclear.

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 dated April 11, 2020, do not include Avigan among the treatment candidates[10].

2.2 Modality of efficacy evaluation

In principle, a drug's proof of efficacy should be based on the confirmation of statistically significant differences through randomized controlled clinical trials with appropriate endpoints.

Avigan originally drew attention as a potential drug for the treatment of COVID-19 because it is said to selectively inhibit viral RNA polymerase to prevent viral replication. It was expected that the drug may also be applicable to SARS-CoV-2, which has the same RNA virus as the influenza virus. However, its robust efficacy against seasonal influenza, that should have been obtained by its mechanism of action, was not observed (i.e., no clinical effects were observed in humans, although the viral load was decreased)[11]. Thus, the clinical efficacy against COVID-19 may be similar.

In the case of COVID-19, it is said that 80% of cases pass with a mild illness or no symptoms, and many people recover spontaneously[12]. Therefore, even if the patient is cured, proof by the principle method of confirming statistical significance in a randomized controlled clinical trial is still necessary to determine that the cure is not spontaneous and is, instead, due to the effect of Avigan.

There have been reports of celebrities being cured after taking Avigan, as if this were an effect of the drug, and reports of comments by experts that fuel excessive expectations based on cases of cures after administration of the drug. However, cases of symptomatic relief after treatment with Avigan do not mean that the drug can be considered effective against COVID-19.

The Ministry of Health, Labor and Welfare (MHLW), in an administrative notice issued on March 23 and April 2, 2020, stated that "MHLW is currently verifying the existing antiviral drugs against COVID-19 by providing financial assistance such as Health and Labour Sciences Research Grants to several research teams[13]" as if the ongoing observational studies can verify Avigan's efficacy against COVID-19. However, the primary role of observational studies is to capture new truths through diligent observation and analysis of individual cases. In the face of new, emerging infectious diseases, it is extremely important to conduct case reports and observational studies to understand the pathogenesis and find appropriate treatments. Observational studies are of the utmost importance, but the accumulation of cases in such studies cannot be used to verify the efficacy of drugs.

In the case of COVID-19, where the number of patients increases with the spread of infection and outcomes can be assessed within a few weeks, efficacy should be clarified in clinical trials, as appropriate randomized controlled clinical trials can be conducted rapidly[14,15].

3 SAFETY

3.1 Side effects such as strong teratogenicity

Concerning Avigan's safety, the following side effects, including strong teratogenicity, were identified through the review at the time of approval[16,17,18,19,20].

3.1.1 Fetal toxicity, teratogenicity

In animal studies, early embryonic lethality (rats) and teratogenicity (monkeys, mice, rats, and rabbits) were observed even at doses similar to or lower than

clinical exposure.

In addition, it has been confirmed that the drug is transferred to semen, and its metabolites are transferred to breast milk.

Therefore, in its warning section, the package insert states that a pregnancy test is mandatory, that contraception is also required for male patients during the administration period and for seven days after the end of administration, and that administration based on written consent is requested for both male and female patients[21].

However, even during clinical studies of the drug, which were supposed to have been strictly controlled, seven pregnancies were observed within 90 days after the end of the study treatment. This indicates that it is difficult to avoid pregnancy in practice. The review report also points out the difficulty of carrying out a pregnancy test before Avigan is prescribed and the fact that influenza patients would be so exhausted that they may not be able to accurately understand the content of the informed consent form. It states "Especially, given the fact that pregnancy occurred even in clinical studies, it is impossible to completely prevent cases in which pregnancy is recognized or occurs after use of favipiravir. Therefore, PMDA has concluded that the teratogenicity risk is a highly significant safety concern of favipiravir at present.[22]"

3.1.2 Other side effects observed in animal experiments

In a one-month oral dose study in juvenile dogs, the following was observed: death during treatment, lung changes, atrophy or regression of lymphoid tissue, hemorrhagic necrosis of hepatocytes, systemic oedema or vascular dilation, degeneration/necrosis or mineralization of papillary muscle in the heart, and the degeneration of skeletal muscle fiber.

In a one-month oral dose study in juvenile rats, the following was observed: abnormal gait, increased CK, histopathological changes in the testis, degeneration and coagulation necrosis of hepatocytes, and atrophy and vacuolization of the skeletal muscle fiber.

In a study of cynomolgus monkeys infected with highly pathogenic avian influenza, in both the favipiravir high-dose group and the low-dose group, one of three animals respectively, a total of two, died. No deaths occurred in the control

group.

3.1.3 Significant potential risks described in the risk management plan

The risk management plan for Avigan lists the following: gout attacks due to increased blood uric acid, shock, anaphylaxis, pneumonia, fulminant hepatitis, hepatic dysfunction, jaundice, toxic epidermal necrolysis, cutaneous mucosal eye syndrome, acute kidney injury, leukopenia, neutropenia, thrombocytopenia, neuropsychiatric symptoms (disturbance of consciousness, abnormal behavior, delirium, hallucination, delusion, convulsion, etc.), and hemorrhagic colitis[23].

3.2 Unknown side effects

It is sometimes said that since Avigan is a previously approved drug, it has an advantage over newly-developed drugs because its side effects are better known.

However, as mentioned above, it was approved through an unusual procedure for stockpiling. Even though it is an approved drug, it has never been distributed commercially and has only been used on a limited number of subjects in clinical trials. Therefore, when it is marketed and used by a large number of people, unknown side effects may occur in addition to the known ones.

Also, of the clinical studies that were conducted at the time of Avigan's approval as an anti-influenza agent and those that were additionally submitted, all studies with relatively large numbers of subjects (500 or more) (US213, US204, 312, US316, and US317) only had five-day repeated doses. However, when used as a treatment for COVID-19, repeated doses for 10 to 14 days are planned[24,25,26]. The total dose and duration of administration will be more than doubled, which may lead to stronger side effects.

4 USE OTHER THAN IN CLINICAL TRIALS (OFF-LABEL USE AS "OBSERVATIONAL STUDIES")

Prime Minister Abe referred to Avigan at a press conference after the declaration of a state of emergency following the spread of COVID-19 on April 7, 2020. He said that the drug's use will be expanded as much as possible to patients who wish to use it within the framework of "observational study."[27]

The framework is designed to accumulate cases of "off-label" use of the drug for

therapeutic purposes at each medical institution. By participating in the study, patients will be able to receive the drug free of charge. Essentially, however, such use is ethically permitted only when there are multiple lines of evidence supporting efficacy and safety, and when sufficient informed consent has been obtained.

However, as mentioned above, the drug has been shown to have strong fetal toxicity and teratogenicity, and there is currently little information to suggest that it is effective against COVID-19.

The guide on COVID-19 pharmacotherapies issued by the Japanese Association for Infectious Diseases states that the timing for initiating antivirals should be based on the requirement that "the patient has developed hypoxemia and requires oxygen administration[28]".

However, there is a concern that various experimental clinical uses, such as early administration and the concomitant use of multiple drugs, will spread and that serious side effects may occur if information is not shared sufficiently. There is another concern that excessive expectations lacking scientific evidence may lead to strong requests for administration by patients who lack the necessary conditions in the medical field.

As mentioned above, observational studies of new infectious diseases are important, but the primary role of such studies is to capture new truths through careful observation and analysis of each case. Widespread expansion of the use of drugs with poor scientific evidence in the name of "observational studies" will, in fact, undermine the interests of patients.

For off-label use of the drug, which is being conducted as an observational study, it is necessary to provide thorough information in writing , and obtain consent with a full understanding of the following: that Avigan's efficacy against COVID-19 has not been confirmed, that there are side effects such as strong teratogenicity, that it was approved for stockpiling in an unusual procedure without efficacy and safety confirmation as an anti-influenza virus drug, and has had little use in clinical settings. However, there are concerns about whether it's possible to establish an environment in which calm, informed consent can be obtained amidst the excessive expectations for the drug.

It is necessary to return to ethical principles and take prudent measures.

5 SUMMARY

At the aforementioned press conference, Prime Minister Abe stated that the stockpile of Avigan will be tripled to two million people[29].

It has been reported that there is a tight situation in the medical field for the treatment of COVID-19. Therefore, expectations for the development of therapeutic drugs are fully understandable. However, as the disease often progresses asymptomatically or mildly rather than severely, we should not overlook the potential harm that may occur if Avigan, which has strong teratogenic and other side effects, is used in patients with mild symptoms or administered prophylactically under excessive expectations without sufficient confirmation of its efficacy.

In light of the above, we urge caution in the use of this product outside clinical trials (off-label use conducted as "observational studies") or in dealing with applications for approval of the drug when filed.

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[1] Information on Avigan Tablets (FUJIFILM Toyama Chemical Co., Ltd.)
http://fftc.fujifilm.co.jp/med/abigan/index.html

[2] Review Report (March 4, 2014)
https://www.pmda.go.jp/files/000210319.pdf

[3] Pharmaceutical interview form (April, 2019 (4th edition)
http://fftc.fujifilm.co.jp/med/abigan/pack/pdf/abigan_if_01.pdf

[4] Minutes of the Meeting of the Pharmaceutical Affairs and Food Sanitation Council, Pharmaceutical Division 2 (February 3, 2014)
https://www.mhlw.go.jp/stf/shingi/0000056624.html

[5] Minutes of the Meeting of the Pharmaceutical Affairs and Food Sanitation Council, Pharmaceutical Division 2 (March 3, 2017)
https://www.mhlw.go.jp/stf/shingi2/0000168147.html

[6] Chang Chen, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial.
https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4

[7] Q. Cai, M. Yang, D. Liu et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering.
https://doi.org/10.1016/j.eng.2020.03.007

[8] Clinical trial by Fujifilm Toyama Chemical

https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-205238

[9] AMED research led by Fujita Health University
https://rctportal.niph.go.jp/s/detail/jr?trial_id=jRCTs041190120

[10] Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Version 1.0.4
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

[11] Ibid., 2.

[12] China CDC Weekly 2020, 2(8): 113-122: Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020
http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51?from=timeline&isappinstalled=0

[13] Request for cooperation with the Ministry of Health, Labour and Welfare Scientific Research Group on Covid-19 (Ministry of Health, Labour and Welfare, Headquarters for the Promotion of Countermeasures to Covid-19, March 23 and April 2, 2020)
https://www.mhlw.go.jp/content/000617744.pdf
https://www.mhlw.go.jp/content/000618587.pdf

[14] Benjamin N, et al. Drug Evaluation during the Covid-19 Pandemic,April 14, 2020 DOI: 10.1056/NEJMp2009457
https://www.nejm.org/doi/full/10.1056/NEJMp2009457

[15] Ivry Zagury-Orly et al. Covid-19 — A Reminder to Reason, April 28, 2020,DOI: 10.1056/NEJMp2009405
https://www.nejm.org/doi/full/10.1056/NEJMp2009405?query=featured_home

[16] Ibid., 2.

[17] Ibid., 3.

[18] Ibid., 4.

[19] Teratogenicity in Non-clinical Trials Explanatory Material (for healthcare professionals) "Teratogenicity Potential of Avigan Tablets"
http://fftc.fujifilm.co.jp/med/abigan/pack/pdf/abigan_description_01.pdf

[20] Drug Risk Management Plan for Avigan Tablet 200mg
http://fftc.fujifilm.co.jp/med/abigan/pack/pdf/abigan_rmp_01.pdf

[21] Package Insert
http://fftc.fujifilm.co.jp/med/abigan/pack/pdf/abigan_package_01.pdf

[22] Ibid., 2.

[23] Ibid., 20.

[24] Japanese Association for Infectious Diseases: "Approach to Treatment with Antiviral Drugs for COVID-19 (1st Edition)"
http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_antiviral_drug_200227.pdf

< Postscript on May 4, 2020 >
The first edition was revised and the second edition was published on May 1.
Japanese Association for Infectious Diseases: "Approach to Treatment with Antiviral Drugs for COVID-19 (2nd Edition)"
http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_drug_200430.pdf

[25] Ibid., 8.

[26] Ibid., 9.

[27] Prime Minister Abe's Press Conference on Covid-19 (April 7, 2020)
https://www.kantei.go.jp/jp/98_abe/statement/2020/0407kaiken.html

[28] Ibid., 24.

[29] Ibid., 27.

The above was viewed between April 25 and 30, 2020.