



The Journey of Clinical Manifestation Covid-19 After Favipiravir Treatment

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Abstract. The Clinical Manifestation Journey of Covid-19 is unpredictable, even after antiviral treatment. Favipiravir is one of the promising antivirals that is expected to stop the development of the disease so that it can eliminate the clinical symptoms of Covid-19. The question is to what extent the drug Favipiravir can do it, therefore this article's objective was to identify the clinical manifestation after Favipiravir treatment at Covid-19 subjects in 3 location studies in Indonesia. This study was a part of the main study related to the clinical trial of the efficacy and safety of Favipiravir for Subjects with moderate Covid-19. The study was conducted 2 times in 2020 and 2021 in 3 main hospitals with Covid-19 patients who came and were hospitalized as a population study. Age > 18 – 59 years old, with Covid-19 confirmation by PCR, voluntary and signed informed consent were inclusion criteria with pregnant women, and lactation and allergy were exclusion criteria. Favipiravir was given a maximum at day 14 plus another standard of care. A total of 66 cases were recruited in this study on day 1 but the number of samples continues to decrease as they are discharged from the hospital, with reduce 15,2% on day 7 and 57.6% on day 14. The result on Day 1 before taking Favipiravir showed 30% cases of fever, 75.8% cough, 10.7% cough, 22.7% sore throat, 45.5% fatigue, 45.5 headaches, 45.5% breathless, 4.5% diarrhea. The result at day 7 were 1.5%, 37.9%, 3.0%, 1.5%, 10.6%, 6.1%, 12.1%, 15.2%, sequentially. And the result at day 14 were 1.5%, 16.7%, 0%, 0,3%, 1.5%, 6.1%, 0%, sequentially. The conclusion of the study was the changes in the clinical manifestations of Covid-19 remain unpredictable after the administration of the drug Favipiravir. In the future, an antiviral that can quickly eliminate the Covid-19 virus is needed so that clinical symptoms can be suppressed and make patients calm in dealing with them.

Keywords: Covid-19 · Clinical Manifestation · Treatment · Favipiravir

1 Introduction

The Clinical Manifestation Journey of Covid-19 caused by SARS-CoV2 is unpredictable, even after being treated with any recommended drug including antiviral treatment. There is no drug of choice for Covid-19 but drug initiation is expected to eliminate the pathogen and help the body to balance its immune response or control the host

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metabolism reaction, then the clinical manifestation related disease will decrease or stop [1]. In Covid-19 cases, many clinical manifestations like fever, cough, dyspnea, diarrhea, headache, etc. showed up a few days after infection even still found with or without any treatment, and this condition showed the SARS-CoV2 is unique, vicious, and even deadly [2, 3]. Even though, drug-like antivirus is still needed to help host recovery from SRAS-CoV2 and the clinical manifestation clearly.

Favipiravir is one of the promising antivirals that is expected to stop the development of the disease Covid-19 [4, 5]. Favipiravir has the capacity to block the synthesis of an RNA virus and clearance the clinical manifestation [6, 7]. The SARS-CoV2 is an RNA virus, and with the potential work of favipiravir for RNA virus, it should eliminate SARS-CoV2 and reduce or stop the inflammation process. The problem is how far the favipiravir as an influenza drug firstly, can help the host to reduce or stop the journey of manifestation.

Favipiravir is one of the antiviral treatments is using to treat Covid-19, especially in mild and moderate cases according to the guideline for Covid-19 in Indonesia [8]. Based on that, one of the criteria to return the patient of Covid-19 is clinical manifestation clearly, and adding 7 days doses of favipiravir with other covid-19 drugs is expected to create it perfectly. With the widespread use of the drug favipiravir in all health care facilities in Indonesia, the information related to its capacity to control Covid-19 disease, especially its effect on the journey of clinical manifestation is very important to know because it is useful for making Covid-19 treatment strategies useful and updated. Therefore this article's objective was to identify the clinical manifestation after Favipiravir treatment at Covid-19 subject.

2 Materials and Methods

This study was a part of the main study related to the clinical trial of the efficacy and safety of favipiravir for Subjects with moderate Covid-19 in Indonesia (unpublished yet). The study was conducted in 2020 and 2021 in 3 main hospitals with Covid-19 patients. The population study was all the subjects who came hospitalized with suspected or get SARS-CoV2 and the sample of this study was all the patients who meet all research criteria. The inclusion criteria were patients with age $> 18 - 59$ years old, Covid-19 confirmation by PCR, voluntary and signed informed consent, then the exclusion criteria were pregnant women, lactation, and allergy were exclusion criteria. The sample size was all the subject groups with favipiravir treatment.

The favipiravir (AviganTM) dose was 2×1600 mg/day and 2×600 mg/day from day 2 to 7 and a maximum of 14. It was given with azithromycin and other drugs based on protocol guidelines. The clinical manifestations were followed from the start subject recruited before taking a drug, on day 7 and maximum day 14. If the patient already had PCR negative and free clinical manifestation for at least 3 days continued, the patient would be sent home as a recovery patient.

The variable clinical manifestations in this study were fever, cough, common cold, sore throat, headache, dyspnea, and diarrhea, this entire variable was commonly and always found in many reported Covid-19 cases.[2, 9] All of the variables were recorded in the structured questionnaire, and asked by the research team in a specific room at the

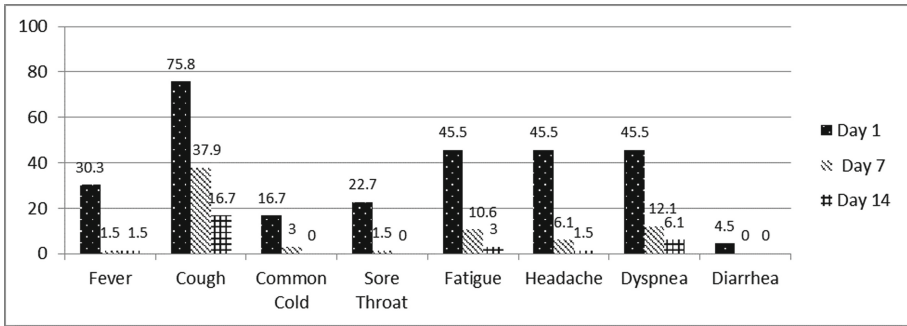


Fig. 1. Percentage of Journey of Clinical manifestation subject study

hospital. All the data was managed by the management data team and analyzed based on the objectives of this study. The analysis data was univariate analysis to identify the characteristic of the clinical manifestation on day 1 (one) before taking a drug, day 7, and day 14 using STATA 16. The ethical clearance was gotten from the National Institute of Health Research and Development Ethics Committee. The entire patient must sign Informed Consent voluntarily before joining this study.

3 Results

A total of 66 cases were recruited in this study with a mean average of 42 (range 20–59) years old and 57.6% a man. The Cough was the most common symptom on day 1, day 7, and day 14, meanwhile other symptoms decreased on days 7 and 14 (Fig. 1). The manifestations of Common cold, sore throat, and diarrheas were clear on day 14. In addition, from the total of 66 cases on day 1, the sample size reduced on day 7 to around 15.2% and 57.6% on day 14. The causes of the decrease of the total subject on days 7 and 14 were related to being severe, withdrawal of consent, and protocol violation cases.

4 Discussion

The clinical manifestations decrease after favipiravir plus standard of care (SoC) treatment but the symptom is still reported as unclear in a few subjects at last day follow-up. This condition gives us an answer that adding an antiviral drug or SoC may not remove all the clinical manifestations even though the SARS-CoV2 was already eliminated in the host subject. The favipiravir was said can shorten the clinical manifestation, especially cough and pyrexia but in fact, it cannot help to stop all the symptoms even though a few symptoms were reduced at the end of the study. [5, 10] The unpredictable SARS-CoV2 after entering the human body will induce an immune response, infiltrate and disrupt the lung, and other organs, this mechanism will retain the clinical manifestation in the subject even after 7 months and will give us a long Covid-19 symptom, and consistent too with study-related clinical manifestation using favipiravir vs arbidol. [2, 3, 6, 11].

Based on various research studies related to the treatment of Covid-19, the best drug to eliminate SARS-CoV2 is still not found. Favipiravir as a potential drug, such

as remdesivir, monoclonal antibodies, etc., cannot help the host to reduce or eliminate all clinical manifestations as expected. As we know above, favipiravir can kill SARS-CoV2 but in fact inflammation in the host can cause many clinical manifestations, and the manifestations can be delayed to heal depending on the host's immune response. So the future possibility of using favipiravir as a weapon to clear all viruses and clinical manifestations of Covid-19 is more challenging. Studies related to favipiravir have shown variation in efficacy ranging from 60–80%. [12] With this condition, there is certainly hope that in the future there will be more question marks for the use of favipiravir to suppress clinical symptoms.

In this study, the cough is a most clinical manifestation from the initial until the last day than others. This is consistent with a study related to Covid-19 that found cough as one of the most clinical manifestations symptomatic in any degree of Covid-19 disease and influences the length of stay of Covid-19 patients. [6, 13, 14] The cough is the clinical manifestation related to lung infiltration of SARS-CoV2 which implicates vagal nerves and hypersensitivity of neuron pathways and can be found until 2 months. [15] The inflammation process that happens in the lung, cannot be disappeared only by eliminating the virus by using antiviral treatment in the lung itself but it is depending on the immune response balance or process of healing itself. In this study, the cough already decreased a half after day 7 and was only found at 16.7% on day 14, this is consistent with the manifestation was gotten better along with negative virus. [16].

The fever, sore throat, fatigue, headache, and dyspnea were still found until day 14 even the percentage below cough. All this condition has the same situation as a cough but the effect has not as long as the cough, it could be related to the receptor ACE more found in the lung than others, so the clinical manifestation is shortened than the cough. [15, 17] The fever manifestation is related to viremia and the second symptom reported in early cases of Covid-19 firstly after entering the respiratory tract. [17, 18] Meanwhile, sore throat had a relation to irritation of the throat because of adhesion at receptors when SARS-COV2 entry into the upper respiratory tract. [2, 18, 19] The mechanism of fatigue is said to be related to the central motor neuron where infection occurs SARS-CoV2 affects III/IV afferents triggering an immunologic reaction that is suspected of causing fatigue that occurred during and after being infected with Covid-19. [20].

The human immune response-related inflammation caused by SARS-COV2 is a mechanism that explains all the symptomatic problems of Covid-19 patients. The clinical manifestation is a sign-related organ problem that causes interaction between receptors and SARS-COV2, but it could be related to a dysfunctional host mechanism to eliminate all the SARS-COV2 [21]. The first time SARS-COV2 enters the human respiratory tract, makes a risk lung dysfunctional, and will trigger the immune response, if the response is dysfunctional too will stimulate an unbalanced immunology scenario. All of the clinical symptoms relate to Covid-19 arise by the mechanism but it could be different per individual and to be unpredictable.

The unpredictable journey of clinical manifestation related to Covid-19 has an impact on health services and the patient. With the Covid-19 still, an endemic problem in world health and the new variant increasing anytime, the journey of clinical manifestation could be increasingly difficult to predict even after getting treatment, then we need more drugs to treat the symptom, and give more burdens including health problems and stigma

for the patient.[22, 23] We need future research related to an antiviral that can quickly eliminate the SARS-CoV2, and others like drug supplement/symptomatic or adjuvant that will help remove clinical manifestation immediately, and the management strategy to help all the long Covid-19 clinical manifestation problem.

This resulting study is consistent to show us the problem of Covid-19 like other study mentioned above but there is still found a few limitations. First, the limitation of this study was a total sample size of only 66 subjects but this condition still can explain the journey of clinical manifestation of Covid-19 after antiviral treatment. The other limitation is this study did not have a comparative drug because this study was a part of the main study related clinical trial of favipiravir.

5 Conclusion

The conclusion of this study was the journey of the clinical manifestations of Covid-19 remains unpredictable after the administration of the drug Favipiravir.

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