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Investigator initiated clinical trial of remdesivir for the treatment of COVID-19 in Japan

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Abstract: Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in Wuhan, China, has spread globally very rapidly. The number of COVID-19 patients increased in Japan from late March to early April 2020. Since COVID-19 treatment methods with antiviral drugs were not established in March 2020, clinical trials began at a rapid pace worldwide. We participated in a global investigator-initiated clinical trial of the antiviral drug remdesivir. It took approximately two months to prepare for and start patient enrollment, 26 days to enroll all patients in Japan, and 32 days from the end of enrollment to the release of the first report, a fairly quick response overall. In the course of this clinical trial, we found some of the critical issues related to conducting an infectious disease clinical trial in Japan need to be addressed and tackled to support a rapid response. These included such things as the necessity of a research network to promote clinical research, a framework for a rapid review system of clinical trial notification, and better cooperation with outsourced teams. Furthermore, for Japan to take the lead in global collaborative research and development in the field of infectious diseases, it is necessary to develop further human resources and organization on a national basis. It is indispensable for Japan to establish a clinical trial system at the national level to prepare for future emerging and re-emerging infectious diseases.

***Keywords*:** SARS-CoV-2, clinical trial, infectious diseases

Introduction

The novel coronavirus identified in Wuhan, China, in December 2019, was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It spread throughout the world as a new type of coronavirus disease (COVID-19) and became a major threat to public health and the economy (*1*). In Japan, the first case of a positive SARS-CoV-2 polymerase chain reaction (PCR) test was reported by the Japanese Ministry of Health, Labor and Welfare (MHLW) on January 16, 2020 (*2*), and the number of cases subsequently increased from late March through early April 2020. The first wave of cases peaked in early April, with more than 600 notifications of infection per day, and the number rapidly declined to around 20 per day in late May (*3*). The second wave has passed the peak in August, and Japan again faces the resurgence of COVID-19, which brought a record number of daily cases, 4,322, as of December 31, 2020.

Because COVID-19 is an emerging infectious disease and treatment methods with antiviral drugs were not yet established in March 2020, clinical trials had begun at a rapid pace around the world, and many are still ongoing. Remdesivir was found to have anti-SARS-CoV activity in a mouse infection model (*4*) and was offered for compassionate use in COVID-19 patients worldwide (*5,6*).

We participated in the U.S. National Institutes of Health (NIH)-led investigator-initiated clinical trial, "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults", as a site and enrolled 15 cases. This trial showed that the use of remdesivir in COVID-19 patients accelerated time to recovery compared to that of a placebo (*7,8*). As a result, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization for remdesivir on May 1 (*9*), and the MHLW has granted fast-track approval for remdesivir as the first treatment for COVID-19 on May 7, 2020 (*10,11*). The FDA approved a new drug application for remdesivir to treat COVID-19 requiring hospitalization on October

22, which allowed remdesivir for sale and marketing in the U.S (*12,13*).

This investigator-initiated clinical trial process was conducted very quickly, at a time when the number of patients infected with SARS-CoV-2 was high, allowing for a large number of case enrollments. To promote clinical trials in the field of infectious diseases in Japan, we reviewed the domestic process from study participation to reporting results, and we identified issues and sought improvements for the rapid implementation of future trials.

Process of the investigator-initiated clinical trial

In early February 2020, the U.S. NIH consulted with the Japanese MHLW about participating in an investigator-initiated international clinical trial of antiviral therapy for COVID-19, and our center, the National Center for Global Health and Medicine (NCGM), agreed to participate in the study. The NIH submitted the first protocol to the FDA on February 18, and the FDA issued a notification that it was safe to proceed on February 19. We participated in this study in the framework of an investigator-initiated clinical trial based on the Japan-Good Clinical Practice (J-GCP) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-GCP (ICH-GCP).

With detailed discussions with the MHLW and the Pharmaceuticals and Medical Devices Agency (PMDA), we submitted our initial clinical trial protocol to the PMDA on February 28. At the same time, we built a research team with the NCGM members and external contractors, and we welcomed a five-member NIH research support team to the NCGM from March 9-19. During the support team's visit to Japan, we worked together to prepare for the clinical trial in accordance with ICH-GCP, including contract signing, clinical trial procedures, in-house microbiology, clinical laboratory systems, investigational drug management procedures, online patient enrollment, staff training, and completion of various documents. We also translated the clinical trial protocol and manual of procedures into Japanese and prepared documents such as an informed consent form in line with J-GCP. After a site initiation visit by a monitoring team sent by the NIH on March 24, our center was approved by the NIH as a clinical trial site on March 25. After the delivery of the investigational drug on March 25, the first patient enrollment at our center was conducted on March 26. With the cooperation of each department, we completed the enrollment of 15 patients at our center on April 20 at 0:00 (Eastern Standard Time). After exchanging data cleansing queries with the NIH team, the “Remdesivir for the Treatment of Covid-19-Preliminary Report" was published in *The New England Journal of Medicine* on May 22, 2020 (*7*).

Why the clinical trial was conducted so quickly

The preparation of an investigator-initiated clinical trial generally takes a large amount of time when considering the process from concept development to research proposal creation, research budget securing, coordination with pharmaceutical companies, research system building, clinical trial consultation, contracting, *etc*. There are several reasons why we were able to achieve this clinical trial at an unprecedented speed. First, and most importantly, the MHLW, PMDA, NCGM staff, Institutional Review Board (IRB) members, and external contractors worked as a team under the direction of the Japanese government to prepare for this clinical trial and enroll patients.

The second reason was the support from the multidisciplinary specialist team from the NIH that stayed in Japan for 11 days to support the preparation of this clinical trial. Of the five members of the NIH team, two were coordinators, one was a microbiologist, one was a pharmacist, and one was a Japanese researcher working on infectious diseases who also served as an interpreter. The coordinator, microbiology technician, and pharmacist answered technical questions from our team while communicating within the NIH team. The Japanese researcher who served as a bridge between the NIH support team and the NCGM team played an important role in the progress of the trial, because it was sometimes difficult for our team to communicate in English for detailed information. Even after the NIH support team returned to the U.S., our team obtained technical advice *via* weekly online meetings; this contributed to the smooth operation of the process. The role of the NIH support team in the rapid preparation and smooth operation of the clinical trial was significant.

Lastly, prompt and flexible review of clinical trial notification by the PMDA was critical to the flow and speed of the preparation process (Figure 1). The PMDA expedited the investigation by swiftly responding to consultations from our team utilizing phone and email and allowing us to submit required documents flexibly, considering the challenging situation in which the study stood. Moreover, we were able to start patient enrollment in one month after the protocol submission for the following reasons: First, the MHLW allowed the clinical trial to begin without waiting for the 30 day investigation period setup for the investigation by the PMDA to be completed (*14*) and second, the PMDA spent a great deal of effort in conducting the investigation in a timely manner. Rapidly starting a clinical trial would have been impossible without the shortened 30-day investigation by the MHLW and the prompt review by PMDA.

Challenges for future clinical trials

The number of cases of SARS-CoV-2 in Japan increased rapidly from late March to early April 2020 and then declined rapidly. If rapid trial preparation and patient enrollment did not take place, the opportunity to find a

treatment method might have been compromised. In the course of this clinical trial, we incurred some challenges in Japan, but we also looked for ways to solve them (Table 1).

First, it is desirable to establish a research network in the field of infectious diseases to support implementing clinical trials, especially administrative work. This type of network has already existed for other diseases in Japan, *e.g.*, the Japan Clinical Oncology Group (JCOG) for cancer treatment research. Due to the shortage of human resources throughout the COVID-19 outbreaks, investigators needed to prepare for this clinical trial while dealing with patients in the medical field. We have realized that administrative work, which is a key to conducting clinical trials without interruption, requires heavy workloads. Fortunately, the team could ask for support from the Center for Clinical Sciences in the NCGM to handle the work. Nevertheless, considering the future outbreaks of infectious diseases, we urgently need to establish a research network to lead administrative tasks for conducting clinical research smoothly.

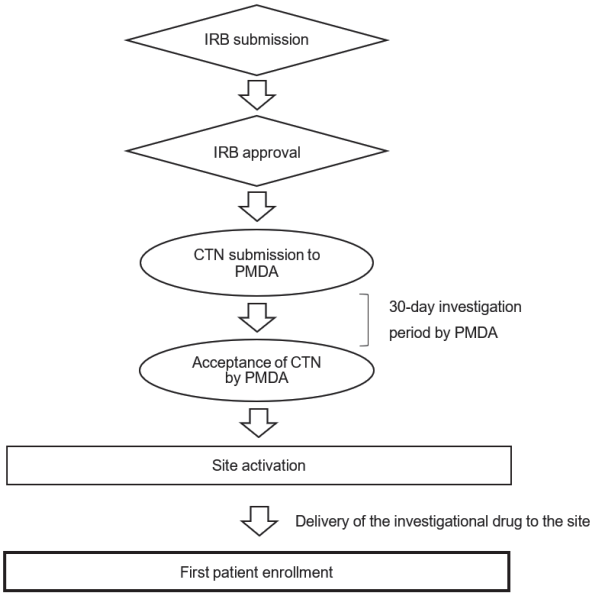

Figure 1. Approval process of investigator-initiated clinical trials in Japan. IRB: Institutional Review Board; CTN: Clinical Trial Notification; PMDA: Pharmaceuticals and Medical Devices Agency.

Second, the investigation period for clinical trial notification in Japan needs to be shortened for responding to an emergency. In this clinical trial, as the PMDA regarded the trial as a special case and made efforts to enable the investigation to be conducted exceptionally quickly, the trial launched without significant delay. Since the SARS-CoV-2 outbreak has proven that infectious diseases can sometimes lead to a rapid increase in the number of patients and have a tremendous social impact, it is necessary to have a first-track review system for clinical trial notification in place to ensure that clinical trials are carried out promptly.

The third issue concerns Site Management Organizations (SMOs), to which we often outsource some duties when conducting investigator-initiated clinical trials. In this clinical trial, it was challenging to reach a contract agreement with SMOs, which could not access sufficient safety information for COVID-19 in the early phase of the pandemic and estimated the risk of infection of the dispatched clinical research coordinators (CRCs) as very high. Although we, fortunately, found a company willing to take the job for the trial, it took more time and cost than usual for commissioning. Discussions need to be continued on how to convince SMOs to commit to clinical trials for infectious diseases after understanding the risk.

The fourth issue is the retention of signed informed consent forms. Because patients must sign the consent document before participating in a clinical trial following

Table 1. Challenges in clinical trials for emerging or re-emerging infectious diseases in Japan

No.	Challenges	Mitigation plans
(1)	Absence of a system to lead administrative tasks for clinical research programs in the field of infectious diseases.	It is desirable to establish a research network leading clinical research and supporting administrative tasks to accelerate clinical research for diagnostic technologies and treatment methods development.
(2)	In the case of outbreaks, the investigation period for clinical trial notification must be shortened.	Consider a fast-track review system as an alternative process.
(3)	Because of insufficient information of a new pathogen, especially in the early phase of the pandemic, it is difficult to recruit SMOs that support clinical trials.	Provide the latest accurate information for SMOs. It still needs to discuss how to convince SMOs to commit to clinical trials for infectious diseases after understanding the risk.
(4)	Retention of the contaminated informed consent forms after signing.	Put the method of using an electric document, which is now allowed by the MHLW, into practice. There are still challenges in using the new method in the medical field. e.g., installing an information network system to store and transfer confidential data securely.
(5)	Lack of capacities and experiences to conduct international clinical trials. The shortage of study specialists and the absence of a coordinate system for the trial is critical.	To strengthen the capacity to carry out and lead international clinical trials, Japan must develop a national coordinate system and promote more human resources development.

Japanese law, it became a problem for the investigators to store signed papers potentially contaminated by droplets from patients. Since the reduction of infectivity after 72 hours was reported (*15*), we isolated the paper documents for at least 72 hours before preserving them. On April 7, 2020, the MHLW announced that, under certain conditions, consent forms signed by patients could be reiterated in the form of electromagnetic records of documents, and electronically signed consent documents (*16*). If we had been able to use this method, the trial would have run more smoothly. Although the rule has been ready, using the method is limited to medical facilities and research institutes capable of setting up and managing an information network system to handle highly confidential personal data. We need to continue the ongoing discussion on putting this method in practice widely.

Finally, if Japan takes the lead in international clinical trials, it will be indispensable to develop a coordinated system at the national level and train more study specialists. The U.S. NIH dispatched expert teams to other countries early in the epidemic. In this trial, we accepted a team with specialists, including a microbiologist, a pharmacist, and a liaison who supports teams bridging the gap between a site and the NIH. Also, outsourced teams were utilized to organize human resources. Significant research funding allows the U.S. NIH to coordinate many global clinical trials hiring people with a high level of expertise. It is considered essential to develop experts who lead in the field of clinical research and build a national organization to coordinate international collaborative clinical studies so that Japan plays a leading role in international collaborative clinical research.

Conclusion

We participated in a clinical trial of remdesivir for the treatment of COVID-19 in Japan through a concerted domestic collaboration and support from the NIH. It took approximately two months to prepare for and start patient enrollment, 26 days to enroll patients, and all of this was done quickly, with 32 days from the end of registration to the release of the first report. Considering that the first wave of COVID-19 patients peaked in early April, and the number of cases declined rapidly after that, speed is critical when we conduct clinical trials for infectious diseases. To address second and third emerging and re-emerging infectious diseases, Japan needs to establish a clinical trial system of infectious diseases. The system must include organizations and a research network to promote research, a framework for the rapid review of clinical trial notification, and cooperation with SMOs. Moreover, for Japan to take the lead in global collaborative research and development, it is necessary to develop human resources and organization on a national basis to coordinate clinical trials over countries.

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References

1. Arshad Ali S, Baloch M, Ahmed N, Arshad Ali A, Iqbal A. The outbreak of Coronavirus Disease 2019 (COVID-19)-An emerging global health threat. J Infect Public Health. 2020; 13:644-646.
2. Ministry of Health, Labor and Welfare. The first confirmed case of COVID-19 in Japan. January 16, 2020. *https://www.mhlw.go.jp/stf/newpage_08906.html* (accessed June 2, 2020) (in Japanese).
3. Ministry of Health, Labor and Welfare. Situation report, Fig. No. of positive cases. *https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou_00006.html#1-1* (accessed October 15, 2020).
4. Sheahan TP, Sims AC, Graham RL, *et al*. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017; 9:eaal3653.
5. Grein J, Ohmagari N, Shin D, *et al*. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020; 382:2327-2336.
6. National Center for Global Health and Medicine. Feel the NCGM, Special Edition. Sep 2020. *https://www.ncgm.go.jp/covid19/PDF/Feel_the_NCGM_SP.pdf* (accessed October 15, 2020) (in Japanese).
7. Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med. 2020 May 22. *https://escholarship.umassmed.edu/covid19/40/* (accessed October 15, 2020)
8. Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020; 383:1813-1826.
9. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. May 1, 2020. *https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment* (accessed January 5, 2021).
10. Ministry of Health, Labor and Welfare. Special Approval for Emergency on Remdesivir for COVID-19. May 8, 2020. *https://www.pmda.go.jp/english/int-activities/0004.pdf* (accessed January 5, 2021).
11. Ministry of Health, Labor and Welfare. Special Approval for Emergency on Remdesivir for COVID-19 in accordance to Pharmaceutical and Medical Device Act. Press Release. May 7 2020. *https://www.mhlw.go.jp/content/000628076.pdf* (accessed January 5, 2021) (in Japanese).

12. U.S. Food and Drug Administration. FDA Approves First Treatment for COVID-19. October 22, 2020. *https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19* (accessed January 5, 2021).
13. U.S. Food and Drug Administration. Frequently Asked Questions for Veklury (remdesivir). Updated December 8, 2020. *https://www.fda.gov/media/137574/download* (accessed January 5, 2021).
14. Handling of Notification of Clinical Trial Plans for Novel Coronavirus Infections. Ministry of Health, Labor and Welfare, ed. March 19 2020. *https://www.mhlw.go.jp/hourei/doc/tsuchi/T200323I0040.pdf* (accessed June 2, 2020) (in Japanese).
15. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382:1564-1567.
16. Handling of the retention of consent documents in clinical trials. Ministry of Health, Labor and Welfare, ed. April 7, 2020. *https://www.mhlw.go.jp/hourei/doc/tsuchi/T200408I0010.pdf* (accessed June 2, 2020) (in Japanese).

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