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Clinical trial experience in Japan and future issues in developing drugs to treat COVID-19

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Abstract: The National Center for Global Health and Medicine plays a central role in the treatment and research of infectious diseases in Japan. It has conducted various research and development activities on drugs to treat coronavirus disease 2019 (COVID-19) with clinical questions as starting points. Clinical trials are essential in developing new treatment modalities, but we have noticed some characteristic difficulties in clinical trials on emerging and re-emerging infectious diseases. For example, since there is no standard of care when an emerging infectious disease starts to spread, establishing an appropriate control group is complicated, and many things are hurried at the start of trials. This means there is little time to arrange a placebo, and conducting blinded, randomized, controlled trials has been difficult. Another issue characteristic of infectious disease has been that progress in enrolling subjects is affected by the spread of the disease. It was also a struggle to select institutions that provide medical care on the front lines of infectious disease and conduct clinical trials regularly. To start multicenter clinical trials expeditiously, a regulated and structured network is thus considered necessary. From the perspective of implementation, it is preferable to conduct decentralized clinical trials (DCTs) that do not depend on people coming to the medical institution, while from the perspective of preventing infections during the spread of COVID-19, wide adoption of eConsent is desirable. Based on the experience of COVID-19, new measures must be taken to prepare for emerging and re-emerging infectious diseases in the future.

***Keywords*:** COVID-19, clinical trial, specified clinical trial, investigator-initiated clinical trial

Introduction

The National Center for Global Health and Medicine (NCGM) is one of Japan's national centers for advanced and specialized medicine, and it plays a central role in treating and researching infectious diseases. In 2009, when novel influenza A (H1N1) was spreading globally, NCGM worked with the Ministry of Health, Labour and Welfare and the National Institute of Infectious Diseases to gather information and provide measures to counter it and inform the general public (*1,2*). During the recent coronavirus disease 2019 (COVID-19) pandemic, three patients with severe disease hospitalized in the NCGM in the early stage were administered remdesivir (RDV) for the first time in Japan through compassionate use. All three patients who received it recovered and were discharged from the hospital. At the same time, various research and development activities on therapeutic drugs started from early in the pandemic. In the early stages, specified clinical trials and investigator-initiated trials on antiviral agents and medical devices were carried out, and efforts were also made to develop antibody preparations and vaccines.

For research and development to progress, a detailed pathological understanding is essential. Therefore, from the early stages of COVID-19, the NCGM collected specimens that would be the foundation for various studies and conducted observational studies (registries) of patients hospitalized for COVID-19 in Japan (*3*) to elucidate the details of the condition.

Clinical trials based on pathological conditions are essential in bringing novel treatment modalities to clinical settings. When possible, double-blinded, randomized, controlled trials are preferable for evaluating treatment modalities. However, while planning and leading clinical trials on COVID-19, we noticed some difficulties peculiar to clinical trials on emerging and re-emerging infectious diseases. The studies that have been performed at our hospital are described, and relevant issues are summarized (Figure 1).

The main clinical trials conducted thus far at the NCGM are outlined below.

Specified clinical trials under the Clinical Trial Act

A multicenter, open-label, randomized, controlled, phase II study to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with

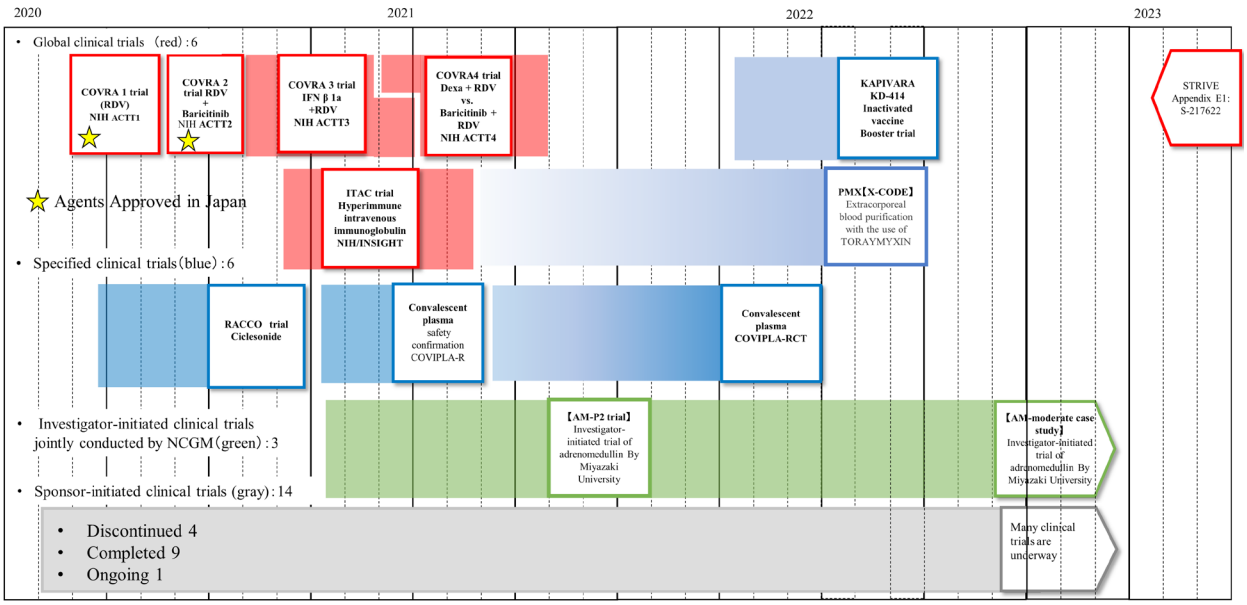

Figure 1. COVID-19-related clinical trials conducted at the National Center for Global Health and Medicine (NCGM) since 2020. Red indicates a global collaborative investigator-initiated clinical trial led by NCGM. Green indicates an investigator-initiated clinical trial in which NCGM participated as a sub-institution, blue indicates a specific clinical study led by NCGM, gray indicates an Industry-sponsored clinical trial.

COVID-19 (RACCO trial)

Enrollment started on March 27, 2020, and was completed on September 17, 2020.

This was the first specified clinical trial planned for COVID-19 at our hospital (*4*). An exploratory phase II trial was started at 22 institutions in Japan led by the NCGM, and 90 people were enrolled. They were randomized into a ciclesonide group and a symptomatic treatment group, and were observed for exacerbation of pneumonia until the eighth day after administration. Exacerbation was seen in 39% (16/41) of the ciclesonide group and 18% (9/48) of the control group. Since significant exacerbation was seen in the ciclesonide group (*5*), it was announced in a press release dated December 23, 2020, that the use of this drug is not recommended for asymptomatic to mild COVID-19 patients.

Exploratory study of the efficacy and safety of direct hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX-DHP) for COVID-19 patients (X-CODE)

Enrollment started on September 28, 2020, and was completed in March 2022 (analysis underway).

This was a multicenter, joint, specified clinical trial to evaluate the efficacy and safety of polymyxin b hemoperfusion (PMX-DHP) blood purification therapy using Toraymyxin® (Toray Medical Co., Ltd, Tokyo, Japan) for moderate to severe COVID-19 (*6*). The control group was a historical control from a COVID-19 registry (COVIREGI) (*3*). The mechanism seems to inhibit the characteristic rapid decrease in lymphocytes in COVID-19, as well as to improve the abnormalities in the coagulation-fibrinolysis system and increase oxygenation by removing activated leukocytes and cytokines, which are risk factors for the aggravation of COVID-19–related pneumonia, with the use of Toraymyxin.

An open-label, randomized, controlled trial to evaluate the efficacy of convalescent plasma therapy for COVID-19 (COVIPLA-RCT)

Enrollment started on February 24, 2021, and was completed in December 2021.

Ahead of this study, a specified clinical trial was conducted to confirm safety. Plasma was collected from people who had contracted COVID-19 and recovered (convalescent plasma) (*7*), and this plasma was administered to mild COVID-19 patients at risk of severe disease in a multicenter, joint, specified clinical trial that investigated the effect in preventing severe disease (*8*). Patients were randomized into a convalescent plasma group and a standard of care group, and the severity of disease was evaluated in an unblinded manner. A point in this study that differs from other antibody studies is that the neutralizing activity of convalescent plasma was measured before administration to subjects. Given that the antibody cocktail therapy Ronapreve® (generic name: casirivimab [genetic recombination]/imdevimab [genetic recombination] [Chugai Pharmaceutical Co., Ltd., Tokyo Japan]) was approved, and enrollment was ended in December 2021.

Exploratory, single-arm study to evaluate the safety and

immunogenicity of KD-414 as a booster vaccine for SARS-CoV-2 in healthy adults (KAPIVARA study)

This was started on October 22, 2021, with follow-up ongoing.

Healthy adults vaccinated twice with a SARS-CoV-2 mRNA vaccine were given a booster with inactivated vaccine KD-414 (*9*). This is a single-center, specified clinical trial to evaluate safety and immunogenicity (*10*). The primary endpoint is immunogenicity after booster vaccination with KD-414 compared with that after primary immunization with an mRNA vaccine.

Investigator-initiated clinical trials led by NCGM

A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT)) (COVRA-1 trial)

Enrollment started on February 21, 2020, and was completed on May 21, 2020.

ACCT-1 was a placebo-controlled, double-blind, comparative trial to evaluate the efficacy and safety of RDV in adult COVID-19 patients hospitalized with moderate to severe disease. A total of 1,063 patients were entered in the trial overall, of whom 15 were entered from the NCGM. An interim report showing the efficacy of RDV was published, and based on those results, RDV was approved in Japan on May 7. In the final analysis, patients who were administered RDV had a median recovery time of 10 days (95% confidence interval [CI]: 9–11), whereas in the patients who received the placebo, it was 15 days (95% CI: 13–18) (rate ratio for recovery 1.29; 95% CI: 1.12–1.49; $p < 0.001$, by the log-rank test) (*11*).

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in Hospitalized Adults (Adaptive COVID-19 Treatment Trial (ACTT-2)) (COVRA-2)

Enrollment started on May 26, 2020, and was completed on July 31, 2020.

ACTT-2 was a double-blind, placebo-controlled trial comparing the combined use of RDV and baricitinib (JAK inhibitor) and the combined use of RDV and a placebo in patients hospitalized with moderate to severe COVID-19. One patient was entered from NCGM. The results of the analysis of the 1,034 patients entered in the trial showed that the recovery time was significantly shorter in the combined RDV and baricitinib group than in the RDV plus placebo group, by about 1 day ($p = 0.03$), confirming the effectiveness of the combination (*12*). Baricitinib was the third drug to receive regulatory approval as a treatment for COVID-19 in Japan, following RDV and dexamethasone.

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT-3)) (COVRA-3)

Enrollment started on July 30, 2020, and was completed on December 21, 2020.

ACTT-3 was a double-blind, comparative trial led by a team at the United States National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) to verify the efficacy of RDV in combination with interferon β-1a. The trial compared subcutaneously administered RDV plus interferon β-1a with subcutaneously administered RDV plus placebo. Worldwide, 969 patients were enrolled, of whom 19 were enrolled at NCGM. In patients hospitalized with COVID-19 pneumonia, combination therapy with interferon β-1a plus RDV was not superior to RDV alone. Patients who required high-flow oxygen at baseline had worse outcomes after interferon β-1a administration than the group that received the placebo (*13*).

An international, multicenter, adaptive, randomized, double-blind, placebo-controlled trial of the safety, tolerability, and efficacy of anti-coronavirus hyperimmune intravenous immunoglobulin for the treatment of adult hospitalized patients at onset of clinical progression of COVID-19 (Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC))

Enrollment started on October 15, 2020, and was completed on October 12, 2021.

The ITAC trial was a randomized, double-blind, placebo-controlled trial led by the NIH and Network for Strategic Initiatives in Global HIV Trials (INSIGHT) that compared hyperimmune intravenous immunoglobulin (hIVIG) and a placebo. Worldwide, 593 patients were enrolled; from Japan, Fujita Health University and NCGM participated and enrolled eight patients and six patients, respectively. The results of this trial demonstrated that hIVIG did not show efficacy against COVID-19 (*14*).

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT-4)) (COVRA-4)

Enrollment started on December 18, 2020, and was completed on August 2, 2021.

ACTT-4 was a double-blind, comparative trial that compared the combination of RDV and dexamethasone

and the combination of RDV and subcutaneously administered baricitinib. Worldwide, 1,010 patients were enrolled, of whom four were enrolled from NCGM. In hospitalized COVID-19 patients who required supplemental oxygen administered by low-flow, high-flow, or non-invasive mechanical ventilation, the mechanical ventilation-free survival by day 29 was the same with baricitinib plus RDV and dexamethasone plus RDV. However, with dexamethasone, there were many more adverse events, treatment-related adverse events, and severe or life-threatening adverse events (*15*).

A multicenter, adaptive, randomized, controlled trial platform to evaluate safety and efficacy of strategies and treatments for hospitalized patients with respiratory infections (Strategies and Treatments for Respiratory Infections & Viral Emergencies (STRIVE))

Enrollment started on February 16, 2023, and is in progress.

STRIVE is a master protocol designed to evaluate the safety and efficacy of unapproved treatments, approved treatments, and their sequential and combined use for the purpose of optimizing the health status of hospitalized patients receiving acute treatment for respiratory infections. Appendix E1 shows a randomized, placebo-controlled, multicenter, joint international clinical trial that evaluates the clinical efficacy when ensitrelvir therapy is added to the standard of care (SOC) in patients hospitalized with COVID-19.

Investigator-initiated clinical trials jointly conducted by NCGM

Prevention of aggravation of mechanical ventilation-required pneumonia caused by COVID-19 using adrenomedullin - Investigator initiated phase IIa trial (AM-P2-COVID)

Enrollment started on November 2, 2020, and was completed on March 1, 2022.

This was a phase II trial led by the University of Miyazaki to examine whether adrenomedullin, a circulation-regulating peptide that shows an anti-inflammatory action, can prevent aggravation in severe COVID-19 patients on mechanical ventilation. Enrollment has ended.

Prevention of aggravation of moderate pneumonia caused by COVID-19 using adrenomedullin - Investigator initiated phase IIa trial (AM-P2-COVID2)

Enrollment started on June 24, 2021, and is in progress.

This is a phase II trial led by the University of Miyazaki to examine whether adrenomedullin administration could inhibit the progression of lung injury and injury of other organs in COVID-19 patients with moderate pneumonia, and whether patients could recover earlier (*16*).

The exploratory study investigating the efficacy and safety of Ephedrine alkaloids-free Ephedra Herb extract (EFE) in patients with COVID-19 in the early stages of infection– Double-blind, randomized, multicenter phase I / II controlled trial–

Enrollment started on March 30, 2021, and was completed on January 7, 2022.

This was an exploratory phase I/II trial led by Kitasato University that examined the efficacy and safety of EFE (*17*) for COVID-19 patients with early infection.

In addition, NCGM is actively working in corporate trials for drug development. To date, it has participated in many sponsor-initiated trials, including for molnupiravir (Lagevrio®, MSD Co.,Ltd., Tokyo, Japan), nirmatrelvir/ritonavir (Paxlovid®, Pfizer Inc., New York, US), tixagevimab/cilgavimab (Evusheld®, AstraZeneca K.K., *Tokyo, Japan*), and tocilizumab (Actemra®, Chugai Pharmaceutical Co., Ltd.).

Future issues

We have planned much studies based on scientific evidence with clinical questions as a starting point. Let us now consider several issues for the future that have become clear from our experience in investigator-initiated clinical trials for emerging infectious diseases.

The RACCO trial is a specified clinical trial targeting COVID-19, and the first in which the NCGM led the planning. Randomization was done, but because of the difficulty of preparing a placebo for inhaled ciclesonide by the start of the trial, it ended up being an open-label comparison with the symptomatic treatment group (*4*). When the study was planned in March 2020, there were still few trials related to COVID-19, and so we felt our way in the planning without establishing endpoints. Since it was an open-label trial with the concept of evaluating the antiviral effect, we decided to make computed tomography images for which the evaluators could be blinded to the primary endpoint (*4*). However, looking back now, that may not have been appropriate. Deciding in the early stage what to make the primary endpoint for a new infectious disease was difficult. In addition, we had no clinical trial network in the field of infectious disease, and so finding institutions with which to conduct a clinical trial was a struggle. Hospitals treating COVID-19 patients had performed few clinical trials up to that time and were unfamiliar with them in some cases, and time was also needed for ethical procedures. Moreover, COVID-19 spread in waves; when it was not prevalent, subjects could not be enrolled, and when cases were abundant, the great burden in care settings meant little progress was made in enrollment (*18*). From our experience in

planning this multicenter clinical study in the early stage of the COVID-19 pandemic, we keenly felt the importance of creating a network during regular times. During that same period, an observational study on the administration of ciclesonide was started in Japan, but since some physicians preferred observational studies in which ciclesonide could be administered with certainty, enrollment was challenging. Starting observational studies without thorough consideration in situations when it is not known whether there will be a treatment effect is in some cases a hindrance to implementing the randomized, comparative trials that are essential for evaluating efficacy and safety. Therefore, an implementation should be carefully considered.

The KAPIVARA trial conducted with healthy adults is a phase II trial assessing safety and efficacy of the inactivated vaccine KD-414 as a booster dose (*7*). It was predicted that inactivated vaccines may produce fewer antibodies than mRNA vaccines; however, from the results of a company phase I/II trial, there were expected to be fewer adverse effects than with mRNA vaccines (*19*). Considering the strong and frequent adverse events seen with mRNA vaccines, there was also predicted to be a certain level of need for inactivated vaccines. This study was planned in the summer of 2021, when the primary immunization of many people in Japan with an mRNA vaccine had been completed, and so it was predicted that if KD-414 were available on the market, it would be used in many situations as a booster dose for people whose primary immunization with an mRNA vaccine had ended. Therefore, KD-414 was given as a booster dose to people whose primary immunization with mRNA was over, and, with reference to guidelines on evaluating vaccines (*20*), information was collected on SARS-CoV-2 antigen-specific antibody titers, neutralizing antibody titers, cell-mediated immunity, cytokine production, and other factors as endpoints of immunogenicity (*10*). However, no method has been established for evaluations when the type of vaccine for primary immunization and booster immunization differ. It was unclear whether antibody titers need to be elevated as much as with mRNA vaccines to prevent COVID-19 infection and an outbreak, and we struggled to set an endpoint.

When obtaining consent for research or treatment, paper consent forms are assumed in Japanese regulations, and it was thus necessary for healthcare workers to meet directly with patients for informed consent. There was also a possibility of infection from paper consent forms, and so caution was required in the handling of consent documents. Our hospital rules specified the use of pens in the patient room when obtaining consent, and that consent forms and papers brought into the patient room should not be taken immediately into clean areas, but first be stored for a fixed time in an intermediate area and then brought into the clean area. In the future, from the perspective of conducting decentralized clinical trials (DCTs) that do not depend on people visiting the medical institution and, from the perspective of preventing infection when COVID-19 is spreading, the wider use of eConsent will be preferred (*21*).

Participation in the series of ACTT trials on RDV was a valuable experience of direct participation from Japan in international clinical trials led by the NIH/NIAID. The NIAID has programs for times of infectious disease outbreaks, including the implementation of clinical trials for Ebola hemorrhagic fever and providing support in other countries before the COVID-19 pandemic. Within several days of the NCGM announcing participation in the ACTT trials, a team consisting of an NIAID research nurse, pharmacist, clinical laboratory technician, and clinical trial office worker came to Japan. We were surprised and deeply grateful for the strong support provided up to the start of the clinical trial. At the same time, the ACTT trial was started at a stage when the COVID-19 situation was unclear, thus, it was a clinical trial with an adaptive design in which revisions were made, such as the criteria for patient enrollment and the validity of endpoints, while the study design itself was being implemented. For that purpose, online conferences were held every week and as needed with the participation of all institutions involved in the clinical trial. These meetings were a place where all stakeholders, including research investigators, pharmaceutical company representatives, government representatives, and biostatisticians, could meet and discuss the content and progress of the trial. We were overwhelmed at how the trial protocol was flexibly adapted to the constantly changing situation of the infectious disease and carried out. All these results were built on the full consideration and preparations from regular times with regard to emerging and re-emerging infectious diseases. The lack of preparation in Japan for COVID-19 is undeniable, and we need to examine these valuable experiences one by one and develop measures for the onset of the next infectious disease.

For our participation in the ACTT trials and their implementation as trials in Japan, the Japanese Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency provided the most rapid and flexible responses allowable within the current pharmaceutical regulations. This was done with total understanding of the significance for the country of participation from Japan in the ACTT trials. However, questions remain on the point of whether the results of these trials conducted in Japan were used to full advantage at the time of actual pharmaceutical approval of RDV and other drugs. Clinical trials conducted in Japan with Japanese subjects have absolute value in evaluating the effectiveness of a drug, but when both time and resources are limited, as in the COVID-19 pandemic, verifying all treatments within Japan can be

difficult. Therefore, ways that will allow the Japanese people to quickly and safely use effective drugs need to be debated and decided from regular times, while maintaining the motivation to conduct clinical trials in Japan. This will involve questions such as how to use the results of clinical trials conducted only in other countries for pharmaceutical approval during future epidemics of new infectious diseases, and how to differentiate them from results of trials in which Japan participated.

Conclusion

There are hindrances in conducting disease-specific clinical trials, such as cases when the time from the outbreak of an infectious disease until the start of treatment is limited, the possibility of infecting healthcare workers exists, or the epidemic spreads in waves. Because of this, our experience with COVID-19 needs to be marshaled, and we need to start preparations, so that we are ready for an outbreak of the next emerging or re-emerging infectious disease. Clinical trials are essential for the development of drugs and treatment methods with evidence, and studies need to be planned with designs matched to the phase of development.

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