Global Health & Medicine. 2022; 4(2):137-140.

CORRESPONDENCE

DOI: 10.35772/ghm.2022.01024

Promotion of proper use of anti-SARS-CoV-2 drugs and SARS-CoV-2 vaccines by hospital pharmacists and establishment of an adverse drug reaction reporting system

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Abstract: Newly developed anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) drugs are being rapidly approved in countries worldwide. These new drugs are being approved after testing with a limited number of cases, and in real-world clinical practice, unknown and potentially serious adverse events that could not be detected in clinical trials may emerge. Accordingly, in the event of an adverse drug reaction for which a causal relationship with these new drugs cannot be ruled out, it is vital to promptly report the details of the case to the regulatory authorities. To date, through close cooperation between physicians and pharmacists, we have reported four cases of adverse drug reactions for which a causal relationship to anti-SARS-CoV-2 drugs cannot be ruled out. Herein, we introduce safety measures taken by pharmacists when using these new drugs in the hospital, and a system for reporting to the regulatory authorities when adverse events occur.

***Keywords*:** regulatory authorities, safety, adverse events, Japan

Introduction

New developments in the drugs to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are occurring daily. In Japan, drugs confirmed to be effective for SARS-CoV-2, including vaccines, have thus far been approved under the Special Approval system and these have been used in numerous cases in real-world clinical settings. Moreover, due to the characteristics of the SARS-CoV-2 virus, new variants are expected to emerge in the future, and many additional drugs capable of treating them are expected to become available. However, from a safety perspective, most of these new drugs are tested in pre-approval clinical trials with a limited number of cases, and in actual clinical settings they may be administered in cases in which the patient background does not match the eligibility criteria of the clinical trial. As such, there may be unknown adverse events that were not detected when the drug was approved or known adverse events that become more severe. Therefore, it is critical to collect and evaluate safety information on medical and pharmaceutical products licensed under Special Approval, and extremely careful monitoring is essential in the months immediately following approval.

In Japan, hospital medical staffs are obligated to make a report to the Pharmaceuticals and Medical Devices Agency (PMDA) if they become aware of a death or event suspected to be an adverse drug reaction (side effect). This is necessary to prevent the occurrence or spread of a health or hygiene hazard (*1*). It is crucial to establish a system at medical institutions to track the condition of patients to whom such drugs have been administered. When an adverse event occurs, it is important to refer the Risk Management Plan (RMP) and the clinical trial data from the time of the approval of the application, and make a report as soon as possible in order to prevent adverse drug reactions from becoming widespread. Herein, we introduce the system for safe usage of new anti-SARS-CoV-2 drugs and SARS-CoV-2 vaccines in use at the Department of Pharmacy, Center hospital of the National Center for Global Health and Medicine (NCGM), and provide examples of adverse event reports created through prompt information gathering and collaboration with physicians.

Current anti-SARS-CoV-2 drugs and vaccines

In Japan, five anti-SARS-CoV-2 drugs Remdesivir (7 May 2020), Baricitinib (23 April 2021), Casirivimab/Imdevimab (19 July 2021), Sotrovimab (27 September 2021), and Molnupiravir (24 December 2021) and three SARS-CoV-2 vaccines COMIRNATY® (14 February 2021), Spikevax® (21 May 2021), and Vaxzebria® (21 May 2021) have been approved under the Special Approval system (as of 4 February 2022).

Special Approval in Japan is a system that allows for the post-approval submission of materials other than the clinical trial documents typically required for application if a drug satisfies the following conditions: *i*) urgent use is necessary in the prevention of the spread of disease, *ii*) no proper method is available except the use of such drug, and *iii*) such drug is authorized for sale in a foreign country (*2*).

The therapeutic effects and safety of the drugs specially approved in Japan have largely been based on data from overseas Phase III trials. These data are Remdesivir (approximately 1,000 subjects) (*3*), Baricitinib (approximately 1,000 subjects) (*4*), Casirivimab/Imdevimab (approximately 5,600 subjects) (*5*), Sotrovimab (approximately 1,000 subjects) (*6*), Molnupiravir (approximately 1,900 subjects) (*7*), COMIRNATY® (approximately 44,000 subjects) (*8*), Spikevax® (approximately 30,000 subjects) (*9*), and Vaxzebria® (approximately 24,000 subjects) (*10*).

In addition to these data, evaluations are made based on data from domestic Phase I and II trials with tens to hundreds of subjects, or from the small number of Japanese patients participating in overseas Phase III trials. Thus, the amount of data from Japanese patients is extremely limited immediately after the approval.

Establishment of a system for introducing anti-SARS-CoV-2 drugs in the hospital

Each time a new anti-SARS-CoV-2 drug receives Special Approval, we create a checklist to confirm patient eligibility for the drug's administration. When the drug is prescribed, it is dispensed only after reviewing the checklist, prescription, and medical chart, and confirming that the eligibility criteria are met. In addition, physicians need to provide a number of instructions for the proper use of the drug when ordering a prescription, such as dosage, flow rate, amount of infusion to be diluted, and administration schedule. Therefore, as a measure to prevent medical errors, we set prescription orders on the electronic medical record system so that physicians can easily and accurately place these orders, enabling all physicians to place the appropriate orders as prescribed in advance.

At the NCGM, clinical pharmacists are assigned to each ward to check the dosage, flow rate, and clinical laboratory values to be monitored to ensure the proper use of drugs, not just specially approved drugs. These pharmacists have a range of roles, for example, checking the details of concomitant medications, adherence, and interactions. When injectable drugs are used, the pharmacists confirm the route of administration to avoid incompatibilities with other drugs, instruct nurses on how to prepare the drugs, and provide information on whether a filter is required for administration. In addition, they monitor for the occurrence of adverse drug reactions. When an adverse drug reaction is suspected, the clinical pharmacists share the information with physicians and the pharmacists of the Drug Information service.

At the NCGM, As shown in Figure 1, physicians and pharmacists work together smoothly to establish a system for prompt reporting of adverse drug reactions, which enables prompt reporting of adverse drug reactions to the PMDA.

The adverse drug reactions reporting system at the NCGM

When the pharmacists of the Drug Information service obtain information on a patient with a suspected adverse

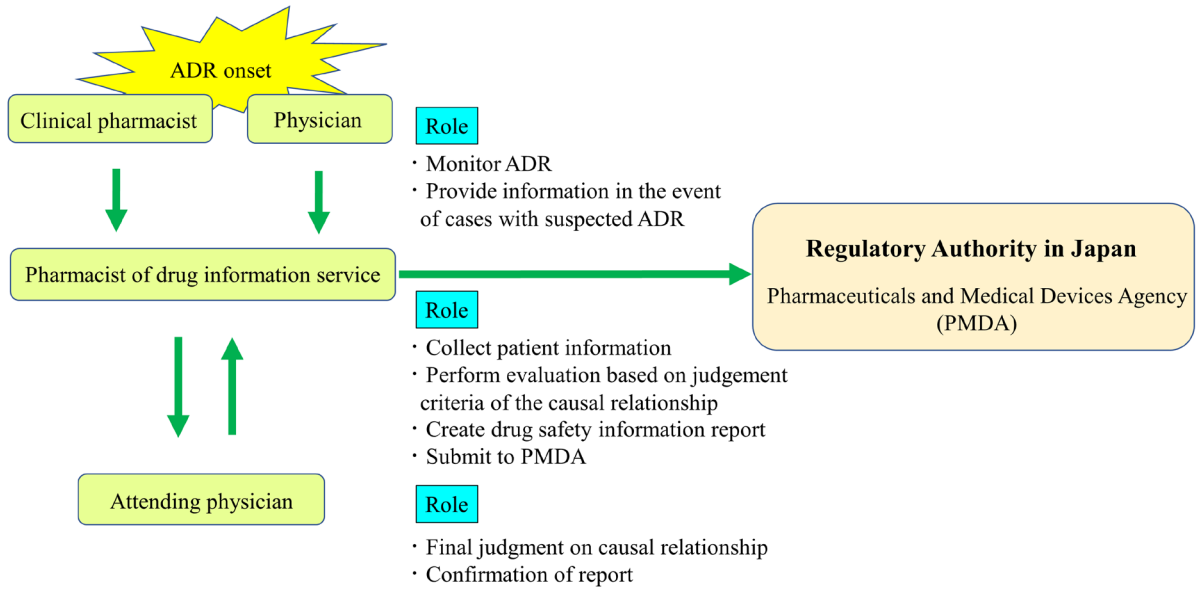

Figure 1. Procedure for reporting suspected adverse drug reactions (ADR) to Pharmaceuticals and Medical Devices Agency (PMDA).

Table 1. Cases of reported adverse drug reactions (ADR) to SARS-CoV-2 drugs or vaccines

Case No.	Sex	Age	Brand name (manufacturer)	Adverse drug reaction	No. of days from ADR onset to PMDA report
1	Male	50s	Remdesivir (GILEAD)	Rash	23
2	Female	60s	COMIRNATY® (Pfizer)	Hypertension and headache	21
3	Female	70s	COMIRNATY® (Pfizer)	Myocardial infraction	21
4	Male	10s	Spikevax® (TAKEDA)	Myocarditis	56

drug reaction from physicians or clinical pharmacists, they collect data on the patient's background (medical history, comorbidities), clinical laboratory values, history of administration of drugs including concomitant drugs, timing and course of the reaction, and severity. Furthermore, after collecting data on adverse events of the suspected drug that have been reported so far, the causal relationship between the suspected drug and the adverse event in the patient is comprehensively verified, and a Drug Safety Information Report (hereafter, DSIR) is prepared. There are several proposed methods for evaluating the degree of association between a suspected drug and an adverse event, but the NCGM evaluates causal relationships based on the criteria proposed in the report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI (*11*) and the Naranjo Scale (*12*). As there are minimal existing data on adverse events for specially approved drugs, causal relationships are carefully investigated based on the chronological clinical course, and the DSIRs are created with special emphasis on the temporal association between the period of drug administration and the onset of the adverse event. DSIRs are submitted to the PMDA after confirming with the physicians responsible for treatment that the final decision of the DSIR is consistent with their opinion.

So far, we have submitted 53 DSIRs in the last three years. For the twelve DSIRs from the past year, the median time to report was 49 days (range 14 to 157 days) from the date the adverse event occurred.

We have submitted the DSIRs to the PMDA for the four cases of adverse events to anti-SARS-CoV-2 drugs or SARS-CoV-2 vaccines specially approved after January 2021 (Table 1). Pharmacists in the drug information service submitted the DSIRs to the PMDA within 21 days of obtaining information in all the cases. In one of the four cases, adverse event information was obtained more than 30 days after the occurrence and as a result, the DSIR was submitted 56 days after onset. DSIRs were completed within 30 days of occurrence in the other three cases.

Case 1 (50s, male)

The second day after Remdesivir administration, an itching sensation was observed on the patients' arms and back, followed by itchiness of the face, trunk, and thighs, and a swollen, red rash which spread across the whole body. The rash disappeared with antihistamine and steroid administration. The Remdesivir was believed to be the cause, and its administration was discontinued thereafter. Afterwards, the patient's fever and pneumonia improved, and the discharge criteria were met, allowing him to be discharged seven days after symptom onset. A DSIR was made because this was a serious case in which a causal relationship between the symptom onset and Remdesivir could not be ruled out.

Case 2 (60s, female)

After receiving her second dose of COMIRNATY® at a different clinic, the patient reported dizziness and her systolic blood pressure was found to be elevated to around 180 mmHg. After this, the patient reported headache in the left temporal region and underwent a head CT scan. This indicated subarachnoid hemorrhage, and the patient was transferred to the NCGM. CT and MRI performed at the NCGM showed no evidence of subarachnoid hemorrhage, and the blood pressure stabilized at 100-120 mmHg with continuous administration of intravenous nicardipine. Subsequently, the symptoms abated, and the patient was discharged five days after symptom onset. Although headache has been reported to occur in 39% of patients ≥ 55 years following the second dose of COMIRNATY® (8), a DSIR was made in this case because there was blood pressure elevation and severe headache requiring hospitalization.

Case 3 (70s, female)

The patient experienced neck pain, nausea, weakness, and cold sweats after receiving her second dose of COMIRNATY®. Her symptoms did not improve after returning home, and she was brought to the NCGM by ambulance where she was diagnosed with myocardial infarction. After hospitalization, percutaneous coronary intervention (PCI) was performed, and she was discharged after eleven days. In addition to hypertension and dyslipidemia, the patient had untreated diabetes, and was thus at high risk for myocardial infarction, but a DSIR was made in this case because the heart attack occurred immediately after vaccination, and the possibility that vaccination triggered the onset of symptoms cannot be ruled out.

Case 4 (10s, male)

Three days after administration of Spikevax®, the

patient reported chest pain and was examined at the NCGM emergency room. Blood test results showed elevation of troponin I and the electrocardiogram showed ST elevation. Based on his clinical course the patient was admitted to the hospital on suspicion of vaccine-associated myocarditis. Over time, the chest pain improved, troponin I dropped to within normal limits, and the ST elevation on the electrocardiogram disappeared, so the patient was discharged after seven days. There are more frequent reports of myocarditis and pericarditis after Spikevax® administration compared to COMIRNATY®, and the Ministry of Health, Labour and Welfare website reports that these cases are often males between 10 to under 30 years of age within about four days of vaccination (*13*).

These findings were not known immediately after Spikevax® was approved, but have become clear as a result of extensive collection and evaluation of cases suspected of adverse events by medical institutions both in Japan and abroad. Although this is a known adverse event, we chose to make a DSIR because these findings may serve as reference data for vaccine selection for male patients in their teens and 20s who plan to get a SARS-CoV-2 vaccine in the future.

Conclusion

Pharmacists can contribute to the proper use of specially approved drugs by confirming the eligibility of patients when dispensing prescriptions and monitoring the drug effects and safety after administration. However, there are cases in which adverse events occur even when drugs are used appropriately.

As specially approved drugs are approved with a limited number of cases, obtaining information on adverse events at an early stage, collaboration between physicians and pharmacists, and prompt and detailed reporting of information on adverse drug reactions will prevent the spread of harm caused by adverse drug reactions and identify previously unknown events and contribute to building evidence and disseminating new information of benefit to patients.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received March 1, 2022; Revised March 28, 2022; Accepted April 4, 2022.

Released online in J-STAGE as advance publication April 9, 2022.

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