Evaluation of the Expression Time of Ganciclovir-Induced Adverse Events Using JADER and FAERS

Go Ando, a Kazuaki Taguchi, a, b Yuki Enoki, b Yuta Yokoyama, a Junko Kizu, a and Kazuaki Matsumoto a, b

a Division of Practical Pharmacy, Keio University Faculty of Pharmacy; 1–5–30 Shibakoen, Minato-ku, Tokyo 105–8512, Japan; and b Division of Pharmacodynamics, Keio University Faculty of Pharmacy; 1–5–30 Shibakoen, Minato-ku, Tokyo 105–8512, Japan.

Received February 16, 2019; accepted August 13, 2019

INTRODUCTION

The use of ganciclovir for cytomegalovirus infection in AIDS, organ transplantation (including hematopoietic stem cell transplantation), and malignant tumors has been approved, and it is the first choice for cytomegalovirus infection in patients with immunodeficiency. On the other hand, the development of adverse reactions, such as leukopenia, thrombocytopenia, anemia, liver dysfunction, and renal hypofunction, at a high frequency is described in the package insert of ganciclovir. Clarifying expression time of the incidence of these adverse reactions enables their prediction, and prevents their development and aggravation to a serious state, facilitating continuous ganciclovir treatment. However, information on onset time of adverse reactions cannot be acquired from the package insert or interview form.

Spontaneous adverse event report databases aim at the early discovery of adverse drug events and clarification of their incidence, and adverse reaction data are accumulated in great amounts by the regulatory authorities of each country. In Japan, the Pharmaceutical and Medical Device Agency (PMDA) has collected spontaneous adverse event reports of drugs for medical use, non-prescription drugs, and drugs requiring guidance since 2004, and more than 300,000 adverse event reports are open to the public as the Japanese Adverse Drug Event Report (JADER). JADER has been utilized in many retrospective studies,1-3 playing a major role in the safety evaluation of drugs in clinical practice sites in Japan.4

The U.S. Food and Drug Administration (FDA) opened the FDA’s Adverse Event Reporting System (FAERS) to the public, which is also a spontaneous adverse event report database similar to JADER.5,6 This system was started in 1996, and data from more than 7 million reports have been collected from the U.S. and other countries. Detecting adverse event signals by data mining of the adverse reaction reports accumulated in these databases will enable the clarification of the incidence of adverse drug events.5

The aim of this study was to evaluate the expression time of ganciclovir-induced adverse events by data mining of the adverse reaction reports, JADER, and FAERS. For this purpose, the number of reported cases of the main adverse reactions (cytopenia, leukopenia, thrombocytopenia, liver damage, and acute renal failure) of ganciclovir in JADER and FAERS were surveyed, and the incidence of these adverse reactions due to ganciclovir and their expression time were evaluated. For signal detection, the reporting odds ratio (ROR) and Weibull distribution, which are frequently used in safety evaluation of drugs, were calculated.7,8

METHODS

Data Analyzed For JADER data, the database updated in April 2016 was downloaded from the PMDA home page (https://www.pmda.go.jp/index.html), and data registered between the 1st quarter of 2004 and the 4th quarter of 2015 were used. For FAERS data, all reports registered by the 4th quar-
ter of 2015 were used. For summation and analysis, CzeekV (https://www.czeek.com/) was employed.

The drug analyzed was ‘ganciclovir’ and only reports in which ‘ganciclovir’ was described as the “suspected drug” were extracted. From FAERS, reports were extracted as a union of ganciclovir preparations among the countries. In cooperation with Kyoto Constella Technologies Co., Ltd., the names of 55 products containing ganciclovir (generic name) were extracted.

For extraction of adverse events listed in JADER and FAERS, the ICH Medical Dictionary for Regulatory Activities (MedDRA) was used. For the names of adverse events included in the analysis, standardized MedDRA queries (SMQ), in which MedDRA terms at the preferred term (PT) level were grouped, was used, and the following 5 types were specified: hematopoietic cytopenia (SMQ: 20000027), hematopoietic leukopenia (SMQ: 2000030), hematopoietic thrombocytopenia (SMQ: 2000031), liver damage (SMQ: 2000005), and acute renal failure (SMQ: 2000003). There are 2 ranges of PT in SMQ: “narrow,” which is used to detect reports likely to present the target adverse event, and “wide,” which is used to detect all possible reports. To accurately identify adverse reactions caused by ganciclovir, the range was specified to “narrow.”

Aggregated Data The numbers of ‘all reported cases,’ ‘reported cases regarding ganciclovir as the suspected drug,’ and ‘reported cases by SMQ analysis’ in JADER and FAERS were summed.

Analytical Method To evaluate each item, the ROR and its 95% confidence interval (95% CI) were used. When the lower limit of the 95% CI of the ROR exceeded 1, it was judged as a signal.

Table 1. Number of Reported Cases and ROR (95% CI) of Each SMQ

<table>
<thead>
<tr>
<th>SMQ</th>
<th>Number of Total Reported Cases</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenia</td>
<td>429 (387162)</td>
<td>12.76 (10.84–15.54)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>273 (46914)</td>
<td>6.17 (5.05–7.54)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>62 (15825)</td>
<td>3.98 (3.83–4.13)</td>
</tr>
<tr>
<td>Liver damage</td>
<td>42 (36918)</td>
<td>1.03 (0.75–1.42)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>35 (7405)</td>
<td>4.57 (3.23–6.46)</td>
</tr>
<tr>
<td>FAERS</td>
<td>1505 (7095703)</td>
<td>13.45 (12.06–15.00)</td>
</tr>
</tbody>
</table>

RESULTS

After excluding reports missing the age or sex, or those with unclear descriptions of the age from all JADER and FAERS data within the specified period, the total number of target cases was 387162 and 7095703 in JADER and FAERS, respectively (Table 1). Of these, the number of reports regarding ganciclovir as the suspected drug was 429 and 1505, respectively. The total number of cases of each adverse event was: cytopenia, 46914 and 230125, respectively; leukopenia, 29694 and 128261, respectively; thrombocytopenia, 15825 and 89265, respectively; liver damage, 36918 and 288090, respectively; and acute renal failure, 7405 and 161760, respectively (Table 1). Of these, the number of adverse events regarding ganciclovir as the suspected drug in each SMQ was: cytopenia, 273 and 467, respectively; leukopenia, 145 and 264, respectively; thrombocytopenia, 62 and 115, respectively; liver damage, 42 and 231, respectively; acute renal failure, 35 and 203, respectively (Table 1).

Number of Reported Cases and ROR (95% CI) of Each SMQ When the ROR (95% CI) of each SMQ in JADER (cytopenia, leukopenia, thrombocytopenia, liver damage, and acute renal failure) was analyzed, signals were detected for cytopenia, leukopenia, thrombocytopenia, and acute renal failure (Table 1). In contrast, the ROR (95% CI) of liver damage was 1.03 (0.75–1.42) with no signal detection (Table 1), suggesting that this adverse reaction is not specific to ganciclovir. On the other hand, unlike the ROR (95% CI) of each SMQ in the JADER analysis, signals were also detected for liver damage (ROR (95% CI): 4.29 (3.73–4.93)), in addition to cytopenia, leukopenia, thrombocytopenia, and acute renal failure.

Onset Time of Adverse Events The numbers of reported cases of adverse events regarding ganciclovir as the suspected drug by onset time in JADER and FAERS are shown in Figs. 1 and 2, respectively. In addition, the onset time of...
each ganciclovir-induced adverse event was analyzed using the Weibull distribution (Figs. S1, S2), and the Weibull distribution parameters are summarized in Table 2. The scale parameter \( \alpha \) values of total adverse events were within 30 in both JADER and FAERS (JADER: (29.4 (24.8–34.7)), FAERS: (26.9 (23.6–30.7)). In addition, the Weibull parameter \( \alpha \) values of each adverse event in both JADER and FAERS suggested that most adverse events occurred within 30d, except for liver damage in JADER (\( \alpha \) (95% CI): 48.4 (23.3–96.6)), acute renal failure in JADER (\( \alpha \) (95% CI): 32.8 (20.9–50.3)), and leukopenia in FAERS (\( \alpha \) (95% CI): 33.7 (25.4–44.3)). Furthermore, most \( \beta \) values of ganciclovir-induced adverse events in JADER and FAERS were less than 1, except for thrombocytopenia (\( \beta \) (95% CI): 1.15 (0.90–1.43)) and acute renal failure (\( \beta \) (95% CI): 1.21 (0.82–1.66)) in JADER, suggesting that the onset time of ganciclovir-induced adverse events is the early failure type.

**DISCUSSION**

Although the therapeutic effects of ganciclovir for cytomegalovirus infection in immunodeficient patients have been confirmed, the incidence of adverse reactions is not low, which is an obstacle for treatment continuation. In this study, using the spontaneous adverse event report databases JADER and FAERS, the incidence of adverse events due to ganciclovir as the suspected drug and their expression time were analyzed.

In the package insert, adverse reactions that decrease each blood cell type (cytopenia, leukopenia, and thrombocytopenia), liver damage, and acute renal failure are described as important adverse reactions of ganciclovir. When the ROR was calculated by these SMQ, signals were detected for cytopenia, leukopenia, thrombocytopenia, and acute renal failure, but no signal was detected for liver damage in JADER (Table 1). In FAERS, signals were detected for all SMQ, including liver damage (Table 1). The range of the 95% CI of the ROR increases and signal detection becomes unlikely when the num-

Fig. 1. Numbers of (A) Total Reported Adverse Events, (B) Cytopenia, (C) Leukopenia, (D) Thrombocytopenia, (E) Liver Damage, and (F) Acute Renal Failure Regarding Ganciclovir as the Suspected Drug by Onset Time in JADER

The following reported case by onset time was not described in the Figure, but included in each analysis: (A) 1124, 1372, 1479, and 1835d, (B) 1479d, and (C) 1479d.
The number of reported cases is small. The total number of reported cases in FAERS was approximately 18-times that in JADER (Table 1), suggesting that the range of the 95% CI of ROR was higher in JADER because of a smaller total number of reported cases, resulting in no signal detection. It is possible that signals will be detected as the number of reported cases increases in the future. Greater importance should be placed on ROR signals with a lower 95% CI limit of 2 or higher.

The overall ROR of each SMQ exceeded 2 in both databases, excluding liver damage in JADER, demonstrating that these SMQ are representative adverse reactions of ganciclovir.

To properly use drugs, clarification of the onset time of adverse reactions is necessary.

### Table 2. The Weibull Parameter of Each Ganciclovir-Induced Adverse Event in JADER and FAERS

<table>
<thead>
<tr>
<th>Event</th>
<th>JADER</th>
<th>FAERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case (n)</td>
<td>Case (n)</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>383 29.4 (24.8–34.7) 0.64 (0.60–0.68)</td>
<td>668 26.9 (23.6–30.7) 0.61 (0.58–0.64)</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>203 20.3 (16.6–24.7) 0.73 (0.67–0.80)</td>
<td>212 25.6 (20.7–31.5) 0.68 (0.62–0.75)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>99 21.0 (15.2–28.7) 0.66 (0.58–0.75)</td>
<td>126 33.7 (25.4–44.3) 0.67 (0.59–0.75)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 11.4 (8.5–15.0) 1.15 (0.90–1.43)</td>
<td>62 15.7 (10.6–23.1) 0.69 (0.57–0.81)</td>
</tr>
<tr>
<td>Liver damage</td>
<td>22 48.4 (23.3–96.6) 0.65 (0.46–0.87)</td>
<td>123 12.0 (9.3–15.4) 0.75 (0.66–0.84)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>17 32.8 (20.9–50.3) 1.21 (0.82–1.66)</td>
<td>88 14.6 (10.0–21.1) 0.61 (0.52–0.70)</td>
</tr>
</tbody>
</table>

![Fig. 2. Numbers of (A) Total Reported Adverse Events, (B) Cytopenia, (C) Leukopenia, (D) Thrombocytopenia, (E) Liver Damage, and (F) Acute Renal Failure Regarding Ganciclovir as the Suspected Drug by Onset Time in FAERS](image-url)
adverse reactions enables medical care workers, including physicians and pharmacists, to take countermeasures against adverse reactions, through which their development and aggravation of adverse reactions can be prevented.13) Focusing on Figs. 1 and 2, approximately 60% of each adverse reaction due to ganciclovir developed within 4 weeks, indicating that the incidence of each adverse event seemed to be developed at early time after ganciclovir administration. Recently, the Weibull distribution is used to detect the signals for adverse events by utilizing time-to-events data.14–17) Thus, we evaluated the time-to-onset of ganciclovir-induced adverse events using Weibull distribution parameters. The results of both scale parameter $\alpha$ and shape parameter $\beta$ of total adverse events in JADER suggested that ganciclovir-induced adverse reactions including cytopenia, leukopenia and liver damage develop early in most cases (the early failure type) (Table 2). However, the $\beta$ values (95% CI) of thrombocytopenia and acute renal failure in JADER indicated that the incidence of these adverse events were ‘the random failure type’ (Table 2). On the other hand, all $\beta$ values in FAERS were less than 1. The contradictory results between JADER and FAERS may be due to the difference in the number of reported cases. As mentioned above, the number of cases influences the signal detection when analyzing extracted data from big databases. In the present study, the numbers of reported cases of thrombocytopenia and acute renal failure in FAERS were approximately 1.5- and 5-times larger than those in JADER (Table 2). Furthermore, all cases of thrombocytopenia in JADER developed within 36d after starting ganciclovir. Thus, sufficient attention to signs of adverse reactions is needed from the early phase when ganciclovir is administered. However, in FAERS, approximately 11% of all cases developed after 113d (Fig. 2A), suggesting that long-term periodic monitoring may be also necessary in addition to attention in the early phase.

The limitations of the present study must be noted. In this study, we evaluated the comparative strength of relationship between ganciclovir and adverse events using the ROR and its 95% CI. Although the ROR provides sufficient evidence to examine the relationship between drugs and single event (adverse effect), a spontaneous reporting system contains numerous biases and confounding variables.18) In previous studies, the ROR was adjusted by logistic regression analysis to minimize the effects of confounding variables when it detects the comparative strength of the relationship between drugs and adverse events.19,20) As the adjusted ROR is expected to provide more beneficial information, further logistic regression analyses, which include confounding variables—such as sex, age, and concomitant drugs, are needed to detect the signals of each ganciclovir-induced adverse effect.

Data from adverse reaction reports of ganciclovir from Japan alone are insufficient with regard to the number of reported cases. By adding the analytical results of overseas big data, such as of FAERS, to the analytical results of JADER, the incidences of adverse events can be clarified. However, the formulation, dose, racial difference, and the system and method of spontaneous adverse reaction reports vary among countries, and application of overseas data to clinical practice sites in Japan is difficult. As accurate analysis of adverse reactions in Japanese will become possible as the number of reported cases of adverse reactions in Japan increases, actively reporting adverse reactions of many drugs, not limited to ganciclovir, may also be an important duty of pharmacists. Development of a method to apply overseas data to clinical practice sites in Japan in consideration of formulations in other countries is also desired.

Acknowledgment This work was supported by a research Grant from Keio University.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

REFERENCES


