Analysis of Prednisolone-Induced Osteoporosis Using the Japanese Adverse Drug Event Report Database

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ABSTRACT -- Purpose: Osteoporosis is an adverse event of prednisolone. This study aimed to assess prednisolone-induced osteoporosis (PIO) profiles and patient backgrounds by analyzing data from the Japanese Adverse Drug Event Report (JADER) database. **Methods:** The current study focused only on orally administered prednisolone. PIO was defined using preferred terms from the Medical Dictionary for Regulatory Activities. Reporting odds ratio (ROR) at 95% confidence interval (CI) and the time-to-onset profile of PIO were used to evaluate adverse events. **Results:** The RORs (95% CI) of the female and male subgroups were 4.73 (4.17–5.38) and 2.49 (2.06–3.00), respectively. The analysis of time-to-onset profiles demonstrated that the median values (interquartile range: 25.0–75.0%) of PIO were 136 (74.0–294.0). The prednisolone treatment duration was significantly longer in the PIO patient group than in the non-PIO patient group. The findings suggest that patients with rheumatoid arthritis, systemic lupus erythematosus, and nephrotic syndrome receiving prednisolone have different age-related PIO profiles. **Conclusions:** Our results suggest that longer prednisolone treatment duration and larger cumulative dose might be risk factors of PIO. The potential risk for PIO should not be overlooked, and careful observation is recommended.

INTRODUCTION

Glucocorticoids are widely used to treat diseases including asthma, rheumatoid arthritis (RA), nephrotic syndrome, and systemic lupus erythematosus (SLE). Osteoporosis is a disease in which bone metabolism is lost, and fractures caused by falling or sneezing are readily revealed, as evidenced by their occurrence in as many as 30–50% of patients receiving glucocorticoid therapy (1). Prednisolone-induced osteoporosis (PIO) is the most common and serious form of secondary osteoporosis (1) and can have a significant social impact on individuals and reduce their quality of life. Therefore, appropriate clinical care is required for this condition.

Various risk factors contribute to osteoporosis, including age, sex, RA, glucocorticoid therapy, and most notably, prednisolone administration. The risk of vertebral fractures may increase even in patients taking <5 mg of prednisolone daily (2). In relation to PIO, several studies have reported daily (2) and cumulative doses (3) of prednisolone. To the best of our knowledge, this is the first study to evaluate PIO in terms of the patient's primary disease, dose, treatment duration, and cumulative dose.

Spontaneous reporting systems (SRSs) such as the Japanese Adverse Drug Event Report (JADER) of the Pharmaceuticals and Medical Devices Agency (PMDA) have been used for pharmacovigilance assessments. They are a valuable tool for assessing the safety of medicines. Similarly, the reporting odds ratio (ROR) is a useful tool to determine the relationship between medicines and adverse events (AEs) (4,5). This study aimed to assess PIO profiles and patients' backgrounds using data from the JADER database. PIO was evaluated by determining and analyzing the RORs and time-to-onset of AEs. The latter is important in assessing the onset duration of side effects.

MATERIALS AND METHODS

Data source

AE reports sent to and fully anonymized by the PMDA constitute the JADER database. To conduct this study, AE records entered in the database from April 2004 to November 2020 were downloaded from the PMDA website (www.pmda.go.jp). The JADER database consists of four tables: DEMO (patient demographic information), DRUG (drug information), HIST (primary disease), and REAC (AE and outcome). Drug information (DRUG) includes the route of administration: oral and the anticipated degree of involvement in AEs: suspected, interacting, and concomitant drugs. The JADER database was integrated into a relational database using FileMaker Pro Advanced 17 (FileMaker, Inc., Santa Clara, CA, USA). Data on suspected drugs and oral administration were extracted and analyzed in this study.

Definition of AEs

The AEs in the JADER database was coded according to the terminology used in the Medical Dictionary for Regulatory Activities/Japanese version 23.1 (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php).

The standardized MedDRA Queries (SMQ) are groupings of MedDRA terms, ordinarily at the preferred term (PT) level, related to a defined medical condition or area of interest. We used the SMQ index "osteoporosis/osteopenia" (SMQ code: 20000178) and 68 PTs. There were 19 PTs with one or more reports related to patients who accepted prednisolone (Table 1 and Figure 1).

Statistical analysis of the parameters of interest from the JADER database

We analyzed the daily dose, treatment duration, cumulative dose, time-to-onset, and primary disease of PIO patients. After calculating the dosage and period, data from patients who received >60 mg of prednisolone per day and those with no written units of prednisolone weight were excluded from the study. This step was taken because the recommendation, according to the package insert for adults, is 5−60 mg of prednisolone orally administered in one to four divided doses daily (6).

Daily dose was calculated by multiplying the dosage and number of divided doses recorded in the DRUG table. When analyzing the treatment duration, we considered a period of over 1,095 days (three years) as 1,095 days (7). If plural duration or dosage per patient were reported, they were analyzed individually. The cumulative dose was calculated by multiplying the daily dosage and treatment duration. Daily dose, treatment duration, and cumulative dose were analyzed using the Anderson–Darling test. We conducted a Wilcoxon rank-sum test to compare the differences between the patients with and without osteoporosis. The contingency table was graphically displayed in a mosaic plot. To compare proportions between multiple categories, Fisher's exact test was applied to a statistical significance test used in the analysis of n × m contingency tables. We worked with the null hypothesis that there are no differences between the classes in the population.

Stratification according to the patients' underlying diseases

When analyzing the diseases underlying PIO, we considered the SMQs for the three predominant diseases. The SMQ for SLE (SMQ code: 20000045) contained 115 PTs, and 11 PTs were summarized with one or more reports (Table 1). For RA, the PT "rheumatoid arthritis" (PT code: 10039073) present in arthritis (SMQ code: 20000216) was used. For nephrotic syndrome, the PT "nephrotic syndrome" (PT code: 10029164) contained in "chronic kidney disease" (SMQ code: 20000213) was used. For patient background analysis, those with two or three of the three diseases were excluded from the study.

Signal detection

ROR is an authorized pharmacovigilance index (8), which was calculated to assess the relationship between prednisolone and osteoporosis in this study. Here, the ROR is the ratio of the odds of reporting AEs versus all other events associated with prednisolone to the reporting odds for all other drugs present in the database. We calculated the ROR using the two-by-two contingency table involving a drug and an AE of interest described in the case reports (Table 2) (8). A signal was defined as the lower limit of the 95% confidence interval (CI) of the ROR being greater than one.

Time-to-onset

Time-to-onset was calculated as the time from the administration of the first dose of the drug to the occurrence of AEs. The median duration, quartiles, and Weibull shape parameters (WSPs) were used to assess time-to-onset data (9,10). The WSP test was used to analyze the time-to-onset data statistically

Table 1. Preferred terms associated with osteoporosis, rheumatoid arthritis, systemic lupus erythematosus and nephrotic syndrome

SMQ CATEGORY	SMQ CODE	PREFERRED TERM	CODE
OSTEOPOROSIS/OSTEOPENIA	20000178	Osteoporosis (114 cases)	10031282
		Osteoporotic fracture (27 cases)	10031290
		Atypical femur fracture (73 cases)	10070884
		Body height below normal (1 case)	10056811
		Bone metabolism disorder (1 case)	10058972
		Femoral neck fracture (34 cases)	10016450
		Femur fracture (50 cases)	10016454
		Fracture (9 cases)	10017076
		Ilium fracture (2 cases)	10021343
		Lumbar vertebral fracture (10 cases)	10049947
		Pathological fracture (8 cases)	10034156
		Pelvic fracture (8 cases)	10061161
		Radius fracture (2 cases)	10037802
		Rib fracture (8 cases)	10039117
		Short stature (6 cases)	10040600
		Spinal compression fracture (94 cases)	10041541
		Spinal fracture (5 cases)	10041569
		Stress fracture (5 cases)	10042212
		Thoracic vertebral fracture (8 cases)	10049948
SYSTEMIC LUPUS ERYTHEMATOSUS	20000045	Lupus nephritis (10 cases)	10025140
		Systemic lupus erythematosus (39 cases)	10042945
		Arthritis (1 case)	10003246
		Pericardial effusion (2 case)	10034474
		Pleural effusion (1 case)	10035598
		Epilepsy (1 case)	10015037
		Seizure (1 case)	10039906
		Autoimmune haemolytic anaemia (1 case)	10073785
		Immune thrombocytopenia (4 cases)	10083842
		Platelet count decreased (2 cases)	10035528
		White blood cell count decreased (1 case)	10047942
ARTHRITIS	20000216	Rheumatoid arthritis (72 cases)	10039073
CHRONIC KIDNEY DISEASE	20000213	Nephrotic syndrome (14 cases)	10029164

SMQ: STANDARDIZED MEDDRA QUERIES

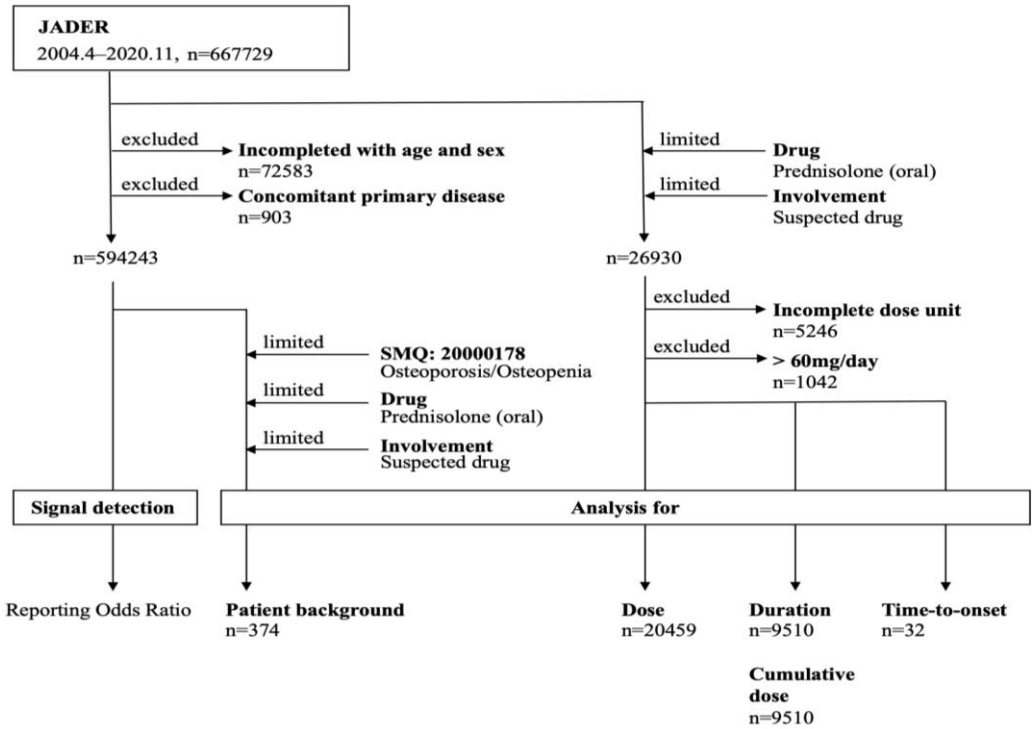

Figure 1. Flowchart of data analysis

and describe the non-constant ratio of incidence of AEs. In the WSP test, β determines the shape of the distribution function. If the β value equals 1, the hazard was constant over time. If both β and the 95% CI of β are >1, the hazards were estimated to increase over time. Finally, if β is <1 and the 95% CI of β excluded 1, the hazards were estimated to decrease over time (4,11,12).

Data analysis involving the Anderson–Darling and Wilcoxon rank-sum tests were performed using JMP Pro 16 (JMP Statistical Discovery, Cary, NC, USA). The Fisher's exact test was performed using R v. 4.1.2 software.

Table 2. Two-by-to contingency table for calculating reporting odds ratio

	Adverse event of interest	All other adverse event of interest	Total
Drug of interest	a	b	a + b
All other drug of interest	c	d	c + d
Total	a + c	b + d	a + b + c + d

Reporting odds ratio (ROR)= (a/c)/(b/d)= ad/bc

95% confidence interval (CI)= exp [log (ROR) ± $1.96\sqrt{1/a + 1/b + 1/c + 1/d}$]

RESULTS

The JADER database contained 667,729 reports from April 2004 to November 2020. The number of AEs corresponding to the number of osteoporosis reports was 5,752. The number of reported cases of osteoporosis in which oral prednisolone was a suspected drug was 374. The RORs (95% CI) of prednisolone administered to female and male subgroups were 4.73 (4.17–5.38) and 2.49 (2.06–3.00), respectively (Table 3). The RORs of PIO in each primary disease, namely RA, SLE, and nephrotic syndrome, were 2.97 (2.34–3.77), 6.11 (4.61–8.11), and 7.75 (4.52–13.30), respectively.

The average (mean ± standard deviation) of the daily dose, treatment duration, and cumulative dose in PIO patients were 14.9±12.2 mg, 121±242 days, and 1387±3764 mg, respectively (Table 4). The distributions of the daily dose, treatment duration, and cumulative dose were inconsistent with normal distribution according to the Anderson–Darling test. According to the Wilcoxon rank-sum test, prednisolone treatment duration in patients with osteoporosis was statistically longer than that in patients without osteoporosis (P=0.0243). The cumulative dose of prednisolone in patients with osteoporosis was statistically larger than that in patients without osteoporosis (P=0.0472). Time-to-onset analysis revealed that the median value (25–75%) of PIO was 136 (74.0–294.0), while the β value (95% CI) of PIO was 1.13 (0.85–1.45).

We used a mosaic plot to summarize the proportion of PIO patients who used oral prednisolone as a suspected drug based on age (Figure 2). In the mosaic plots of PIO patients, the following significantly different categorical features were detected using Fisher's exact test: All: P=0.00050 (Figure 2A), Male: P=0.00028 (Figure 2B), and Female: P=0.00005 (Figure 2C). A Fisher's exact test using the relevant contingency table revealed that gender was not significant for RA, SLE, and nephrotic syndrome (Table 5).

DISCUSSION

Prednisolone is widely used in clinical practice. However, PIO accounts for 20% of all osteoporosis cases and is regarded as a major clinical problem (13). Unfortunately, the available information on the effectiveness of prevention and treatment of PIO is insufficient, and adequate preventive measures are not being taken (1,13). To contribute to the ongoing research on PIO prevention and treatment, we analyzed AE signals for PIO in the JADER database. Our results suggest that patients with RA, SLE, and nephrotic syndrome receiving prednisolone possess different PIO profiles and should be carefully monitored.

Many studies have focused on the daily and cumulative doses of prednisolone. Some studies have stated that the daily dose may be associated with osteoporosis (2), while others report that the cumulative dose may be strongly linked to osteoporosis (3). In our study, the cumulative dose seemed to influence PIO and the treatment duration was significantly longer in the PIO patient group than in the non-PIO patient group (Table 4).

The time-to-onset profiles of PIO were systematically analyzed using the JADER database. According to our analysis, the median duration of PIO was 136 days, consistent with the results of another study that indicated that the peak time-to-onset was 3–6 months (14).

We investigated the relationship between the primary disease and PIO. Our results indicated a relationship between PIO and RA in patients over the age of 50 years (Figure 2 and Table 5). In Japan, the

Table 3. Reporting odds ratio for osteoporosis

	Prednisolone	Total (n)	Case (n)	ROR (95% CI)
Total	+	13429	374	3.82 (3.43–4.25)
Female	+	7432	259	4.73 (4.17–5.38)
Male	+	5997	115	2.49 (2.06–3.00)
Primary disease				
Rheumatoid arthritis	+	3054	70	2.97 (2.34–3.77)
	-	20254	265	1.70 (1.50–1.93)
Systemic lupus erythematosus	+	1107	51	6.11 (4.61–8.11)
	-	19670	145	0.929 (0.787–1.10)
Nephrotic syndrome	+	241	14	7.75 (4.52–13.3)
	-	1304	6	0.579 (0.260–1.29)

ROR: Reporting Odds Ratio. CI: Confidence Interval.

Table 4. Comparison of daily dose, treatment duration and cumulative dose

	Osteoporosis	n	Mean±SD	P-value
Daily dose (mg)	+	489	14.9±12.2	0.290
	-	19970	16.9±14.7	
Treatment duration (days)	+	190	121±242	0.0243*
	-	9320	97.0±207	
Cumulative dose (mg)	+	190	1387±3764	0.0472*
	-	9320	1154±3230	

* Wilcoxon rank-sum test

Table 5. Characteristics of case-associated with Nephrotic syndrome, Systemic lupus erythematosus, and Rheumatoid arthritis.

		Age								
	Total	**<10**	**10–19**	**20–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**≧80**
Rheumatoid arthritis										
Male	10	0	0	0	0	0	0	2 (20.0%)	5 (50.0%)	3 (30.0%)
Female	60	0	0	0	0	0	10 (16.6%)	23 (38.3%)	21 (35.0%)	6 (10.0%)
Systemic lupus erythematosus										
Male	8	0	1(12.5%)	0	1(12.5%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	0	2 (25.0%)
Female	43	1 (2.3%)	1(2.3%)	0	9(20.9%)	10 (23.3%)	13 (30.2%)	7 (16.3%)	1 (2.3%)	1 (2.3%)
Nephrotic syndrome										
Male	11	2 (18.2%)	2(18.2%)	0	7(63.6%)	0	0	0	0	0
Female	3	1 (33.3%)	1(33.3%)	0	0	0	0	0	0	1 (33.3%)
Others										
Male	86	4 (4.7%)	8 (9.3%)	1 (1.2%)	13 (15.1%)	6 (7.0%)	6 (7.0%)	31 (36.0%)	9 (10.5%)	8 (9.3%)
Female	153	1 (0.7%)	5 (3.3%)	3 (2.0%)	5(3.3%)	15 (9.8%)	26 (17.0%)	33 (21.6%)	47 (30.7%)	18 (11.8%)

mean age at RA onset increased from 55.8 years in 2002–2003 to 59.9 years in 2012–2013 (15). The non-vertebral fracture rate increases sharply with age in females, and age is strongly associated with the increasing frequency of fractures in the vertebrae and at the proximal end of the femur (16). However, our data suggest that there is no statistical gender difference in the incidence of PIO in RA. Inflamed synovial tissues produce pro-inflammatory factors (mainly TNFα, IL1, and IL6) that can interfere with the differentiation and function of osteoblasts and osteoclasts in RA (17,18). In addition to these factors, the risk of osteoporosis may increase because of a decline in physiological function with an increase in age.

SLE affects many organs, particularly the kidneys with a rate of 50% (21). Lower bone mineral density is observed in SLE patients (20). It is about nine times more common in women than in men and is often diagnosed in the reproductive age (19). In our study, the percentage of SLE among PIO cases in females in the 30–39, 40–49, and 50–59 age groups were 64%, 40%, and 27%, respectively. Thus, SLE may be a risk factor for PIO; however, thus far, no detailed study has been conducted on this issue. As prednisolone is used to treat SLE, apprpriate measures must be taken to prevent PIO occurrence.

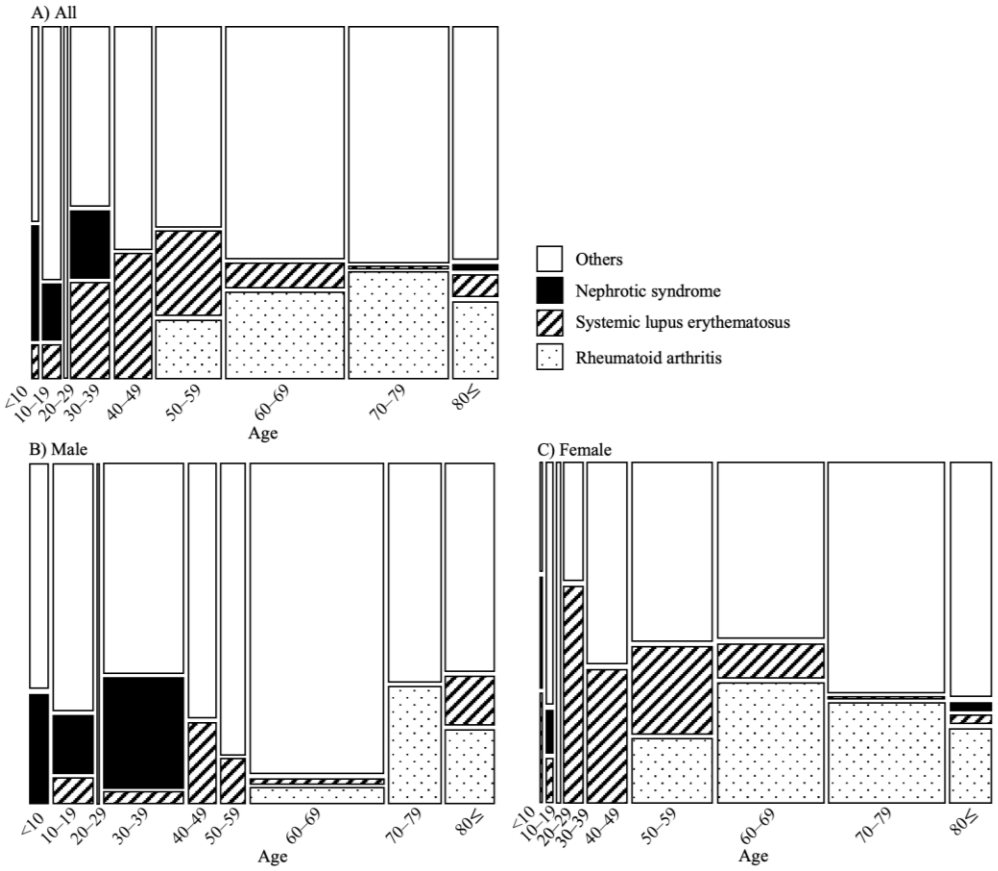

Figure 2. Stratification of the percentage of patients with the primary disease based on age. Mosaic plots of contingency tables were constructed using the age (X) and primary disease (Y) of patients who developed PIO. Proportions on the X-axis represent the number of observations at each level of the X variable. The mosaic plot is divided into rectangles, and the vertical length of each rectangle is proportional to the magnitude of the Y variable at each level of the X variable.

As prednisolone is the treatment of choice for managing nephrotic syndrome, it may possibly interfere with the growth of children (22). Other studies have shown that males are overrepresented in pediatric nephrotic syndrome, and as patients get older, the difference between men and women seems to disappear (23). Our results also showed a high percentage of male patients with concomitant nephrotic syndrome under 20 and 30–39 years of age, above which the prevalence of nephrotic syndrome decreased. However, there was no statistical gender difference in the incidence of PIO in nephrotic syndrome.

As the JADER database is an SRS, several limitations of the present analysis should be noted. First, SRSs are subject to over-reporting, under-reporting, missing data, exclusion of healthy individuals, lack of denominators, and presence of confounding factors (24,25). Second, it is difficult to draw general conclusions from subgroups with small population size without avoiding some bias owing to the imbalance in the number of cases. Third, detailed background information, such as genetic information and medical history, was not included. Therefore, further epidemiological studies should be conducted to confirm our results. Finally, as this study focused only on orally administered prednisolone, further research on other routes of administration is required.

CONCLUSION

In conclusion, patients with RA, SLE, and nephrotic syndrome who receive prednisolone are potentially at risk for osteoporosis. Our results suggest that longer prednisolone treatment duration and larger cumulative dose might be risk factors of prednisolone-induced osteoporosis. Despite the limitations associated with SRS data, our results promote the understanding of this condition, and will

help in developing clinical practices for the efficient management of the related adverse events.

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CONFLICT OF INTEREST. Shiori Hasegawa is an employee of Kaneichi Pharmaceutical. Co., Ltd. Mari Iwata is an employee of Kifune Pharmacy. The rest of the authors have no conflict of interest.

AUTHOR CONTRIBUTIONS. Wataru Wakabayashi and Mitsuhiro Nakamura contributed to the overall concept and design of the study. Wataru Wakabayashi, Mizuki Tanaka, and Mitsuhiro Nakamura wrote the main manuscript. Shiori Hasegawa, Mayuko Masuta, Hiroaki Uranishi and Mitsuhiro Nakamura created the relational JADER database system used in the work. Mizuki Tanaka, Kiyoka Matsumoto, Riko Satake, Misaki Inoue, Yu Yoshida, Keita Oura, Takaaki Suzuki and Mari Iwata carried out data extraction and statistical analysis. Mika Maezawa contributed important intellectual content in the statistical analysis. Shiori Hasegawa, Mika Maezawa, Hiroaki Uranishi, and Mayuko Masuta revised the article critically for important intellectual content. All authors have reviewed the manuscript.

ETHICS APPROVAL. Ethical approval was not sought for this study because it was a retrospective observational study without any research subjects. All results were obtained from data openly available online from the PMDA websites.

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