

Assessment of Time-to-onset and Outcome of Lung Adverse Events With Pomalidomide from a Pharmacovigilance Study

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Abstract. *Background/Aim:* Pomalidomide is an immunomodulatory drug that is used to treat multiple myeloma. We examined the time-to-onset and outcome of lung adverse events (LAEs) related to pomalidomide in Japanese patients based on information obtained from the spontaneous reporting system of the Japanese Adverse Drug Event Report database (JADER) of the Pharmaceuticals and Medical Devices Agency. *Patients and Methods:* We analyzed adverse events (AEs) reports recorded between April 2004 and March 2021 from JADER. Data on LAEs were extracted, and the relative risk of AEs was estimated using the reporting odds ratio and 95% confidence interval. We analyzed 1,772,494 reports and identified 2,918 reports of AEs caused by pomalidomide. Of these, 253 LAEs were reportedly associated with pomalidomide. *Results:* Signals were detected for five LAEs: pneumonia, pneumocystis jirovecii pneumonia, bronchitis, pneumonia bacterial, and pneumonia pneumococcal. Pneumonia was the most frequently mentioned condition (68.8%). The median time-to-onset of pneumonia was 66 days, but some cases of pneumonia occurred as late as 20 months after the start of administration. Fatal outcomes were observed in two of the five AEs wherein signals were detected and were due to pneumonia and bacterial pneumonia. *Conclusion:* Serious

outcomes can occur after pomalidomide administration. It has been suggested that these LAEs occur relatively early after pomalidomide administration. Since some situations can result in fatal consequences, patients should be monitored for the emergence of these AEs over a prolonged period of time, especially for pneumonia.

Pomalidomide, a thalidomide derivative, is an immunomodulatory drug (IMiD) that is used to treat multiple myeloma (MM). Pomalidomide is administered orally; thus, injections are not necessary, and treatment can be provided on an outpatient basis. Pomalidomide is used in salvage therapy in combination with other agents in cases of nonresponse to standard therapy or relapse/refractory MM (1, 2). Clinical use of IMiDs, such as pomalidomide, has significantly improved long-term survival and quality of life for patients with MM (3). The main therapeutic mechanisms of pomalidomide are its immunomodulatory, antiproliferative, and antiangiogenic effects (4-6). In addition, Yamamoto *et al.* recently demonstrated that pomalidomide has superior anticancer activity by degrading ARID2 in addition to its known targets (7). ARID2 is highly expressed in relapsed/refractory MM.

However, pomalidomide can cause several adverse events (AEs). Of these, hematological toxicity is the most common serious AE, and others include fatigue, constipation, diarrhea, rash, and thrombosis (1, 2, 8). In contrast, lung adverse events (LAEs) attributable to pomalidomide have received little attention in clinical trials, despite their life-threatening potential. Furthermore, although pomalidomide has been widely used in patients since its launch, no detailed information on LAEs from post-marketing monitoring has been reported. Inadequate management of AEs may force the discontinuation of pomalidomide therapy until the events are controlled, which may result in patient disadvantages, such as decreased efficacy.

The spontaneous AEs reporting database is a database maintained by regulatory authorities as part of post-

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Key Words: Pomalidomide, lung adverse events, Japanese Adverse Drug Event Report database (JADER).



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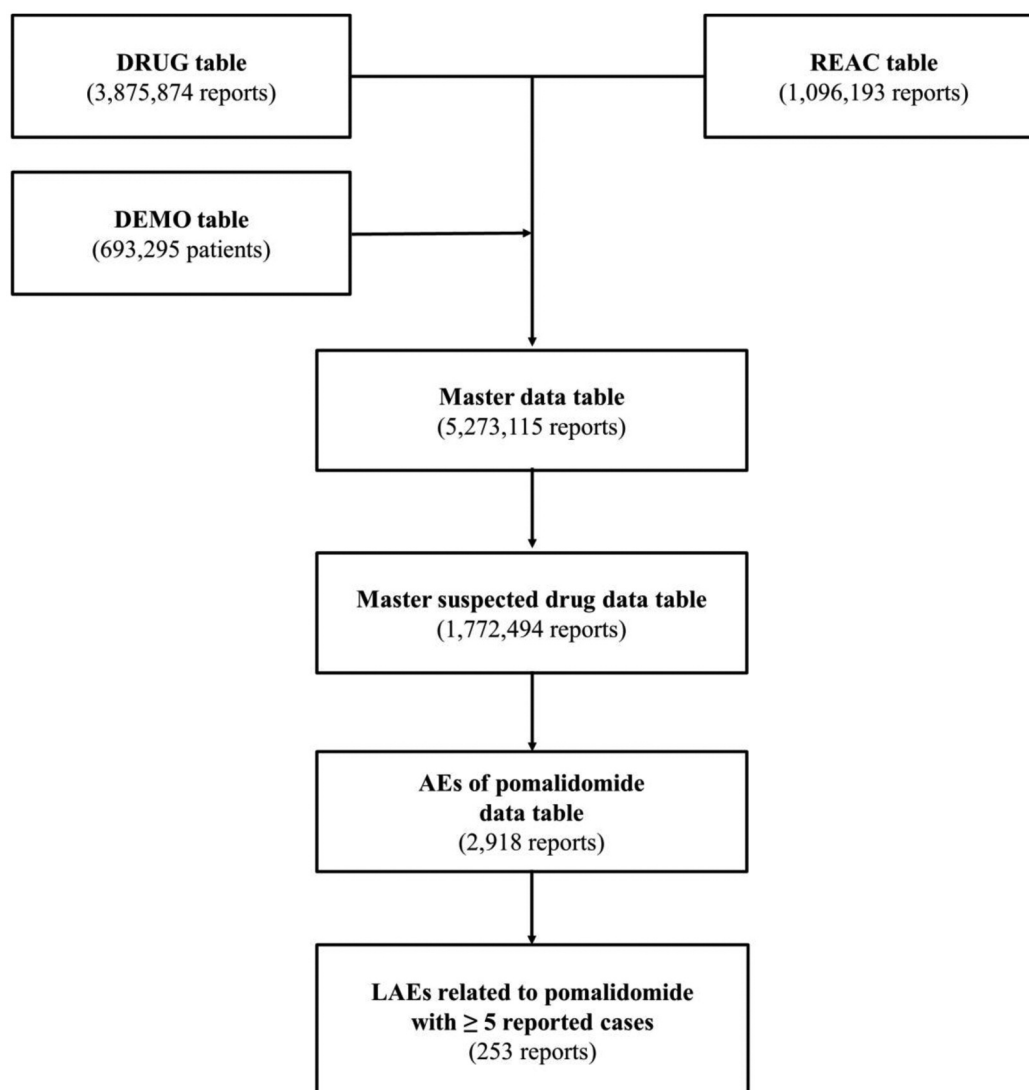


Figure 1. Process of constructing a data analysis table.

marketing drug safety measures. Using the spontaneous AEs reporting database to identify safety signals may be a valid strategy to hypothesize about possible drug relationships to unknown or potential AEs. Therefore, we examined the time-to-onset and outcome of LAEs related to pomalidomide in Japanese patients based on information obtained from the spontaneous reporting system of the Japanese Adverse Drug Event Report database (JADER) of the Pharmaceuticals and Medical Devices Agency (PMDA).

Patients and Methods

Data sources. We used data from the public release of the JADER database. This database is available for free download from the PMDA website (9) and includes AE cases. We analyzed AE reports

recorded between April 2004 and March 2021. The data structure of the JADER consists of four datasets: patient demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history (HIST). The REAC table uses the Medical Dictionary for Regulatory Activities/Japanese version 24.1 to codify the AEs, which are indicated as “Preferred Terms (PT)”. Initially, we removed duplicate cases from the DRUG and REAC tables. We then used the identification number of each AE case to merge corresponding case data from the DRUG, REAC, and DEMO tables. The medication contributions to the AEs were classified as “suspected medicine”, “concomitant medicine”, and “interaction.” We only extracted cases that were classified as “suspected medicine”, which included 1,772,494 reports. We analyzed this data table and obtained 2,918 reports of AEs caused by pomalidomide. Of these, 253 LAEs were reported to be associated with pomalidomide (Figure 1).

Definition of AEs. For each LAEs, we used data with at least five reports. Each lung-related AE coded according to the terminology recommended by the Medical Dictionary for Regulatory Activities was collectively referred to as LAE in this study.

Signal detection. We evaluated the association of LAEs with pomalidomide based on the reported odds ratios (RORs). ROR is frequently used in the spontaneous reporting database as an indicator of the relative risk of AEs. We used the analysis data table and constructed 2x2 tables based on two classifications: the presence or absence of the LAEs and the presence or absence of suspected pomalidomide use. We next calculated the ROR as the reporting rate of a LAE caused by pomalidomide divided by the rate of the same adverse event caused by all other drugs present in the database. LAE signals were considered positive when the lower limits of the 95% confidence intervals (95% CIs) of the ROR were >1 (10).

Time-to-onset analysis. The onset time of LAE was calculated based on the report by Hirooka *et al.* (11), and the principle onset time was "(onset date of AE) - (start date of administration) + 0.5" (12). The time-to-onset of AEs for analysis was limited to 2 years (730 days) (13).

The scale parameter α of the Weibull distribution determines the scale of the distribution function. It is the quantile where 63.2% of AEs occur (14). A large value of the scale indicates a wide distribution, whereas a small value of the scale indicates a narrow distribution. The shape parameter β represents the change in hazard over time in the absence of a reference population. When β is equal to 1, the hazard is estimated to be constant over time. If β is less than 1 and the 95%CI of β excluded the value 1, this indicates the hazard decreased over time, and if β is greater than 1 and the 95%CI of β excluded the value 1, the hazard increased over time (14).

Ethics approval. Ethics approval was not sought for this study, given the database-related, observational design without direct involvement of any research subjects. All results were obtained from data openly available online from the PMDA website. All data from the JADER were fully anonymised by the relevant regulatory authority before we accessed them. Thus, all methods were performed in accordance with the relevant guidelines and regulations.

Statistical analyses. We calculated the RORs, 95% CIs, and p-values using Fisher's exact tests. All data were analyzed using JMP Pro® version 16.2 (SAS Institute Inc., Cary, NC, USA), with $p < 0.05$ indicating statistical significance.

Results

Signal of LAEs related to pomalidomide. The patient characteristics are shown in Table I. LAEs related to pomalidomide were more common in patients in their 70s (38.7%), followed by those in their 60s (29.2%). Approximately 54.9% of the patients were male.

Pneumonia was the most common LAE with pomalidomide, with 174 cases, followed by pneumocystis jirovecii pneumonia, or interstitial lung disease (Table II). Signals were detected in

Table I. Characteristics of the patients exhibiting lung adverse events (LAEs) related to pomalidomide.

Variable	Value (%)
Number of patients	253
Sex	
Male	139 (54.9)
Female	111 (43.9)
Unknown	3 (1.2)
Age	
30s	1 (0.4)
40s	4 (1.6)
50s	14 (5.5)
60s	74 (29.2)
70s	98 (38.7)
80s	53 (20.9)
90s	1 (0.4)
Unknown	8 (3.2)

five categories: pneumocystis jirovecii pneumonia, bronchitis, pneumonia bacterial, and pneumonia pneumococcal. The ROR and 95%CI for each LAE were 4.53 (95%CI=3.88-5.28; $p < 0.001$) for pneumonia, 1.93 (95%CI=1.28-2.91; $p = 0.003$) for pneumocystis jirovecii pneumonia, 8.79 (95%CI=5.36-14.42; $p < 0.001$) for bronchitis, 1.98 (95%CI=1.06-3.68; $p = 0.041$) for pneumonia bacterial, and 5.14 (95%CI=2.13-12.40; $p = 0.003$) for pneumonia pneumococcal.

Time-to-onset of LAEs related to pomalidomide. Figure 2 shows a histogram of the time-to-onset of the five LAE signals detected, all of which occurred between 66 and 264 days after pomalidomide administration (Figure 2).

Median values (quartiles, 25-75%) to time of onset were as follows: 66 (22-178) days for pneumonia, 140 (99-297) days for pneumocystis jirovecii pneumonia, 73 (34-231) days for bronchitis, 66 (9-202) days for pneumonia bacterial, and 264 (119-460) days for pneumonia pneumococcal. The Weibull distribution of histograms of time-to-onset showed that the 95%CI range for the shape parameter β for pneumocystis jirovecii pneumonia was $\beta = 1$, and for the other LAEs $\beta < 1$ (Table III).

Outcome after the occurrence of AEs. Figure 3 shows the percentage of outcomes (recovered, remission, not recovered, death, unclear) after the onset of five AEs. Of the five LAEs for which signals were detected, fatal outcomes were observed for two, pneumonia and pneumonia bacterial.

Discussion

In this study, we focused on lung toxicity caused by pomalidomide, and the AEs for which a signal was detected were pneumonia, pneumocystis jirovecii pneumonia,

Table II. Numbers of reports and RORs of the lung adverse events (LAEs) related to pomalidomide.

Variable	Cases (n)	Non-cases (n)	Rate (%)	ROR	95%CI	p-Value
Pneumonia	174	2,744	5.96	4.53	3.88-5.28	<0.001
Pneumocystis jirovecii pneumonia	23	2,895	0.79	1.93	1.28-2.91	0.003
Interstitial lung disease	19	2,899	0.65	0.23	0.14-0.36	<0.001
Bronchitis	16	2,902	0.55	8.79	5.36-14.42	<0.001
Pneumonia bacterial	10	2,908	0.34	1.98	1.06-3.68	0.041
Pulmonary embolism	6	2,912	0.21	0.92	0.41-2.05	1.000
Pneumonia pneumococcal	5	2,913	0.17	5.14	2.13-12.40	0.003

“Cases” indicates the number of reported cases of LAEs. Bold *p*-values represent statistically significant results. We used more than five reports for each type of LAE. All analyzed data were obtained from the JADER. The hypothesis tests were two-sided, and statistical significance was set at $p < 0.05$. *p*-Values were calculated using Fisher’s exact test. ROR: Reporting odds ratio; 95%CI: 95% confidence interval; JADER: Japanese Adverse Drug Event Report database.

Table III. The medians and Weibull parameters of lung adverse events (LAEs).

Adverse effects	Case (n)	Median (day) (25-75%)	Scale parameter α (95%CI)	Shape parameter β (95% CI)
Pneumonia	139	66 (22-178)	118.24 (95.03-146.25)	0.82 (0.72-0.93)
Pneumocystis jirovecii pneumonia	19	140 (99-297)	213.94 (133.17-336.20)	1.08 (0.72-1.51)
Bronchitis	15	73 (34-231)	129.94 (65.98-246.16)	0.87 (0.56-1.25)
Pneumonia bacterial	8	66 (9-202)	87.27 (23.02-304.98)	0.66 (0.34-1.09)
Pneumonia pneumococcal	4	264 (119-460)	323.72 (134.89-750.26)	0.62 (0.31-1.63)

“Cases” indicate the number of reported cases of LAEs. The detected LAEs signals were analyzed to determine the time to onset. 95%CI: 95% confidence interval.

bronchitis, pneumonia bacterial, and pneumonia pneumococcal. Among these, pneumonia was the most common (68.8%, 174/253 cases), and fatality occurred at a frequency of 10.3% (18/174 cases).

Although AEs of pneumonia related to pomalidomide have been reported (1, 2, 8), the timing of the onset of pneumonia was not well understood. However, the present results suggest a trend toward a higher incidence of pneumonia early after pomalidomide administration, according to the Weibull distribution. Pomalidomide has a higher incidence of severe pneumonia in patients older than 65 years (8), and a higher incidence of grade 3/4 neutropenia (15). Additionally, patients with MM are often older and considered to have a higher risk for pneumonia (16-18). Therefore, more attention should be paid to immunodeficiency and infections caused by pomalidomide, and information on the timing of the onset of pneumonia would be very useful clinically. AE data from clinical trials before a drug is approved are obtained from a relatively small population under various constraints. However, after approval, new trends in AEs may be discovered through repeated drug use in patients with various characteristics. Therefore, pharmacovigilance, which aims to monitor drug safety, is important for the proper use of all drugs (19-21).

In this study, the incidence rate of pneumonia did not increase in a dose-dependent manner. However, since pneumonia was observed in some cases approximately 20 months or more after the start of treatment, continuous monitoring throughout the entire dosing period is recommended. Among the five AEs in which signals were detected, fatal outcomes were also observed in bacterial pneumonia as well as pneumonia. Clinicians should pay close attention to the development of LAE due to pomalidomide, as it can have a fatal outcome. Bacterial pneumonia, similar to pneumonia, was suggested to occur relatively early after pomalidomide administration. In MM, susceptibility to bacterial infections is increased primarily due to abnormalities in humoral immunity, causing significant morbidity and mortality (22). Thus, patients with pomalidomide may also be at risk of bacterial pneumonia. In this study, the median time to onset of both pneumonia and bacterial pneumonia was 66 days. Accordingly, clinicians should pay particular attention to the occurrence of pneumonia and pneumonia bacterial approximately 2 months after pomalidomide administration.

This study has some limitations. The adverse drug cases in the JADER were reported voluntarily. Thus, spontaneous reporting systems, such as the JADER, are subject to

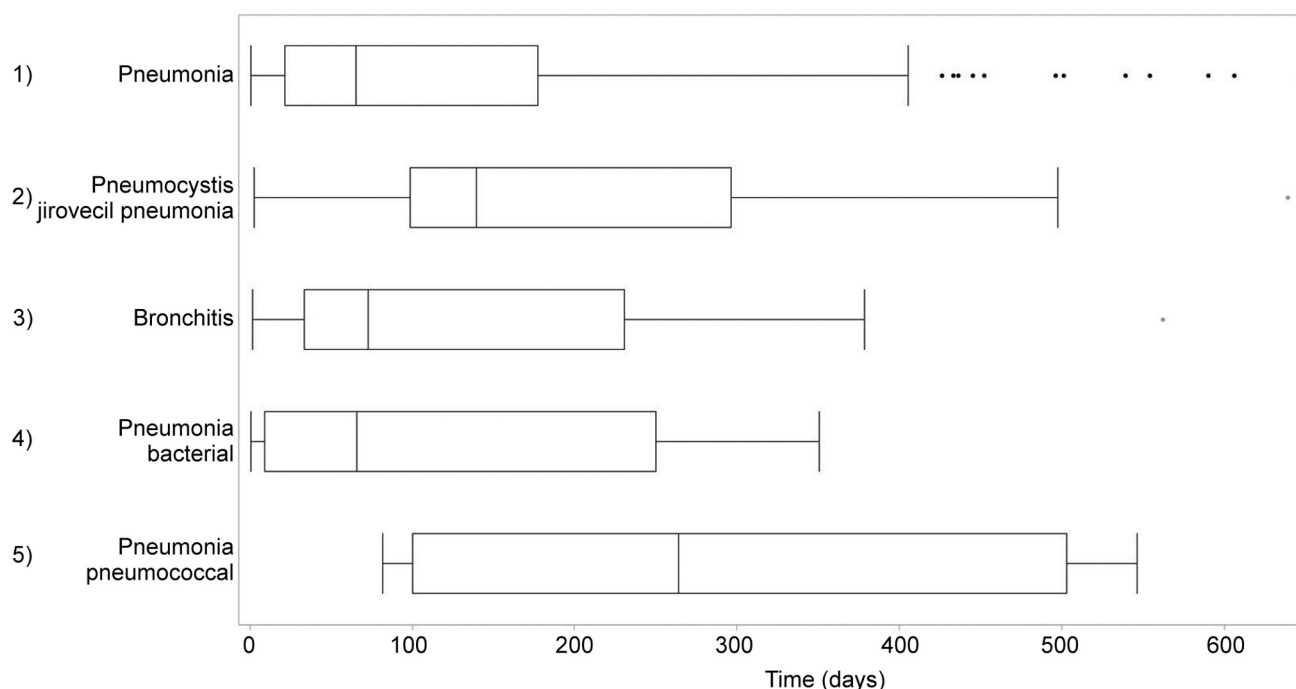


Figure 2. A histogram of lung adverse events (LAEs) for 1) pneumonia, 2) pneumocystis jirovecii pneumonia, 3) bronchitis, 4) pneumonia bacterial, 5) pneumonia pneumococcal.

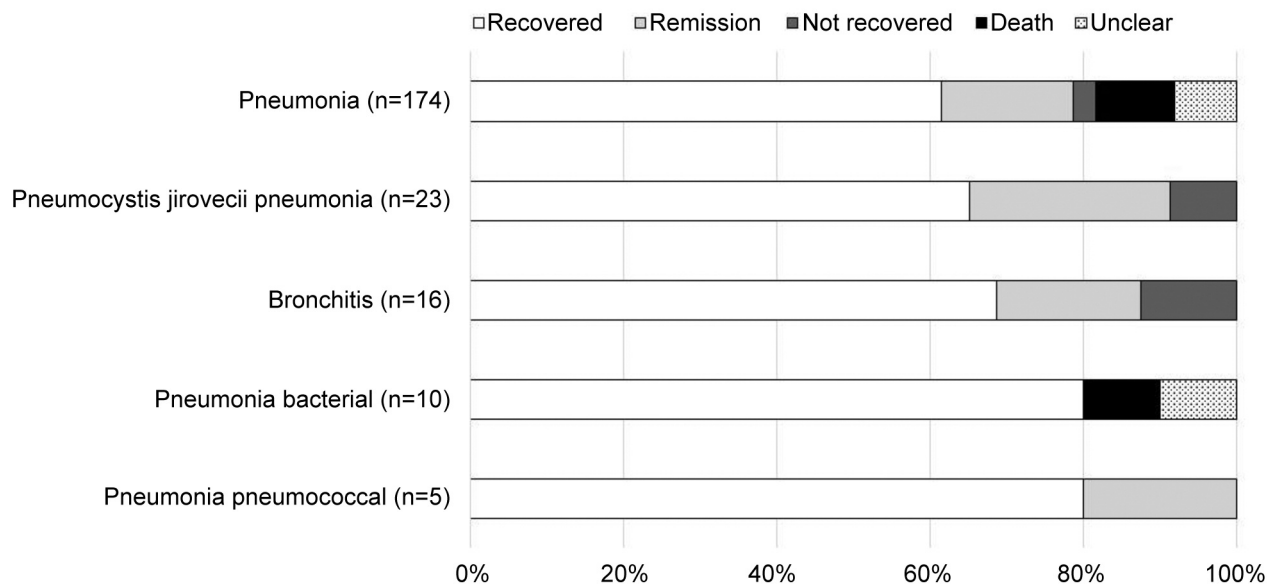


Figure 3. Percentage of four lung adverse events (LAEs) related to pomalidomide based on the outcomes.

overreporting, underreporting, missing data, lack of a denominator, and the presence of confounding factors (*e.g.*, concomitant medications, comorbidities, and severity of AEs) (10). Consequently, it is impossible to calculate the true

incidence of LAEs. Although the JADER has more clinical details than other spontaneous reporting system databases, such as the FDA Adverse Events Reporting System, further studies are required to address these limitations.

However, the results of this study were based on extracted data representing AEs that the reporting persons considered to be most likely associated with pomalidomide. Therefore, our report provides useful information for monitoring LAEs related to pomalidomide.

Conclusion

We focused on LAEs caused by pomalidomide as post-marketing AEs. Pneumonia and pneumonia bacterial can be serious outcomes after pomalidomide administration. It has been suggested that these LAEs occur relatively early after pomalidomide administration; however, we found evidence of LAEs occurring up to 20 months later. Since some outcomes can result in significant consequences, patients should be monitored for the emergence of these AEs over a prolonged period of time, especially for pneumonia.

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose in relation to this study.

Authors' Contributions

Yuka Kawahara, Saeko Murata and Tadashi Shimizu: Data curation; Writing – original draft; Writing – review and editing; Data curation; Writing – review and editing. Yoshihiro Uesawa: Writing – review and editing. Mayako Uchida: Conceptualization; Supervision; Writing – review and editing.

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