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Evaluation of the Time to Onset and Outcome of Lenalidomide-induced Thrombosis and Embolism Using Spontaneous Reporting Database

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Abstract. *Background/Aim: Lenalidomide (LND) is an oral antineoplastic agent used in the treatment of various malignant hematologic diseases, including multiple myeloma. Major adverse events of LND include myelosuppression, pneumonia, and thromboembolism. Thromboembolism is an adverse drug reaction (ADR) associated with poor outcomes, therefore anticoagulants are administered prophylactically. However, LND-induced thromboembolism has not been clearly characterized from clinical trials. The purpose of this study was to evaluate the incidence, timing, and outcome details of thromboembolism caused by LND using the JADER (Japanese Adverse Drug Event Report) database. Patients and Methods: ADRs due to LND reported from April 2004 to March 2021 were selected. Data on thromboembolic adverse events were analyzed and relative risks were estimated using reported odds ratios (RORs) and 95% confidence intervals (CIs). In addition, the time of onset and outcome of thromboembolism were analyzed. Results: There were 11,681 adverse events attributed to LND. Of these, 306 were thromboembolisms. The most frequently reported thrombosis with the highest ROR was deep vein thrombosis (DVT) (165 cases, ROR=7.12, 95%CI=6.09-8.33). The median onset of DVT (quartiles, 25-75%) was 80 (28-155) days. The parameter value (β) was 0.87 (0.76-0.99), suggesting the onset of DVT early in treatment. The prognosis of DVT due to LND was recovery and remission in 34% and 43% of patients, respectively, but 7.9% did not recover. Conclusion: DVT is the most frequent thromboembolism in LND, and early treatment is important.*

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Key Words: Lenalidomide, thrombosis and embolism, Japanese adverse drug event report database, signal, time to onset.

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Lenalidomide (LND) is used as an oral anticancer drug for multiple myeloma (MM), myelodysplastic syndrome (MDS) T-cell leukaemia-lymphoma and follicular lymphoma. Adverse drug reactions (ADRs) of LND are characterized by hematologic toxicity, pneumonia and other infections, and thromboembolism. Hematologic toxicity is frequent but reversible. In contrast, pneumonia and thromboembolism are serious ADRs due to LND. Thromboembolism develops with sudden onset of symptoms such as sudden swelling, tingling, or numbness in one lower extremity (rarely the upper extremity), chest pain, sudden shortness of breath, and paralysis of the extremities. Thromboembolism is often an irreversible outcome, leading to obstructed organ dysfunction. However, the clinical features of thromboembolism caused by LND are varied and limited in the number of cases. Therefore, a detailed pathogenic profile, including outcome, is lacking.

Pharmacological vigilance against thromboembolism needs to be validated in a larger patient population. ADR data obtained in clinical trials prior to drug approval is information obtained from a relatively small patient population with clearly defined patient backgrounds. In actual clinical practice, however, the use of an approved drug in a large number of patients with a variety of backgrounds

reveals previously unknown ADR profiles. Pharmacovigilance, which aims to monitor the safety of medicines, is conducted using a spontaneous reporting system (SRS) that reflects actual clinical practice (1). In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has established the JADER (Japanese Adverse Drug Event Report) database as an SRS. Several ADR profiles have been reported using this database (2, 3). These data can be used to promptly provide information to healthcare professionals and patients to reduce the risk of ADRs. This study aimed to retrospectively analyse the JADER database to determine the type and time profile of thromboembolism in patients receiving LND.

Patients and Methods

Data source. We used data from the public releases of the JADER database. The PMDA website (4) offers a free download of this database, which contains cases of ADRs. We analyzed ADR reports recorded between April 2004 and March 2022. The data structure of the JADER consists of four datasets: Patient demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history (HIST). We used the identification number of each ADR case to merge corresponding case data from the drug information, ADRs, and patient demographic information tables. We then extracted only cases classified as "suspected medicines".

We examined the reports of spontaneous ADRs that were sent to the PMDA's JADER database to assess the relationship between LND use and thrombosis and embolism. Each thrombosis and embolism ADR coded according to the terminology recommended by the Medical Dictionary for Regulatory Activities/Japanese version 25.1 (5) was collectively referred to as thrombosis and embolism in this study.

Statistical analyses. Data on thrombosis and embolism with more than five reported cases were extracted, and the relative risk of ADRs was estimated using the reporting odds ratio (ROR). ROR is frequently used in the spontaneous reporting database as an indicator of the relative risk of ADRs. We used the analysis data table and constructed 2×2 tables based on two classifications: the presence or absence of "thrombosis and embolism" and the presence or absence of suspected LND use. The ROR was calculated by dividing the reported rate of ADRs attributable to LND by the reported rate of the same ADRs attributable to all other drugs in the database. The signal of ADRs was considered positive if the lower limit of the 95% confidence interval (95%CI) of the ROR was >1 (1).

The time to onset of ADR was calculated, and the number of cases was counted for reports in which the date of onset of ADRs, date of start of administration, and date of end of administration were described in year/month/day or year/month (6). The onset time was calculated as follows: "(onset date of ADR)−(administration start date)+0.5" in principle (7). The time to onset of ADRs for analysis was limited to 2 years (730 days). The Weibull distribution is represented by a scale parameter α and a shape parameter β. Depending on the value of the shape parameter β, the upper limit of β value of 95%CI <1 indicates that the hazard increases initially and then decreases (early failure type), a β value containing 1 or almost 1 and a 95%CI of 1 indicate that the hazard remains constant throughout the exposure period (random failure type), and the lower limit of β value of 95%CI >1 indicates that the hazard increases over time (wear-out failure type) (8). All statistical analyses were performed using JMP Pro® 16.2 (SAS Institute, Cary, NC, USA).

Table I. *Characteristics of the patients exhibiting thrombosis and embolism related to lenalidomide.*

Variable	Value (%)
Number of patients	306
Sex	
Male	168 (54.9)
Female	136 (44.4)
Unknown	2 (0.98)
Age, years	
40s	10 (3.27)
50s	27 (8.82)
60s	94 (30.7)
70s	114 (37.3)
80s	47 (15.4)
90s	3 (0.98)
Unknown	11 (3.59)

Results

Incidence of LND-induced thrombosis and embolism. We joined three tables, DRUG (4,134,536 reports), REAC (1,280,060 reports), and DEMO (775,566 patients), by the ID number. We removed duplicate data from the DRUG and REAC tables (9). Of these, all data included in the category of "suspected drugs" were extracted and used as the "data table" (2,021,907 reports).

We analyzed this data table and obtained 11,681 reports of ADRs caused by LND. Of these, 306 cases of thrombosis and embolism were reported to be associated with LND (Figure 1). The patient characteristics are shown in Table I. Approximately 54.9% of the patients were male. According to the age distribution of the study population, thrombosis and embolism were more common in patients in their 70s (37.3%), followed by those in their 60s (30.7%).

There were eight types of thrombosis and embolism caused by LND. Signals were detected for all eight types of thrombosis and embolism (Table II).

Time to onset of LND-induced thrombosis and embolism. A histogram of the time to onset of the eight detected types of thrombosis and embolism signals showed they occurred from 24 to 123 days after LND administration (Figure 2). The median onset times (quartiles, 25-75%) of deep vein thrombosis, pulmonary embolism, thrombosis, venous thrombosis limb, embolism venous, venous thrombosis, pulmonary artery thrombosis, and thrombophlebitis caused

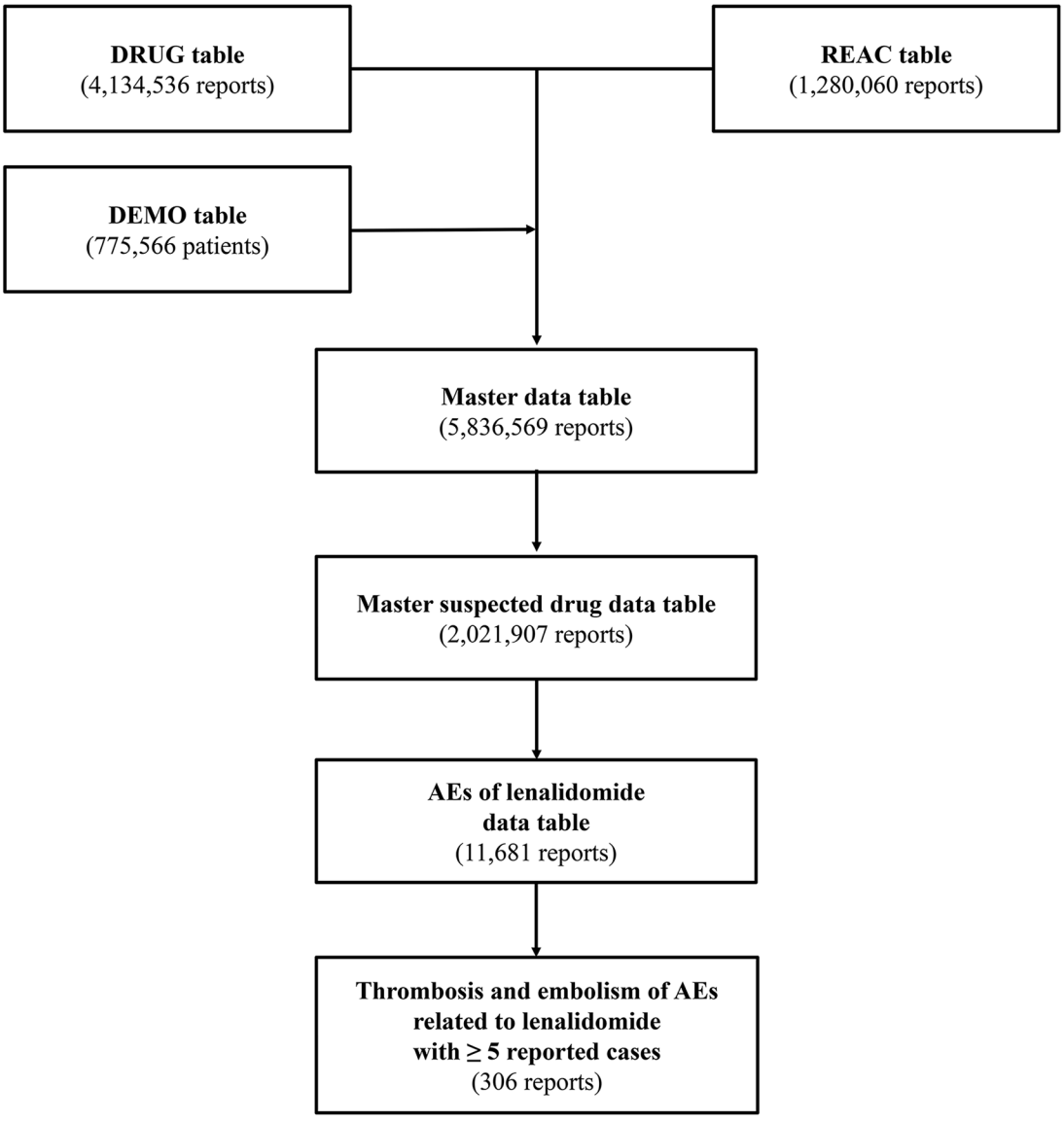

Figure 1. *Process of constructing a data analysis table. DEMO: Case list data; DRUG: drug information data; REAC: adverse events data; AEs: adverse events.*

by LND were 80 (28-155), 69 (27-189), 123 (63-175), 73 (22-196), 53 (34-62), 33 (25-104), 33 (18-45), and 24 (21-446) days, respectively. The Weibull distribution of the histogram of the time to onset showed that the range of 95%CI for the shape parameter β of the thrombosis, embolism venous, venous thrombosis, and pulmonary artery thrombosis was >1. The shape parameter β of other ADRs were <1 (Table III).

Outcome after the occurrence of adverse events. The percentage of outcomes (recovered, remission, not recovered, with sequelae, death, unclear) after the onset of eight ADRs is shown in Figure 3. Fatal outcomes were observed in five of the eight ADRs for which signals were detected.

Discussion

MM patients have a particularly high incidence of thromboembolism compared to patients with other cancers. Furthermore, LND increases the incidence of thromboembolism, especially when combined with high doses of DEX (LND/DEX *vs.* DEX alone: 11% *vs.* 5%; high dose DEX *vs.* low dose DEX: 26% *vs.* 12%) (9, 10). Therefore, anticoagulation, including aspirin, is used to

Table II. *Numbers of reports and reporting odds ratios (RORs) of the thrombosis and embolism related to lenalidomide.*

Variable	Cases (n)	Non-cases (n)	Rate (%)	ROR	95%CI	*p*-Value
Deep vein thrombosis	165	11,516	1.41	7.12	6.09-8.33	<0.001
Pulmonary embolism	55	11,626	0.47	2.21	1.69-2.88	<0.001
Thrombosis	22	11,659	0.19	2.59	1.70-3.94	<0.001
Venous thrombosis limb	21	11,660	0.18	4.77	3.09-7.36	<0.001
Embolism venous	19	11,662	0.16	7.70	4.86-12.20	<0.001
Venous thrombosis	9	11,672	0.08	3.33	1.72-6.43	0.002
Pulmonary artery thrombosis	8	11,673	0.07	2.03	1.01-4.09	0.067
Thrombophlebitis	7	11,674	0.06	5.31	2.50-11.27	<0.001

"Cases" indicates the number of reported cases of thrombosis and embolism related to lenalidomide. Italicized *p*-values represent statistically significant results. We used more than five reports for each type of thrombosis and embolism. All analyzed data were obtained from the Japanese Adverse Drug Event Report database. The hypothesis tests were two-sided, and statistical significance was set at $p<0.05$. *p*-values were calculated using Fisher's exact test. 95%CI: 95% Confidence interval.

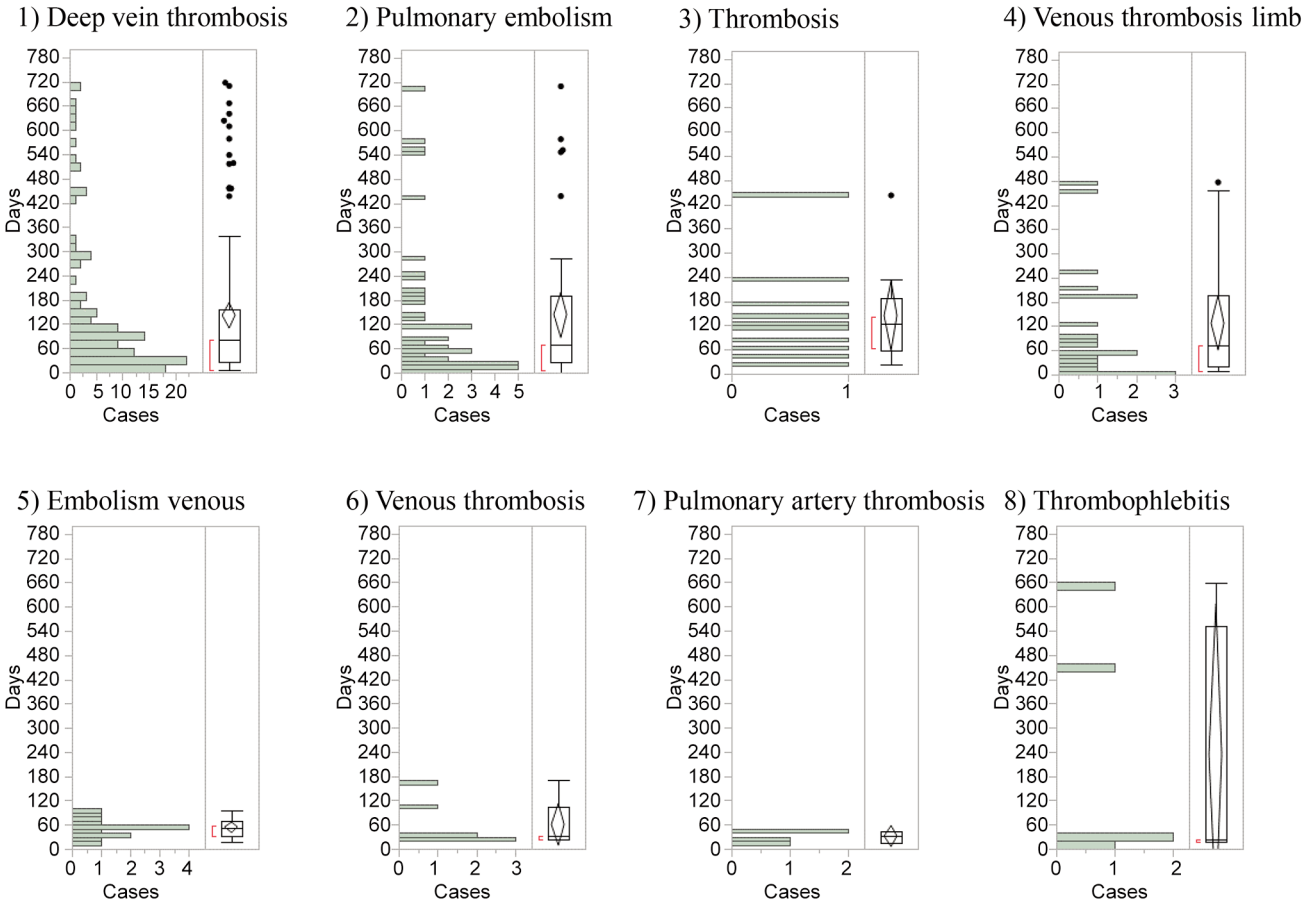

Figure 2. *A histogram of thrombosis and embolism for 1) Deep vein thrombosis, 2) Pulmonary embolism, 3) Thrombosis, 4) Venous thrombosis limb, 5) Embolism venous, 6) Venous thrombosis, 7) Pulmonary artery thrombosis, 8) Thrombophlebitis.*

prevent thromboembolism caused by LND. However, even with the use of aspirin, it is difficult to completely prevent thromboembolism caused by LND.

The symptoms and diagnosis of thromboembolism vary depending on the site of occlusion, such as cerebral infarction, myocardial infarction, pulmonary embolism

Table III. *The medians and Weibull parameters of thrombosis and embolism related to lenalidomide.*

Adverse effects	Case (n)	Median (day) (25-75%)	Scale parameter α (95%CI)	Shape parameter β (95%CI)
Deep vein thrombosis	121	80 (28-155)	130.27 (104.44-161.51)	0.87 (0.76-0.99)
Pulmonary embolism	41	69 (27-189)	127.92 (84.72-189.74)	0.82 (0.64-1.03)
Thrombosis	10	123 (63-175)	159.52 (92.12-267.27)	1.36 (0.80-2.05)
Venous thrombosis limb	19	73 (22-196)	122.34 (69.63-207.87)	0.92 (0.63-1.27)
Embolism venous	13	53 (34-62)	60.36 (47.13-76.12)	2.60 (1.61-3.83)
Venous thrombosis	7	33 (25-104)	64.74 (31.29-128.09)	1.28 (0.67-2.07)
Pulmonary artery thrombosis	4	33 (18-45)	35.12 (19.79-60.88)	2.50 (0.93-5.22)
Thrombophlebitis	5	24 (21-446)	172.77 (28.35-949.77)	0.66 (0.29-1.22)

"Cases" indicate the number of reported cases of thrombosis and embolism related to lenalidomide. The detected thrombosis and embolism signals were analyzed to determine the time to onset. 95%CI: 95% Confidence interval.

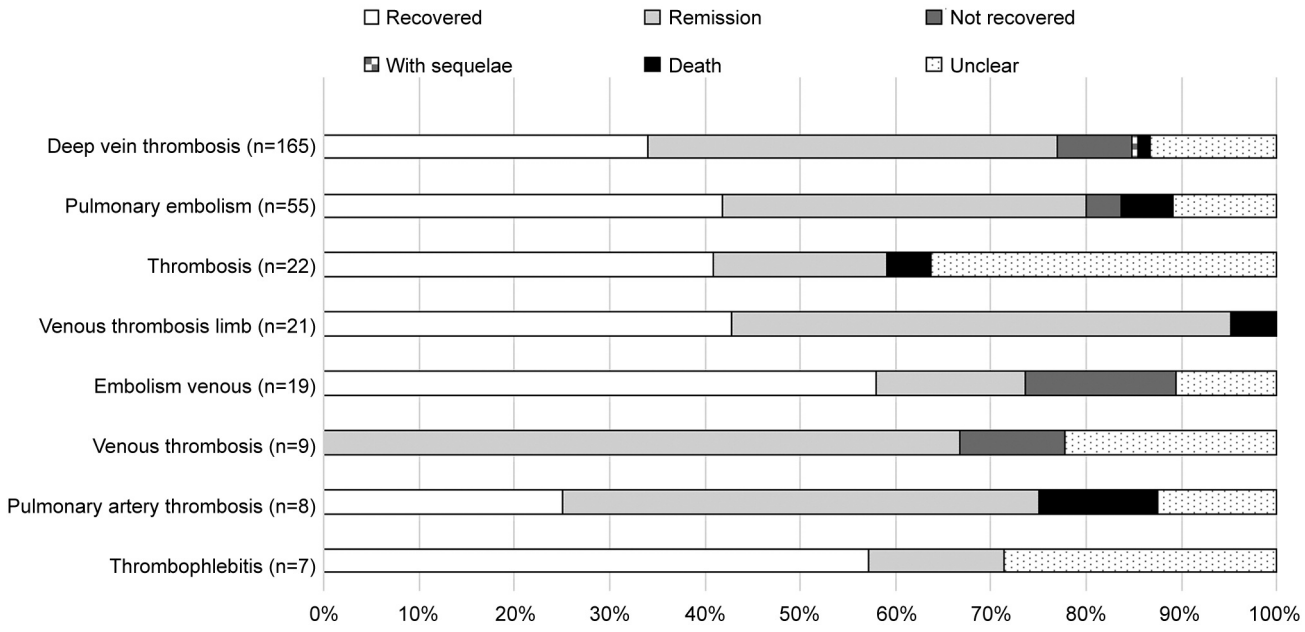

Figure 3. *Percentage of eight adverse drug reactions associated with lenalidomide by the outcome.*

(PE), and DVT. In the present results, positive RORs for all eight ADRs (deep vein thrombosis, pulmonary embolism, thrombosis, limb vein thrombosis, venous embolism, venous thrombosis, pulmonary artery thrombosis, and thrombophlebitis) were detected, indicating a diversity of symptoms according to thromboembolic site. A common feature of thromboembolism is its sudden onset. The early detection of thromboembolism necessitates that patients and healthcare providers are aware of these symptoms.

In various clinical trials, details regarding the time of onset and outcome of thromboembolism caused by LND are not provided. A total of 43 out of 443 patients newly diagnosed with MM developed VTE following treatment with the combination of LND and DEX , mostly within 4 months (10). In addition, DVT occurred in 6 out of 205 patients with MDS on LND, with 5 of them occurring mostly within the first 3 months of treatment (11). Our data similar to this, with a median onset of 80 days. Our data also appeared objective and reliable since they derive from a large analysis of 306 thromboembolisms accumulated over 17 years since 2004. The only ADR with a β of the Weibull distribution significantly less than 1 was VTE, which indicates early onset after treatment. The median onset was 80 days. Conversely, ADR with β greater than 1 were venous embolisms, which showed a tendency to appear over time. The median time of onset was 53 days. The reason for the difference in the incidence of thrombosis and embolism

is unclear, but the fact that there were only 13 cases of venous embolism may have had an influence. Except for thrombosis, most ADRs had a median onset between 60-90 days. In clinical trials using LND, overall survival exceeded 3 years (12). Alertness to thromboembolism for approximately 60-90 days after initiation of therapy during a long treatment period is important information for an LND treatment strategy.

The current study also provided information on treatment outcomes. The outcome of VTE, which had a high number of reports and RORs, was recovery in 77% and death in only 1.2% of the cases. In contrast, the outcome for pulmonary artery thrombosis and PE was death in 6.3%. These results are consistent with the poor prognosis of PE among thromboembolisms in the general elderly population. The 1-week survival rate for PE is 71%, and 25% of PE is detected as sudden death (13). The present results reveal the severity of pulmonary thrombosis and PE among thromboembolisms caused by LND.

The study has several limitations. First, unlike clinical trials and observational studies, the JADER database is based on self-reports. Therefore, not all patients who received LND were followed. Furthermore, toxicity expression results are likely to be over-reported. Second, the calculated onset date data do not reflect all reported data because data that do not include the start date of treatment were excluded. Third, risk factors affecting thromboembolism and concomitant medications are not evaluated in the JADER database. Fourth, whether the diagnosis of thromboembolism is based on a reliable diagnosis such as echocardiography remains unclear.

Conclusion

This study revealed that VTE is the most common thromboembolism and tends to occur early (within 3 months) after LND treatment. The findings should allow physicians and pharmacists to be more aware of the details of thromboembolism during LND treatment. Furthermore, it may provide important information to alert patients using LNDs to the early detection of symptoms.

Conflicts of Interest

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

Authors' Contributions

Junya Sato, Naru Yamamoto, and Yuka Kawahara: Data curation; Writing – original draft; Writing – review and editing. Tadashi Shimizu: Writing – review and editing. Mayako Uchida: Data curation, Conceptualization; Supervision; Writing – review and editing.

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