Analysis of Time-to-onset and Onset-pattern of Interstitial Lung Disease
after the Administration of Monoclonal Antibody Agents

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The aim of this study has been to investigate the time-to-onset and onset-pattern of drug-induced interstitial lung disease (DILD) after the administration of monoclonal antibodies through the use of the spontaneous adverse reaction reporting system of the Japanese Adverse Drug Event Report database. DILD datasets for adalimumab, bevacizumab, cetuximab, denosumab, golimumab, infliximab, nivolumab, panitumumab, pembrolizumab, tocilizumab, and trastuzumab were used to calculate the median time-to-onset of DILD, as well as the Weibull distribution parameters. The median time-to-onset of DILD for pembrolizumab and infliximab was within 1 month. The median time-to-onset of DILD for cetuximab, nivolumab, panitumumab, bevacizumab, golimumab, trastuzumab, and tocilizumab ranged from 1 to 2 months. The median time-to-onset of DILD for denosumab and adalimumab was more than 2 months. Infliximab, trastuzumab and tocilizumab, and denosumab were estimated to fit the early failure type profile of the Weibull distribution parameters. Cetuximab, nivolumab, panitumumab, bevacizumab, golimumab, and adalimumab were estimated to fit the random failure type profile. Pembrolizumab was estimated to fit the wear out failure type profile. Cluster analysis was performed to classify the time-to-onset patterns of DILD. Hierarchical cluster analysis showed 3 clusters. The findings of this study established both the most likely time period and onset-pattern of DILD that can occur in patients after the administration of monoclonal antibody agents.

Key words—interstitial lung disease; monoclonal antibody agent; adverse reaction; time-to-onset; Weibull parameter

INTRODUCTION

The Pharmaceuticals and Medical Devices Agency (PMDA) has created and released a spontaneous adverse reaction reporting system for the Japanese Adverse Drug Event Report (JADER) database. The JADER is a unitized large-scale database that reflects the realities of clinical practice. This database has been recognized as one of the primary tools for pharmacovigilance assessments, and it used to conduct risk analysis of adverse reactions.1–6 Several studies have previously indicated the time-to-onset of adverse reactions using JADER and/or U.S. Food and Drug Administration Adverse Event Reporting System.7–9

The overall aim of this study has been to investigate the time-to-onset and the onset-pattern of drug-induced interstitial lung disease (DILD) following the administration of monoclonal antibody agents using the JADER database.

DILD is one of the most serious adverse reactions associated with the use of molecularly-targeted drugs. Currently, there are more than 450 different drugs that have been implicated in DILD.10 Suggested DILD mechanisms include, 1) the induction of pulmonary fibrosis caused by a direct toxic reaction to the drugs, 2) drugs acting as potential antigens or haptons, and causing immune-mediated lung toxicity, and 3) drugs causing phospholipidosis in alveolar macrophages and in type 2 cells. Since DILD is considered to be a clinically serious and potentially life-threatening toxicity, the immediate administration of an appropriate treatment is required in these patients. In addition, the clinical features of these early onset cases are characterized by a rapid progression and high mortality rate after the administration of gefitinib.11 Furthermore, an increase has especially been noted in the amounts of data for DILD in tandem with several new biologic agents, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI), anti-EGFR antibody, mammalian target of rapamycin (mTOR) inhibitors, immune checkpoint inhibitors, Bcr-Abl TKI, and multi-kinase inhibitors.12–25 Several studies have also reported that the incidence of DILD is higher in Japan versus other countries, with this trend more prominently observed in the post-marketing surveillance studies of EGFR TKIs and the anti-EGFR antibody.11,14,20,25

Several studies have shown that the post-marketing
spontaneous reporting database can be a valuable resource for estimating the time-to-onset of adverse reactions for the Weibull analysis.\textsuperscript{26-34} Furthermore, we postulated that cluster analysis could be applied to classifying the time-to-onset patterns of DILD.\textsuperscript{35,36} Our previous study demonstrated that the median time-to-onset of DILD for small molecule molecularly-targeted drugs such as dasatinib, erlotinib, everolimus, gefitinib, lapatinib, osimertinib, and temsirolimus ranged from 1 to 2 months.\textsuperscript{37} In addition, the median time-to-onset of the DILD for alectinib, imatinib, and tofacitinib ranged from 2 to 3 months, while the median time-to-onset of the DILD for sunitinib and sorafenib ranged from 8 to 9 months. The Weibull distributions for bortezomib, crizotinib, erlotinib, afatinib, gefitinib, dasatinib, nilotinib, lapatinib, imatinib, and sorafenib were estimated to fit the early failure type profile, while those for osimertinib and everolimus were estimated to fit the wear out failure type profile. The Weibull distributions for temsirolimus, alectinib, tofacitinib, and sunitinib were estimated to fit the random failure type profile. Cluster analysis for small molecule molecularly-targeted drugs showed that there were 4 clusters. It appears that the differences observed between the clusters may be indicative of the mechanism of action for some of these small molecule molecularly-targeted drugs. Thus, it is important to determine how the DILD occurrence varies over time during the administration of molecularly-targeted drug therapy.

MATERIALS AND METHODS

After accessing the PMDA website, the JADER database was downloaded for the period from April 2004 to October 2017.\textsuperscript{38} This database, which consists of 4 data tables, includes a patient demographics information table, drug information table, adverse events table (REAC), and primary illness table. The adverse events in REAC are coded according to the terminology preferred by the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J ver. 20.1).\textsuperscript{39} To extract the DILD from REAC, the interstitial lung disease (Preferred Term: Standardized MedDRA Queries; 20000042) was used. The lowest level term group for the interstitial lung disease in MedDRA includes many different syndromes (e.g., acute diffuse infiltrative lung disease, chronic interstitial pneumonia, follicular bronchiolitis, interstitial lung fibrosis, interstitial pneumonia, pneumonia interstitial diffuse, interstitial pneumonia aggravated, etc.). Both the drug information (2998521 cases), along with the adverse event and outcome information (749188 cases), were integrated into our time-to-onset database using JMP 13.2 (SAS Institute Inc., Cary). However, duplicate cases are known to exist in these tables, thus, these reports can have an impact on evaluation and analysis. In order to exclude any overlap from these previously reported cases, all duplicate reported cases based on the associated identification number were removed. In addition, any forms in which there were blanks or where the data were not correctly described were excluded. All data within the mean of ±3S.D. were used for the data analysis. Time-to-onset of DILD was calculated from the time of the patient’s prescription to the first occurrence of DILD. After data cleaning, any datasets for the time-to-onset of DILD for adalimumab, bevacizumab, cetuximab, denosumab, golimumab, infliximab, nivolumab, panitumumab, pembrolizumab, tocilizumab, and trastuzumab that had more than 50 cases were then used to calculate the Weibull parameters. The reporting odds ratio (ROR) was used for quantitative signal detection.\textsuperscript{3,4,6,8,28-30} The RORs [95% confidence interval (95% CI)] of DILD for adalimumab, bevacizumab, cetuximab, denosumab, golimumab, infliximab, nivolumab, panitumumab, pembrolizumab, tocilizumab, and trastuzumab were 2.02 (95% CI, 1.76–2.33), 1.69 (95% CI, 1.56–1.83), 4.17 (95% CI, 3.75–4.64), 1.38 (95% CI, 1.15–1.66), 1.99 (95% CI, 1.59–2.50), 1.79 (95% CI, 1.61–1.99), 7.03 (95% CI, 6.40–7.72), 5.76 (95% CI, 5.04–6.58), 7.42 (95% CI, 5.84–9.44), 1.17 (95% CI, 1.01–1.35), and 3.46 (95% CI, 3.09–3.87), respectively.

The scale parameter of the Weibull distribution is used to determine the scale of the data distribution function, with the scale parameter defined as 63.2% of the lower side of the Weibull distribution.\textsuperscript{26-34} Thus, when a larger value for the scale parameter is present, this stretches the distribution, while the presence of a smaller value for the scale parameter will shrink the data distribution. The shape parameter of the Weibull distribution can be used to define a hazard without having to refer to a reference population. For example, if the shape parameter is less than 1 and the 95% CI of the shape parameter is also less than the value 1, the hazard is considered to have rapidly decreased over time (an early failure type pro-
Table 1. Median Time-to-onset of DILD with Monoclonal Antibody Agents

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Case</th>
<th>Onset (d)</th>
<th>Significant difference (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>73</td>
<td>20 1−78</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>253</td>
<td>31 1−987</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>315</td>
<td>42 1−282</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>513</td>
<td>47 1−343</td>
<td></td>
</tr>
<tr>
<td>Panitumumab</td>
<td>219</td>
<td>49 1−365</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>448</td>
<td>50 1−476</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>60</td>
<td>55 7−644</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>196</td>
<td>55.5 1−791</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>124</td>
<td>57 1−1253</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>66</td>
<td>64.5 1−928</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>155</td>
<td>126 4−1370</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Histograms and Fitting Curves for the Weibull Distribution of the Time-to-onset of DILD
(A) Pembrolizumab, (B) cetuximab, (C) nivolumab, (D) panitumumab, (E) bevacizumab, (F) infliximab, (G) trastuzumab, (H) golimumab, (I) denosumab, (J) tocilizumab, and (K) adalimumab.

If the shape parameter is equal to or nearly 1 and the 95% CI of the shape parameter includes the value 1, the hazard is estimated to have been constant over time (a random failure type profile). If the shape parameter is greater than 1 and the 95% CI of the shape parameter excluded the value 1, the hazard is considered to have a maximum value at a specific time (a wear out failure type profile).

Cluster analysis was carried out using the estimated values of median onset time, the scale parameter, and the shape parameter. A hierarchical cluster analysis using Ward’s method was utilized to generate a dendrogram for estimation of the number of likely clusters. The estimations for Weibull parameters and
Table 2. Time-to-onset Analysis of Monoclonal Antibody Agents Using Weibull Distributions

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Weibull Distribution</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scale parameter</td>
<td>95% CI</td>
<td>Shape parameter</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>24.8</td>
<td>20.5–29.9</td>
<td>1.30</td>
</tr>
<tr>
<td>Infliximab</td>
<td>53.4</td>
<td>45.8–62.1</td>
<td>0.863</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>62.2</td>
<td>55.6–69.3</td>
<td>1.06</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>72.9</td>
<td>66.3–80.0</td>
<td>0.973</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>77.6</td>
<td>67.1–89.5</td>
<td>0.976</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>83.1</td>
<td>74.9–92.0</td>
<td>0.953</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>86.4</td>
<td>71.6–104</td>
<td>0.802</td>
</tr>
<tr>
<td>Golimumab</td>
<td>113</td>
<td>81.8–153</td>
<td>0.871</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>123</td>
<td>94.8–159</td>
<td>0.724</td>
</tr>
<tr>
<td>Denosumab</td>
<td>164</td>
<td>118–227</td>
<td>0.787</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>233</td>
<td>194–279</td>
<td>0.924</td>
</tr>
</tbody>
</table>

Statistical analysis was performed using JMP 13.2. Statistical analysis was performed using the Steel-Dwass test on each pair. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

The median time-to-onsets of DILD for pembrolizumab, infliximab, cetuximab, nivolumab, panitumumab, bevacizumab, golimumab, trastuzumab, tocilizumab, denosumab, and adalimumab were 20, 31, 42, 47, 49, 50, 55, 55.5, 57, 64.5, and 126 d, respectively (Table 1). The median time-to-onset of DILD for adalimumab was 6 times longer than that for pembrolizumab. The median time-to-onset of DILD for pembrolizumab was significantly shorter than that found for the other drugs. Similarly, the median time-to-onset of DILD for infliximab was significantly shorter than that found for all of the other drugs, with the exception of cetuximab. The median time-to-onset of DILD for denosumab was significantly longer than that observed for cetuximab and nivolumab. In addition, the median time-to-onset of DILD for adalimumab was significantly longer than that observed for all other agents, with the exception of denosumab.

The histograms of the time-to-onset of DILD for infliximab, trastuzumab, denosumab and tocilizumab, showed rapid decreases with time (F, G, I, and J in Fig. 1). Since the upper 95% CI for the shape parameter was less than 1, the DILD onset time profiles of these drugs were estimated to be similar to the early failure type profiles of the Weibull distribution (Table 2). The DILD onset time profiles for cetuximab, nivolumab, panitumumab, bevacizumab, golimumab, and adalimumab were estimated to fit the random failure type profile based on the 95% CI of the shape parameter including the value 1 (B, C, D, E, H, and K in Fig. 1). The time-to-onset of DILD cases for pembrolizumab demonstrated that there was broad distribution along with a maximum value at a specific time (A in Fig. 1). Both the estimated shape parameters and the 95% CI of the shape parameter for pembrolizumab exceeded 1. Therefore, the onset-pattern of DILD for pembrolizumab was estimated to be the wear out failure type profile.

Figure 2 shows the hierarchical cluster analysis that generated the dendrogram for estimation of the 3 clusters. Cluster 1, which included pembrolizumab, infliximab, cetuximab, nivolumab, panitumumab, and bevacizumab, exhibited a median time-to-onset of DILD that ranged from 20 to 50 d. With regard to the profiles, infliximab showed an early failure type profile, while cetuximab, nivolumab, panitumumab, and bevacizumab showed random failure type profiles, and pembrolizumab showed a wear out failure type profile. Cluster 2, which included golimumab, trastuzumab, tocilizumab, and denosumab, showed a median time-to-onset of DILD that ranged from 55 to 64.5 d. With regard to the profiles, trastuzumab, tocilizumab and denosumab exhibited early failure type profiles, while golimumab exhibited a random failure type profile. Cluster 3 included only adalimumab, which exhibited a random failure type profile with 126 d as its median time-to-onset of DILD.

DISCUSSION

Many reports of post-marketing surveillance stud-
ies (special drug use-results survey and long-term use studies) for monoclonal antibody agents indicated the incidence, grade, and/or time-to-onset of DILD. The findings of this study established both the most likely time period and onset-pattern of DILD that can occur in patients after the administration of specific monoclonal antibody agents.

The median time-to-onset and onset-pattern of the DILD after administration of monoclonal antibody agents in this study, and small molecule molecularly-targeted drugs in our previous study with the same mechanism of action, were compared. The median time-to-onset of DILD for the monoclonal antibodies of EGFR, cetuximab (42 d) and panitumumab (49 d), showed that these occurred later than those observed for the small molecule molecularly-targeted drugs of the EGFR TKIs, erlotinib (21 d), gefitinib (24 d), and osimertinib (34.5 d). In addition, the DILD onset time profiles for cetuximab and panitumumab were estimated to be the random failure type. However, the profiles for erlotinib and gefitinib were estimated to be the early failure type, while osimertinib was estimated to be the wear out failure type profile. The median time-to-onset of DILD for the monoclonal antibody of HER2, trastuzumab, was 55.5 d, while those for the small molecule molecularly-targeted drugs of the HER2 receptor inhibitors, afatinib and lapatinib, were 26.5 and 53 d, respectively. The DILD onset time profiles for trastuzumab, afatinib, and lapatinib were estimated to fit the early failure type profile. The median time-to-onset values of DILD for both monoclonal antibody and small molecule molecularly-targeted drug for HER2 were almost the same. Furthermore, the onset-pattern of DILD for the agents used to target HER2 represented the early failure type profile.

Bevacizumab, which is the monoclonal antibody of vascular endothelial growth factor receptors (VEGFR), inhibited the wound healing process during recovery from a lung injury. The median time-to-onset of bevacizumab-induced DILD was 50 d with a random failure type profile, while the median time-to-onset of DILD for the small molecule molecularly-targeted agents, sunitinib and sorafenib, which inhibit multiple receptor tyrosine kinases including VEGFR inhibitors, were 247 d with a random failure type profile and 262 d with an early failure type profile, respectively. The present study showed that there was also a wide range for the time-to-onset of DILD for the monoclonal antibody agents for tumor necrosis factor α (TNFα)-targeted therapy. The median time-to-onsets of DILD for infliximab and golimumab, were 31 and 55 d, respectively, while it was 126 d for adalimumab. Several studies have reported that the time-to-onset of DILD for monoclonal antibody agents for the immune checkpoint that blocks the interaction between programmed death 1 (PD-1) and its ligands (PD-L1 and PD-L2), nivolumab and pembrolizumab, ranged from 3 to 8 weeks. The median time-to-onset of DILD for nivolumab in this study was 47 d, with a random failure type profile, while it was 20 d for pembrolizumab with a wear out failure type profile.

Cluster analysis was performed to classify the time-to-onset patterns of DILD. The cluster analysis for small molecule molecularly-targeted drugs showed that there were 4 clusters in our previous study. Cluster 1 described a subgroup with early to later onset DILD and an early or a random failure type profile, which included the proteasome inhibitor, Bcr-Abl TKI, JAK inhibitor, and ErbB family TKI. Cluster 2 described a subgroup with early onset DILD and early failure or a random failure type profile, which included EGFR TKI, ALK TKI, ErbB family inhibitor, and mTOR inhibitor. Cluster 3 described a subgroup with a later onset time and random or wear out failure type profiles, which included EGFR TKI, mTOR inhibitor, and ALK TKI. Cluster 4 was described as a subgroup with the latest onset DILD and an early or a random failure type profile, which included the multiple receptor TKI with both PDGFR and VEGFR inhibition. Thus, it appears that the differences observed between the clusters may indicate the mechanism of action for some of these small molecule molecularly-targeted drugs. The present cluster analysis for monoclonal antibody agents showed that there were 3 clusters. Cluster 1 describes a subgroup with a median onset time from 20 to 50 d and early, random, or wear out failure type profiles; these include the chimeric antibody (infliximab, and cetuximab), the humanized antibody (pembrolizumab and bevacizumab), and the human-type antibody (nivolumab and panitumumab). Cluster 2 describes a subgroup with a median onset time from 55 to 64.5 d and early or random failure type profiles; these include the humanized antibody (trastuzumab and tocilizumab), and the human-type antibody (golimumab and denosumab). Cluster 3 includes...
Adalimumab (human-type antibody), which exhibited a random failure type profile with a median time-to-onset of the DILD of 126 d. Based on these findings, further research is required to examine the associations between the physicochemical and/or other properties of monoclonal antibody agents and the time-to-onset of the DILD.

Abe et al. reported that any interpretation of data from small sample sizes (notably, less than 100 case reports) should be performed cautiously, as the variance of the regression line estimated by the Weibull analysis would be increased when small sample sizes are present. Thus, since there were fewer than 100 case reports for pembrolizumab, golimumab, and denosumab in this study, the present findings for these agents may not be conclusive. Secondly, the fact that the time-to-onset of the DILD in this study was performed using only 11 agents also needs to be taken into consideration. It should be noted, however, that there has been a recent increase in the amount of data reported for monoclonal antibody agents responsible for causing DILD, with these cases including information on cetuximab pegol, ipilimumab, ramucirumab, and other new agents in the JADER database.

While post-marketing spontaneous reporting of suspected adverse reactions has been shown to be a valuable resource, there are several problems associated with spontaneous reporting databases, such as the JADER, that need to be taken into consideration. These problems include: 1) the size and characteristics of the target population are often unclear, which indicates that the range of adaptation of the obtained results cannot be definitively defined; 2) despite bias in the information, it is difficult to evaluate the magnitude of the influence; 3) countless prognostic factors and covariates are confounded, thereby making it hard to investigate which of these might have truly influenced the results; 4) there is no means for confirming the causal relationship, even if a suspected side effect is found; and 5) there is difficulty ascertaining the accuracy of the report. As a result, careful attention needs to be paid to any interpretation of the results from the JADER database.

In conclusion, the results of our present study showed that with the exception of denosumab (64.5 d) and adalimumab (126 d), the time-to-onset of DILD for monoclonal antibody agents ranged from 1 to 2 months after the initial administration. Furthermore, with the exception of pembrolizumab, the onset-patterns for the monoclonal antibody agents were estimated to be either the early failure type profile or the random failure type profile. Perhaps more importantly, our present study was able to demonstrate the likely range of time in which DILD might be found, in addition to the most likely time period that DILD could actually occur in patients after the administration of monoclonal antibody agents. As a result, these findings could potentially lead to more concrete pharmacovigilance in the use of these agents.

Finally, to determine the onset of drug-induced blood disorders at an early stage, the specific time of monitoring laboratory tests is described in the package insert of small molecule molecularly-targeted drugs. Although the incidence of DILD is described in the package insert, and included in the interview form, of monoclonal antibody agents, the time to onset of DILD is not described. During the administration of monoclonal antibody agent therapy, it is important to determine how DILD occurrence varies over time. It is considered necessary to describe, both in the package insert and on the interview form, not only the incidence of side effects, but also the time to onset.

Conflict of Interest The authors declare no conflicts of interest.

REFERENCES

35) Wiemken T. L., Kelley R. R., Fernandez-Bo


