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Analysis of drug-induced interstitial lung disease using the Japanese Adverse Drug Event Report database

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Abstract

Objectives: Drug-induced interstitial lung disease occurs when exposure to a drug causes inflammation and, eventually, fibrosis of the lung interstitium. Drug-induced interstitial lung disease is associated with substantial morbidity and mortality. The aim of this retrospective study was to obtain new information on the time-to-onset profiles of drug-induced interstitial lung disease by consideration of other associated clinical factors using the Japanese Adverse Drug Event Report database.

Methods: We identified and analyzed reports of drug-induced interstitial lung disease between 2004 and 2018 from the Japanese Adverse Drug Event Report database. The reporting odds ratio and 95% confidence interval was used to detect the signal for each drug-induced interstitial lung disease incidence. We evaluated the time-to-onset profile of drug-induced interstitial lung disease and used the applied association rule mining technique to uncover undetected relationships, such as possible risk factors.

Results: The reporting odds ratios (95% confidence intervals) of drug-induced interstitial lung disease due to temsirolimus, gefitinib, sho-saiko-to, sai-rei-to, osimertinib, amiodarone, alectinib, erlotinib, everolimus, and bicalutamide were 18.3 (15.6–21.3), 17.8 (16.5–19.2), 16.3 (11.8–22.4), 14.5 (11.7–18.2), 12.5 (10.7–14.7), 10.9 (9.9–11.9), 10.6 (8.1–13.9), 9.6 (8.8–10.4), 9.4 (8.7–10.0), and 9.2 (7.9–10.6), respectively. The median durations (day (interquartile range)) for drug-induced interstitial lung disease were as follows: amiodarone (123.0 (27.0–400.5)), methotrexate (145.5 (67.8–475.8)), fluorouracil (86.0 (35.5–181.3)), gemcitabine (53.0 (20.0–83.0)), paclitaxel (52.0 (28.5–77.5)), docetaxel (47.0 (18.8–78.3)), bleomycin (92.0 (38.0–130.5)), oxaliplatin (45.0 (11.0–180.0)), nivolumab (56.0 (21.0–135.0)), gefitinib (24.0 (11.0–55.0)), erlotinib (21.0 (9.0–49.0)), temsirolimus (38.0 (14.0–68.5)), everolimus (56.0 (35.0–90.0)), osimertinib (51.5 (21.0–84.8)), alectinib (78.5 (44.3–145.8)), bicalutamide (50.0 (28.0–147.0)), pegylated interferon-2α (140.0 (75.8–233.0)), sai-rei-to (35.0 (20.0–54.5)), and sho-saiko-to (33.0 (13.5–74.0)) days. Association rule mining suggested that the risk of drug-induced interstitial lung disease was increased by a combination of amiodarone or sho-saiko-to and aging.

Conclusion: Our results showed that patients who receive gefitinib or erlotinib should be closely monitored for the development of drug-induced interstitial lung disease within a short duration (4 weeks). In addition, elderly people who receive amiodarone or sho-saiko-to should be carefully monitored for the development of drug-induced interstitial lung disease.

Keywords

Drug-induced interstitial lung disease, the Japanese Adverse Drug Event Report database, pharmacovigilance, time-to-onset profile

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Introduction

Interstitial lung disease is a group of diffuse parenchymal lung disorders associated with substantial morbidity and mortality.[1] Drug-induced interstitial lung disease (DIILD) occurs when drug exposure causes inflammation and eventually fibrosis of the lung interstitium.[2] Chemotherapeutic drugs (e.g. bleomycin and gefitinib), amiodarone, anti-inflammatory drugs (e.g. methotrexate), biological drugs, and various other drugs can cause DIILD (www.pneumotox.com).[2,3] As DIILD is considered a serious adverse event (AE) and represents a serious clinical problem, all healthcare professionals should be aware of a potential DIILD as soon as possible. Early intervention may prevent the progression of AEs and permanent changes.[4] However, the detailed time-to-onset profiles of DIILD in clinical settings are not clear.

The frequency of DIILD is reported to be higher in Japan than that in other countries.[5] Lung injuries related to molecular-targeted drugs have been reported. Reports related to gefitinib first occurred in 2002 in Japan and those related to the antirheumatic drug leflunomide were reported 1 year later.[5] The Ministry of Health, Labor and Welfare in Japan has issued the Manual for Handling Disorders due to Adverse Drug Reactions with a focus on DIILD. AEs during the post-marketing phase in Japan are reported and managed by the Pharmaceuticals and Medical Devices Agency (PMDA). The agency has established a spontaneous reporting system (SRS) for the Japanese Adverse Drug Event Report (JADER) database. The JADER is the largest database in Japan and reflects the realities of clinical practices.

The aim of this retrospective pharmacovigilance study was to assess the incidence of DIILD by using the JADER database. We focused on the time-to-onset profile of DIILD. Furthermore, association rule mining has been proposed as a new analytical technique to identify undetected relationships such as possible risk factors between variables in the SRS database.[6,7] We evaluated potential association rules between DIILD and demographics.

Materials and methods

Data source

Healthcare professionals, marketing approval holders, patients, and consumers voluntarily send AE reports to the PMDA. All AE report data were accumulated in the PMDA and were fully anonymized by the PMDA to form the JADER database. JADER data from April 2004 to June 2018 are publicly available and can be downloaded from the PMDA website (www.pmda.go.jp). For this retrospective study, we built a relational database, which integrated the data tables, by using the FileMaker Pro 13 software.

Definition of interstitial lung disease

In accordance with the terminology preferred by the Medical Dictionary for Regulatory Activities (MedDRA, www.pmrj.jp/jmo/php/indexj.php) version 19.0, we used the following preferred term (PT) for DIILD: *interstitial lung disease* (PT code: 10022611).

Drug selection

The number of drugs known to produce various patterns of DIILD is increasing. In this study, we first listed 82 drugs, each of which had more than 100 reported DIILD cases in the JADER database. Second, from the Drug-Induced Respiratory Disease Website (www.pneumotox.com), we listed 598 drugs from the website in the categories of interstitial/parenchymal lung disease, pulmonary edema—acute lung injury—ARDS, and pathology. From these categories, the following patterns were identified: "Interstitial/parenchymal lung disease: pneumonitis (ILD), acute, severe (may occasion an ARDS picture)" (pattern Ia, 155 listed drugs); "Interstitial/parenchymal lung disease: pneumonitis (ILD)" (pattern Ib, 329 listed drugs); "Interstitial/parenchymal lung disease: eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)" (pattern Ic, 192 listed drugs); "Interstitial/parenchymal lung disease: pulmonary fibrosis (not otherwise specified)" (pattern Ig, 84 listed drugs); "Pulmonary edema—acute lung injury—ARDS" (pattern IIb, 254 listed drugs); "Pathology: cellular NSIP pattern" (pattern XVa, 51 listed drugs); "Pathology: organizing pneumonia (OP/BOOP) pattern" (pattern XVc, 70 listed drugs). Third, we compared the 598 listed drugs from the Drug-Induced Respiratory Disease Website (www.pneumotox.com) and the drugs in the JADER database with between 50 and 99 reported DIILD cases. Fourth, we listed the 18 drugs that matched the drugs in the Drug-Induced Respiratory Disease Website. Fifth, regardless of the number of reported DIILD cases related to each drug, we compared the drugs that were reported in the JADER database and drugs reported in previous studies.[2,8] Ten drugs (sirolimus, simvastatin, fluvastatin, daptomycin, lapatinib, interferon beta, interferon gamma, pravastatin, pitavastatin, and ipilimumab) that were not listed by the fourth procedure were added. In total, we identified 110 (82 + 18 + 10) drugs for analysis (Table 1). Thus, Table 1 is considered to include almost all drugs that can be practically analyzed.

Statistics

Reporting odds ratio. The reporting odds ratio (ROR) is the authorized pharmacovigilance index and was calculated using two-by-two contingency tables of the presence or absence of a particular drug and a particular AE in the case reports.[9] An association was considered disproportionate when the lower limit of the 95% confidence interval (CI) was >1 (Figure 1).[9,10] Two or more cases were required to define the signal.[11]

Time to onset. Time-to-onset duration was calculated from the time of the patient's first prescription to the occurrence of

Table 1. Number of reports and ROR for drug-induced interstitial lung disease.

Category	ATC code[a]	Drugs	Total (n)	Case (n)	Non-case (n)	ROR[b] (95% CI)
		Total	534688	24123	–	–
H2-receptor antagonists	A02BA03	Famotidine	3469	172	3297	1.1 (0.9–1.3)
Proton pump inhibitors	A02BC03	Lansoprazole	4434	240	4194	1.2 (1.1–1.4)
Aminosalicylic acid and similar agents	A07EC01	Salazosulfapyridine	1864	108	1756	1.3 (1.1–1.6)
	A07EC02	Mesalazine	1558	133	1425	2.0 (1.7–2.4)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH01	Sitagliptin	2054	148	1906	1.6 (1.4–1.9)
	A10BH02	Vildagliptin	2371	74	2297	0.7 (0.5−0.9)
Platelet aggregation inhibitors	B01AC04	Clopidogrel	4638	229	4409	1.1 (0.9–1.3)
	B01AC05	Ticlopidine	2180	57	2123	0.6 (0.4−0.7)
	B01AC23	Cilostazol	2244	107	2137	1.1 (0.9−1.3)
Direct thrombin inhibitors	B01AE07	Dabigatran	2466	92	2374	0.8 (0.7−1.0)
Direct factor Xa inhibitors	B01AF01	Rivaroxaban	4691	165	4526	0.8 (0.7–0.9)
	B01AF02	Apixaban	4800	133	4667	0.6 (0.5–0.7)
Antiarrhythmics, class III	C01BD01	Amiodarone	1993	665	1328	10.9 (9.9–11.9)
Dihydropyridine derivatives	C08CA01	Amlodipine	3672	100	3572	0.6 (0.5−0.7)
Phenylalkylamine derivatives	C08EA02	Bepridil	734	133	601	4.7 (3.9–5.7)
Angiotensin II receptor blockers (ARBs), plain	C09CA03	Valsartan	3548	131	3417	0.8 (0.7–1.0)
	C09CA06	Candesartan	1925	121	1804	1.4 (1.2–1.7)
HMG CoA reductase inhibitors	C10AA01	Simvastatin	318	14	304	1.0 (0.6–1.7)
	C10AA03	Pravastatin	922	40	882	1.0 (0.7–1.3)
	C10AA04	Fluvastatin	638	19	619	0.6 (0.4–1.0)
	C10AA05	Atorvastatin	2748	104	2644	0.8 (0.7–1.0)
	C10AA07	Rosuvastatin	1517	71	1446	1.0 (0.8–1.3)
	C10AA08	Pitavastatin	813	41	772	1.1 (0.8–1.5)
Glucocorticoids	H02AB02	Dexamethasone	5952	144	5808	0.5 (0.4–0.6)
Tetracyclines	J01AA08	Minocycline	1637	152	1485	2.2 (1.8–2.6)
Carbapenems	J01DH02	Meropenem	1940	103	1837	1.2 (0.97−1.4)
Combinations of sulfonamides and trimethoprim, incl. derivatives	J01EE01	Sulfamethoxazole • Trimethoprim	2737	104	2633	0.8 (0.7−1.0)
Macrolides	J01FA09	Clarithromycin	4066	101	3965	0.5 (0.4−0.7)
Fluoroquinolones	J01MA12	Levofloxacin	4187	196	3991	1.0 (0.9–1.2)
Other antibacterials	J01XX09	Daptomycin	353	20	333	1.3 (0.8–2.0)
Antibiotics	J04AB02	Rifampicin	1600	76	1524	1.1 (0.8−1.3)
Other drugs for treatment of tuberculosis	J04AK02	Ethambutol	1253	50	1203	0.9 (0.7−1.2)
Antivirals for treatment of HCV infections	J05AP01	Ribavirin	10394	319	10075	0.7 (0.6–0.7)
Nitrogen mustard analogues	L01AA01	Cyclophosphamide	5129	390	4739	1.8 (1.6–1.9)
Folic acid analogues	L01BA01	Methotrexate	18336	1899	16437	2.6 (2.4–2.7)
	L01BA04	Pemetrexed	2431	347	2084	3.6 (3.2–4.0)
Pyrimidine analogues	L01BC02	Fluorouracil	7796	801	6995	2.5 (2.3–2.7)

(Continued)

Table 1. (Continued)

Category	ATC code[a]	Drugs	Total (n)	Case (n)	Non-case (n)	ROR[b] (95% CI)
	L01BC05	Gemcitabine	4454	1161	3293	7.8 (7.3–8.3)
	L01BC06	Capecitabine	3561	209	3352	1.3 (1.1-1.5)
	L01BC53	Tegafur·Uracil	1635	108	1527	1.5 (1.2–1.8)
	L01BC53	Tegafur•Gimeracil•Oteracil	6618	639	5979	2.3 (2.1–2.5)
Vinca alkaloids and analogues	L01CA02	Vincristine	2939	145	2794	1.1 (0.9–1.3)
	L01CA04	Vinorelbine	758	175	583	6.4 (5.4–7.6)
Podophyllotoxin derivatives	L01CB01	Etoposide	3017	123	2894	0.9 (0.7–1.1)
Taxanes	L01CD01	Paclitaxel	6900	944	5956	3.5 (3.2–3.7)
	L01CD02	Docetaxel	6403	1066	5337	4.4 (4.1–4.7)
Anthracyclines and related substances	L01DB01	Doxorubicin	3804	186	3618	1.1 (0.9–1.3)
	L01DB03	Epirubicin	1547	138	1409	2.1 (1.7–2.5)
	L01DB10	Amrubicin	1245	116	1129	2.2 (1.8–2.6)
Other cytotoxic antibiotics	L01DC01	Bleomycin	418	104	314	7.0 (5.6–8.8)
Platinum compounds	L01XA01	Cisplatin	8673	260	8413	0.7 (0.6–0.7)
	L01XA02	Carboplatin	5281	332	4949	1.4 (1.3–1.6)
	L01XA03	Oxaliplatin	8001	682	7319	2.0 (1.8–2.2)
Monoclonal antibodies	L01XC02	Rituximab	3979	209	3770	1.2 (1.0–1.4)
	L01XC03	Trastuzumab	2469	380	2089	3.9 (3.5–4.3)
	L01XC06	Cetuximab	2746	451	2295	4.2 (3.8–4.7)
	L01XC07	Bevacizumab	9440	505	8935	1.2 (1.1–1.3)
	L01XC08	Panitumumab	1393	302	1091	5.9 (5.2–6.7)
	L01XC11	Ipilimumab	545	41	504	1.7 (1.3–2.4)
	L01XC13	Pertuzumab	683	122	561	4.6 (3.8–5.6)
	L01XC17	Nivolumab	4419	991	3428	6.3 (5.9–6.8)
	L01XC18	Pembrolizumab	2148	622	1526	8.8 (8.0–9.7)
	L01XC21	Ramucirumab	1570	91	1479	1.3 (1.1−1.6)
Protein kinase inhibitors	L01XE01	Imatinib	4399	348	4051	1.8 (1.6–2.0)
	L01XE02	Gefitinib	2736	1217	1519	17.8 (16.5–19.2)
	L01XE03	Erlotinib	2748	836	1912	9.6 (8.8–10.4)
	L01XE04	Sunitinib	3320	106	3214	0.7 (0.6–0.8)
	L01XE05	Sorafenib	4922	136	4786	0.6 (0.5–0.7)
	L01XE06	Dasatinib	1256	85	1171	1.5 (1.2–1.9)
	L01XE07	Lapatinib	731	36	695	1.1 (0.8–1.5)
	L01XE09	Temsirolimus	652	300	352	18.3 (15.6–21.3)
	L01XE10	Everolimus	3671	1093	2578	9.4 (8.7–10.0)
	L01XE13	Afatinib	786	178	608	6.2 (5.3–7.4)
	L01XE16	Crizotinib	1027	147	880	3.6 (3.0–4.2)
	L01XE35	Osimertinib	653	241	412	12.5 (10.7-14.7)

(Continued)

Table 1. (Continued)

Category	ATC code[a]	Drugs	Total (n)	Case (n)	Non-case (n)	ROR[b] (95% CI)
	L01XE36	Alectinib	243	81	162	10.6 (8.1–13.9)
Other antineoplastic agents	L01XX19	Irinotecan	5545	650	4895	2.9 (2.6–3.1)
	L01XX32	Bortezomib	2219	153	2066	1.6 (1.3–1.9)
	L01XX33	Celecoxib	3222	110	3112	0.7 (0.6–0.9)
	L01XX41	Eribulin	840	104	736	3.0 (2.4−3.7)
Gonadotropin releasing hormone analogues	L02AE02	Leuprorelin	1436	229	1207	4.0 (3.5–4.7)
Anti-androgens	L02BB03	Bicalutamide	849	255	594	9.2 (7.9–10.6)
Colony stimulating factors	L03AA02	Filgrastim	635	117	518	4.8 (3.9−5.9)
Interferons	L03AB02	Interferon beta	1555	38	1517	0.5 (0.4–0.7)
	L03AB03	Interferon gamma	32	6	26	4.9 (2.0–11.9)
	L03AB11	PEG INF-2α	3386	305	3081	2.1 (1.9–2.4)
Selective immunosuppressants	L04AA10	Sirolimus	44	5	39	2.7 (1.1–6.9)
	L04AA13	Leflunomide	630	55	575	2.0 (1.5–2.7)
	L04AA24	Abatacept	1186	84	1102	1.6 (1.3−2.0)
	L04AA29	Tofacitinib	981	74	907	1.7 (1.4–2.2)
Tumor necrosis factor alpha (TNF-α) inhibitors	L04AB01	Etanercept	4050	402	3648	2.4 (2.1–2.6)
	L04AB02	Infliximab	4605	347	4258	1.7 (1.6–1.9)
	L04AB04	Adalimumab	2452	227	2225	2.2 (1.9–2.5)
	L04AB05	Certolizumab Pegol	863	66	797	1.8 (1.4−2.3)
	L04AB06	Golimumab	1047	86	961	1.9 (1.5−2.4)
Interleukin inhibitors	L04AC07	Tocilizumab	4187	209	3978	1.1 (0.97–1.3)
Calcineurin inhibitors	L04AD01	Ciclosporin	6602	121	6481	0.4 (0.3–0.5)
	L04AD02	Tacrolimus	10478	268	10210	0.6 (0.5–0.6)
Other immunosuppressants	L04AX04	Lenalidomide	4247	99	4148	0.5 (0.4−0.6)
Acetic acid derivatives and related substances	M01AB05	Diclofenac	3552	106	3446	0.6 (0.5−0.7)
Propionic acid derivatives	M01AE	Loxoprofen	6372	304	6068	1.1 (0.9–1.2)
Penicillamine and similar agents	M01CC02	Bucillamine	1095	251	844	6.4 (5.5–7.3)
Preparations inhibiting uric acid production	M04AA01	Allopurinol	3202	142	3060	1.0 (0.8–1.2)
Salicylic acid and derivatives	N02BA01	Aspirin (acetylsalicylic acid)	7477	109	7368	0.3 (0.3−0.4)
Carboxamide derivatives	N03AF01	Carbamazepine	5568	76	5492	0.3 (0.2−0.4)
Other antiepileptics	N03AX16	Pregabalin	4659	158	4501	0.7 (0.6–0.9)
Detoxifying agents for antineoplastic treatment	V03AF04	Levofolinate	3989	410	3579	2.4 (2.2–2.7)
Herbal Medicines		Sai-rei-to	325	132	193	14.5 (11.7–18.2)
		Sho-saiko-to	152	66	86	16.3 (11.8–22.4)
Others		Iguratimod	487	86	401	4.6 (3.6−5.7)

ROR: reporting odds ratio; CI: confidence interval; HCV: Hepatitis C Virus.
[a]Anatomical therapeutic classification.
[b]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

$$\text{Reporting Odds Ratio (ROR)} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$95\%\ \text{Confidence Interval (CI)} = e^{\ln(\text{ROR}) \pm 1.96 \sqrt{1/a+1/b+1/c+1/d}}$$

Figure 1. Two-by-two contingency table for analysis.

the AEs.[7,12] It is necessary to take the correct truncation into account when estimating the time to onset of AEs from SRS data. We chose an analysis period of 730 days after the start date of administration to focus attention on the onset of AEs within 2 years. The median duration, quartiles, and the Weibull shape parameters (WSPs) were used to evaluate the time-to-onset data.[7,12] The scale parameter, α, of the Weibull distribution determines the scale of the distribution function. A larger scale value stretches the distribution, whereas a smaller scale value shrinks the data distribution. The shape parameter, β, of the Weibull distribution determines the shape of the distribution function. A larger shape value produces a left-skewed curve, whereas a smaller shape value produces a right-skewed curve. In the analysis of the SRS, the shape parameter of the Weibull distribution was used to indicate hazards without a reference population as follows: when β was equal to 1, the hazard was estimated to be constant over time; if β was greater than 1 and the 95% confidence interval (CI) of β excluded the value 1, the hazard was considered to increase over time (wear-out failure type); finally, if β was less than 1 and the 95% CI of β excluded the value 1, the hazard was considered to decrease over time (initial-failure type).[7,13–17] Data analyses were performed by using JMP, version 12.0.1 (SAS Institute Inc., Cary, NC, USA).

Association rule mining. Association rule mining has been proposed as an analytical approach for discovering interesting relationships among the possible risk factors and variables in the SRS database. The method is focused on finding frequent co-existing associations among a collection of items.[6,7] Given a set of transactions T (each transaction is a set of items), an association rule can be expressed as X (the antecedent (left-hand-side, lhs) of the rule) → Y (the consequent (right-hand-side, rhs) of the rule), where X and Y are mutually exclusive sets of items.[6,7] The *Apriori* algorithm was applied to find association rules. *Support, confidence*, and *lift* were used as indicators to decide the relative strength of the rules. These indices were calculated as follows:

$$\textit{Support} = \text{Number of transactions with both X and Y/Total number of transactions} = \{X \cap Y\} / \{D\} = P(X \cap Y)$$

$$\textit{Confidence} = \text{Number of transactions with both X and Y/Total number of transactions with X} = P(X \cap Y) / P(X)$$

Confidence corresponds to the conditional probability P (Y|X) and *Confidence* measures the reliability of the interference made by a rule.

$$\textit{Expected confidence} = \text{Number of transactions with Y/Total number of transactions} = P(B)$$

$$\textit{Lift} = \textit{Confidence} / \textit{Expected Confidence} = P(X \cap Y) / P(X)P(Y)$$

Lift is the factor by which the co-occurrence of X and Y exceeds the expected probability of X and Y co-occurring, had they been independent. *Lift* is the ratio between the *confidence* of the rule and the *support* of the itemset as a consequence of the rule. The *lift* can be expressed as the confidence divided by P (Y). The *lift* can be evaluated as follows: $lift = 1$, if X and Y are independent; $lift > 1$, if X and Y are positively correlated; $lift < 1$, if X and Y are negatively correlated. Furthermore, we calculated the chi-square values to evaluate the association rules[18]

$$\textit{Chi-squared} = D(lift - 1)^2 \frac{Support * Confidence}{(Confidence - Support) * (Lift - Confidence)}$$

Association rule mining was performed using the *apriori* function of the *arules* library in the *arules* package of the R software (version 3.3.3). *Support* and *lift* were visualized using the R-extension package *arulesViz* which implements novel visualization techniques to explore association rules.

Results

The JADER database contained 534,688 reports. The number of AE reports corresponding to DIILD was 24,123 reports (Table 1). The number of AEs associated with the top 10 reported drugs, methotrexate, gefitinib, gemcitabine, everolimus, docetaxel, nivolumab, paclitaxel, erlotinib, fluorouracil, and oxaliplatin was 1899, 1217, 1161, 1093, 1066, 991, 944, 836, 801, and 682, respectively. The top 10 RORs (95% CIs) with drugs, temsirolimus, gefitinib, sho-saiko-to, sai-rei-to, osimertinib, amiodarone, alectinib, erlotinib, everolimus, and

bicalutamide were 18.3 (15.6–21.3), 17.8 (16.5–19.2), 16.3 (11.8–22.4), 14.5 (11.7–18.2), 12.5 (10.7–14.7), 10.9 (9.9–11.9), 10.6 (8.1–13.9), 9.6 (8.8–10.4), 9.4 (8.7–10.0), and 9.2 (7.9–10.6), respectively. In contrast, the ROR signals of HMG CoA reductase and antithrombotic agents such as platelet aggregation inhibitors, direct thrombin inhibitors, and direct factor Xa inhibitors were not detected.

For the time-to-onset analysis, we extracted combinations that had complete information for the date of treatment initiation and the date of AE onset. The median durations (day) (interquartile range) for DIILD were as follows: amiodarone (123.0 (27.0–400.5)), methotrexate (145.5 (67.8–475.8)), fluorouracil (86.0 (35.5–181.3)), gemcitabine (53.0 (20.0–83.0)), paclitaxel (52.0 (28.5–77.5)), docetaxel (47.0 (18.8–78.3)), bleomycin (92.0 (38.0–130.5)), oxaliplatin (45.0 (11.0–180.0)), nivolumab (56.0 (21.0–135.0)), gefitinib (24.0 (11.0–55.0)), erlotinib (21.0 (9.0–49.0)), temsirolimus (38.0 (14.0–68.5)), everolimus (56.0 (35.0–90.0)), osimertinib (51.5 (21.0–84.8)), alectinib (78.5 (44.3–145.8)), bicalutamide (50.0 (28.0–147.0)), PEG IFN-2α (140.0 (75.8–233.0)), sai-rei-to (35.0 (20.0–54.5)), and sho-saiko-to (33.0 (13.5–74.0)) days, respectively (Figure 2). Among the drugs which demonstrated the lower limit of the 95% CI of the ROR was >1, >50% of the DIILD cases associated with minocycline, amrubicin, carboplatin, gefitinib, erlotinib, dasatinib, afatinib, crizotinib, bortezomib, filgrastim, or certolizumab pegol were observed within 4 weeks. >50% of the reports of DIILD following administration of amiodarone, methotrexate, PEG IFN-2α, leflunomide, or etanercept were recorded more than 4 months of treatment initiation. The WSP β (95% CI) of amiodarone, nivolumab, gefitinib, and sho-saiko-to was 0.77 (0.70–0.84), 0.90 (0.85–0.95), 0.78 (0.74–0.82), and 0.76 (0.59–0.95), respectively. The lower limits of the 95% CI of the WSP β value for daptomycin, vinorelbine, paclitaxel, amrubicin, bevacizumab, everolimus, and PEG INF-2α were greater than 1.

To evaluate the risk factors for DIILD by using demographic data, such as age, patient history, and administered drugs, we applied the *Apriori* algorithm (minimum *support* and minimum *confidence* threshold, 0.00001 and 0.01, respectively) and *maxlen* was restricted to 3. The result of the mining algorithm for DIILD was a set of 11 rules, respectively (Table 2). {sho-saiko-to, 50–59 years}, {sho-saiko-to, 60–69 years}, {sho-saiko-to, 70–79 years} ⇒ {DIILD}, {sho-saiko-to-ka-kikyo-sekko, 70–79 years} ⇒ {DIILD} demonstrated high *lift* scores (Table 2, id(8–11) and Figure 3). The association rules of the combination of {amiodarone, 50–59 years}, {amiodarone, 60–69 years}, {amiodarone, 70–79 years}, {amiodarone, 80–89 years}, {amiodarone, ⩾90 years} ⇒ {DIILD} demonstrated high *support* and *lift* scores (Table 2, id(3–7) and Figure 3).

Discussion

In this study, we evaluated the relationship between the drug and DIILD by using data from the SRS database. The exact frequency of drug-induced pulmonary toxicity is unknown.[3] Although global incidence of DIILD is not clearly known, at least 2.5%–3.0% of cases are drug induced.[19,20] Several studies have indicated that drug-induced pulmonary toxicity is underdiagnosed worldwide.[3] We summarized the incidence of DIILD, the ROR values, and time-to-onset profile from the SRS database. It is considered to be more comprehensive information indicating the occurrence of DIILD reflecting the actual clinical use than has been published previously.

DIILD can occur at any time during treatment.[21] We applied time-to-onset analysis to validate the results, and found that >50% of the DIILD cases associated with carboplatin, gefitinib, erlotinib, dasatinib, afatinib, crizotinib, bortezomib, and so on were observed within 4 weeks in the real-world data set. DIILD occurring after 4 months of amiodarone, methotrexate, PEG IFN-2α, leflunomide, or etanercept administration should not be overlooked.

It is suggested that risk factors for amiodarone-related DIILD were cumulative dose, and a combination of high doses over longer periods.[22] The cumulative incidence of amiodarone-related DIILD was 4.2%, 7.8%, and 10.6% after 1, 3, and 5 years, respectively, during 48-month follow-up periods in a retrospective study.[23] The time-to-onset duration of amiodarone was 123.0 days in our study using the JADER data set. Amiodarone-related DIILD was likely to be initial-failure type. For methotrexate, Kremer et al.[24] reported a mean time to DIILD onset of 23 days (range = 3–112 days). In other studies, time to DIILD onset has been as long as 4 years.[25] The onset of DIILD due to methotrexate was 145.5 days in our study. A nationwide Japanese study of gemcitabine determined a median time of onset of 65 days.[2] The onset of DIILD due to gemcitabine was 53.0 days in our study. The median DIILD initiation time in patients with germ cell tumors receiving high-dose bleomycin was 4.2 months (126 days).[26] The median DIILD initiation time of bleomycin was 92.0 days in our study. DIILD onset of epidermal growth factor receptor (EGFR)-directed monoclonal antibodies such as cetuximab and panitumumab demonstrated a broad range of times (median = 101 days, range = 17–431 days).[27] The time-to-onset durations of cetuximab and panitumumab were 45.0 and 55.0 days in our study, respectively. For immune checkpoint inhibitors such as programmed cell death 1 (PD-1) inhibitors (nivolumab (DIILD onset in the JADER data set: 56.0 days), pembrolizumab (DIILD onset in the JADER data set: 40.0 days)), time to onset ranged from 0.2 to 27.4 months, with DIILD occurring within 2 months of treatment initiation in 42% of patients.[2] No clear relationship has been observed between DIILD onset and dose or duration of treatment.[28] Gefitinib (DIILD onset in the JADER data set: 24.0 days) and erlotinib (DIILD onset in the JADER data set: 21.0 days) are EGFR-targeting agents. The incidence of DIILD associated with gefitinib and erlotinib was highest within 4 weeks (28 days) of the initiation of treatment.[29,30] DIILD induced by gefitinib was likely

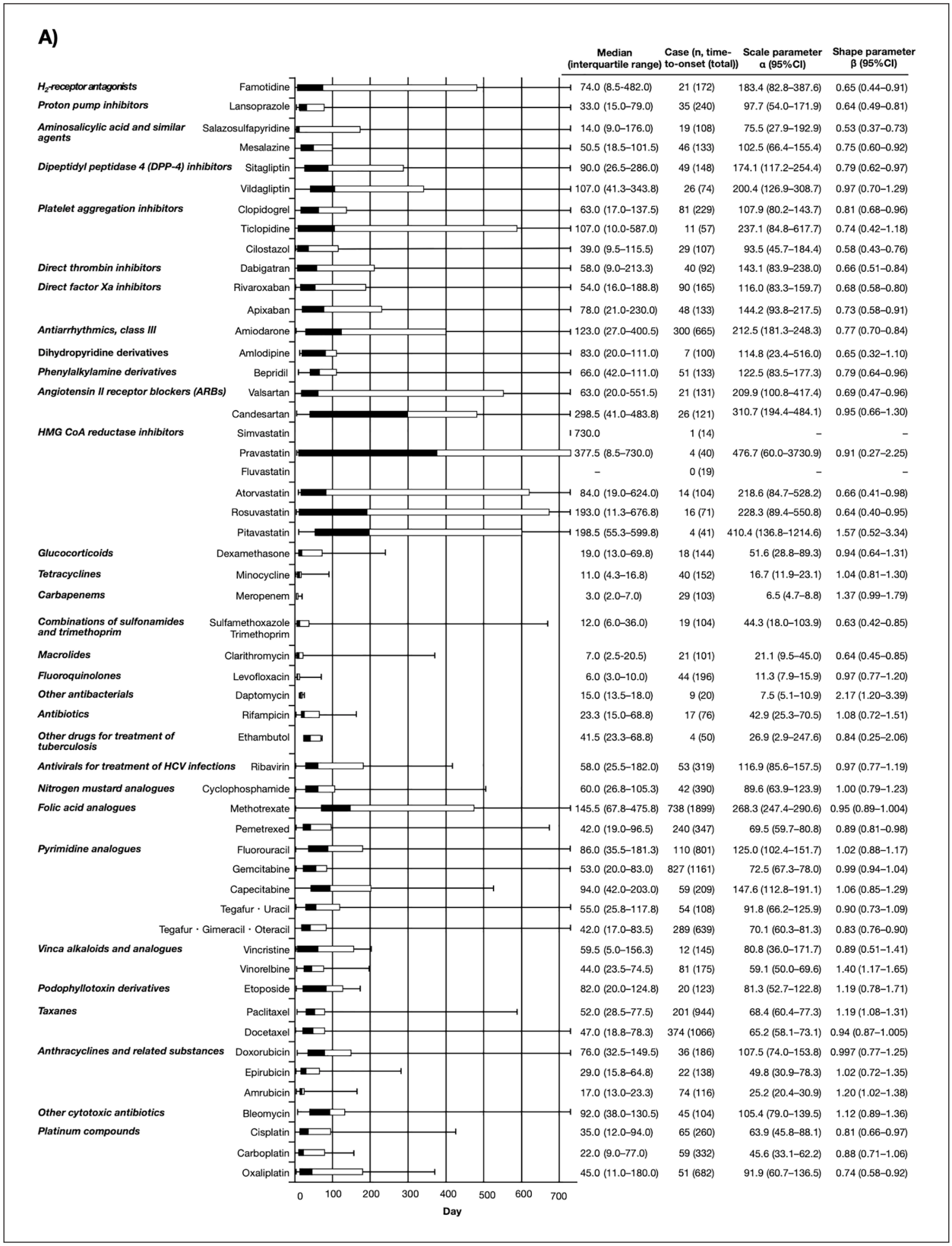

Figure 2. *(Continued)*

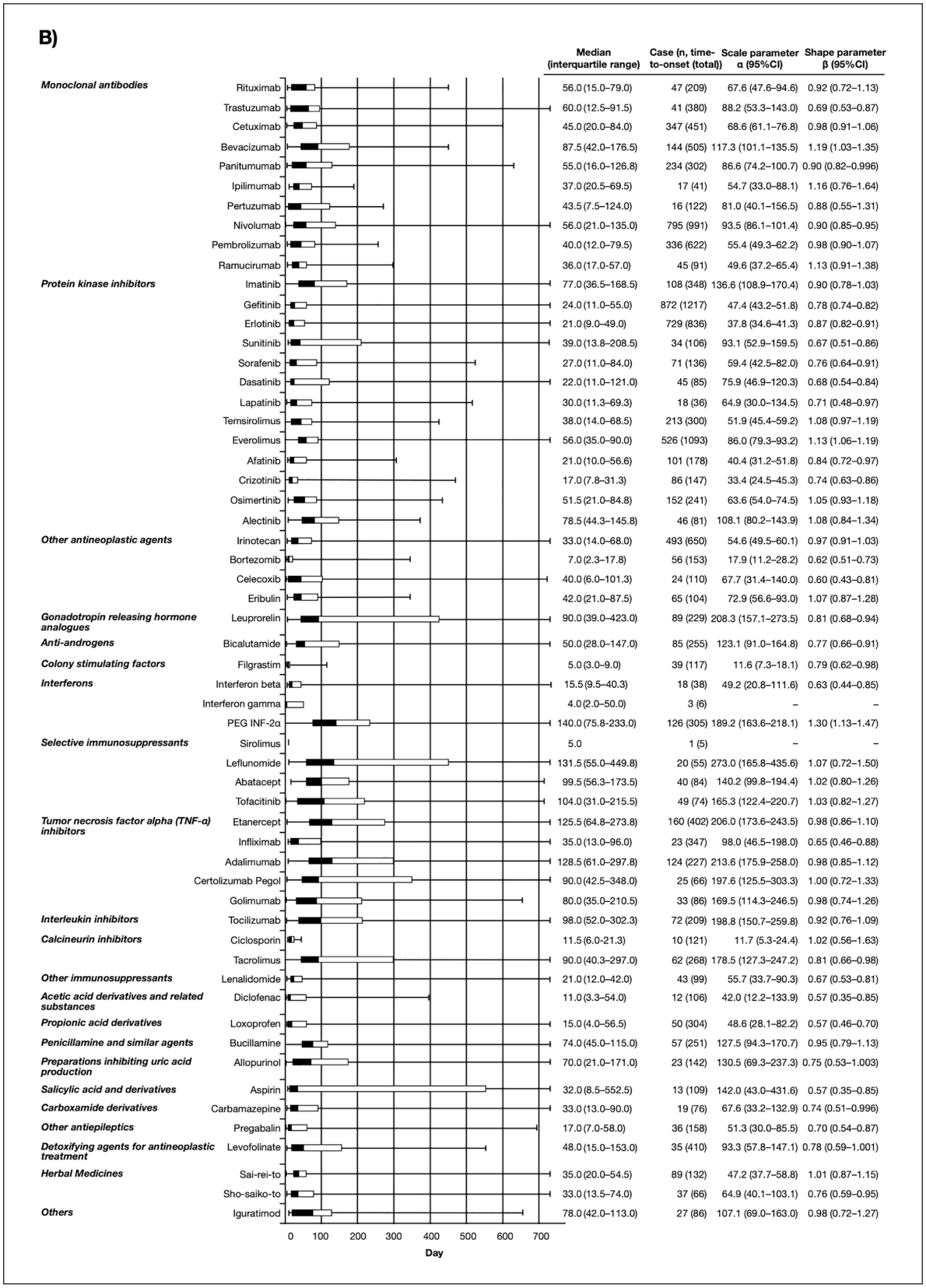

Figure 2. A box plot of drug-induced interstitial lung disease. The bottom end is minimum value. The top end is maximum value. The bottom of black box is 25th percentile. The top of white box is 75th percentile. The line joining the white and black is median. Panel A contains the drugs from ATC code A02BA03 to ATC code L01XA03 in the Table 1. Panel B contains the drugs from ATC code L01XC02 to ATC code V03AF04 in the Table 1.

Table 2. Association parameters of rules of Drug-Induced Interstitial Lung Disease (DIILD) based on the administered drug and the stratified age group (sort by lift).

Id	lhs[a]		rhs[b]	*Support*	*Confidence*	*Lift*	χ^2
[1]	{amiodarone, 40–49 years}	⇒	{DIILD}	0.00015	0.52288	1.17	3.52
[2]	{amiodarone, 30–39 years}	⇒	{DIILD}	0.00001	0.06667	1.49	0.90
[3]	{amiodarone, 50–59 years}	⇒	{DIILD}	0.00011	0.18182	4.06	142.24[c]
[4]	{amiodarone, ⩾90 years}	⇒	{DIILD}	0.00019	0.21277	4.75	315.56[c]
[5]	{amiodarone, 60–69 years}	⇒	{DIILD}	0.00034	0.27492	6.14	820.47[c]
[6]	{amiodarone, 70–79 years}	⇒	{DIILD}	0.00048	0.29702	6.64	1288.35[c]
[7]	{amiodarone, 80–89 years}	⇒	{DIILD}	0.00025	0.29797	6.66	673.40[c]
[8]	{sho-saiko-to, 50–59 years}	⇒	{DIILD}	0.00019	0.03030	6.77	505.12[c]
[9]	{sho-saiko-to-ka-kikyo-sekko, 70–79 years}	⇒	{DIILD}	0.00011	0.31579	7.06	320.15[c]
[10]	{sho-saiko-to, 70–79 years}	⇒	{DIILD}	0.00049	0.38806	8.67	1863.67[c]
[11]	{sho-saiko-to, 60–69 years}	⇒	{DIILD}	0.00036	0.48718	10.89	1810.41[c]

[a]lhs: left-hand-side (antecedents).
[b]rhs: right-hand-side (consequents).
[c]Statistical significance: χ^2 value ⩾4.

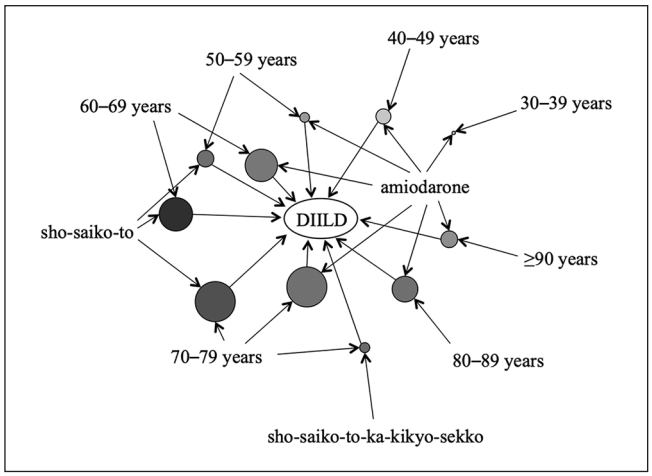

Figure 3. Association rules for drug-induced interstitial lung disease based on the JADER database between April 2004 and June 2018. The arguments of plot in the *arulesViz* were set as follows: method = "graph," measure = "*support*," shading = "*lift*." The measures of *support* were used in visualization as area of circle. The measures of *lift* were used for the shading of color of the circle. *Support* and *lift* were visualized using the R-extension package *arulesViz* which implements novel visualization techniques to explore association rules.

to be initial-failure type. Crizotinib, an oral tyrosine kinase inhibitor, induced DIILD several months after the initiation of treatment (median, 8.5 (6.5–11.5) months (255 days)).[31] In contrast, the onset of DIILD due to crizotinib was 17.0 days in our study. A distinct discrepancy in crizotinib was observed in the time-to-onset duration between the literature data and our result; however, we do not have a plausible explanation for this discrepancy. For leflunomide (DIILD onset in the JADER data set: 131.5 days), DIILD was reported in most patients within 20 weeks (140 days) in a study in Japan.[32] Our findings for the time to onset were not clearly linked to the literature data. However, we could demonstrate similar trends in most of the drugs considered in this study. Information from the SRS database and the literature data might be considered complementary.

There are many unclear points about the causative substances and underlying mechanisms of DIILD, which is diagnosed on the basis of clinical, physiological, and radiological findings consistent with interstitial lung disease.[2] Some of the known risk factors of DIILD include follows: age, drug interaction, genetic variations, ethnicity, dose, sex, radiation-induced lung injury, pulmonary edema, smoking, progression of the underlying disease, and use or non-use of corticosteroid therapy.[3,4]

In general, old age is associated with an increased risk of drug toxicity.[3] In a retrospective review of the pulmonary toxicity of bleomycin, Simpson et al.[33] showed that for cases in which pulmonary toxicity was fatal, the patients were older than the remaining patients, and in patients aged over 40 years, especially those with renal function in the lower range of normal, the risk of developing fatal toxicity might exceed 10%.[3] We detected the possible association rule related to DIILD for the combination of sho-saiko-to or amiodarone and aging (⩾50 years). Furthermore, the other rule of association {sho-saiko-to-ka-kikyo-sekko, 70–79 years} was observed in the antecedent (lhs). Thus, elderly patients receiving sho-saiko-to or amiodarone should be advised to adhere to appropriate treatment plan.

Sho-saiko-to contains seven crude drugs.[34] Among them, *Bupleurum* root and *Scutellaria* root are thought to be the potential causes of lung injury.[34] Many Chinese herbal medicines contain *Bupleurum* root and *Scutellaria* root, and herbal medicines such as saiko-ka-ryukotsu-borei-to and sai-rei-to can induce DIILD in a manner similar to that associated with sho-saiko-to.[35,36] It remains to be elucidated whether one or both drugs affect the lungs. Until then, it is a reasonable

assumption that DIILD associated with sho-saiko-to was caused by *Bupleurum* root and *Scutellaria* root.[34]

Drug interaction by concomitant drug use is a risk factor of AEs. As people age, they develop more chronic diseases and, accordingly, use more drugs. It is reported that amiodarone inhibits CYP1A2, CYP3A4, CYP2C9, and CYP2D6.[37–39] As the medication that is metabolized by any of these enzymes will be affected by plasma levels, it is likely that patients using amiodarone use other drugs which might increase the risk to DIILD occurrence. We evaluated the dose dependency of amiodarone on DIILD. The average dose of amiodarone for cases with DIILD (n = 778) and without DIILD (n = 1351) was 211.2 ± 154.3 (mean ± standard deviation) and 191.4 ± 174.9 mg/day, respectively. There were no statistically significant differences in our results. We did not evaluate the effects of concomitant drugs further.

Gefitinib plasma levels might be affected when using drugs that are metabolized by CYP2D6, such as metoprolol.[37,38] In our study, the number of all AE reports related to gefitinib was 2736. The number of cases of DIILD related to gefitinib was 1217. The combination of gefitinib and metoprolol was 8, and 4 cases were related to DIILD among them (8 cases). We did not examine the potential drug-by-drug bias of gefitinib and metoprolol because there were too few cases for a robust analysis.

Erlotinib and smoking are also a bad combination because of the induction of CYP1A2 and the subsequent lower plasma levels.[38–40] Even doubling up the dose (300 mg instead of 150 mg) is not sufficient,[41] but it can increase the incidence of DIILD, even without the presence of a polymorphism in one or several of these enzymes. As variability in drug response among patients is multifactorial, genetic variations in metabolizing enzymes may enhance the drivers of DIILD. Both clinical and genetic risk stratification (pharmacogenomics) may lead to a more accurate prevention of drug-induced lung damage in the future.

Our study has some limitations that should be considered. First, the JADER database does not contain detailed background information, such as genetic information, lifestyle habit (e.g. smoking), medical history (e.g. treatment regimen and pre-existing lung disease). For example, as detailed information is lacking from the studied population, factors affecting latency time (time to occurrence of the DIILD), such as concomitant infections that increase the degree of oxidative stress and cell injury or the occurrence of renal impairment, that influence pharmacokinetics and therefore serum drug levels,[2,42] are not evaluated. Second, the SRS is subject to over-reporting, under-reporting, missing data, exclusion of data from healthy individuals, lack of a denominator, and presence of confounding factors.[9] Therefore, ROR is not applicable to inferences of comparative degrees of causality. ROR only offers a rough indication of signal strength. Several approaches can be used to control for covariates, such as multiple-logistic regression,[43] Bayesian logistic regression,[44] and propensity score.[45] These approaches may be useful for further analysis of SRS. Third, in the association rule mining method, the researcher determined the parameters (*support, confidence*, and *maxlen*) according to the data set and purpose of the research. Therefore, further epidemiological studies may be required to confirm the results of this study.

Conclusion

Despite the limitations inherent to the SRS, we showed the potential risk of DIILD in a real-life setting. The present analysis showed that patients receiving gefitinib, erlotinib, afatinib, or crizotinib should be closely monitored for the development of DIILD within a short duration (4 weeks). In contrast, patients receiving methotrexate, leflunomide, etanercept, amiodarone, or PEG INF-2α should be carefully monitored for the development of DIILD over a longer duration (more than 4 months). Patients who are co-administered amiodarone, sho-saiko-to, and sho-saiko-to-ka-kikyo-sekko should also be carefully monitored for the development of DIILD.

Declaration of conflicting interests

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Ethical approval

Ethical approval was not sought for this study because the study was an observational study without any research subjects. All results were obtained from data openly available online from the PMDA website. All data from the JADER database were fully anonymized by the regulatory authority before we accessed them.

Informed consent

Informed consent was not sought for the present study because the study was an observational study without any research subjects. All results were obtained from data openly available online from the Pharmaceuticals and Medical Devices Agency (PMDA) website (www.pmda.go.jp). All data from the JADER database were fully anonymized by the regulatory authority before we accessed them.

Trial registration

This clinical trial was not registered because the study was an observational study without any research subjects. All results were obtained from data openly available online from the Pharmaceuticals and Medical Devices Agency (PMDA) website (www.pmda.go.jp). All data from the JADER database were fully anonymized by the regulatory authority before we accessed them.

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