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 (145.5 (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

Date received: 18 July 2019; accepted: 20 February 2020

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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.\(^5,7\) 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 Ilb, 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.\(^2,4\) Ten drugs (sirolimus, simvastatin, fluvastatin, daptomycin, lapatinib, interféron beta, interféron 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<sup>a</sup> | Drugs | Total (n) | Case (n) | Non-case (n) | ROR<sup>b</sup> (95% CI) |
|----------|------------------------|-------|-----------|----------|-------------|--------------------------|
| 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 peptide 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)
| Category | ATC code | Drugs | Total (n) | Case (n) | Non-case (n) | RORb (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      | 5.956       | 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) |
| 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) |
| Category                                                                 | ATC code | Drugs               | Total (n) | Case (n) | Non-case (n) | RORb (95% CI) |
|--------------------------------------------------------------------------|----------|---------------------|-----------|----------|--------------|---------------|
| Other antineoplastic agents                                             | L01XE36  | Alectinib           | 243       | 81       | 162          | 10.6 (8.1–13.9) |
|                                                                          | 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  | Leuprolrelin        | 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 (2.9–5.9)  |
| 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                                                       | V03AF04  | Levofolinate        | 3989      | 410      | 3579         | 2.4 (2.2–2.7)  |
|                                                                          |          | 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.

"Anatomical therapeutic classification.

"Reporting odds ratio."
the AEs.\textsuperscript{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.\textsuperscript{7,12} The scale parameter, $\alpha$, 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, $\beta$, 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 $\beta$ was equal to 1, the hazard was estimated to be constant over time; if $\beta$ was greater than 1 and the 95% confidence interval (CI) of $\beta$ excluded the value 1, the hazard was considered to increase over time (wear-out failure type); finally, if $\beta$ was less than 1 and the 95% CI of $\beta$ excluded the value 1, the hazard was considered to decrease over time (initial-failure type).\textsuperscript{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.\textsuperscript{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) $\rightarrow$ $Y$ (the consequent (right-hand-side, rhs) of the rule), where $X$ and $Y$ are mutually exclusive sets of items.\textsuperscript{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:

- **Support** = Number of transactions with both $X$ and $Y$ / Total number of transactions
- **Confidence** = Number of transactions with both $X$ and $Y$ / Total number of transactions with $X$
- **Lift** = Confidence / Expected Confidence

$\text{Lift} = \frac{P(\text{Y}|\text{X})}{P(\text{Y})}$

$Lift$ 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 $P(\text{Y})$. The lift can be evaluated as follows: $\text{lift} = 1$, if $X$ and $Y$ are independent; $\text{lift} > 1$, if $X$ and $Y$ are positively correlated; $\text{lift} < 1$, if $X$ and $Y$ are negatively correlated. Furthermore, we calculated the chi-square values to evaluate the association rules.\textsuperscript{18}

$\text{Chi-squared} = \frac{(\text{Support} \times \text{Confidence})}{(\text{Expected Confidence} - \text{Support}) \times (\text{Expected Confidence} - \text{Confidence})}$

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 (44.3–185.4)), bicalutamide (50.0 (28.0–147.0)), PEG IFN-2α (140.0 (75.8–233.0)), sei-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 monocycline, amrubin, 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, lefunomide, 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. 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. 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. 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. 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. 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). 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). 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. No clear relationship has been observed between DIILD onset and dose or duration of treatment. 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.
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 | \(\chi^2\) |
|----|-----------|-----------|---------|------------|------|------------|
| [1] | {amiodarone, 40–49 years} ⇒ (DIILD) | 0.00015 | 0.52288 | 1.17 | 3.52 |
| [2] | {amiodarone, 30–39 years} ⇒ (DIILD) | 0.00011 | 0.06667 | 1.49 | 0.90 |
| [3] | {amiodarone, 50–59 years} ⇒ (DIILD) | 0.00019 | 0.18182 | 4.06 | 142.24\(^c\) |
| [4] | {amiodarone, ≥ 90 years} ⇒ (DIILD) | 0.00034 | 0.27492 | 6.14 | 820.47\(^c\) |
| [5] | {amiodarone, 60–69 years} ⇒ (DIILD) | 0.00048 | 0.29702 | 6.64 | 1288.35\(^c\) |
| [6] | {amiodarone, 70–79 years} ⇒ (DIILD) | 0.00025 | 0.29797 | 6.66 | 673.40\(^c\) |
| [7] | {amiodarone, 80–89 years} ⇒ (DIILD) | 0.00019 | 0.03030 | 6.77 | 505.12\(^c\) |
| [8] | {sho-saiko-to, 50–59 years} ⇒ (DIILD) | 0.00011 | 0.31579 | 7.06 | 320.15\(^c\) |
| [9] | {sho-saiko-to-ka-kikyo-sekko, 70–79 years} ⇒ (DIILD) | 0.00049 | 0.38806 | 8.67 | 1863.67\(^c\) |
| [10] | {sho-saiko-to, 70–79 years} ⇒ (DIILD) | 0.00036 | 0.48718 | 10.89 | 1810.41\(^c\) |
| [11] | {sho-saiko-to, 60–69 years} ⇒ (DIILD) | 0.00034 | 0.18182 | 4.06 | 142.24\(^c\) |

\(^a\)lhs: left-hand-side (antecedents).
\(^b\)rhs: right-hand-side (consequents).
\(^c\)Statistical significance: \(\chi^2\) 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: 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%.\(^1\) 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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was partially supported by Japan Society for the Promotion of Science KAKENHI grant number, 17K08452. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

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 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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