Evaluation of Drug-Induced Photosensitivity Using the Japanese Adverse Drug Event Report (JADER) Database

Satoshi Nakao,† Haruna Hatahira, a Sayaka Sasaoka, a Shiori Hasegawa, a Yumi Motoooka, a Natsumi Ueda, a,d Junko Abe, a,b Akiho Fukuda, a Misa Naganuma, a Hiroyuki Kanoh, a Mariko Seishima, c Motoyuki Ishiguro, d Yasutomi Kinosada, e and Mitsuhiro Nakamura*,a

a Laboratory of Drug Informatics, Gifu Pharmaceutical University; 1–25–4 Daigaku-Nishi, Gifu 501–1196, Japan; b Medical Database Co., Ltd.; 3–11–10 Higashi, Shibuya-ku, Tokyo 150–0011, Japan; c Department of Dermatology, Gifu University Graduate School of Medicine, Gifu University; 1–1 Yanagido, Gifu 501–1194, Japan; d Ishiguro Clinic; 6–37 Masakikita-machi, Gifu 502–0881, Japan; and e United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University; 1–1 Yanagido, Gifu 501–1194, Japan.

Received July 11, 2017; accepted September 21, 2017

Drug-induced photosensitivity (DIP) refers to the development of cutaneous disorders caused by the combined effects of different medications and light. The aim of this study was to obtain new information on drug risk comparisons and on DIP onset profiles, including seasonal variations, for clinically used prescription drugs. We analyzed reports of DIP recorded in the Japanese Adverse Drug Event Report (JADER) database using a reporting odds ratio (ROR). We also used Weibull proportional-hazards models for each drug to examine the patterns of DIP. The JADER database contains 430587 reports recorded from April 2004 to November 2016. The ROR values (95% confidence interval [CI]) of losartan/hydrochlorothiazide (HCTZ), valsartan/HCTZ, and ketoprofen were 214.5 (162.1–283.9), 104.7 (66.3–165.5), and 117.9 (76.6–181.5), respectively. For time-to-onset analysis, the median durations (interquartile range) for DIP caused by losartan/HCTZ, valsartan/HCTZ, and ketoprofen were 56 (41–78), 49 (38–88), and 8 (2–14) days, respectively. The lower limit of the 95% CI for the Weibull shape parameter β value for losartan/HCTZ was greater than 1. More than half of the reports of DIP onset following the administration of ketoprofen were recorded within 10 d of treatment initiation. The seasonal variation of photosensitivity reactions was shown to follow an annual sinusoidal pattern with a peak in April and May. Based on the results, losartan/HCTZ, valsartan/HCTZ, and ketoprofen should be used carefully in clinical practice to avoid DIP.

Key words photosensitivity; Japanese Adverse Drug Event Report database; seasonal variation; ketoprofen; hydrochlorothiazide

Drug-induced photosensitivity (DIP) refers to the development of cutaneous disorders caused by the combined effects of a variety of medications (oral, intravenous, and dermal) and light.1) Although the pathogenesis of DIP reactions is not fully understood, they can be classified as phototoxic or photoallergic drug eruptions.2) The clinical manifestation of phototoxicity is an exaggerated sunburn with blistering, desquamation, and hyperpigmentation, while that of photoallergy is dermatitis.3) Many drugs are associated with photosensitivity. The common photosensitizing medications include antibiotics, antifungals, antihistamines, cholesterol-lowering drugs, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives and estrogens, phenothiazines, psoralsens, retinoids, sulfonamides, sulfonyleureas used for type 2 diabetes, and alpha-hydroxy acids used in cosmetics.4,5)

Incidentes of DIP are generally reported as less than 5% or as unknown based on the information provided in package inserts in Japan.5–7) Since DIP is a rare adverse event (AE), evaluation of the association between a suspected medication and DIP onset is difficult. The Japanese Adverse Drug Event Report (JADER) database is a spontaneous reporting system (SRS) that has been released by the Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory authority of Japan. Recently, losartan potassium-hydrochlorothiazide combination was primarily reported in the JADER database as suspected to induce DIP onset.8) This was a thought-provoking study; however, by only totaling the reported number of DIP cases, this could represent a simplified analysis. We examined the AE profiles for DIP using several established indices for pharmacovigilance analysis.9,10) SRSs can be used to evaluate drug-associated AEs through disproportionality analysis, which usually involves the crude reporting odds ratio (ROR) for the signal detection of rare and severe AEs. In general, the crude ROR is unsuitable for inferring the comparative strength of causal relationships between drugs and AEs, and only offers a rough indication of the signal strength (i.e., generating hypotheses to search for unknown potential AEs).9,11) It might be acceptable to compare crude RORs of a particular event within a particular context to examine the possibility of an interaction between the drug and AE.9,11) In addition, the crude ROR can be used as a technique that allows for adjustments through logistic regression analyses to mitigate the effects of confounding factors.11–16)

The time-to-onset profile of DIP for certain medications has not been adequately examined using SRS. Analysis of time-to-onset using the Weibull shape parameter (WSP) has recently been proposed to detect the signals for AEs by utilizing time-to-event data without requiring a reference population.17–20) The WSP can describe the varying incidence of AEs and can

1Present address: Division of Pharmacy, Ehime University Hospital; Shitsukawa, Toon, Ehime 791–0204, Japan.

* To whom correspondence should be addressed. e-mail: mnakamura@gifu-pu.ac.jp
evaluate hazard functions for detecting AEs. Information using WSP could be of complementary value for pharmacovigilance analysis using ROR. There have been no previous published reports on time-to-onset analyses for DIP using JADER.

DIP, which is affected by the weather and light, is associated with seasonal variations and has an obviously intuitive plausibility. Marrero et al. analyzed reports of several AEs using the U. S. Food and Drug Administration Adverse Events Reporting System (FAERS) and demonstrated seasonal and regional variations for DIP.21) According to data from Japan recorded in FAERS, the reported incidences show an annual sinusoidal pattern. Nomura et al. reported that there are differences in the reported numbers of AEs between the JADER and FAERS; however, the number of shared reports between JADER and FAERS is unknown.22) Regional differences in drug prescriptions or genetic backgrounds might be responsible for the differences in AEs.22) The number of reports published in the JADER database is larger than that recorded in the FAERS database. Therefore, we evaluated the seasonal variation of DIP using a logistic regression model.

This is the first study to evaluate whether a signal related to DIP can be detected using the ROR, which was developed for the pharmacovigilance index of SRS analysis and time-to-onset analysis. The aim of this study was to obtain new information regarding risk comparisons of drugs and onset profiles of DIP, including seasonal variations, for prescription drugs used clinically.

MATERIALS AND METHODS

The JADER dataset, including the information recorded between April 2004 and November 2016, was downloaded from the PMDA website (www.pmda.go.jp). The JADER database consists of four tables: 1) DEMO (patients’ demographic information such as the gender, age, and weight); 2) DRUG (drug name, causality, etc.); 3) REAC (AEs, outcome, etc.); and 4) HIST (medical history, primary illness, etc.). We built a relational database, which integrated the four data tables, using the FileMaker Pro 13 software (FileMaker, Santa Clara, CA, U.S.A.). In the DRUG table, the causality of each drug was assigned a code according to its association with adverse drug reactions, such as a “suspected drug,” “concomitant drug,” or “interacting drug.” The analysis was restricted to reports where drugs were recorded as a “suspected drug.”

The AE definitions used in this study corresponded to those provided by the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J, www.pmj.jp/jmo/php/index.php) ver. 19.0. We evaluated the preferred term (PT) “photosensitivity reaction” (PT code: 10034972) for DIP, according to MedDRA/J. We evaluated terms related to DIP as follows: “solar dermatitis” (PT code: 10041303), “photodermatosis” (PT code: 10051246), “actinic cheilitis” (not listed in MedDRA/J as PT). A flowchart for the construction of the data analysis table is involved in Fig. 1.

When analyzing drugs associated with DIP, we calculated ROR, which is an established index for pharmacovigilance research, to detect the incidence of DIP. ROR was calculated from a two-by-two contingency table and is the ratio of the odds of reporting AEs versus all other events associated with the drug of interest compared with the reporting odds for all other drugs present in the database. For signal detection, general qualitative judgments were used. Detection of a signal was dependent on signal indices exceeding a predefined threshold. ROR values of less than 1 indicated no potential exposure–event associations, and those of more than 1 indicated potential exposure–event safety signals. The safety signals were considered significant when the estimated ROR and the lower limit of the corresponding 95% confidence interval (CI) exceeded 1. At least two cases were required to define a signal.9,23)

Use of ROR allows for adjustment through logistic regression analysis and offers the advantage of controlling for covariates.11–16) We calculated the adjusted ROR according to previous reports.15,16) For the calculation of adjusted ROR, only reports with complete information of reporting year, sex, age, and month of photosensitivity reaction onset were extracted. The reports were stratified by age as follows: ≤ 19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years. To construct the logistic model, gender, reporting year, stratified age groups, and reporting month were coded. The following logistic model was used for analysis:

\[
\text{Log (odds)} = \beta_0 + \beta_Y + \beta_S + \beta_A + \beta_M
\]

where \( Y \) is reporting year, \( S \) is sex, \( A \) is age-stratified group, and \( M \) is month of photosensitivity reaction onset.

The 20–29-year-old group was used as a reference group to calculate RORs adjusted for age variations. Since the re-
porting ratio of November was the lowest among months, it was used as a reference group to calculate RORs adjusted for month variations. A Wald test can be used to evaluate the effect of adding a particular term. Because the difference in −2 log-likelihood follows a chi-square distribution with one degree of freedom, in this case, adding an interaction term was statistically significant (p<0.05).

The median of the period until the DIP onset from the time of the first prescription for each subject, as well as the interquartile range and WSP were used for the evaluation of the time-to-onset profile. We chose an analysis period of 150d after the beginning of administration. The rate of the AE occurrence after prescription is thought to depend on the causal mechanism and will often vary over time; in contrast, AEs not associated with the drug will occur at a constant background rate. The WSP test is used for the statistical analysis of time-to-onset data and can describe a non-constant ratio of the incidence of AEs. The scale parameter α of the Weibull distribution determines the scale of the distribution function. A larger scale value (α) stretches the distribution, while a smaller scale value shrinks the data distribution. The shape parameter β of the Weibull distribution determines the shape of the distribution function. The WSP β value indicates the hazard without a reference population; when β is equal to 1, the hazard is estimated to be constant over time. If β is greater than 1 and the 95% CI of β excludes the value of 1, the hazard is considered to increase over time.17–20,24,25

We investigated the relation between the number of reports and seasonality of DIP. We analyzed the onset day of AEs and then obtained the number of AE reports per month between April 2004 and November 2016 from REAC table of JADER. We calculated the reporting ratio per month by dividing the number of DIP reports by the number of all AE reports for each month.

All data analyses were performed using JMP 11.0 (SAS Institute, Cary, NC, U.S.A.).

RESULTS

The JADER database contains 430587 reports submitted from April 2004 to November 2016, and we identified 330 DIP events. The number of reports for “photosensitivity reaction” (PT code: 10034972) as DIP, “solar dermatitis,” “photodermatitis,” and “actinic cheilitis” were 330, 9, 3, and 1, respectively. We further focused on DIP. In Table 1, we summarize the target drugs such as angiotensin II receptor blocker (ARB) and hydrochlorothiazide (HCTZ) diuretic combinations (ARB/HCTZs), NSAIDs including ketoprofen (topical), thiazide diuretics (oral), pirenidone (oral), and other drugs. For ketoprofen, DIP was observed only for topical administration. The numbers of DIP reports for losartan/HCTZ, valsartan/HCTZ, and ketoprofen (topical) were 68, 21, and 24, respectively. The AE signals, by ROR (95% CI), were detected for losartan/HCTZ, valsartan/HCTZ, and ketoprofen (topical), simprevir, ribavirin, and pirenidone (Table 1).

The adjusted RORs and 95% CIs are summarized in Table 2. Signals for the item of reporting year (β) were detected (p<0.0001). In contrast, a signal was not detected with Wald testing for any age groups (Table 2).

For the evaluation of seasonal variation, we extracted DIP cases from each month (the numbers of cases from January to December: 12, 21, 28, 47, 52, 35, 24, 22, 15, 11, 3, and 12). The DIP reporting ratio values per month are presented in Fig. 2. These data followed an annual sinusoidal pattern with peaks in April (0.11%) and May (0.12%). Signals were detected for comparing DIP onset month suing November as reference. The adjusted RORs for DIP onset month in April and May were 15.3 (95% CI, 5.6–63.1, p<0.0001) and 16.1 (95% CI, 6.0–66.3, p<0.0001), respectively (Fig. 2).

For the time-to-onset analysis, we extracted combinations that had complete information for the date of treatment initiation and the date of the AE onset. We evaluated six drugs for which the number of cases was more than five (Table 3). Figure 3 shows a histogram of the number of DIP cases from day 0 to day 150. The median durations (interquartile range) for DIP caused by losartan/HCTZ and ketoprofen (topical) were 56 (41–78) and 8 (2–14) days, respectively. More than half of the reports of DIP onset following administration of ketoprofen (topical) were recorded within 10d of the initiation of treatment (Fig. 3). Furthermore, the scale parameter α value of ketoprofen (topical) was 14.1 (6.9–27.5), and the lower limit of the 95% CI of the β value was greater than 1 for losartan/HCTZ.

DISCUSSION

DIP is a problem that can be encountered with a variety of medications. Our analysis showed significant RORs for several drugs (Table 1). The number of reported cases of DIP with losartan/HCTZ, valsartan/HCTZ, and ketoprofen (topical) were high and ROR signals were detected. It has been reported that combining any product with HCTZ is associated with a risk of photosensitivity.2,26 The risk of DIP associated with ARB/HCTZ has been reported by regulatory authorities such as the PMDA and WHO. ARB/HCTZ showed higher RORs compared to those of ARB or HCTZ alone (Table 1). One plausible reason for the high ROR value might be the increase ARB/HCTZ use in this decade, in Japan. ARB/HCTZ first used in Japan in 2006.37 In the JADER database, DIP reporting for HCTZ diuretic-containing formulations was observed since 2006.8 Furthermore, an effect for “reporting year” was observed in the results of the adjusted ROR (p<0.0001). As another reason, media attention and publicity resulting from advertising or regulatory actions such as safety information27 from the PMDA might result in increased reporting and could generate a higher-than-expected reporting ratio, a phenomenon known as “notoriety bias.”28,29

For more than 50 years, HCTZ has been associated with DIP; it also might provoke exaggerated sunburn and can cause lupus and lichen planus-like eruptions.3,30 However, DIP reporting after treatment with HCTZ alone had decreased.31 The ROR for HCTZ alone was lower compared to that of ARB/HCTZ. Thus, DIP might be affected by trends in medication.3,32 To the best of our knowledge, DIP reporting with ARB alone was scare.

Ketoprofen (topical) has been shown to cause most cases of NSAIDs induced photosensitivity.9 The European Medicines Agency recommends that topical ketoprofen should only be used when prescribed by a physician.13 The rate of DIP occurrence described in the package insert for pirenidone is 51.7%.34 Compared with those of other suspected drugs evaluated in our study, the DIP incidence is high for pirenidone. The results obtained in this study, through the analysis of data...
from the JADER database, seem to be reasonable when compared to those reported in the literature.

In contrast, we detected signals for DIP for several drugs and vaccines such as lornoxicam, flurbiprofen, human papillomavirus quadrivalent (types 6, 11, 16, and 18) recombinant vaccine (Gardasil®), and human papillomavirus bivalent (types 16 and 18) recombinant vaccine (Cervarix®), which have no AE warnings lists in their package inserts in Japan.35–38) A more detailed analysis focusing on these drugs should be the subject of future investigation.

DIP is triggered by UV radiation in individuals taking certain medications and might involve different mechanisms such as phototoxic reactions (PTR), photoallergic reaction (PAR), pellagra, pseudoporphyrria, lichenoid, and lupus erythematosus reactions.3) PTR rapidly manifests as acute dermatitis in an individual exposed to a photosensitizing agent. This leads to direct cellular damage, might induce immunological inflammation, and usually occurs within minutes to hours after exposure to the agent and UV.3,39) PTR appears similar to a sunburn and is clinically restricted to the skin that has been exposed to sunlight.39) PTRs are dose-dependent and occur more commonly than PARs, which depend on individual predisposition and involve specific immunologic reactions including antigen recognition by specific T-cells.40) Symptoms of PARs are similar to those of contact dermatitis, and the condition is not dose-related. PAR only occurs after an individual has already been sensitized to the agent, and typically develops within 24–72 h after exposure or after multiple weeks of continuous exposure.2,41,42) Consequently, desquamation and residual hyperpigmentation occur and can persist for more than 1 year.3) PAR manifests as eczematous, pruritic lesions, which might spread to areas of the skin that were not previ-
Photosensitivity Reaction

Table 2. Crude and Adjusted ROR of Photosensitivity Reaction

<table>
<thead>
<tr>
<th>Total</th>
<th>Case$^a$</th>
<th>Crude ROR$^b$ (95% CI$^c$)</th>
<th>Adjusted ROR$^b$ (95% CI$^c$)</th>
<th>$p$-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>430587</td>
<td>330</td>
<td>0.9 (0.9−1.0)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Reporting year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211590</td>
<td>172</td>
<td>1.1 (0.9−1.4)</td>
<td>1.1 (0.8−1.4)</td>
</tr>
<tr>
<td>Age (y.o.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>29900</td>
<td>39</td>
<td>1.8 (1.3−2.5)</td>
<td>1.4 (0.7−3.1)</td>
</tr>
<tr>
<td>20−29</td>
<td>14674</td>
<td>10</td>
<td>0.9 (0.5−1.7)</td>
<td>1 (as reference)</td>
</tr>
<tr>
<td>30−39</td>
<td>24904</td>
<td>17</td>
<td>0.9 (0.5−1.4)</td>
<td>1.0 (0.4−2.4)</td>
</tr>
<tr>
<td>40−49</td>
<td>31844</td>
<td>23</td>
<td>0.9 (0.6−1.4)</td>
<td>1.1 (0.5−2.6)</td>
</tr>
<tr>
<td>50−59</td>
<td>54103</td>
<td>36</td>
<td>0.9 (0.6−1.2)</td>
<td>0.9 (0.4−1.9)</td>
</tr>
<tr>
<td>60−69</td>
<td>92858</td>
<td>77</td>
<td>1.1 (0.9−1.4)</td>
<td>1.2 (0.6−2.5)</td>
</tr>
<tr>
<td>70−79</td>
<td>98380</td>
<td>88</td>
<td>1.2 (1.0−1.6)</td>
<td>1.3 (0.7−2.8)</td>
</tr>
<tr>
<td>80−89</td>
<td>47015</td>
<td>21</td>
<td>0.6 (0.4−0.9)</td>
<td>0.7 (0.3−1.6)</td>
</tr>
<tr>
<td>≥90</td>
<td>6108</td>
<td>2</td>
<td>0.4 (0.1−1.7)</td>
<td>0.6 (0.1−2.2)</td>
</tr>
<tr>
<td>Month (onset)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24924</td>
<td>12</td>
<td>0.6 (0.3−1.1)</td>
<td>4.0 (1.3−17.7)</td>
</tr>
<tr>
<td>2</td>
<td>25604</td>
<td>21</td>
<td>1.1 (0.7−1.7)</td>
<td>6.9 (2.4−29.1)</td>
</tr>
<tr>
<td>3</td>
<td>27280</td>
<td>28</td>
<td>1.4 (0.9−2.0)</td>
<td>8.1 (2.9−34.1)</td>
</tr>
<tr>
<td>4</td>
<td>26590</td>
<td>47</td>
<td>2.5 (1.9−3.4)</td>
<td>15.3 (5.6−63.1)</td>
</tr>
<tr>
<td>5</td>
<td>27686</td>
<td>52</td>
<td>2.7 (2.0−3.7)</td>
<td>16.1 (6.0−66.3)</td>
</tr>
<tr>
<td>6</td>
<td>28860</td>
<td>35</td>
<td>1.7 (1.2−2.3)</td>
<td>9.5 (3.4−39.5)</td>
</tr>
<tr>
<td>7</td>
<td>28121</td>
<td>24</td>
<td>1.1 (0.7−1.7)</td>
<td>7.3 (2.5−30.5)</td>
</tr>
<tr>
<td>8</td>
<td>26822</td>
<td>22</td>
<td>1.1 (0.7−1.7)</td>
<td>6.6 (2.3−28.1)</td>
</tr>
<tr>
<td>9</td>
<td>24178</td>
<td>15</td>
<td>0.8 (0.5−1.3)</td>
<td>5.2 (1.7−22.4)</td>
</tr>
<tr>
<td>10</td>
<td>25701</td>
<td>11</td>
<td>0.5 (0.3−1.0)</td>
<td>3.2 (1.0−14.5)</td>
</tr>
<tr>
<td>11</td>
<td>24956</td>
<td>3</td>
<td>0.1 (0.0−0.5)</td>
<td>1 (as reference)</td>
</tr>
<tr>
<td>12</td>
<td>23982</td>
<td>12</td>
<td>0.6 (0.4−1.1)</td>
<td>3.8 (1.2−16.9)</td>
</tr>
</tbody>
</table>

$^a$ Number of patients with photosensitivity reaction, $^b$ Reporting Odds Ratio, $^c$ Confidence Interval. *Probability>Chi-square, **$p$<0.05.

Fig. 2. Monthly Reporting Ratio of Photosensitivity Reactions

Bar graphs are monthly reporting ratios of photosensitivity reactions. Line graph is adjusted ROR.

ously exposed to the sun.39) PAR occurs in patients of any age.3) Both ketoprofen (topical) and HCTZ can be responsible for PAR and PTR.39,43) Women are affected more commonly than men.3) However, based on our data, we could not detect significant differences between men and women [median of men (interquartile range): 55 (42−84); median of women (interquartile range): 56 (35−80)]. As the number of medication in older population is generally higher than that in younger population, the number of DIP report increased in a population age-dependent manner.31,44) Similar results were obtained for the number of reporting. On the contrary, it is reported that PAR occurs in patients of any age.3) We also could not observe an age-related effect based on the results from the Wald tests in logistic regression analysis. We believe that this warrants further study.

The time-to-onset analysis using the WSP method allows for the detection of potential AEs without requiring a control population.31,38) Thus, we examined the time-to-onset of DIP
using the WSP test. To the best of our knowledge, no time-to-onset analyses for DIP have been systematically performed using the JADER database. The median of the time-to-onset for ketoprofen topical treatment was almost 10 d. Topical ketoprofen administration might induce phototoxic, photoallergic, and photoaggravated contact dermatitis. PTR can occur within a few hours of sun exposure.

1) Based on our results, special attention should be paid to the possibility of DIP onset with topical ketoprofen and careful observation is recommended soon after the administration for at least 2 weeks.

The time-to-onset profiles of ARB/HCTZs were different from those of topical ketoprofen. The medians for ARB/HCTZs were approximately 50 d. The WSP $\beta$ value for losartan/HCTZ was 2.6 (2.1–3.3), and therefore, the hazard was considered to increase over time (Table 3). PARs might not occur until several days after sun exposure. In our case, an eruption appeared several months after the first administration of ARB/HCTZ; therefore, the DIP reaction caused by ARB/HCTZ was more likely to be a PAR rather than a PTR. Our time-to-onset analysis was conducted to obtain new information regarding the onset profiles of DIP for prescription drugs.

We demonstrated an annual sinusoidal pattern for DIP with

Fig. 3. A Histogram and the Weibull Shape Parameter of Photosensitivity Reactions for 1) Losartan/Hydrochlorothiazide, 2) Ketoprofen (Topical), 3) Valsartan/Hydrochlorothiazide, 4) Simeprevir, 5) Ribavirin, and 6) Pirfenidone

Table 3. The Medians and Weibull Parameter of Each Drug

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Case (n)</th>
<th>Median (day) (25–75%)</th>
<th>Scale parameter</th>
<th>Shape parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan/Hydrochlorothiazide</td>
<td>44</td>
<td>56 (41–78)</td>
<td>70.5 (62.2–79.6)</td>
<td>2.6 (2.1–3.3)</td>
</tr>
<tr>
<td>Valsartan/Hydrochlorothiazide</td>
<td>13</td>
<td>49 (38–88)</td>
<td>40.0 (24.3–63.9)</td>
<td>1.4 (0.8–2.0)</td>
</tr>
<tr>
<td>Ketoprofen (topical)</td>
<td>15</td>
<td>8 (2–14)</td>
<td>14.1 (6.9–27.5)</td>
<td>0.9 (0.6–1.3)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>18</td>
<td>28 (19–58)</td>
<td>29.4 (19.0–44.3)</td>
<td>1.4 (0.9–2.0)</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>14</td>
<td>29 (21–60)</td>
<td>31.7 (20.0–48.7)</td>
<td>1.5 (0.9–2.3)</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>5</td>
<td>85 (59–135)</td>
<td>49.1 (14.3–161.6)</td>
<td>1.2 (0.4–2.5)</td>
</tr>
</tbody>
</table>
a peak in April and May using the reporting ratio and the adjusted RORs (Fig. 2). According to the Japan dataset in the FAERS database, the highest frequency of photosensitivity reactions is observed from May to June. Information regarding the comparison between seasonal UV radiation profiles and DIP onset profiles are very important for clinicians. We referred to the average daily maximum UV index charts recorded from 1997 to 2008 in Tokyo from the website of the Japan Meteorological Agency. The UV index is a rating scale, with numbers from 1 to 11, and indicates the amount of skin-damaging UV rays reaching the Earth's surface during the day. Moreover, UVA (320–400 nm) generally causes much more photosensitivity than UVB (290–320 nm). In Japan, UVA radiation in spring is almost equal to that in summer. The annual sinusoidal pattern of the daily maximum UV index chart showed a peak in July and August in Tokyo. Furthermore, UVA (320–400 nm) generally causes much more photosensitivity than UVB (290–320 nm). In Japan, UVA radiation in spring is almost equal to that in summer. The annual sinusoidal pattern of the daily maximum UV index chart showed a peak in July and August in Tokyo.46,47) Moreover, UVA (320–400 nm) generally causes much more photosensitivity than UVB (290–320 nm).3) In Japan, UVA radiation in spring is almost equal to that in summer.28–30) The annual sinusoidal pattern of the daily maximum UV index chart showed a peak in July and August in Tokyo. Thus, since PTR is related and PAR is not related to UV radiation in individuals administered drugs partially explains the high DIP risk in spring in Japan.

Clinicians should encourage the use of sunscreens and protective clothing (long-sleeve shirts, pants, and broad-brimmed hats) to limit sun exposure.3) Broad-spectrum sunscreens provide protection against UVA and UVB radiation. Sun protection factor (SPF) 15 is the minimum value needed to provide measurable protection; however, a sunscreen with an SPF value of 30 or higher is recommended.3) Rarely, some sunscreen ingredients can cause photosensitivity themselves.3)

Our study had some limitations worth noting. SRSS such as JADER are passive reporting systems and are therefore subject to numerous biases and confounding variables.9) Since SRSS such as JADER do not include control populations, the ROR is defined as the ratio of reported cases of a defined AE of interest versus all other AEs for the drug of interest, compared to the reporting odds for all other drugs present in the database. The ROR is different from the reporting odds for all other drugs present in the database. Thus, since spring is a more pleasant season than summer in Japan, individuals might be slow to undertake anti-sunburn measures in April and May. We consider that this inattention to UV radiation in individuals administered drugs partially explains the high DIP risk in spring in Japan.

Clinicians should encourage the use of sunscreens and protective clothing (long-sleeve shirts, pants, and broad-brimmed hats) to limit sun exposure.3) Broad-spectrum sunscreens provide protection against UVA and UVB radiation. Sun protection factor (SPF) 15 is the minimum value needed to provide measurable protection; however, a sunscreen with an SPF value of 30 or higher is recommended.3) Rarely, some sunscreen ingredients can cause photosensitivity themselves.3)

CONCLUSION

The JADER database, wherein clinicians report their concerns about potential drug-induced AEs, has been recognized as a tool for pharmacovigilance that reflects the realities of clinical practice. This study was the first to evaluate the correlation between DIP and medications using an SRS analysis strategy. We demonstrated a potential risk of DIP associated with ketoprofen (topical) and ARB/HCTZs, based on the number of reported DIP cases, ROR, and time-to-onset analysis. We can infer that patients receiving suspected drugs should be closely monitored, specifically, 2 weeks for topical ketoprofen and 5 months for ARB/HCTZ. When discussing the prevention of DIP, seasonal variation is an important factor for patient comfort and safety, as well as for therapeutic efficacy. Our results show that patients should be closely monitored for DIP in April in Japan. It is important to provide education to patients regarding anti-sunburn measures. We expect that our study will make a valuable contribution to the information available for clinicians and will help improve the management of DIP.

Acknowledgment This research was partially supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number, 17K08452.

Conflict of Interest Junko Abe is an employee of Medical Database. The rest of the authors have no conflict of interest.

REFERENCES

13) Van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG.


