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Drug-Induced Rhabdomyolysis Atlas (DIRA) for idiosyncratic adverse drug reaction management

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Drug-induced rhabdomyolysis (DIR) is an idiosyncratic and fatal adverse drug reaction (ADR) characterized in severe muscle injuries accompanied by multiple-organ failure. Limited knowledge regarding the pathophysiology of rhabdomyolysis is the main obstacle to developing early biomarkers and prevention strategies. Given the lack of a centralized data resource to curate, organize, and standardize widespread DIR information, here we present a Drug-Induced Rhabdomyolysis Atlas (DIRA) that provides DIR-related information, including: a classification scheme for DIR based on drug labeling information; postmarketing surveillance data of DIR; and DIR drug property information. To elucidate the utility of DIRA, we used precision dosing, concomitant use of DIR drugs, and predictive modeling development to exemplify strategies for idiosyncratic ADR (IADR) management.

Introduction

Rhabdomyolysis is a serious syndrome caused by a direct or indirect injury to skeletal muscle, which can lead to severe complications, such as acute renal failure [1]. As one of the major forms of rhabdomyolysis, DIR is idiosyncratic in nature and, thus, difficult to study [2–4]. The incidence of DIR is approximately 1 in 100,000. However, the real incidence could be significantly higher, given the wide exclusive and combined use of drugs [5]. Serious regulatory decisions have been made, including labeling changes or even a market withdrawal, because of DIR. For example, cerivastatin was withdrawn from US market because of 52 deaths attributed to rhabdomyolysis and resulting kidney failure [6,7]. In addition, important safety labeling changes to cholesterol-lowering statin drugs have been made because of drug-induced liver injury (DILI) and DIR (www.fda.gov/Drugs/DrugSafety/ucm293101.htm).

Drugs in certain therapeutic categories appear to more likely to cause rhabdomyolysis. For example, statins, also known as HMG-CoA reductase inhibitors, are used to lower cholesterol and treat cardiovascular disease; however, statin-induced rhabdomyolysis has been widely reported [8,9]. Currently, serum creatine kinase (CK) and serum and urine myoglobin serve as clinical biomarkers for rhabdomyolysis diagnosis. Other strategies, such as magnetic resonance imaging (MRI) image, prothrombin time (PT), and activated partial thromboplastin time (aPTT), might be also useful for rhabdomyolysis diagnosis [10,11]. However, the lack of an agreed detection level of those clinical parameters limits their diagnostic performance [11]. The major divergence in diagnostic criteria is related to the time muscle injury onset and the strength of clinical parameters. For example, the serum CK value typically increased from 2 to 12 h after the onset of injury, peaking between 24 h and 72 h, and declining in ~7–10 days [12]. Therefore, the time of diagnosis is key to accurately measuring the severity of muscle injury. Furthermore, CK levels vary among individuals. Generally, a CK level five times that of the normal value is considered as a standard diagnostic criterion for rhabdomyolysis diagnosis. However, higher CK values (i.e., ten times that of the normal value) have been suggested as a cut-off

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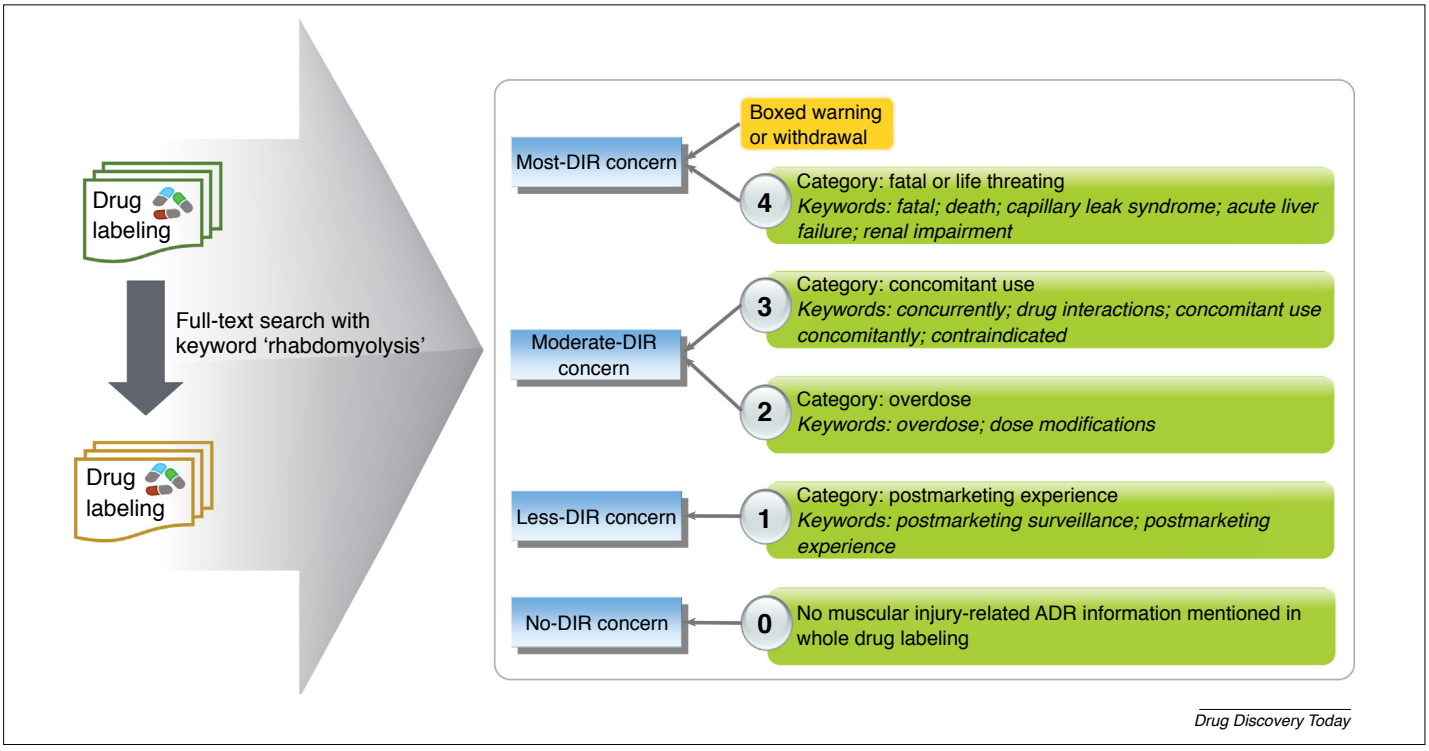

FIGURE 1

Classification scheme for drug-induced rhabdomyolysis (DIR) potential based on US Food and Drug Administration (FDA)-approved drug labeling. The FDA-approved drug labeling containing the keyword 'rhabdomyolysis' was extracted. Then, for each drug labeling, the severity score was assigned based on predefined keywords based on *a priori* knowledge. Finally, DIR concerns were determined based on the severity scores (i.e., most-DIR concern: Boxed warning or withdrawal drugs, and drugs with severity score 4; Moderate-DIR concern: drugs with severity score 2 and 3; Less-DIR concerns: drugs with severity score 1; and No-DIR concern: drugs with severity score 0).

for younger patients [13]. Furthermore, few effective biomarkers exist for the early detection of DIR in the preclinical setting. DIR is currently detected based mainly on clinical observations and postmarketing surveillance data from cohort studies, controlled population studies, and spontaneous reporting systems. Unfortunately, few case reports of DIR are available; those that are available are scattered throughout the literature, electronic medical records, and pharmacovigilance databases, delaying any progress in the development of early prevention and predictive models.

A classification scheme of the potential of a drug to cause rhabdomyolysis in humans is imperative to facilitate community efforts to develop early prediction strategies and to identify effective DIR diagnostic biomarkers. Here, we report a DIR classification scheme that was developed based on drug labeling information. In addition, postmarketing DIR surveillance data from the US Food and Drug Administration (FDA) Spontaneous Adverse Events Reporting System (FAERS) were extracted to represent DIR incidence information. Moreover, drug properties, such as chemical structures, therapeutic categories, and daily doses, were also curated. All information was centralized and managed under a web-based application: the DIRA (www.ADRatlas.com/DIRA). The utility of DIRA is exemplified below based on key aspects of idiosyncratic ADR (IADR) management, including precision dosing, concomitant use of drugs, and predictive model development.

Drug-induced rhabdomyolysis classification

It is challenging to develop a reproducible procedure to assess rhabdomyolysis risk for drugs. To annotate drugs for their DIR potential, major attributes, including seriousness, causality, severity, and expectedness, should be taken into consideration. However, no centralized resource comprising all the relevant information for DIR has existed previously. Drug labeling is a compilation of information about a drug product necessary for its safe and effective use, written primarily for the healthcare practitioner, approved by the FDA, and regulated by law (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57). Drug labeling contains consistent and up-to-date drug safety information and has been well established as one of most stable resources to annotate ADR risk for drugs. Inspired by the Liver Toxicity Knowledge Base (LTKB) project led by the FDA [14,15], a DIR classification scheme was developed based on drug labeling information (Fig. 1). Details of the proposed DIR classification scheme are described below.

DIR-related labeling extraction

To extract DIR-related drug labeling, we applied the following steps: (i) human drug labeling containing the keyword 'rhabdomyolysis' [16]; (ii) drug labeling with a single active ingredient; (iii) only drugs administered via the oral or parenteral route; and (iv) latest version of drug labeling. Consequently, a 172-drug list was generated for further DIR classification. The details of the labeling curation process are described in the Supplementary information online.

Distribution of DIR information across labeling sections

ADR information described in different labeling sections represents different levels of ADR seriousness. For example, the Boxed Warning (BW) section is used to concisely summarize certain contraindications or serious warnings, particularly those that can lead to death or serious injury according to the Code of Federal Regulations (21CFR201.57, www.accessdata.fda.gov/scripts/

TABLE 1

Severity levels of DIR based on descriptions in drug labeling

Severity score	DIR category	Keywords	Example description in drug labeling
4	Fatal or life threating	Fatal; death; capillary leak syndrome; acute liver failure; renal impairment	These serious adverse reactions include death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema
3	Drug interaction induced	Concurrently; drug interactions; concomitant use concomitantly; contraindicated	As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly
2	Overdose driven	Overdose; dose modifications	Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses
1	Postmarketing experience	Postmarketing experience	The following infrequent adverse experiences have been reported in postmarketing surveillance, in addition to those mentioned above: angioedema, erythema, urticaria, bronchospasm, cyanosis/ hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis, and rhabdomyolysis

cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57). Thus, the most serious ADR information is usually described in the BW section. Furthermore, the same ADR information is repeatedly mentioned in multiple labeling sections. For example, ADR information mentioned in the BW section is usually also emphasized in other sections, such as the Warnings and Precautions (WP) and Adverse Reaction (AR) sections. Rhabdomyolysis information of 172 drugs was described in over ten different labeling sections (Fig. S1 in the Supplemental information online). Among those sections, rhabdomyolysis information of five drugs (iopromide, ioversol, succinylcholine chlorid, tolcapone, and baclofen) was mentioned in the BW section. Most DIR information was described in the WP (77 drugs) and AR sections (97 drugs). Furthermore, rhabdomyolysis information was also embedded in the Drug Interactions (18 drugs), Contraindications (14 drugs), Overdosage (15 drugs), and Dosage and Administration (five drugs) sections, given that drug interaction and overdose are established as major causes of DIR [17,18].

DIR severity based on labeling content

The language used for describing DIR in drug labeling follows a relatively clear pattern, which enables one to determine the level of DIR severity. Here, we developed a four-level system to assign the 172 drugs into different severity categories (Table 1). Severe DIR had highest severity score (4), and contained DIR drugs that cause serious clinical outcomes, such as death, acute renal failure or impairment, and capillary leak syndrome. Moderate DIR comprised drugs with severity score of 2 and 3, mainly relating to DIR from either the concomitant use of the drug with other drugs or overdose. Mild DIR with severity score 1 was defined by postmarketing experience without severe clinical outcomes. The percentage of severe DIR drugs (score 4) across labeling sections was as follows: BW (100%), WP (65%), dosage-related sections (i.e., Overdosage section and Dosage and Administration section: 24%), and AR (2%) (Fig. S2 in the Supplemental information online). The distribution of severity scores was consistent with the degree of ADR seriousness in the different labeling sections, as regulated by the Code of Federal Regulations 21CFR201.57 [14].

Determination of DIR potential

The DIR potential determination scheme was developed by integrating both labeling section information and the severity level described above (Fig. 1). However, the DIR potential is a matter of concern rather than a regulatory decision. Furthermore, the DIR annotation scheme is a drug-centric approach that does not take host heterogenicity into consideration. Moreover, the current DIR classification was solely based on FDA-approved drug labeling information and, thus, dosages and indications of some drugs might be different in other countries. The 172 drugs were classified into three levels regarding their DIR potential: Most DIR concern [drugs withdrawn from the market because of rhabdomyolysis (e.g., cerivastatin); drugs with DIR information described in the BW section (i.e., five BW drugs); and drugs with a severity score of 4 were considered as Most-DIR concern drugs regardless of any DIR information mentioned in any labeling section]; Moderate DIR concern (drugs with severity scores 2 and 3); and Less DIR concern (drugs with severity score 1).

Furthermore, a list of No-DIR concern drugs was also curated, which could serve as a list of negative controls for model development. Here, the No-DIR concern drugs were defined as those with no muscular injury-related ADR information mentioned in any of the drug labeling sections. Specifically, the SIDER 4.1 database [19] containing drug and ADR relationships was used, where the ADR information was standardized with Preferred Terms (PTs) using well-established Medical Dictionary for Regulatory Activities (MedDRA) terminology (www.meddra.org/). First, we mapped PTs onto their primary System Organ Classes (SOCs), which represented the corresponding organ information for certain ADRs. Then, drugs without any related PTs that belonged to the SOC 'Musculoskeletal and connective tissue disorders' were extracted. Finally, we selected 40 drugs as No-DIR concern drugs. We also took into account the diversity of drug therapeutic categories and drug physicochemical properties when selecting No-DIR concern drugs.

Following the proposed scheme, a benchmark DIR data set with 213 drugs was obtained, containing 55 Most-DIR concern drugs; 44 Moderate-DIR concern drugs; 74 Less-DIR concern drugs; and 40 No-DIR concern drugs (Table S1 in the Supplemental information online).

Postmarketing surveillance data for DIR

Postmarketing surveillance for ADR and *ad hoc* safety studies are crucial to drug safety monitoring and IADR management. Efforts, such as FAERS and the Sentinel Initiative, facilitate relevant pharmacovigilance studies [20,21]. Given the limited DIR signal observed in clinical trials, postmarketing surveillance is an effective ap-

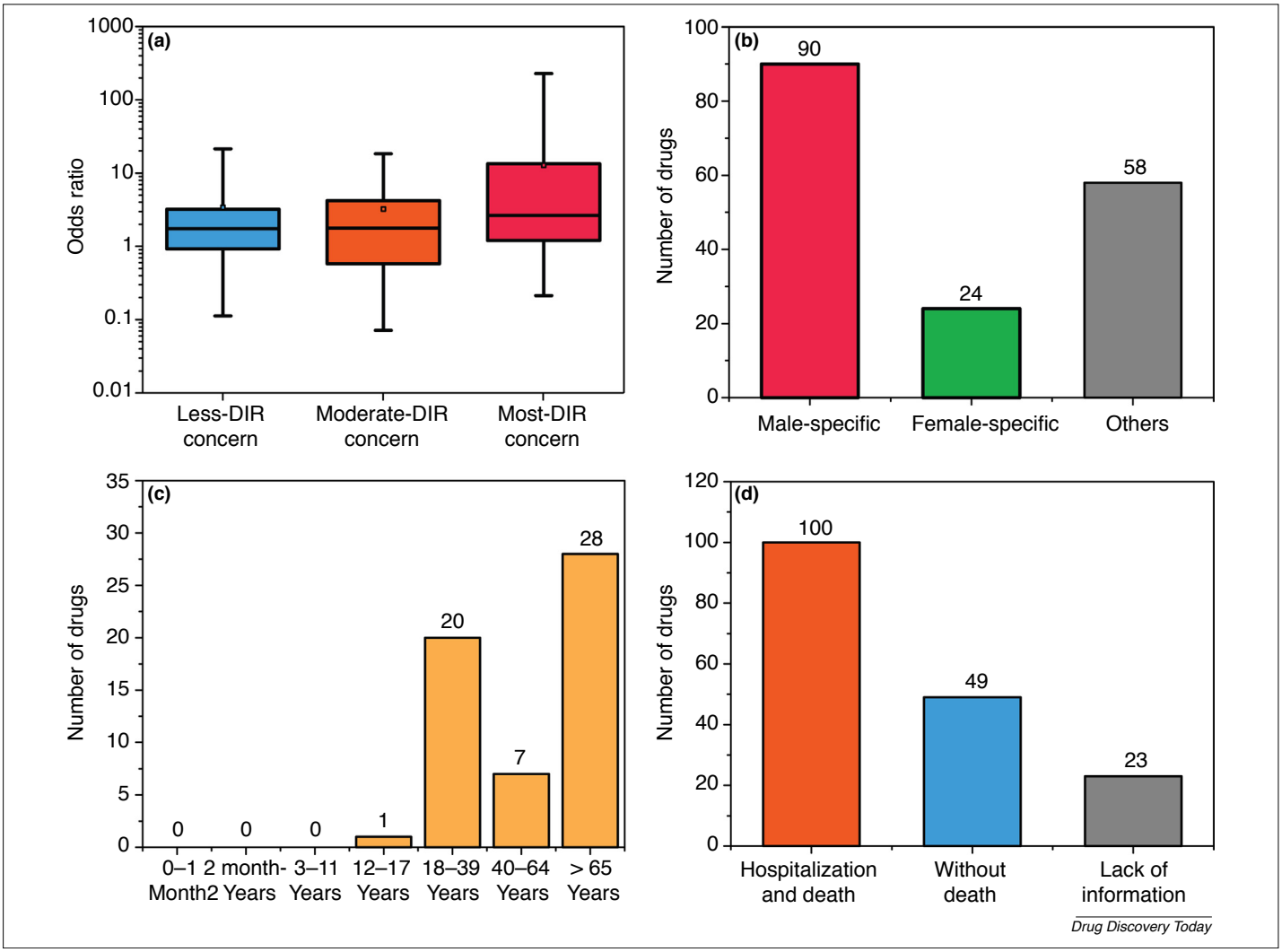

FIGURE 2

Rhabdomyolysis-related case reports of drug-induced rhabdomyolysis (DIR) drugs based on the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). **(a)** Odds ratio distributions for different DIR classification categories; **(b)** gender difference for DIR drugs; **(c)** age distribution of DIR drugs; **(d)** clinical outcomes for DIR drugs.

proach to detect potential safety signals, to identify the population susceptibility of ADR (i.e., gender differences and age distributions), and to generate hypotheses for further verification in mechanistic studies.

The FAERS case reports of 172 DIR positive drugs (cerivastatin excluded) were extracted from the PharmaPendium database (www.pharmapedium.com). The odds ratio (OR) was calculated to measure the DIR potential of the 172 drugs based on case reports in FAERS (details in Table S2 in the Supplemental information online). Figure 2a illustrates the correlation between the ORs of DIR drugs and the proposed DIR classification categories. It showed that the average OR increased from Less-DIR concern to Most-DIR concern. Furthermore, some Less-DIR drugs had high OR values, which could highlight the need for further evaluation of their DIR potential. Figure 2b represents the gender differences in DIR drugs. Approximately 24 DIR drugs (14.0%) were female specific (female:male ratio $\geq$1.5), 90 DIR drugs (52.3%) were male specific (male:female ratio $\geq$1.5), and the other 58 drugs showed either no gender difference or gender information was not available. Furthermore, patients aged 65 or more were more susceptible to DIR (Fig. 2c), which was also reported by some case studies [22]. Moreover, we found that 58.1% DIR drugs tended to cause severe clinical outcomes, such as hospitalization and death, which further demonstrated the seriousness of DIR in the clinical setting (Fig. 2d).

Precision dosing

One of the key pillars of precision medicine practice is to vary the dose regimen for subpopulation groups to eliminate the occurrence of unexpected ADRs [23]. Overdose as one of the risk factors for rhabdomyolysis has been widely reported [24]. However, the overdose effects for DIR are mainly identified and associated with statin drugs, and the underlying mechanisms are still elusive.

The benchmark DIR data set developed allows the systematic investigation of dosage distribution across drugs in different therapeutic categories. In the benchmark DIR data set, 17 drugs that caused DIR by overdosage were mentioned in FDA-aprroved drug labeling (Table S3 in the Supplemental information online). Among them, nine drugs (52.9%) belong to N06 – Psychoanaleptics, which are used to treat central nervous system-related diseases, such as depression. We further extracted the Anatomical Therapeutic Chemical (ATC) code and drug

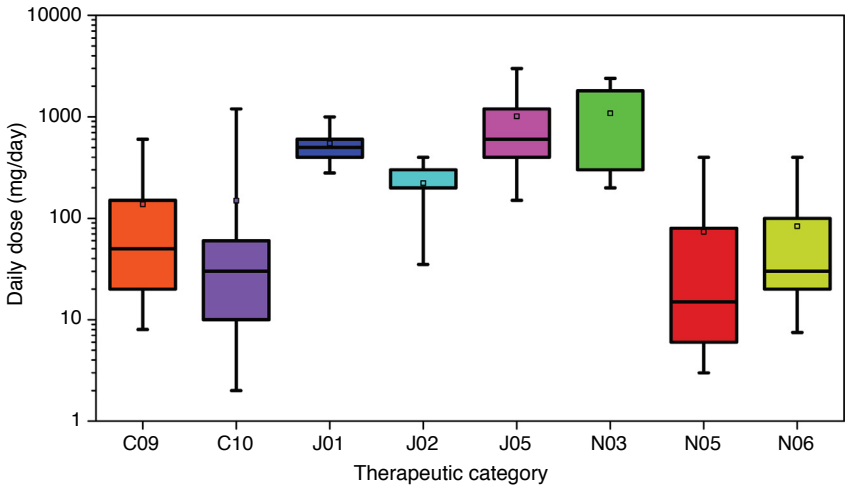

FIGURE 3

Human daily dose distribution of drug-induced rhabdomyolysis (DIR) drugs based on WHO ATC/DDD Index 2018. The second level of the Anatomical Therapeutic Chemical (ATC) Classification System was used to represent the therapeutic categories of DIR drugs. For DIR drugs used in multiple therapeutic categories, the corresponding human daily dose was collected. The daily dose distribution of eight therapeutic categories was then box plotted.

daily dose (DDD) of all DIR drugs from the WHO ATC/DDD Index 2018 (www.whocc.no/atc_ddd_index/) to further investigate dosage variance among the DIR drugs from different therapeutic categories (Table S3 in the Supplemental information online). It showed that drugs in some therapeutic categories (i.e., J05 – Antivirals for systemic use, N03 – Antiepileptics, and J01 – Antibacterials for systemic use) have relatively higher daily doses (Fig. 3). The formulation of drugs is also an influential factor. The formulation of drugs with the highest approved dose appeared more likely to cause DIR compared with lower dose formulations. For example, the FDA recommended limiting the highest approved dose of simvastatin (80 mg) because of increased risk of muscle damage, including rhabdomyolysis (www.fda.gov/Drugs/DrugSafety/ucm256581.htm).

Concomitant use

Concomitant drug use significantly increases the risk of DIR [25,26]. Notably, some drugs concomitantly used with statins tend to have a high probability of causing rhabdomyolysis if the drug is primarily metabolized by cytochrome P450 enzymes, such as CYP3A4 and CYP2C9, because most statins are also metabolized by those enzymes (e.g., lovastatin and simvastatin by CYP3A4 and fluvastain by CYP2C9). Some preclinical models have been established to clarify the mechanism of rhabdomyolysis following the co-administration of drugs. For example, Watanable *et al.* [27] developed a mouse model for the mechanistic study of rhabdomyolysis resulting from the concomitant use of statin and fibrate. Furthermore, some miRNAs, such as miR-206, have been identified that are correlated with the increased risk for DIR [28].

We listed all the concomitated drug pairs (i.e., 30 DIR drugs and their concomitant drugs) that could potentially cause DIR based on drug labeling (Table S4 in the Supplemental information online). The most concomitated drugs highlighted in the drug labeling were statins. To further expand our understanding of the role of concomitated drugs in rhabdomyolysis, the top ten concomitant drugs for each DIR drug were extracted based on FAERS case reports and presented in our web application. The concomitant drugs in FAERS reflect the real-world usages of drugs, which expands the scope of concomitated drugs and their impact on rhabdomyolysis. For example, as one of most popular concomitated drugs, aspirin was enriched in 14 out of the 30 DIR drugs. Case reports revealed that aspirin appears to cause muscle damage, although the underlying mechanism is unknown [29,30]. Thus, the concomitant usage of aspirin with other DIR drugs could increase the risk of rhabdomyolysis. Therefore, these concomitant drug pairs could be used to develop preclinical models for uncovering underlying mechanism of DIR.

Predictive toxicology

Available clinical biomarkers for DIR have limited diagnosis power [3]. More importantly, no biomarkers have been established and qualified for the early detection of DIR. Advances in machine learning (e.g., deep learning) and bioengineering technology (e.g., induced pluripotent stem cells) provide an unprecedented opportunity to promote drug safety evaluation [31,32]. A few prediction models based on chemical structures for DIR prediction have been reported [33]. However, their performance was limited by the number of drugs available and a lack of negative compounds. Nevertheless, the 213 DIR drugs proposed could facilitate *in silico* model development for early DIR prediction. Furthermore, many cell-based *in vitro* assay data have been generated with the help of high-throughput screening (HTS) techniques, such as quantitative HTS [34]. The efforts include the Tox21 and ToxCast projects led by EPA, which covered more than 10 000 compounds and over 400 bioassay endpoints [35]. Moreover, transcriptomic data sets, such as LINCS project, also cover most of the approved drugs and lead compounds in clinical trials. Data from some advanced cell culture systems, such as induced pluripotent stem cells, are also included [36]. Thus, we

encourage the development of integrative approaches to fuse different data types, which could facilitate the mechanistic understanding of DIR and further improve the performance of early prediction models.

Concluding remarks

The underlying mechanisms of DIR are still not well understood. One of the hurdles to conducting DIR studies is a lack of centralized resources that collect information and provide a standard scheme of DIR classification. Thus, we developed a DIR classification scheme inspired by the well-established LTKB project [14], with 213 drugs annotated with their DIR potential. Our benchmark DIR data set could be used for preclinical model development and serve as a basis for establishing *in silico* strategies. Furthermore, we developed DIRA (www.ADRatlas.com/DIRA), a web-based application that provides a user-friendly platform for researchers to query and download DIR-related information (Fig. 3). To the best of our knowledge, DIRA is the first attempt to centralize DIR information in the pharmaceutical community.

Genomics is a fast-moving field contributing to advances in drug development and safety evaluations. Some potential pharmacogenomics (PGx) biomarkers (e.g., *SLCO1B1*, *CPT2*, and *AMPD*) for DIR have been reported in epidemiological and genetic research [37]. Some pharmacogenomics descriptions for the effects of polymorphisms on the efficacy and/or safety for DIR drugs (e.g., rosuvastatin) have been provided in drug labeling (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c067a2c7-d306-4ae0-b722-b5855d269d98). However, until now, no biomarkers for DIR have been clearly established and incorporated into regulatory decision-making processes. Furthermore, Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines have been designed to facilitate understanding of how available genetic test results of DIR should be used for decision making by physicians (https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/). One example is SLCO1B1 and the simvastatin-induced myopathy guideline developed by CPIC, which facilitates the clinical implementation of DIR-related PGx biomarkers [38]. This situation could improve with the publication of more case reports and a better understanding of the links between DIR PGx biomarkers and clinical outcomes.

The debate about whether drug labeling could serve as 'gold standard' to annotate drug safety potential is ongoing. Several caveats to drug labeling, such as a lack of incidence information and ambiguous language used for ADR descriptions, could generate divergent annotations when implementing the proposed strategy for new drugs. To overcome these shortcomings, we used postmarketing surveillance data to help researchers to make a decision. Furthermore, DIRA has been developed as an interactive platform that can be improved in response to users' suggestions, criticisms, and comments. We hope that the proposed DIR annotation and DIRA database could trigger community efforts in DIR research and promote IADR management.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2018.06.006.

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