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Drug-induced Rhabdomyolysis Atlas (DIRA) for Idiosyncratic Adverse Drug Reaction Management

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Abstract

Drug-induced rhabdomyolysis (DIR) is an idiosyncratic, rare and fatal adverse drug reaction (ADR) characterized in severe muscle injuries accompanied by multiple-organ failure. Limited knowledge and evidence regarding pathophysiology and natural history of rhabdomyolysis are the big obstacles to developing early biomarkers and prevention strategies. Given that lack of centralized data resource to curate, organize, and standardize widespread DIR information, we present a **Drug-induced Rhabdomyolysis Atlas (DIRA)** to fulfill the gap. DIRA provides three folds of DIR related information including (1) a classification scheme for drugs' potential to cause rhabdomyolysis based on drug labeling information; (2) post-marketing surveillance data of DIR; and (3) DIR drug property information. To elucidate the utility of DIRA, we employed precision dosing, concomitant use of DIR drugs, and predictive modeling development to exemplify strategies for idiosyncratic adverse drug reaction (IADR) management.

Keywords

rhabdomyolysis; muscle injury; idiosyncratic adverse drug reaction; drug safety

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Introduction

Rhabdomyolysis is a serious syndrome caused by a direct or indirect injury to skeletal muscle, which could lead to severe complications such as acute renal failure [1]. Drug-induced rhabdomyolysis (DIR) as one of the major forms of rhabdomyolysis is of an Idiosyncratic nature and thus difficult to study [2–4]. The incidence of DIR is approximately 1 in 100,000. However, the risk may be significantly increased considering wide exclusive and combined use of drugs [5]. Some serious regulatory decisions have been made including labeling changes or even a market withdrawal due to DIR. One example is cerivastatin; the drug was withdrawn from U.S. market due to 52 deaths attributed to rhabdomyolysis that lead to kidney failure [6,7]. Also, Important safety labeling changes to cholesterol-lowering statin drugs have been made due to drug-induced liver injury (DILI) and DIR (<https://www.fda.gov/Drugs/DrugSafety/ucm293101.htm>).

Drugs in the certain therapeutic category seem more likely to cause rhabdomyolysis. For example, statins, also known as HMG-CoA reductase inhibitors, are used to lower cholesterol and treat cardiovascular disease. Statin-induced rhabdomyolysis has been widely reported [8,9]. Currently, serum creatine kinase (CK) and serum and urine myoglobin are served as clinical biomarkers for rhabdomyolysis diagnosis. However, no agreed detection level of those clinical parameters limits their diagnostic performance [10]. Furthermore, few effective biomarkers exist for early detection of DIR in the preclinical setting. DIR is currently detected mainly based on clinical observation and post-marketing surveillance data from cohort studies, controlled population studies, and spontaneous reporting systems. Unfortunately, few case reports of DIR are available, and they are scattered in literature, electronic medical records, and pharmacovigilance database, resulting in the lurch of the progress of early prevention and predictive model development.

A classification scheme of drug's potential to cause rhabdomyolysis in humans is imperative to facilitate the community efforts to develop early prediction strategies and to identify effective DIR diagnostic biomarkers. Here, a DIR classification scheme was developed based on drug labeling information. Furthermore, post-marketing DIR surveillance data from U.S. Food and Drug Administration (FDA) Spontaneous Adverse Events Reporting System (FAERS) were extracted to represent incidence information of DIR. Moreover, drug properties such as chemical structure, therapeutic categories, and daily dose were also curated. All information is centralized and managed under web-based application named **Drug-induced Rhabdomyolysis Atlas (DIRA)**, (<https://www.ADRAtlas.com/DIRA>). The utility of DIRA was exemplified with some key aspects of idiosyncratic adverse drug reaction (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. Until now, there does not exist a centralized resource consisting of all the attribute information for DIR. Drug

labeling is a compilation of information about a drug product necessary for safety and effective use written by primarily for the healthcare practitioner, approved by U.S. FDA, and regulated by law (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57>). Drug labeling contains the consistent and update-to-date drug safety information and has been well-established as one of most stable resources to annotate ADR risk for drugs. Inspired by Liver Toxicity Knowledge Base (LTKB) project led by U.S. FDA [11,12], DIR classification scheme was developed based on drug labeling information (Figure 1). Details of proposed DIR classification scheme were described in the following subsections.

DIR-related labeling extraction

To extract DIR-related drug labeling, we applied the following steps: (a) human drug labeling containing keyword “*rhabdomyolysis*” [13]; (b) drug labeling with single active ingredient; (c) only drugs administered through oral or parenteral route; (d) the latest version of drug labeling. Consequently, a 172-drug list was generated for further DIR classification. The details of the labeling curation process were described in Supplementary Materials and Methods.

Distribution of DIR information across labeling sections

ADR information described in different labeling sections has divergent seriousness degree. For instance, Boxed Warning (BW) section is used to concisely summarize certain contraindications or serious warnings, particularly those that may lead to death or serious injury according to the Code of Federal Regulations (21CFR201.57, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57>). Thus, the most seriousness ADR information is usually described in BW section. Furthermore, the same ADR information is repeatedly mentioned in multiple labeling sections. For example, ADR information mentioned in BW section is usually also emphasized in other sections such as Warnings and Precautions (WP) and Adverse Reaction (AR) sections. Rhabdomyolysis information of 172 drugs was described in over ten different labeling sections (Supplementary Figure S1). Among those sections, rhabdomyolysis information of 5 drugs including iopromide, ioversol, succinylcholine chlorid, tolcapone, and baclofen was mentioned in BW section. Most DIR information was described in WP (77 drugs) and AR sections (97 drugs). Furthermore, rhabdomyolysis information was also embedded in the Drug Interactions section (18 drugs), Contraindications section (14 drugs), Overdosage section (15 drugs), and Dosage and Administration section (5 drugs), since drug interaction and overdose are established as major reasons causing DIR [14,15].

DIR severity based on labeling content

The language used for describing DIR in drug labeling has a relatively clear pattern, which enables the DIR severity determination. Here, we developed a 4-level system to assign the 172 drugs into different severity categories (Table 1). The severe DIR with highest severity score is 4, which contains DIR drugs cause serious clinical outcomes such as death, acute renal failure or impairment, and capillary leak syndrome. Moderate DIR consists of drugs with severity score 2 and 3, and the reasons for drugs causing DIR in this category are mainly due to concomitant use with other drugs or overdose. Mild DIR with severity score 1

is defined based on post-marketing experience without severe clinical outcomes. Percentage of severe DIR drugs (score 4) across labeling sections is in descending order for BW (100%), WP (65%), dosage related sections (i.e., Overdosage section and Dosage and Administration section: 24%), and AR (2%) (Supplementary Figure S2). The distribution of severity scores is consistent with seriousness degree of ADR in different labeling sections regulated by the Code of Federal Regulations 21CFR201.57 [11].

Determination of DIR potential

The DIR potential determination scheme was developed by integrating both labeling section information and severity level mentioned above (Figure 1). However, it was worth pointing out the DIR potential is a matter of concern other than a regulatory decision. Furthermore, the DIR annotation scheme is drug-centric approach without taking into consideration of the host heterogeneity. The 172 drugs were classified into three levels regarding their DIR potential named Most DIR concern, Moderate DIR concern, Less DIR concern. Furthermore, a list of No-DIR concern drugs was also curated.

1. **Most-DIR concern:** first, drugs withdrawal from the market due to rhabdomyolysis was included (i.e. cerivastatin). Second, drugs with DIR information described in BW section (i.e. 5 BW drugs) were also attributed to Most-DIR concern category. Third, drugs with severity score 4 (highest scores) are considered as Most-DIR concern drugs regardless DIR information mentioned in any labeling section.
2. **Moderate-DIR concern:** Drugs with severity scores 2 and 3.
3. **Less-DIR concern:** Drugs with severity score 1.
4. **No-DIR concern:** It is of great importance to define a list of drugs without any DIR concern, which could be served as negative controls for model development. Here, the No-DIR concern drugs were defined as no muscular injury related ADR information mentioned in whole drug labeling. Specifically, SIDER 4.1 database [16] containing drug and ADR relationship was employed, where the ADR information was standardized with Preferred Terms (PTs) by using well-established Medical Dictionary for Regulatory Activities (MedDRA) terminology (<https://www.meddra.org/>). First, we mapped PTs onto their primary System Organ Classes (SOCs), which represented the corresponding organ information of certain ADR. Then, drugs without any related PTs belong to SOC - *Musculoskeletal and connective tissue disorders* were extracted. Finally, we selected 40 drugs with double-checking their drug labeling as No-DIR concern drugs. Meanwhile, we also took the diversity of drug therapeutic categories and drug physical-chemical properties into consideration when selecting No-DIR concern drugs.

Following the proposed scheme, a benchmark DIR dataset containing 213 drugs was obtained, containing Most-DIR concern (55 drugs), Moderate-DIR concern (44 drugs), Less-DIR concern (74 drugs), and No-DIR concern (40 drugs) (see Supplementary Table S1).

Post-marketing Surveillance data for DIR

Post-marketing surveillance for ADR and *ad hoc* safety studies are crucial to drug safety monitoring and IADR management. Efforts such as FDA Adverse Event Reporting System (FAERS) and Sentinel Initiative have been made and tremendously facilitate the pharmacovigilance studies [17,18]. Given that limited DIR signal observed in the clinical trials, post-marketing surveillance is an effective complement approach to detect potential safety signals, to identify population susceptibility of ADR (i.e., gender difference and age distributions), and to generate hypothesis for further mechanistic studies verification.

The FAERS case reports of 172 DIR positive drugs (cerivastatin excluded) were extracted from PharmaPendium database (<https://www.pharmapendium.com>). The odds ratio was calculated to measure DIR potential of the 172 drugs based on case reports in FAERS (details in Supplementary Material and Methods and Table S2). Figure 2A illustrated the correlation between odds ratio of DIR drugs and the proposed DIR classification categories. It showed that the average ratio odds were increased from Less-DIR concern to Most-DIR concern. Furthermore, we noticed that some Less-DIR drugs had a high odds ratio value, which may raise concern for further evaluation of their DIR potential. Figure 2B represented the gender difference of DIR drugs. Approximately 24 DIR drugs (14.0%) are female-specific (Female: Male ratio = 1.5), 90 DIR drugs (52.3%) is male-specific (Male: Female ratio = 1.5), and other 58 drugs are either no gender difference or gender information not available. Furthermore, patients with age more than 65 are more susceptible to DIR (Figure 2C), which was also reported by some case studies [19]. Moreover, we found that about 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 (Figure 2D).

Precision Dosing

One of the key pillars of precision medicine practice is to vary dose regimen for subpopulation group to eliminate the occurrence of unexpected ADRs [20]. Overdose as one of the risk factors for rhabdomyolysis has been widely reported [21]. However, the overdose effect for DIR are mainly identified and associated with statin drugs, and the underlying mechanism is still elusive.

The benchmark DIR dataset developed allows systematic investigation of dosage distribution across drugs in different therapeutic categories (see Supplementary Table S3). There are 17 DIR drugs caused by overdosage in the benchmark DIR dataset. Of 17 drugs, 9 drugs (52.9%) belong to **N06** - Psychoanaleptics, which are used to treat central nervous related diseases such as depression. We further extracted the Anatomical Therapeutic Chemical (ATC) code and drug daily dose (DDD) of all DIR drugs from World Health Organization (WHO) ATC/DDD Index 2018 (https://www.whocc.no/atc_ddd_index/). It illustrated that drugs in some therapeutic categories (i.e., **J05** - Antivirals for systemic use, **N03** - Antiepileptics, and **J01** - Antibacterials for systemic use) have a relatively higher daily dose (see Figure 3). On the other hand, the formulation of drugs is also an influential factor. Formulation of highest approved drugs seems more likely to cause DIR compared to lower dose formulation. For example, FDA recommended limiting highest approved dose of

simvastatin (80 mg), due to increased risk of muscle damage including rhabdomyolysis (<https://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>).

Concomitant Use

Concomitant drug use significantly increases the risk of DIR [22,23]. Notably, some drugs are concomitantly used with statins tends to have a high probability to cause rhabdomyolysis if the drug is primarily metabolized by cytochrome P450 enzymes such as CYP3A4 and CYP2C9, since most statins (e.g., lovastatin and simvastatin for CYP3A4 and Fluvastatin for CYP2C9) are also metabolized by those enzymes. Some preclinical models have been established to clarify the mechanism of rhabdomyolysis by coadministration of drugs. For example, Watanabe et al. [24] developed a mouse model for the mechanistic study of rhabdomyolysis by concomitant use of statin and fibrates. Furthermore, some miRNAs such as miR-206 were identified that were correlated with the increase of risk for DIR.

We listed all the concomitated drug pairs that could potentially cause DIR mentioned in drug labeling (see Supplementary Table S4). Furthermore, the top ten concomitant drugs for each DIR drug were extracted based on FAERS case reports and presented in our web application. 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 early detection of DIR. Advance in machine learning (e.g., deep learning) and bioengineering technology (e.g., iPSC stem cells) provides an unprecedented opportunity to promote drug safety evaluation [25,26]. A few prediction models based on chemical structures for DIR prediction have been reported [27]. However, the performance of models was limited by the number of drugs and lack of negative compounds. With that said, the proposed 213 DIR drugs could greatly facilitate in silico model development for early DIR prediction. Furthermore, a huge amount of cell-based in vitro assay data has been generated with the help of high throughput screening techniques such as qHTS [28]. The efforts including Tox21 and ToxCast projects led by EPA, which covers more than 10k compounds and over 400 bioassay endpoints [29]. Moreover, the transcriptomic data such as LINCS project also covers most approved drugs and lead compounds in clinical trials. Some advanced cell culture such as iPSC stem cell data was also included [30]. The integrative approaches to fuse different data types are highly encouraged, which could facilitate the mechanistic understanding of DIR and further improve the performance of early prediction models.

Closing Remarks

The underlying mechanism of drug-induced Rhabdomyolysis has not been well understood. One of the hurdles to conducting DIR study is lack of centralized resources to collect dispersed information and provide a standard scheme of DIR classification. To break the dilemma, we developed a DIR classification scheme inspired by well-established LTKB

project [11], which contains 213 drugs annotated with their DIR potential. The benchmark DIR dataset could be used for preclinical model development and serve as ground truth for establishing *in silico* strategies. Furthermore, we developed a **Drug-induced Rhabdomyolysis Atlas (DIRA)**, (<http://www.ADRAtlas.com/DIRA>), a web-based application to provide a user-friendly platform for the researchers to query and download DIR related information (Figure 3). To our best knowledge, DIRA is the first attempt at centralizing DIR information in the community.

Genomics has become a fast-moving field and contributed to advances in drug development and safety evaluations. Some potential pharmacogenomics (PGx) biomarkers (e.g. *SLCO1B1*, *CPT2* and *AMPD*) for DIR such as have been reported in epidemiological and genetic studies [31]. Some pharmacogenomics description for polymorphism on efficacy and/or safety for DIR drugs (e.g. rosuvastatin) has been mentioned in drug labeling (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c067a2c7-d306-4ae0-b722-b5855d269d98>). However, till now, none of biomarkers for DIR have been clearly established and incorporated into regulatory decision making process. The situation may be changed with more case reports and better understanding of causality between DIR PGx biomarkers and clinical outcomes.

Catfight on whether drug labeling could serve as “gold standard” to annotate drug safety potential is still on. Several obvious caveats of drug labeling such as lack of incidence information and ambiguity language used for ADR description may generate divergent annotation when implementing the proposed strategy for new drugs. To complement the shortcoming, we employed post-marketing surveillance for researchers to make compromise decision. Furthermore, DIRA aims to be an interactive platform to absorb the users’ suggestion, critics, and comments for gradually improving annotation quality. We hope the proposed DIR annotation and DIRA database could trigger community efforts for DIR research and promote IADR management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Classification scheme for drug-induced rhabdomyolysis (DIR) potential based on FDA approved drug labeling

Figure 2. Rhabdomyolysis related case reports of drug-induced rhabdomyolysis (DIR) drugs from 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; (4) Clinical outcomes for DIR drugs

Figure 3.
Human daily dose distribution of drug-induced rhabdomyolysis drugs based on WHO ATC/DDD Index 2018

Table 1

Severity levels of DIR based on description in drug labeling

Severity score	DIR categories	Keywords	Example description in drug labeling
4	Fatal or life threatening	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	Post-marketing experience	post-marketing Experience	Post-marketing Experience: The following infrequent adverse experiences have been reported in post-marketing surveillance, in addition to those mentioned above: angioedema, erythema, urticaria, bronchospasm, cyanosis/hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis, and rhabdomyolysis.