MOLECULAR, CELLULAR, AND IMMUNOLOGICAL BASIS FOR SEVERE ADVERSE DRUG REACTIONS

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12/12/2013
LEADING CAUSES OF DEATH IN USA IN 1994

Heart disease 743,460
Cancer 529,904
Stroke 150,108
SADRs 106,000
Pulmonary disease 101,077
Accidents 90,523
Pneumonia 75,719
Diabetes 53,894

Lazarou et al., JAMA, 279, 1208 (1998)
### SEVERE DRUG-INDUCED DISEASES

<table>
<thead>
<tr>
<th>System</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Skin</td>
<td>Granulocytopenia</td>
</tr>
<tr>
<td>Renal</td>
<td>Thrombocytopenia</td>
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<tr>
<td>Pulmonary</td>
<td>Aplastic anemia</td>
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<tr>
<td>Neurological</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Lupus</td>
<td></td>
</tr>
</tbody>
</table>
HAPTEN HYPOTHESIS AND DRUG-INDUCED ALLERGIC REACTIONS

Drug or Metabolite + → B and T Cell Responses

Toxicity ←
Drug Protein Conjugate Formed in a Cell

Secreted

Injured Cell

Immature Dendritic Cell

Ag Processing

B Cell

IgG, IgE, IgA

Ag Presentation by MHC Class I and II

Regulatory T Cells

Migration to Periphery

Block Drug Allergy

Migration to Periphery

Drug Allergy

B Cell

IgG, IgE, IgA

HMGB-1, HSPs, Uric Acid, dsRNA, ssRNA, CpG DNA, Lipopeptides

Migrate to Lymph Nodes

Immunization of T Cells

CD4^+ CD8^+

IL-10, PGE_2, TGF-β

Migrate to Lymph Nodes

Toleration of T Cells

CD4^+ CD8^+
THREE WAYS T CELLS MAY BE ACTIVATED BY DRUG-HLA COMPLEXES

Camous et al., Current Opinion in Immunology, 24, 730 (2012)
REGULATORY T CELLS HAVE A ROLE IN TOLERANCE

Alpdogan and van den Brink, Semin. Oncol, 39, 629 (2012)
T CELL INHIBITORY MOLECULES CTLA-4 AND PD-1 HAVE ROLES IN TOLERANCE

Figure 2. T cell–antigen-presenting cell (APC) interaction with costimulatory molecules. CTLA-4, cytotoxic T-lymphocyte antigen 4; TCR, T-cell receptor; MHC, major histocompatibility complex; ICOS, inducible T-cell costimulator; PD-1, programmed death-1; PD1-L, programmed death-1 ligand.

Alpdogan and van den Brink, Semin. Oncol, 39, 629 (2012)
DRUG-INDUCED SKIN DISEASE
MILD FORM OF CUTANEOUS TOXICITY

[Image of skin with lesions]
STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)
<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Anticonvulsants</th>
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</thead>
<tbody>
<tr>
<td>Aminopenicillins</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Imidazole antifungals</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
</tr>
<tr>
<td>Sulfonamides (esp. TMP-SMX)</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Chlormezanone</td>
</tr>
<tr>
<td>NSAIDs (esp. oxicam derivatives)</td>
<td>Nevirapine</td>
</tr>
</tbody>
</table>

Borchers, et al., Autoimmunity Reviews, 7, 598 (2008)
Subject: FDA MedWatch - Acetaminophen: Drug Safety Communication - Association with Risk of Serious Skin Reactions

Date: Thursday, August 1, 2013 6:30:12 PM ET

From: FDA MedWatch
To: pohl@nih.gov

Acetaminophen: Drug Safety Communication - Association with Risk of Serious Skin Reactions

AUDIENCE: Dermatology, Primary Care, Pharmacy

ISSUE: FDA notified healthcare professionals and patients that acetaminophen has been associated with a risk of rare but serious skin reactions. Acetaminophen is a common active ingredient to treat pain and reduce fever; it is included in many prescription and over-the-counter (OTC) products. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. These reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Other drugs used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDS, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions, which is already described in the warnings section of their drug labels.
FDA Drug Safety Communication: FDA warns of serious skin reactions with the anti-seizure drug Onfi (clobazam) and has approved label changes

View and print full Drug Safety Communication (PDF - 60KB)

Safety Announcement

[12-3-2013] The U.S. Food and Drug Administration (FDA) is warning the public that the anti-seizure drug Onfi (clobazam) can cause rare but serious skin reactions that can result in permanent harm and death. We have approved changes to the Onfi drug label and the patient Medication Guide to describe the risk of these serious skin reactions. Patients taking Onfi should seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Health care professionals should discontinue use of Onfi and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

These rare but serious skin reactions, called Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur at any time during Onfi treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when Onfi is stopped and then re-started. All cases of SJS and TEN in the FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death.

Onfi is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome. Serious skin reactions have not generally been associated with other benzodiazepines.
Roychowdhury and Svensson,
AAPS J., 7, E834 (2005)
Chung and Hung, Allergology Internat. 59, 325 (2010)
Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population

Takeshi Ozeki1, Taisei Mushiroda1, Amara Yowang1, Atsushi Takahashi2, Michiaki Kubo2, Yuji Shirakata4, Zenro Ikezawa4, Masafumi Iijima4, Tetsuo Shihohara7, Koji Hashimoto4, Naoyuki Kamata1 and Yusuke Nakamura1,8

1Research Group for Pharmacogenomics, 2Research Group for Medical Informatics and 3Research Group for Genotyping, RIKEN Center for Genome Medicine, Yokohama 230-0045, Japan, 4Department of Dermatology, Ehime University Graduate School of Medicine, Ehime 791-0295, Japan, 5Department of Dermatology, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan, 6Department of Dermatology, Showa University School of Medicine, Tokyo 142-8555, Japan, 7Department of Dermatology, Kyorin University School of Medicine, Tokyo 161-8611, Japan and 8Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan

Received September 12, 2010; Revised November 28, 2010; Accepted December 6, 2010

An anticonvulsant, carbamazepine (CBZ), is known to show incidences of cutaneous adverse drug reactions (cADRs) including Stevens—Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS). To identify a gene(s) susceptible to CBZ-induced cADRs, we conducted a genome-wide association study (GWAS) in 53 subjects with the CBZ-induced cADRs, including SJS, TEN and DIHS, and 882 subjects of a general population in Japan. Among the single nucleotide polymorphisms (SNPs) analyzed in the GWAS, 12 SNPs showed significant association with CBZ-induced cADRs, and rs1633021 showed the smallest P-value for association with CBZ-induced cADRs ($P = 1.18 \times 10^{-13}$). These SNPs were located within a 430 kb linkage disequilibrium block on chromosome 6p21.33, including the HLA-A locus. Thus, we genotyped the individual HLA-A alleles in 61 cases and 376 patients who showed no cADRs by administration of CBZ (CBZ-tolerant controls) and found that HLA-A*3101 was present in 60.7% (37/61) of the patients with CBZ-induced cADRs, but in only 12.5% (47/376) of the CBZ-tolerant controls (odds ratio = 10.8, 95% confidence interval 5.9–19.6, $P = 3.64 \times 10^{-15}$), implying that this allele has the 60.7% sensitivity and 87.5% specificity when we apply HLA-A*3101 as a risk predictor for CBZ-induced cADRs. Although DIHS is clinically distinguished from SJS and TEN, our data presented here have indicated that they share a common genetic factor as well as a common pathophysiological mechanism. Our findings should provide useful information for making a decision of individualized medication of anticonvulsants.

Ozeki, et al., Human Molecular Genetics, 20, 1034 (2011)
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

- Skin pathology, mild to severe
- Fever
- Liver, kidney, lung, heart, and CNS
- Lymphocytosis, eosinophilia, and lymph-adenopathy
- Human herpes virus 6 reactivation
- Carbamazepine, phenytoin, phenobarbital, zonisamide, lamotrigine, sulfalazine, and allopurinol
- 10% fatality

Cacoub, et al., The American Journal of Medicine, 124, 588 (2011)
Tohyama and Hashimoto, J. of Dermatology., 38, 222 (2011)
DRUG-INDUCED LIVER DISEASE
Preclinical Strategy to Reduce Clinical Hepatotoxicity Using In Vitro Bioactivation Data for >200 Compounds

Melanie Z. Sabetia,1 Melinda J. Reesa,2 Andrew W. Harrell,1 Maxine A. Taylor,† Ian A. Baines,† Liangli Chen,1 Jackie C. Bloomer,† Eric Y. Yang2 Hanna M. Ellis2, Jeffrey L. Ambrose2, Ceryn A. Lovett,1 Andrew D. Ayton,† and Stephen E. Clarke†

1Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Park Road, Ware, Hertfordshire SG12 6DR, United Kingdom
2Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Five Moore Drive, P.O. Box 13390, Research Triangle Park, North Carolina, United States
†Safety Assessment, GlaxoSmithKline, Upper Montauk, 709 Sandels Road, King of Prussia, Pennsylvania 19406, United States

ABSTRACT—Drug-induced liver injury is the most common cause of market withdrawal of pharmaceuticals, and thus there is considerable need for better prediction models for DILI early in drug discovery. We present a study involving 223 marketed drugs (5% associated with clinical hepatotoxicity; 49% non-hepatotoxic) to assess the concurrence of in vitro bioactivation data with clinical hepatotoxicity and how such data led to a decision tree to help reduce late-stage candidate attrition. Data from various P450 metabolite-dependent inhibition (MDI) factors for all common drug-metabolizing P450 enzymes were generated for 179 of these compounds. MDI factor data generated for 70 compounds,orrent binding data obtained for 53 compounds, and clinical dose data obtained for all compounds. Individual data for all 223 compounds were presented here and interrogated to determine what level of an alert to consider termination of a compound. The analysis showed that 76% of drugs with a daily dose of 100 mg were non-hepatotoxic (p < 0.0001). Drugs with a daily dose of ≥ 100 mg or with OATP substrate propensity, marked P450 MDI, or covalent binding ≥ 200 pmol/mg were significantly more likely to be hepatotoxic (45% in each case). Combining dose with each hepatotoxicity assay increased this association significantly (80–100% p < 0.0001). These analyses were then used to develop the decision tree and the tree tested using 10% of the compounds with sufficient data (49% hepatotoxic; 51% non-hepatotoxic). This resulted in the outcome where the decision tree was correctly terminated before candidate selection in 91% of cases.

ACETAMINOPHEN LIVER INJURY

1. Glucuronide
2. Sulfate
3. NAPQI
4. Mercapturic Acid
5. Cell Death
SIGNALING PATHWAY IN AILI

OTHER DRUGS MAY CAUSE LIVER INJURY BY DAMAGING THE MITOCHONDRIA

- Troglitazone
- Diclofenac
- Nimesulide
- Mefenamic acid
- Tolcapone
- Valproic acid
- Leflunomide
- Amiodarone
- Trovafloxacin

- Simvastatin
- Perhexiline
- Isoniazid
- Dantrolene
- Sulindac
- Lamivudine
- Stavudine
- Fialuridine

Mitochondrial Superoxide Dismutase and Glutathione Peroxidase in Idiosyncratic Drug-Induced Liver Injury

M. Isabel Lucena,1,11* Elena García-Martín,2,12 Raúl J. Andrade,3,11 Carmen Martínez,4,12 Camilla Stephens,1,11 Jhon D. Ruíz,4,12 Eugenia Uzurrum,1,11 M. Carmen Fernandez,5,11 Manuel Romero-Gómez,5,11 Augustin Castiella,7 Ramon Planas,8,11 José Antonio Durán,9 Ana Melcón De Dios,9 Carlos Guarner,10,11 German Soriano,10,11 Yolanda Borraz,1,11 and José A. G. Agundez4,12*

Drug-induced liver injury (DILI) susceptibility has a potential genetic basis. We have evaluated possible associations between the risk of developing DILI and common genetic variants of the manganese superoxide dismutase (SOD2 Val16Ala) and glutathione peroxidase (GPX1 Pro200Leu) genes, which are involved in mitochondrial oxidative stress management. Genomic DNA from 185 DILI patients assessed by the Council for International Organizations of Medical Science scale and 270 sex- and age-matched controls were analyzed. The SOD2 and GPX1 genotyping was performed using polymerase chain reaction restriction fragment length polymorphism and TaqMan probed quantitative polymerase chain reaction, respectively. The statistical power to detect the effect of variant alleles with the observed odds ratio (OR) was 98.2% and 99.7% for bilateral association of SOD2 and GPX1, respectively. The SOD2 Ala/Ala genotype was associated with cholestatic/mixed damage [OR = 2.3; 95% confidence interval (CI) = 1.4-3.8; corrected P (Pc) = 0.0058], whereas the GPX1 Leu/Leu genotype was associated with cholestatic injury (OR = 5.1; 95%CI = 1.6-16.0; Pc = 0.0112). The presence of two or more combined risk alleles (SOD2 Ala and GPX1 Leu) was more frequent in DILI patients (OR = 2.1; 95%CI = 1.4-3.0; Pc = 0.0006). Patients with cholestatic/mixed injury induced by mitochondria hazardous drugs were more prone to have the SOD2 Ala/Ala genotype (OR = 3.6; 95%CI = 1.4-9.3; Pc = 0.02). This genotype was also more frequent in cholestatic/mixed DILI induced by pharmaceuticals producing quinone-like or epoxide metabolites (OR = 3.0; 95%CI = 1.7-5.5; Pc = 0.0008) and S-oxides, dioxines, nitrosation radicals, or iminium ions (OR = 16.0; 95%CI = 1.8-146.1; Pc = 0.009). Conclusion: Patients homozygous for the SOD2 Ala allele and the GPX1 Leu allele are at higher risk of developing cholestatic DILI. SOD2 Ala homozygotes may be more prone to suffer DILI from drugs that are mitochondria hazardous or produce reactive intermediates. (HEPATOLOGY 2010;52:303-312)
CLINICAL FINDINGS SUGGEST THAT THE INNATE AND ADAPTIVE IMMUNE SYSTEMS HAVE A ROLE IN DILI

- Fever and skin rash often associated with DILI.
- Hepatic lesions often contain neutrophils, eosinophils and/or lymphocytes.
- Onset is often more rapid on re-exposure.
- Specific HLA associations have been found.
- Drug-protein adducts, drug metabolites and parent drugs have been found to activate T cells in the blood.
- Serum antibodies have been shown to react with drug-protein adducts, and unaltered carrier proteins of reactive metabolites.
DAMPS RELEASED FROM INJURED CELLS CAN ACTIVATE INNATE IMMUNE CELLS

<table>
<thead>
<tr>
<th>MOLECULE</th>
<th>RECEPTOR</th>
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<tbody>
<tr>
<td>ATP</td>
<td>P2X7</td>
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<tr>
<td>Cytochrome c</td>
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</tr>
<tr>
<td>Defensins</td>
<td>CCR6, TLR4</td>
</tr>
<tr>
<td>Galectins</td>
<td>CD2</td>
</tr>
<tr>
<td>HMGB1</td>
<td>TLR4, RAGE</td>
</tr>
<tr>
<td>Heat Shock Proteins</td>
<td>TLR4, CD14, CD19</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
<td>TLR2, TLR4</td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>TLR9, NLRP3</td>
</tr>
<tr>
<td>Nuclear DNA</td>
<td>TLR9</td>
</tr>
<tr>
<td>S100 Proteins</td>
<td>RAGE</td>
</tr>
<tr>
<td>Thioredoxin</td>
<td>Many Proteins</td>
</tr>
<tr>
<td>Uric Acid Crystal</td>
<td>NLRP3</td>
</tr>
</tbody>
</table>

Kubes and Mehal, Gastroenterology 2012
PAMPS CAN ALSO ACTIVATE CELLS OF THE INNATE IMMUNE SYSTEM

- Bacterial tri- and diacylated lipopeptides can activate TLR1/2 and TLR2/6, respectively
- Bacterial LPS can activate TLR4
- Bacterial flagellin can activate TLR5
- Bacterial unmethylated CpG DNA can activate TLR9
- Viral dsRNA can activate TLR 3
- Viral ssRNA can activate TLR7 and 8

*Seki and Brenner, Hepatology, 48, 322 (2008)*
INNATE IMMUNE CELLS AND WHAT THEY HAVE BEEN SHOWN TO DO IN DILI MODEL STUDIES

**Cells:** Dendritic cells, neutrophils, NK and NKT cells, macrophages, Kupffer cells, and even hepatocytes

**Protoxicant Factors:** ROS and RNS, IFN-γ, IL-1β, IL-17, IL-18, osteopontin, MIF, IL-6, and chemokines

**Protective Factors:** IL-4, IL-6, IL-10, IL-13, COX-2, and Nrf2
The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury

E. BJÖRNSSON, E. KALAITZAKIS & R. OLSSON

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Correspondence to:
Dr E. Björnsson, Department of Internal Medicine, Sahlgrenska University Hospital, SE-411 45 Gothenburg, Sweden.
E-mail: einar.bjornsson@medic.gu.se

SUMMARY

Background
Drug-induced liver injury may be immunologically mediated or metabolically induced. Peripheral eosinophilia and liver eosinophilia in suspected drug-induced liver injury generally supports the role of drug aetiology.

Aim
To assess the importance of eosinophilia and hepatic necrosis on outcome in patients with suspected drug-induced liver injury.

Methods
We performed search of MEDLINE for case reports on drug-induced liver injury associated with: amoxicillin/clavulanic acid, carbamazepine, diclofenac, disulfiram, erythromycin, flucloxacillin, halothane, isoniazid, phenytoin, sulindac and trimethoprim/sulfamethoxazol.

HALOTHANE-INDUCED LIVER INJURY

$ : B ; F : C 8$

$ @ < A : B ; C D ^ 1 8 B A , @ @ ? C 8 ^ { 2 } 8 E 9 < C E 8 E$

$ # < I @ G >$
HALOTHANE CAUSES PERIVENOUS LIVER INJURY IN FEMALE BALB/CJ MICE 24 HOURS AFTER HALOTHANE
HISTOLOGY OF EOSINOPHILS AND NEUTROPHILS PURIFIED BY CELL SORTING 24 HOURS AFTER HALOTHANE

A  B

C  D
IMMUNOHISTOCHEMICAL STAINING OF EOSINOPHIL MAJOR BASIC PROTEIN IN PERIVENOUS REGIONS OF LIVER INJURY

A

<table>
<thead>
<tr>
<th>12h HAL</th>
<th>H&amp;E</th>
<th>MBP</th>
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<tbody>
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<td>![H&amp;E Image]</td>
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</table>
# HLA ASSOCIATIONS IN DILI

Table 1. HLA associations in DILI detected by genotyping.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Drug</th>
<th>Type of study</th>
<th>Ethnicity of subjects</th>
<th>Replication</th>
<th>Reference</th>
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<tbody>
<tr>
<td>HLA-A</td>
<td>*3303</td>
<td>Ticlopidine</td>
<td>Candidate gene</td>
<td>Japanese</td>
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<td>(Hiraia et al., 2008)</td>
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<tr>
<td>HLA-B</td>
<td>*5701</td>
<td>Fluoxetine</td>
<td>GWAS</td>
<td>European (UK)</td>
<td>Yes</td>
<td>(Daly et al., 2009)</td>
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<tr>
<td>HLA-DRB1</td>
<td>*1501</td>
<td>Amoxicillin-clavulanate</td>
<td>Candidate gene and GWAS</td>
<td>European (UK, U.S. and Spanish)</td>
<td>Yes</td>
<td>(Hautekeete et al., 1999; O’Donchue et al., 2000; Donaldson et al., 2010; Lucena et al., 2011)</td>
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<tr>
<td>HLA-A</td>
<td>*0201</td>
<td></td>
<td>GWAS</td>
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<td>(Andrade et al., 2004)</td>
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<tr>
<td>HLA-B</td>
<td>*1801</td>
<td></td>
<td>GWAS</td>
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<tr>
<td>HLA-DRB1</td>
<td>*1501</td>
<td>Various</td>
<td>Candidate gene</td>
<td>European (Spanish)</td>
<td>No</td>
<td>(Kindmark et al., 2008)</td>
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<tr>
<td>HLA-DRB1</td>
<td>*1501</td>
<td>Lumiracoxib</td>
<td>GWAS</td>
<td>Various</td>
<td>Yes</td>
<td>(Martin et al., 2005; Yuan et al., 2011)</td>
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<tr>
<td>HLA-DRB1</td>
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<td>Ximelagatran</td>
<td>GWAS/candidate gene</td>
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<td>HLA-DRB1</td>
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<td>Isoniazid</td>
<td>Candidate gene</td>
<td>Indian</td>
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</tr>
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</table>

*A.K. Daly and C.P. Day, Drug Metab. Rev., 2011*
**T CELL REACTIVITY IS ASSOCIATED WITH DRUGS CAUSING ALLERGIC HEPATITIS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
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<tr>
<td>Cotrimoxazole</td>
<td>Chlorpromazine</td>
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<tr>
<td>Ketoconazole</td>
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<td>Captopril</td>
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<td>α-Methyldopa</td>
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<tr>
<td>Enalapril</td>
<td>Propylthiouracil</td>
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_Gut, 41, 534 (1997)_
### CELLULAR TARGETS OF HALOTHANE HEPATITIS PATIENTS’ SERUM ANTIBODIES (% REACTIVITY)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>TFA-Protein</th>
<th>Native-Protein</th>
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<td>PDI</td>
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<td>5</td>
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<tr>
<td>PDI isoform</td>
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<td>25</td>
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<td>Carboxylesterase</td>
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<td>5</td>
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<td>Calreticulin</td>
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<td>ERP72</td>
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<td>25</td>
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<tr>
<td>GRP94</td>
<td>65</td>
<td>28</td>
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<tr>
<td>CYP2E1</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>
Limited contribution of common genetic variants to risk for liver injury due to a variety of drugs


Background and aims Drug-induced liver injury (DILI) is a serious adverse drug event that is suspected to have a heritable component. We carried out a genome-wide association study of 783 individuals of European ancestry who experienced DILI due to more than 200 implicated drugs.

Methods DILI patients from the US-based Drug-Induced Liver Injury Network (n = 401) and three international registries (n = 382) were genotyped with the Illumina 1Mduo BeadChip and compared with population controls (n = 3001). Potential associations were tested in 307 independent Drug-Induced Liver Injury Network cases.

Results After accounting for known major histocompatibility complex risk alleles for fluoroacetilin-DILI and amoxicillin/clavulanate-DILI, there were no genome-wide significant associations, including in the major histocompatibility complex region. Stratification of DILI cases according to clinical phenotypes (injury type, latency, age of onset) also did not show significant associations. An analysis of hepatocellular DILI (n = 285) restricted to system in DILI. However, the lack of genome-wide association study findings supports the idea that strong genetic determinants of DILI may be largely drug-specific or may reflect rare genetic variations, which were not assessed in our study. Pharmacogenetics and Genomics 22:784-795 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: drug-induced liver injury, genome-wide association study, pharmacogenetics

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CARDIAC DISEASE CAUSED BY DRUG-INDUCED LONG QT SYNDROME
ECG tracing of a normal heart rhythm.

In atrial fibrillation, the tracing shows tiny, irregular "fibrillation" waves between heartbeats. The rhythm is irregular and erratic.
DRUG-INDUCED-LONG QT SYNDROME AND TORSADES DE POINTES

Table 2
Examples of drugs with QT interval prolonging potential\(^a\) (Haverkamp et al., 2000; www.Torsades.org, 2004; Tristani-Firouzi et al., 2001; Recanatini et al., 2005)

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>disopyramide, procainamide, quinidine</td>
</tr>
<tr>
<td></td>
<td>amiodarone, dofetilide, ibutilide, sotalol</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>chlorpromazine, droperidol, haloperidol, pimozide, sertindole, thioridazine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>fluoroquinolones (gatifloxacin, grepafloxacin, moxifloxacin, sparfloxacine)</td>
</tr>
<tr>
<td></td>
<td>macrolide antibiotics (clarithromycin, erythromycin)</td>
</tr>
<tr>
<td></td>
<td>azole antymycotics (fluconazole, ketoconazole)</td>
</tr>
<tr>
<td></td>
<td>antimalarials (chloroquine, halofantrine, mefloquine, quinine)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>astemizole, terfenadine</td>
</tr>
<tr>
<td>GI stimulants</td>
<td>cisapride, domperidone</td>
</tr>
<tr>
<td>Opioid agonists</td>
<td>levacetylmethadol, methadone</td>
</tr>
<tr>
<td>Antianginals</td>
<td>bepridil, lidoflazine, prenylamine</td>
</tr>
<tr>
<td>Miscellanea</td>
<td>arsenic trioxide, budipine, terodiline</td>
</tr>
</tbody>
</table>

\(^a\) The list is not intended as exhaustive.

RISK FACTORS FOR DRUG-INDUCED TORSADES DE POINTES

• Hypokalemia and hypomagnesemia
• Bradycardia
• Cardiac hypertrophy and congestive heart failure
• High drug serum concentrations
• Female
• Polymorphisms

A Large Candidate Gene Survey Identifies the KCNE1 D85N Polymorphism as a Possible Modulator of Drug-Induced Torsades de Pointes

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Background—Drug-induced long-QT syndrome (diLQTS) is an adverse drug effect that has an important impact on drug use, development, and regulation. We tested the hypothesis that common variants in key genes controlling cardiac electric properties modify the risk of diLQTS.

Methods and Results—In a case-control setting, we included 176 patients of European descent from North America and Europe with diLQTS, defined as documented torsades de pointes during treatment with a QT-prolonging drug. Control samples were obtained from 207 patients of European ancestry who displayed <50 ms QT lengthening during initiation of therapy with a QT-prolonging drug and 837 control subjects from the population-based KORA study. Subjects were successfully genotyped at 1424 single-nucleotide polymorphisms (SNPs) in 18 candidate genes including 1386 SNPs tagging common haplotype blocks and 38 nonsynonymous ion channel gene SNPs. For validation, we used a set of cases (n=57) and population-based control subjects of European descent. The SNP KCNE1 D85N (rs1805128), known to modulate an important potassium current in the heart, predicted diLQTS with an odds ratio of 9.0 (95% confidence interval, 3.5–22.9). The variant allele was present in 8.6% of cases, 2.9% of drug-exposed control subjects, and 1.8% of population control subjects. In the validation cohort, the variant allele was present in 3.5% of cases and in 1.4% of control subjects.

Conclusions—This high-density candidate SNP approach identified a key potassium channel susceptibility allele that may be associated with the rare adverse drug reaction torsades de pointes. (Circ Cardiovasc Genet. 2012;5:91-99.)
Genome Wide Analysis of Drug-Induced Torsades de Pointes: Lack of Common Variants with Large Effect Sizes

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Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes

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Marked prolongation of the QT interval and polymorphic ventricular tachycardia following medication (drug-induced long QT syndrome, dLQTS) is a severe adverse drug reaction (ADR) that phenocopies congenital long QT syndrome (cLQTS) and is one of the leading causes for drug withdrawal and relabeling. We evaluated the frequency of rare non-synonymous variants in genes contributing to the maintenance of heart rhythm in cases of dLQTS using targeted capture coupled to next-generation sequencing. Eleven of 31 dLQTS subjects (36%) carried a novel missense mutation in genes with known congenital arrhythmia associations or with a known cLQTS mutation. In the 26 Caucasian subjects, 23% carried a highly conserved rare variant predicted to be deleterious to protein function in these genes compared with only 2–4% in public databases (P < 0.003). We conclude that the rare variation in genes responsible for congenital arrhythmia syndromes is frequent in dLQTS. Our findings demonstrate that dLQTS is a pharmacogenomic syndrome predisposed by rare genetic variants.

The Pharmacogenomics Journal advance online publication, 15 May 2012; doi:10.1038/tpj.2012.14

Keywords: adverse drug reaction; next-generation sequencing; sudden cardiac death
Refining the Human iPSC-Cardiomyocyte Arrhythmic Risk Assessment Model

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Human induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMs) are capable of detecting drug-induced clinical arrhythmia, Torsade de Pointes (TdP), and QT prolongation. Efforts herein employ a broad set of structurally diverse drugs to optimize the predictive algorithm for applications in discovery toxicology and cardiac safety screening. The changes in the beat rhythm and rate of a confluent monolayer of hiPSC-CMs by 88 marketed and 30 internal discovery compounds were detected with real-time cellular impedance measurement and quantified by measures of arrhythmic beating (IBSEP), lowest concentration inducing ≥ 20% arrhythmia (irregular, atypical) beats in 3 consecutive 20-s sweeps, and predicted proarrhythmic score (PPS)-IBSEP or changes in beat rate (BRSEP, the lowest concentration inducing a reduction in beat rate of ≥ 20% at 3 consecutive

Key Words: cardiotoxicity; arrhythmia; stem cells; cardiomyocytes; label-free technology; investigative toxicology.

Cardiovascular liabilities of new chemical entities continue to be a significant source of attrition across the entire drug discovery and development process (Laverty et al., 2011). Among the most common drug-induced cardiovascular findings encountered are disturbances in the electrical activity of the myocardium. Cardiac arrhythmias, particularly Torsade de Pointes (TdP), can have serious and sometimes fatal consequences. Accordingly, detection of arrhythmia in the drug discovery process is mandated through a panel of in vitro and in vivo tests outlined by regulatory agencies prior to entry into clinical trials (ICH S7A and S7B) and again dur-
BIOLOGICS ALSO CAUSE SEVERE ADVERSE DRUG REACTIONS
TNF-α ANTAGONISTS

• These drugs are used to treat rheumatoid arthritis, Crohn’s disease, ulcerative colitis, psoriasis, and other inflammatory diseases.

• They inhibit TNF-α signaling by directly binding soluble and membrane bound TNF-α and all contain at least in part a human IgG antibody component.

• They have also been associated with tuberculosis, hepatitis B, lymphoma, seizures, aplastic anemia, and liver injury.
Liver Injury From Tumor Necrosis Factor-α Antagonists: Analysis of Thirty-four Cases

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**Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

BACKGROUND & AIMS: Tumor necrosis factor (TNF)-α antagonists have been associated with drug-induced liver injury (DILI). We reviewed cases of DILI in the United States to identify those associated with use of TNF-α antagonists.

METHODS: We searched the U.S. DILI Network (DILIN) database, from 2003 to 2011, for cases associated with TNF-α antagonists. Mean Rouselle-Uclaf Causality Assessment Method scores were calculated. A DILIN severity score was assigned according to a previously published scale, and we identified 6 subjects likely to have DILI associated with use of TNF-α antagonists. We also searched PubMed for articles that reported hepatotoxicity from TNF-α antagonists, identifying 28 additional cases suitable for analysis.

RESULTS: The drugs presumed to have caused DILI were infliximab (n = 26), etanercept (n = 4), and adalimumab (n = 4). The anti-TNF-α agent was the probable cause of 12 cases of DILI (35%), a very likely cause for 21 (62%), and a definite cause for 1 (3%). Median latency was 13 weeks (range, 2–104); however, 7 cases (20%) had latency periods longer than 24 weeks. Twenty-two of 33 subjects who underwent serologic analysis (67%) tested positive for anti-nuclear and/or smooth muscle antibodies. Of these, 22, 17 underwent liver biopsy; 13 subjects had histologic features of autoimmune hepatitis. The 22 subjects with autoimmune features had longer median latency (16 vs 10 weeks) and higher peak levels of alanine aminotransferase (784 vs 528 U/L) than the 12 without such features. There was 1 case of severe cholestasis. All but one subject improved after discontinuation of the implicated drug; 12 subjects received corticosteroid therapy. No deaths were attributed to liver injury, although one patient with preexistent cirrhosis required liver transplantation.

CONCLUSIONS: Acute liver injury caused by TNF-α antagonists may be a class effect because multiple agents in this category have been implicated. The most common presentation is an autoimmune phenotype with marked hepatocellular injury, but a mixed non-autoimmune pattern or predominant cholestasis also occurs. The prognosis is usually good after drug discontinuation, although some patients may benefit from a course of corticosteroids. ClinicalTrials.gov: Number, NCT0043930
Antibody-Drug Conjugates: Modes of Toxicity

Melissa M. Schutten, DVM, PhD, DACVP
Safety Assessment Pathology

NorCal Society of Toxicology Meeting
September 27, 2012
Anatomy of an Antibody-Drug Conjugate (ADC)

Antibody targeted to tumor
- Humanized monoclonal Ab (IgG1)
- mAb with Fc modifications (modulate ADCC, CDC activity)
- Other mAb fragments

Linker stable in circulation
- Linker biochemistry
  - Acid labile (hydrazone)
  - Enzyme dipeptides (cleavable)
  - Thioether (uncleavable)
  - Hindered disulfide (uncleavable)
- Site of conjugation
  - Fc, HC, LC

Very potent chemotherapeutic drug
- Tubulin polymerization inhibitors
  - Maytansines (DM1, DM4)
  - Auristatins (MMAE, MMAF)
- DNA damaging agents
  - Calicheamicins
  - Duocarmycins
  - Anthracyclines (doxorubicin)
Modes of Anti-tumor Activity of ADCs

Tumor cytotoxicity is target-directed
ADC-Ag binding → internalization in lysosomes → ADC degradation → release of toxin intracellularly → tumor cell death

Tumor cytotoxicity is target-enhanced (bystander effect)
ADC-Ag binding → extracellular cleavage of toxin → release of toxin in local tumor environment → diffusion of toxin intracellularly to neighboring tumor cells → tumor cell death
Modes of Toxicity of ADCs

Systemic release of toxin
- Instability of linker
- Catabolism of ADC

Unwanted ADC-mediated cytotoxicity
- Targeted binding to normal tissues expressing antigen
- Off-target (cross reactive) binding to normal tissues
- Non-antigen-mediated ADC uptake (e.g., Fc-mediated uptake, pinocytosis)
PERSPECTIVES

Proposed mechanism of off-target toxicity for antibody–drug conjugates driven by mannose receptor uptake

Boris Gorovits · Corinna Krinos-Fiorotti

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Abstract Antibody–drug conjugates (ADCs) are developed with the goal of increasing compound therapeutic index by specific and targeted delivery of a toxic payload to the site of action while considerably reducing damage to normal tissues. Yet, off-target hepatic toxicities have been reported for several ADC. Locations of these off-target toxicities coincide with the reported locations of cell surface mannose receptor (MR). The relative proportion of agalactosylated glycans on the Fc domain (G0F vs. G1F and G2F components) in monoclonal antibody (mAb)-based biotherapeutics is closer to some disease state IgG rather than to a normal serum-derived immunoglobulin. The lack of the terminal galactose on a G0F glycan creates an opportunity for the mAb to interact with soluble and cell surface MRs. MR is a known multi-domain lectin that specifically binds and internalizes glycoproteins and immune complexes with relatively high G0F content and

Introduction

Monoclonal antibody (mAb)-based biotherapeutics are typically modified post-translationally by the intracellular machinery of a producing host cell in a manner similar to naturally produced immunoglobulins. The N-glycosylation site is located on the asparagine (Asn-297) amino acid within the CH2 domain and consists of biantennary core oligosaccharides with various degrees of terminal galactosylation. Glycans found at this site are generally categorized based on the number of terminal galactoses (G), that is, G0F, G1F and G2F. Although the nature of the oligosaccharides found within the Fc region is similar to that on serum-derived immunoglobulins, the G0F/G1F/G2F distribution on commercial mAbs is closer to that found on immunoglobulins from disease state sera where the relative fraction of the G0F component is elevated [1, 2]. The lack of the terminal gal-
SUMMARY

- Severe drug reactions are often idiosyncratic, rare, and even occur with biologic drugs.
- Many toxicities appear to be mediated at least in part by the innate and adaptive immune systems.
- GWAS of common genetic variations have yet to identify disease-specific risk factors.
- Whole genome deep sequencing is needed to identify disease-associations with coding and non-coding rare genetic variations.
- Animal models have to be developed to better understand the mechanisms of these rare drug-induced diseases.