BIOCHEMICAL MECHANISMS OF DRUG TOXICITIES

Lance R. Pohl, Pharm.D., Ph.D.
Chief, Section of Molecular and Cellular Toxicology
Laboratory of Molecular Immunology
pohll@nih.gov
12/15/2011
ADVERSE DRUG REACTIONS (ADRS)

- Minor
- Severe
  - 6.2-6.7% hospitalized patients in USA
  - over 2 million hospitalized patients
  - similar findings in Europe and Australia
  - tens of billions of dollars cost burden

LEADING CAUSES OF DEATH IN USA IN 1994

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>743,460</td>
</tr>
<tr>
<td>Cancer</td>
<td>529,904</td>
</tr>
<tr>
<td>Stroke</td>
<td>150,108</td>
</tr>
<tr>
<td>SADRs</td>
<td>106,000</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>101,077</td>
</tr>
<tr>
<td>Accidents</td>
<td>90,523</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>75,719</td>
</tr>
<tr>
<td>Diabetes</td>
<td>53,894</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System</th>
<th>Condition</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>
</tr>
<tr>
<td>Pulmonary</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Neurological</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Lupus</td>
<td></td>
</tr>
</tbody>
</table>
**DRUG WITHDRAWN IN USA**

- Azaribine, psoriasis, **blood clots**, 1976
- Ticrynafen, blood pressure, **liver injury**, 1980
- Benoxaprofen, NSAID, **liver injury**, 1982
- Zomepirac, NSAID, **anaphylaxis**, 1983
- Nomifensine, anti-depressant, **hemolytic anemia**, 1986
- Suprofen, NSAID, **kidney failure**, 1987
- Temafloxacin, antibiotic, **kidney failure**, 1992
- Fenfluramine, appetite suppression, **heart valve disease**, 1997
- Terfenadine, anti-histamine, **fatal arrhythmia**, 1998
- Bromfenac, NSAID, **liver injury**, 1998
- Mibefradil, blood pressure, **muscle damage and fatal arrhythmia**, 1998
DRUG WITHDRAWN IN USA

- Etretinate, psoriasis, birth defects, 1999
- Grepafloxacin, antibiotic, fatal arrhythmia, 1999
- Astemizole, antihistamine, fatal arrhythmia, 1999
- Cisapride, heartburn, fatal arrhythmia, 2000
- Troglitazone, diabetes, liver toxicity, 2000
- Cerivastatin, cholesterol reduction, muscle damage leading to kidney failure, 2001
- Trovafloxacin, antibiotic, liver toxicity, 2001
- Rofecoxib, NSAID, heart attack, stroke, 2004
- Valdecoxib, NSAID, skin disease, 2005
- Pemoline, ADHD, liver toxicity, 2005
- Levomethadyl, opiate dependence, fatal arrhythmia, 2008
- Avandia, diabetes, heart attack, 2010
- Darvon, analgesic, fatal arrhythmia, 2010
TYPE A ADRs

- 80% of ADRs
- Relatively frequent and often predictable
- Excessive or diminished pharmacologic effects
- Drug-drug interactions and polymorphisms in metabolizing enzymes and transporters
- Mild to severe ADRs
- Often uncovered preclinically

EXAMPLES OF TYPE A ADRS

- Drowsiness from antihistamines
- Hypotension from antihypertensive therapy
- Excess bleeding from warfarin
- Acetaminophen
TYPE B ADRs

- 20% of ADRs
- Rare, unpredictable, and highly host-dependent
- Mild to severe ADRs
- Rarely uncovered preclinically in animals or in clinical trials
- Mechanisms often unknown but may be due to:
  
  **Allergic Reactions**
  **Rare Polymorphisms**
  **Imbalance in Cellular Homeostasis**
  **Environmental Factors**
HAP TEN HYPOTHESIS AND DRUG-INDUCED ALLERGIC REACTIONS

Drug or Metabolite + Toxicity ↔ B and T Cell Responses
Drug Protein Conjugate Formed in a Cell

Secreted
Injured Cell

Immature Dendritic Cell

Ag Processing

IgG, IgE, IgA

B Cell

Ag Presentation by MHC Class I and II

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

Migrate to Lymph Nodes
Immunization of T Cells

CD4+, CD8+

IL-10, PGE2, TGF-β

Migrate to Lymph Nodes
Tolerization of T Cells

CD4+, CD8+

Migration to Periphery
Drug Allergy

Regulatory T Cells
Migration to Periphery
Block Drug Allergy

Migration to Periphery
Drug Allergy

B Cell

IgG, IgE, IgA
IgE-MEDIATED ANAPHYLACTIC DRUG REACTIONS

Alcuronium    Sulfamethoxazole
Cephalosporins Suxamethonium
Penicillins   Thiopentone
Protamine     Trimethoprine
Streptokinase Tubocurarine

MECHANISM OF DRUG-INDUCED ANAPHYLAXIS

1. Airway smooth muscle contraction leading to bronchospasm
2. Increase permeability of blood vessels and mucous gland secretion
3. Inflammation (eosinophils and neutrophils)
4. Respiratory, gastrointestinal, cutaneous, and cardiovascular systems can be involved

Histamine, leukotrienes, and cytokines
DRUG-INDUCED SKIN DISEASE
MILD FORM OF CUTANEOUS TOXICITY
STEVENS JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)
<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Anticonvulsants</th>
</tr>
</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></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>NSAIDs (esp. oxicam derivatives)</td>
<td></td>
</tr>
</tbody>
</table>

Roychowdhury and Svensson, AAPS J., 7, E834 (2005)
HLA-B*1502 ASSOCIATED WITH CBZ-INDUCED SJS/TENS

- Seen in south-east Asians but not in Caucasians
- 98.3% (59/60) CBZ-SJS/TEN positive
- 4.2% (6/144) CBZ-tolerant positive
- High sensitivity/specificity of this test can be used to screen patients receiving CBZ

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, Atushi Takahashi², Michiaki Kubo³, Yuji Shirakata⁴, Zenro Ikezawa⁵, Masafumi Iijima⁶, Tetsuo Shihohara⁷, Koji Hashimoto⁴, Naoyuki Kanatani¹ 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 rs1630021 showed the smallest P-value for association with CBZ-induced cADRs (P = 1.18 × 10⁻¹⁸). 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 5.9–19.8, P = 3.64 × 10⁻¹⁷), 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.

T. Ozeki, et al., Human Molecular Genetics, 20, 1034 (2011)
DRUG-INDUCED HYPERSENSITIVITY SYNDROME

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

P. Cacoub, et al., The American Journal of Medicine, 124, 588 (2011)
DRUG-INDUCED CARDIAC DISEASE
DRUG-INDUCED-LONG QT SYNDROME AND TORSADES DE POINTES

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>disopyramide, procainamide, quinidine</td>
</tr>
<tr>
<td>class IA</td>
<td>amiodarone, dofetilide, ibutilide, sotalol</td>
</tr>
<tr>
<td>class III</td>
<td>chlorpromazine, droperidol, haloperidol, pimozide, sertindole, thioridazine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>fluoroquinolones (gatifloxicin, grepafloxicin, moxifloxicin, sparfloxicin)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>macrolide antibiotics (clarithromycin, erythromycin)</td>
</tr>
<tr>
<td></td>
<td>azole antymycotics (fluconazole, ketoconazole)</td>
</tr>
<tr>
<td></td>
<td>antimalarias (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

METHODS USED TO PREDICT DRUG-INDUCED TORSADES DE POINTES

- *In vitro* assays with cells expressing the K ion channel have been used.
- Cardiomyocytes derived from human embryonic stem cell may replace these other tests.
- The best cardiomyocytes for these tests would be from diseased individuals.

Patient-Specific Induced Pluripotent Stem-Cell Models for Long-QT Syndrome

Alessandra Moretti, Ph.D., Milena Bellin, Ph.D., Andrea Welling, Ph.D., Christian Billy Jung, M.Sc., Jason T. Lam, Ph.D., Lorenz Bott-Flügel, M.D., Tatjana Dorn, Ph.D., Alexander Goedel, M.D., Christian Höhnke, M.D., Franz Hofmann, M.D., Melchior Seyfarth, M.D., Daniel Sinnecker, M.D., Albert Schöning, M.D., and Karl-Ludwig Laugwitz, M.D.

ABSTRACT

BACKGROUND

Long-QT syndromes are heritable diseases associated with prolongation of the QT interval on an electrocardiogram and a high risk of sudden cardiac death due to ventricular tachyarrhythmia. In long-QT syndrome type 1, mutations occur in the KCNQ1 gene, which encodes the repolarizing potassium channel mediating the delayed rectifier I\textsubscript{K1} current.

METHODS

We screened a family affected by long-QT syndrome type 1 and identified an autosomal dominant missense mutation (R190Q) in the KCNQ1 gene. We obtained dermal fibroblasts from two family members and two healthy controls and infected them with retroviral vectors encoding the human transcription factors OCT3/4, SOX2, KLF4, and c-MYC to generate pluripotent stem cells. With the use of a specific protocol, these cells were then directed to differentiate into cardiac myocytes.
DRUG-INDUCED LIVER DISEASE
DRUG-INDUCED LIVER DISEASE IS THE MAJOR CAUSE OF ACUTE LIVER FAILURE

• Preclinical development of drugs is often stopped because of this toxicity.

• As are clinical trials of drugs.

• And the withdrawal of drugs postmarketing.
ACETAMINOPHEN LIVER INJURY

Glucuronide

HN-C-CH₃

O

OH

HN-C-CH₃

HN-C-CH₃

HN-C-CH₃

Sulfate

Cyt P-450
NADPH/O₂

HN-C-CH₃

O

NAPQI

HN-C-CH₃

HN-C-CH₃

O

S-protein

+ protein

+ GSH

MERCAPTURIC ACID

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

Polymerase γ Gene POLG Determines the Risk of Sodium Valproate-Induced Liver Toxicity

Joanna D. Stewart,1 Rita Horvath,1 Enrico Baruffini,2 Iliana Ferrero,3 Stefanie Bulst,3 Paul B. Watkins,4 Robert J. Fontana,5 Christopher P. Day,6 and Patrick F. Chinnery1,7

Sodium valproate (VPA) is widely used throughout the world to treat epilepsy, migraine, chronic headache, bipolar disorder, and as adjuvant chemotherapy. VPA toxicity is an uncommon but potentially fatal cause of idiosyncratic liver injury. Rare mutations in POLG, which codes for the mitochondrial DNA polymerase γ (polγ), cause Alpers-Huttenlocher syndrome (AHS). AHS is a neurometabolic disorder associated with an increased risk of developing fatal VPA hepatotoxicity. We therefore set out to determine whether common genetic variants in POLG explain why some otherwise healthy individuals develop VPA hepatotoxicity. We carried out a prospective study of subjects enrolled in the Drug Induced Liver Injury Network (DILIN) from 2004 to 2008 through five US centers. POLG was sequenced and the functional consequences of VPA and novel POLG variants were evaluated in primary human cell lines and the yeast model system Saccharomyces cerevisiae. Heterozygous genetic variation in POLG was strongly associated with VPA-induced liver toxicity (odds ratio = 23.6, 95% confidence interval [CI] = 8.4-65.8, \( P = 5.1 \times 10^{-7} \)). This was principally due to the p.Q1236H substitution which compromised polγ function in yeast. Therapeutic doses of VPA inhibited human cellular proliferation and high doses caused nonapoptotic cell death, which was not mediated through mitochondrial DNA depletion, mutation, or a defect of fatty acid metabolism. Conclusion: These findings implicate impaired liver regeneration in VPA toxicity and show that prospective genetic testing of POLG will identify individuals at high risk of this potentially fatal consequence of treatment. (HEPATOLOGY 2010;52:1791-1796)
Mitochondrial Superoxide Dismutase and Glutathione Peroxidase in Idiosyncratic Drug-Induced Liver Injury

M. Isabel Lucena, Elena García-Martín, Raúl J. Andrade, Carmen Martínez, Camilla Stephens, Jhon D. Ruiz, Eugenia Uzurrurn, M. Carmen Fernandez, Manuel Romero-Gomez, Augustín Castiella, Ramon Planas, José Antonio Durán, Ana Melcón De Dios, Carlos Guerza, Germain Soriano, Yolanda Borraz, and José A. G. Agundez

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 reactionrestriction 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 cholesterol/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; P = 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; P = 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; P = 0.022). 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; P = 0.0008) and S-oxides, dioxines, nitrosation radicals, or iminium ions (OR = 16.0; 95%CI = 1.8-146.1; P = 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)
SECONDARY PHASE OF LIVER INJURY IS CAUSED BY ACTIVATION OF THE INNATE IMMUNE SYSTEM

DAMPs are released from injured cells: HMGB-1, MIF, HSPs, Uric Acid, DNA

Innate immune cells are activated by DAMPs: Dendritic cells, neutrophils, NK and NKT cells, macrophages, Kupffer cells, eosinophils, basophils and mast cells

Protoxicant Factors released from activated cells: ROS and RNS, IFN-γ, IL-1β, IL-17, IL-18, osteopontin, MIF, IL-6, and chemokines

Protective Factors released from activated cells: IL-4, IL-6, IL-10, IL-13, COX-2, and Nrf2

INFLAMMATORY CELL INVOLVEMENT IN AILI IN IL-10^{-/-} MICE
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 umethylated CpG DNA can activate TLR9
• Viral dsRNA can activate TLR 3
• Viral ssRNA can activate TLR7 and 8

E. Seki and D.A. Brenner, Hepatology, 48, 322 (2008)
DRUG-INDUCED ALLERGIC HEPATITIS
## HALOTHANE HEPATITIS PATIENTS’ SERUM ANTIBODIES (% REACTIVITY)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>TFA-Protein</th>
<th>Native-Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDI</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>PDI isoform</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>Carboxylesterase</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Calreticulin</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>ERP72</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>GRP94</td>
<td>65</td>
<td>28</td>
</tr>
<tr>
<td>CYP2E1</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>
# Antibodies Associated with Other Drugs Causing Hepatitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tienilic acid</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Dihydralazine</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Ethanol</td>
<td>CYP2E1, CYP3A4</td>
</tr>
<tr>
<td>Carbamazapine</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

*T. Mizutani, et al., Drug Metab. Rev., 1, 235 (2005)*
<table>
<thead>
<tr>
<th>Drugs Associated with Both Idiosyncratic DILI and Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid\textsuperscript{44}</td>
</tr>
<tr>
<td>minocycline\textsuperscript{45}</td>
</tr>
<tr>
<td>α-methyldopa\textsuperscript{46–48}</td>
</tr>
<tr>
<td>hydralazine\textsuperscript{47,49}</td>
</tr>
<tr>
<td>nitrofurantoin\textsuperscript{50,51}</td>
</tr>
<tr>
<td>propylthiouracil\textsuperscript{52,53}</td>
</tr>
<tr>
<td>methimazole\textsuperscript{54,55}</td>
</tr>
<tr>
<td>aminogluthethimide\textsuperscript{56,57}</td>
</tr>
<tr>
<td>diclofenac\textsuperscript{58,59}</td>
</tr>
<tr>
<td>allopurinol\textsuperscript{60,61}</td>
</tr>
<tr>
<td>phenylbutazone\textsuperscript{62,63}</td>
</tr>
<tr>
<td>phenytoin\textsuperscript{64,65}</td>
</tr>
<tr>
<td>carbamazepine\textsuperscript{66,67}</td>
</tr>
<tr>
<td>sulfonamides\textsuperscript{68,69}</td>
</tr>
<tr>
<td>phenothiazines\textsuperscript{70,71}</td>
</tr>
<tr>
<td>terbinafine\textsuperscript{72,73}</td>
</tr>
<tr>
<td>statins\textsuperscript{74,75}</td>
</tr>
<tr>
<td>leflunomide\textsuperscript{76,77}</td>
</tr>
<tr>
<td>zafirlukast\textsuperscript{78–80}</td>
</tr>
</tbody>
</table>

\textsuperscript{J. Uetrecht, Seminar in Liver Disease, 29, 383 (2009)}
T CELL REACTIVITY ASSOCIATED WITH DRUGS CAUSING ALLERGIC HEPATITIS

<table>
<thead>
<tr>
<th>Drugs Causing Allergic Hepatitis</th>
<th>Drugs Causing Allergic Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Amineptine</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Dothiepine</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Captopril</td>
<td>Glibenclamide</td>
</tr>
<tr>
<td>α-Methyldopa</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Propylthiouracil</td>
</tr>
</tbody>
</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>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>*3303</td>
<td>Ticlopidine</td>
<td>Candidate gene</td>
<td>Japanese</td>
<td>No</td>
<td>(Hiraia et al., 2008)</td>
</tr>
<tr>
<td>HLA-B</td>
<td>*5701</td>
<td>Flucloxacillin</td>
<td>GWAS</td>
<td>European (UK)</td>
<td>Yes</td>
<td>(Daly et al., 2009)</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>*1501</td>
<td>Amoxicillin-</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>
</tr>
<tr>
<td>HLA-A</td>
<td>*0201</td>
<td></td>
<td>GWAS</td>
<td></td>
<td></td>
<td>(Andrade et al., 2004)</td>
</tr>
<tr>
<td>HLA-B</td>
<td>*1801</td>
<td></td>
<td>GWAS</td>
<td></td>
<td></td>
<td>(Singer et al., 2010)</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>*0701</td>
<td>Ximelagatran</td>
<td>GWAS/candidate gene</td>
<td>Various</td>
<td>No</td>
<td>(Spraggs et al., 2011)</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>*01</td>
<td>Nevirapine</td>
<td>Candidate gene</td>
<td>European</td>
<td>No</td>
<td>(Sarma et al., 2002)</td>
</tr>
<tr>
<td>HLA-DQA1</td>
<td>*0201</td>
<td>Lapatinib</td>
<td>Candidate gene</td>
<td>Various</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>*0201</td>
<td>Isoniazid</td>
<td>Candidate gene</td>
<td>Indian</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

HEPATOTOXIC DOSE OF APAP DEPLETES LYMPHOCYTES WITHIN 24 HOURS

CELLULAR BASIS OF LIVER TOLERANCE

Summary

• Drug-drug interactions are the major cause of ADRs, but are often predictable and avoidable.
• Most SADRs are rare, highly host-dependent, difficult to predict, and likely involve multiple genetic and environmental factors and the innate and adaptive immune systems.
• It is anticipated that future animal model studies and global-wide genomic, proteomic and metabolomic studies will lead to the discover of useful biomarkers, susceptibility factors, and safer drugs.
• Currently, the best way to avoid SADRS is to design new drugs that are not metabolized to reactive metabolites and are very potent.