¿Cómo Realizar el diagnóstico de DILI?: presente y futuro

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Punta Cana 22 Septiembre 2018
I have no relevant financial disclosures
Agenda

• Current state of DILI diagnosis
• New biomarkers
• Clinical case
Rare condition, not well known

Variable symptoms

Absence of diagnostic biomarkers

Exclusion-based diagnosis

Challenging clinical diagnosis
Suspicion of DILI!

- Clinical stepwise approach
- Formal causality assessment process
Stepwise approach to drug-induced liver injury (DILI) diagnosis

Abnormal biochemistry / acute hepatitis

DILI suspicion

Features supporting toxic etiology
Skin involvement, Kidney injury, Previous DILI episodes

Careful enquiry of exposure to HDS, drugs, OTC (record start and stop dates)

Potential pitfalls
Lack of information (e.g. dose, duration), several medications, Hidden HDS and OTCs intake

Search in hepatotoxicity resources (Liver tox)

Calculate biochemical pattern of liver injury

- Hep
  - $R \geq 5$
- Mix
  - $2 > R < 5$
- Chol
  - $R \leq 2$

Search for alternative causes

- Viral infections (HAV, HBV, HCV, HEV, EBV, CMV)
- Alcoholic liver disease, Hepatic ischemia
- Autoantibody titres, ↑IgG
- Benign / malignant biliary obstruction
- Primary biliary cholangitis
- Primary sclerosing cholangitis

Consider liver biopsy if

- Negative or incomplete dechallenge
- Acute or chronic atypical presentation: (vascular disease, chronic hepatitis, fibrosis, microvesicular steatosis)
- Autoimmune hepatitis

EASL CPG DILI. J Hepatol 2018;
# Causality classification categories

<table>
<thead>
<tr>
<th>Causality category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1=definite</td>
<td>The drug is considered as the cause: clear time course, exclusion of other causes, typical pattern of drug-induced liver injury and/or histology suggestive of drug-induced liver injury, absence of other drugs, positive rechallenge if available</td>
</tr>
<tr>
<td>2=Probable</td>
<td>Chronological criteria are suggestive; the etiological work-up reasonably excludes other classical challenging causes; the study drug appears to be the most likely cause even if there is not specific clinical/histological data suggesting specifically the role of a drug</td>
</tr>
<tr>
<td>3=possible</td>
<td>Some criteria are missing or there is a challenging diagnosis; e.g., another drug given within a compatible period; absence of ultrasound examination in a cholestatic/mixed pattern liver injury; absence of adapted viral screening in a cytolytic liver injury (HAV, HBV, HCV, etc).</td>
</tr>
<tr>
<td>4=unlikely</td>
<td>Another cause appears more likely or chronology very atypical</td>
</tr>
<tr>
<td>5=Excluded</td>
<td>Another cause is definitely responsible or time course not compatible; e.g. ALT has already significantly increased before the real onset of the treatment; or onset more than 8 weeks after discontinuation of the treatment; histological pattern not compatible</td>
</tr>
<tr>
<td>6=Not assessable</td>
<td>Available data are too scant to allow a reasonable assessment: not clear chronology; not clear results for liver abnormalities; no data for the etiological assessment</td>
</tr>
</tbody>
</table>
Causality assessment approaches

- Expert opinion
  - Structured
  - Unstructured
- Instruments
  - Algoritms/Scales
  - Probabilistic/Bayesian
  - RUCAM/CIOMS
  - Naranjo
  - Maria & Victorino

DILIN
Causality assessment scales

- Council for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM)

- Maria & Victorino’s clinical diagnostic scale (CDS)

- Naranjo Adverse Drug Reaction Probability Scale (not liver specific!)
CIOMS/RUCAM

Total score

- $\geq 8$: highly likely
- $6 - 7$: probable
- $3 - 5$: possible
- $\leq 2$: unlikely

Latency: 0 to +2
Course after De-challenge: -2 to +3
Risk factors: 0 to +2
Comedication: -3 to 0
Exclusion of other etiologies: -3 to +2
Data on drug hepatotoxicity: 0 to +2
Re-challenge: -2 to +3
# RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury

## 1 Time to onset:

<table>
<thead>
<tr>
<th>Type</th>
<th>Hepatocellular Type</th>
<th>Cholestatic or Mixed Type</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incompatible</td>
<td>Reaction occurred before starting the drug or more than 15 days after stopping the drug (except for slowly metabolized drugs)</td>
<td>Reaction occurred before starting the drug or more than 30 days after stopping the drug (except for slowly metabolized drugs)</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Unknown</td>
<td>When information is not available to calculate time to onset, then case is:</td>
<td>Insufficiently documented</td>
<td></td>
</tr>
</tbody>
</table>

### 1a From the beginning of the drug:

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggestive</td>
<td>5–90 days</td>
<td>1–15 days</td>
<td>5–90 days</td>
<td>1–90 days</td>
<td>+2</td>
</tr>
<tr>
<td>Compatible</td>
<td>&lt;5 or &gt;90 days</td>
<td>&gt;15 days</td>
<td>&lt;5 or &gt;90 days</td>
<td>&gt;90 days</td>
<td>+1</td>
</tr>
</tbody>
</table>

### 1b From the cessation of the drug:

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compatible</td>
<td>≤15 days</td>
<td>≤15 days</td>
<td>≤30 days</td>
<td>≤30 days</td>
<td>+1</td>
</tr>
</tbody>
</table>

## 2 Course:

### 2a After cessation of the drug:

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly suggestive</td>
<td>Decrease ≥ 50% within 8 days</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Suggestive</td>
<td>Decrease ≥ 50% within 30 days</td>
<td>Decrease ≥ 50% within 180 days</td>
</tr>
<tr>
<td>Compatible</td>
<td>Not applicable</td>
<td>Decrease &lt;50% within 180 days</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>No information OR Decrease ≥ 50%, after the 30th day</td>
<td>Persistence or increase or no information</td>
</tr>
<tr>
<td>OR Against the role of the drug</td>
<td>Decrease &lt;50%, after the 30th day OR Recurrent increase</td>
<td>No situation</td>
</tr>
</tbody>
</table>

### 2b If the drug is continued:

<table>
<thead>
<tr>
<th>Type</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Initial Treatment</th>
<th>Subsequent Treatment</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inconclusive</td>
<td>All situations</td>
<td>All situations</td>
<td></td>
<td></td>
<td>-2</td>
</tr>
</tbody>
</table>

## 3 Risk factors:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ethanol</th>
<th>Ethanol or Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Absence</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age of the patient ≥ 55 years</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Age of the patient &lt; 55 years</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## CIOMS/RUCAM REPORT FORM

### RUCAM Causality Assessment of a Drug in a Case of Acute Liver Injury (continued)

<table>
<thead>
<tr>
<th>4 Concomitant drug(s):</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or no information or concomitant drug with incompatible time to onset</td>
<td>0</td>
</tr>
<tr>
<td>Concomitant drug with compatible or suggestive time to onset</td>
<td>-1</td>
</tr>
<tr>
<td>Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset</td>
<td>-2</td>
</tr>
<tr>
<td>Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)</td>
<td>-3</td>
</tr>
</tbody>
</table>

### 5 Search for nondrug causes:

#### Group I (6 causes):
- Recent viral infection with HAV (IgM anti-HAV antibody) or HBV (IgM anti-HBc antibody) or HCV (anti-HCV antibody and circumstantial arguments for non-A, non-B hepatitis; Biliary obstruction (ultrasonography); Alcoholism (AST/ALT ≥ 2); Acute recent hypotension history (particularly if underlying heart disease).

#### Group II:
Complications of underlying disease(s); clinical and/or biological context suggesting CMV, EBV or herpes virus infection.

- All causes—groups I and II—reasonably ruled out | +2 |
- The 6 causes of group I ruled out | +1 |
- Five or 4 causes of group I ruled out | 0 |
- Less than 4 causes of group I ruled out | -2 |
- Non drug cause highly probable | -3 |

### 6 Previous information on hepatotoxicity of the drug:

- Reaction labeled in the product characteristics | +2 |
- Reaction published but unlabeled | +1 |
- Reaction unknown | 0 |

### 7 Response to readministration:

| Positive | Doubling of ALT with the drugs alone | Doubling of AP (or TB) with the drug alone | +3 |
| Compatible | Doubling of ALT with the drugs already given at the time of the first reaction | Doubling of AP (or TB) with the drugs already given at the time of the first reaction | +1 |
| Negative | Increase of ALT but less than N in the same conditions as for the first administration | Increase of AP (or TB) but less than N in the same conditions as for the first administration | -2 |
| Not done or not interpretable | Other situations | Other situations | 0 |

### Investigator Signature

Investigator’s signature: __________________________________________ Date signed: ________ / ______ / ______
CIOMS/RUCAM: Main limitations

- Lack of clear instruction
  - R value based on initial or peak analytical values?

- Time to onset
  - Delayed onset, typically seen with amoxicillin-clavulanate, scores less

- Course of reaction
  - Lack of or little follow-up data, atypical (e.g., fatal and chronic) cases → scores less

- Risk factors
  - Are alcohol consumption, pregnancy and age general risk factors for DILI development?
CIOMS/RUCAM: Main limitations

- **Concomitant drugs**
  - require independent evaluation, which ignore enhanced DILI risk due to drug-drug interactions
  - concomitant drugs taken during the same time often have identical probability scores
  - Sporadic acetaminophen intake can reduce the score of more probable causative agents

- **Previous information on hepatotoxicity potential**
  - Dependent on the user’s interpretation
CIOMS/RUCAM Reproducibility

Within reviewer differences

Between reviewer differences

*Rochon et al Hepatology, 2008; 48(4): 1175-11836
Clinical challenges in DILI diagnosis

- Autoimmune hepatitis
- DILI caused by herbal and dietary supplements
- Underlying liver disease
- Multiple drugs
Autoimmune hepatitis and DILI

Suspected DILI cases with autoimmune features could be:

- Autoimmune hepatitis (drug-independent) coinciding with drug intake
- Autoimmune hepatitis unmasked by drug
- DILI with autoimmune hepatitis-like features
DILI caused by herbal and dietary supplements (HDS)

Increasing use of HDS products
Easily obtained (no need for medical prescription)
Highly advertised
Dissatisfaction with conventional medicines
Presumed to be safer due to their ‘natural’ origin

Increasing rate of HDS-induced liver injury
Chronic viral hepatitis
- Check potential increase in viral load
- Chronic viral hepatitis can be a risk factor for specific forms of DILI, eg HBV and anti-TBC hepatotoxicity

Cirrhosis
- Close attention to temporal sequence between drug intake/cessation and liver enzyme alterations
- Liver profile values prior to drug intake to be used instead of ULN

DILI with underlying hepatic conditions

Chalasani et al, Gastroenterology 2015

p = 0.009
DILI and multiple drug treatments

- Pay close attention to each drug’s temporal sequence
- Consider specific latency features, i.e., delayed onset
- Consider typical phenotypes of the potential causative agents
- Inquire about previous exposure to any of the drugs

It is not always possible to determine a single causative agent!
MetaHeps: a new tool for DILI causality assessment in polymedicated patients

- Monocyte-derived hepatocyte-like (MH)
- High sensitivity and specificity
- Requires validation

Kullak-Ublick GA, Andrade RJ et al. Gut 2017
Current liver biomarkers in DILI

**General liver injury serum biomarkers**

- **ALT**
  - Leakage biomarkers indicating cell injury, highly expressed in hepatocytes and biliary cells but not specific to these cell types

- **AST**

- **ALP**

- **TBL**
  - Liver specific biomarker that reflects liver dysfunction, but appears later during disease progression
Exploratory circulating biomarkers for DILI

- Hepatocyte
  - Hepatocyte Injury
  - miR-122
  - Keratin-18 (FL)
  - Keratin-18 (CC)
  - GLDH
  - Apoptosis
  - Mitochondrial Dysfunction

- Immune cell
  - HMGB1
  - M-CSF1
  - Reconstitution
  - HMGB1-Acetyl
  - Immune Cell Activation

courtesy: Jonathan Moggs
miRNAs in DILI patients

Starkey Lewis et al, Hepatology, 2011
Starkey Lewis et al, Hepatology, 2013
Published biomarker study

Collaborative effort between:

- Safer and Faster Evidence-Based Translation (SAFE-T), Europe
- Critical Path Institute’s Predictive Safety Testing Consortium (PSTC), USA
- Drug-Induced Liver Injury Network (DILIN), USA

Candidate Biomarkers for the Diagnosis and Prognosis of Drug-Induced Liver Injury: An International Collaborative Effort

Rachel J. Church,1,2* Gerd A. Kullak-Ublick,3,4* Jiri Aubrecht,5 Herbert L. Bonkovsky,6 Naga Chalasani,7 Robert J. Fontana,8 Jens C. Goepfert,9 Frances Hackman,10 Nicholas M. P. King,11 Simon Kirby,10 Patrick Kirby,12 John Marcinak,12 Sif Ornarsdottir,13 Shelli J. Schomaker,5 Ina Schuppe-Koistinen,14 Francis Wolenski,12 Nadir Arber,15 Michael Merz,3,16 John-Michael Sauer,11 Raul J. Andrade,17 Florian van Bömmel,18 Thierry Poynard,19* and Paul B. Watkins1,2*
SAFE-T data

Mechanism-based biomarkers
HMGB1 and Cytokeratin 18: immune activation and necrosis

ALT (U/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DILI</td>
<td>123</td>
</tr>
<tr>
<td>HV</td>
<td>181</td>
</tr>
</tbody>
</table>

Acetylated HMGB1 (ng/mL)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DILI</td>
<td>121</td>
</tr>
<tr>
<td>HV</td>
<td>154</td>
</tr>
</tbody>
</table>

Full length K18 (U/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DILI</td>
<td>113</td>
</tr>
<tr>
<td>HV</td>
<td>192</td>
</tr>
</tbody>
</table>
SAFE-T data

Biomarker values at DILI initiation classified by causative drug and healthy volunteers (HV)

MCSFR (ng/mL), immune activation
SAFE-T data

Biomarker values at DILI initiation classified by fulfillment of Hy’s law* criteria

MCSFR (ng/mL), immune activation

*Hy’s law definition: ALT >3 × ULN and TBL >2 × ULN
DILIN data: Presentation biomarker data by outcome up to month 6

ALT (U/L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Related Death/Transplant</td>
<td>16</td>
</tr>
<tr>
<td>Chronic DILI</td>
<td>21</td>
</tr>
<tr>
<td>Recovery</td>
<td>127</td>
</tr>
</tbody>
</table>

AUROC value Liver related death/transplant vs. Recovery: 0.57

Church et al Hepatology 2018 in press
DILIN data:
Presentation biomarker data by outcome up to month 6

Total bilirubin (µmol/L)

<table>
<thead>
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<th>N</th>
</tr>
</thead>
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<td>Liver Related Death/Transplant</td>
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</tr>
<tr>
<td>Recovery</td>
<td>127</td>
</tr>
</tbody>
</table>

AUROC value Liver related death/transplant vs. Recovery: 0.85

Church et al Hepatology 2018 in press
DILIN data: 
Presentation biomarker data by outcome up to month 6

Osteopontin (ng/ml)

AUROC value Liver related death/transplant vs. Recovery: 0.83

Church et al Hepatology 2018 in press
Genome-wide association studies

- Genotyping for many (500,000 to 1 million) genetic polymorphisms (SNPs) using array-based technology
  - These polymorphisms occur throughout the genome on all genes and account for most common genetic variability
- Open nature of method means most possible genetic associations screened for
- Successful implementation usually requires large numbers of samples (cases and controls)
- Pharmacogenetic applications
  - Adverse drug reactions
  - Response to drugs such as warfarin and clopidogrel
Susceptibility to Amoxicillin-Clavulanate-Induced Liver Injury Is Influenced by Multiple HLA Class I and II Alleles


201 amoxicillin-clavulanate DILI patients (96 English, 56 American and 49 Spanish cases) and 532 controls
Chromosome 6, HLA associations

**AmoxClav**
- HLA-DRB1*1501-DQB1*0602 (class II)
- HLA –A*0201 (class I) North European

201 amoxicillin-clavulanate DILI patients
(96 English, 56 American and 49 Spanish cases) and 532 controls

Lucena et al, *Gastroenterology* 2011
Association of Liver Injury From Specific Drugs, or Groups of Drugs, With Polymorphisms in HLA and Other Genes in a Genome-Wide Association Study

- HLA-A*33:01 is a strong risk factor for terbinafine DILI (n=14): OR 40.53 [12.51-288.9](p = 6.7x10^{-10})
- All A*33:01 positive terbinafine cases carry HLA A*33:01-B*14:02-C*08:02 haplotype
  - OR_{haplotype} 70; (p=8.7x10^{-13}).

Flucoxacillin: HLA-B*57:01 OR=80.6
AmoxClav, lumiracoxib: HLA-DRB1*1501-DQB1*0602
HLA-A*0201
Ximelagatran DRB1*0701-DQA1*0201
Lapatinib DRB1*0701-DQA1*0201
Flupirtine DRB1*16:01-DQB1*05:02
Terbinafine (chol/mix injury) HLA-A*33:01

DILI GWAS: chromosome 6 (HLA genes)

OR=80,
low predictive positive value
High predictive negative value

<table>
<thead>
<tr>
<th>Test: HLA type</th>
<th>% positive in DILI cases</th>
<th>% positive in ‘normal’ population</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*15:01</td>
<td>57%-67% (Amoxicillin-clavulanate)</td>
<td>15%-20%</td>
</tr>
<tr>
<td>B*57:01</td>
<td>84%-87% (Flucloxacillin)</td>
<td>6%</td>
</tr>
<tr>
<td>A*31:01</td>
<td>17% (Carbamazepine)</td>
<td>2%</td>
</tr>
<tr>
<td>DRB1<em>16:01-DQB1</em>05:02</td>
<td>25% (Flupirtine)</td>
<td>1%</td>
</tr>
<tr>
<td>A*33:01</td>
<td>80% (Ticlopidine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (Methyldopa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (Enalapril)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43% (Fenofibrate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43% (Terbinafine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40% (Sertraline)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20% (Erythromycin)</td>
<td></td>
</tr>
<tr>
<td>B*35:02</td>
<td>16% (Minocycline)</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
Clinical Case

- 35-year-old man, previously healthy
- June 2018 he complained from abdominal discomfort, jaundice, light-colored stools, dark urine and itching
- He had been taken terbinafine for skin fungal infection until a week before symptoms. No acetaminophen.
- No recent travels, no personal history or risk factors for liver disease
- Peak AST 261 U/L, ALT 519 U/L, GGT 144 U/L, ALP 173 U/L, total bilirubin 6.1 mg/dL (conjugated bilirubin 4.4 mg/dL)
- Coagulation parameters were normal
Stepwise approach to drug-induced liver injury (DILI) diagnosis

- Abnormal biochemistry / acute hepatitis
  - DILI suspicion

**Features supporting toxic etiology**
- Skin involvement,
- Kidney injury,
- Previous DILI episodes

**Careful enquiry of exposure to HDS, drugs, OTC**
- (record start and stop dates)

**Potential pitfalls**
- Lack of information (e.g. dose, duration), several medications,
- Hidden HDS and OTCs intake

**Search in hepatotoxicity resources**
- (Liver tox)
TERBINAFINE

OVERVIEW

Introduction
Terbinafine is an orally and topically active allylamine fungicidal agent which is used to treat superficial fungal infections of the skin and nails. Terbinafine has been clearly linked to rare instances of acute liver injury that can be severe and sometimes fatal.

Background
Terbinafine (ter’bin a feen) is a synthetic allylamine derivative that has potent activity against many dermatophytes that affect skin and nails, including Epidermophyton floccosum, Trichophyton mentagrophytes and Trichophyton rubrum. The antifungal activity of terbinafine is believed to be due to the selective inhibition of fungal squalene epoxidase, which increases squalene to toxic levels, thus killing the fungal cell. Terbinafine was approved for use in the United States in a topical form in 1992 and as an oral antifungal agent in 1998. Topical terbinafine is available over-the-counter as a 1% cream or spray for treatment of dermatophyte infections of the skin (tinea pedis, cruris or corporis). Oral terbinafine is available by prescription only in tablets of 250 mg generically and under the brand name of Lamisil. Oral terbinafine is used in the therapy of onychomycosis or fungal infections of the fingernails or toenails (tinea unguium) typically in a dose of 250 mg once daily for 6 weeks (fingernails) or 12 weeks (toenails). The most common side effects of terbinafine include gastrointestinal disturbances, headache, change in taste and rash.

Hepatotoxicity
Drug induced liver injury due to terbinafine was identified shortly after its introduction into clinical use. Clinical cases have been reported with a range of severity. In the United Kingdom, dedicated databases maintain records of cases. The information is available from the following link:

Drug-Induced Liver Injury in the UK (DILIT)
Introduction
Terbinafine is an orally and topically active allylamine fungicidal agent which is used to treat superficial fungal infections of the skin and nails. Terbinafine has been clearly linked to rare instances of acute liver injury that can be severe and sometimes fatal.

Background
Terbinafine (ter’ bin a feen) is a synthetic allylamine derivative that has potent activity against many dermatophytes that affect skin and nails, including Epidermophyton floccosum, Trichophyton mentagrophytes and Trichophyton rubrum. The antifungal activity of terbinafine is believed to be due to the selective inhibition of fungal squalene epoxidase, which increases squalene to toxic levels, thus killing the fungal cell. Terbinafine was approved for use in the United States in a topical form in 1992 and as an oral antifungal agent in 1998. Topical terbinafine is available over-the-counter as a 1% cream or spray for treatment of dermatophyte infections of the skin (tinea pedis, cruris or corporis). Oral terbinafine is available by prescription only in tablets of 250 mg generically and under the brand name of Lamisil. Oral terbinafine is used in the therapy of onychomycosis or fungal infections of the fingernails or toenails (tinea unguium) typically in a dose of 250 mg once daily for 6 weeks (fingernails) or 12 weeks (toenails). The most common side effects of terbinafine include gastrointestinal disturbances, headache, change in taste and rash.

Hepatotoxicity
Drug induced liver injury due to terbinafine was identified shortly after its introduction into medical use. Oral therapy with terbinafine is associated with elevations in serum aminotransferases in less than 1% of patients and the elevations are generally asymptomatic and resolve without stopping therapy. The estimated probability of developing elevated serum aminotransferase levels requiring stopping treatment is about 0.31% for 2 to 6 weeks’ treatment and 0.44% for treatment longer than 8 weeks.

Clinically apparent liver injury from terbinafine occurs rarely (1 in 50,000 to 120,000 prescriptions), but many case reports and even case series have been described in the literature. Liver injury usually arises within the first 6 weeks of therapy. The pattern of injury can be either hepatocellular or cholestatic initially, but typically evolves into a cholestatic pattern which can be prolonged (Cases 1 and 2). Some cases may progress to vanishing bile duct syndrome. Signs of hypersensitivity (rash, fever, eosinophilia) are not common and, when present, are generally mild-to-moderate in severity. Autoantibody formation is rare. In addition, cases with severe hepatocellular injury with acute liver failure have been described. These instances are marked by precipitous onset with marked elevations in serum aminotransferase levels and progressive jaundice and hepatic failure. Terbinafine has also been implicated in cases of Stevens-Johnson syndrome, in which case the hepatic injury may be overshadowed by rash and allergic symptoms.

Likelihood score: B (highly likely cause of clinically apparent liver injury).
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A</td>
<td>The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described</td>
</tr>
<tr>
<td>Category B</td>
<td>The drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described</td>
</tr>
<tr>
<td>Category C</td>
<td>The drug is probably linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series</td>
</tr>
<tr>
<td>Category D</td>
<td>Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury</td>
</tr>
<tr>
<td>Category E</td>
<td>Despite extensive use, no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is not believed or is unlikely to cause liver injury</td>
</tr>
<tr>
<td>Category E*</td>
<td>The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is unproven, but suspected to cause liver injury</td>
</tr>
<tr>
<td>Category X</td>
<td>Finally, for medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as “unknown”</td>
</tr>
</tbody>
</table>
# Drugs in category B

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class/Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amodiaquine</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>Muscle relaxant</td>
</tr>
<tr>
<td>Cyproterone</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Levofloxacin/Ofloxacin</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Antimicrobial</td>
</tr>
</tbody>
</table>
Stepwise approach to drug-induced liver injury (DILI) diagnosis

Abnormal biochemistry / acute hepatitis

DILI suspicion

Features supporting toxic etiology
Skin involvement, Kidney injury, Previous DILI episodes

Careful enquiry of exposure to HDS, drugs, OTC (record start and stop dates)

Potential pitfalls
Lack of information (e.g. dose, duration), several medications, Hidden HDS and OTCs intake

Search in hepatotoxicity resources (Liver tox)

Calculate biochemical pattern of liver injury

<table>
<thead>
<tr>
<th>Hep</th>
<th>Mix</th>
<th>Chol</th>
</tr>
</thead>
<tbody>
<tr>
<td>R ≥ 5</td>
<td>2 &gt; R &lt; 5</td>
<td>R ≤ 2</td>
</tr>
</tbody>
</table>

R = ALT x ULN/ALP x ULN

Search for alternative causes

- Viral infections (HAV, HBV, HCV, HEV, EBV, CMV)
- Alcoholic liver disease, Hepatic ischemia
- Autoantibody titres, ↑ IgG
- Benign / malignant biliary obstruction
- Primary biliary cholangitis
- Primary sclerosing cholangitis

Consider liver biopsy if

- Negative or incomplete dechallenge
- Acute or chronic atypical presentation: (vascular disease, chronic hepatitis, fibrosis, microvesicular steatosis)
- Autoimmune hepatitis

EASL CPG DILI. J Hepatol 2018;
Clinical Case

- No evidence of hepatitis A, B, C or E.
- Other viral hepatitis such as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and human immunodeficiency virus (HIV) also excluded.
- Autoimmune serology: ASMA + 1/320, antiF-actin Ab+. IgG normal
- Abdominal ultrasound: no liver abnormalities.
- Colangiography by MR: no bile duct abnormalities
- Liver biopsy: Cholestasis, portal inflammation, eosinophil, no fibrosis
Clinical Case

- Differential diagnosis:

  autoimmune hepatitis (ASMA +)

  vs

  Terbinafine induced liver injury (drug exposure)

What tools can we use to further discriminate between both entities?
<table>
<thead>
<tr>
<th>Case</th>
<th>Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT_ULN</td>
<td>8.5</td>
</tr>
<tr>
<td>AP_ULN</td>
<td>1.47</td>
</tr>
<tr>
<td>R</td>
<td>5.7</td>
</tr>
<tr>
<td>DILI Type</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Exposure</td>
<td>first</td>
</tr>
<tr>
<td>Time from drug intake until reaction</td>
<td>2</td>
</tr>
<tr>
<td>Risk factors_Alcohol</td>
<td>0</td>
</tr>
<tr>
<td>Risk factors_Age ≥ 55 y</td>
<td>0</td>
</tr>
<tr>
<td>Course of reaction</td>
<td>2</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>0</td>
</tr>
<tr>
<td>Exclusion of non-drug</td>
<td>2</td>
</tr>
<tr>
<td>Previous information on hepatotoxicity</td>
<td>2</td>
</tr>
<tr>
<td>Response to re-administration</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td>8</td>
</tr>
<tr>
<td>DILI</td>
<td>Probable</td>
</tr>
</tbody>
</table>
## Genetic Tests as DILI biomarkers

<table>
<thead>
<tr>
<th>Test: antibodies</th>
<th>% positive in AIH cases</th>
<th>% + in ‘normal’ population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA 1:60</td>
<td>68%-75%</td>
<td>15% (&lt;40 ♂) - 24% (&gt;40 ♂)</td>
</tr>
<tr>
<td>ASMA</td>
<td>52%-59%</td>
<td>Up to 43%</td>
</tr>
<tr>
<td>IgG &gt;1600 mg/dL</td>
<td>86%</td>
<td>5%</td>
</tr>
<tr>
<td>Anti-LKM</td>
<td>4%-20%</td>
<td>1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test: HLA type</th>
<th>% positive in DILI cases</th>
<th>% + in ‘normal’ population</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*15:01</td>
<td>57%-67% (Amoxicillin-clavulanate)</td>
<td>15%-20%</td>
</tr>
<tr>
<td>B*57:01</td>
<td>84%-87% (Flucloxacillin)</td>
<td>6%</td>
</tr>
<tr>
<td>A*31:01</td>
<td>17% (Carbamazepine)</td>
<td>2%</td>
</tr>
<tr>
<td>DRB1<em>16:01-DQB1</em>05:02</td>
<td>25% (Flupirtine)</td>
<td>1%</td>
</tr>
<tr>
<td>A*33:01</td>
<td>80% (Ticlopidine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (Methyldopa)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (Enalapril)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43% (Fenofibrate)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>43% (Terbinafine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40% (Sertraline)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20% (Erythromycin)</td>
<td></td>
</tr>
<tr>
<td>B*35:02</td>
<td>16% (Minocycline)</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
Clinical Case

The subject was carrier of $HLA\ A^{*33:01}$

Final diagnosis: Terbinafine-induced liver injury
Take home messages

• Idiosyncratic drug-induced liver injury remains a difficult to diagnose liver disease
• A detailed clinical history and exhaustive work-up for alternative etiologies is paramount
• RUCAM scale may help in the diagnostic approach but need to be refined
• New circulating biomarkers hold promise for improved sensitivity and prognosis in hepatotoxicity but biomarkers specific for DILI have yet to be identified
• Testing of genetic variants associated with the risk of DILI is not helpful for preventive purposes but may be of value for diagnosis in selected cases
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ORISE