Role of Liver Histopathology in Drug-Induced Liver Injury

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FDA-PhRMA-AASLD Drug-Induced Liver Injury Workshop
March, 2010
Liver Biopsies and DILI

• The utility of the liver biopsy, beyond its use as a sophisticated diagnostic test, has not been defined in DILI.
  – What information can the liver biopsy provide?
  – How do findings on liver biopsy correlate with the biochemical presentation?
  – Can the liver biopsy help predict outcome?
An Illustrative Case

- 42 y.o. male with chronic hepatitis B
- Enrolled in a 6 month trial of a promising anti-HBV drug Fialuridine
- Previously participated in a 4 week trial (10 months prior to current trial) of the same drug, no symptoms of toxicity noted
• At week 11, the drug was stopped due to symptoms of neurotoxicity
• Three weeks later complained of lethargy, weakness, anorexia, myalgias and nausea
• Labs: Bili 5.8, PT 15.4, Alb 2.8, Ammonia 77, lactate 18.8
Explanted Liver
What did we learn from the pathology?

- **Overall pattern**: Microvesicular steatosis superimposed on pre-existing chronic hepatitis B
- **Not a pattern of fulminant hepatitis**, progression of underlying liver disease or confluent necrosis
- Microvesicular steatosis is frequently the result of mitochondrial injury from drugs and toxins (notably ddl and AZT), also seen in rare disorders like acute fatty liver of pregnancy, alcoholic foamy degeneration

Pathology confirmed DILI, excluded competing injury patterns, accounted for underlying disease and provided a clue to the mechanism of injury
Role of Liver Biopsy in DILI

- Characterize the morphologic changes
  - Morphologic changes may confirm drug injury by matching known/reported patterns
  - Morphologic changes may suggest mechanism of injury
- Assess the degree of injury
- Rule out other causes of hepatic injury
- May help to make diagnosis of DILI in complex cases by careful clinical-pathological correlation
- Sometimes biopsy can exclude DILI, permitting continued use of a necessary drug
<table>
<thead>
<tr>
<th>Morphologic Change</th>
<th>Toxic Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvesicular Steatosis</td>
<td>Inhibition of mitochondrial $\beta$–oxidation; hepatocellular energy shortage via mitochondrial injury</td>
</tr>
<tr>
<td>Zonal necrosis</td>
<td>Metabolite toxicity associated with P450 enzyme gradients, oxidative status</td>
</tr>
<tr>
<td>Hepatocellular cholestasis</td>
<td>Inhibition of bile transport proteins</td>
</tr>
<tr>
<td>Duct destruction</td>
<td>Concentration of toxic metabolites in bile; injury to peribiliary vascular plexus</td>
</tr>
<tr>
<td>Sinusoidal obstruction syndrome</td>
<td>Endothelial cell damage</td>
</tr>
</tbody>
</table>
Biopsy Evaluation in DILIN

• Blinded histologic review by a single hepatopathologist
• Classification of the overall disease pattern into one of eighteen categories
• Semi-quantitative evaluation of 50 individual features
DILIN Liver Disease Patterns
(after Zimmerman)

- Acute Hepatitic
- Chronic Hepatitic
- Acute Cholestatic
- Chronic Cholestatic
- Mixed Hepatitic-Cholestatic
- Granulomatous
- Macrosteatotic
- Microsteatotic
- Steatohepatitic
- Necrosis, zonal
- Necrosis, non-zonal
- Submassive necrosis
- Vascular
- Hepatocellular alteration
- Nodular Regenerative Hyperplasia
- Unclassifiable mixed
- Minimal changes
- Absolutely normal
DILIN – Histologic Feature Recording

- **Inflammation (11)** - Mod. Ishak HAI (4 scales), granulomas, plasma cells, eos, PMNs, lymphoid aggregates, bridging necrosis, lipogranulomas
- **Fibrosis (2)** - Ishak stage, perisinusoidal fibrosis
- **Steatosis (3)** - Micro/macro, location, grade (HALT-C method)
- **Cholestasis/Ducts (10)** – Overall degree, Hepatocellular, canalicular, cholangiolar, ductal, chronic, ductular reaction, duct injury, duct paucity, acute cholangitis
- **Hepatocellular injury (6)** - Ballooning, apoptosis, coagulative/confluent necrosis (location and degree), lobular disarray, hepatocyte rosettes
- **Vascular (6)** - VOD, Venulitis, Portal venopathy, hemorrhage, sinusoidal dilation/peliosis, NRH
- **Miscellaneous changes (6)** - Ground glass, inclusions, Mallory’s hyalin, stellate cells, glycogenosis, talc
- **Special stains (5)** - Iron (hepatocellular, REC), Copper, PAS
- **Size** (No. of portal areas)
Acute Hepatitic Injury
(DILIN case- Probable Atomoxitine DILI)

- Lobular predominant lymphocytic-plasmacytic infiltration +/- hepatocellular degeneration, lobular disarray, no cholestasis
- DDx: Acute Viral or Autoimmune Hepatitis, Early chronic hepatitis or PBC, Non-specific reactive changes
- Ex: Isoniazid, sulfamides, rifampin
Chronic Hepatitic Injury
(DILIN case – Likely Nitrofurantoin injury)

• Portal predominant, interface hepatitis, portal-based fibrosis, no cholestasis
• DDx: Chronic viral or autoimmune hepatitis, early PBC/PSC
• Isoniazid, minocycline, methyldopa
Acute Cholestatic
DILIN Case – Probable Azithromycin injury

- Pure hepatocellular or canalicular cholestasis, mild injury and inflammation, mild portal changes
- DDx: Sepsis, post-surgical, acute LDO, cholestasis of pregnancy, benign recur cholestasis
- Androgens/Estrogens, Chlorpromazine, Erythromycin
Chronic Cholestatic
DILIN case – Likely Cefuroxime injury

• Duct injury/paucity with cholate stasis, copper accum, fibrosis, may have chronic hep changes
• DDx: PBC, PSC, Chronic LDO, chronic hepatitis with duct injury, GVHD
• Ex: Chlorpromazine, imipramine, thiabendazole
Mixed Hepatitic-cholestatic injury
(DILIN Case – Likely Sevoflurane injury)

- Combination of hepatitis (usually acute) with canalicular/hepatocellular cholestasis, duct injury
- Acute cholestatic viral hepatitis, GVHD
- Isoniazid, phenylbutazone, chlorpropamide, diphenylhydantoin
Zonal Necrosis
(Acetaminophen Injury)

• Coagulative/confluent necrosis and/or hepatocyte drop-out in a zonal or pan-acinar pattern with little inflammation
• Hypoxic-ischemic injury, shock
• Acetaminophen
Relationship of Biopsy Findings to Biochemical Tests and Presentation
Issues

• Is the biochemically defined injury “R” reflective of the histological injury pattern?
  – Typical for publications to equate elevated transaminases to “hepatitis” or “necrosis” etc.

• “R” is typically defined at the “onset” of injury—is there another time point which would be a better comparator?

• How do individual histologic findings relate to serum enzyme levels?
Hypothetical DILI Enzyme Profile

- ALT MAX
- AP MAX
- BIOPSY

Time (days)

X ULN

ALT MAX
AP MAX
BIOPSY
ONSET
Data Analysis

• All DILIN cases with biopsies adjudicated as Probable, Very Likely or Definite DILI
• Laboratory data (AST, ALT, AP, tBili, R) at 5 points defined by profile or protocol
  – Onset, ALT Max, AP Max, At Biopsy, Baseline
  – “At biopsy” labs were within 7 days
Relative Frequency of Pathology Patterns in DILIN Patients with at Least Probable Causality Determination

N = 106

“Other” Includes
1 Granulomatous Hep
2 Steatohepatitic
2 Hepatocyte Alteration
3 Unclassifiable
### Distribution of Pathology by Onset Biochemical Injury

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Total</th>
<th>Hepatocellular</th>
<th>Mixed</th>
<th>Cholestatic</th>
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<td>Totals with Bx Eval</td>
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<td>53</td>
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Chi square p=0.11

(55%) (26%) (20%)
### Distribution of Pathology by Biochemical Injury at Biopsy

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<th>Cholestatic</th>
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<td>41</td>
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Chi square p=0.018

(53%) (21%) (27%)
Variation of “R” at Onset with Pathologic Pattern of Injury
# Range of Injury by Pattern

(Comparison to Zimmerman)

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<th>DILIN (onset labs)</th>
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<th>Zimmerman</th>
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<tr>
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<td>ALT/ULN</td>
<td>AP/ULN</td>
<td>ALT/ULN</td>
<td>AP/ULN</td>
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<td>0.7-4x</td>
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<td>0.6-4x</td>
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<td>1-6x</td>
<td>1-5x</td>
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<td>Mixed H-C</td>
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<td>1-5x</td>
<td>1-10x</td>
<td>&gt;3x</td>
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<td>Zonal Necrosis</td>
<td>6-140x</td>
<td>0.7-1.4</td>
<td>100-1000x</td>
<td>1-3x</td>
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<td>Feature</td>
<td>Serum Biochemistries at Time of Biopsy</td>
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<td></td>
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<tr>
<td>------------------------------</td>
<td>----------------------------------------</td>
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<tr>
<td></td>
<td>R $\geq$ 5</td>
<td>ALT $\geq$ 5xULN</td>
<td>AP $\geq$ 2xULN</td>
<td>tBili $\geq$ 3</td>
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<td>Interface Hepatitis</td>
<td>0.025</td>
<td>0.0016</td>
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<td>&gt;0.2</td>
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<td>Lobular Inflammation</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
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<td>Portal Inflammation</td>
<td>&gt;0.2</td>
<td>0.18</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
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<td>Granulomas</td>
<td>0.057</td>
<td>&gt;0.2</td>
<td>0.0005</td>
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<td>Plasma Cells</td>
<td>0.043</td>
<td>0.0009</td>
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<td>Eosinophils</td>
<td>&gt;0.2</td>
<td>0.18</td>
<td>0.19</td>
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<td>Bridging Necrosis</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
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<tr>
<td>Canalicicular Cholestasis</td>
<td>&gt;0.2</td>
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<td>&gt;0.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Chronic Cholestasis</td>
<td>0.089</td>
<td>&gt;0.2</td>
<td>0.11</td>
<td>&gt;0.2</td>
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<tr>
<td>Ductular Reaction</td>
<td>0.11</td>
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<tr>
<td>Ductular Injury</td>
<td>(0.047)</td>
<td>&gt;0.2</td>
<td>0.037</td>
<td>0.0007</td>
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<tr>
<td>Ballooning</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
<td>(0.016)</td>
<td>&gt;0.2</td>
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<tr>
<td>Apoptosis</td>
<td>0.0001</td>
<td>&gt;0.0001</td>
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<td>Coag/Confluent Necrosis</td>
<td>0.15</td>
<td>0.005</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
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</table>
Distribution of Inflammation Severity with respect to ALT at Biopsy

**Interface Hepatitis**
- ALT<5ULN
- ALT>5ULN

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<tr>
<th>Interface</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>ALT&lt;5ULN</td>
<td>5</td>
<td>15</td>
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<td>45</td>
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<tr>
<td>ALT&gt;5ULN</td>
<td>10</td>
<td>25</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

p=0.0016

**Lobular Inflammation**
- ALT<5ULN
- ALT>5ULN

<table>
<thead>
<tr>
<th>Lobular</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
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<tr>
<td>ALT&gt;5ULN</td>
<td>10</td>
<td>25</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

p<0.0001
Distribution of Necrosis Severity with respect to ALT at Biopsy

- **Bridging/MultiLob Necrosis**
  - ALT<5ULN: 100%
  - ALT>5ULN: 90%
  - p=0.0016

- **Acidophil bodies**
  - 0: 50%
  - <1/hpf: 40%
  - 1-3/hpf: 30%
  - >3/hpf: 20%
  - p<0.0001
Canalicular Cholestasis and Duct Injury in Relation to total Bilirubin at Biopsy

Duct Injury

- None
- One Duct
- Mult Ducts

Canalicular Cholestasis

- Absent
- Present

p=0.0077

p<0.0001
Relationship of Biochemistry to Histology

• Biochemical Classification using “R” only loosely correlates with the actual histologic injury pattern
  – Patients with “cholestatic” R values can have an acute hepatitis pattern on biopsy
  – Patients with “hepatocellular” R values can have acute or chronic cholestasis
  – Biochemical classification not useful for variant patterns: e.g. granulomatous and steatohepatitic

• Individual biochemical tests (ALT, AP, Bilirubin) do correlate with some histologic features in a rational way

• Some histological features, such as the cell types involved in the injury, are not reflected in laboratory tests
Liver Histology and Outcome in DILI
• Meta-analysis of 570 case reports of DILI with liver biopsy
• Study evolved from a study of disulfiram DILI in which these factors were associated with outcome
• “Eosinophilia” was recorded if patient had any degree of eosinophilic infiltrate on biopsy
• “Hepatic necrosis” was recorded if biopsy was described as having any of the following: “centrilobular drop-out, centrilobular necrosis, confluent necrosis, panlobular necrosis, submassive necrosis and massive necrosis”
• These factors were related to fatal outcome

<table>
<thead>
<tr>
<th></th>
<th>Not-Fatal</th>
<th>Fatal</th>
<th>p</th>
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<tbody>
<tr>
<td>Eosinophilia</td>
<td>48%</td>
<td>18.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatic Necrosis</td>
<td>24%</td>
<td>84%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Histopathology and Outcome in the DILIN cohort

• Reviewed pathology data and DILIN severity score on patients in the database with both a biopsy reviewed and causality completed with DILI causality of probable or greater

• 111 patients met this criterion

• Age 49.8 (7.8 to 87.2 years)

• 41% Male

• Analyzed individual histologic observations including necrosis, inflammation, fibrosis, cholestasis and others comparing fatal vs non-fatal and severe/fatal vs less than severe
DILIN Severity Score

**Mild**
Elevated ALT, AST or AP, tBili <2.5, no coagulopathy (INR<1.5)

**Moderate**
Elevated ALT, AST or AP, and tBili >2.5 or coagulopathy (INR>1.5)

**Moderate-Hospitalized**
As for Moderate but patient is either hospitalized for DILI or pre-existing stay is prolonged

**Severe**
Elevated ALT, AST or AP, with tBili >2.5 and either hepatic decompensation or other DILI-related organ failure

**Fatal**
DILI related death or transplantation
<table>
<thead>
<tr>
<th>Condition</th>
<th>Mild</th>
<th>Moderate</th>
<th>Mod-Hosp</th>
<th>Severe</th>
<th>Fatal</th>
<th>Total</th>
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<td><strong>Total</strong></td>
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### Relationship of Most Common Pathology Pattern with Outcome

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<tr>
<th>Pathology Pattern</th>
<th>Mild</th>
<th>Moderate</th>
<th>Mod-Hosp</th>
<th>Severe</th>
<th>Fatal</th>
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<tr>
<td>Acute Hepatitis</td>
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<td>5</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>27</td>
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<td>3</td>
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<tr>
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<tr>
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<tr>
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<td>2</td>
<td>2</td>
<td>8</td>
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<td><strong>Total</strong></td>
<td><strong>22</strong></td>
<td><strong>21</strong></td>
<td><strong>44</strong></td>
<td><strong>16</strong></td>
<td><strong>8</strong></td>
<td><strong>111</strong></td>
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</table>
Histologic Features and Outcome

- Individual features assessed on biopsy were evaluated for non-random association with either severe/fatal or fatal outcome.
- Analysis somewhat limited by the small number of fatal cases (8/111).
- Very few features showed any suggestion of correlation with outcome with a few exceptions:
  - Granulomas associated with better outcome.
  - Eosinophils showed a non-significant trend to better outcome.
  - The presence of multiacinar or bridging necrosis but not the degree of confluent necrosis was associated with poor outcome.
  - Ductular reaction was associated with poor outcome.
Granulomas and Eosinophils

**Granulomas**

- No Granulomas: 46 cases
- Microgran: 58 cases
- Epith Gran: 6 cases

**Eosinophils**

- None/Mild: 56 cases
- Increased: 54 cases

- p=0.008
- p=0.06

(46) (58) (6) (56) (54)
Necrosis

Bridging Necrosis or Multiacinar Necrosis

Percent of Cases

Not Present: (77)
Present: (33)

Not Fatal
Fatal

p=0.004

Confluent Necrosis Fraction

<33%:
(99)

>33%:
(11)

Not Fatal
Fatal

p=0.18
Ductular Reaction

Percent of Cases

<table>
<thead>
<tr>
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<th>Not Severe</th>
<th>Severe/Fatal</th>
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<tr>
<td>None/Mild</td>
<td>(67)</td>
<td>(42)</td>
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<td>Prominent</td>
<td>(42)</td>
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</table>

p=0.004

Not Severe | Severe/Fatal

<table>
<thead>
<tr>
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<th>Not Fatal</th>
<th>Fatal</th>
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<tbody>
<tr>
<td>None/Mild</td>
<td>(67)</td>
<td>(42)</td>
</tr>
<tr>
<td>Prominent</td>
<td>(42)</td>
<td>(42)</td>
</tr>
</tbody>
</table>

p=0.005
Ductular Reaction

• Ductular reaction is a lesion characterized by small ductules, often without a visible lumen, fibrosis and inflammatory cells

• In impaired hepatic regeneration, it has been shown to be a secondary pathway of hepatocyte progenitor replication

• In some chronic liver diseases, it has been associated with replicative failure in primary hepatocytes
  – Richardson MM et al., Gastroenterology 2007;133: 80–90;
Conclusions

• Biochemical classification of injury along with the results of specific laboratory tests at most allow an educated guess at the histologic pattern of injury

• Specific features on biopsy may be useful in prognosis

• Liver biopsy remains a valuable tool that may give insight into mechanism of injury, potential for chronicity and help with difficult clinical differential diagnoses
Acknowledgments

DILIN Investigators

– Herbert Bonkovsky (*Petr Protiva*)-UConn
– Naga Chalasani-IU
– Timothy Davern-UCSF
– Robert Fontana-UMich
– Paul Watkins-UNC
– William Lee-UTSW
– Andrew Stolz-USC
– Jayant Talwalkar-Mayo
– Victor Navarro-Jefferson/UPenn
– James Rochon-DCRI
– Jose Serrano-NIDDK Project Officer