A Pre-marketing ALT Signal Predicts Post-Marketing Liver Safety

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Background: Drug induced liver injury risk

- Drug-induced hepatotoxicity is one of the leading causes of drug attrition during drug development and drug withdrawal post-marketing
- Leading cause of acute liver failure in the US
- Critical to identify sensitive measures that signal the potential for drug-induced liver injury (DILI) during drug development

Background: Identifying drugs with potential for hepatotoxicity

- Idiosyncratic hepatocellular injury can occur with many drugs but annual incidence of serious injury is low (1/100,000)
- Clinical trials often lack the sample size necessary to find severe injury so may be difficult to see prior to marketing
- Mild elevations in serum transaminases, however, can commonly be seen during pre-marketing clinical trial phases and these elevations are reasonably sensitive markers of hepatocellular injury

Background: Identifying drugs with potential for hepatotoxicity

• In clinical trials, nearly all drugs associated with hepatotoxicity have been accompanied by an increased frequency of ALT $\geq 3\times$ULN relative to placebo or control*

• Relationship b/w increased incidence of ALT $\geq 3\times$ULN in clinical trials and post-marketing published hepatotoxicity case reports^

• Incidence of ALT $\geq 3\times$ULN may provide a simple metric to identify a drug’s pre-marketing hepatotoxicity potential

• The most accurate value of this increased incidence and its correlation with clinically significant DILI remain in question

Specific Aims

• To quantify whether a specific increase of ALT $\geq 3\times$ULN in active treatment groups over placebo in pre-marketing clinical trials could predict post-marketing liver safety

• Investigate whether other information including hepatic metabolism and daily drug dose could add utility to hepatotoxicity prediction
Methods

- Retrospective review of all FDA new drug applications (NDA) of new chemical entities between 2001 and 2006
- Drugs used in randomized, placebo-controlled, phase II-III clinical trials
- Publically available databases: DailyMed, FDA website
  - Collected data using medical and statistical reviews and product labeling
  - Daily dose, hepatic metabolism information, etc.

www.fda.gov
Methods: Hepatotoxicity Assessment
- Pre-marketing Liver Safety Signal

Incidence of ALT $\geq 3\times$ULN in Treatment Group

- Incidence of ALT $\geq 3\times$ULN in Placebo Group

Excess risk of ALT $\geq 3\times$ULN

“ALT Signal” = Pre-marketing liver safety signal

(Primary predictor of post-marketing liver hepatotoxicity)
Methods: Hepatotoxicity Assessment - Post-marketing Liver Safety Signal

- FDA Adverse Events Reporting System (FDA AERS)
  - Database of > 3 million spontaneous adverse event reports
- Liver safety of the study drugs in the post-marketing period through the first-quarter of 2009
- Disproportionality analysis (DPA) used to examine reporting frequency of drug-adverse event pair relative to background in the entire database
  - Computes adjusted relative reporting ratio or Empirical Bayes Geometric Mean (EBGM) with associated lower and upper bounds of a 2-sided 90% confidence limits (EB05, EB95)

EBGM of 5 indicates a drug-liver safety event combination reported 5x more than expected
  – Threshold for signal detection: EB05 > 2

Primary post-marketing liver safety signal = EB05 > 2

Primary post-marketing outcome:
  – Dichotomized signal EB05 > 2 vs. EB05 < 2

Secondary post-marketing outcome: odds ratio (OR) of the relative reporting frequency of liver events after adjusting for age, gender, and co-reported medications

Methods: Hepatotoxicity Assessment -Post-marketing Liver Safety Signal

Univariate analysis between the pre-marketing excess risk of association of ALT ≥ 3xULN (“ALT signal”) and the dichotomized post-marketing outcome EB05 ≥ 2 or EB05 < 2 for each drug

Logistic regression to evaluate the ROC curve in order to determine the best predictive value for the “ALT signal”

Multiple logistic regression analysis to assess the impact of daily drug dose and significant hepatic metabolism on the accuracy of a pre-marketing liver safety signal to predict EB05 ≥2
102 Drugs Identified 2001-2006

22 Drugs excluded:
- Intranasal
- Inhaled
- Topical
- Radiologic or dialysis agent
- Nutritional supplement
- Systemic absorption < 25%

80 Drugs

54 Drugs excluded:
- Active comparator
- No Phase II or III studies
- No ALT information

26 Drugs

8 Drugs excluded:
- No ALT ≥ 3xULN data

28 Drugs

19 Drugs with ALT > 3xULN data

9 Drugs excluded:
- No ALT > 3 x ULN data

9 Drugs excluded:
- Insufficient information in FDA or Daily Med database

1 drug overlapping with original cohort

18 Drugs from placebo-controlled, randomized, Phase II and III clinical trials with ALT > 3xULN data

37 Medium-High Risk Drugs (Llanos, et al. 2010)

18 New Drugs with ALT ≥ 3xULN data

36 Drugs in Final Analysis
## Results: Pre-marketing Liver Signal

<table>
<thead>
<tr>
<th>ALT signal</th>
<th>Incidence Active treatment</th>
<th>Incidence Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT $\geq$ 3x ULN, median (IQR)</td>
<td>0.66% (0.27 – 1.9)</td>
<td>0.36% (0.2 – 1.08%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excess risk of ALT $\geq$ 3x ULN (Incidence Tx – Incidence Plc)</th>
<th>range</th>
<th>median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>range</td>
<td>-0.9% to 9%</td>
<td>0.2% (0.045 – 1.08%)</td>
</tr>
</tbody>
</table>

Safety population: median (IQR): 2384 (977-3477)
Results: Post-marketing Liver Safety Signals

- All 36 drugs had at least one liver safety event reported in the FDA AERS database
- Number of reported cases ranged from 8 to 3731
- Median EBGM: 1.038 (IQR: 0.519 – 2.05)
- 19.4% (n=7) were associated with positive post-marketing liver safety signal (EB05 ≥ 2)
- Two additional drugs were associated with a post-marketing liver signal after adjusting for co-reported medications (fenofibrate, acamprosate)
### Results: 36 Drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trial Size</th>
<th>Daily Dose &gt; 50mg</th>
<th>Hepatic Metabolism</th>
<th>EXCESS_RISK (Ia-Ic)</th>
<th>EB05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>1742</td>
<td>1</td>
<td>0</td>
<td>-0.001</td>
<td>1.79</td>
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<tr>
<td>Acarbose</td>
<td>2254</td>
<td>1</td>
<td>0</td>
<td>0.02</td>
<td>2.436</td>
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<tr>
<td>Alefacept</td>
<td>1289</td>
<td>0</td>
<td>0</td>
<td>0.005</td>
<td>0.285</td>
</tr>
<tr>
<td>Bosentan</td>
<td>938</td>
<td>1</td>
<td>1</td>
<td>0.09</td>
<td>6.022</td>
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<tr>
<td>Darifenacin Slow Release</td>
<td>6469</td>
<td>0</td>
<td>1</td>
<td>0.0015</td>
<td>0.287</td>
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<tr>
<td>Dutasteride</td>
<td>2449</td>
<td>0</td>
<td>1</td>
<td>0.0016</td>
<td>0.52</td>
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<tr>
<td>Eletriptan</td>
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<td>0</td>
<td>1</td>
<td>0.0027</td>
<td>0.48</td>
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<td>Eplerenone</td>
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<td>0.0038</td>
<td>1.664</td>
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<td>Eszopiclone</td>
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<td>0.0017</td>
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<td>Ezetimibe</td>
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<td>Fenofibrate</td>
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<td>Frovatriptan</td>
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<td>Nevirapine</td>
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<td>Olanzapine</td>
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<td>Olmesartan</td>
<td>2676</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

## Results: 36 Drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
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<th>Hepatic Metabolism</th>
<th>EXCESS_RISK (Id-Ic)</th>
<th>EB05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone</td>
<td>1011</td>
<td>0</td>
<td>0</td>
<td>0.0003</td>
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<tr>
<td>Pegvisomant</td>
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<td>0</td>
<td>0</td>
<td>-0.009</td>
<td>0.951</td>
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<td>Pioglitazone</td>
<td>2319</td>
<td>0</td>
<td>1</td>
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<td>1.219</td>
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<tr>
<td>Pravastatin</td>
<td>19768</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>Ramelteon</td>
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<td>1</td>
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<td>Rosiglitazone</td>
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<td>Simvastatin</td>
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<td>Solifenacin</td>
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<td>0.0017</td>
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<td>Tadalafil</td>
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<td>Tegaserod</td>
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<td>Tizanidine</td>
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<td>Zidovudine</td>
<td>881</td>
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<tr>
<td>Zileuton</td>
<td>966</td>
<td>1</td>
<td>1</td>
<td>0.017</td>
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<tr>
<td>Ziprasidone</td>
<td>3055</td>
<td>1</td>
<td>1</td>
<td>0.0052</td>
<td>0.601</td>
</tr>
</tbody>
</table>
Drugs with EB05 ≥ 2 had significantly higher excess risk of ALT > 3 x ULN (ALT signal)

*p = 0.019
Results: ROC curve

AUC = 0.79

Excess Risk (ALT Signal) > 1.2%

Sensitivity = 62.5%
Specificity = 92.9%
## Results: Logistic Regression Models to Predict Post-marketing EB05 > 2

<table>
<thead>
<tr>
<th>Model</th>
<th>Excess risk of ALT &gt; 3xULN (continuous variable)</th>
<th>Excess risk of ALT &gt; 3xULN (dichotomized: &gt;0.012 or &lt; 0.012)</th>
<th>Hepatic metabolism</th>
<th>Daily dose &gt;50mg</th>
<th>AUC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>*</td>
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<td></td>
<td>0.788</td>
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<td>0.744</td>
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<tr>
<td>4</td>
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<td>0.936</td>
<td>0.0025</td>
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<tr>
<td>5</td>
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<td>0.877</td>
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<td><strong>0.931</strong></td>
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<td>11</td>
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<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Results: Predicting Post-Marketing Liver Safety Signals Using Pre-Marketing Data

<table>
<thead>
<tr>
<th>Excess risk of ALT $&gt; 3$xULN $&gt; 1.2%$</th>
<th>Daily dose of $&gt; 50\text{mg}$</th>
<th>Proportion of positive liver signals</th>
<th>Proportion of negative liver signals</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>1.60%</td>
<td>98.40%</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>27.60%</td>
<td>72.40%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>21.80%</td>
<td>78.20%</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>86.90%</td>
<td>13.10%</td>
</tr>
</tbody>
</table>
In Summary...

- Systematic analysis of 36 marketed drugs with graded ALT data in Phase II-III placebo-controlled trials
- "ALT Signal" of greater than 1.2% significantly associated with post-marketing liver safety events
- Good positive predictive value (86%) of post-marketing liver safety events when the daily-dose exceeds 50mg and the ALT signal is > 1.2%
- Excellent negative predictive value of post-marketing liver safety events when both of these signals are negative (98%)
- Simple and easy to use model that can inform the drug development process
# Strengths and Limitations

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Real world data from clinical trials</td>
<td>Limitations of FDA AERS</td>
</tr>
<tr>
<td>Diverse drug classes</td>
<td>Unable to assess causality</td>
</tr>
<tr>
<td>Large safety populations of included drugs</td>
<td>Effect of low incidence of hepatotoxicity in approved drugs</td>
</tr>
<tr>
<td>≥ 3 years of follow-up data in FDA AERS</td>
<td>Unable to assess impact of nonclinical data (reactive metabolites, mitochondrial dysfunction, etc)</td>
</tr>
<tr>
<td>Combined info with other pre-clinical predictors (dose, hepatic metab)</td>
<td>Cannot determine risk /benefit</td>
</tr>
</tbody>
</table>
Conclusions

• A pre-marketing excess risk of ALT > 3xULN of > 1.2% in active treatment vs. placebo identifies a drug’s potential toxicity during drug development
  – Guide surveillance: likely safe vs heightened vigilance?
  – Use to guide decisions early in development to save time and money
  – Inform regulatory review

• Important to predict safety
  – Use as part of an algorithm with other predictors to determine benefit/risk

• Future directions
  – Validate in a larger dataset
  – Addition of other clinical and non-clinical predictors to improve accuracy
Acknowledgements

Christine Hunt (formerly GSK)
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Michael Ames – Clinical Statistics
Nancy Yuen - Global Clinical Safety and Pharmacovigilance
GSK Hepatotoxicity Board

Ayako Suzuki

Duke/GSK Hepatology Fellowship
Thank You

"I have the results of your liver scan. You don’t have all your ducts in a row."

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