FDA Drug Development Issues in Patients with Liver Disease

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*The opinions expressed are those of the author and do not necessarily reflect those of the FDA.

Topics

- Development issues
  - Nonclinical assessment
  - Early and late development
  - How are risk/benefit decisions made
  - Regulatory consequences
- Increasing evaluation of products in patients with HIV and liver disease

Nonclinical Studies

- Animal studies
  - Attempt to identify signals that might be applicable to humans
    - Ability to predict human idiosyncratic, often uncommon or rare, drug-induced toxicity is not good

Hepatic Impairment Study

- For development of dosing recommendations
- If hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite
- If the drug and/or active metabolite is eliminated to a lesser extent (<20 percent)
- If labeling or literature sources suggest that it has a narrow therapeutic range
- Enrollment by severity rather than underlying cause
  - Childs-Pugh score
  - No requirement for HIV

Early Studies

- What populations should drugs be studied in?
  - The population that will receive them
  - Testing drugs in a full demographic sample
  - Are dose adjustments for renal and hepatic impairment needed?
  - Full range of concomitant illnesses and medications
- The question is when and how to minimize risk?

Early Studies

- Non-clinical hepatotoxicity signal
  - Yes
    - Should be directed at serious and life-threatening illnesses or probably not developed
  - No
    - Initial trials in relatively healthy patients
    - Patients with active liver disease usually excluded

Later Studies

- Evidence of injury or no injury
  - No evidence in early studies
    - Phase 2/3 as usual
    - Monitoring, retesting, follow-up abnormal labs
  - Evidence of injury
    - Patients with pre-existing liver disease should be included
    - Could be stratified
    - Monitor frequently
    - Establish stopping rules
    - Follow-up critical

Detecting Serious Hepatotoxicity

- May have low incidence
- Confounders (especially HIV)
  - Alcohol
  - Other Drugs
  - Underlying illnesses
    - Chronic hepatitis B and C
    - Other liver diseases
- Need earlier detection: Biomarkers?

Hy's Rule for Drug-Induced Hepatotoxicity

- If both drug-induced hepatocellular injury and jaundice occur (transaminase and bilirubin elevations occur together in the absence of biliary obstruction)

Mortality (or its surrogate, liver transplantation) of at least 10% may be expected

Limitations to Hy's Rule

- FDA experience: Hy's rule is a consistent predictor
- Not defined quantitatively
  - What magnitude increase in transaminase and bilirubin levels is predictive?

Does Liver Biopsy Help to Diagnose Acute Hepatotoxicity?

- No, or very little
  - No pathognomonic histologic lesion for hepatoxicity, which may look like almost any kind of liver disease not caused by a drug
  - May help rule out other processes

Are There Biomarkers Available to Predict Hepatotoxicity?

- Non-invasive biomarkers (ALT, AST, ALP, TBL) are not predictors of hepatotoxicity to come, but hepatotoxicity that has already happened
- Findings do not predict what will come if the drug administration is continued
- Most people with serum enzyme rises caused by drugs adapt to them by alterations in liver enzyme and transporter activities and become tolerant of the drug
  - Only 1 or 2 per 300 with serum ALT rises in response to isoniazid fail to adapt and have to stop the drug permanently to avoid progressing to liver failure and death

Approach for Suspect Cases

- FDA uses ALT/AST ≥3 times ULN and T. BILI ≥2 times ULN
  - Drug should be stopped in study participant
  - Causality assessment
  - Correlate with clinical symptoms and Risk/Benefit difference
- In some individuals abnormalities resolve despite continuation of drug

Causality Assessment

- Latency
- Rate of resolution (dechallenge)
- Risk Factors (age, race, etc)
- Exclusion of other causes (viral hepatitis, ischemia, biliary tract disease, alcohol)
- Concomitant drugs
- Like-reactions
- Rechallenge

Drug induced liver disease edited by Kaplowitz and DeLeve 2003.

Options for Regulatory Action-Pre Approval

- Risk/benefit difference
  - **Discontinuation of drug development**
  - Partial or Full Clinical Hold
  - No studies in certain populations
    - Treatment-naïves (may have safer alternatives)
    - Healthy volunteers (may be too high a risk for no benefit)
  - Identify patients at risk and monitor

Options for Regulatory Action-Post Approval

- Risk/benefit difference
  - Add or increase BLACK BOX or other WARNINGS
  - Pharmacovigilance program
  - Risk management strategy
    - MedGuide
    - Restrict distribution
  - **Remove drug from market**

Pre-marketing Example: Aplaviroc

- 39 year old male, antiretroviral naïve
- Grade 4 hepatic cytolysis 59 days after initiating treatment with APL (800 mg bid) and ZDV/LAM
- Hospitalized:
  - Nausea and asthenia
  - Total bilirubin 2.7 mg/dL – direct 1.7 mg/dL
  - ALT 2888 U/L, AST 1938 U/L, LDH 1475 U/L
  - APTT and INR within normal limits
  - PT ranged 78.5% to 82% of normal
  - Liver biopsy compatible with drug-induced hepatitis

Pre-market Example: Aplaviroc

- Causality assessment
  - "Like-reaction" reports
    - Ten reports of treatment-emergent Grade 3/4 increases in AST, ALT or total bilirubin
    - 4 Cases considered clinically relevant
    - Cases occurred at all dose levels of APL
  - Risk factor assessment
  - Data request and assessment

Pre-market Example: Aplaviroc

- Partial Clinical Hold
  - No studies in treatment-naïve or healthy volunteers
  - Studies in treatment-experience continue with revisions
    - Reconsent for participation
    - Exclude patients with HBV, HCV, history of liver disease, > Grade 1 ALT/AST and > ULN bilirubin
    - LFT/bilirubin monitoring every 2 weeks through Week 24
    - Monthly safety summaries and line-listings for all increases in ALT/AST and bilirubin
- Development stopped

Post Approval Example: Darunavir

- PI for treatment experienced HIV-1 infected adults
  - Approved 6/23/2006
  - Label included PRECAUTION about hepatic impairment
  - Periodic Adverse Drug Experience Report
    - Fatalities
    - Other hepatotoxicity events

Post Approval Example: Darunavir

- **PRECAUTION**
  - Hepatic Impairment: Darunavir is primarily metabolized by the liver, increased plasma concentrations are expected in patients with hepatic impairment
  - There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment
  - Patients with pre-existing liver dysfunction, including chronic active hepatitis, should be monitored according to standard practice. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered

Post Approval Example: Darunavir

- Literature search
- Mining of FDA adverse event reports
- 43 cases
  - 27 not co-infected
  - 16 co-infected
- 24 cases causality “possible”
  - Deaths, hepatic necrosis, hepatic failure, hepatitis, acute hepatitis, cirrhosis

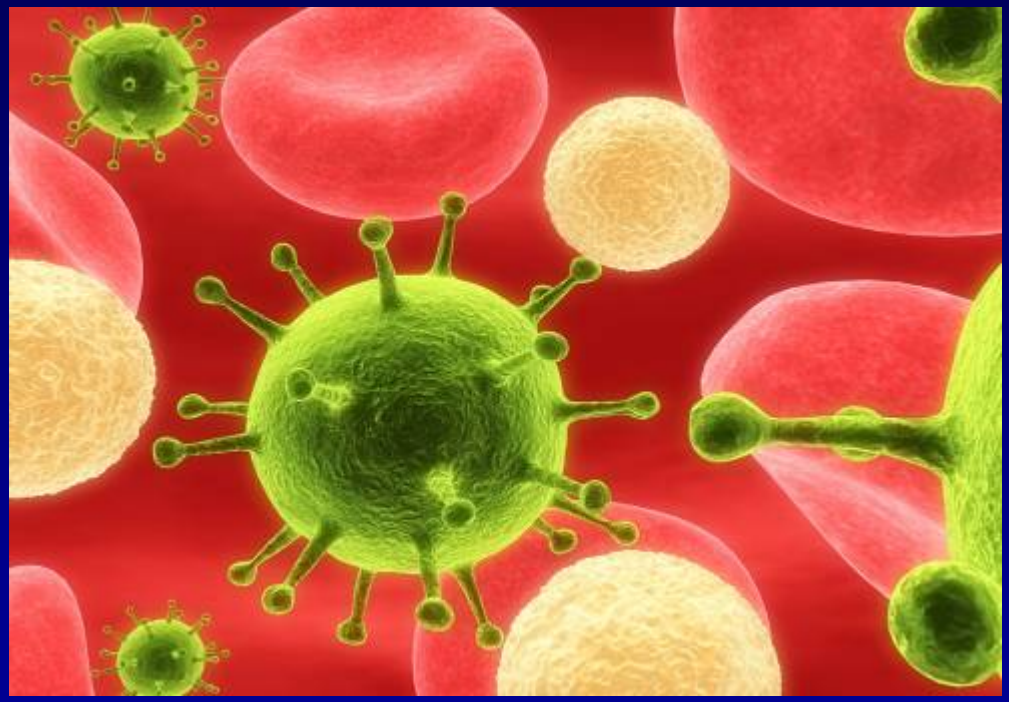
Post Approval Example: Darunavir

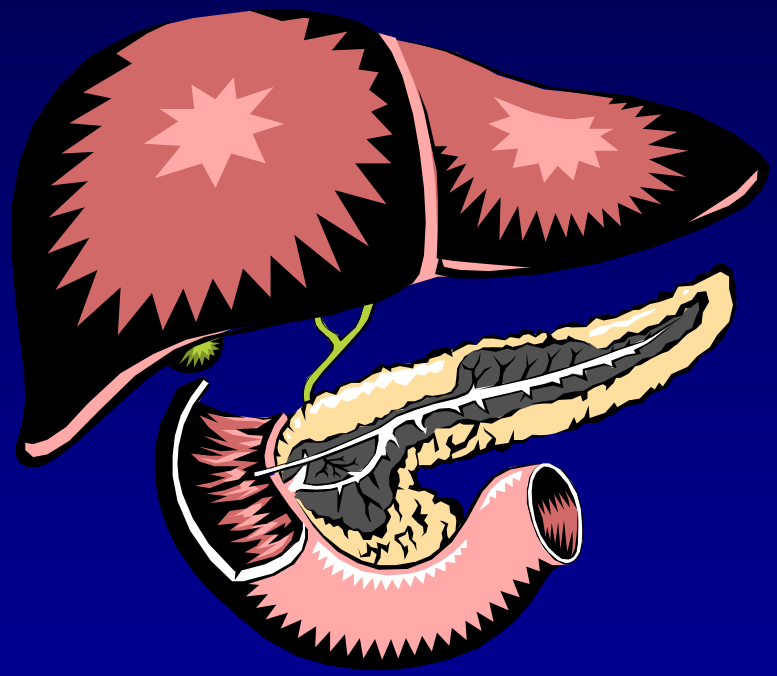
- **New WARNING**
  - Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported, including some fatalities
  - Generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having hepatitis B or C co-infection, and/or developing immune reconstitution syndrome
  - Appropriate laboratory testing should be conducted prior to initiating therapy and patients should be monitored during treatment
  - If there is evidence of new or worsening liver dysfunction, interruption or discontinuation of treatment must be considered

Hepatotoxicity Summary

- Often difficult to assess
  - Unpredictable
  - Infrequent/rare
  - Confounded/incomplete reports
- Approach
  - Review clinical cases
  - Look at biomarkers—Hy's Rule
  - Causality assessment
    - Like reactions—event characteristics
  - Balance risks and benefits

Increasing Trials in Patients with HIV and Liver Disease





Pre-Approval Issues

- Studies in patients with advanced liver disease and co-infection requested during development
  - No regulatory requirement
  - Proposals slow in coming
  - Companies very risk averse
- Inclusion/exclusion criteria limited
  - Usually ALT <5 × ULN
  - No co-infection
  - Compensated liver disease

Post-Marketing Studies

- Studies conducted by the applicant after approval that are intended to further refine the safety, efficacy or optimal use of a product, or to ensure consistency and reliability of product quality. These commitments can either be agreed-upon by the FDA and the applicant, or required by FDA under certain circumstances
- Prior to the passage of FDAAA, FDA could require PMCs in the following situations:
  - Subpart H approvals [21 CFR 314.510 and 601.41], which requires subsequent studies to demonstrate clinical benefit
  - Deferred pediatric studies [21 CFR 314.55(b) and 601.27(b)], where studies are required under PREA
  - Animal Efficacy Rule Clinical Efficacy and Safety Studies [21 CFR 314.610(b)(1) and 601.91(b)(1)], where studies to demonstrate safety and efficacy in humans are required at the time of use

Post-Marketing Studies

- FDAAA now allows the FDA to **require** post marketing studies to address safety concerns
  - To assess a known serious risk related to the drug involved
  - To assess signals of serious risk related to the drug
  - To identify an unexpected serious risk when available data indicate the potential for such risk
- Will FDA be able to use co-infection or advanced liver disease as a “safety” reason for a post-marketing requirement?
  - We believe YES

Enrollment Issues: Post-Approval

- Require or request PM trials
- Proposals slow in coming
- Inclusion/exclusion criteria limited
  - Usually ALT <5 × ULN
  - Sometimes co-infection
  - Rarely decompensated liver disease

Tipranavir PMC Trial

- Safety and activity of TPV/r in HIV, HCV and HBV co-infected patients
- Pharmacokinetics and potential for TDM
- TPV/r + SOC ART
- No mention of anti-HBV or HCV therapy

Tipranavir PMC Trial

- Inclusion/Exclusion criteria
  - HIV + Chronic HCV or HBV infection
  - ALT and AST <DAIDS Grade 3
  - No decompensated liver disease, including presence or history of ascites, variceal bleeding, or hepatic encephalopathy or having ever been diagnosed with Child Pugh class B or C

What Can FDA Do?

- Pre-approval
  - Continue to engage in discussions and request plans to evaluate co-infected and those with decompensated disease
  - Attempt to broaden inclusion criteria
  - Request interaction studies early
  - Offer incentives for a priority review
    - Pre and post liver transplant

What Can FDA Do?

- Post-approval
  - PM trials directed at evaluation of HIV co-infected patients and patients with advanced liver disease

What Can Sponsors and Investigators Do?

- Sponsors
  - Design and conduct trials that will answer regulatory and management questions
- Investigators and cohorts
  - Design and conduct trials that will answer management questions

Summary

- FDA attempts to have comprehensive approach to products with potential for hepatotoxicity
  - Pre clinical, clinical studies
  - Post marketing
- Increasing trials in HIV, co-infection and advanced liver disease
  - FDA: encourage trials pre and post marketing
  - Sponsors/investigators: design and conduct trials that answer important regulatory and management questions

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