Impact of Aging in Liver on HCV Progression

Robert A. Branch, MD
Center for Clinical Pharmacology
University of Pittsburgh

Presented at the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, 22-23 June 2011, Cambridge, USA
A Time for Hope

Alternative drugs that have demonstrated efficacy

Old Drugs
- Pegylated Interferon α
- Ribaviron

New Drugs
- Telaprevir
- Boceprevir
- Interferon lambda
A Time to Fear

Lack of knowledge: How to optimize individual therapy?

Drug Factors
- Efficacy
- Side effects
- Economics
- Variability in disposition

Host Factors
- Age
- Gender
- Ethnicity
- Genetics

Viral Factors
- Genotype
- Mutation rate
- Resistance

Natural history of HCV-induced liver disease
What a prescribing physician would like to know?

- Drug
- Genetic Constitution
- Age
- Diseases
- Drugs
- Efficacy
- Toxicity

Exposure : Response

Cp

Time
If drugs are approved by FDA, what should we know now?

Information that the FDA does ask for:

**PHASE I**
- Identification therapeutic target
- Preclinical safety
- Formulation
- Preliminary safety
- Preliminary drug disposition

**PHASE II**
- Identification clinical target
- More safety/dose ranging
- PK variability
- PD variability
- Variability in special populations – aging, liver disease

**PHASE III**
- Expand study size for defined clinical target
- More safety at fixed doses
- Simplify protocol
- Prove efficacy – usually over placebo
How are these general principles relevant to the contemporary management of HCV induced liver disease?

Variability in **natural history**
- Clinical target for drug testing
- Clinical target for drug use

Variability in **virus**
- Genotype
- Risk of resistance/multi-drug use
- What is a cure? (How long to treat?)

Variability in **drug factors**
- Need for combination therapy
- Dose range limitations
- Strategy for resistance

Variability in **host**
- Concomitant disease (HIV, Alcohol)
- Genotype (Interferon lambda 3)
- Age
- Side effects to drugs vs. clinical disease
What is the relevance of aging to the HCV epidemic?

- What is the impact of aging and liver disease on drug disposition?
- What stage of the disease are we managing?
  - therapy
  - prevention
- What is the impact of aging and drug therapy on host/virus interaction?
At the time of drug approval: we should know the pharmacokinetic implications of…

1. Aging
2. Liver Disease

…on HCV targeted drugs
Fundamental Principles of Pharmacology

Schematic of steady state plasma levels with fixed dose

Plasma Concentration

Time

Low clearance

Medium clearance

High clearance

Response

Drug Response

Efficacy

Toxicity

Therapeutic Window

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Individual Variation

Individualized Benefit Plane for a Drug in Aging

Assumes active parent drug

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Drug Disposition in Aging

Aging variability reduces:
- GFR
- CYP Phase 1 drug metabolism

Aging does not influence:
- glucuronidation

Intersubject Variation

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Drug Disposition in Liver Disease

Physiological Determinants of Hepatic Drug Elimination

- Intrinsic Hepatic Clearance
- Metabolism
- Bile
- Drug Delivery
- Blood Flow & Binding
Intact Hepatocyte Hypothesis

Reduced number of functionally intact hepatocytes - intrahepatic portosystemic shunt

Drug Disposition in Liver Disease

generalized schematic for many drugs

Drug Exposure Measured by the AUC or Cmax

Severity of Liver Disease

Intersubject Variation
Selective Regulation of CYP in Liver Disease

Superfamily of Cytochrome P450 (CYP)

Families

CYP1
CYP1A2
Caffeine

CYP2

CYP2C9
Flurbiprofen

CYP2C19
Mephenytoin

CYP3
CYP3A4
Dapsone

CYP2E1
Chlorzoxazone

Subfamilies

A
B
C
D
E

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Selective Regulation of CYPs in Chronic Liver Disease

Progressive, Sequential Effect Model of Liver Disease on Drug Clearance

Individual Variation

Individualized Benefit Plane for a Drug in Liver Disease

What the FDA wants to know in drug development

What the FDA wants to know in drug development

Assumes active parent drug
What is the relevance of aging to the HCV epidemic?

- What is the impact of aging and liver disease on drug disposition?
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  - prevention
- What is the impact of aging and drug therapy on host/virus interaction?
What type of HCV-induced liver disease are we managing?

Interindividual Variation

Clinical Disease

Threshold

Viremia

HCV Infection

Age (years)

20 30 40 50 60 70

Acute Hepatitis
Chronic Hepatitis
Cirrhosis
Hepatocellular Cancer
No Disease

Threshold

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HCV Epidemic in US

1980s – HCV pre-screening use of blood products

- Hemophylia
- Surgery
- Trauma

1980s – present

- Risk takers
- HIV
- Drug abuse

Multi cohort natural history model of HCV induced liver disease

(Davis et al, Gastroenterology 138, 513-521, 2010)
Schematic of Natural History of Hepatitis C Virus Induced Liver Disease

Davis et al, Gastroenterology 138, 513-521, 2010
Estimated Proportion of Cases of Patients with HCV Induced Liver Disease that have Progressed to Cirrhosis

Model predicts 1 million patients in 2030

Adapted from: G.L. Davis et al, Gastroenterology 138, 513-521, 2010
What stage of HCV-induced liver disease are we managing? Therapeutic versus prevention targets.

**Clinical Disease**

- HCV Infection
- Acute Hepatitis
- Chronic Hepatitis
- Cirrhosis
- Hepatocellular Cancer

**Viremia**

- No Disease
- Viremia
- Clinical Disease

Ideal target for drug testing: Acute Hepatitis, Chronic Hepatitis, Cirrhosis

Therapeutic Need: HCV Infection, Acute Hepatitis, Chronic Hepatitis, Cirrhosis, Hepatocellular Cancer

Age (years)

- 20
- 30
- 40
- 50
- 60
- 70

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What is the relevance of aging to the HCV epidemic?

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- What is the impact of aging and drug therapy on host/virus interaction?
What is the impact of aging and drug therapy on host/HCV interaction?

We do not know:

- Emergence of resistance
- Can we prevent?
  - acute inflammatory response
  - fibrosis towards cirrhosis
  - mutations leading to HCC
- Relationship of extent viremia to disease

We assume:

- Suppression of viremia is a surrogate for HCV – liver response
A Time for Hope

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New Drugs
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Drug Response

- Efficacy
- Toxicity
Evolution of a Drug in its Development

Conceptual Idea

Preclinical Development

IND to CDER of FDA
Office of Review

12 Subspeciality Divisions, Such as Anti-Viral, Cardio-Renal

× Safety

Phase I

Pharmaceutical Science

◆ Biopharmaceutics
◆ Preclinical to Clinical Translation
◆ Clinical Pharmacology

× Efficacy

Phase II

× Comparative Efficacy

Phase III

NDA Review & Approval

Phase IV

Post-Marketing Surveillance

Therapeutic Niche
If drugs are FDA approved, why don’t we know more now?

Information that the FDA does not ask for:
- Comparative effectiveness to what is on the market
- Effectiveness for indications outside inclusion criteria of phase III studies
- Economics for drug marketing

What information is not yet complete?
- Guide to optimize personalized therapy
- Knowledge of full range of adverse effects
Challenges to HCV Drug Therapy

Therapeutic Objective
- Prevention
- Therapeutic

Drug
- Intersubject variability
- Additive vs. synergy
- Interactions
- Side effects

Host
- Pharmacogenetics PK/Pd
- Genotype (interferon lambda 3)
- Aging
- Concurrent liver disease

Environment
- Multi-drug therapy
- Intersubject variability in natural history
- Concomitant Disease (HIV, alcohol)

Virus
- Genotype susceptibility
- Mutation rate
- Drug resistance
- What is a cure?