A New Kind of Coffee Connection!

Ruhl CE and Everhart JE.

Gastroenterology 129(6)1928-1936;200
Mechanism of protective effect of coffee unknown

- Constituents such as caffeine, cafestol, and kahweol protective in experimental studies
- Antioxidant effect
- Insulin sensitizing effect
- Coffee drinkers have higher levels of plasma adiponectin and lower levels of CRP and TNF alpha
Multiple Studies Show that Coffee is Hepatoprotective

- Coffee drinkers have lower levels of liver enzymes
- Coffee drinkers have less hepatic fibrosis
- Coffee drinkers have less hospitalization and mortality from chronic liver disease
- Coffee drinkers have a reduced risk of developing primary hepatocellular carcinoma
Kaldi the shepherd from Kaffa
“Coffee is so good, the infidels should not have exclusive use of it.”

Pope Vincent III
Coffee Protects Against Liver Disease
References: Coffee and Liver Disease, 2012
Sanjiv Chopra, MD, MACP


Large prospective study; Coffee consumption inversely associated with total and cause-specific mortality.

Hepatitis C Is Diverse and Complex to Effectively Treat

<table>
<thead>
<tr>
<th>Viral Factors</th>
<th>Patient Factors</th>
<th>Health Factors</th>
<th>Treatment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Genotype</td>
<td>• Gender</td>
<td>• Co-infection</td>
<td>• Resistance</td>
</tr>
<tr>
<td>• Viral load</td>
<td>• Race</td>
<td>• Comorbidities</td>
<td>• Safety</td>
</tr>
<tr>
<td>• Mutations</td>
<td>• Age</td>
<td>• Prior treatment outcomes</td>
<td>• Dosing</td>
</tr>
<tr>
<td></td>
<td>• IL28B status</td>
<td></td>
<td>• Treatment duration</td>
</tr>
<tr>
<td></td>
<td>• Adherence</td>
<td></td>
<td>• Access</td>
</tr>
</tbody>
</table>
Mild Chronic Hepatitis C

To Treat or Not to Treat?

1. _________________ 100 years (B,E)

2. Progression

3. Treatment Responder

4. Treatment Non-Responder

5. More Effective Treatment in Future
Mild Disease: Treatment?

When you come to a fork in the road, take it!

Yogi Berra
Baseball Hall of Fame Catcher
To Treat or Not to Treat: A Constellation of Considerations

- Genotype virus
  - Genotype Patient (IL28)
- Histologic stage
  - 20%+ life time risk Of cirrhosis
- Duration of infection
- Personal plans
  - (marriage, pregnancy)
- Age
- Family and other support
- Patient "mindset"
- ALT
- Occupation
- Extrahepatic Features
  - (Fatigue, EMC, PCT)
- HIV coinfection
- Contraindications & comorbidities
  - Insulin Resistance

PinK AALSD CME 2009
Milestones in Therapy of CHC:
Average SVR Rates from Clinical Trials

Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
2011 Advances in Treatment of Chronic Hepatitis C

- Two protease inhibitors (PI’s) Telaprevir and Boceprevir approved by FDA for Genotype I patients

- Triple therapy viz., Peg IFN, Ribavirin plus a PI:
  - 75% of naïve patients have a SVR.
  - 75% of relapsers to dual Rx have a SVR.
  - 35% of Non-responders to dual Rx have a SVR.

Marcellin P et al. Gastroenterology 2011;140:459
TVR + PR: Adverse Events

Significantly higher rates of rash, anemia, and anorectal signs/symptoms in TVR arms vs control

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>TVR + PR RGT/48 n = 1797</th>
<th>PR48 n = 493</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>56%</td>
<td>34%</td>
</tr>
<tr>
<td>Anemia</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>Anorectal discomfort</td>
<td>29%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Telaprevir Film Coated Tablets. Prescribing Information, May 2011.
BOC + PR: Adverse Events

Significantly higher rates of anemia, neutropenia and dysgeusia in BOC arms vs control

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>BOC + PR RGT/48 n = 1225</th>
<th>PR48 n = 467</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35%</td>
<td>16%</td>
</tr>
</tbody>
</table>

SVR prevents liver-related death

10-year occurrence

SVR: 1.9% (95% CI 0.0-4.1)
non-SVR: 27.4% (95% CI 22.0-32.8)

Follow-up time, years
LR-Mortality, %

SVR eliminates liver failure

Van de Meer et al Submitted 2012
What’s In Our Near Future? More Triple Therapy

• Single DAA plus IFN backbone plus ribavirin (RBV)
  – Second-generation PIs
  – Nucleoside polymerase inhibitors
  – Nonstructural protein (NS)5A inhibitors

• Considerations
  – RVR > 90%
  – Sustained virologic response (SVR): 80%
  – Tolerability and side effects
  – RGT
  – 12–16 weeks of therapy for IL-28B CC genotype
Sofosbuvir + PEG/RBV: GT 1, 4, 5, 6

Study Weeks

12
24

NEUTRINO:
Treatment-naïve patients, multicenter, open-label study

N=327

Sofosbuvir 400 mg QD + PEG 180 μg/week + RBV

SVR 12
NEUTRINO SVR12 Results

- No on-treatment virologic failure (all relapses)
- Most common AEs occurring in ≥20% subjects were fatigue, headache, nausea, insomnia, and anemia
The Goal of Combination Regimens

- Profound suppression of broad range of viral variants, including pre-existing variants
- Prevention of emergent resistance (pre-existing or de novo)

- Different drugs can contribute variably to each goal. Not all components must be direct-acting antivirals (DAAs).
Promising Therapeutic Targets for Direct-Acting Antiviral Drug Development

Hepatitis C Virus Polyprotein

**Structural Proteins**
- Core
- E1
- E2
- P7

**Nonstructural Proteins**
- NS2
- NS3
- 4A
- NS4B
- NS5A
- NS5B

**Protease Inhibitors**
- High potency
- Multigenotypic coverage
- Intermediate to high barrier to resistance

**NS5A Inhibitors**
- High potency
- Multigenotypic coverage
- Low to intermediate barrier to resistance

**NS5B Nucleoside Inhibitors**
- Intermediate potency
- Pangenotypic coverage
- High barrier to resistance

**NS5B Non-nucleoside Inhibitors**
- Intermediate potency
- Limited genotypic coverage
- Low barrier to resistance

Differentiating Attributes of Future Therapy Beyond Cure

Prioritization Criteria

- Sustained virologic response rate: Most important
- Side effects
- Drug-drug interaction
- Cost
- Dosing/Treatment duration
- Pan-genotypic: Secondary attributes determining treatment with non-inferior SVR
- Class of therapy
- Number of direct-acting antiviral drugs: Least important

Abbreviation: SVR, sustained virologic response.
Source: Leerink physician interviews. Leerink Swann Consulting.
All Oral Therapies – How They Differentiate?

1. Genotype / subtype
2. Prior IFN/PI response
3. Efficacy
   - Standard population
   - Special populations – are there any?
4. Treatment duration
   - Is it the same for all
5. Resistance
6. Drug-Drug-Interactions
7. Safety and Tolerability
8. Pill Burden
9. Ribavirin – yes / no
## Evolution of Therapies for GT1

<table>
<thead>
<tr>
<th>Timing</th>
<th>Treatment Paradigm</th>
<th>Treatment Regimens</th>
<th>SVR for GT1</th>
</tr>
</thead>
</table>
| 2011         | Triple Therapy                      | • Telaprevir + PEG-IFN + RBV  
• Boceprevir + PEG-IFN + RBV                                                   | • Naive \(\cong 70\%^{1,2}\)  
• Exp \(\cong 40\%^{1,2}\)                                                  |
| 2013 - 2014  | Triple Therapy: Next Generation     | • Sofosbuvir + PEG-IFN + RBV  
• Simeprevir + PEG-IFN + RBV  
• Faldeprevir + PEG-IFN + RBV                                                | • Naive \(\cong 89\%^{3}\)  
• Naive \(\cong 80\%^{4}\)  
• Naive \(\cong 89\%^{5}\)                                                  |
| 2015         | IFN-free Therapy Wave 1             | • Multiple combinations in development                                             | Expected  
• Naive = >90%  
• Exp = >80%                                                  |
| 2016 +       | IFN-Free Therapy Wave 2             | • Multiple combinations in development  
• Pangenotypic                                                                | Expected  
• Naive = >90%  
• Exp = >90%                                                  |

Abbreviations: GT1, HCV genotype 1; IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.
Sofosbuvir + Ledipasvir + RBV

ELECTRON Results: in GT1 Naive/Null Responders

- Nonrandomized phase 2 study in GT1 noncirrhotics
- AE profile consistent with RBV toxicity profile; 1 patient discontinued due to AE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EOT, %</th>
<th>SVR4, %</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>100</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>Null responders</td>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Null responders</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Sofosbuvir 400 mg QD; ledipasvir 90 mg QD; weight-based RBV 1000-1200 mg/d

Abbreviations: EOT, end of treatment; GT1, HCV genotype 1; RBV, ribavirin; SVR4, 4-week sustained virologic response; SVR12, 12-week sustained virologic response.

COSMOS study: Sofosbuvir + Simeprevir in GT1 Null-Responders
- No benefit of RBV

Sofosbuvir 400 mg QD + Simeprevir 150 mg QD ± RBV x 12 wks

SVR$_{8\text{wks}}$ (%)

- RBV +: 26/27 (96%)
- RBV -: 13/14 (93%)

Lawitz et al., CROI 2013, Abstract 155LB
The future of HCV therapy

Statements and predictions

- Ribavirin will disappear
- 3 DAAs (vs 2 DAAs) may
  - further shorten therapy
  - lead to higher SVR rates (in particular in cirrhosis)
- Response to previous (IFN-based) therapy will be less relevant
- Cirrhosis (more granular differentiation) is expected to become the key baseline predictor for SVR
Conclusions

• Screening strategies will increase awareness of HCV
• New treatment paradigms will make linkage to care easier for patients
• Global Access will be key to eradication
• New all oral treatments will provide
  – Higher cure rates
  – Increased tolerability
  – Enhanced resistance profiles
  – Convenient dosing
  – Shorter treatment durations
  – Broad genotypic coverage
  – Efficacy in hard to treat patients