HEPATITIS C
and
METABOLIC MANIFESTATIONS

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Prevalence of Hepatitis C in VN

• HCV prevalence was estimated at 2%–9% among adults

• Higher prevalence rates in special populations
  – IVDA - 55.6%
  – Dialysis – 26.6%
  – Sex workers – 8.7%
  – Blood transfusion – 6%

Nakata S et al. J Gastro Hepatol, 1994
Tran HT et al. Hepatol Res. 2003; 26:275-280
Genotype of Hepatitis C in VN

Ho Chi Minh City
• Genotype 6: 53%
• Genotype 1: 32.6%
• Genotype 2: 18.6%
• Genotype 3: 0%

Ha Noi and Central
• Genotype 1: 60%
• Genotype 6: 35.8%
• Genotype 3: 1.8%
• Genotype 2: 0.4%

Virology, 2014 November; 0:197-206
## BODY MASS INDEX

<table>
<thead>
<tr>
<th></th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian BMI</td>
<td>25-29.9 kg/m²</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>Asian BMI</td>
<td>23-27.4 kg/m²</td>
<td>&gt;27.5 kg/m²</td>
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</tbody>
</table>
Prevalence of Obesity in VN

<table>
<thead>
<tr>
<th></th>
<th>Overweight %</th>
<th>Obesity %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIETNAM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>9.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Females</td>
<td>10.9</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td>34.5</td>
<td>34.9</td>
</tr>
</tbody>
</table>

Ashtari S; World J Hepatol, 2015 July8: 1788-1796
Insulin Resistance

• A condition in which organs do not respond properly to body produced insulin

• insulin resistance score (HOMA-IR) = fasting plasma glucose (mmol/l) X fasting serum insulin (mU/l)/ 22.5.

• Low HOMA-IR values indicate high insulin sensitivity

• High HOMA-IR values indicate low insulin sensitivity (insulin resistance).
Metabolic Syndrome

a group of risk factors increases risk for heart disease, diabetes and stroke

• Abdominal Obesity
  – Waist circumference > 102cm in men
  – Waist circumference > 88cm in women
• Hypertriglyceridemia >150mg/dl
• Low HDL level: <40 mg/dl in men; <50mg/dl in women
• High blood pressure (>130/85mm/Hg)
• High fasting glucose (>110mg/dl)
Prevalence of Metabolic Syndrome in VN

• 15.8% in age >54
• 16.3% in Red River Delta Region

Binh et al. Endocrine Disorders, 2014, 14:77
Huy Tran. J Geriatric Cardiology, Dec 2004
Fatty Liver Disease

- Normal
- NALDF
- NASH

- Steatosis
- Ballooning degeneration
- Lobular inflammation
- Mallory hyaline
- Perisinusoidal fibrosis
Fatty Liver Disease

NASH

Steatosis alone

By itself

HCV

10%-20%

Cirrhosis

Benign

Aggressive
Risk factors for NALDF/NASH

• Diabetes
• Metabolic Syndrome
• Hyperlipidemia
• Obesity (high BMI)
Metabolic Effects of Hepatitis C

- Insulin Resistance
- Diabetes
- Metabolic Syndrome
- Steatosis
Prevalence of IR in HCV

1. Prospective, single-center, observational cohort study of 500 CHC patients¹
   • 32.4% overall prevalence of IR excluding diabetic patients (n=38%)
   • 40.1% prevalence of IR in GT 1 and 4 patients

2. Retrospective, single-center, study of 69 CHC, genotype 1 patients²
   • 64% prevalence of IR

3. Prospective, single-center, study of 201 CHC, genotype 1 patients³
   • 52.7% prevalence of IR

Insulin Resistance and HCV Viral Load

- IR defined as a HOMA > 3
- High viral load > 600,000 IU/mL
- HVL associated with IR 55.3% versus 42.3% for LVL, p=0.009

Association of Insulin Resistance and Fibrosis Progression

- IR associated with moderate to severe inflammation
- HOMA increased significantly with fibrosis stage (p<0.001)
- By logistic regression, IR independently associated with significant fibrosis

Association of Insulin Resistance and Fibrosis Progression

- 260 patients with CHC, 48% GT 1
- Single Center experience
- IR is a predictor of the stage of fibrosis and rate of fibrosis progression

Mean HOMA:

GT 1: 3.2  GT 3: 2.4

Hui et al, Gastroenterology 2003;125;1695-1704
Diabetes in non-cirrhotic HCV patients

HCV and Diabetes

- After adjustment for confounders, patients with HCV (>40 yrs) were more likely to have type 2 DM: OR 3.77 (95% CI, 1.80-3.87)
Chronic HCV Infection: Insulin Resistance and Diabetes

• HCV infection is associated with the development of insulin resistance (precursor of type 2 diabetes mellitus)
• HCV infection predisposes to insulin resistance regardless of liver disease severity
• Though the relationship is not understood, the incidence of diabetes is increased in patients with HCV. In fact, it is greater than 3 fold greater if the HCV-infected patients are also over 40 years old.
• Prevalence of diabetes mellitus
  – Increasing in HCV-infected subjects compared to general population, and to patients with other etiologies of liver disease
• Further, HCV associated with diabetes and/or insulin resistance increases the risk for HCC and accelerated liver fibrogenesis
• Treatment of HCV in diabetics is associated with reduced risk of end stage renal disease and ischemic stroke

HCV and Metabolic Syndrome

SVR GT 1:
MS: 21.6%
No MS: 42.7%

HCV and Metabolic Syndrome


P < 0.001
# Metabolic Syndrome vs HCADS

Table 1. Metabolic Syndrome *versus* Hepatitis C-Associated Dysmetabolic Syndrome (HCADS)—A comparison at a glance.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Metabolic Syndrome</th>
<th>HCADS</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D</td>
<td>Yes</td>
<td>Yes</td>
<td>[3]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Yes</td>
<td>[3]</td>
</tr>
<tr>
<td>Visceral Obesity</td>
<td>Yes</td>
<td>Preliminary evidence suggests that HCV patients have abdominal fat distribution</td>
<td>[3]</td>
</tr>
<tr>
<td>Atherogenic dyslipidemia</td>
<td>Yes</td>
<td>Acquired, reversible hypcholesterolemia</td>
<td>[6]</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>Not included among diagnostic criteria but often found as a concurrent or precursor finding</td>
<td>In chronic HCV patients, steatosis is two- to three-fold more prevalent than in chronic hepatitides of other etiologies. HCV genotype 3 is associated with a higher prevalence and more severe steatosis</td>
<td>[3,6]</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Not included in diagnostic criteria but often associated on pathophysiological grounds Whether the full-blown MetS adds to the risk of its individual components, particularly T2D, is controversial</td>
<td>Strongly associated with severity of steatosis</td>
<td>[3,190]</td>
</tr>
<tr>
<td>Accelerated atherogenesis</td>
<td></td>
<td>Individuals with HCV infection (particularly those with T2D and hypertension) have an excess of cardiovascular morbidity and mortality</td>
<td>[3,191]</td>
</tr>
<tr>
<td>HCC risk</td>
<td>Both the MetS and T2D increase the risk of HCC. This likely results via NAFLD/NASH even in non-cirrhotic livers</td>
<td>Concurrent T2D and chronic HCV infection lead to increased risk of HCC. Steatosis and overweight/obesity possibly play a role</td>
<td>[168,192,193]</td>
</tr>
</tbody>
</table>
HCV and Steatosis

• Sources of Steatosis in HCV
  – In chronic hepatitis C, steatosis is common (40%-70%)
  – Sources of steatosis:
    • Viral factors
    • Host factors
Source of Steatosis in HCV

- BMI / obesity
- Diabetes / insulin resistance
- Increased leptin (?)

Metabolic syndrome


Source of Steatosis in HCV

- HCV genotype 3
  - Fayyzi M et al. *Hepatology* 1997
  - Rubbia-Brandt et al. *J Hepatology* 2000
  - Rubbia-Brandt et al. *Histopatology* 2001
  - Poynard T et al. *Hepatology* 2003
  - Sharma P et al. *DDS* 2004
  - Rubbia-Brandt et al. *Gut* 2004

- HCV core protein (?)
  - Moriya K et al. *J of Gen Virology* 1997
  - Perlemuter G et al. *FASEB* 2002
Viral Factors in Hepatic Steatosis

- Chronic Hepatitis C: N=755
- Steatosis: 41.7%
- Independent predictors of steatosis:
  - HCV genotype 3, obesity (BMI), ETOH (current), and age

HCV genotype 3 is the most important viral factor associated with steatosis
Interactions of HCV on steatosis

Figure 1. Summary of interactions of hepatitis C virus (HCV) on hepatic steatosis, insulin resistance (IR), oxidative stress, and hepatocellular injury. Arrows signify increases or activation; blunt ends signify inhibition.

Apo B=apolipoprotein B; ECM=extracellular matrix; FA=fatty acid; FFA=free fatty acid; HCV core=HCV core protein; IL-6=interleukin-6; MTP=micronosomal triglyceride transfer protein; ROS=reactive oxygen species; SREBP=sterol regulatory element-binding protein; TG=triglyceride; TGF-β=transforming growth factor β; TNF-α=tumor necrosis factor α; VLDL=very-low-density lipoprotein.

Proposed pathogenesis for hepatic steatosis in patients with CHC

Harrison SA, Clin Gastro Hepatol 2008
Metabolic Effects of HCV and HCC
Insulin Resistance and Incidence of HCC

Fig. 3 Cumulative incidence of HCC according to insulin resistance (cut-off HOMA IR: 3.0) for non-SVR patients with a mild fibrosis (F3-2) and b advanced fibrosis (F3). HCC, hepatocellular carcinoma; HOMA, homeostasis model assessment of insulin resistance; SVR, sustained virological response.
HCC Risk Remains High After SVR With PegIFN ± RBV

- Retrospective VA cohort study of HCV-infected pts treated with pegIFN ± RBV from 1999-2009 (N = 22,028)
- HCC incidence rate 3.27/1000 PY with SVR vs 13.2/1000 PY without SVR (HR: 0.358)

<table>
<thead>
<tr>
<th>Predictor of HCC Following SVR*</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis at time of SVR</td>
<td>4.45 (2.53-7.82)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Age at SVR, yrs (vs younger than 55 yrs)</td>
<td></td>
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</tr>
<tr>
<td>55-64</td>
<td>2.40 (1.53-3.77)</td>
<td>.0002</td>
</tr>
<tr>
<td>65 or older</td>
<td>4.69 (2.04-10.78)</td>
<td>.0003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.07 (1.35-3.20)</td>
<td>.0010</td>
</tr>
<tr>
<td>HCV GT (vs GT1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.56 (0.32-1.01)</td>
<td>.0522</td>
</tr>
<tr>
<td>3</td>
<td>1.91 (1.14-3.18)</td>
<td>.0131</td>
</tr>
</tbody>
</table>

* Cox proportional hazards model adjusted for competing risk of death.
Metabolic Effects of HCV and HCC

- Insulin Resistance has a strong impact on the development of HCC in non-cirrhotic patients
- Type II Diabetes is established factor for cirrhosis and HCC especially with chronic HCV patients
- NALDF patients can develop HCC without evidence of cirrhosis

Hayashi et al. Infectious Agents and Cancer 2016, 11:9
Metabolic Effects on HCV Treatment Response with Peg Interferon
SVR Decreased in Insulin Resistant Patients with HCV Genotype 1

Normal = fasting glucose < 100 mg/dL; High = fasting glucose >100 mg/dL.
Subjects through fasting glucose > 140 mg/dL were excluded.
The Impact of Superimposed Steatosis or Its Risk Factors on HCV Treatment (cont)

Treatments: IFN α-2b 3 MU TIW + RBV 1000 –1200 mg/day for 48 wks or Peg-IFN α-2b 1.5 μg/kg/wk for 4 wks followed by 0.5 μg/kg/wk for 44 wks + RBV 1000 – 1200 mg/day or Peg-IFN α-2b 1.5 μg/kg/wk + RBV 800 mg/day for 48 wks

Why Is There A Decreased Response with PegInterferon?
The Impact of Superimposed Steatosis or Its Risk Factors on HCV Treatment (cont)

• Insulin may prevent IFN-mediated HCV suppression

  Sanyal AJ et al. AASLD 2004

• Obesity may inhibit IFN signaling in the liver

  Walsh M et al. Gut 2005
Obesity

Increased/altered cytokine release and function\textsuperscript{2,3}

HCV core protein disrupts JAK/STAT pathway as well\textsuperscript{4,5}

Increased Inflammation

Oxidative Stress

Impaired IFN-\alpha Signaling\textsuperscript{1}

SVR

\textsuperscript{5} Luquin E, et al. Antiviral Res. 2007;76:194-197.
The Impact of Superimposed Steatosis or Its Risk Factors on HCV Treatment (cont)

- Hepatitis C and steatosis (N=19)
- Three-month weight reduction program
  - Weight loss 5.9±3.2 kg
  - Decrease in waist of 9.0±5.0 cm
  - Fasting insulin 16±7 to 11±4 mmol/l
  - ALT improved (16/19)
- Patients with paired biopsy (N=10)
  - 9 pts showed reduction in steatosis, improvement in fibrosis (3:1), and activated stellate cells
Metabolic Effects on HCV treatment with DAA
The ASTRAL Phase 3 Program (N=1408)

<table>
<thead>
<tr>
<th>Study</th>
<th>GT</th>
<th>TN, TE</th>
<th>NC, CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTRAL-1</td>
<td>1, 2, 4–6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRAL-2</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>ASTRAL-3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRAL-4</td>
<td>1–6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTRAL-5</td>
<td>1–4</td>
<td></td>
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</tbody>
</table>

- **Primary endpoints**
  - SVR12
  - Discontinuations due to AEs

Integrated Efficacy Analysis of SOF/VEL for 12 Weeks

Retrospective integrated analysis of data from 1,035 SOF/VEL patients in ASTRAL-1, -2, and -3

### Baseline Demographics

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>GT1 n=328</th>
<th>GT2 n=238</th>
<th>GT3 n=277</th>
<th>GT4 n=116</th>
<th>GT5 n=35</th>
<th>GT6 n=41</th>
<th>Total N=1035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>73 (22)</td>
<td>29 (12)</td>
<td>80 (29)</td>
<td>27 (23)</td>
<td>5 (14)</td>
<td>6 (15)</td>
<td>220 (21)</td>
</tr>
<tr>
<td>Platelets &lt;100 x 10³/µL</td>
<td>21 (6)</td>
<td>4 (2)</td>
<td>25 (9)</td>
<td>8 (7)</td>
<td>1 (3)</td>
<td>3 (7)</td>
<td>62 (6)</td>
</tr>
<tr>
<td>Albumin &lt;3.5 mg/dL</td>
<td>6 (2)</td>
<td>1 (&lt;1)</td>
<td>8 (3)</td>
<td>6 (5)</td>
<td>0</td>
<td>0</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Fibroscan ≥15 kPa</td>
<td>30 (16)</td>
<td>9 (7)</td>
<td>40 (20)</td>
<td>17 (19)</td>
<td>4 (17)</td>
<td>5 (19)</td>
<td>105 (16)</td>
</tr>
<tr>
<td>HCV RNA ≥800,000 IU/mL</td>
<td>255 (78)</td>
<td>186 (78)</td>
<td>191 (69)</td>
<td>74 (64)</td>
<td>26 (74)</td>
<td>31 (76)</td>
<td>763 (74)</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>110 (34)</td>
<td>44 (18)</td>
<td>71 (26)</td>
<td>52 (45)</td>
<td>11 (31)</td>
<td>3 (7)</td>
<td>291 (28)</td>
</tr>
<tr>
<td>Black race</td>
<td>25 (8)</td>
<td>19 (8)</td>
<td>3 (1)</td>
<td>14 (12)</td>
<td>0</td>
<td>0</td>
<td>61 (6)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>36 (11)</td>
<td>53 (22)</td>
<td>7 (3)</td>
<td>11 (10)</td>
<td>16 (46)</td>
<td>0</td>
<td>123 (12)</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>20 (6)</td>
<td>18 (8)</td>
<td>21 (8)</td>
<td>8 (7)</td>
<td>3 (9)</td>
<td>0</td>
<td>70 (7)</td>
</tr>
<tr>
<td>HbA1c ≥6.5%</td>
<td>21 (6)</td>
<td>9 (4)</td>
<td>13 (5)</td>
<td>10 (9)</td>
<td>3 (9)</td>
<td>4 (10)</td>
<td>60 (6)</td>
</tr>
<tr>
<td>NS5A RAVs (15% cut off)</td>
<td>50 (15)</td>
<td>146 (61)</td>
<td>31 (11)</td>
<td>69 (59)</td>
<td>3 (9)</td>
<td>19 (46)</td>
<td>318 (31)</td>
</tr>
</tbody>
</table>

The ASTRAL-1, -2, and -3 studies enrolled patients with baseline characteristics historically associated with poor response
Integrated Efficacy: SVR12

ASTRAL-1, -2, -3

SVR12 (%)

- **Total**: 98%
  - GT 1: 98%
    - 2 relapse
    - 2 LTFU
      - 1 D/C
    - 323 / 328
  - GT 2: 99%
    - 1 D/C
    - 237 / 238
  - GT 3: 95%
    - 11 relapse
    - 2 D/C
    - 264 / 277
  - GT 4: 100%
    - 116 / 116
  - GT 5: 97%
    - 1 death
    - 34 / 35
  - GT 6: 100%
    - 41 / 41

Agarwal, EASL 2016, Poster SAT-195
## SVR12 per negative predictor

<table>
<thead>
<tr>
<th>Patients, n(%)</th>
<th>GT1 n=328</th>
<th>GT2 n=238</th>
<th>GT3 n=277</th>
<th>GT4 n=116</th>
<th>GT5 n=35</th>
<th>GT6 n=41</th>
<th>Total n=1035</th>
</tr>
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<tbody>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99 (72/73)</td>
<td>100 (29/29)</td>
<td>91 (73/80)</td>
<td>100 (27/27)</td>
<td>100 (5/5)</td>
<td>100 (6/6)</td>
<td>96 (212/220)</td>
</tr>
<tr>
<td>No</td>
<td>98 (251/255)</td>
<td>99 (207/208)</td>
<td>97 (191/197)</td>
<td>100 (89/89)</td>
<td>97 (28/29)</td>
<td>100 (35/35)</td>
<td>99 (801/813)</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 x 10^3/μL</td>
<td>95 (20/21)</td>
<td>100 (4/4)</td>
<td>88 (22/25)</td>
<td>100 (8/8)</td>
<td>100 (1/1)</td>
<td>100 (3/3)</td>
<td>94 (58/62)</td>
</tr>
<tr>
<td>≥100 x 10^3/μL</td>
<td>99 (303/307)</td>
<td>99 (233/234)</td>
<td>96 (242/252)</td>
<td>100 (108/108)</td>
<td>97 (33/34)</td>
<td>100 (38/38)</td>
<td>98 (957/973)</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 mg/dL</td>
<td>100 (6/6)</td>
<td>100 (1/1)</td>
<td>88 (7/8)</td>
<td>100 (6/6)</td>
<td>0</td>
<td>0</td>
<td>95 (20/21)</td>
</tr>
<tr>
<td>≥3.5 mg/dL</td>
<td>98 (317/322)</td>
<td>99 (236/237)</td>
<td>96 (257/269)</td>
<td>100 (110/110)</td>
<td>97 (34/35)</td>
<td>100 (41/41)</td>
<td>98 (995/1014)</td>
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<tr>
<td>FibroScan</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 kPa</td>
<td>100 (30/30)</td>
<td>100 (9/9)</td>
<td>90 (36/40)</td>
<td>100 (17/17)</td>
<td>100 (4/4)</td>
<td>100 (5/5)</td>
<td>96 (101/105)</td>
</tr>
<tr>
<td>&lt;15 kPa</td>
<td>98 (154/158)</td>
<td>99 (118/119)</td>
<td>97 (152/156)</td>
<td>100 (74/74)</td>
<td>95 (19/20)</td>
<td>100 (22/22)</td>
<td>98 (539/549)</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced</td>
<td>99 (109/110)</td>
<td>100 (44/44)</td>
<td>90 (64/71)</td>
<td>100 (52/52)</td>
<td>100 (11/11)</td>
<td>100 (3/3)</td>
<td>97 (283/291)</td>
</tr>
<tr>
<td>Naïve</td>
<td>98 (214/218)</td>
<td>99 (193/194)</td>
<td>97 (200/206)</td>
<td>100 (64/64)</td>
<td>96 (23/24)</td>
<td>100 (38/38)</td>
<td>98 (732/744)</td>
</tr>
<tr>
<td>NS5A RAVs (15% cut off)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With RAVs</td>
<td>96 (48/50)</td>
<td>100 (146/146)</td>
<td>87 (27/31)</td>
<td>100 (69/69)</td>
<td>100 (3/3)</td>
<td>100 (19/19)</td>
<td>98 (312/318)</td>
</tr>
<tr>
<td>Without RAVs</td>
<td>99 (275/278)</td>
<td>99 (89/90)</td>
<td>96 (236/245)</td>
<td>100 (46/46)</td>
<td>97 (31/32)</td>
<td>100 (21/21)</td>
<td>98 (698/712)</td>
</tr>
</tbody>
</table>

Agarwal, EASL 2016. Poster #SAT-195
Diabetes and Hyperlipidemia Compromise SVR with DAA treatment

- Overall SVR: 81%
- Lower SVR if pretreatment fasting glucose >126mg/dl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male)</td>
<td>37 (68.5)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>54.6 ± 22.3</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>29.6 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Pre Treatment Stage Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>32 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Previous Interferon History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>31 (57.4)</td>
<td></td>
</tr>
<tr>
<td>No Response</td>
<td>18 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>5 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Pre-Treatment HCV RNA (IU/mL)</td>
<td></td>
<td>2,703,207 ± 1,407,000</td>
</tr>
<tr>
<td>ALT (IU/mL)</td>
<td></td>
<td>79.5 ± 49.9</td>
</tr>
<tr>
<td>Serum Creatinine (g/dL)</td>
<td></td>
<td>0.91 ± 0.3</td>
</tr>
<tr>
<td>Total Bilirubin (g/dL)</td>
<td></td>
<td>1.2 ± 1</td>
</tr>
<tr>
<td>Platelets (x10^3)</td>
<td></td>
<td>132.2 ± 77.3</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31 (57.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16 (29.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of Concomitant Metabolic Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (20.4)</td>
<td></td>
</tr>
</tbody>
</table>

Does Eradication of HCV improves its Metabolic Effects
Treatment Response Improves IR

- HOMA-IR decreased in HCV patients who achieved SVR but not in non responders and relapsers

SVR With PegIFN + RBV Reduces Development of New-Onset Insulin Resistance

- Extended follow-up sub-study of the MIST study
  - Non-diabetic, white HCV-infected patients treated with pegIFN + RBV (n=399)
    - Male: 58%
    - Age: 51.8 years
    - BMI >25 kg/m^2: 46%
    - Genotype 1/4: 50%
    - Fibrosis stage >4: 29%
    - HOMA score: 1.15
- SVR rate: 63%
- New-onset insulin resistance (matched measurements)
  - 10.7% (n=38/354)

Rate of De-Novo Insulin Resistance

SVR May Lower Cumulative Incidences of HCV-Related Comorbidities

- Two retrospective studies in Japan showed that SVR reduced the cumulative incidences of type 2 diabetes mellitus\(^1\) and hemorrhagic stroke\(^2\)

\[\text{Type 2 Diabetes}^1\]

\[\text{Hemorrhagic Stroke}^2\]

- Antiviral treatment has shown benefit for other comorbidities, such as lymphoma,\(^3\) end-stage renal disease,\(^4\) and ischemic stroke\(^4\)

Patient cohorts from the Toranomon Hospital, Japan: 2842 CHC patients were treated with an IFN-based regimen between September 1990 and March 2007\(^1\); 4649 CHC patients were treated between September 1990 and May 2010.\(^2\)

HCV clearance was defined as clearance of HCV RNA at 6 months after the cessation of therapy. \(^a\)Cox regression analysis.

Treatment Response Improves Steatosis

<table>
<thead>
<tr>
<th></th>
<th>Genotype 3</th>
<th>Other Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of at least one grade</td>
<td>77%</td>
<td>29%</td>
</tr>
<tr>
<td>Disappearance of steatosis</td>
<td>46%</td>
<td>29%</td>
</tr>
</tbody>
</table>

T. Poynard et al. Hepatology, July 2003, 75-85
Eradication of Hepatitis C

- Improve and resolve Insulin resistance and Diabetes
- Improve and resolve steatosis especially in genotype 3
- Reduce and prevent HCC

T. Poynard et al. Hepatology, July 2003, 75-85
SUMMARY
Hepatitis C

Insulin Resistance → Diabetes → Obesity → Metabolic Syndrome

Steatosis → Liver Cancer

Cirrhosis
Summary

• Treat hepatitis C - treat early!
• Eradication of HCV may reduce Insulin Resistance and prevent Diabetes, Metabolic syndrome and Steatosis
• Weight reduction before treatment if patients are treated with Interferon and have BMI greater than 27kg/m²
• HCC surveillance in treatment response cirrhotic and diabetic patients
• Alcohol reduction