A Sad Story...

V Di Martino*

*Advisory board/lectures/travel facilities: Abbvie, BMS, Gilead, MSD
Case report (1)

- Mr T. Philippe 55 yrs old
- Past IV drug user (1985)
- Morbid obesity (149kgs/1.90m; BMI=41.3kg). Gastric band in 2006: Macroscopic aspect of liver cirrhosis during surgery. Hep C genotype 4 subsequently diagnosed.
- Good efficacy of gastric band: losses 41 Kgs within 10 months. Persistent Diabetes.

In December, 2013, listed for liver transplantation

In January, 2014, receives Sofosbuvir + RBV 3 months then sofosbuvir + daclatasvir 3 months.

How SVR could be beneficial for this patient?

- Improvement of survival
- Decreased risk of hepatocellular carcinoma
- No longer need for liver transplantation
- Improvement of diabetes
- Decreased risk of stroke and coronary disease
- All the above
How SVR could be beneficial for this patient?

• Improvement of survival
• Decreased risk of hepatocellular carcinoma
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• Improvement of diabetes
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• All the above
Persistent HCV viremia is associated with liver-related mortality

REVEAL-HCV Cohort study on 23,820 patients including 1095 patients HCV positive

**HCC-related mortality**

- Cumulative mortality (%)
- Years
- HCV positive, viremic
- HCV positive, non viremic
- HCV negative

**Liver-related mortality**

- Cumulative mortality (%)
- Years
- HCV positive, viremic
- HCV positive, non viremic
- HCV negative

Impact of SVR on liver related mortality and HCC

Muticentric cohort study in 530 patients who received IFN based therapy between 1990 and 2003.

van der Meer et al. JAMA. 2012; 308(24): 2584-93.
Impact of SVR on HCV-related mortality: Meta-analysis on 34,563 patients

Hill et al. AASLD 2014. Abstract 44.
Impact of SVR on the outcome of HCV-related liver disease: Meta-analysis on 34,563 patients

Hill et al. AASLD 2014. Abstract 44.
Regression of HCV cirrhosis: a true event

<table>
<thead>
<tr>
<th>The study</th>
<th>Nr of pre-treatment cirrhotics with SVR</th>
<th>Cirrhosis regression among SVR</th>
<th>Mean/median follow-up time months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberge, 2004</td>
<td>18</td>
<td>6 (33%)</td>
<td>6</td>
</tr>
<tr>
<td>Maylin, 2008</td>
<td>14</td>
<td>9 (64%)</td>
<td>6 (range 0-14 y)</td>
</tr>
<tr>
<td>Mallet, 2008</td>
<td>35</td>
<td>22 (63%) if one stage less, (17/35, 49% if 2 stages less)</td>
<td>11-17</td>
</tr>
<tr>
<td>Everson, 2008</td>
<td>40 (F3-F4)</td>
<td>20 (50%)</td>
<td>19.8</td>
</tr>
<tr>
<td>Poynard, 2002</td>
<td>37</td>
<td>25 (68%)</td>
<td>21±4</td>
</tr>
<tr>
<td>Arif, 2003</td>
<td>6</td>
<td>5 (83%)</td>
<td>27±9</td>
</tr>
<tr>
<td>George, 2009</td>
<td>8</td>
<td>6 (75%)</td>
<td>At least 48</td>
</tr>
<tr>
<td>Pol, 2004</td>
<td>17</td>
<td>4 (24%)</td>
<td>55.2±26.4</td>
</tr>
<tr>
<td>Reichard, 1999</td>
<td>3</td>
<td>3 (100%)</td>
<td>60±22</td>
</tr>
<tr>
<td>D’Ambrosio, 2012</td>
<td>38</td>
<td>23 (61%)</td>
<td>61 (range 48-104)</td>
</tr>
</tbody>
</table>

113 pat with pre-tx cirrhosis and liver biopsies after SVR

Akhtar E et al, Liver Int 2015
Impact of SVR on cirrhosis-related complications and mortality

French cohort study conducted between 1988 and 2001, in 96 patients with histologically-proven HCV cirrhosis

RVS may induce cirrhosis reversion that cancels the risk of cirrhosis-related complications and mortality. The identification of the ‘reversers’ is challenging.

HCV and extrahepatic mortality

- Significant association between HCV and:
  - diabetes (OR = 1.8) 1*
  - cardiovascular disorders (OR=2.37) 2*
  - stroke (OR= 2.7) 3*
  - Renal disorders (HR if< 59 yrs= 7.8 vs. 3.2) 4*
  - Neurocognitive disorders 3
  - Extrahepatic malignancies (breast: OR = 2) 5

* Impact of metabolic syndrome

Graph: Extrahepatic mortality according to HCV status

- HCV positive, viremic
- HCV positive, non viremic
- HCV negative

Key:
- p<0.001 pour comparaison intergroupes
- p=0.002 for détectable vs. Indétectable HCV RNA

References:
HCV clearance reduces hepatic and extrahepatic mortality: the concept of ‘HCV-related chronic inflammation’

- **HCV infection**
  - < 30 %: **Cure**
  - > 70 %: **Chronic Infection**
  - > 95 %: **Chronic Hepatitis**
  - > 20 %: **Cirrhosis**
  - > 20 %: **HCC**

- **Acute Hepatitis**
  - > 95 %: **Chronic Hepatitis**
  - > 70 %: **Lymphotropism**
  - 1 à 2 %: **Cryoglobulinemia**
  - 40 %: **Cryoglobulinemic vasculitis**

Liver disease, ‘chronic inflammation’, Cryoglobulinemic vasculitis
HCV Infection and diabetes
Meta-analysis of 14 retrospective studies

B. Multivariate estimates
Study (year)

Mehta SH (2000)*
Howard AA (2003)**
Butt A (2007)***
Huang J-F (2007)****
Li-Ng M (2007)*****
Marzouk D (2007)******
Costa L (2008)*******

Overall (OR=1.68, 95% CI 1.15, 2.20)

White DL et al, J Hepatol 2008
Clearance of HCV improves insulin resistance

Decreased HOMA-IR and HOMA-B in sustained responders but not in other groups

Kawaguchi Am J Gastroenterol 2007
SVR prevents *de novo* diabetes

Age 50 yrs  cirrhosis  Pré-diabetes

**A**

Cumulative development rate of T2DM (%)

$P < 0.001$

SVR (N = 535)

Non-SVR (N = 975)

**B**

Cumulative development rate of T2DM (%)

$P = 0.017$

SVR (N = 54)

Non-SVR (N = 139)

**C**

Cumulative development rate of T2DM (%)

$P = 0.005$

SVR (N = 90)

Non-SVR (N = 151)

Arase, *Hepatology* 2009
Cerebrovascular deaths and HCV infection

Community-based prospective cohort study of 23,665 residents in Taiwan
Median follow-up 16.9 years

Anti-HCV +ve participants

Lee M-H et al. Stroke 2010;41:2894–2900
# Impact of HCV on coronary artery disease

**High bias risk studies removed**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (HR) and 95% CI</th>
<th>OR</th>
<th>LCI</th>
<th>UCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varsaille (2004)</td>
<td>4.20 (1.40)</td>
<td>1.40</td>
<td>13.00</td>
<td></td>
</tr>
<tr>
<td>Volzke (2004)</td>
<td>1.55 (0.92)</td>
<td>0.92</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>Butt (2007)</td>
<td>0.74 (0.71)</td>
<td>0.71</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Ramdeen (2008)</td>
<td>5.71 (1.67)</td>
<td>1.67</td>
<td>19.60</td>
<td></td>
</tr>
<tr>
<td>Butt (2009) (HR)</td>
<td>1.27 (1.22)</td>
<td>1.22</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
<td>Tsui (2009) (HR)</td>
<td>1.74 (0.92)</td>
<td>0.92</td>
<td>3.32</td>
<td></td>
</tr>
</tbody>
</table>

**Decreased risk of CAD**

**Increased risk of CAD**

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LCI, lower confidence interval; OR, odds ratio; UCI, upper confidence interval

Impact of SVR on myocardial perfusion

217 HCV infected patients without overt cardiac disorder

Variations of myocardial scintigraphy according to response to treatment

Baseline

End of Treatment

6 months post Treatment

SVR

Relapse

Non response

SPECT: single-photon emission computed tomography

HCV infection and cancer

Relative risk of cancers in patients HCV+ vs. HCV

<table>
<thead>
<tr>
<th>Site</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>2.51</td>
<td>&lt; 0.0004</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.03</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rectum/Colon</td>
<td>1.88</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Liver</td>
<td>68.67</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.79</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Myeloma</td>
<td>3.41</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3.59</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Head&amp;Neck</td>
<td>2.56</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lung</td>
<td>2.44</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.05</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.05</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>All sites including HCC</td>
<td>2.33</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>All sites excluding HCC</td>
<td>1.84</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Nyberg AH et al. EASL 2015, Abs. 0058
benefits of SVR on extrahepatic mortality is also visible in cirrhotic patients!

**CIRVIR**: French multicenter prospective cohort study conducted between March, 2006 and June, 2012 in 1323 patients with HCV-related histologically-proven cirrhosis

• Patient was not delisted but maintained in ‘temporary contra-indication’
• In September, 2015 abdominal US was ‘normal’. aFP=30 UI/mL
• In October 2015, abdominal pain. -> CT scan
CT scan findings: multinodular HCC with macrovascular invasion
Impact of SVR on the prognosis of HCV-related liver disease: Meta-analysis on 34,563 patients.
Residual risk of HCC and hepatic decompensation in sustained responders: the CirVir cohort (1323 cirrhotic patients)

Risk of HCC according to Metabolic syndrome and SVR: the CirVir cohort

Nahon et al. EASL 2015. Abstract P0328.
Diabetes: risk factor of HCC and mortality in patients with HCV cirrhosis

Fig. 2. Probability of survival in patients with cirrhosis according to MELD score and diabetes status at inclusion (MELD <10 and no DM vs. MELD <10 and DM, \( P = 0.005 \); MELD <10 and no DM vs. MELD \( \geq 10 \) and no DM, \( P < 0.001 \); MELD <10 and no DM vs. MELD \( \geq 10 \) and DM, \( P < 0.001 \); MELD <10 and DM vs. MELD \( \geq 10 \) and no DM, \( P = 0.045 \); MELD <10 and DM vs. MELD \( \geq 10 \) and DM, \( P = 0.019 \); MELD \( \geq 10 \) and no DM vs. MELD \( \geq 10 \) and DM, \( P = 0.6 \); and \( P < 0.001 \) for the overall comparison by the log-rank test).

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD &lt;10 and no DM</td>
<td>102  78  63  49  40  22  14  1</td>
</tr>
<tr>
<td>MELD &lt;10 and DM</td>
<td>55   40  29  19  13  7  4  0</td>
</tr>
<tr>
<td>MELD ( \geq 10 ) and no DM</td>
<td>104  48  28  18  12  6  2  0</td>
</tr>
<tr>
<td>MELD ( \geq 10 ) and DM</td>
<td>81   30  20  13  9  5  3  0</td>
</tr>
</tbody>
</table>

ElKrief, Hepatology 2014
Diabetes: risk factor of HCC and mortality in patients with HCV cirrhosis

Table 5. Multivariate Cox Regression Analysis Evaluating Baseline Factors Associated With the Occurrence of Major Complications of Cirrhosis During Follow-up

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD score ≥10</td>
<td>1.904</td>
<td>1.124</td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.631</td>
<td>0.985</td>
<td>0.057</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.754</td>
<td>1.016</td>
<td>0.044</td>
</tr>
<tr>
<td><strong>Renal Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>2.471</td>
<td>1.154</td>
<td>0.020</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.352</td>
<td>1.318</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Bacterial Infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD score ≥10</td>
<td>2.527</td>
<td>1.452</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.098</td>
<td>1.227</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>HE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>0.756</td>
<td>0.364</td>
<td>0.452</td>
</tr>
<tr>
<td>MELD score ≥10</td>
<td>6.868</td>
<td>2.927</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GI Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None of the baseline variables were included in multivariate analysis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HCC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>2.017</td>
<td>1.196</td>
<td>0.009</td>
</tr>
<tr>
<td>MELD score ≥10</td>
<td>0.605</td>
<td>0.351</td>
<td>0.070</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.938</td>
<td>1.129</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Variables with a P value ≤0.05 in multivariate Cox's regression analysis were included in Cox's multivariate analysis (Supporting Table 7).
Alcohol increases the risk of hepatocellular carcinoma in patients with HBV and HCV infection

*Odds ratio of Hepatocellular carcinoma*

---

*Donato F, Am J Epidemiol 2002*
The majority of hospitalized HCV infected patients has comorbidities

- French PMSI Database 2008-2012
- 28,953,755 adults admitted at least once

<table>
<thead>
<tr>
<th>Comparison of HCV positive vs HCV negative patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Alcohol related disorders</td>
</tr>
<tr>
<td>&gt; 1 severe comorbidity</td>
</tr>
</tbody>
</table>
Case report (4)

• Sorafenib started on November, stopped on December for encephalopathy associated with deterioration of liver function.

• Patient still on waiting list... awaiting death
In summary

• The rationale of gains attributed to SVR in terms of extrahepatic morbidity/mortality is strong since numerous studies indicate the impact of HCV viremia on extrahepatic disorders, but

• At an individual level, This gain is inconstant, depending on comorbidities

• At a population level (long-term follow-up cohort studies including untreated patients) the magnitude of the gain also depends on whether patients were selected for receiving HCV treatment (Interferon+++)

• No data available to date with SVR obtained with DAAs.
In summary (2)

• In patients with advanced fibrosis/cirrhosis who develop SVR, HCC can occur, particularly in the event of associated diabetes or metabolic syndrome or alcohol consumption.

• Improvement of some hepatic or extrahepatic conditions after SVR doesn’t guarantee that everything will improve and that HCC will not occur.

• All F3/F4 patients MUST be followed all life long regardless of additional risk factors for HCC or outcome of liver function after SVR.