The long term impact of treatment on the outcome of Hepatitis C

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Acıbadem University
Turkey
Currently, Very Few HCV Patients Are Treated

2.7-3.9 million infected
50% HCV detected
32% to 38% referred for care
7% to 11% treated

<table>
<thead>
<tr>
<th>Retrospective studies</th>
<th>Prospective studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervals from exposure</td>
<td>9-29 years</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>17-55% (mean 42%)</td>
</tr>
<tr>
<td>HCC</td>
<td>1-23%</td>
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<tr>
<td>Liver deaths</td>
<td>4-15%</td>
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</tbody>
</table>

See LB. *Hepatology, 2002;36:535. Hatzakis A et al. JIVH, 2011;18:51*
### Natural history of hepatitis C from retrospective, prospective and retrospective-prospective cohort studies (B)

#### Retrospective -Prospective Cohort Studies

- **Children and young men or women**
  - Exposure interval: 9-45 years
  - Cirrhosis: 0.3-5.9% (mean 2.1%)
  - HCC: 0
  - Liver deaths: 0-2.1%

- **Middle-aged people with post-transfusion hepatitis**
  - Exposure interval: 23 years
  - Cirrhosis: 15%
  - HCC: 1.9%
  - Liver deaths: 2.8%

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EXPECTATIONS FROM HCV TREATMENT WITH ANTIVIRALS

- Reduce the risk of:
  - Developing HCC
  - Liver decompensation / complications of LC
  - Liver related death
  - Overall death in HCV cirrhosis

- Improve quality of life
- Decrease the disease burden in the community
- Control the economic burden associated with advanced disease
To which extent these expectations are fulfilled with antiviral therapies?
Effects of a Sustained Virologic Response on Outcomes of Patients With Chronic Hepatitis C

- Achievement of SVR after treatment is associated with:
  - Improvements in disease progression,
  - Liver histology,
  - Health-related quality of life,
  - Reduced risk of HCC and
  - Liver-related mortality
• An SVR reduced liver-related mortality among patients with chronic hepatitis C (3.3- to 25-fold),
• The incidence of hepatocellular carcinoma (1.7- to 4.2-fold),
• Hepatic decompensation (2.7- to 17.4-fold).

# Liver Disease Progression and Hepatic Decompensation in Sustained Viral Responders and Nonresponders

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>pts</th>
<th>Antiviral used</th>
<th>Mean Follow-up</th>
<th>SVR %</th>
<th>Progression/decompensation SVR</th>
<th>Non SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrosis</strong></td>
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</tr>
<tr>
<td>Bruno et al.</td>
<td>2001</td>
<td>Italy</td>
<td>47</td>
<td>IFN</td>
<td>8.5</td>
<td>100%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Shiratori</td>
<td>2000</td>
<td>Japan</td>
<td>487</td>
<td>IFN</td>
<td>3.7</td>
<td>37.6%</td>
<td>1.1%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2007</td>
<td>Taiwan</td>
<td>892</td>
<td>IFN, IFN/R264</td>
<td>5</td>
<td>70.6%</td>
<td>3.8%</td>
<td>10.3%</td>
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<tr>
<td>George et al</td>
<td>2008</td>
<td>USA</td>
<td>150</td>
<td>IFN/RBV146, Peg/RBV</td>
<td>5</td>
<td>100%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced Fibrosis</strong></td>
<td></td>
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<tr>
<td>Trapero-Marugan et al</td>
<td>2011</td>
<td>Spain</td>
<td>5</td>
<td>PEG IFN/RBV</td>
<td>6.3</td>
<td>100%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Iacobellis et al</td>
<td>2007</td>
<td>Italy</td>
<td>61</td>
<td>PEG IFN/RBV</td>
<td>2.5</td>
<td>21.3%</td>
<td>23.1%</td>
<td>68.8%</td>
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</table>
Liver-Related Mortality in Sustained Viral Responders and Nonresponders

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>pts</th>
<th>Antiviral used</th>
<th>Mean Foll-up</th>
<th>SVR %</th>
<th>Liver-related deaths, SVR</th>
<th>Non SVR</th>
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</thead>
<tbody>
<tr>
<td><strong>All stages of fibrosis</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Arase et al</td>
<td>2007</td>
<td>Japan</td>
<td>500</td>
<td>IFN, 31 IFN/RBV</td>
<td>7.4</td>
<td>(28%)</td>
<td>(1.4%)</td>
<td>(8.9%)</td>
</tr>
<tr>
<td>Coverdale et al</td>
<td>2004</td>
<td>Australia</td>
<td>343</td>
<td>IFN-alfa</td>
<td>6.81</td>
<td>(14.6%)</td>
<td>(2%)</td>
<td>(8.2%)</td>
</tr>
<tr>
<td>Kasahara et al</td>
<td>2004</td>
<td>Japan</td>
<td>2668</td>
<td>IFN</td>
<td>6</td>
<td>(27.7%)</td>
<td>(0.14%)</td>
<td>(3.5%)</td>
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<tr>
<td>Yoshida et al</td>
<td>2002</td>
<td>Japan</td>
<td>2430</td>
<td>IFN</td>
<td>5.4</td>
<td>(33.6%)</td>
<td>(0.24%)</td>
<td>(2%)</td>
</tr>
<tr>
<td><strong>Advanced fibrosis</strong></td>
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<td></td>
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<tr>
<td>Morgan et al</td>
<td>2010</td>
<td>USA</td>
<td>526</td>
<td>PEG-IFN/RBV</td>
<td>7.5</td>
<td>(26.6%)</td>
<td>(0.7%)</td>
<td>(6%)</td>
</tr>
<tr>
<td>Bruno et al</td>
<td>2007</td>
<td>Italy</td>
<td>920</td>
<td>IFN</td>
<td>8</td>
<td>(13.5%)</td>
<td>(1.7%)</td>
<td>(11.4%)</td>
</tr>
<tr>
<td>Braks et al</td>
<td>2007</td>
<td>France</td>
<td>113</td>
<td>IFN, 40 IFN/RBV, 38 PEG-IFN/RBV</td>
<td>7.7</td>
<td>(32.7%)</td>
<td>(0%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>Mallet et al</td>
<td>2008</td>
<td>France</td>
<td>96</td>
<td>IFN, 34 IFN/RBV, 208PEG/RBV</td>
<td>9.8</td>
<td>(40.6%)</td>
<td>(8.6%)</td>
<td>(31.1%)</td>
</tr>
<tr>
<td>Veldt et al</td>
<td>2007</td>
<td>Mcenter</td>
<td>479</td>
<td>IFN, 130 IFN/RB, 10 PEG, 208PEG/RBV</td>
<td>2.1</td>
<td>(29.6%)</td>
<td>(0.7%)</td>
<td>(7.1%)</td>
</tr>
</tbody>
</table>
**Sustained Virological Response to Interferon-α Is Associated with Improved Outcome in HCV-related Cirrhosis: A Retrospective Study**

Savino Bruno,1 Tommaso Stroffolini,2 Massimo Colombo,3 Simona Bollani,1 Luisa Benvegnù,4 Giuseppe Mazzella,5 Antonio Ascione,6 Teresa Santantonio,7 Felice Piccinino,8 Pietro Andreone,9 Alessandra Mangia,10 Giovanni B. Gaeta,11 Marcello Persico,12 Stefano Fagiuoli,13 Piero L. Almasio,14

on behalf of the Italian Association of the Study of the Liver Disease (AISF).

$n$: 920    SVR: 13.5% IFN Alpha mono for 1 year. Follow up 8 years

**Conclusion:** in patients with HCV-related cirrhosis, SVR after IFN therapy is associated with

- A reduction of liver-related mortality
- Lower rate of complications
- Lower HCC development.
IFN therapy not only improves hepatic inflammation and fibrosis, but also leads to a reduction in the incidence of HCC, particularly in patients achieving a sustained virological response (SVR)

Clinical events in patients with and without (SVR) in HCV pts with advanced fibrosis


N:479  CVR: 29.6%, NCVR: 70.3 %
Clinical events in patients with and without (SVR) in HCV pts with advanced fibrosis


N: 479  CVR: 29.6%, NCVR: 70.3%
Long-term follow-up of the German HCV (1b)-contaminated anti-D cohort

Recipients of HCV(1b) contaminated anti-D immunoglobulin 1978/79 (n=2867)

25 years of follow up (n=1980)

Patients lost to fU (n=1343)

Continuous surveillance (n=537)

Inclusion of additional patients of the original cohort (n=181)

35 years of follow-up (n=718)
Clinical outcome of HCV at 35 years after infection in German Hepatitis C Virus (1b)-Contaminated Anti-D Cohort

Wiese M et al, Hepatology 2014

- Overall cohort:
  - 9.3% (n=67)
- Spontaneous recovery:
  - 4.2% (n=30)
  - 1.1% (n=2)
  - 1.1% (n=2)
- Treatment naive:
  - 4.8% (n=9)
  - 2.5% (n=5)
  - 1.5% (n=3)
- SVR:
  - 6.6% (n=13)
  - 0.7% (n=1)
- Non SVR:
  - 6% (n=9)
  - 3.3% (n=6)
  - 0.7% (n=1)
  - 0.7% (n=1)

- F3 fibrosis:
  - 14.2% (n=28)
- HCC:
  - 15.3% (n=28)
- Cirrhosis:
  - 18% (n=28)
- Death:
  - 18% (n=28)
After inoculation of HCV

- 9.3% of patients showed clinical signs of liver cirrhosis at 35 years after infection
- Those with self limited HCV and those with SVR had less progression to cirrhosis
- Obesity and overweight increased the rate of fibrosis progression to cirrhosis and decreased survival in 35 years of follow up
Effect of IFN on the development of HCC

<table>
<thead>
<tr>
<th>Design</th>
<th>Treated (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishiguchi 95</td>
<td>RCT</td>
<td>4</td>
</tr>
<tr>
<td>Mazzella 96</td>
<td>NRCT/P</td>
<td>3</td>
</tr>
<tr>
<td>Fattovich 97</td>
<td>NRCT/P</td>
<td>4</td>
</tr>
<tr>
<td>Bruno 97</td>
<td>NRCT/P</td>
<td>7</td>
</tr>
<tr>
<td>Serfaty 98</td>
<td>NRCT/P</td>
<td>4</td>
</tr>
<tr>
<td>IIHCSG 98</td>
<td>NRCT/R</td>
<td>9</td>
</tr>
<tr>
<td>Imai 98</td>
<td>NRCT/R</td>
<td>25</td>
</tr>
<tr>
<td>Benvegnu 98</td>
<td>NRCT/R</td>
<td>5.6</td>
</tr>
<tr>
<td>Valla 99</td>
<td>RCT</td>
<td>11</td>
</tr>
<tr>
<td>Ikeda 99</td>
<td>NRCT/R</td>
<td>4.8</td>
</tr>
<tr>
<td>Inoue 2000</td>
<td>NRCT/R</td>
<td>2.2</td>
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</table>
## HCC Occurrence in Sustained Viral Responders and Nonresponders

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<thead>
<tr>
<th>Study</th>
<th>Year</th>
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<th>Mean Follow-up</th>
<th>SVR %</th>
<th>SVR</th>
<th>Non SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arase et al</td>
<td>2007</td>
<td>Japan</td>
<td>500</td>
<td>469 IFN, 31 IFN/ RBV</td>
<td>7.4</td>
<td>140/500 (28%)</td>
<td>13/140 (9.3%)</td>
<td>58/360 (16.1%)</td>
</tr>
<tr>
<td>Coverdale et al</td>
<td>2004</td>
<td>Australia</td>
<td>343</td>
<td>IFN</td>
<td>6.81</td>
<td>50/343 (14.6%)</td>
<td>1/50 (2%)</td>
<td>23/293 (7.8%)</td>
</tr>
<tr>
<td>Tanaka et al</td>
<td>2000</td>
<td>Japan</td>
<td>594</td>
<td>IFN</td>
<td>4.8</td>
<td>175/594 (29.5%)</td>
<td>3/175 (1.7%)</td>
<td>30/419 (7.2%)</td>
</tr>
<tr>
<td>Kobayashi et al</td>
<td>2007</td>
<td>Japan</td>
<td>1124</td>
<td>1039 IFN, 85 IFN/ RBV</td>
<td>5.5</td>
<td>373/1124 (33.2%)</td>
<td>13/373 (3.5%)</td>
<td>61/751 (8.1%)</td>
</tr>
<tr>
<td>Hung et al</td>
<td>2006</td>
<td>Taiwan</td>
<td>132</td>
<td>IFN/ RBV</td>
<td>3.1</td>
<td>73/132 (55%)</td>
<td>5/73 (6.8%)</td>
<td>11/59 (18.6%)</td>
</tr>
<tr>
<td>Bruno et al</td>
<td>2007</td>
<td>Italy</td>
<td>920</td>
<td>IFN</td>
<td>8</td>
<td>124/920 (13.5%)</td>
<td>7/124 (5.6%)</td>
<td>122/759 (16.1%)</td>
</tr>
<tr>
<td>Hirakawa et al</td>
<td>2008</td>
<td>Japan</td>
<td>1193</td>
<td>1032 IFN, 161 IFN/ RBV</td>
<td>8.3</td>
<td>1193/1193 (100%)</td>
<td>9/1193 (0.75%)</td>
<td></td>
</tr>
<tr>
<td>Mallet et al</td>
<td>2008</td>
<td>France</td>
<td>96</td>
<td>61 IFN, 34 IFN/ RBV, 1 PEG-IFN/ RBV</td>
<td>9.8</td>
<td>39/96 (40.6%)</td>
<td>3/39 (8.6%)</td>
<td>14/57 (24.6%)</td>
</tr>
<tr>
<td>Cardoso et al</td>
<td>2010</td>
<td>France</td>
<td>307</td>
<td>33 IFN ± RBV, 22 PEG-IFN, 252 PEG-IFN/ RBV</td>
<td>3.5</td>
<td>103/307 (33%)</td>
<td>6/103 (5.8%)</td>
<td>40/204 (19.6%)</td>
</tr>
</tbody>
</table>
• Risk factors for HCC in patients with CHC include male sex, age older than 50 years, co-morbidities and the presence of cirrhosis.
In 97% of patients with CHC, SVR is durable without evidence of disease progression,

SVR may be associated with subsequent improvement in portal hypertension and perhaps partial regression of fibrosis as shown by transient elastography

Patients with pre-treatment cirrhosis are at continuing low risk for hepatocellular carcinoma

• Up to 5%-6 % of patients with SVR may develop HCC on long-term follow up
  
  • Sato A et al. Japan. Intern Med 2013,
  • Asahina Y et al. Hepatology 2013
  • Lok A et al. Gastroenterology 2009
A retrospective analysis and a prospective study of patients followed up for 6.8 years conducted in Japan showed that HCC risk was reduced, but not abolished, in patients with cirrhosis

Impact Of Peginterferon And Ribavirin Therapy on Hepatocellular Carcinoma: Incidence And Survival In Hepatitis C Patients With Advanced Fibrosis

• **307** chronic HCV patients with bridging fibrosis (n = 127) or cirrhosis (n = 180) treated with IFN (different regimens) and followed for 3.5 years were analysed

• **33%** achieved SVR

• **non-SVR patients had**
  - 4.72 fold higher rate of HCC
  - 6.70 fold higher rate of liver-related complications and
  - 6.10 fold higher rates of liver-related death than SVR patients

*Cardoso et al.* J Hepatol 2010;52:652–657
IMPACT OF PEGINTERFERON AND RIBAVIRIN THERAPY ON HEPATOCELLULAR CARCINOMA: INCIDENCE AND SURVIVAL IN HEPATITIS C PATIENTS WITH ADVANCED FIBROSIS


Fig. 1. Cumulative incidence of hepatocellular carcinoma stratified according to response to treatment (p < 0.001, by log-rank test). SVR, sustained virological response.

Fig. 2. Cumulative incidence of liver-related complications stratified according to response to treatment (p <0.001, by log-rank test). SVR, sustained virological response.
Why HCC may still develop despite SVR

- Patients with advanced fibrosis /cirrhosis
- Concomitant diseases (diabetes, NAFLD, ASH)
- Small HCC present before SVR
The risk of HCC was associated with:

- Age (patients 45-60 & >60 had 8-9 times increased risk for developing HCC compared to patients <45)
- Severity of liver disease
- Diabetes mellitus'

Continued HCC surveillance among patients with cirrhosis and SVR is recommended.
OTHER BENEFITS OF HCV TREATMENT?
Cognitive Functions Improve After Successful Viral Eradication

Significant improvement in neurocognitive function was observed 12 months after the end of successful viral eradication with pegylated α-interferon-2b and ribavirin

Kraus MR et al. HEPATOLOGY 2013;58:497-504.
Health Related Quality of Life (HRQL) improves with Treatment in Chronic HCV

*Bezemer et al. BMC Gastroenterology 2012, 12:11*

DITTO study group

SF-36 in MALES at baseline and at 24 weeks after completion of treatment (follow-up).

SF-36 in FEMALES at baseline and at 24 wks after completion of treatment (follow-up).
HRQOL is influenced by

- Presence of cirrhosis
- Age,
- Gender,
- Country (cross cultural differences)
- Response to treatment.
- Awareness of response status to therapy
Conclusions

• There is beneficial effect of viral clearance in HCV patients on progression of liver disease, decompensation, mortality and HCC development

• HCC may still develop in responders at all stages of fibrosis but especially in pts with advanced fibrosis and cirrhosis

• People at risk should undergo surveillance for HCC even after SVR

• With the availability of newer and more effective therapies, SVR rates can be increased and HCC incidence rates can be reduced in HCV-infected persons
I'M AN INCURABLE OPTIMIST!

Everything is going well!
Opportunities are many!
The world is great!
I am a winner!
Something wonderful is going to take place!
I am a success!
Everything is fine!
I will fulfil my dreams!
It's going to happen!

Go for it today!
Incurable optimism better than dark pessimism

- Better results expected from newer treatments
- Access to treatment and affordability is crucial
- Early diagnosis = Better outcome
- Molecular prediction of cancer risk / genomic profiling
- Identification of patients at risk for HCC and in the need of surveillance after SVR
“Intellectuals solve problems; geniuses prevent them.”