HCV Therapy with DAAs Prevents Liver Transplants

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There is no debate that hepatitis C can be cured (SVR) with DAA’s.
Caveats

1. DAA therapy ~ SVR
Caveats

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2. Data extrapolated from IFN-related SVR
What happens to the liver after viral eradication (SVR)?

- Fibrosis
- Liver decompensation
- Hepatocellular carcinoma
- Liver transplantation
- Death
SVR leads to regression of fibrosis

• N=3010, pooled from 4 large prospective studies
• Paired liver biopsies before and 24 weeks after IFN therapy
• Results:
  – Reversal of cirrhosis was observed in 49% (75/153) patients with baseline cirrhosis.
  – Six factors were independently associated with the absence of significant fibrosis after treatment:
    • baseline fibrosis stage (odds ratio [OR]=0.12; P<0.0001)
    • sustained viral response (OR=0.36; P<0.0001)
    • age < 40 years (OR=0.51; P<0.001)
    • Body mass index <27 kg/m² (OR=0.65; P<0.001)
    • no or minimal baseline activity (OR=0.70; P=0.02)
    • viral load <3.5 millions copies per milliliter (OR=0.79; P=0.03).
What happens to the liver after viral eradication (SVR)?

REGRESSION
- Fibrosis
- Liver decompensation
- Hepatocellular carcinoma
- Liver transplantation
- Death

STOP

PROGRESSION
SVR reduces liver decompensation

- n=479, multicenter, retrospective cohort study
- Consecutively treated patients with advanced fibrosis or cirrhosis
- Liver failure: ascites, bleeding esophageal varices, jaundice, hepatic encephalopathy

Figure. Kaplan-Meier curves showing the occurrence (95% CI) of clinical events in patients with and without sustained virologic response (SVR).

SVR improves liver function in decompensated cirrhotics

Solar – SOF/LDV, Ally - SOF/DCV, Astral -SOF/VPV

Table 2. Changes in measurements of hepatic decompensation following DAA therapy among patients with chronic HCV infection and advanced liver disease.

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<td>Time at evaluation</td>
<td>SVR-4</td>
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<td>MELD changes</td>
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CTP, Child-Turcotte-Pugh score; DAA, direct-acting antiviral; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SVR, sustained virological response (at 4; 12 or 24 weeks after DAA therapy).
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What happens to the liver after viral eradication (SVR)?

REGRESSION

✓ Fibrosis
✓ Liver decompensation
• Hepatocellular carcinoma
• Liver transplantation
• Death

PROGRESSION
SVR reduces the risk for HCC

- A systematic review of 34 studies, including 5 meta-analyses

- Overwhelming consensus of the results... patients who achieve SVR have a considerably reduced risk for HCC in comparison with untreated patients or those who fail to achieve SVR

- One meta-analysis:
  - 29 studies
  - N=3310 cirrhotics
  - RR=0.35 (p<0.00001)

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Figure 2. Forrest plot for HCC development in patients with HCV cirrhosis: comparison of treated patients with antiviral therapy (IFN or IFN and RBV) and untreated patients.

Smith-Palmer J, Cerri K, Valentine W. BMC Infectious Diseases;2015:1-19
Singal A et al. Clin Gastroenterol Hepatol 2010;8:192-199
Tenet: There are always exceptions to every rule
And when HCC does occur...

Fig. 2. The BCLC staging system for HCC. M, metastasis classification; N, node classification; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
What happens to the liver after viral eradication (SVR)?

- **REGRESSION**
  - Fibrosis
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  - Hepatocellular carcinoma
    - Liver transplantation
    - Death

- **STOP**

- **PROGRESSION**
SVR reduces need for LT in HCV with advanced fibrosis

- n=530, international, multicenter long term study of IFN-based treatment
- Median follow up: 8.4 years (IQR, 6.4-11.4)
- SVR vs no SVR
  - HR=0.26 (p<0.001) for all cause mortality
  - HR=0.06 (p<0.001) for liver-related mortality and LT
  - HR=0.19 (p<0.001) for HCC
  - HR=0.07 (p<0.001) for liver failure

Van der Meer et al, JAMA 2012;308:2584-2593.
SVR leads to delisting from the LT waitlist

- N=103 consecutive listed patients without HCC, treated with DAA in 11 European centers

Fig. 2: Competing risk cumulative incidence of patients. (A) Patients that were inactivated, dropped out, underwent LT or died. (B) Of those patients that were delisted, dropped out, underwent LT or died.
SVR leads to delisting

- N=103 consecutive listed patients without HCC, treated with DAA in 11 European centers

35% inactivated at 6 mos

20% delisted at 6 mos

Inactivated patients:
- MELD improvement of 4 points (p<0.0001)
- CTP improvement of 3 points (p<0.0001).
SVR leads to delisting

- N=103 consecutive listed patients without HCC, treated with DAA in 11 European centers

35% inactivated at 6 mos

20% delisted at 6 mos

Belli LS et al. J Hepatol 2016;65:524-531
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- Fibrosis
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  - Death
SVR reduces all-cause mortality in HCV patients

- Meta-analysis of 31 studies, n=33,360
- Median: 5.4 years (IQR, 4.9-7.5)
- HR=0.50 for general population
- HR=0.26 for cirrhotic group

Fig. 2. Percent reduction in all-cause mortality in patients with SVR. Achievement of SVR results in significant reductions in all-cause mortality. This is seen in the general population of HCV-infected patients, as well as subgroups with cirrhosis and with HCV-HIV coinfection [14].
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STOP

PROGRESSION
Can DAA’s (SVR) prevent liver transplantation? YES!
Rebuttal
Indications for LT in waitlisted patients: latest SRTR report

OPTN/SRTR 2015 Annual Data Report: Liver

W. R. Kim\textsuperscript{1,2}, J. R. Lake\textsuperscript{1,3}, J. M. Smith\textsuperscript{1,4}, M. A. Skeans\textsuperscript{1}, D. P. Schladt\textsuperscript{1}, E. B. Edwards\textsuperscript{5,6}, A. M. Harper\textsuperscript{5,6}, J. L. Wainright\textsuperscript{5,6}, J. J. Snyder\textsuperscript{1,7}, A. K. Israni\textsuperscript{1,7,8}, B. L. Kasiske\textsuperscript{1,8}
Trends of HCV as indication for adding to the waitlist for LT

Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation

David Goldberg,1,2,3,*, Ivo C. Ditah,4,∗ Kia Saeian,5 Mona Lalehzari,5 Andrew Aronsohn,6 Emmanuel C. Gorospe,7 and Michael Charlton8

Gastroenterology 2017;152:1090-1099
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The prevention of LT with SVR (DAA’s)
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- Advanced fibrosis/cirrhosis
- No or early fibrosis
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