HCC and Direct acting antivirals for HCV after resection of HCC: Friend or Foe?

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Natural course of hepatitis C virus Infection

Initial infection; acute hepatitis

Spontaneous viral loss

Chronic Hepatitis (fibrosis)
Minimal → Moderate → Marked

Compensated cirrhosis

Decompensated cirrhosis → HCC

6-12 months
20-40+ years
HCV-related mechanisms of carcinogenesis

Vescovo et al. Clinical Microbiology and Infection, 2016
Hepatitis C Virologic Cure Associated With Improved Outcomes

Mechanisms of IFN for HCC prevention

1. Antiproliferative effects
2. Direct antiviral effects
3. Direct antitumor effects
   - induction of proapoptotic genes
   - upregulation of tumor suppressors
   - inhibition of angiogenesis
   - \( \uparrow \) antitumor immune responses
     : upregulate NK cell activity
     : increase circulating levels of Th cell

# DAA-based treatment
- Antiviral effect
- No clear direct antitumor or anti-inflammatory effects
Current All-Oral Therapies Highly Effective, Simple, Well Tolerated

- IFN: Interferon
- PBV: Ribavirin
- PegIFN: Peginterferon
- DAA: Direct-Acting Antivirals

<table>
<thead>
<tr>
<th>Year</th>
<th>Standard Interferon (IFN)</th>
<th>Ribavirin (RBV)</th>
<th>Peginterferon (pegIFN)</th>
<th>PegIFN/RBV ± DAA</th>
<th>All-Oral DAA ± RBV</th>
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</thead>
<tbody>
<tr>
<td>1991</td>
<td>6</td>
<td>16</td>
<td>34</td>
<td>39</td>
<td>55</td>
</tr>
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<td>1998</td>
<td>34</td>
<td>42</td>
<td>55</td>
<td>70+</td>
<td>90+</td>
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<tr>
<td>2001</td>
<td>42</td>
<td>39</td>
<td>70+</td>
<td>90+</td>
<td>95+</td>
</tr>
<tr>
<td>2011</td>
<td>55</td>
<td>70+</td>
<td>90+</td>
<td>90+</td>
<td>95+</td>
</tr>
<tr>
<td>2013</td>
<td>70+</td>
<td>90+</td>
<td>90+</td>
<td>90+</td>
<td>95+</td>
</tr>
<tr>
<td>Current</td>
<td>95+</td>
<td>95+</td>
<td>95+</td>
<td>95+</td>
<td>95+</td>
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</tbody>
</table>
Direct Acting Antiviral Agents

...Previr

- NS3-4A protease inhibitor
- Boceprevir
- Telaprevir
- Simeprevir
- Paritaprevir
- Asunaprevir

...Asvir

- NS5A inhibitor
- Daclatasvir
- Ledipasvir
- Ombitasvir

...Buvir

- NS5B inhibitor
- Polymerase inhibitor
- Dasabuvir
- Sofosbuvir
- Beclabuvir
Modulation of HCV-related HCC development by anti-HCV therapies

- SVR by DAAs: 30-40%
- SVR by interferon: ~1%
- SVR by interferon: < Up to ~5%?
- SVR by DAAs: < Up to ~5%?

Host risk factors:
- Metabolic disorders
- High AFP, inflammation

Viral risk factors:
- Core gene variants
- Genotype 3
Soon Sun Kim <cocorico99@gmail.com>

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 교수님들께

최근에 J Hepatology에 나온 논문 중에

DAA 치료 후 HCC가 recurrence가 더 잘 된다는 논문이 있습니다.

AASLD에서도 잡깐 언급이 있었고, 아직 단정하기는 어렵지만 (이해하기도 어렵고)

저도 DAA 치료 중 재발하는 환자가 최근에 있어서 좀 걱정이 됩니다.

진료에 참고하시길 바랍니다.

김순선 올림.
Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy

María Reig¹,‡, Zoe Mariño²,‡, Christie Perelló³, Mercedes Iñarrairaegui⁴, Andrea Ribeiro¹, Sabela Lens², Alba Díaz⁵, Ramón Vilana⁶, Anna Darnell⁶, María Varela⁷, Bruno Sangro⁴, José Luis Calleja³, Xavier Forns²,‡, Jordi Bruix¹,§,‡

¹Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; ²Liver Unit, Hospital Clinic, IDIBAPS, University of Barcelona, CIBERehd, Barcelona, Spain; ³Liver Unit, Hospital Universitario Puerta de Hierro, CIBERehd, IDIHPHM, Madrid, Spain; ⁴Unidad de Hepatología, Clínica Universidad de Navarra, IDISNA, CIBERehd, Pamplona, Spain; ⁵Department of Pathology, BCLC Group, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, Spain; ⁶Department of Radiology, BCLC Group, Hospital Clinic Barcelona, University of Barcelona, Spain; ⁷Liver Unit, Hospital Universitario Central de Asturias, Oviedo, Spain

- HCV-related early HCC who achieved complete response after resection (n=20), ablation (n=32) or TACE (n=6)
- Incidence of HCC recurrence immediately after DAA Tx: 27.6%
Consecutive patients (n = 344) who had hepatitis C-related cirrhosis of Child Pugh A or B. Patients received various DAA combinations.

During 24-week follow-up, HCC was detected in 26 (7.6%) patients.
- 17 of 59 (28.81%) patients with previous HCC
- 9 of 285 patients (3.16%) without previous HCC

Conti F et al. J Hepatol 2016
Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma

Three French prospective multicenter ANRS cohorts of > 6,000 DAA treated patients who underwent curative HCC therapies
- Cirrhotic, non-cirrhotic, liver transplant patients
- No evidence was found to support an increased risk of HCC recurrence in patients with DAA; 12.7% in treated group vs. 20.5% in untreated group

ANRS collaborative study group. J Hepatol 2016
Explanation for the link between DAA therapy and increased HCC occurrence - Breakdown of immune surveillance -

- A fall of antigenic load promotes a hyporesponsive state of memory-helper T cells
- Rapid decline of HCV viral load by DAAs leads to the reconstitution of innate immunity and downregulation of type II and III IFNs, their receptors, and interferon stimulated genes
- The lack of interferon activation may allow growth of malignant cells. Immune distortion could favor the growth of existing precancerous lesions
- Lack of immune surveillance and immune attack might allow tumors to grow more rapidly
IFN-free cure of HCV infection alters the soluble inflammatory milieu in patients with liver cirrhosis which could affect HCC surveillance by CD8+ T cells

Sekyere et al. EASL 2017. Abstract
Modulation of the NK cell compartment during IFN-free therapy for chronic HCV Infection

- Immunological Analysis During Interferon-Free Therapy for Chronic Hepatitis C Virus Infection Reveals that viral Load Reduction Decreases NK Cell–Related Cytokines in Serum and TRAIL Expression

Explaination for the link between DAA therapy and increased HCC occurrence
-Regenerative stimulus with oncogenic potential-

- As HCV is cleared, a major regenerative stimulus occurs and as the liver regenerates and repairs itself, small tumors that were present and not clinically detected might accelerate their growth.

- Liver regeneration promotes rapid tumor growth or carcinogenesis after resection for HCC. Recurrence could be accelerated by DAA boosting the growth of invisible HCC.
Explanation for the link between DAA therapy and increased HCC occurrence
- Kinetics of viral eradication -

- Viral eradication under IFN-based regimen translates into a reduction of HCC incidence. The reason for such a difference is probably related to the kinetics of viral eradication that is faster under DAAs.

- Abrupt resolution of infection within days or weeks affects immune cell populations, which will no longer guarantee tumor cell destruction and consequently allow the wake-up of dormant cancer clones.
De Novo or Recurrent HCC after DAA studies at EASL 2017
HCC Recurrence Following HCV DAA Therapy

10 pts had second HCC recurrence or progression

- Tumor recurrence after DAA therapy for HCV patients with previously treated HCC discloses a more aggressive pattern and faster tumor growth

No Increased Risk of HCC Recurrence in Patients Following Interferon-free DAAs

- QuintilesIMS PharMetrics Plus™ claims dataset (2006-2016)
- 143 out of >4,000 HCC-HCV patients initiated an HCV Tx after HCC Tx
- 93 IFN-free DAAs and 50 IFN-containing regimens

There was no significant difference in risk of HCC recurrence with IFN-free DAA-based when compared to IFN-containing treatment regimens, regardless of time since HCV treatment initiation.

Telep L, EASL 2017
HCC Recurrence Equivalent With DAAs and IFN

- Meta-analysis and meta-regression analysis comparing risk of HCC after SVR with DAA- vs IFN-based therapy in 41 studies (N = 13,875)

<table>
<thead>
<tr>
<th>Meta-Regression Results</th>
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**HCC occurrence**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR</th>
<th>Adjusted* RR</th>
<th>95% CI</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Average follow-up</td>
<td>0.88</td>
<td>0.77</td>
<td>0.62, 0.97</td>
<td>0.03</td>
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<tr>
<td>Average age</td>
<td>1.11</td>
<td>1.06</td>
<td>0.99, 1.14</td>
<td>0.08</td>
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<tr>
<td>Treatment</td>
<td>2.77</td>
<td>0.75</td>
<td>0.22, 2.52</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**HCC recurrence**

<table>
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<tr>
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<th>Adjusted* RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average follow-up</td>
<td>0.86</td>
<td>0.79</td>
<td>0.55, 1.15</td>
<td>0.19</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>1.11</td>
<td>0.96, 1.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.36</td>
<td>0.62</td>
<td>0.11, 3.45</td>
<td>0.56</td>
</tr>
</tbody>
</table>

- No difference in HCC occurrence or recurrence between DAA-treated and IFN-treated patients achieving SVR

Waziry R, EASL 2017
De Novo or Recurrent HCC studies at EASL 2017

- Majority reported **NO increase** in HCC *De Novo* occurrence (12/14) or recurrence (9/14) after DAAs when compared with “IFN based” or “untreated” patients

*4 studies reported both De Novo and Recurrence data*
Link between DAA therapy and HCC
- In defense of DAA -

- Selection bias
  - DAAs are used to treat patients with impaired liver function that could not have been treated with IFN
- Inclusion of patients
  - non-curative therapy for HCC
- Insufficient follow up duration
- Short duration between HCC treatment and initiation of DAA therapy
- Long median time between last imaging study and initiation of DAA
Link between DAA therapy and HCC - Recommendations -

1. HCC screening and close follow up is necessary for high risk patients even after achievement of SVR
2. Follow patients who have had recent HCC therapy a little more closely after successful HCV treatment
3. Wait until it is clear that the tumor has been adequately treated without evidence of recurrence prior to undertaking HCV therapy
4. Balance the risks and benefits in each individual patient to guide the optimal time for treatment initiation
5. Randomized prospective trials and large database studies will be required, not only to better quantify HCC recurrence risk but also to identify patients who may be predisposed for development of an aggressive HCC phenotype
6. Studies should aim at identifying biomarkers for predicting HCC development in patients who achieved SVR
Does the DAA therapy increase a patient’s risk of HCC recurrence?