About These Slide

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Journal of Hepatology

- Founded in 1980
- "The Journal of Hepatology publishes original papers, reviews, case reports and letters to the Editor concerned with clinical and basic research in the field of hepatology"
- Published monthly
- Impact Factor 2016: 12.468
- Official journal of EASL
Relationship between serum HBV-RNA levels and intrahepatic viral as well as histologic activity markers in entecavir-treated patients. *Wang et al*

- Serum HBV-RNA are valuable when circulatory HBV-DNA is suppressed by NA-therapy
- Determine intrahepatic viral activity in sHBV-RNA and its contributes to liver histology changes in NA therapy
- Cross-section of serum + biopsies treated with entecavir with undetectable sHBV-DNA in China
- sHBV-RNA (2.33-4.80 log10 copies/ml) detected in 35/47 patients (74.47%)
  - Correlated with intrahepatic HBV-RNA; ratio of intrahepatic HBV-RNA to cccDNA; histological grading
- Re. quasispecies:
  - sHBV-RNA dynamic and more genetically homogenous to intrahepatic HBV-RNA compared to cccDNA
- **sHBV-RNA reflect intrahepatic viral transcriptional activity and associated with disease progression despite suppression of circulating HBV-DNA**
- sHBV-RNA: use for non-invasive diagnostic marker for disease progression?
- Development of novel therapeutics?
- Limitations: only Chinese, no longitudinal observations

*J Hepatol* 2018; 68:16-24
Natural History of Chronic HBV: The 4 Phases and Relevance to Treatment Decisions

**HBV DNA**

**ALT**

**HBeAg**

**Anti-HBe**

<table>
<thead>
<tr>
<th>IMMUNE TOLERANCE</th>
<th>IMMUNE CLEARANCE</th>
<th>IMMUNE CONTROL</th>
<th>IMMUNE ESCAPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High HBV DNA, Normal LFTs, HBeAg positive</td>
<td>High HBV DNA, Abnormal LFTs, HBeAg positive</td>
<td>Low HBV DNA, Normal LFTs, HBeAg neg; anti-HBe pos</td>
<td>High HBV DNA, Abnormal LFTs, HBeAg neg; anti-HBe pos</td>
</tr>
<tr>
<td>Monitor every 6-12 months</td>
<td>At risk of progression to cirrhosis and HCC therefore should be referred for consideration of treatment</td>
<td>Monitor every 6-12 months</td>
<td>At risk of progression to cirrhosis and HCC therefore should be referred for consideration of treatment</td>
</tr>
</tbody>
</table>
Durability of hepatitis B surface antigen seroclearance in untreated and nucleos(t)ide analogue-treated patients. *Yip et al*

- Is NA-induced HbsAg seroclearance (SC) durable?
- SC of HBsAg = functional cure of CHB
- Impact of HBsAb and duration of NA-therapy on the durability of SC
- Retrospective HK cohort; 2000-2016
- 154743 CHB, 4080 with negative HBsAg
- Looked at spontaneous and NA-induced SC
- 5-year cumulative probability of maintaining SC:
  - Comparable with spontaneous and NA-induced SC (88.1% vs. 92.2%, Log-rank test p=0.964)
  - Similar +/- HBsAb (95.4% vs. 95.5%, Log-rank test, p=0.602)
- Seroreversion (SR) in 3 (2%) with consolidation therapy for 6-12 months, none for >12 months
- **NA-induced HBsAg SC is as durable as spontaneous**
- HBsAb not essential for maintaining SC after NA-therapy - therefore development of HBsAb not required before ceasing in those who have SC

<table>
<thead>
<tr>
<th>4080 HBsAg –ve</th>
<th>Confirmed HBsAg SC</th>
<th>HBsAg SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous HBsAg SC n=3563</td>
<td>1771 (49.7%)</td>
<td>75 (2.1%)</td>
</tr>
<tr>
<td>NA induced HBsAg SC n=475</td>
<td>320 (67.4%)</td>
<td>14 (2.9%)</td>
</tr>
</tbody>
</table>

*J Hepatol 2018; 68:63-72*
A novel orally available small molecule that inhibits hepatitis B virus expression. *Mueller et al*

- Standard treatment reduces viraemia but rarely results in sustained HBsAg loss
- Need to identify novel therapies that restore virus specific immune responsiveness
- Discovery of orally bioavailable small molecule inhibitor of HBV gene expression - **RG7834**
- **RG7834** selectivity against CHB evaluated in mice model of CHB +/- entecavir
- **RG7834** significantly reduced levels of HBsAg and lowered viraemia
- Time course RNA-seq analysis - fast and selective reduction mRNAs
- **RG7834** led to a mean HBsAg reduction of 1.09 log10 compared to entecavir
- Combo of **RG7834**, entecavir and IFN led to significant reductions of both HBV DNA and HBsAg levels
- Future preclinical studies necessary

_J Hepatol 2018; 68:412-420_
Eliminating HCV by 2030

**HCV WHO targets:**

- ✓ 65% reduction in mortality
- ✓ 80% reduction in incidence

... compared with 2015 baseline
The contribution of alcohol use disorder to decompensated cirrhosis among people with hepatitis C: An international study. *Alavi et al*

- **DAA era = ambitious HCV targets ?compromised by AUD**
- **Aim:** evaluate contribution of AUD to people with decompensated cirrhosis with HCV
- **Definitions AUD and decomp. cirrhosis**
- **Retrospective population level data**
- **BC/NSW/Scotland - HCV notifications 1995-2011/12/13 linked to hospital admissions 2001-12/13/14 for decomp. cirrhosis**
- **Assessed age standardised decomp. cirrhosis incident rates, associated factors and computed AUD-associated PAFs**

<table>
<thead>
<tr>
<th></th>
<th>HCV</th>
<th>Decomp. Cirrhosis Dx</th>
<th>Decomp. Cirrhosis + AUD</th>
<th>Age at Dx decomp. cirrhosis</th>
<th>AUD associated with decomp. Cirrhosis</th>
<th>PAFs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BC</strong></td>
<td>58487</td>
<td>4.6%</td>
<td>28%</td>
<td>54 IQR 48-60</td>
<td>aHR 1.92 95% CI 1.76-2.10</td>
<td>13% 95% CI 11-15%</td>
</tr>
<tr>
<td><strong>NSW</strong></td>
<td>84529</td>
<td>3.7%</td>
<td>32%</td>
<td>50 IQR 45-56</td>
<td>aHR 3.68 95% CI 3.38-4.00</td>
<td>25% 95% CI 23-27%</td>
</tr>
<tr>
<td><strong>Scotland</strong></td>
<td>31924</td>
<td>4.3%</td>
<td><strong>50%</strong></td>
<td>46 IQR 39-53</td>
<td>aHR 3.88 95% CI 3.42-4.40</td>
<td><strong>40% 95% CI 36-44%</strong></td>
</tr>
</tbody>
</table>

- AUD major contribution to HCV liver disease across all settings (esp. Scotland)
- **Need to combine DAA treatment with management of AUD if WHO targets to be met**

*J Hepatol 2018; 68:393-401*
Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. Fraser et al

- Prevention of HCV transmission among PWID = critical for eliminating HCV

- Estimate impact of current and scaled-up HCV treatment with and without scaling up OST/NSPs across Europe over next 10 years

- 11 European settings

- Collected data on HCV transmission among PWID, stratifying PWID according to intervention status (+/- OST/NSP), HCV treatment status

- HCV transmission model to setting-specific data to project HCV prevalence and incidence among PWID

J Hepatol 2018; 68:402-411
Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *Fraser et al*

**2016...**
- HCV prevalence: <25% (Slovenia, Czech) to >55% (Finland, Sweden)
- HCV treatment: <2% (Amsterdam, Hamburg, Norway, Denmark, Sweden, Finland) to 5% (Slovenia, Czech)

**2026...**
- Current treatment rates: reductions in prevalence (38-63%) in Czech, Slovenia, Amsterdam
- Double treatment rates: reduce prevalence (12-24%) in Belgium, Denmark, Hamburg, Norway, Scotland. NOT in Sweden, Finland
- **80% scaling-up of OST/NSPs with current DAA rates: reduce prevalence (18-97%) in all sites**
- Current treatment rates: reduce incidence to <2% in Slovenia and Amsterdam
  - Increases in current treatment rates needed to achieve the same impact elsewhere; 1.4 to 3x (Czech and France), 5-17x (Scotland, Hamburg, Norway, Denmark, Belgium and Sweden) to 200x (Finland)
- **Scale-up OST/NSP to 80% reduces HCV treatment scale-up needed by 20-80%**

*J Hepatol 2018; 68:402-411*
Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *Fraser et al*

- Scale-up of HCV treatment AND harm reduction interventions needed to minimize HCV transmission among PWID
- Cost effective to add in OST/NSPs compared to DAAs
- Platforms needed to deliver DAAs

*J Hepatol* 2018; 68:402-411
Retreatment with direct-acting antivirals of genotypes 1-3-4 hepatitis C patients who failed an anti-NS5A regimen in real world. *Halfon et al*

- "real world study"
- HCV DAA treatment failure associated with RASs
- Analyse retreatment on baseline NS5A RASs after 1st-line DAA failure
- 2014-2016: 2995 HCV patients exposed to NS5A-inhibitors in 6 French liver centres: 80 (2.7%) relapsed
- Studied 24/80 who failed SVR with 1st line DAA
- SVR12 achieved in 23/24 with 2nd line DAA
- 1 relapsed - baseline Y93N NS5A RAS
- Baseline NS5A RASs found in 20/24: 16/20 retreated with NS5A-inhibitor as 2nd line
- Longer treatment given 2nd line: 24 weeks DAA 1st line 5/24 (21%) vs. 2nd line 15/24 (63%) (Fisher p = 0.0043)
- Failed regimen: *ombitasvir*+*paritaprevir*+*ritonavir*+*dasabuvir*+*ribavirin*
Retreatment with DAA of genotypes 1-3-4 Hepatitis C patients who failed an anti-NS5A regimen in real world. *Halfon et al*

- Showed retreatment of after first line NS5A based regimen failure is effective (96% SVR)
- Real world (88-96%) vs. clinical studies (90-96%) = similar SVR rates
- Limitation: number of patients and disparate regimens
- Baseline RASs did not seem to impact retreatment outcome

**Future:**
- Dual or triple therapy regimens
- Shorter treatment
Protective effect of coffee consumption on all-cause mortality of French HIV-HCV co-infected patients. *Carrieri et al*

- Coffee = anti-inflammatory and hepatoprotective
- Relationship between coffee consumption and risk of all-cause mortality in co-infection
- ANR3 CO13 HEPAVIH - 5 yr follow-up from 2005 in 21 French centres
- Enrolled: 1246; Eligible: 1028 patients
- Annual medical/psychosocial/behavioural data
- 77 deaths = Mortality rate 1.64/100py 95%CI 1.31-2.05
- Leading cause of death: HCV-related
- 1st visit: 26.6% elevated coffee consumption = 50% reduced risk of all-cause mortality [0.5 CI 0.3-0.9 p=0.032]
- ≥3 coffees/day halves mortality risk
- Limitation: standardizing self-reported coffee intake
- ?polyphenols implicated

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV related (inc. HCC)</td>
<td>33 (43)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Cancer unrelated</td>
<td>9 (12)</td>
</tr>
<tr>
<td>AIDS</td>
<td>8 (10)</td>
</tr>
</tbody>
</table>

*J Hepatol 2017; 67:1157-1167*
Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression

Reem Waziry, Behzad Hajarizadeh, Jason Grebely, Janaki Amin, Matthew Law, Mark Danta, Jacob George, Gregory J. Dore

J Hepatol 2017; 67:1204-1212
Background

- Primary liver CA - 5th ♂ 9th ♀ with poor prognosis
- HCC attributed to HCV
- DAA most promising strategies for reducing burden of HCC
- IFN reduces risk of HCC by 77% in cirrhotic patients
- However...
  - Reig et al (Semin Liver Dis 2017; 37:109-118) suggested that DAAs may increase risk of HCC recurrence - created uncertainty

Aim

1. Compare rate of HCC occurrence following SVR with DAA or IFN therapy in patients with HCV-related cirrhosis
2. Compare rate of HCC recurrence following SVR with DAA or IFN therapy in patients with HCV who received curative HCC treatment

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

J Hepatol 2017; 67:1204-1212
Methods

- Literature search: 2000 - 2017
- Studies included assessed HCC outcomes by type and response to HCV therapy
- Data extraction using standardised form
- Risk of bias: Newcastle-Ottawa scale
- Main outcome factors:
  - HCC occurrence following SVR
  - HCC recurrence following SVR and curative HCC treatment
- Studies summarised as averages for continuous variables and proportions for categorical variables
- Incidence rates of HCC calculated per 100 person-years (py)
- Random-effects meta-analysis: determine estimate of HCC incidence rate per 100 py with SVR
- Meta-regression analysis: difference in incidence rates between HCV therapy types after adjustment for age and follow-up
- Sensitivity analysis: assess impact of excluding studies with <1 year follow-up
- Q with chi-square and I² statistics: heterogeneity between studies

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

J Hepatol 2017; 67:1204-1212
Results

6715 citations retrieved

- **344 HCC occurrence eligible**
  - 26 HCC occurrence (IFN=17, DAA=9) included
    - 11523 patients (5521 IFN, 6002 DAA)
    - IFN vs DAA
    - Average FU longer in IFN: 5 vs. 1 years
    - Patients younger in IFN: 52 vs. 60 yo
    - More likely to be Male: 62% vs. 57%
    - Child Pugh A: 100% vs. 66%
    - Geographical distribution more diverse in IFN

- **421 HCC recurrence eligible**
  - 17 HCC recurrence (IFN=7, DAA=10) included
    - 2352 patients (1485 IFN, 867 DAA)
    - IFN vs. DAA
    - Average FU longer on IFN: 5 vs. 1.3 years
    - Patients similar age: 66 vs. 64 yo
    - More likely to be Male: 82% vs. 67%
    - Lower AFP at baseline: 14 vs. 22ng/ml
    - Similar proportion of curative treatment for their initial HCC: 100% vs. 96%
    - Child Pugh A: 100% vs. 66%
    - Geographical distribution less diverse in IFN

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*J Hepatol 2017; 67:1204-1212*
HCC occurrence following SVR

- A IFN: 1.14/100 py (95% CI 0.86-1.52)
- B DAA: 2.96/100 py (95% CI 1.76-4.96)

HCC recurrence following SVR

- C IFN: 9.21/100 py (95% CI 7.18-11.81)
- D DAA: 12.16/100 py (95% CI 5.00-29.58)

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Results

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Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

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J Hepatol 2017; 67:1204-1212
Results
Incidence rates per 100 py

HCC occurrence following SVR
A and B: Incidence lower with longer follow-up and younger age

HCC recurrence following SVR
C and D: Incidence lower with longer follow-up and younger age

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

J Hepatol 2017; 67:1204-1212
Results
Meta-regression after adjusting for study follow-up and age

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

Table 3. Meta-regression analysis of factors associated with occurrence of hepatocellular carcinoma following HCV cure (Observations = 26).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>DAA</td>
<td>2.77</td>
<td>1.46–5.25</td>
</tr>
<tr>
<td>Average follow-up, years</td>
<td>0.88</td>
<td>0.80–0.97</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>1.03–1.18</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>1.01</td>
<td>0.99–1.03</td>
</tr>
</tbody>
</table>

Table 4. Meta-regression analysis of factors associated with recurrence of hepatocellular carcinoma following HCV cure (Observations = 17).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
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</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>DAA</td>
<td>1.36</td>
<td>0.49–3.76</td>
</tr>
<tr>
<td>Average follow-up, years</td>
<td>0.86</td>
<td>0.70–1.05</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>0.96–1.28</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>1.01</td>
<td>0.97–1.05</td>
</tr>
</tbody>
</table>

DAA: NOT associated with higher HCC occurrence or recurrence compared to IFN

J Hepatol 2017; 67:1204-1212
Results

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

Study Type

<table>
<thead>
<tr>
<th></th>
<th>HCC Occurrence</th>
<th>HCC Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average sample size</td>
<td>443 (range; 21-2279)</td>
<td>139 (range; 8-899)</td>
</tr>
<tr>
<td>Prospective</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Retrospective</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Prospective-Retrospective</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Subgroup analyses

- IFN studies and HCC occurrence (adjusting for follow-up and age) showed SVR highly associated with reduced HCC risk (RR = 0.37; 95% CI 0.25-0.54: p<0.001)

Sensitivity analysis

- Excluded studies (n=6) with <1 yr follow-up - therapy type (IFN ref.) not associated with higher risk of HCC occurrence (RR=0.67; 95% CI 0.16-2.77; p=0.56) or recurrence (RR=0.57; 95% CI 0.21-1.55; p=0.25)
Discussion

- Considerable controversy past year
- No evidence that DAAs impact on rate of HCC; when adjusted for age and follow-up
- HCV cure following DAA should reduce risk of HCC to similar extent as IFN - sub-group analysis estimated 63% reduction
- Higher cure rates of DAAs mean the impact on HCC incidence is higher
- Data shows apparent “higher risk” of HCC associated with DAAs
  - Older age and advanced cirrhosis are predictors of HCC and this higher risk population being treated with DAAs
  - Therefore higher HCC risk in those treated with DAAs resulted in 3x higher HCC incidence (3.1 vs. 1.1/100 py)
- Incidence will depend on other factors… screening, mechanisms of detection, timing of follow-up

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

J Hepatol 2017; 67:1204-1212
Discussion

- Timing of HCC detection in most studies was at EOT (19/24), therefore undiagnosed HCC at baseline more likely to be Dx “new HCC” post-treatment if duration is short [DAA 12-24 weeks) vs. IFN (24-48 weeks)]

- Cohort effect - higher initial HCC risk with progressive lowering with time relates to both a higher baseline HCC risk profile for DAA treatment.
  - Possibility that many of the early post-treatment HCC cases detected were NOT new…

- Difficulty distinguishing HCC recurrence between progressions de novo vs new lesions

- Recommend continued HCC screening for cirrhotic patients post DAA treatment

Concludes:

- *No evidence to support a hypothesis of differential impact of IFN and DAA based cure on risk of HCC occurrence and recurrence*

- *No reason to withhold or defer DAA therapy*

*Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.*

J Hepatol 2017; 67:1204-1212
My thoughts

- Well-designed meta-analysis and regression
- Contributes to clinical debate
- Reig *et al* – biased because DAAs allow treatment of sicker older patients… and allow them to live long enough for a pre-existing cancer to manifest. Pre-DAAs these patients would not have been treated and would have died of ESLD without knowing they were pre-symptomatic with HCC
- Small number of studies, many retrospective
  - No large randomized controlled clinical trials
  - Unethical to randomize DAA therapy?
- Need for larger prospective studies with longer term follow-up
- Geographical variation eg all IFN-based Japanese, DAA-based European

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

*J Hepatol* 2017; 67:1204-1212
My thoughts

- Pooled heterogeneity
  - Sample size, inclusion criteria, treatment schedule, screening programs etc.
  - Interest limited by the relevant clinical heterogeneity

- Explore if study design (prospective vs. retrospective) source of heterogeneity by sensitivity analysis, and uni- and multi-variate meta-regressions

- Key variables not included
  - Tumour burden, Barcelona clinic liver cancer stage
  - Presumably due to lack of data

- Statistical conclusions (no association between DAA therapy and HCC risk) are valid and in keeping with study aims

Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression.

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