Do direct acting antivirals cure chronic hepatitis C?

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57% of the 71 million people with chronic hepatitis C infection, which corresponds to a prevalence of 1.6%. Nearly 400 000 people with chronic hepatitis C die each year, mostly from cirrhosis and hepatocellular carcinoma. 1 In the United States, hepatitis C is the most common cause of chronic liver disease and the most frequent indication for liver transplantation. 2

Direct acting antivirals (DAAs) are relatively new drugs that have been hailed as a cure for chronic hepatitis C. 1, 2 The drugs are taken orally and the treatment duration varies between eight and 24 weeks. The chosen DAA regimen is based on several factors, including the infecting genotype and pre-existing viral mutations, natural history and stage of the disease, availability of drugs, prior treatment history, and potential adverse effects. 3

Guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the World Health Organisation recommend early treatment with DAAs for all patients with chronic hepatitis C. 4, 5 These guidelines define successful treatment as sustained virological response (SVR), which is the inability to demonstrate hepatitis C virus RNA in the blood 12-24 weeks after the end of treatment and thereafter. 6, 7

However, the clinical implications of achieving sustained virological response are unclear. 8 The evidence for using sustained virological response as a surrogate marker for improvement in mortality, liver cancer, and liver related complications consists of observational studies that are often uncontrolled and subject to confounding. 9, 10 The use of the word “cure” is not adequate because some patients who achieve sustained virological response can relapse years later with genetically identical viruses, suggesting that the virus latentely existed in the body during that time, and patients who achieve sustained virological response can progress to end stage liver disease. 11

It is uncertain if DAAs offer a meaningful clinical benefit in terms of reduced hepatitis related complications and mortality in these patients.

What is the evidence of uncertainty? (box 1)

The Cochrane systematic review (138 randomised clinical trials, 25 232 participants) evaluated 51 different DAAs compared with placebo or no intervention. Eighty four trials involved DAAs on the market or still under development (13 466 participants). 1 Fifty seven trials were on DAAs that have since been withdrawn. 2 Most trials primarily assessed effects on...
sustained virological response and there were relatively limited data on clinically important outcomes and none on long term effects.²

There was no evidence to judge the effects of DAAs on the clinically important outcomes: ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, and hepatocellular carcinoma. Meta-analysis of the effects of all DAAs on the market or under development showed no evidence of a difference with regard to all cause mortality in DAAs recipients compared with controls (2996 participants, 11 trials, very low quality evidence).³ The number of patients with hepatitis C morbidity and mortality observed in the trials was low and it is uncertain how DAAs affect these outcomes.⁴ DAAs achieved sustained virological response in more patients compared with controls (6886 participants, 32 trials, low quality evidence).² Table 1 lists the main results of the Cochrane review.

DAAs do not seem to influence the risk of serious adverse events (for example, death, hospitalisation, persisting adverse events⁵) compared with placebo or no intervention.² Several non-serious adverse effects, such as nausea and dizziness, were reported with DAAs but were not systematically assessed in the review. Follow-up ranged from 1 week to 120 weeks with an average of 34 weeks. All trials and outcome results were at high risk of bias.² No blinded trials on health related quality of life were identified.²

Is ongoing research likely to provide relevant evidence?

We identified two ongoing randomised clinical trials assessing the effects of DAAs compared with no intervention in patients with chronic hepatitis C. Both trials assess safety outcomes, such as serious adverse events and adverse events. We do not expect these will contribute to evidence on the clinical effects of DAAs, as both trials plan to randomise approximately 150 participants with chronic hepatitis C and assess sustained virological response (from 4 to 24 weeks after treatment) as the primary outcome.²

What should we do in light of the uncertainty?

International guidelines recommend early treatment with DAAs in all patients with chronic hepatitis C,⁶ except those with limited life expectancy as a result of non-hepatic causes. We suggest doctors discuss with patients the uncertain long term clinical benefit of DAAs, the risks, and the costs of treatment. Explain to your patient that these drugs will likely clear the virus from their blood; however, there is no evidence so far that DAA treatment will reduce long term risks of liver related complications. They might still develop cirrhosis or cancer and could need a liver transplant eventually. Explain measures to decrease the risk of transmission (for example, avoid unsafe injection practices or unsafe blood transfusions) and to curtail behaviours associated with accelerated liver disease (for example, alcohol use, drug abuse, and obesity).¹⁵

Patients will usually require referral to a specialist, either in primary or secondary care, to discuss appropriate treatment options, and to initiate and monitor treatment. Stakeholders should implement a fairer pricing framework. An analysis of pricing of some of the most commonly used DAAs, sofosbuvir and ledipasvir/sofosbuvir, across 30 countries published in 2016 concluded that DAAs are unaffordable globally.¹⁶ The high costs of these drugs necessitate robust clinical evidence before they can be recommended to all patients with chronic hepatitis C.²

Recommendaations for further research

- Study design: randomised clinical trials with low risks of bias, design errors, and random errors
- Population: patients with chronic hepatitis C̊
- Intervention: direct acting antivirals
- Comparison: placebo
- Outcomes: patient centred clinical outcomes such as all cause mortality, serious adverse events, liver morbidity (ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma), and quality of life in addition to sustained virological response.

² Since progression to end stage liver disease occurs over a period of decades, we recommend trials in patients with advanced fibrosis (for example, stage 3 or 4) and/or patients who are at risk of more rapid progression (for example, connected with HIV).

³ For quality of life trials, we recommend strict blinding of all study participants (including investigators): blinding should include withholding the results of the hepatitis C related tests, including sustained virological response results and other liver related blood tests, from participants.

How patients were involved in the creation of this article

A carer of a patient with chronic hepatitis C reviewed our paper. She suggested we emphasise the importance of considering patient centred outcomes in research on DAAs and while making treatment decisions including impact on quality of life, long term benefit, and mortality. We have outlined the uncertain clinical benefits of DAAs for clinicians to discuss with patients, and the outcomes that future trials on DAAs must consider.

What patients need to know

- Direct acting antivirals (DAAs) are relatively new but costly drugs for chronic hepatitis C
- DAAs have been shown to eradicate hepatitis C virus from the blood (sustained virological response), but their effects on clinically important outcomes are unknown
- No long term randomised clinical trials have shown whether DAAs reduce mortality, affect the risk of liver complications due to chronic hepatitis C, or improve quality of life
- There is an absence of evidence on whether new drugs for hepatitis C cure the disease

Education into practice

- How would you offer treatment advice to a patient with newly diagnosed chronic hepatitis C?
- Based on reading this article, is there anything that you will do differently in your practice?
- How many patients in your practice have hepatitis C? Have they been offered DAAs? How are they being monitored?

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3 Chopra S, Arora S. Clinical manifestations and natural history of chronic hepatitis C virus infection. UpToDate. 2011;52:889-900. doi:10.1093/und/ctr076.10.21427356
13 Koretz RL, Lin KW, Ioannidis JP, Lenzer J. Is widespread screening for hepatitis C justified?BMJ 2015;350:g7809. 10.1136/bmj.g7809 25587052

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# Table

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<tr>
<th>Outcomes</th>
<th>Absolute effects</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (trials)</th>
<th>Quality of evidence (GRADE)</th>
<th>Comments</th>
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<tr>
<td></td>
<td>Risk with placebo or no intervention</td>
<td>Risk with direct acting antivirals (95% CI) (TSA adjusted CI)</td>
<td></td>
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<tr>
<td>All cause mortality at maximum follow-up</td>
<td>2 per 1000 (1 to 42)</td>
<td>7 per 1000 (0.53 to 26.18), (0.71 to 1.33)</td>
<td>2996 (11 RCTs)</td>
<td>Very low</td>
<td>It was not possible to perform TSA because of too few events</td>
</tr>
<tr>
<td>Proportion of participants with one or more serious adverse events at maximum follow-up</td>
<td>541 per 1000 (200 to 281)</td>
<td>56 per 1000 (49 to 55)</td>
<td>52 per 1000 (0.75 to 1.15), (TSA adjusted CI 0.71 to 1.33)</td>
<td>15 817 (43 RCTs)</td>
<td>Very low</td>
</tr>
<tr>
<td>Proportion of participants with no sustained virological response at maximum follow-up</td>
<td>6886 (32 RCTs)</td>
<td>RR 0.44 (0.37 to 0.52), (TSA adjusted CI 0.42 to 0.55)</td>
<td>238 per 1000 (200 to 281)</td>
<td>Low</td>
<td>TSA showed that the boundary for benefit was crossed. This indicates that DAAs achieve sustained virological response in more patients compared with control if risk of bias and other threats to the validity can be disregarded</td>
</tr>
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GRADE Working group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality**: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

**Very low quality**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Footnotes:

1. TSA: Trial sequential analysis
2. Downgraded two levels because of very serious risk of bias in the included trials and two levels due to very serious imprecision (none of the TSA boundaries are crossed so the information size is too low)
3. Downgraded two levels due to very serious risk of bias in the included trials and one level due to serious indirectness (the components of this composite outcome consisted of events with very different degrees of severity, which limits the interpretability of this outcome result)
4. Downgraded two levels because of very serious risk of bias in the included trials
5. CI: confidence interval; OR: odds ratio; RCT: randomised clinical trial; RR: relative risk

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