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PRACTICE

UNCERTAINTIES

Do direct acting antivirals cure chronic hepatitis C?

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What you need to know

- Direct acting antivirals (DAAs) are relatively expensive drugs that have been promoted as a cure for chronic hepatitis C
- There is insufficient evidence to judge if DAAs reduce mortality or other liver related complications from chronic hepatitis C
- Discuss with your patient the uncertain clinical benefit, and the risks and costs of these drugs, to make a shared decision on treatment

Globally, an estimated 71 million people have chronic hepatitis C infection, which corresponds to a prevalence of 1.6%.[1 2] 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.[3]

Direct acting antivirals (DAAs) are relatively new drugs that have been hailed as a cure for hepatitis C.[1 2 4] DAAs target specific proteins of the hepatitis C virus, thereby disrupting replication.[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.[5]

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.[6-8] These guidelines define successful treatment as sustained virological response—that is, the inability to demonstrate hepatitis C virus RNA in the blood 12-24 weeks after the end of treatment and thereafter.[6-8]

However, the clinical implications of achieving sustained virological response are unclear.[2] 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.[9-12] 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 latently existed in the body during that time, and patients who achieve sustained virological response can progress to end stage liver disease.[13]

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)

Box 1: Search strategy and study selection

We have drawn on evidence from our Cochrane review published in 2017 where we searched for all ongoing, published, and unpublished randomised clinical trials assessing the effects of DAAs compared with placebo or no intervention for chronic hepatitis C. We searched in the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, Medline, Embase, Science Citation Index Expanded, LILACS, and BIOSIS; three Chinese databases, Google Scholar, TRIP Database, ClinicalTrials.gov, EMA, WHO International Clinical Trials Registry Platform, FDA, and pharmaceutical company sources.[2] We included adults diagnosed with chronic hepatitis C, regardless of sex, ethnicity, occupation, country of residence, duration of infection, and stage of disease. Patients who had received earlier treatment and those who were treatment naive were both included. We have not identified other relevant trials since the review was published.

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).[2] Fifty seven trials were on DAAs that have since been withdrawn.[2] Most trials primarily assessed effects on

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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 DAA recipients compared with controls (2996 participants, 11 trials, very low quality evidence).[2] 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.[2] 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 events[14]) 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,[6-8] 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]

Recommendations for further research

- Study design: randomised clinical trials with low risks of bias, design errors, and random errors
- Population: patients with chronic hepatitis C[1]
- 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[2] in addition to sustained virological response

[1] 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, coinfected with HIV).

[2] 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?

Provenance: Commissioned, externally peer reviewed.

Contributors: JCJ wrote the first draft. All authors approved the final version, and JCJ is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare no competing interests. All authors of this present paper are also authors of the Cochrane review and editors in the Cochrane Hepato-Biliary Group.

1 World Health Organization. Global hepatitis C report. 2017. http://www.whoint/mediacentre/factsheets/fs164/en

2 Jakobsen JC, Nielsen EE, Feinberg J, etal . Direct-acting antivirals for chronic hepatitis C. *Cochrane Database Syst Rev* 2017. 10.1002/14651858.CD012143.pub3.

3 Chopra S. Clinical manifestations and natural history of chronic hepatitis C virus infection. *UpToDate* 2017. http://www.uptodate.com/index2017.

4 Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011;52:889-900. 10.1093/cid/cir076 21427396

5 Chopra S, Arora S. Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection. *UpToDate* .2018. http://www.uptodate.com/index.

6 AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;62:932-54. 10.1002/hep.27950 26111063
7 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. 2016. *J Hepatol* 2017;66:153-94.27667367
8 World Health Organization. Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version WHO Guidelines Approved by the Guidelines Review Committee2016. http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/
9 Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 2013;158:329-37. 10.7326/0003-4819-158-5-201303050-00005 23460056
10 van der Meer AJ, Veldt BJ, Feld JJ, etal . Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584-93. 10.1001/jama.2012.144878 23268517
11 Veldt BJ, Heathcote EJ, Wedemeyer H, etal . Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007;147:677-84. 10.7326/0003-4819-147-10-200711200-00003 18025443
12 Chopra S, Arora S. Diagnosis and evaluation of chronic hepatitis C virus infection.*UpToDate* 2018. http://www.uptodate.com/index.
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
14 International Conference on Harmonisation Expert Working Group (ICH-EWG). International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice in CFR & ICH Guidelines. 1997;1.
15 Chopra S, Pockros PJ. Overview of the management of chronic hepatitis C virus infection.*UpToDate* 2017. http://www.uptodate.com/index
16 Iyengar S, Tay-Teo K, Vogler S, etal . Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. *PLoS Med* 2016;13:e1002032. 10.1371/journal.pmed.1002032 27243629

Table

Table 1| Summary of main findings from Cochrane review on DAAs

DAAs on the market or under development versus placebo or no intervention for chronic hepatitis C

Outcomes	Absolute effects		Relative effect (95%) CI, (TSA adjusted CI)[1]	No of participants (trials)	Quality of evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with direct acting antivirals (95% CI)				
All cause mortality at maximum follow-up	2 per 1000	7 per 1000 (1 to 42)	OR 3.72 (0.53 to 26.18), (-)	2996 (11 RCTs)	Very low[2]	It was not possible to perform TSA because of too few events
Proportion of participants with one or more serious adverse events at maximum follow-up	56 per 1000	52 per 1000 (49 to 55)	OR 0.93 (0.75 to 1.15), (TSA adjusted CI 0.71 to 1.33)	15 817 (43 RCTs)	Very low[3]	TSA showed that the boundary for futility was crossed. This leads us to conclude that the possible intervention effect, if any, is less than 20%
Proportion of participants with no sustained virological response at maximum follow-up	541 per 1000	238 per 1000 (200 to 281)	RR 0.44 (0.37 to 0.52), (TSA adjusted CI 0.42 to 0.55)	6886 (32 RCTs)	Low[4]	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

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 CI: confidence interval; OR: odds ratio; RCT: randomised clinical trial; RR: relative risk.