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- Co-Ordination Editor, The Cochrane Hepato-Biliary Group
- No conflicts

Chronic hepatitis C

- Globally, an estimated 71 million people have chronic hepatitis C infection, which corresponds to a prevalence of 1.6%
- The WHO global report on hepatitis C estimates that nearly 400,000 people die each year

Direct-acting antivirals (DAAs)

Cochrane Library

Cochrane Database of Systematic Reviews

Direct-acting antivirals for chronic hepatitis C (Review)

Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, Poropat G, Djurisic S, Weiss KH, Bjelakovic M, Bjelakovic G, Klingenberg SL, Liu JP, Nikolova D, Koretz RL, Gluud C

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Direct-acting antivirals for chronic hepatitis C.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012143.
DOI: 10.1002/14651858.CD012143.pub3.

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Hierarchy of evidence

Simulations and systematic review 2003

Evaluating non-randomised intervention studies

JJ Deeks[1*]
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AJ Sowden[3]
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In collaboration with the International Stroke Trial and the European Carotid Surgery Trial Collaborative Groups

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Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;**7**(27).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

Historical examples

- **Leeches**
- **Aminoglycosides for sepsis**
- **Starch for sepsis**
- **Preventive vitamins**
- **Antidepressants**
- **DAAs for chronic hepatitis C?**

Direct-acting antivirals (DAAs)

Guidelines from AASLD, EASL, and the WHO all recommend early treatment with DAAs for all patients with chronic hepatitis C

These guidelines define successful treatment as sustained virological response, i.e. the inability to demonstrate hepatitis C virus RNA in the blood 12-24 weeks after the end of treatment and thereafter

Sustained virological response (SVR)

- Showing an association (or a correlation) between short-term outcomes and long-term clinical outcomes does not validate a surrogate outcome
- Patients who develop SVRs might have underlying characteristics that would predict that they would have better long-term outcomes even if no treatment was provided
- “A correlate does not a surrogate make” (Flemming 1996)

Sustained virological response (SVR)

- The evidence behind using SVR as a surrogate marker for improvement in mortality, liver cancer, and liver-related complications consists only of observational studies
- The use of the word “cure” is not correct because some patients who achieve sustained virological response progress to end-stage liver disease

What are the clinical benefits and harms of DAAs for chronic hepatitis C?

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Methods

- All ongoing, published, and unpublished randomised clinical trials assessing the effects of DAAs compared with placebo or no intervention for chronic hepatitis C
- Adults diagnosed with chronic hepatitis C, regardless of sex, ethnicity, occupation, country of residence, duration of infection, and stage of disease. Both treatment-naive and treatment-experienced participants were included

Methods

- 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 companies

Results

- We identified 138 randomised clinical trials (25,232 participants) assessing the effects of 51 different DAAs
- Eighty-four of the included trials involved DAAs on the market or under development (13,466 participants)

Results

- 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
- Most trials primarily assessed effects on sustained virological response and there were limited data on clinically important outcomes and none on long-term effects

All-cause mortality

- 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
- Meta-analysis showed no difference with regard to all-cause mortality in DAA recipients compared with controls (2996 participants, 11 trials) (DAA 15/2377 (0.63%) versus control 1/617 (0.16%); OR 3.72, 95% CI 0.53 to 26.18, very low-quality evidence)

Serious adverse events (ICH-GCP)

- Meta-analysis and Trial Sequential Analysis showed that DAAs compared with placebo or no intervention do not seem to influence the risk of serious adverse events
- DAA 5.2% versus control 5.6%;
- OR 0.93, 95% CI 0.75 to 1.15,

  15,817 participants, 43 trials

Serious adverse events (ICH-GCP)

Other outcomes?

- There was no evidence on the effects of DAAs on the clinically important outcomes: ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, and hepatocellular carcinoma
- No blinded trials on health-related quality of life were identified

It should not be sufficient to show that an intervention clears hepatitis C virus from the blood, it needs to be shown that an intervention decreases the risk of hepatitis C-related complications!

Conclusion

There is insufficient evidence to judge if DAAs have beneficial or harmful effects on clinical outcomes for patients with chronic hepatitis C

Thank you for your attention!