

Is there sufficient evidence to repeal three decades of clinical research on chronic hepatitis C?

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Main text

A recently published systematic review on the treatment of chronic hepatitis C (CHC) with direct-acting antivirals (DAAs) performed by the Cochrane's Collaboration has reached highly controversial conclusions. [1-2] The authors selected included 138 randomized controlled trials (RCT) with no restriction on patients' stage of disease and the type of DAA combinations. They concluded that there was no evidence either to confirm or to reject the premise that DAAs had any clinical effects and they also stated that sustained virological response (SVR) was an unreliable surrogate marker to assess clinical efficacy. We would like to differ on both these counts. Their results are in discordance with current international guidelines [3-4] the opinion of the of scientific societies for the study of liver diseases in Europe [5] and in America [6] and the endorsement of the World Health Organization (WHO) which state that DAAs can eliminate HCV by 2030 [7-9]. These results reflect an underestimation of the actual value of observational evidence in the context of the current knowledge of CHC clinical management. [10-11]

Current knowledge on CHC

First identified in 1989 [12] Hepatitis C virus (HCV) was associated with severe degenerative processes affecting different tissues and organs including liver damage, metabolism imbalance, immunological deregulation and increased risk of cancer. [13] Studies on the natural history of CHC established that about 15%-20% of subjects exposed to HCV die as a direct consequence of the infection. Therapy against CHC in the '90s involved using a host targeted therapy with alpha interferon plus ribavirin (a weak antiviral compound). DAAs were introduced in 2014. Evidence from clinical studies has demonstrated that DAA combinations have extraordinary efficacy and safety with rate of resolution of infection ranging between 80-100%. [14-18]

SVR (i.e. undetectable HCV RNA over a certain period of time) has been always considered the best surrogate marker for natural and drug induced resolution of HCV infection. Meta-analyses performed on recent RCTs and non-randomized studies have provided strong evidence that patients with SVR experienced significantly lower morbidity and mortality than viremic ones [19-21]. An example of the potential impact of SVR on patients' health is reported in Figure 1 which shows an original overview on five meta-analyses comparing the risk of hepatocellular carcinoma in patients who either did or did not achieve SVR. Overall this analysis suggests that SVR reduce the risk of HCC by 3 to 5 times.

Limitation

The main limitation of the Cochrane review is that its study design, thought formally impeccable, was not tailored to answer the critical clinical questions on CHC management. There are several drawbacks of the study.

Firstly, the study lacks a clinically oriented restriction framework for defining which study population(s) and which intervention(s) are under assessment. [22] Restriction is a strategy commonly employed for controlling confounding bias at the study design by the selection of a homogeneous study sample and comparable

interventions, so that study results are solid within the defined set of assumptions. It is noteworthy that controlling confounding bias at study design level is pivotal in meta-analyses of aggregated data which can hardly manage confounding at the level of analysis (ecological fallacy). [23] The Cochrane review polled results from studies including subjects with radically different clinical background and receiving heterogeneous combinations of DAAs (and interferon). Therapies with DAA can never be considered as a unique intervention. Instead, there is solid evidence that DAAs should be used in specific combinations and defined posology according to diseases stage, exposure to previous treatments, HCV genotype and viral profile of resistance.[2-3] Ignoring that, several combinations of DAA which have been marketed since 2014, are currently considered either sub-optimal (e.g. those including only one DAA) or too toxic (e.g. those including first and second generation DAA plus interferon) [24] may produce results that are inconsistent with the real world clinical practice. In particular, 57 out of 138 RCTs (41%) included in the Cochrane review were studies carried out on DAAs which were never marketed or have already been withdrawn. Moreover, even the analysis to assess efficacy (i.e. SVR) carried out with 33 RCTs including only experimental or approved DAAs can hardly inform clinical decisions. In fact, most of these 33 RCTs had an experimental arm consisting in a single DAA in addition to interferon and ribavirin (currently not recommended). Overall only 3 out of 33 RCTs included in this analysis assessed interferon-free DAA combinations and only 2 of those included an experimental arm consisting in a currently recommend DAA combination.

Secondly, while inclusion criteria based on patients' clinical features and type of interventions were exceedingly wide, criteria for selection of the studies according to design were remarkably strict and only explanatory RCTs, [25] with a control group receiving no DAA, were included. This decision resulted in the exclusion of pivotal information from large phase III trials (including DAAs in parallel arms) and non-randomized studies that resemble current use of DAAs much better than the included RCTs. [26] Even if non-randomized studies fail now and then in prediction of the real effects of new medical interventions, evidence from observational studies may be as credible as those from RCTs to assess unintended events, such as adverse drug reactions. [27] In addition, it is well expected that a set of explanatory RCTs with short follow-up and not entirely focused on patients with cirrhosis would have been severely underpowered to assess sequelae of HCV infections that characterize the final stage of CHC; such as liver morbidity and reduction of life quality. [10]

Finally, the Cochrane review appears to assume that SVR, which has been used for the last 25 years as the main surrogate marker to assess the success of anti-HCV therapy, is fundamentally unreliable as it has never been validated in a formal RCT. This implies that one should also repeal all the current knowledge about clinical management of CHC. In our opinion, the notion that robust enough evidence to guide clinical decisions can only come from RCTs, is based on two crucial misconceptions. Firstly, the idea that randomization is always feasible, which if false as the ethical basis of RCTs [28] relies on the principle of clinical equipoise (i.e. lack of evidence that the experimental treatment is better than the standard of care) and individual uncertainty (i.e. investigators

and patients are uncertain about the merits of the experimental treatment). With regard to CHC, the time of equipoise and uncertainty has well expired since the time of dual therapy with interferon and ribavirin. Thus, randomizing patients for no therapy, to study the effect of SVR on the evolution of CHC (i.e. the natural history) is rather unethical both in term of the risk for the individual patients (who will progress towards end stage liver diseases) and the risk for the community (achieving SVR reduces the infectivity and is crucial step for HCV elimination). [6,29-30] Secondly, the misconception that observational studies are an alternative to experimentation rather than a set of complementary approaches. Observational studies served to investigate non-randomizable conditions and, in fact, interpret correctly the results obtained from RCTs themselves. [18,31]

Merits and perspective

Despite these drawbacks the Cochrane review has several merits. It highlights that DAAs are not the miracle drugs that has been publicly perceived. [7] To prove or disprove this, there is a need to measure the real impact of DAAs both on patients and community welfare.

DAAs are radically innovative compounds. In contrast to interferon based therapy which exert their effect by targeting host cells, [32] DAAs have no effects on host, including those (desirable) on liver fibrosis modulation [33] and enhancement of cellular immunity against cancer. [34] Thus, the questions on whether and how much SVR obtained by DAAs translates into recovery from liver damage, systemic abnormalities and finally improve patients' quality of life is legitimate. Indeed, recent observational studies emphasizes that ALT (a marker of liver cytolysis) normalize in most but not all patients who achieve SVR with DAAs, suggesting that clearance of infection does not always revert damage at cellular level. [35] In addition, from a public health point of view it is pivotal to define the effectiveness (i.e. the general impact) of an extended use of DAAs with the aim of the elimination of HCV. [4] In particular, pros and cons of extended use of molecular testing and expensive therapy with DAAs should be tailored on availability of local resources, patterns of risk for re-infections in special populations and the topical needs of the local communities.

We suggest that future research on CHC should take forward the implementation of high quality quantitative studies to measure how SVR translate into health improvement. These studies need solid and measurable clinical endpoints to assess recovery form CHC associated conditions which may significantly impact on patient's life quality and expectancy; such as: recovery form metabolic imbalance (e.g. insulin resistance), reduction of liver damage (e.g. fibrosis) and improvement of liver function in patients who achieved SVR when cirrhosis was already established. In addition, large population studies are also needed to assess the impact of DAAs on reduction of late CHC sequelae and to explore the potential of DAAs for HCV eradication at a global level.

Conclusion

The results of Cochrane review can hardly inform current clinical decisions. In fact, the systematic review and meta-analyses are mainly based on CHC treatments which are no longer recommend and on outcomes that cannot

be assessed by explanatory RCTs with short follow-ups. At present there is a need to build up reliable models for making more accurate predictions about patient's prognosis and the efficacy of novel treatments and prevention interventions.

RCTs may be practically unfeasible to assess the effect of new DAAs on long term outcomes such as the reduction of the overall mortality and the recovery for extra-hepatic conditions in patients with CHC at an early clinical stage. In these circumstances medical science should be capable of judging quality and take advantage from observational evidence and building on preexisting knowledge. Since currently recommended DAA combinations have already proved to have extraordinary efficacy in obtaining SVR, future studies should be aimed to assess whether SVR: A) coincides with the eradication of HCV infection; B) improves life expectancy; C) can stop, or even revert, hepatic damage; D) is associated with the improvement extra-hepatic conditions related to CHC. Long lasting observational cohort studies are, in our opinion, the best way to assess all these issues.

Moreover, from a public health point of view, there is a need for the implementation of population studies aimed to assess the risk of re-infection and the capability to effectively reach special populations. In fact, as a vaccine is not available, the results of public health programmes aimed to eliminate HCV infection at national and supranational level will mainly depend on the capability to identify social niches of HCV transmission, to provide treatment to difficult-to-reach people and to prevent the risk of reinfection in people with high risk behaviors. In these setting large population studies and, potentially, well-designed population trials such as those implemented for the prevention of HIV (e.g. cluster randomized trials) [36] may be necessary.

Conflict of interests: authors declare non-conflict of interest

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Figure 1. Meta-analyses overview. We searched Pubmed for meta-analyses which: A) directly assess the effect of SVR on the risk of hepatocellular carcinoma; B) included 3 studies or more; C) were published over the last 15 years (i.e. since January 2003). In this way we found 5 large meta-analyses including a total of 45 individual studies (2 RCT, 12 prospective cohorts and 31 historical studies; each study can be included in more than one meta-analysis). The figure reports information of 45,428 cases of CHC (20,891 with SVR and 24,537 without SVR) at different stage of liver diseases and different exposure to interferon and ribavirin. Overall the analysis suggests that SVR reduce the risk of HCC by 3 to 5 times. Heterogeneity was low and due to a unique study. N. Studies indicates the number of studies included in each meta-analysis.

Methodological note. The string used for the search was: (("Hepatitis C"[Mesh] OR "Hepatitis C, Chronic"[Mesh]) AND "Carcinoma, Hepatocellular"[Mesh]) AND "Meta-Analysis"[Publication Type] AND ("2003/01/01"[PDAT] : "2017/12/01"[PDAT])).

We reviewed 46 studies. We excluded 41 studies: 29 focused on condition different from SVR in CHC; 6 focused on HCC recurrence; 4 evaluated adjuvant therapies for HCC; 1 because included only 2 studies and 1 because it was published in Chinese only. We did not provide a unique estimate of pooled effect as a single study may be included in more than one meta-analysis

Reference

- [1] Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database of Systematic Reviews* 2017;6:CD012143
- [2] Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database Syst Rev.* 2017;9:CD012143.
- [3] American Association for the Study of the Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C available at <https://www.hcvguidelines.org/>
- [4] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol.* 2017;66:153-94.
- [5] European Association for the Study of the Liver. Response to the Cochrane systematic review on DAA-based treatment of chronic hepatitis C. *J Hepatol.* 2017;67:663-4.
- [6] American Association For The Study Of Liver Diseases. AASLD Expresses Concern for Cochrane Review of DAA. Available at <https://www.aasld.org/about-aasld/press-room/aasld-expresses-concern-cochrane-review-daas>
- [7] Lanini S, Easterbrook PJ, Zumla A, Ippolito G. Hepatitis C: global epidemiology and strategies for control. *Clin Microbiol Infect.* 2016;22:833-8 PubMed .
- [8] World Health Organization Global Health Sector Strategy On Viral Hepatitis 2016–2021 Towards Ending Viral Hepatitis available at <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1>
- [9] WHO endorses direct-acting antivirals for treatment of hepatitis C <http://www.who.int/hepatitis/news-events/direct-acting-antiviral-cure-hepatitis-c/en/>
- [10] The Lancet Gastroenterology Hepatology. Clinical effects of antivirals for hepatitis C: context is critical. *Lancet Gastroenterol Hepatol.* 2017;2:539.

- [11] Avorn J. In defense of pharmacoepidemiology--embracing the yin and yang of drug research. *N Engl J Med*. 2007 Nov 29;357:2219-21.
- [12] Ippolito G, Capobianchi MR, Lanini S, Antonelli G. Is hepatitis C virus eradication around the corner only 25 years after its discovery? *Int J Antimicrob Agents*. 2015;45:111-2 PubMed ..
- [13] Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol*. 2014;61:S58-S68.
- [14] Sacks HS. Review: In chronic hepatitis C virus infection, oral direct-acting antivirals have high sustained virologic response. *Ann Intern Med*. 2017;167:JC3.
- [15] Berden FA, Aaldering BR, Groenewoud H, IntHout J, Kievit W, Drenth JP. Identification of the Best Direct-Acting Antiviral Regimen for Patients With Hepatitis C Virus Genotype 3 Infection: A Systematic Review and Network Meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15:349-59.
- [16] Ferreira VL, Assis Jarek NA, Tonin FS, Borba HH, Wiens A, Pontarolo R. Safety of interferon-free therapies for chronic hepatitis C: a network meta-analysis. *J Clin Pharm Ther*. 2016;41:478-85.
- [17] Borba HH, Wiens A, Steimbach LM, Perlin CM, Tonin FS, Pedroso ML et al. Network meta-analysis of first- and second-generation protease inhibitors for chronic hepatitis C genotype 1: efficacy based on RVR and SVR 24. *Eur J Clin Pharmacol*. 2017;73:1-14.
- [18] Chen K, Lu P, Song R, Zhang J, Tao R, Wang Z et al. Direct-acting antiviral agent efficacy and safety in renal transplant recipients with chronic hepatitis C virus infection: A PRISMA-compliant study. *Medicine (Baltimore)*. 2017;96:e7568.
- [19] Bang CS, Song IH. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. *BMC Gastroenterol*. 2017;17:46.
- [20] Messori A, Badiani B, Trippoli S. Achieving Sustained Virological Response in Hepatitis C Reduces the Long-Term Risk of Hepatocellular Carcinoma: An Updated Meta-Analysis Employing Relative and Absolute Outcome Measures. *Clin Drug Investig*. 2015;35:843-50.
- [21] Singal AK, Singh A, Jaganmohan S, Guturu P, Mummadi R, Kuo YF et al. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Clin Gastroenterol Hepatol*. 2010;8:192-9.
- [22] Pocock SJ, Stone GW. The Primary Outcome Fails - What Next? *N Engl J Med*. 2016;375:861-70 PubMed
- [23] Govan L, Ades AE, Weir CJ, Welton NJ, Langhorne P. Controlling ecological bias in evidence synthesis of trials reporting on collapsed and overlapping covariate categories. *Stat Med*. 2010;29:1340-56 PubMed .

- [24] Lanini S, Mammone A, Puro V, Girardi E, Bruzzi P, Ippolito G. Triple therapy for hepatitis C improves viral response but also increases the risk of severe infections and anaemia: a frequentist meta-analysis approach. *New Microbiol.* 2014;37:263-76.
- [25] Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. Criteria for distinguishing effectiveness from efficacy trials in systematic reviews. AHRQ Publication No. 06-0046. Rockville, MD: Agency for Healthcare Research and Quality. April 2006.
- [26] Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ.* 1996 ;312:1215-8 PubMed .
- [27] Vandembroucke JP. When are observational studies as credible as randomized trials? *Lancet.* 2004;363:1728-31 PubMed .
- [28] Lanini S, Zumla A, Ioannidis JP, Di Caro A, Krishna S et al. Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa? *Lancet Infect Dis.* 2015;15:738-45 PubMed .
- [29] Raspberry W. Shades of Tuskegee. *Washington Post.* 1997:A19.
- [30] Lanini S, Abbate I, Puro V, Soscia F, Albertoni F, Battisti W et al. Molecular epidemiology of a hepatitis C virus epidemic in a haemodialysis unit: outbreak investigation and infection outcome. *BMC Infect Dis.* 2010;10:257.
- [31] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342:1887-92 PubMed .
- [32] Hervas-Stubbs S, Perez-Gracia JL, Rouzaut A, Sanmamed MF, Le Bon A, Melero I. Direct effects of type I interferons on cells of the immune system. *Clin Cancer Res.* 2011;17:2619-27 PubMed .
- [33] Sobesky R, Mathurin P, Charlotte F, Moussalli J, Olivi M, Vidaud M et al. Modeling the impact of interferon alfa treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. The Multivirc Group. *Gastroenterology.* 1999;116:378-86 PubMed .
- [34] Parker BS, Rautela J, Hertzog PJ. Antitumour actions of interferons: implications for cancer therapy. *Nat Rev Cancer.* 2016;16:131-44 PubMed .
- [35] Welsch C, Efinger M, von Wagner M, Herrmann E, Zeuzem S, Welzel TM et al. Ongoing liver inflammation in patients with chronic hepatitis C and sustained virological response. *PLoS One.* 2017;12:e0171755.

[36] Weiss SM, Zulu R, Jones DL, Redding CA, Cook R, Chitalu N. The Spear and Shield intervention to increase the availability and acceptability of voluntary medical male circumcision in Zambia: a cluster randomised controlled trial. *Lancet HIV*. 2015;2:e181-9.