Clinical effects of antivirals for hepatitis C: context is critical

An article published in *The Guardian* on June 8, 2017, led with the startling headline that "'Miracle' hepatitis C drugs costing £30k per patient 'may have no clinical effect'". The article was reporting on a Cochrane review of randomised clinical trials of direct-acting antivirals (DAAs) for individuals with chronic hepatitis C virus (HCV) infection, which concluded that "DAAs on the market or under development do not seem to have any effects on risk of serious adverse events [but] we could neither confirm nor reject that DAAs had any clinical effects". Given the excitement surrounding the development of DAAs, which form the bedrock on which efforts to eliminate HCV by 2030 are based, what is the basis for these surprising conclusions?

The primary outcomes of the Cochrane review were hepatitis C-related morbidity, serious adverse events, and quality of life; secondary outcomes included all-cause mortality, various common sequelae of advanced liver disease (eg, ascites, variceal bleeding, etc), and sustained virological response (SVR; defined as achieving undetectable HCV RNA over a certain period of time after treatment). However, a close look at the review reveals that no data were available for hepatitis C-related morbidity and only 16 deaths from any cause were reported among nearly 3000 patients included in that analysis, rendering interpretation of these endpoints essentially meaningless. Likewise, only one study among the 138 identified by the review reported on the effect of DAAs on quality of life, making assessment impossible. Meta-analysis showed no difference between those treated with DAAs compared with controls in terms of the risk of serious adverse events (odds ratio 0·93, 95% CI 0·75–1·15), whereas treatment with DAAs significantly reduced the odds of not achieving an SVR (relative risk 0·44, 95% CI 0·37–0·52).

The scarcity of data for hepatitis C-related morbidity and all-cause mortality is unsurprising, given the short follow-up available for many of the trials of DAAs—it takes many years for these outcomes to become apparent. Furthermore, the aim of many of these trials was to demonstrate virological efficacy; they are neither designed nor adequately powered to assess mortality. That only one study investigating the effect of DAAs on quality of life was included in the Cochrane review might be explained by the review's cut-off date for inclusion (October, 2016). Several trials have reported quality-of-life data in recent months, and suggest that the use of DAAs is associated with improvements in quality of life—outcomes that are just as important to patients as hard clinical endpoints, if not more so.

The crux of the study's conclusion seems to be the fact that SVR—although a widely used primary endpoint for trials of HCV treatment—has never been formally validated as a robust surrogate endpoint for hepatitis C-related morbidity or mortality, and therefore is not an adequate measure of clinical effect. Despite the lack of gold-standard validation of SVR in a randomised trial that shows that treatment improves both SVR and later clinical outcomes, a large body of accumulated evidence indicates associations between SVR and improvements in liver function, fibrosis, cirrhosis-related complications, extrahepatic outcomes, and all-cause mortality. Population-level data also indicate that mortality and need for liver transplantation for chronic hepatitis C have decreased since the introduction of DAAs, and multivariate analyses have repeatedly shown that SVR is the strongest predictor of better outcomes, independent of known clinical prognostic factors. It should also be noted that achieving SVR reduces the infectivity of a patient, thus reducing person-to-person transmission and helping to break the chain of infection—a vital step towards elimination.

It is unfortunate that alarmist headlines and a lack of substantial discussion of the clinical context and implications of the findings might deter patients from seeking appropriate, potentially life-saving treatment and regulators and insurers from approving and paying for DAAs. Regrettably, the window of opportunity for conducting the necessary randomised trials to formally validate SVR as a surrogate endpoint has now closed, given that it would now be unethical to randomise patients to receive no treatment. One must accept that medicine is not an exact or perfect science, and that although DAAs are not without their problems—chief among them their high financial burden—the overwhelming indication is that they help patients to live healthier lives.

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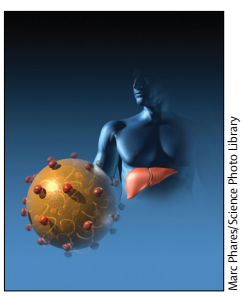

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For ***The Guardian* article** see https://www.theguardian.com/society/2017/jun/08/miracle-hepatitis-c-drugs-costing-30k-per-patient-may-have-no-clinical-effect

For the **Cochrane review** see *Cochrane Database Syst Rev* 2017; **6:** CD012143