The Cochrane Review Conclusion for Hepatitis C DAA Therapies is Wrong

Paul Y. Kwo, MD, FACG[1], Mitchell L. Shiffman, MD, FACG[2] and David E. Bernstein, MD, FACG[3,4]

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Gastroenterologists and hepatologists have been privileged to be part of the identification and subsequent successful treatment of multiple diseases that have caused significant morbidity and mortality in the United States and worldwide. The seminal observations that *Helicobacter pylori* caused gastritis, ulcer disease, and gastric cancer have led to large screening programs to diagnose and treat this infection, and due in part to these efforts, the incidence of ulcer disease and gastric cancer has been on the decline in many parts of the world (1–3). A recent meta-analysis demonstrated that colorectal cancer incidence and mortality in patients with nonmalignant findings are significantly reduced after colonoscopy (4,5). Of note, these significant findings of reduced cancer rates and mortality were not reported within the first 2 years of these treatments and screening modalities being implemented, but rather have been noted years or decades later.

To this list, we are now adding chronic hepatitis infection C, a major cause of morbidity and mortality in the United States and worldwide (6). Hepatitis C-related cirrhosis remains the most common predisposing factor for the development of liver cancer in the United States and has been the leading indication for orthotopic liver transplant in the United States and Europe for the past 2 decades (7,8).

The treatment of chronic hepatitis C virus (HCV) evolved slowly for two decades. Since the late 1990s, the treatment of hepatitis C with interferon or pegylated (peg)-interferon, without and then with ribavirin led to overall sustained virologic response (SVR) rates or cure of ~33–50% between 2005 and 2015. Unfortunately, the toxicities associated with interferon-based treatment severely limited the effectiveness of this therapy. Patients with significant comorbidities or decompensated liver disease could not tolerate therapy, and even those without other medical comorbidities had difficulty tolerating interferon-based therapy lasting 6–12 months (9).

In 2014, we entered the era of solely oral direct-acting anti-viral agents (DAAs) for hepatitis C with combinations of sofosbuvir and simeprevir and sofosbuvir and ribavirin leading to markedly improved SVR rates.. Today, several pangenotypic oral anti-viral regimens can cure HCV in 97–99% of persons regardless of genotype in as little as 8–12 weeks (10–13). Moreover, these DAAs are well tolerated, and have been shown to be highly effective with essentially identical SVR rates being achieved in real-world clinical practices as was seen in structured clinical trials (14,15) This is a marked departure from studies in the interferon era, where the SVR results reported in community practice settings could be significantly lower than those observed in clinical trials, particularly in difficult to treat populations (16).

Numerous clinical trials in patients who had been treated with interferon-based therapy have clearly demonstrated that an SVR was associated with meaningful clinical end points including regression of fibrosis, reduction in portal pressure, reduction in the risk of liver cancer, and reduction of liver-related and all-cause mortality (17–19) Other long-term studies have clearly demonstrated that achieving an SVR following interferon-based therapy is associated with a significant reduction in the risk of developing extrahepatic manifestations of HCV including cryoglobulinemia, B-cell lymphoma, and insulin resistance (20–22).

While we are just 3 years into the DAA era, initial results demonstrate an obvious positive impact on the natural history of HCV. High SVR rates have been observed in patients with decompensated cirrhosis; a population that could not safely be possibly be treated with interferon-based therapy, and this has translated into a marked reduction in the number of new patients with hepatitis C that are listed for orthotopic liver transplant in the United States (23,24). While reports are preliminary, ~20% of candidates for liver transplantation with chronic HCV who are successfully treated with DAAs have sufficient improvement in liver function that they have been removed from the liver transplant waiting list (25). As was seen with successful interferon-based therapy, improvements in extrahepatic manifestations of hepatitis C including resolution of cryoglobulinemia and improvement in renal function are also seen when an SVR is achieved with DAA therapy (26). Finally, while data is still early, Health Related Quality

[1]Division of Gastroenterology/Hepatology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California, USA; [2]Bon Secours Liver Institute of Virginia, Bon Secours Medical Group, Newport News and Richmond, Virginia, USA; [3]Division of Hepatology and Center for Liver Diseases, North Shore Long Island Jewish Health Care System, Manhasset, New York, USA; [4]Division of Hepatology and Sandra Atlas Bass Center for Liver Diseases, Northwell Health, Manhasset, New York, USA. **Correspondence:** Paul Y. Kwo, MD, FACG, Indiana University School of Medicine, 975 West Walnut, IB 327, Indianapolis, Indiana 46202-5121, USA. E-mail: pkwo@stanford.edu

of Life measurements improve in the DAA era following SVR (27). Indeed, when a patient infected with hepatitis C presents to us for evaluation, we can now tell them that a cure is to be expected.

The Cochrane group has done an outstanding job of evaluating the merit and impact of various medical therapies across many disciplines of medicine. Their approach is to group and analyze many clinical trials and to determine the overall benefit of a particular therapy for a particular disorder. Their approach has not been to extrapolate the benefits of therapy upon other related health disorders, or to extrapolate the benefits of a therapy beyond the limits of what the studies evaluated. Indeed, the Cochrane group noted in their recent assessment of DAAs that most of the outcome results were short-term results and therefore could neither confirm nor reject any long-term effects of DAAs (28).

It is therefore surprising and disappointing that the recent Cochrane database review of DAAs for chronic hepatitis C concluded that DAA administration has little or no clinical relevance to patients with hepatitis C, stating that it was questionable if SVR has any clinical relevance (28). This manuscript correctly concluded that (i) the currently available DAAs offer high rates of SVR and cure HCV infection in nearly all patients treated with these medications and (ii) that there was no benefit of such treatments within the study duration that the DAAs were evaluated on the primary end points defined by the Cochrane group, which were hepatitis C-related morbidity, serious adverse events, and quality of life. However, none of these elements were considered primary end points of the DAA trials analyzed by this Cochrane analysis. This latter point represents a gross departure from the typical Cochrane methodology, which limits itself to the end points of the clinical trials examined and does not extrapolate these end points. Previously, the Cochrane group concluded that peg-interferon offers a superior SVR rate compared with standard interferon; that there is no discernable benefit of using peg-interferon-α2a or -α2b; and that medicinal herbs had no demonstrable impact on treating HCV or the natural history of HCV (5,29,30). In each of these other reviews, the Cochrane group analyzed the data and made conclusions based solely on the merits of the data they analyzed. The Cochrane group has not previously evaluated the long-term benefits of a sustained virological response in hepatitis C patients treated with interferon-based therapy. While the most recent analysis by the Cochrane group came to the correct conclusion that DAA therapy was effective in achieving SVR, the authors of this manuscript then over reached and came to conclusions based on an extrapolation of SVR to potential benefits, which were not evaluated within any of the studies included in their review.

As a result, the recent Cochrane database review on DAAs for chronic hepatitis C conclusion that DAA administration has little or no clinical relevance to patients with hepatitis C was in our opinion outrageous, as was their questioning of the clinical relevance of an SVR or hepatitis C cure. Their recent conclusions were drawn from an analysis of 138 trials evaluating DAA efficacy in the treatment of hepatitis C, of which 57 trials included DAAs that were not licensed with an average treatment duration of 14 weeks and average total follow-up duration of 34 weeks. The primary outcome of these trials was SVR, and other clinical end points, including decompensation events such as ascites, encephalopathy, varices, the need for liver transplantation, and liver cancer were not evaluated.. Two long-term studies completed in the interferon era have assessed survival, hepatic decompensation, and the development of hepatocellular cancer in patients with hepatitis C as primary end points. These studies lasted several years in duration, evaluated patients with advanced fibrosis and cirrhosis, and demonstrated that an SVR is associated with an reduction in liver-related mortality, all-cause mortality, and the development of hepatocellular carcinoma (31–33).

The end point for all clinical trials of DAA therapies conducted to date has been SVR. This end point is required for the registration of new HCV therapies across the world and one which regulatory agencies have identified as a predictor of short- and long-term benefit. Certainly, one would not expect improvement in mortality or morbidity to occur in a 6-month period, which is the typical length for most DAA treatment trials and follow-up, as even untreated cirrhotic patients with hepatitis C can live for many years without decompensation (34). There are a limited number of DAA trials that have examined clinical outcomes in decompensated patients with cirrhosis. The primary end point for these trials was also SVR, but these trials were also able to demonstrate improvements in MELD (model for end-stage liver disease) scores and CPT (Child–Pugh–Turcotte) scores within 12 weeks of completing therapy (35–37).

Across the world, there have been multiple groups advocating for universal access to these highly effective, DAAs, and many organizations, both governmental and nongovernmental, have set a goal of worldwide elimination of hepatitis C by 2030. We hope the Cochrane database review is not misinterpreted to suggest there are no benefits to achieving SVR with DAA therapy. The ample data from the interferon era, coupled with the short-term improvements in DAA-treated individuals not captured in the trials examined by the Cochrane group review, suggest that the strategy of eliminating hepatitis C will provide multiple benefits by reducing the number of individuals requiring liver transplant for hepatitis C, reducing the rates of hepatitis C-related cirrhosis, reduce the rates of liver cancer, reducing the many extrahepatic manifestations of hepatitis C and improving overall quality of life and survival in these patients. As gastroenterologists and hepatologists, we are on the right track with our current treatment strategies and goals for hepatitis C, and we should not turn back. The Cochrane conclusion is a disservice to patients and all of those who care for those with hepatitis C and should be amended or retracted. We hope that this poorly informed report will not deter the robust worldwide effort to eradicate hepatitis C infection in the next two decades.

CONFLICT OF INTEREST

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