Comments on Cochrane Review on Direct-Acting Antivirals for Hepatitis C

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Abbreviations:

DAA: direct acting antiviral, HCV: hepatitis C virus, IFN: interferon, SVR: sustained virological response

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A recent Cochrane Review with the stated objective to assess the benefits and harms of direct-acting antiviral (DAA) therapy for people with chronic hepatitis C virus (HCV) infection raised alarms within the hepatology and infectious diseases communities because the authors concluded there was insufficient evidence to confirm or reject an effect of DAA therapy on HCV-related morbidity (cirrhosis, hepatic decompensation or hepatocellular carcinoma) or all-cause mortality (1). The authors also concluded that the clinical relevance of sustained virological response (SVR) obtained with DAAs is questionable, as it is a non-validated surrogate outcome. The Review further stated that all DAA trials and outcome results were at high risk of bias, so their results presumably overestimated benefit and underestimated harm. Indeed, the plain language summary stated that the lack of valid evidence and the possibility of potentially harming people with chronic hepatitis should be considered before treating people with hepatitis C with DAAs. Based on the findings of this Review, the authors concluded that additional randomized clinical trials assessing the long-term clinical effects of DAAs are needed.

To understand how these conclusions were reached, it is important to recognize that only randomized clinical trials comparing DAAs versus no intervention or placebo were selected for review. A total of 138 trials met the strict selection criteria when the search ended in October 2016 of which 84 involved DAAs on the market or under development, while others represented studies of either investigational drugs never approved or agents approved but no longer marketed.

The paucity of data supporting an effect of DAAs on HCV-related morbidity and all-cause mortality is not surprising because DAAs currently on the market in the United States had been approved for less than four years. Recognizing the natural history of HCV infection, during which clinical outcomes may take years to become apparent, that late relapse after achieving SVR is rare (2, 3), and the mounting evidence that SVR decreases HCV-related morbidity and

mortality, the Food and Drug Administration (FDA) accepted SVR as a valid surrogate and a practical endpoint for clinical trials of DAAs. Due to the rapid movement in the field of HCV therapeutics and the dramatic improvement in efficacy and safety of investigational DAAs, the inclusion of a control group receiving IFN-based regimens would not be ethical. The FDA provided guidance to industry for acceptable efficacy analyses including the use of historical control response rates, recognizing the lack of equipoise by many providers and patients for non-DAA containing study arms. Thus, most clinical trials on DAA therapy conducted in the last 5 years did not have an untreated control group, which excluded them from this Review. Some trials did have control groups randomized to placebo, but these patients received active treatment with DAAs after the randomized phase of the trial was completed. Thus, the long-term outcome of DAA therapy versus no treatment could not be compared. Given the high rates of SVR with DAA therapies, a study randomizing patients to a prolonged placebo arm would be unethical in chronic HCV infection.

A key issue raised in this Review is whether SVR is a valid surrogate endpoint for clinical outcomes. In this regard, experience from earlier HCV therapies (based on IFN-containing regimens), for which long term follow-up data are now available, clearly demonstrate numerous health benefits including a decrease in liver inflammation as reflected by improved aminotransferase levels and a reduction in the rate of progression of liver fibrosis as reflected in paired liver biopsy studies (4). Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from four randomized trials of 10 different IFN-based regimens, 39% to 73% of patients who achieved an SVR had improvement in liver fibrosis and necrosis in liver biopsies separated by a mean of 20 months (4). Cirrhosis resolved in half of the cases. Portal hypertension, splenomegaly and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons with advanced fibrosis, SVR is associated with a more

than 70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation (5-7). It is precisely for these reasons that the Food and Drug Administation recommended SVR as the primary endpoint for all contemporary HCV trials. In the scientific community, SVR achieved with IFN-based therapies is a well-accepted virologic surrogate for clinical cure. Based on these data, there is every reason to expect that analogous clinical benefits will be observed in patients who achieved SVR via DAAs after a sufficient follow-up period.

While these long-term follow-up data are awaited, early experience with DAAs support clear improvements in clinical outcomes that can be measured in the short term. Cure of HCV infection immediately reduces symptoms and organ dysfunction from severe extrahepatic manifestations including cryoglobulinemic vasculitis, a complication affecting up to 10% of HCV-infected patients (8, 9). Historically, HCV-infected persons with non-Hodgkin lymphoma and other B-cell lymphoproliferative disorders achieved complete or partial remission in up to 75% of cases following successful IFN-based therapy for HCV infection (10-13). Recent data show that DAA regimens produce similar remission rates in non-Hodgkin lymphoma and even higher rates of SVR (14). Perhaps the most striking evidence of direct clinical improvement comes from data demonstrating the success of DAAs in patients with decompensated liver disease for whom SVR was associated with improved model for end-stage liver disease (MELD) scores and albumin levels in the majority of patients with Child B and C cirrhosis (15, 16). Indeed, success in this group in many cases obviates the need for liver transplantation, meaning that more donor organs could become available to other patients on the waitlist (17). In those who still required liver transplantation, SVR prior to transplant prevents reinfection of the liver graft allowing these patients to derive long-term benefit from this life-saving procedure (15) (18-20).

The Review indicated only 1 of 84 trials of DAAs on the market or in development assessed health-related quality of life but many studies clearly demonstrated that DAA therapy improves patient-reported outcomes (21-23). Thus, even without long term follow-up to prove a survival benefit, there is a convincing body of literature supporting the clinical benefit of SVR offered by use of DAAs to reduce symptoms and disease complications.

We are therefore troubled by the implications of this Review for the ongoing international efforts to halt the HCV epidemic, and to give patients back their futures. In the face of the National Academies of Science, Engineering, and Medicine reports that elimination of HCV is possible by 2030 with optimal implementation of high efficacy therapy (24) (25), we believe that the Cochrane Review does a grave disservice to these efforts and to patients living with chronic HCV infection, a disease responsible for tens of thousands of deaths around the world each year. Furthermore, we believe that long-term trials with an untreated control arm would be unethical given our current state of knowledge, especially as persons viremic with HCV can continue to transmit this infection to other individuals. We therefore stand behind our Associations' recommendations that all patients with HCV should be treated to prevent complications of this curable disease (26) and we will continue to fight for the global elimination of this viral infection. In light of the evidence that we have cited, we urge the Cochrane Review authors and/or editors to retract or to revise their conclusions.

Conflict of Interest:

Anna S. Lok – has received research grants to her institution from Bristol-Myers Squibb and Gilead.

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