



Summary of Recently Published Studies on Treatments for Hepatitis C ***Working Document***

Prepared for a PCORI Patient Stakeholder Workshop by David Hickam, MD, MPH, Danielle Whicher, PhD, MHS, and Victoria Szydlowski

October 17, 2014

Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036
www.pcori.org



Introduction

This working document was produced to supplement [Treatment for Hepatitis C Virus Infection in Adults](#) by Roger Chou, MD, Daniel Hartung, PharmD, MPH, Basmah Rahman, MPH, Ngoc Wasson, MPH, Erika Cottrell, PhD, and Rongwei Fu, PhD, published by Agency for Healthcare Research and Quality in November 2012. Chou et al., was based on research published through August 2012 on antiviral agents approved by the FDA prior to this time. This document summarizes studies published since August 2012 and includes information on several more recent antiviral agents.

To prepare this document, a search of the Medline and Cochrane Collaboration databases was performed for the period August 2012 through August 2014 using search terms for hepatitis C and terms for either randomized controlled trials or controlled clinical trials. Non-human studies and non-English-language citations were excluded. The search included no restrictions on the treatments used in the studies.

The search produced a total of 2,112 citations. The titles and abstracts of all citations were screened for possible relevance, based on whether the study examined the treatment of hepatitis C with any antiviral agent or combination of agents. Studies that examined treatment with regimens containing only interferon and/or ribavirin were excluded. Studies were included if they contained data about efficacy and/or harms of the treatments. The screening was not performed in duplicate.

Following the screening of the titles and abstracts, a total of 101 citations were judged possibly relevant. All were retrieved and reviewed in full text, and 39 then judged to include non-duplicated data on the efficacy or harms of one or more antiviral agents. These studies examined a total of 19 different therapeutic agents. The results were compiled only for those agents examined in at least two studies, which included a total of 36 of the relevant studies. Of the studies that examined treatment efficacy, all used sustained virologic response at either 12 or 24 weeks as the primary outcome measure. The scope of these studies is briefly summarized below.

Telaprevir and **boceprevir** are protease inhibitors that were approved for use in the United States in 2011. Of a total of eight studies, two were comparisons of regimens containing telaprevir to regimens containing boceprevir, and the remaining six examined regimens containing telaprevir (but not boceprevir). These studies enrolled a total of 3749 participants. All but one study examined combination regimens in which telaprevir or boceprevir were combined with interferon and ribavirin. One study was a randomized trial comparing a triple drug combination containing telaprevir to a triple drug combination containing boceprevir. These studies provide evidence that both telaprevir and boceprevir improve response rates when added to the combination of interferon and ribavirin. The studies also provide information about treatment-related harms, including renal impairment, anemia, and skin reactions (including rare cases of severe skin reactions).

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase that was approved for use in the United States in 2013. Seven studies of sofosbuvir were identified. These studies enrolled a total of 2,009 patients. Three studies focused exclusively on patients diagnosed with HCV genotype 1, and four focused exclusively on patients diagnosed with HCV genotypes 2 and 3. All studies of HCV genotype 1 patients, two of which were RCTs, examined the combination of sofosbuvir and the NS5A replication complex inhibitor **ledipasvir**, with and without ribavirin. Three of the four studies in HCV genotype 2 and 3 patients compared the combination of sofosbuvir and ribavirin; one study also included interferon. The fourth study examined the combination of sofosbuvir and **daclatasvir**. These studies provide evidence that most patients, even those who previously failed interferon-based treatment regimens, can achieve sustained virologic response when treated with sofosbuvir-based treatment regimens. All studies also provide information about rates of common side effects associated with sofosbuvir regimens, the most common of which were headache, fatigue, and nausea. In 2013, the FDA approved the combination of sofosbuvir and ribavirin for the treatment of Hepatitis C genotypes 2 and 3. It also approved the combination of sofosbuvir, ribavirin, and interferon for the treatment of genotypes 1 and 4. On October 10, 2014, the FDA approved the combination of sofosbuvir and ledipasvir for the treatment of genotype 1 patients.

Daclatasvir is a NS5A replication complex inhibitor that has not yet been approved by the FDA for clinical use in the United States. Seven studies of daclatasvir that included 541 participants were identified. The studies examined the use of daclatasvir in combination with **asunaprevir** (a protease inhibitor not yet approved by the FDA), sofosbuvir, or interferon/ribavirin. Clinical trials have shown that the combination of daclatasvir and asunaprevir is highly efficacious for achieving a virologic response among people with genotype 1b but may be less efficacious among people with other genotypes. Adverse effects include hepatic abnormalities, fatigue, headaches, and nausea. The combination of daclatasvir and asunaprevir has been proposed as a fixed drug combination for treating hepatitis C.

Paritaprevir (ABT-450) is a protease inhibitor that has not yet been approved by the FDA for clinical use in the United States. Five studies of paritaprevir were identified. These studies enrolled a total of 2,190 patients. All studies examined the combination regimen of paritaprevir and the protease inhibitor **ritonavir**. Two of these were placebo controlled studies of paritaprevir and ritonavir in combination with **dasabuvir**, **ombitasvir**, and ribavirin. Dasabuvir is a nonnucleoside polymerase inhibitor, and ombitasvir is a NS5A replication complex inhibitor. One of these two studies was a four-arm trial of paritaprevir and ritonavir in combination with dasabuvir, ribavirin, and ombitasvir. One study evaluated paritaprevir, ritonavir, ombitasvir, daclatasvir with or without ribavirin. These studies provide evidence that the combination regimen of paritaprevir and ritonavir improve response rates when combined with: ombitasvir, daclatasvir, and ribavirin; dasabuvir and ribavirin; or ombitasvir, dasabuvir, and ribavirin. The studies also provide information about adverse events, with four studies reporting serious adverse events, three studies reporting grade 3/4 adverse events, and three studies reporting grade 3/4 laboratory abnormalities.

Faldaprevir (a protease inhibitor) and/or **deleobuvir** (a NS5B polymerase inhibitor) were examined in a total of five studies. Both have been withdrawn from further development by the manufacturers because of poor efficacy. Information from these studies was not compiled.

In conclusion, since August 2012, there has been a large body of clinical research on many antiviral agents with potential usefulness for treating hepatitis C. This research has led to several agents moving through the regulatory approval process. Two agents (sofosbuvir and ledipasvir) have recently received FDA approval as components of multi-drug regimens.

Included Studies

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