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# Is Sofosbuvir Safer and More Effective Than Peginterferon for Treatment of Chronic Hepatitis C Virus Infection in Treatment-Naïve Patients?

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**Is Sofosbuvir safer and more effective than Peginterferon for  
treatment of chronic Hepatitis C Virus infection in treatment-  
naïve patients?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

**Objective:** The objective of this selective EBM review is to determine whether or not Sofosbuvir plus Ribavirin is safer and more effective than Peginterferon plus Ribavirin for treatment of chronic Hepatitis C Virus infection in treatment-naïve patients.

**Study Design:** Systematic review of three English language primary studies, published in 2013.

**Data Sources:** Three randomized control trials, two of which are open-label, active-controlled and one that is double-blind, placebo-controlled, comparing Sofosbuvir and Ribavirin versus other chronic HCV modalities found via PubMed in peer-reviewed journals.

**Outcomes Measured:** Safety was measured by self-reported adverse events, routine laboratory tests, physical exams, vital signs, and electrocardiography and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Efficacy was determined by sustained virological response at 12 or 24 weeks post-treatment (SVR12 and SVR24, respectively), which is classified as a HCV RNA concentration below the limit of detection of 15 IU/mL or 25 IU/mL

**Results:** Gane, et al<sup>5</sup> compared the treatment effects of 400mg Sofosbuvir and Ribavirin (RBV) with that of Sofosbuvir plus RBV and Peginterferon (PEG) for 12 weeks in patients with chronic HCV. Analysis resulted in an equal incidence of SVR24, but with less adverse events in the experimental group. In Lawitz, Lalezari, et al<sup>6</sup>, patients received 12 weeks with either 400mg Sofosbuvir, RBV, and PEG or placebo, PEG, and RBV. SVR24 was higher in the Sofosbuvir group, however more adverse events of fatigue were reported compared to the placebo group. Lawitz, Mangia, et al<sup>7</sup> examined the difference in treatment with 12 weeks of 400mg Sofosbuvir and RBV versus 24 weeks of PEG and RBV. Statistical analysis showed an equal rate of SVR12 between the two groups, yet treatment with Sofosbuvir was safer.

**Conclusions:** It can be deduced from these three RCTs that Sofosbuvir plus RBV is safer, yet, statistically, nearly equal in efficacy to treatment with PEG and RBV. Given that PEG is a weekly injection with many unfavorable side effects, it would be more beneficial to receive treatment with Sofosbuvir and RBV for treatment of chronic HCV infection

**Key Words:** Hepatitis C, Sofosbuvir, treatment

## INTRODUCTION

Hepatitis C Virus (HCV) is an infectious RNA virus that invades the liver and is transmitted primarily via exposure to infected blood, such as through intravenous drug abuse.<sup>1</sup> Following an acute HCV infection, approximately 85% of cases become chronic, or when the infection lasts greater than 3-6 months.<sup>1,2</sup> This paper evaluates three randomized control trials (RCTs) – two of which are open-label, active-controlled and one which is double-blind, placebo-controlled – comparing the safety and efficacy of Sofosbuvir and Ribavirin in the treatment of chronic HCV.

The Center for Disease Control and Prevention (CDC) has estimated that chronic HCV infection affects 3.2 million people in the United States alone.<sup>2</sup> In 2011, it was projected that the total healthcare cost associated with HCV infection was an average of \$6.5 billion.<sup>3</sup> Of those infected with HCV, 75-85% will become a chronic infection, 60-70% will develop chronic liver disease, 5-20% will develop cirrhosis, and 1-5% will die.<sup>2</sup> Additionally, chronic HCV infection can increase one's chance of developing hepatocellular carcinoma and, due in part to its high prevalence in the population, is the leading cause for liver transplantation.<sup>4</sup>

Unfortunately, there is no vaccine available to protect against HCV, only initiation of preventative measures. Once infected, a person with HCV will usually be asymptomatic unless severe liver disease and consequences ensue.<sup>2</sup> Furthermore, during the acute phase, liver function tests may be elevated, but once the HCV becomes chronic, the levels may normalize.<sup>1,2</sup> HCV infection, then, may only be exposed on routine laboratory screening.<sup>4</sup> HCV infection is determined by detection of anti-HCV antibodies through enzyme immunoassay (EIA). The HCV can be further quantified by its RNA concentration through polymerase chain reaction

(PCR).<sup>1</sup> There are 6 major genotypes of HCV that are recognized, with genotype 1 being the most common.<sup>2</sup>

The mainstay of treatment for chronic HCV infection has been a combination of anywhere from one to three different drugs. The most utilized method is treatment with Peginterferon-alfa 2a (PEG), a weekly subcutaneous injection, for 24-48 weeks.<sup>5</sup> Not only does PEG carry many side effects such as cytopenia and flu-like symptoms, but also many patients are reluctant, or even unable, to adhere to the once weekly injections.<sup>5</sup> Although PEG can be administered as a monotherapy, efficacy is rather low. The nucleoside inhibitor Ribavirin is used as an adjunctive treatment, boosting the effectiveness of PEG and other therapies. Even with the combination of ribavirin, however, the sustained virologic response (SVR) rate may be anywhere from 45-80%, depending upon the HCV genotype. In the presence of liver disease or other comorbidities, the SVR may be even lower.<sup>1</sup>

Newer drugs used to combat chronic HCV include the protease inhibitors Telaprevir and Boceprevir, both of which were approved by the FDA in 2011. Although either of these drugs in combination with PEG and ribavirin increased the efficacy of treatment to a SVR rate from 66-75% in genotype 1 patients, effective in other genotypes has not been studied. Additionally, dosing schedules, drug interactions, and side effects of these drugs have limited their extensive use in chronic HCV treatment.<sup>6</sup>

A nucleotide polymerase inhibitor, Sofosbuvir, is the newest drug on the market for the treatment of chronic HCV infection. FDA approved in December 2013, Sofosbuvir can be given as a once daily oral dose and is thought to be safer and more effective and efficient than the current treatment modalities.

## OBJECTIVE

The objective of this selective EBM review is to determine whether or not Sofosbuvir plus Ribavirin is safer and more effective than Peginterferon plus Ribavirin for treatment of chronic Hepatitis C Virus in treatment-naïve patients.

## METHODS

Specific criteria were utilized in the selection of studies to establish as much parallel as possible for proper comparison. The populations studied included previously untreated men and women 18 years of age or older with chronic HCV infection. All three interventions included the once-daily oral administration of Sofosbuvir 400mg and Ribavirin (RBV). In one study, the intervention also included a once-weekly injection of PEG. For the two interventions of Sofosbuvir plus RBV, one study compared it to treatment with the addition of PEG and the other study compared it to PEG plus RBV. The third intervention, Sofosbuvir plus PEG and RBV, was compared to a placebo plus PEG and RBV. The three studies included in this systematic review were randomized control trials (RCTs), each measuring both safety and efficacy. Two of the RCTs were open-label, active-controlled and the other one was double-blind, placebo-controlled.

Research was done by the author using the key words “Sofosbuvir,” “chronic HCV,” and “HCV treatment” via the PubMed database. All articles were in English and published in peer-reviewed journals in 2013. Articles were chosen according to their relevance to the clinical question with outcomes that were patient oriented (POEMs)

Inclusion criteria contained studies that were RCTs and included patients who were 18 years and older with chronic HCV infection (**Table 1**). Exclusion criteria included significant

comorbidities, such as Hepatitis B infection or Human Immunodeficiency Virus (HIV), and previous treatment for their HCV infection (**Table 1**). Statistics reported in the studies included sustained virologic response (SVR) rate, 95% confidence interval (CI), and p-values. The author calculated relative risk reduction (RRR), absolute risk increase (ARI), absolute risk reduction (ARR), numbers needed to harm (NNH), and numbers needed to treat (NNT).

**Table 1: Demographics and characteristics of included studies**

| Study                                    | Type | # of pts | Age (yrs) | Inclusion Criteria  | Exclusion Criteria  | W/D | Interventions   |
|--|------|----------|-----------|---|---|-----|---|
| Gane, et al <sup>5</sup> 2013            | RCT  | 21       | 18+       | ≥18 y/o; Tx naïve; Chronic HCV infection (serum HCV RNA level, >50,000 IU/mL)   | Cirrhosis; HepB or HIV infection  | 0   | Sofosbuvir 400mg plus Ribavirin (RBV) VS. Sofosbuvir 400mg plus RBV and Peginterferon (PEG) |
| Lawitz, Lalezari et al <sup>6</sup> 2013 | RCT  | 73       | 18-70     | 18-70 y/o; Tx naïve; Chronic HCV genotype 1 infection; [HCV RNA] ≥50,000 IU/mL; Adequate hematologic and biochemical parameters   | Cirrhosis; HepB or HIV infection; Psychiatric illness; Pulmonary or cardiac disease; Seizure disorder or other serious comorbid disorders   | 16  | Sofosbuvir 400mg plus RBV and PEG VS. Placebo plus PEG and RBV                              |
| Lawitz, Mangia et al <sup>7</sup> 2013   | RCT  | 499      | 18+       | ≥18 y/o; Tx naïve; BMI of 18 kg/m; Chronic genotype 2 or 3 HCV infection with serum HCV RNA ≥10,000 IU/mL; Subjects or their partner(s) must be of non-childbearing potential or use effective contraception until 6 months after the last dose of study medication | HepB or HIV infection; liver, pulmonary, or cardiac disease; psychiatric illness, immunologic disorder; hemoglobinopathy; seizure disorder or anticonvulsant use, poorly controlled diabetes; cancer; acute pancreatitis; abnormal hematologic & biochemical parameters | 36  | Sofosbuvir 400mg plus RBV VS. PEG plus RBV  |

## **OUTCOMES MEASURED**

In each of the three RCTs, safety was measured by self-reported adverse events, such as fatigue and headache, and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. All three studies determined efficacy by the sustained virological response at 12 and 24 weeks post-treatment (SVR12 and SVR24, respectively), which is classified by a HCV RNA concentration below the limit of detection of 15 IU/mL or 25 IU/mL, depending upon the lab used. For each trial, HCV RNA was quantified using the COBAS AmpliPrep/COBAS TaqMan HCV Test. It has been shown that SVR12 and SVR24 are highly correlated with virus eradication signifying no further need for treatment. Furthermore, these endpoints greatly reduce HCV complications, including mortality, as well as decrease the chance of a relapse.<sup>8</sup>

## **RESULTS**

This systematic review assesses three RCTs for the efficacy and tolerability of Sofosbuvir plus Ribavirin (RBV) compared to other modalities involving Peginterferon (PEG) for treatment of chronic HCV infection. Each of the trials contained comparable study designs with dichotomous data, which was used in intention-to-treat analysis. Additionally, all analysis was performed with a 95% confidence interval (95% CI).

In the first study, Gane et al<sup>5</sup> enrolled 21 patients with chronic HCV genotypes 2 and 3 into an open-label, active-controlled RCT. All 21 patients received 12 weeks of 400mg Sofosbuvir plus RBV. 11 of the 21 patients were randomized to the control group, which received 12 weeks of concurrent PEG treatment. Enrollees were followed for 24 weeks post-treatment. Every patient completed the trial and acquired sustained virological response (SVR)



at 24 weeks post-treatment. With a 95% CI (69 to 100), statistical analysis of the experimental group (experimental event rate, or EER) in comparison with the control group (control event rate, or CER) revealed a relative benefit increase (RBI), an absolute benefit increase (ABI), and a numbers needed to treat (NNT) of 0 (**Table 2**).

Gane et al<sup>5</sup> also addressed the safety of treatment with Sofosbuvir and Ribavirin. The most common self-reported adverse events during the trial were headache, fatigue, insomnia, nausea, rash, and anemia. In regards to fatigue, 45% of patients in the control group (CER) reported the symptom as opposed to 10% in the experimental group (EER). This resulted in a calculated relative risk reduction (RRR) of -77.8%, an absolute risk reduction (ARR) of -35%, and a number needed to harm (NNH) of -2 (**Table 3**). This negative NNH means that for every 2 patients treated, one fewer will experience the adverse event of fatigue in the experimental group compared to the control group.

In Lawitz, Lalezari and colleagues<sup>6</sup>, a double-blind, placebo-controlled RCT, 48 patients with HCV genotype 1 were assigned to the experimental group to receive treatment for 12 weeks with 400mg Sofosbuvir, RBV, and PEG. 26 patients, placed in the control group, were allotted to receive placebo, PEG, and RBV for 12 weeks. Of the 47 people who began treatment in the experimental group and 26 who started in the control group, 42 and 14 people completed the study, respectively. However, intention-to-treat analysis included everyone who began treatment.

In the Sofosbuvir group, 89% of patients acquired sustained virological response (SVR) at 24 weeks post-treatment (EER) as opposed to 58% of patients in the placebo group (CER). As shown in **Table 2**, statistical analysis with a 95% CI (11 to 49) exposed a RBI of 58%, an ABI of 14%, and a numbers needed to treat (NNT) of 4. This positive NNT suggests that for every 4

patients treated in the experimental group, one more will achieve SVR24 than compared to the control group. Additionally, the p-value for the study equaled 0.0006 (**Table 2**).

The most common adverse events reported by Lawitz, Lalezari, et al<sup>6</sup> were fatigue, headache, nausea, and chills. Using fatigue for comparison, 68% in the experimental group (EER) reported the symptom as opposed to 54% in the placebo group (CER). This resulted in a RRR of 26%, an ARR of 14%, and a NNH of 8. This implies that for every 8 patients treated, one more will have fatigue in the experimental group compared to the control group (**Table 3**).

In the third study, Lawitz, Mangia et al<sup>7</sup> conducted an open-label, active-controlled RCT, dubbed the FISSION study, using patients with HCV genotypes 2 and 3. Of the 499 patients who started treatment, 256 underwent treatment in the experimental group with 400mg Sofosbuvir plus RBV for 12 weeks. The other 243 patients, assigned to the control group, received PEG and RBV for 24 weeks. All subjects who received at least one dose of study drug were analyzed in the group to which they were randomized. Both the experimental and control groups obtained an equal percentage of patients that acquired sustained virological response at 12 weeks post-treatment (SVR12). Since CER and EER were both 67%, statistical analysis resulted in a RBI, ABI, and NNT of 0. A 95% CI (-7.5 to 8.0) and p-value of <0.001 were also reported (**Table 2**).

Similar to the other two RCTs, the most self-reported adverse events in Lawitz, Mangia et al<sup>7</sup> were fatigue, headache, nausea, and insomnia. Using fatigue for calculations, 55.1% of patients in the control group (CER) and 35.9% in the experimental group (EER) experienced this adverse event. This resulted in a RRR of -34.8%, an ARR of -19.2%, and a NNH of -6, which suggests that for every 6 patients treated, one fewer will experience the adverse event of fatigue in the Sofosbuvir group compared to the control group (**Table 3**).

**Table 2: Efficacy of Treatment (Experimental vs. Control)**

| Study                                | CER (%) | EER (%) | RBI (%) | ABI (%) | NNT | 95% CI      | p-value |
|--------------------------------------|---------|---------|---------|---------|-----|-------------|---------|
| Gane, et al <sup>5</sup>             | 100     | 100     | 0       | 0       | 0   | 69 to 100   | -----   |
| Lawitz, Lalezari, et al <sup>6</sup> | 58      | 89      | 53      | 14      | 4   | 11 to 49    | 0.0006  |
| Lawitz, Mangia, et al <sup>7</sup>   | 67      | 67      | 0       | 0       | 0   | -7.5 to 8.0 | <0.001  |

**Table 3: Adverse Event of Fatigue from Treatment (Experimental vs. Control)**

| Study                                | CER (%) | EER (%) | RRR (%) | ARR (%) | NNH (%) |
|--------------------------------------|---------|---------|---------|---------|---------|
| Gane, et al <sup>5</sup>             | 45      | 10      | -77.8   | -35     | -2      |
| Lawitz, Lalezari, et al <sup>6</sup> | 54      | 68      | 26      | 14      | 8       |
| Lawitz, Mangia, et al <sup>7</sup>   | 55.1    | 35.9    | -34.8   | -19.2   | -6      |

## DISCUSSION

This systematic review compared three RCTs for the safety and efficacy of Sofosbuvir and Ribavirin in the treatment of chronic HCV infection using participants who were 18 years of age or older with treatment-naïve chronic HCV genotypes 1, 2, or 3. In Gane et al<sup>5</sup>, a 12-week regimen of Sofosbuvir plus RBV proved to be safer but just as effective as Sofosbuvir plus PEG and RBV for treatment of chronic HCV genotypes 2 and 3. People with cirrhosis were excluded from participating in this study. Cirrhosis has been associated with a reduced response to treatment, thus results may be skewed. Furthermore, the sample size of both the experimental and control groups were both small at 10 and 11 participants, respectively. Results, then, may be insufficient.

Lawitz, Lalezari and colleagues<sup>6</sup> examined the chronic HCV genotype 1 treatment regimen of Sofosbuvir 400mg plus PEG and RBV in comparison to placebo, PEG, and RBV for

12 weeks. Results show that Sofosbuvir-PEG-RBV was more effective yet had more adverse events than the control group. It should be noted that most of the adverse events in the experimental group, such as that of fatigue, were noticed during treatment with PEG and RBV as opposed to Sofosbuvir. As with Gane et al<sup>5</sup>, people with cirrhosis were excluded from participating in the study which could have altered the results.

In the 3<sup>rd</sup> study, Lawitz, Mangia et al<sup>7</sup>, the 12-week regimen of Sofosbuvir plus RBV showed fewer adverse events but equal efficacy to PEG-RBV for treatment of HCV genotypes 2 and 3. In this study, 20% and 21% of participants in the experimental and control groups, respectively, had cirrhosis, which affected treatment efficacy and incidence of adverse events. Furthermore, efficacy was only measured to week 12 post-treatment (SVR12), which, although sufficient, could have been measured to week 24 (SVR24) for better results.

In regards to safety, the author chose to only address one of the most common self-reported adverse events, making it an outcome that directly affects the patient, or rather, patient-oriented evidence that matters (POEM). It is known, however, that treatment with PEG can cause hematologic anomalies such as cytopenia.<sup>5</sup> It should be noted that this was seen in each of the three RCTs when participants were treated with PEG. Furthermore, in the large cohort FISSION study in Lawitz, Mangia et al<sup>7</sup> it was discovered that “adverse events associated with various organ systems” were consistently higher in the PEG-RBV control group as opposed to the experimental group of Sofosbuvir-RBV.<sup>7</sup>

Overall, Sofosbuvir, itself, has been well tolerated in all clinical trials, thus far. Potential drug interactions include certain anticonvulsants, antimycobacterials, HIV protease inhibitors, and the herbal supplement St. John's wort.<sup>9</sup> Each of these interactions may decrease the level of available Sofosbuvir. It has also been discovered that Sofosbuvir has a high genetic barrier for

resistance, meaning that, unless there are many crucial genetic mutations, it should remain an effective treatment. The biggest downside to Sofosbuvir, which was only recently FDA approved in December 2013, is that it costs a staggering \$1,000 for one 400mg pill, resulting in a total cost of \$84,000 after completion of a 12-week course.<sup>9</sup> Although highly effective, efficient, and safe, the elated price may deter insurance companies or individuals from covering the treatment.

### CONCLUSION

In conclusion, it can be deduced that Sofosbuvir plus RBV is safer, yet, statistically, nearly equal in efficacy to treatment with PEG and RBV. Given that PEG is a weekly subcutaneous injection with many side effects, it would be more beneficial to receive treatment with Sofosbuvir.

While each RCT carried similar results, future large cohort studies should be done with standardized parameters such as using one specific genotype or fully excluding or including participants with cirrhosis. Although the RCTs included smaller analyses that addressed these variations, the primary end points of safety and efficacy included all patients. Additionally, to further confirm efficacy in each RCT and rule out relapse of HCV, a one-year post-treatment SVR measurement should be done.

Each of these three RCTs examined additional treatment regimens besides the experimental and control groups. Such alterations included a different dose of Sofosbuvir or varying amounts of PEG treatments. For commonality's sake, the author of this systematic review chose the most suitable comparison groups. With that said, the only RCT that specifically contrasted the treatment of Sofosbuvir and RBV with that of PEG and RBV was Lawitz, Mangia, et al<sup>7</sup>. Although this study had the largest cohort, it compared treatment with

the experimental group for 12 weeks versus 24 weeks for the control group. One might argue that given a reduced treatment time of 12 weeks, the results would have pointed in favor of Sofosbuvir plus RBV for the best efficacy. Additionally, the study observed treatment in patients with genotypes 2 and 3, rather than the more common genotype 1 HCV infection. Therefore, for a more accurate analysis, another RCT could be performed comparing 12 weeks of Sofosbuvir and RBV treatment with 12 weeks of PEG and RBV in patients with genotype 1 HCV infections.

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