

# The Quest for Optimal Therapy: Sofosbuvir and Ribavirin in Chronic Hepatitis C - A Systematic Review

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## Abstract

### Background

Chronic Hepatitis C (CHC) infection leads to liver cirrhosis, liver failure and hepatocellular carcinoma. It is mostly treated with Sofosbuvir and ribavirin or in combination with other Direct-acting antivirals (DAA's).

### Method

This was a systematic review Comparing the safety and efficacy of Sofosbuvir and ribavirin in Chronic Hepatitis C. Studies including patients taking Sofosbuvir and ribavirin, or both were included with a specific focus on Cirrhosis patients.

### Results

Sustained Virological Response (SVR) from included studies showed above 90% overall. The study found that Sofosbuvir and Ribavirin were safe and effective in mild and moderate cirrhosis, but SVR rates dropped to 57% for decompensated cirrhosis.

### Conclusion

Sofosbuvir and ribavirin are the most effective, well-tolerated, and shortest treatment for chronic hepatitis C, making it a curable disease.

### Keywords

Sofosbuvir, Ribavirin, Chronic Hepatitis-C, Cirrhosis, Safety, Efficacy.

## Introduction

Chronic hepatitis C (CHC) is a liver disease caused by the hepatitis C virus (HCV). It is a major global health problem, with an estimated 71 million people living with CHC worldwide [1]. CHC can lead to liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[1].

In the past, treatment for CHC was difficult and often ineffective; the development of direct-acting antivirals (DAAs) has revolutionized treatment [22]. DAAs are highly effective and have a much better safety profile than older treatments [2].

Sofosbuvir is a DAA approved for the treatment of CHC [4]. It is often used in combination with ribavirin, another antiviral drug [11]. Ribavirin is not always necessary, but it can improve the efficacy of sofosbuvir in some [23]. Usually the treatment is taken for 8 or 12

weeks, depending on the genotype of HCV and the presence of liver Damage. It is taken orally, once a day.

The standard of care for the treatment of CHC is a combination of sofosbuvir and [24]. Sofosbuvir is a direct-acting antiviral (DAA) that targets the HCV polymerase, while ribavirin is an older antiviral drug used to treat CHC for many years [9].

The safety and efficacy of sofosbuvir and ribavirin in the treatment of CHC have been well-studied [5]. Several randomized controlled trials (RCTs) have shown that the combination therapy is highly effective, with sustained virological response (SVR) rates of 80% to 90% in most studies [17].

However, there is still some uncertainty about the relative safety and efficacy of sofosbuvir and ribavirin compared to other treatment regimens. This systematic review will assess the evidence from RCTs and other observational studies to compare the safety and effectiveness of sofosbuvir and ribavirin with different treatment regimens for CHC.

## Method

### Methodology and Search Strategy

Our method and results for systematic review are reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020 guidelines following our screening selection[18].

We consider PubMed, Medline, and PMC to look for articles using Medical Subject Headings (MeSH) and keywords to highlight the most relevant reviews and studies for analysis. The keywords included: "Sofosbuvir," "Ribavirin," "Chronic hepatitis-C" , "Safety", "Efficacy" and "Cirrhosis". Used Booleans to put together the keywords for an algorithm to use in PubMed. The articles were screened to highlight those most relevant to the search question and selected according to the inclusion/exclusion criteria.

## Inclusion and Exclusion Criteria

The selection choice was from randomized controlled trials (RCT'S) and Observational studies published from 2018 to 2023. All selected articles were peer-reviewed

and published in the English language. Grey literature was excluded. Our selection for eligibility followed the population, intervention, comparisons, and outcomes (PICO) model. The inclusion and exclusion criteria are shown in Table 1.

Inclusion Criteria	Exclusion Criteria
Adult patients with Chronic hepatitis-C (age 18 or above). Patients receiving treatment for chronic hepatitis. Patients taking Sofosbuvir in or Ribavirin or combination. Patients who developed Cirrhosis of the liver. Patients from any geographical region of the world. Randomized Controlled Trials and observational studies were included.	Children (age less than 18). Pregnant patients with CH. Transplant patients with CH. Chronic hepatitis-C patients with other comorbidities (eg-Kidney disease, bone disease) and receiving treatment regimens for other comorbidities. Studies that were conducted before 2017. Patients with acute hepatitis C.

Table 1 showing Inclusion and Exclusion criteria.

### Data extraction

The data retrieval and review were completed by two separate researchers independently. In the case of disagreements, the researchers would discuss the data for its relevance and design to eligibility criteria, to reach an accord. A third researcher was counseled for objectivity if a decision could not be made.

### Critical appraisal of studies

We critically appraised our screened articles using the Cochrane risk of bias tool, New castle Ottawa tool, JBI checklist.

The bias risk for RCT's were looked at seven causes of potential bias. The quality assessment for RCT's using Cochrane bias tool is shown in Table 2.

Table 2

Article	Random sequence generation - Selection bias	Allocation of concealment - Selection bias	Blinding of both participants and evaluators - Performance Bias	Blinding of assessment during outcome collection - Detection bias	Incomplete outcome data - Attrition bias	Selective reporting - Reporting bias	Other bias/Comments
Orr et al. 2019 [1]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Pellicelli et al. 2020 [7]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	

Table 2 showing Quality assessment of randomized controlled trials using Cochrane bias tool.

The bias risk for observational studies looked mainly at selection, comparability and outcome domains. The quality assessment for observational studies using the new castle Ottawa tool is shown in Table 3.

Table 3

Study	Selection	Comparability	Outcome	Overall risk of bias
Tang et.al 2018 [2]	+	+	-	-
Yeon et.al 2018 [3]	-	+	-	-
Butt et.al 2019 [4]	+	+	-	-
Kim et.al 2018 [5]	-	+	-	-
Chen et.al 2020 [8]	+	+	-	-
Xu et.al 2018 [9]	-	+	+	-
Orr et.al 2020 [10]	+	+	+	+
Jang et.al 2020 [11]	-	+	-	-
Mita et.al 2023 [12]	+	+	+	+
Tmu et.al 2019 [13]	+	+	+	-
Smirne et.al 2021 [14]	+	+	+	-
Liu et.al 2021 [15]	+	+	+	-
Abdelkawy et.al 2020 [16]	+	+	+	-
Han et.al 2021 [17]	+	+	+	+

Table 3 showing Quality assessment of observational studies using new castle Ottawa tool.

Judgment:

x = High

- = Some concerns

+ = Low

The bias risk for Case report was looked at by using JBI checklist shown in Table 4.

Table 4

JBI checklist questions	Miyasaka et.al 2020 [6]
1. Were patient's demographic characteristics clearly described?	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes
6. Was the post-intervention clinical condition clearly described?	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes
8. Does the case report provide takeaway lessons?	Yes

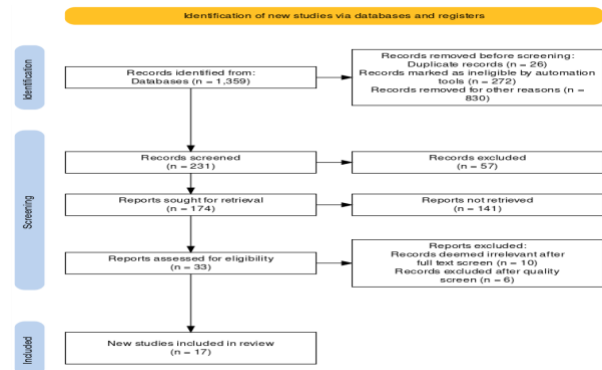
Table 4 showing Quality assessment of a case report using JBI checklist questions.

## Results

### Literature Search and Study Selection

The MeSH strategy and PubMed search generated thirteen hundred and fifty-nine articles from keywords, eligibility criteria, and databases. This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. Twenty-six articles were excluded due to duplication. Upon reading the titles and abstracts, fifty-seven articles were excluded. We were left with thirty-three articles after filtering to include articles that fit inclusion and exclusion criteria. Of the remaining articles, ten seemed irrelevant after a full-text screen, and six didn't meet the quality check criteria. Seventeen final articles met the criteria and were included, of which two were RCTs, fourteen were observational studies, and one was a case report. Our PRISMA flow diagram is shown below in Figure 1.

### PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.



### Definition:

Sustained Virological Response (SVR) : HCV cure following therapy is not confirmed until HCV RNA remains undetectable at 12 weeks after the end of treatment. This is known as sustained virologic response (SVR) and can be considered viral cure, as relapse after 12 weeks is exceedingly rare [30].

A brief overview of the studies included is given in Table 5

Table 5 Showing baseline characteristics of the studies included.

Article	Study design	Inclusion criteria	Outcome	Conclusion
Orr et al. 2019[1]	RCT	HCV patients who were treatment naive, willing to undergo liver biopsy, detectable HCV RNA at baseline, 18 or above.	Predominant cellular change during treatment was a decrease in CD8+ T-cell density in both parenchymal and non-parenchymal regions of the liver.	Decrease in CD8+ T-cell density during DAA treatment may be a reflection of the antiviral activity of the drugs.
Tang et al. 2018[2]	Prospective observational study	CHC patients, 18 or above, untreated or treatment experienced patients with compensated liver disease.	SVR rate- 72.4% in generic Sofosbuvir and 75.7% in brand name Sofosbuvir group.	No statistically significant difference in SVR and safety profiles between the generic Sofosbuvir group and the brand name sofosbuvir with ribavirin group.
Yeon et al. 2018[3]	Retrospective cohort	181 patients were followed for 12 weeks after the end of treatment.	SVR rate was 95.9% comparable to the SVR rates of newer DAA treatments.	Sofosbuvir plus ribavirin is still an effective treatment option for genotype 2 chronic hepatitis C in Koreans. Newer DAA treatments are generally the preferred option.
Butt et al. 2019[4]	Prospective observational study	Chronic active HCV infection as demonstrated by an Anti-HCV (ELISA) test.	SVR rate was 98% for treatment naive patients and 96.6% for treatment experienced patients.	Sofosbuvir and Ribavirin is a safe and effective treatment for CHC genotype 3 with high SVR rates in both treatment naive and treatment

				experienced patients.
Kim et al. 2018[5]	Retrospective cohort study	18 or above, CHC virus genotype 2 infection as determined by PCR.	SVR rate was 98.8% for treatment naive and 97.2% for treatment experienced patients.	The study found Sofosbuvir and ribavirin is safe for genotype 2 even in cirrhotic or non-cirrhotic patients.
Miyasaka et al. 2020[6]	Case report	Patients who were Hbsag +ve at baseline and remained Hbsag +ve after SVR. Detectable HBV DNA levels after SVR.	Acute hepatitis B in a patient who has been Hbsag +ve for at least 6 months and has undetectable HBV DNA levels. Incidence was 2.5%.	HBV reactivation is a very rare but serious complication of Sofosbuvir and ribavirin treatment for HCV infection.
Pelllicelli et al. 2020[7]	RCT	Patients with CHC genotype 3 infection and compensated cirrhosis. 18 or above.	SVR rate was 98%. SVR rate was not significantly different between patients with Child Pugh A and B cirrhosis.	Sofosbuvir plus Ribavirin/ Daclatasvir is safe and effective regardless of cirrhosis severity.
Chen et al. 2020[8]	Retrospective Cohort study	18 or above. Patients with CHC genotype 2 infection.	Incidence of anemia in study was 10%.	Anemia had a negative impact on SVR rates. Patients with anemia were less likely to achieve SVR than patients without anemia.
Xu et al. 2018[9]	Observational study	18 or above, Patients with HCV infection.	SVR rate was 96% in patients treated with Sofosbuvir and ribavirin with or without interferon.	Sofosbuvir and ribavirin has same safety and efficacy with or without Interferon, so it is good for who are not eligible for interferon based treatment.
Orr et al. 2020[10]	Retrospective cohort study	CHC genotype 1 patients, 18 or above.	Patients who relapsed had lower pretreatment neutrophil counts and higher post treatment NK cell counts. Also patients with Cirrhosis relapsed more.	People with weaker immune system and preexisting liver disease are more likely to relapse.
Jang et al. 2020[11]	Retrospective observational study	CHC genotype 2 patients.	SVR - 95%. With regardless of Ribavirin dose. The treatment was well tolerated with most common adverse events being anemia, nausea and fatigue.	A reduced Ribavirin dose can be considered as SVR rates and adverse events are similar.
Mita et al. 2023[12]	Prospective observational study	CHC genotypes 3,4,5 and 6.	SVR rates were 83.7%.	Sofosbuvir and ribavirin is shown to be safe and effective in genotypes 3,4,5, and 6 in Japan people.
Tmu et al. 2019[13]	Retrospective observational study	Genotype 1 or 4. Decompensated cirrhosis with child Pugh class B or C patients.	SVR rates were 57%.	SVR rates were lower than other studies showing that the treatment is less effective for cirrhotic patients, but safety was same.
Smirne et al. 2021[14]	Retrospective observational study	Genotype 2 patients	SVR - 98.3%. Efficacy and safety were same in both flat dose Ribavirin and weight-based dose Ribavirin is same. SVR rates were similar in both	Sofosbuvir based therapies are safe and effective for Chronic hepatitis C genotype 2 even with mild and moderate cirrhosis.

			Child Pugh A and B cirrhosis.	
Liu et al. 2021[15]	Retrospective Observational study	HCV Genotype 1a,1b,2,3,4,5 or 6. Chronic HCV patients with Child Pugh B or C cirrhosis.	SVR-89.7% in overall population, 94.1% in the modified intention to treat (mITT) population, 100% in the per protocol (PP) population.	Sofosbuvir/Velpat asvir plus Ribavirin is a safe and effective treatment for CHC and Child Pugh B,C cirrhosis, helping in improving the lives of patients.
Abdelkawy et al. 2020[16]	Retrospective observational Study	HCV Genotype 4 infection	SVR 12 rate-92.0%. No significant association between the genetic variations in the SLC 28A2, ABCB1, and ABCB11 genes and the SVR 12 rate. However, the ABCB12677G>TSNP and the ABCB11 1331T>C SNP were statistically associated with higher plasma concentrations of Ribavirin at week 4 of therapy.	SNP genotyping for ABCB1 and ABCB11 genes can help personalize medicine for ribavirin treatment by identifying patients who are more likely to respond to the drug.
Han et al. 2021[17]	Retrospective observational study	HCV Genotype 2 infection.	SVR 12 rate-92.8%. The predictors of SVR 12 were rapid virological response (RVR) and no previous history of hepatocellular carcinoma (HCC).	The patients who had RVR and no previous history of HCC were more likely to achieve SVR 12 with Sofosbuvir and ribavirin treatment.

## Discussion

### *Effectiveness and safety of Sofosbuvir in combination with Ribavirin.*

The safety and efficacy of Sofosbuvir and ribavirin have been well-established in clinical trials. Sofosbuvir and ribavirin are generally well-tolerated, with the most common adverse events being fatigue, headache, nausea, and vomiting [23]. The long-term safety of Sofosbuvir and ribavirin is still being studied, but there is no evidence to suggest that these medications cause any long-term harm.

In terms of efficacy, Sofosbuvir and ribavirin have been shown to be highly effective in treating chronic hepatitis C. Sustained virologic response (SVR) rates with Sofosbuvir and ribavirin are typically over 90%, regardless of HCV genotype or patient [28]. This means that over 90% of patients who complete treatment with Sofosbuvir and ribavirin will achieve a cure.

Direct-acting antiviral (DAA) treatment is effective for most patients with chronic hepatitis C virus (HCV) infection, but some fail to achieve sustained virologic response (SVR)[1]. A study found that both generic and brand name sofosbuvir with ribavirin are effective, with a sustained virologic response (SVR) of 72.4% and 75.7%, respectively. However, bioequivalency studies of all generic DAAs need to be performed before wider use

of such drugs for the treatment of hepatitis C [2]. A study in Pakistan found that sofosbuvir (SOF) in combination with ribavirin (RIB) is safe and effective for the treatment of chronic HCV genotype 3. The study found that 99.1% of patients achieved SVR, regardless of whether they had previously been treated with antiviral medications [4]. A study in Korea found that a 12-16 week treatment with sofosbuvir plus ribavirin is remarkably effective and well tolerated in patients with chronic HCV genotype 2 infection. The most common adverse event was anemia, which occurred in 11% of patients [5].

A study reported a rare case of hepatitis B virus (HBV) reactivation in a patient with hepatitis C virus (HCV) infection after direct-acting antiviral agents (DAAs) therapy. The patient was treated with nucleotide analog, and her condition improved [6]. A study also found that the most effective and safe treatment for genotype 3 HCV cirrhosis patients is the DCV/SOF/RBV flat-dose regimen. The DCV/SOF regimen was the least effective, and the DCV/SOF/RBV weight-based dose regimen was associated with a higher incidence of anemia [7]. Another study found that severe anemia was not uncommon during sofosbuvir plus ribavirin therapy for chronic hepatitis C genotype 2 patients. The study found that chronic kidney disease, low baseline hemoglobin level, and low baseline platelet count were independent risk factors for severe anemia. The study also found that severe anemia, dose reduction, or average dose of ribavirin was not associated with sustained virologic response (SVR) [8]. A study in China found that sofosbuvir and ribavirin-based treatment can cure most patients with chronic hepatitis C, even those with cirrhosis. The treatment rapidly decreased viral load and sustained virological response (SVR) in 8 of 9 patients. The study also found that the interferon-inducible protein-10 (IP-10) decreased after treatment, and its levels may be a biomarker for the prognosis of HCV [9]. Finally, a study found that patients who relapsed after hepatitis C virus (HCV) therapy had lower pre-treatment neutrophil counts and higher post-treatment natural killer (NK) cell counts than patients who did not relapse. They also had different expressions of genes associated with interferon signaling, T-cell dysfunction, and T-cell co-stimulation. The study also identified a pre- and post-treatment gene expression signature that could predict relapse, but it was not yet robust enough to be used in clinical practice [10].

Studies have shown that sofosbuvir-based therapies are effective and well-tolerated in patients with chronic hepatitis C virus (HCV) infection, regardless of genotype, previous antiviral treatment, or liver disease severity [11,12,13,14,15].

Two studies were conducted to investigate the efficacy and safety of treatments for hepatitis C virus (HCV) infection. The first study found that genetic variations in the ABCB1 and ABCB11 genes were associated with ribavirin (RBV) plasma trough levels and clinical outcomes, such as sustained virological response (SVR), in Egyptian patients with HCV genotype 4. The

study authors concluded that genetic testing for these genes could help to personalize treatment for patients with HCV genotype 4 [16]. The second study found that sofosbuvir/ribavirin (SOF/RBV) was effective and well-tolerated in most Korean patients with HCV genotype 2 (HCV GT2) infection, with an SVR12 rate of 92.8%. The study also found that rapid virological response (RVR) and no previous history of hepatocellular carcinoma (HCC) were positive predictors of SVR12 [17]. In summary, both studies suggest that genetic testing and clinical factors can be used to personalize treatment for patients with HCV infection.

#### *Comparison with other treatments*

Sofosbuvir and ribavirin have been compared with other treatments for chronic hepatitis C, including pegylated interferon and ribavirin, and interferon-free regimens. Sofosbuvir and ribavirin have been shown to be more effective than pegylated interferon and ribavirin, and they have a shorter treatment [25]. Sofosbuvir and ribavirin are also more effective than interferon-free regimens, and they have a lower risk of [29].

#### *Implications for clinical practice*

Sofosbuvir and ribavirin are the first-line treatment for chronic hepatitis [26]. They are highly effective and well-tolerated, and they have a shorter treatment duration than previous [27]. As a result, Sofosbuvir and ribavirin are the preferred treatment for most patients with chronic hepatitis C.

#### **Limitations**

This review was limited by the fact that it only included published studies. There may be unpublished studies that have not yet been reported. Additionally, the studies included in this review were conducted in different settings, and the results may not be generalizable to all patients with chronic hepatitis C.

Overall, Sofosbuvir and ribavirin are a major advance in the treatment of chronic hepatitis C. They are more effective and better tolerated than previous treatments, and they have a shorter treatment duration. As a result, Sofosbuvir and ribavirin have revolutionized the treatment of chronic hepatitis C and have made it a curable disease.

#### **Conclusions and future directions**

Sofosbuvir and ribavirin are the standard of care for the treatment of chronic hepatitis C. They are more effective and better tolerated than previous treatments, and they have a shorter treatment duration. As a result, Sofosbuvir and ribavirin have revolutionized the treatment of chronic hepatitis C and have made it a curable disease. Future directions for research include the development of new Sofosbuvir-based regimens that are even more effective and better tolerated. Additionally, research is ongoing to evaluate the long-term safety of Sofosbuvir and ribavirin.

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