



ORIGINAL ARTICLE

Study of the effects of Sofosbuvir-based treatments on liver stiffness in chronic Hepatitis C patients using transient Elastography

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is a global public health problem affecting millions of people worldwide. Chronic HCV infection causes long-term complications as liver cirrhosis and its consequences as hepatocellular carcinoma. The inadequate and improperly tolerated treatment options contributed to the health burden of chronic HCV. New treatment therapies had evolved that implied direct-acting antivirals (DAAs) that targeted different hepatitis C virus genomic sites. DAAs demonstrated better efficacy, patient compliance, and tolerance than former antiviral therapy. transient elastography is established as a noninvasive method for assessing hepatic fibrosis in HCV patients. Aim of the study: to demonstrate the effectiveness of DAAs (sofosbuvir-based therapy) in treating chronic HCV infection and improving hepatic fibrosis through assessment using TE. Relevant articles were identified by searching PubMed and Google Scholar databases.

Conclusions: This literature review revealed significant improvement in hepatic fibrosis assessed by TE in HCV patients treated by sofosbuvir-based antiviral therapy.

Keywords: HCV, Sofosbuvir, TE, direct-acting antivirals

INTRODUCTION:

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease in the world [1]. Around 180 million people are thought to be chronically unwell worldwide, although the majority are oblivious to their condition [2].

Direct-acting antiviral (DAA) medications have changed the way HCV is treated in recent years; they were first used in clinical settings in 2014–2015. With higher SVR rates, simpler, shorter regimens, and a decreased incidence of therapy-related side effects in HCV patients, they demonstrated a bright future for HCV treatment [3].

For many years, liver professionals have focused their research and discussions on the regression fibrosis of the liver. However, recent research has demonstrated that fibrosis regression can happen in a range of chronic

liver diseases, including persistent viral hepatitis [4].

According to several studies, administering strong antiviral medications to CHC patients may cause liver fibrosis to regress by enhancing hepatic necro-inflammation, lessening harm in long-term recipients, and delaying the onset of relapses [5].

These days, transient elastography (TE) has the advantages of significant accuracy and repeatability as an established noninvasive method for assessing hepatic fibrosis in patients with HCV [6].

It has been shown that several non-invasive laboratory techniques, including In HCV patients, FIB-4 and APRI are accurate indicators of hepatic fibrosis and for staging chronic liver disorders prior to antiviral therapy. Additionally, they have been utilized to evaluate the effects of antiviral medication

and monitor chronic hepatitis patients over an extended time [7].

TE is thought to be helpful in the diagnosis of cirrhosis (F4 fibrosis) and in differentiating between significant (\geq F2) and non-significant data (F0 and F1) fibrosis [8].

Hepatitis C Virus Infection

The RNA is a virus belonging to the Flaviviridae family that is referred to as the hepatitis C virus (HCV). Acute C-hepatitis can be transmitted by HCV infection; after acute infection, 50–80% of patients get chronic hepatitis C. A chronic inflammatory disease process brought on by a persistent HCV infection may result in liver fibrosis, cirrhosis, hepatocellular cancer, and even death. In many parts of the world, hepatitis C is the primary reason for liver transplantation [9].

Hepatitis C can cause liver cirrhosis or possibly hepatocellular cancer if left untreated (HCC) [10].

Epidemiology

According to the World Health Organization (WHO), the global prevalence of chronic HCV infection remains as high as 58 million, including 3.2 million cases in adolescents and children [11]. In addition, there are approximately 1.5 million new infections per year [11]. WHO estimated that in 2019, 290,000 people died of hepatitis C. Mortality was mostly a result of complications of the chronic disease with cirrhosis and hepatocellular carcinoma (HCC) [11].

The highest burden of disease is in the Eastern Mediterranean Region and European Region, with 12 million people chronically infected in each region. In the Southeast Asia Region and the Western Pacific Region, an estimated 10 million people in each region are chronically infected. Nine million people are chronically infected in the African Region and 5 million in the Region of the Americas. [11].

The World Health Organization (WHO) announced Egypt as the first country to achieve “gold tier” status on the path to elimination of hepatitis C as per WHO criteria. Achieving the gold tier means that Egypt has fulfilled the programmatic

requirements that facilitate the reduction of new hepatitis C infections and deaths to levels that position the country to end the hepatitis C epidemic. [12]. Egypt is accustomed to having one of the highest prevalence of HCV infection worldwide. The Egyptian Ministry of Health launched a national campaign for the screening and management of HCV to reduce its burden [13].

WHO unanimously endorsed the 2016–2021 Viral Hepatitis Agenda in the First Global Health Sector Plan, which this updated plan was in line with. Signatories to the WHO pledged to eradicate viral hepatitis as a danger to public health by 2030. According to the WHO, elimination was characterized as a 90% decrease in incidence and a 65% decrease in mortality relative to the 2015 baseline [14].

DAA's regimens for chronic HCV infection

Globally, there are six genotypes of the hepatitis C virus (HCV) [14]. According to a recent comprehensive assessment, genotype 1 (GT1) accounts for 49% of all adult HCV infections worldwide. Genotypes 3 (GT3), 4 (GT4), and 5 (GT5), and genotype 6 (GT6), are next in order of prevalence, at 18%, 17%, 11%, and 2%, respectively [15].

The effectiveness of HCV antiviral therapy is evaluated using the sustained virology response (SVR) rate [16]. SVR denotes the observation of an undetectable viral load (HCV RNA $<$ 15 IU/mL) 12 weeks post-treatment (SVR12) [16].

The following illustrates a concise approach for the detection, treatment, and monitoring of long-term HCV infection in adults and teenagers [11].

A paradigm shift is occurring in the treatment of chronic hepatitis C virus (HCV) infection, as new Rapidly taking the place of the long-used combination of PEGylated interferon and ribavirin are direct-acting antiviral medications or DAAs. Today's finest DAA combinations require 8–12 weeks of treatment to cure almost all patients. Compared to traditional interferon and ribavirin therapy, oral therapies are more well-tolerated, have shorter half-lives, fewer side effects, and have higher rates of sustained viral response [17].

Treatment for HCV infection aims to cure the virus to: (i) prevent death and serious extrahepatic manifestations; (ii) enhance people's quality of life and remove stigma; and (iii) avoid consequences from liver and extrahepatic disorders linked to HCV, such as fibrosis, cirrhosis, and decompensation of cirrhosis, and hepatic necro-inflammation; (TasP) [18].

Combinations of DAAs are frequently used to prevent the emergence of antiviral resistance [19].

Table (1) illustrates how direct-acting antivirals (DAAs) are categorized based on how they work [19]. Pre-treatment requirements for patients with chronic HCV are illustrated in **Table (2)** [2].

Sofosbuvir Based Treatment

"Sofosbuvir" became the first NS5B RNA-polymerase inhibitor authorized for use in HCV therapy in 2014. When compared to IFN-based treatments. DAA-containing interferon-free regimens lead to increased rates of SVR and exhibit a better safety profile. As a result, these treatment plans are frequently employed to treat chronic hepatitis C. By November 2015, the primary treatment in Egypt's National Program SOF/DCV, with or without RBV, was used to treat chronic HCV [21].

Among the directly acting antiviral medications now being developed, sofosbuvir is particularly intriguing because of its high efficacy, few side effects, oral delivery, and great resistance to resistance [22].

Figure (1) illustrates how the liver's Sofosbuvir activation pathway works [23].

Three all-oral combination treatments were approved: ombitasvir + paritaprevir + ritonavir + dasabuvir; Sofosbuvir plus simeprevir; and Sofosbuvir plus ledipasvir in 2014. It was shown that all three regimens were quite successful, with SVR rates getting close to 100% [24].

Several clinical studies have looked at sofosbuvir's efficacy and safety in individuals with varying HCV genotypes and medication combinations. Twelve to twenty-four weeks of treatment are available, including

Sofosbuvir at its highest effective dose being 400mg [22].

The effectiveness Dependence of Sofosbuvir-based treatment plans on the measurement of liver stiffness using transient elastography. Hepatic fibrosis is a condition associated with hepatic necro-inflammation that is characterized by a balance between the synthesis and breakdown of extracellular matrix [25].

Hepatic fibrosis severity and extent are indicators of how the disease will advance and aid in the identification of patients who need antiviral therapy, the course of treatment, and the choice of a plan of care [26].

A novel ultrasound-based technique called transient elastography was developed as a liver stiffness assessment tool in place of liver biopsies. Liver fibrosis severity can vary swiftly and precisely assessed using TE, a non-invasive method. Furthermore, it permits reexamination of hepatic fibrosis in those with chronic liver disease [27].

Shousha et al SVR rate was 93.6% with significant improvement in liver stiffness observed in his 2017 cohort study involving 155 patients who received Sofosbuvir and daclatasvir ± weight-based ribavirin (RBV), sofosbuvir and simeprevir, sofosbuvir, weekly PEGylated interferon, and weight-based RBV (Peg IFN) for 12 weeks. (LSM) (P value > 0.001) [28].

Khattab et al conducted a prospective study on 75 HCV patients at 2021 who had Sofosbuvir plus weight-based ribavirin (RBV) for 12 weeks together with daclatasvir. Patients in the research showed a substantial improvement in liver stiffness in both dual and triple therapy, with a P value of 0.005, and reached SVR 100% [29].

Alswat et al APRI dropped from 0.81 (0.7) to 0.34 (0.2) and FIB-4 dropped from 1.99 (1.4) to 1.35 (0.9) in the study of changes in individuals with chronic hepatitis C infection who react well to direct-acting antivirals but have hepatic fibrosis. There was a significant difference observed on follow-up following treatment and total virus eradication [30].

Likewise, **Elsharkawy et al.** performed a retrospective analysis on 337 patients

receiving sofosbuvir/simeprevir treatment, and sofosbuvir/daclatasvir, either with or without ribavirin. The results showed a 92% SVR and dramatically reduced liver stiffness in SVR12 [5].

In 2021, **Mohammed et al.** conducted a prospective trial including 50 HCV patients receiving daclatasvir and sofosbuvir therapy. The patients obtained 96% SVR and a substantial ($p \sim 0.05$) improvement in LSM by Fibro Scan between baseline and six months after therapy [31].

Furthermore, patients saw a significant improvement in dual-wavelength shear-wave elastography (2 D-SWE) with a p-value of 0.013 in a retrospective study conducted by **Lee et al.** on 68 patients treated with daclatasvir + sofosbuvir with 100% SVR [32]. **Nozaki et al.** studied 119 patients receiving for 12 weeks, take ledipasvir 90 mg/sofosbuvir 400 mg, sofosbuvir 400 mg, and 200–1000 mg/day of ribavirin. The

findings demonstrated that all genotype-2 patients and 98% of genotype-1 patients obtained SVR at that time. Regression of fibrosis was linked to the achievement of SVR following antiviral therapy. showed a strong correlation with LSM 48 weeks following the start of treatment [33].

400 patients received Sofosbuvir / Daclatasvir ± Ribavirin (SOF/DCV± RBV), Sofosbuvir/± Ribavirin (SOF/SIM±RBV), or Sofosbuvir / PEG-interferon / Ribavirin (PEGIFN/SOF/RBV) for 12 weeks with 94.6 SVR and a significant decrease in LSM following SVR12. **Perazzo et al.** retrospective observational study included 400 patients [34].

Study characteristics

The patients in our assessment of the literature come based on 11 studies. The characteristics and findings of the included studies are shown in Table 3.

Table (1): Classification of direct-acting antivirals (DAAs) according to their mechanism of action [19].

NS5A Serine Protease Inhibitor	Protease Inhibitor NS3/4A	NS5B Polymerase Inhibitor (Non-Nucleoside Analogue)	NS5B Polymerase Inhibitor (Nucleotide Analogue)
Daclatasvir	Glecaprevir	Dasabuvir	Sofosbuvir
Elbasvir	Grazoprevir	Deleobuvir	
Ledipasvir	Paritaprevir		
Ombitasvir	Simeprevir		
Pribrentasvir	Voxilaprevir		
Velpatasvir			

Table (2): Direct Acting Antiviral Class Attributes [20]

	Protease Inhibitors	Nucleoside Inhibitors	Nonnucleoside Inhibitors	NS5A Inhibitors
Potency	High	Intermediate	Intermediate	High
Genotype coverage	Multiple genotypes	Pangenotypic	Limited genotypes	Multiple genotypes
Barrier to resistance	Low-intermediate	High	Low	Low-intermediate
Drug-drug interactions	Many	Few	Moderate	Moderate

Table (3): Study characteristics

Author	Year	Study Design	Sample Size	Treatment	Treatment Duration	SVR12 rate	Study Outcome
Shousha et al	2017	Cohort study	155	Sofosbuvir and daclatasvir ± weight based ribavirin (RBV), sofosbuvir and simeprevir, sofosbuvir and weight-based RBV plus weekly PEGylated interferon (Peg IFN) for 12 weeks.	12 weeks	93.6%	Significant improvement in liver stiffness(LSM) (P value< 0.001
Elsharkawy et al	2017	Retrospective study	337	sofosbuvir/simeprevir, sofosbuvir/ribavirin, and sofosbuvir/ daclatasvir with or without ribavirin	12 weeks	92%	Liver stiffness measurements were significantly lower in SVR12
Mohammed et al	2021	prospective study	50	Sofosbuvir and daclatasvir	12 weeks	96 %	significant improvement (p <0.05) LSM by Fibro Scan from baseline compared to 6 months post-treatment
Lee et al	2020	Retrospective study	68	daclatasvir plus sofosbuvir	12 weeks	100%	Significant improvement of two dimensional shear-wave elastography (2 D-SWE) p value 0.013
Khattab	2021	Prospective study	75	Sofosbuvir and daclatasvir ± weight based ribavirin (RBV)	12 weeks	100%	significant improvement in liver stiffness in both dual and triple therapy P value 0.005
Alkhattib et al	2019	Prospective cohort study	162	Sofosbuvir and daclatasvir ± weight based ribavirin (RBV)	12 weeks	95.1	Significant decline in LSM values using SWE. (P <0.001).
Alswat et al	2021	Retrospective cohort study.	172	Sofosbuvir and daclatasvir ± weight based ribavirin (RBV)	12 weeks	100%	Significant decline in LSM values using SWE. (P <0.001).
El-Kady et al	2021	prospective study	300	Sofosbuvir + Simeprevir ± Ribavirin as dual or triple therapy Sofosbuvir + Daclatasvir ± Ribavirin as dual or triple therapy	12 weeks	100%	fibro scan parameters showed a significant decrease in both groups compared to the baseline.
Nozaki et al	2021	prospective cohort study	119	ledipasvir 90mg/sofosbuvir 400mg and sofosbuvir 400mg + 200–1000mg/day ribavirin,	12 weeks	98% of the genotype-1 patients and all the genotype-2 patients achieved SVR at 12weeks.	Achievement of SVR after antiviral therapy was associated with fibrosis regression. correlated well with LSM at week 48 after treatment initiation
Perazzo et al	2019	retrospective observational study	400	Sofosbuvir / Daclatasvir ± Ribavirina (SOF/DCV± RBV), Sofosbuvir / ± Ribavirina (SOF/SIM±RBV) or Sofosbuvir/PEG-interferon/Ribavirina (PEGIFN/SOF/RBV)	12 weeks	94.6	significant decreasing of LSM after SVR12 was observed i

SVR12: Sustained virologic response at 12 weeks after treatment is completed,
LSM: Liver Stiffness Measurement

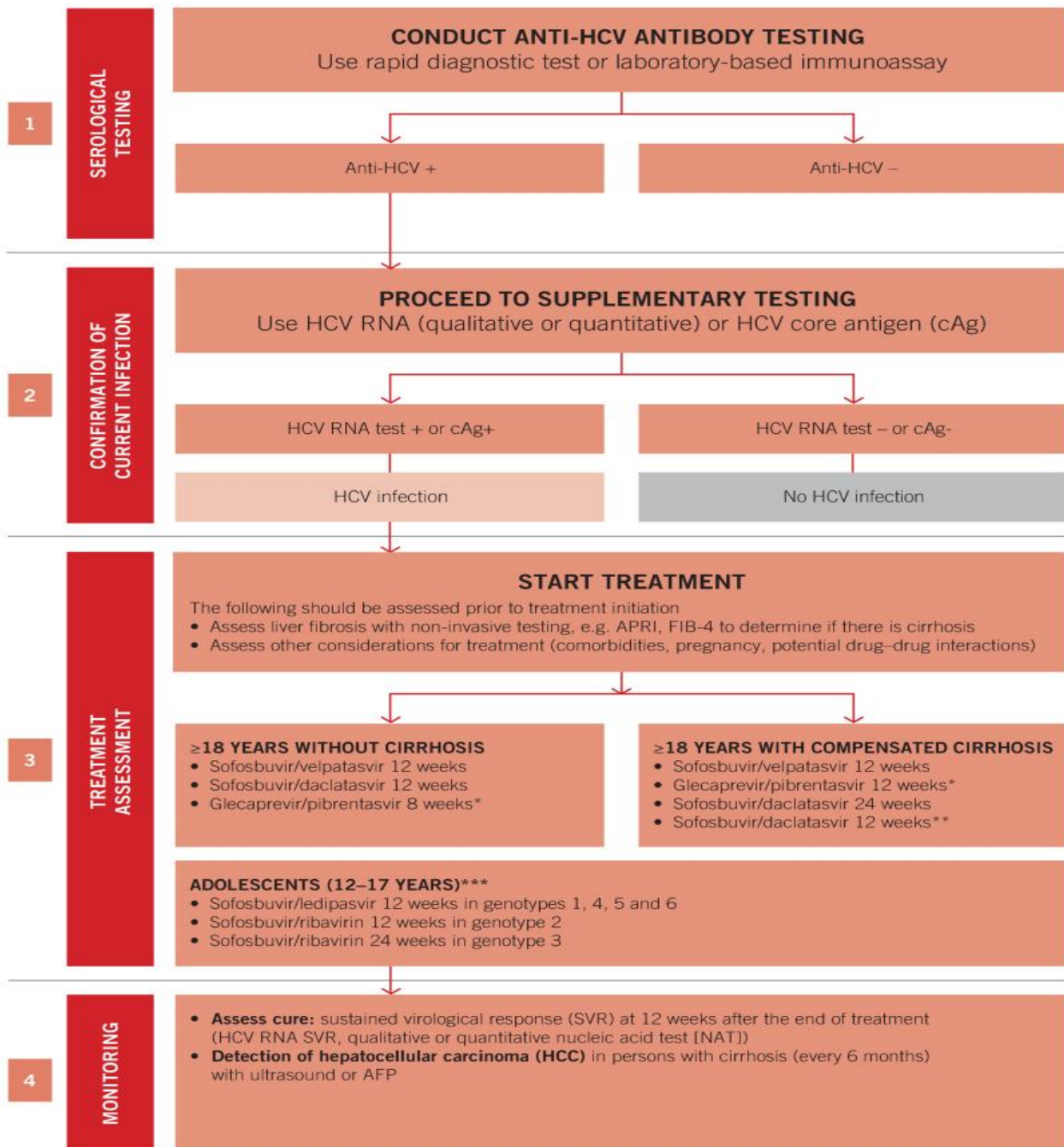


Figure (1): Summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection in adults and adolescents [11].

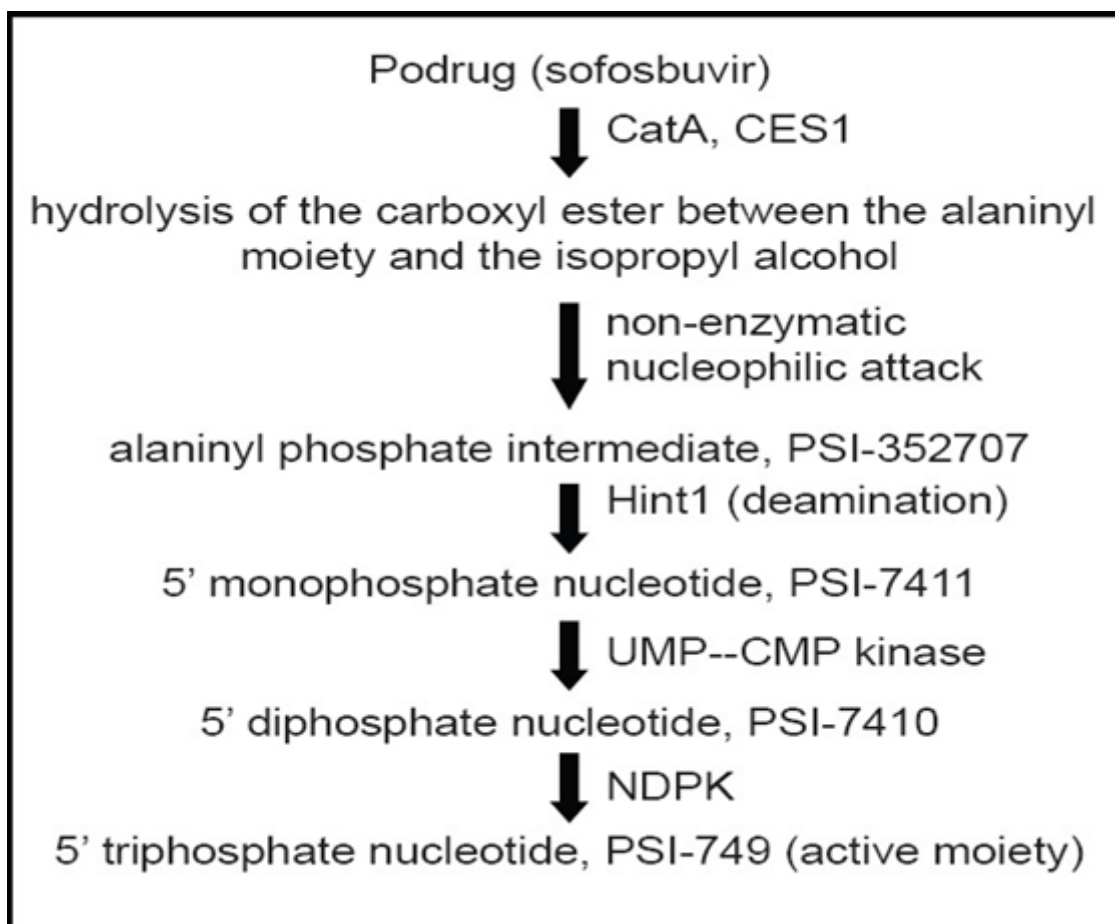


Figure (2): Activation of sofosbuvir in liver.

CatA -human cathepsin A; CES1- carboxylesterase 1; Hint1 - histidine triad nucleotide-binding protein 1; NDPK – nucleoside diphosphate kinase; UMP–CMP kinase-uridine monophosphate–cytidine monophosphate kinase[22].

Conclusions:

Through noninvasive After receiving sofosbuvir treatment for chronic hepatitis C patients, our review of the literature using transient elastography to detect liver stiffness found a regression of hepatic inflammation and fibrosis-based therapy.

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