SOFOSBUVIR: NEW AND PROMISING TREATMENT FOR HEPATITIS C VIRUS INFECTION- A REVIEW

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ABSTRACT

Hepatitis C is a life threatening disease caused by Hepatitis C virus. Until recently, ribavirin in combination with peg interferon was considered to be the standard in treatment for HCV infection. However, the need for a newer agent became evident when patients with advanced liver disease, liver transplant receivers, hard to treat hepatitis and in those who can’t tolerate or receive peg interferon therapy came into picture. Sofosbuvir, a viral nucleotide HCV polymerase inhibitor was formulated to provide a solution for such difficulties. With the introduction of sofosbuvir, a greater cure rate with minimum treatment duration for HCV infection was made into a reality and when in combination with either ribavirin with or without peg interferon, visibly out ranked the older standards in therapy.

KEYWORDS: Hepatitis C, Peg interferon, Ribavirin, Sofosbuvir, Efficacy, Safety.

INTRODUCTION

Hepatitis C is a life threatening disease caused by a virus known as the Hepatitis C Virus [HCV].[1] This disease manifest in two phases. The first phase of the disease is called the ‘acute phase’ wherein the patient is typically asymptomatic. Acute phase is usually followed by a second ‘chronic phase’ of the disease, wherein the patients are likely to progress from nonspecific symptoms of liver insult such as fatigue, loss of appetite, flu-like symptoms, etc. to more specific symptoms such as jaundice, dark yellow urine and/or delayed wound healing.[2,3] However, it is not necessary that patients with acute hepatitis C infection will progress into the chronic phase of the infection. Unfortunately, for those patients who enter
into the chronic phase, the risk for liver cirrhosis is increased by 15-30% in addition to the risk for hepatocellular carcinoma, which is increased to 17 folds.[4,1,5]

**NEED FOR A NEWER AGENT**

Until recently, ribavirin in combination with peg interferon was considered to be the standard in treatment for HCV infection.[6] However, the need for a newer agent became evident when patients with advanced liver disease, liver transplant receivers, hard to treat hepatitis, and those who can’t tolerate or receive peg interferon therapy came into picture.[7,8] Sofosbuvir, a viral nucleotide HCV polymerase inhibitor of was formulated to provide a solution for such difficulties and also, was aimed in achieving a greater cure rate with minimum treatment durations for patients with HCV infection.[8]

**MECHANISM OF ACTION**

Sofosbuvir [Fig 1] is a newer antiviral drug which upon its conversion in the liver to its active form serves as a nucleotide polymerase inhibitor. The activated drug (2’-deoxy-2’-α-fluoro-β-C-methyluridine-5’-triphosphate), acts as a defective substrate for the RNA polymerases. Once this analogue is bound to the RNA polymerases, further synthesis of viral RNAs are inhibited which in turn leads to the termination of viral replication.[6,9,10,11]

![Chemical structure of sofosbuvir](image)

**Fig 1: Chemical structure of sofosbuvir**

**SOFOSBUVIR AS A NEWER THERAPEUTIC MODALITY**

So far, 6 different strains of HCV (also known as “genotype”) have been identified. Treatment with sofosbuvir was found to be very effective against all the HCV genotypes in bringing about a rapid reduction in its viral load.[12] Combination therapy of sofosbuvir with either ribavirin with or without peg interferon is strictly recommended over monotherapy in order to reduce the incidences of viral S282T mutations as demonstrated by ELECTRON phase 2 study, and to effectively reduce the viral RNA load.[13,14] A study conducted has observed that when sofosbuvir was used alone for treatment in patients with HCV genotypes
2 or 3, 60% patients had sustained virological response [SVR] defined as undetectable viral RNA post therapy, at 24 weeks. However, when added to ribavirin with or without peg interferon, a 100% in SVR was observed at 24 weeks.[8]

COMPARATIVE EFFICACY OF SOFOSBUVIR AS A COMBINATION THERAPY
Sofosbuvir should only be given in combination with other anti-HCV medications. The duration of treatment and the selection of anti-HCV drug for combination therapy with sofosbuvir are further dependent upon the type of HCV genotype in a patient.[13]

1. In patients with HCV Genotype 2 or 3 infection
Studies have shown that chronic infection with HCV genotype 2 or 3 can be treated by using a combination of sofosbuvir and ribavirin without interferon.[15] Therefore, for this review, data from different studies were compiled to determine the efficacy profile of sofosbuvir used in combination with ribavirin with or without peg interferon. Following were the comparisons made

(i) In comparison with placebo
When efficacy of sofosbuvir/ribavirin combination was compared with a placebo in patients with HCV genotype 2 or 3 for a duration of 12 weeks, the result obtained was a remarkable 78% of patients achieving SVR at 12 weeks post therapy with sofosbuvir/ribavirin combination. But for those patients that have received a placebo, none of them turned negative to Hepatitis C.[16,17]

(ii) In comparison with the older standard therapy
A study has shown that sofosbuvir/ribavirin combination when given to patients for whom treatment with peg interferon/ribavirin combination (older standard therapy) was not an option, 12-16 weeks of treatment with sofosbuvir/ribavirin combination could be considered as an effective alternative.[16] Interestingly, it was found that the response rates to sofosbuvir/ribavirin combination were higher in patients with HCV genotype 2 infections as opposed to genotype 3 infections and for those patients with genotype 3 infections, the response rate was found to be lower in those with cirrhosis when compared to those without cirrhosis.[6,16]
2. In patients with HCV Genotype 1, 4, 5, or 6 infection
The response rate in treatment naïve patients was observed to be higher when sofosbuvir was added to peg interferon and ribavirin as demonstrated by the NEUTRINO trial. From this study it was observed that 90% patients had achieved SVR with sofosbuvir/ribavirin/ peg interferon combination therapy at 12 weeks.\(^{[18,19]}\)

PLACE IN THERAPY FOR SOFOSBUVIR
The latest NICE guidelines (February 2015) on HCV infection recommends sofosbuvir to be used only for those patients who are intolerant or ineligible to interferon and/or have cirrhosis [Table 1]. However, an exception to this criterion remains to those patients with HCV genotype 1 infection.\(^{[13,20]}\) A detailed recommendation on sofosbuvir use is laid below.

Table 1: Latest NICE guidelines on HCV infection

<table>
<thead>
<tr>
<th>HCV Genotypes</th>
<th>Sofosbuvir+Peginterferon alpha+Ribavirin</th>
<th>Sofosbuvir+Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>Recommended</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Not licensed</td>
<td>Recommended only for Treatment naïve patients* who can’t receive interferon, or Treatment experienced patients**</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Recommended only for Treatment naïve patients and have cirrhosis, or Treatment experienced patients</td>
<td>Recommended only if Patients have cirrhosis, and cannot receive interferon</td>
</tr>
<tr>
<td>Genotype 4,5,6</td>
<td>Recommended only if Patients have cirrhosis</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*Treatment naïve patients: Patients who had not had treatment for HCV  
**Treatment experienced patients: Patients who had received treatment but has not adequately responded to interferon based treatment

The optimal treatment duration for HCV genotype 1, 2, or 4 can be 12 weeks.\(^{[9]}\) However, the response rate of sofosbuvir/ribavirin combination in people with HCV genotype 3 infection was found to be lower in comparison to any other genotypes, in turn suggesting that in patients with HCV genotype 3 infections, a longer duration of treatment may be required.\(^{[6]}\) According to the FUSION study, 16 weeks therapy with sofosbuvir/ribavirin combination was considered superior to 12 week therapy as it brought about an increased cure rate in those with HCV genotype 3 infections who didn’t respond to previous therapy with interferon.\(^{[17]}\) In addition, results from BOSON study identified that 24 week therapy with sofosbuvir/ribavirin combination brought a still higher cure rate when compared to 16 week
Results from these two studies in turn suggested that for patients with HCV genotype 3 infection, therapy may be prolonged to up to 24 weeks to achieve higher curative rate.

**PHARMACOKINETIC PROFILE OF SOFOSBUVIR**

Sofosbuvir is having a very favourable pharmacokinetic profile. The peak plasma concentration following the oral administration of sofosbuvir was found to be 0.5-2 hours irrespective of food intake. The drug is rapidly absorbed with approximately 61-65% bound to human plasma proteins. Sofosbuvir is metabolized in the liver by human cathepsin A (CatA), carboxylesterase 1 (CES1) and Histidine triad nucleotide binding protein 1 (Hint 1) with no evidence of CYP450 or UGT mediated metabolism. The drug has three routes of elimination: urine (80%), feces (14%) and respiration (2.5%) with the highest elimination occurring via the kidneys. The median terminal half-lives of sofosbuvir and its major metabolite are 0.4 and 27 h, respectively.

No dose adjustments are required for patients with creatinine clearance >30 mL/min or with moderate and severe hepatic dysfunction. However, for those patients with creatinine clearance <30 mL/min or are under hemodialysis sofosbuvir is contraindicated.

There is a lack of information on sofosbuvir use in patients with decompensated cirrhosis, < 18 and > 65 years of age, coinfection with hepatitis B virus and lactation. Therefore the use of the drug under these circumstances is not recommended until further studies are made available. However, pregnancy should be avoided in both female patients and female partners of male patients for at least 6 months following cessation of therapy since sofosbuvir is usually given in combination with ribavirin with or without peg interferon; and ribavirin being a known teratogen.

**DRUG INTERACTIONS**

Since sofosbuvir has no evidence of CYP450 or UGT mediated metabolism, the drug has limited potential for interactions with other drugs. However, regardless of its nature, drug-drug interactions must be always sort out prior to initiating any combination therapy with sofosbuvir.

Drug interactions were not seen with other direct acting antivirals (e.g. daclatasvir, ledipasvir, and simeprevir), immunosuppressive agents (e.g: tacrolimus and cyclosporine), or several
antiretroviral agents (e.g. zidovudine, emtricitabine, lamivudine, efavirenz, tenofovir, atazanavir, darunavir, raltegravir and ritonavir).[12,24] However, since sofosbuvir is a substrate for p-glycoprotein, avoidance of its combination with rifampicin, st johns wort, modafinil, phenytoin, phenobarbital, tipranivir and ritonavir is recommended since these drugs can significantly decrease sofosbuvir plasma concentrations leading to a reduced therapeutic effect.[6]

ADVERSE DRUG REACTIONS
Sofosbuvir at a dose of 400mg once daily is safe and generally well tolerated. The commonest adverse effects observed being fatigue, headache, nausea, insomnia, and rash. Rare reports of anemia and neutropenia were also observed. However, studies are indicative of these adverse effects to be mostly attributable to its concurrent use with ribavirin or peg interferon/ribavirin combination.[6,8,25]

COST EFFECTIVE ANALYSIS
Sofosbuvir is found to be the one drug which when used in combination with anti-HCV medications has brought the highest cure rate in HCV infection till date. However, the drug comes at a price of $1000 per 400mg pill.[26] Since, the drug is expensive; a study aimed to determine the population that benefitted the most while taking cost into perspective concluded that the drug is most benefitted when its used for treatment experienced patients with HCV genotype 2 or 3 infection and in those patients with cirrhosis.[15]

CONCLUSION
Sofosbuvir marked a new era in the treatment of HCV infection. With its advent, a higher cure rate with minimum treatment duration for HCV infection was made into a reality. Sofosbuvir in combination with either ribavirin or ribavirin/peg interferon clearly out ranked the older standards in therapy. However, since the drug is expensive and is only recommended for a select populous, this wonder drug is just an inaccessible option for many patients.

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BIBLIOGRAPHY


