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# EFFECTIVENESS OF SOFOSBUVIR DRUG IN THE TREATMENT OF HEPATITIS C INFECTION IN POST RENAL TRANSPLANT PATIENT

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## ABSTRACT

Hepatitis C is an infection caused by the Hepatitis C virus that attacks the liver and leads to inflammation. Being a communicable disease Hepatitis C has now become of the major reason for morbidity and mortality. The evidence suggests that chronic hepatitis c plays a detrimental role in survival among patients on maintenance dialysis or renal transplant recipient promotes the antiviral treatment of hepatitis c virus (HCV) among chronic kidney disease patients. Interferon based regimens have provided limited efficacy and safety among chronic kidney disease patients, whereas the advent of new direct acting antiviral for the treatment of hepaitisc (launched over the past 5 years) have given the opportunity to reach sustained virologic response rate of 90% for many patient groups. Sofusbovir has high efficacy in treating HCV in patients who were counteracted to the drug interferon. The viral load of the patients shows almost undetectable after 4weeks of treatment. It is also efficient in treating all genotype. Thus, the antiviral regimens based on direct acting antivirals promise to play a pivotal role in the eradication of hepatitis c among kidney disease patients. Direct acting antiviral are very expensive; in an era of cost containment this is a crucial point either in developed and developing countries.

**KEYWORDS:** Hepatitis C, Anti Viral, Ribavirin, Interferon, Viral Load, Direct-Acting Antiviral, Sobosfovir.

## INTRODUCTION

**H**epatitis C virus (HCV) infection is a global public health problem. Approximately 130 to 170 million people experience chronic HCV infection, which has a global prevalence of 2%-3%.In 2002, worldwide, 27% of 783000 deaths from cirrhosis and 25% of 619000 deaths from hepatocellular carcinoma were attributed to HCV infection. The appearance of direct-acting antiviral agents (DAAs), which specifically target HCV proteins, has provided insights into the current situation.[1]

The current treatment for hepatitis C virus (HCV) genotype 1 chronic infection is the addition of direct-acting antivirals (DAAs) with a protease inhibitor (telaprevir or boceprevir) to the pegylated interferon (PEG-IFN) and ribavirin (RBV) regimen.[3] In 2014, sofosbuvir, simeprevir and faldaprevir was made available, each in combination with PEG-IFN/RBV triple therapy. All the HCV enzymes are essential for HCV replication, and are potential drug discovery targets. Therefore, DAAs with different viral targets, including NS3 protease inhibitors, nucleoside/nucleotide analogue and nonnucleoside inhibitors of the RNA-dependent RNA polymerase, and NS5A replication complex inhibitors are under development.[2]

The emergence of a new and novel treatment for chronic hepatitis C signals a major change in the standard of care. In addition, our understanding of the definition and benefits of effective treatment has recently expanded. The goal of treatment in all infected individuals, regardless of which of the six major genotypes (G1–6) are present, has been and continues to be the achievement of a sustained virological response (SVR) in which circulating HCV RNA is undetectable with the use of a highly sensitive assay following treatment. Initially, SVR was measured at 24 weeks (SVR24) after the end of treatment.[6] In 2013, sufficient data from clinical trials were available to demonstrate that SVR measured at 12 weeks post-treatment (SVR12) showed a high concordance with SVR24[12].[2]

## EPIDOMOLOGY

Globally, hepatitis C virus (HCV) has infected an estimated 130 million people, most of who are chronically infected. HCV-infected people serve as a reservoir for transmission to others and are at risk for developing chronic liver disease, cirrhosis, and primary hepatocellular carcinoma (HCC). It has been estimated that HCV accounts for 27% of cirrhosis and 25% of HCC worldwide. HCV infection has likely been endemic in many populations for centuries. However, the wave of

increased HCV-related morbidity and mortality that we are now facing is the result of an unprecedented increase in the spread of HCV during the 20th century. Two 20th century events appear to be responsible for this increase; the widespread availability of injectable therapies and the illicit use of injectable drugs.[4]

Since the isolation of complementary DNA of hepatitis C virus (HCV) by Choo et al., in 1989, hepatitis C has been recognized as one of the main causes of chronic liver disease worldwide. Prevention and control of hepatitis C depend on a complex evaluation of global distribution of HCV infection, determination of its risk factors, and assessment of factors that accelerate disease progression. Moreover, due to the lack of a vaccine or some form of post-exposure prophylaxis, an accurate epidemiological assessment to plan primary prevention actions in any given population.[7]

**PREVELENCE AND INCIDENCE**

The estimated global prevalence of HCV infection is 2.2%, corresponding to about 130 000 000 HCV-positive persons worldwide. Because many countries lack data, this estimate is based on weighted averages for regions rather than individual countries. Region-specific estimates range from < 1.0% in Northern Europe to > 2.9% in Northern Africa. The lowest prevalence (0.01%-0.1%) has been reported from countries in the United Kingdom and Scandinavia; the highest prevalence (15%-20%) has been reported from Egypt. An estimated 27% of cirrhosis and 25% of HCC worldwide occur in HCV-infected people.[5]

In contrast, the age-specific prevalences of HCV infection increase steadily with age in Turkey, Spain, Italy, Japan, and China. In these countries, persons > 50 years old account for most infections, which suggest a cohort effect in which the risk for HCV infection was higher in the distant past, i.e., 40-60 years previously. In many countries with this pattern, the greatest variations in HCV prevalence occur geographically. In Italy, Japan and China, for example, there are hyperendemic areas of the country in which older persons have an HCV prevalence 20-fold greater than the average overall and 1.5-2-fold greater than the prevalence among older persons in other areas of the country. The highest HCV prevalence in the world occurs in Egypt, where the prevalence of infection increases steadily with age, and high rates of infection are observed among persons in all age groups. This pattern indicates an increased risk in the distant past followed by an ongoing high risk for acquiring HCV infection, although there are regional differences in average overall prevalence.[5]

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**RISK AND TRANSMISSION FACTORS**

The investigation of the risk factors for HCV infection can be done by prospective or retrospective studies, and several studies indicate as main risk factors: transfusion of blood and blood products from non-tested blood donors; organ transplantation from infected donors; IV drug use; therapy with injected drugs with contaminated (or not safe) equipment; hemodialysis; occupational exposure to blood; prenatal infection; and sexual transmission.[3] Moreover, due to the great variety of human Activities with potential exposure to blood, several possible biologic transmission models exist, such as tattoo, piercing, barber shop, scarification rituals, circumcision, and acupuncture. Among the different risk factors, the ones described most often in literature include blood transfusion, IV drug use, and invasive therapies with contaminated (or unsafe) equipment. However, a significant variation on the importance of each of those factors in disease transmission was observed over time in each region.[8]

**BOOD TRANSFUSION AND EXPOSURES IATROGENIC EXPOSURES**

Transfusion-associated HCV infection was a worldwide risk before HCV testing became available. It has been virtually eliminated in those countries that implemented routine HCV testing of donors, but in others, receipt of blood transfusions remains an important source for infection. Some countries continue to use commercial donors to supplement their blood supplies, have not considered blood safety a priority, and lack the resources to implement donor screening.[1] Of even greater importance in the spread of HCV, are unsafe therapeutic injections performed by both professionals and non-professionals. It has been estimated that approximately 2 million HCV infections are acquired annually from contaminated health care injections, and may account for up to 40% of all HCV infections worldwide.[2] In many developing countries, supplies of sterile syringes may be inadequate or nonexistent, non-professionals often administer injections outside the medical setting, and injections are often given to deliver medications that could otherwise be delivered by the oral route. Reuse of glass syringes during the early campaign to treat schistosomiasis in Egypt appeared to be responsible for the largest outbreak of iatrogenic transmission of a blood borne pathogen ever recorded.[5] In addition to unsafe injection practices, lack of attention to appropriate cleaning and disinfection of equipment used in hospital and dental settings also may be a source for HCV transmission.[9]

**INTRAVENOUS DRUG USE**

After reduction in HCV transmission by blood products transfusion, sharing contaminated material by IV drug users became the greatest risk factor for transmission of disease. Intravenous drug use was one of the main types

of HCV transmission in the last 40 years in countries like the United States and Australia, being currently the main risk factor in developed countries. In these countries, IV drug use is responsible for approximately 70% to 80% of HCV contaminations in the last 30 years.[10]

A study by Thorpe et al. demonstrated that the prevalence of HCV infection among IV drug users has varied from 70% to 90%21, and it seems to increase with the time of use. However, some studies have demonstrated that even the recent users (less than six months) can present rates higher than 75%21. In Brazil, statistics are scarce. However, in a study that evaluated the prevalence of anti HCV in IV drug users in the city of Santos, showed a rate of 75%, comparable to rates reported by most countries.[8]

**VERTICAL TRANSMISSION**

Rates of vertical HCV transmission range from 0% to 20%, with a mean of approximately 5% in most studies. Risk factors for vertical transmission include elevated maternal viral load, prolonged labor, internal fetal monitoring, and HIV-HCV coinfection. Coinfected mothers were 3.8 times more prone to transmit HCV to the fetus. Breast feeding did not contribute significantly to HCV transmission.[10]

**SEXUAL TRANSMISSION**

The risk associated with sexually transmitted HCV is not yet fully understood, and this risk factor is one of the most controversial in the epidemiology of hepatitis C among different results in different studies. A higher prevalence of HCV infection has been observed among patients treated in clinics specialized in sexually transmitted diseases, among prostitutes and their partners and among patients with HIV-HCV coinfection. Other risk factors related to sexual behavior seem to contribute for the higher transmission rate of HCV, including: higher number of sexual partners46, presence of other sexually transmitted diseases, such as trichomoniasis, HIV/AIDS, syphilis, and Chlamydia, low use of condoms, traumatic sexual experience and male homosexuality. Additionally, male-female transmission seem to be easier than female-male transmission. Despite this evidence, studies with monogamous couples demonstrated low risk of sexual transmission. Moreover, the possibility of intrafamilial transmission by sharing personal hygiene material or occasional exposure to contaminated blood hinders interpretation of studies assessing sexual transmission of HCV.[9]

**DIAGNOSIS**

The diagnosis of viral hepatitis involves epidemiological, clinical, and laboratory findings. Typical results are described in all these areas for each of the types of viral hepatitis. The clinician, however, must remember that atypical presentations commonly occur and that a diagnosis should not hinge on any single epidemiological, clinical, or laboratory finding. In particular, laboratory tests vary depending on many. Factors including when during the disease course the specimen was obtained, how it was handled, and whether the most appropriate tests were ordered. False-positive and negative results occur for many reasons, some known and some unknown. Performance characteristics differ for different method versions of the same diagnostic test. Both serologic and molecular assays are useful in the diagnosis of viral hepatitis. This article will attempt to describe the usefulness of these various assays and point out critical factors and problems in interpreting their results.[8]

**Who should get tested for Hepatitis C**

- Anyone who has injected drugs, even just once or many years ago.
- Anyone with certain medical conditions, such as chronic liver disease and HIV or AIDS.
- Anyone who has received donated blood or organs before 1996.
- Anyone born from 1945 through 1965.
- Anyone with abnormal liver tests or liver disease.
- Health and safety workers who have been exposed to blood on the job through a needle stick or injury with a sharp object.
- Anyone on hemodialysis.
- Anyone born to a mother with Hepatitis C.

**Getting tested for Hepatitis C**

Doctors use a blood test, called a Hepatitis C Antibody Test, to find out if a person has ever been infected with Hepatitis C. The Hepatitis C Antibody Test, sometimes called the Anti-HCV Test, looks for antibodies to the Hepatitis C virus. Antibodies are chemicals released into the bloodstream when someone gets infected. Hepatitis C Antibody Test Results When getting tested for Hepatitis C, ask your doctor when and how you will find out your results. The test results usually take anywhere from a few days to a few weeks to come back. A new rapid test is available in some health clinics.[7]

**Diagnosing Hepatitis C**

If the antibody test is reactive, an additional blood test is needed to determine if a person is currently infected with Hepatitis C. This test is called a RNA test. Another name used for this test is a PCR test. If the RNA test is negative, this means a person does not have Hepatitis C. If the RNA test is positive, this means a person currently has Hepatitis C and should talk to a doctor experienced in diagnosing and treating the disease.[10]

**HEPATITIS C VIRUS**

Hepatitis C virus (HCV) is an RNA flavivirus believed to be transmitted only through blood. HCV is primarily transmitted parenterally by intravenous drug users, but needle-stick injury, contaminated medical equipment, and blood spills are also potential sources of transmission. Sexual and maternal-fetal transmission also occur. Many HCV victims became infected through blood transfusions in the 1970s and 1980s, but because of the implementation of blood donor screening assays,

by 1996 the rate of post transfusion HCV infection had declined to 0.1%.3 The most unique characteristic of HCV is its ability to persist in the host. Although 70% to 80% of acute infections are asymptomatic, 70% to 80% of HCV-infected patients go on to develop chronic infections. There are serious long-term consequences with chronic HCV infection. Epidemiological studies show that within 20 years after development of chronic HCV infection, 20% to 30% of patients will have cirrhosis, and 1% to 5% will have hepatocellular carcinoma.[6]

**Serologic Assays**

The only commercially available, FDA-approved tests to aid in the diagnosis of HCV infection are antibody detection assays. A second-generation EIA is the screening assay of choice for HCV antibody (anti-HCV), followed by a supplemental assay depending on the presence or absence of risk factors. In a low-risk population, such as blood donors, a second, more specific, antibody assay, the HCV 3.0 Strip Recombinant Immunoblot Assay (RIBA, Chiron Corporation, Emery-ville, Calif.), is recommended. In the case of blood donors, the FDA mandates the use of the RIBA as the supplemental assay. Persons with risk factors for HCV exposure should be tested by a molecular method (qualitative HCV RNA PCR) as the supplemental assay. Because of the long window period between HCV exposure and the development of detectable antibody (20 to 150 days, mean of 50 days), antibody screening may not be useful for diagnosing new HCV infection. In addition, because anti-HCV can be a lifelong marker (which does not indicate immunity), antibody testing alone cannot distinguish between acute, chronic, or resolved infections. Molecular testing is necessary to deter- mine whether an infection is ongoing or resolved. The RIBA uses recombinant HCV encoded antigens (c33c, NS5) and synthetic HCV encoded peptides (cloop, 5-1-lp, c22p) as bands-on test strips to detect antibody in patient serum. The RIBA is considered positive when bands corresponding to at least two antigens are detected. An indeterminate result is obtained when only one band is detected. Indeterminate RIBA results may occur in recently infected persons who have not completely seroconverted, in a chronically infected person, or the result may be false positive.[9]

**Molecular Assays**

Because HCV RNA can be detected in serum within 1 to 2 weeks after acute infection (compared with a "window period" of 20 to 150 days for serology), molecular assays provide clinicians and blood banks with the first diagnostic sign of acute HCV infection. Detection is also possible in patients unable to mount an antibody response because of age or immune status. In addition, molecular testing is recommended for confirmatory testing of high-risk patients with positive anti-HCV EIA serology results or to resolve indeterminate EIA results.[10]

**Transcription Mediated Amplification**

Transcription mediated amplification (TMA) is a new technology developed by Gen-Probe (San Diego) and Bayer (Emeryville, Calif.) that may have important implications for the diagnosis of HCV.28 The target for this assay is also the 5'UTR. Although not a PCR method, it is subject to the same precautions and limitations. The VERSANT"' HCV RNA Qualitative TMA assay is available for investigational use only, and test performance characteristics have not been fully established. The qualitative TMA testing for HCV is available in the United States as a service of the Bayer Reference Testing Laboratory (Emeryville, Calif.). This assay may provide a more sensitive detection method than RT-PCR. The company reports the detection of fewer than 50 HCV copies/mL and less than 5 HCV IU/mL. This sensitivity allows early identification of virus replication and is also useful to verify viral clearance. Specificity is reported to be greater than 99.5%. The test incorporates contamination prevention systems and internal controls to maximize reproducibility and minimize operator- dependent variability. In a study in which 47 patient samples had tested negative for HCV with commercial PCR assays, the VERSANT"' HCV Qualitative RNA Assay showed that 36% of patient samples were positive with the new TMA test. After being tested with the conventional PCR test, all of these patients had relapsed after treatment was stopped.[5]

Both serologic and molecular assays are useful in the diagnosis of viral hepatitis. They may detect early infections before other signs of disease appear, differentiate acute from chronic infections, and detect persistence of viremia or verify development of immunity. Molecular assays may also be used to monitor responses to antiviral therapy, and in the future, be a primary method to screen blood and organ donors (NAT). EIA serologies are used to diagnose acute HAV infections or establish immune status. Similar immunoassays are used to detect HBV infections, verify persistence of antigenemia and degree of infectivity, and indicate immunity (including the response to vaccination). HBV molecular assays can shorten the diagnostic window period, verify persistence of viremia, including monitoring response to antiviral therapy, and be useful in NAT screening of donors. Molecular assays play a major role in HCV diagnosis where serologic tests can document past or present infection but cannot differentiate one from the other. A variety of molecular tests can be used as sensitive (and early) detectors of viremia (and serve as confirmatory tests for positive serologies and as donor NAT methods), document its persistence as an indicator of chronic infection, and monitor responses to antiviral therapy. Both qualitative and quantitative molecular assays are available, and their efficient use requires familiarity with the sensitivity and dynamic ranges of each method.[6]

**CAUSES**

HCV is caused by a virus transmitted through blood-to-blood contact.[2]

A virus is a microscopic, infectious particle that contains nucleic acid. HCV is an RNA virus. Viruses lie in a dormant state until entering the living cell of a host, where it will then hijack the cell s hardware to replicate itself. Reserch suggest that chronic HCV infection consist of millions, billions of actual viruses circulating with in the body. At last six distinct HCV genotypes and 70 subtype have been identified.[2]

HCV is not transmitted through casual contact, respiratory droplets, sharing food, kissing, or through mosquito bites.[2]

For a blood-to-blood infection to occur, blood from an infected person must enter the body of someone who is not infected. By far, the biggest risk factor for becoming infected with drug HCV is injectable drug use; specifically sharing needles or equipment used to inject drug. A speck of blood so small that it is not viewable to the naked eye can carry hundreds of hepatitis C virus particles. Cleaning with alcohol or rinsing with soap and water, even letting the needle and syringe air-dry for several days will not kill the virus. Once it is injected in to the body, even if on only one occasion, exposure has occurred and infection is quite possible. Around 30% of persons who inject drugs are infected with HCV with in the first two years of using.[2]

**PATHOGENISIS**

The immune response has a unique role in the pathogenesis of viral hepatitis because it contributes both to viral infection control and healing as well as in developing chronic infection and liver cirrhosis. HCV is a non-cytopathic virus that induces acute or chronic liver disease and interacts in a complex way with the immune system. The immune response (innate and adaptive) represents the first line of defense against viral replication; on its part, HCV has complex mechanisms to elude this immune response. Interactions between HCV and host immune response in the first weeks after exposure may substantially influence the subsequent evolution and the prognosis of infection.[10]

However, immunology studies showed a delay of the cellular adaptive immune response of 1-2 months and of the humoral response of 2-3 months . These observations led to the hypothesis that HCV manages to surpass the adaptive immune response. This hypothesis is backed up by the rarity of symptomatic C virus infections, as we know that clinical signs and especially jaundice are caused by liver injuries mediated by T lymphocytes.[10]

Another observation is that in HCV infection, the adaptive immune response seems to ignore significant viral levels for several weeks while in HBV infection the limited HBV antigen levels (in the early stages of infection) seem to be responsible for delaying the adaptive immune response.[10]

After the first weeks from exposure, the initial (rapid) peak of viral replication is followed by a period of 4-6 weeks during which HCV-RNA may slightly elevate or remain stable, in the absence of specific HCV B and T lymphocytes and liver inflammation induction.[10]

Serum aminotransferase levels begin to rise 2-8 weeks after exposure, and at 8-12 weeks, when their levels reach the maximum value, HCV-RNA levels diminish. Anti HCV antibodies presence is variable, becoming detectable at the time of aminotransferases peak, later or not at all.[10]

**TREATMENT**

Acute and chronic hepatitis C virus (HCV) infection remains a serious health problem worldwide, however, there has been advancement in the treatment of HCV infection due to standard treatment using pegylated interferon and ribavirin. Recent studies indicates that therapy for HCV is becoming more individualized. In addition to considering genotype and viral RNA levels before treatment, achievement of an early virologic response (EVR) and a rapid virologic response (RVR) is now possible during therapy. Moreover, problem patients, such as non-responders, relapsers, HIV or HBV co- infected patients, patients with liver cirrhosis, and pre- or post-liver transplantation The transition from acute to chronic infection is only partly understood. However, early treatment with pegylated interferon (PEG-IFN) alpha to prevent chronic infection is effective in up to 95% of patients with acute hepatitis. Determining the optimal treatment for chronically infected individuals is a remaining question. To date, standard treatment for chronically infected patients is the combination of PEG-IFN alpha with ribavirin. Recent studies have demonstrated that a relatively high number of patients acquire sustained virologic response (SVR), defined as non-detectable serum virus RNA levels by qualitative PCR 6 months after end of treatment, and this is the primary goal of therapy. However, a large number of patients remain viraemic and chronically infected. In addition, many patients suffer from severe side effects while receiving this combination therapy. These are the reasons for attempts to find medications with higher SVRs, better tolerability and shorter treatment regimens. Moreover, alternative therapeutic regimens, such as an effective therapeutic or prophylactic vaccine for HCV infection, are being sought after and developed.[8]

**TREATMENT FOR ACUTE INFECTION**

An optimal treatment for acute HCV infections has not been established. There are several studies showing excellent responses using IFNa. The best results, with a SVR in over 95% of the patients, were achieved by using 5 million international units (MIU) of IFN daily for 4 wk, followed by 5 MIU three times weekly for another 20 wk. This treatment was well tolerated in most cases.

Another recent study achieved a SVR in 87% of patients, using 6 MIU of IFN injected intramuscularly daily for 4 wk. In acute HCV, genotype and RNA serum levels seem to have no influence on treatment outcomes. While undergoing treatment, patients need to be monitored at least every four weeks for transaminases, HCV antibodies and serum RNA levels.[7]

**TREATMENT OF CHRONIC HEPATITIS C.**

The primary treatment goal for chronic HCV infection is, as mentioned previously, sustained virologic response (SVR). With the recommended treatment, SVR can be achieved in about 55% of patients who are chronically infected with genotype 1 of HCV, while with genotype 2 and 3 the efficacy is 80% or greater. The standard therapy is PEG-IFN alpha-2a or PEG-IFN alpha-2b subcutaneously in combination with twice daily oral doses of ribavirin. The combination has proven to be more efficient than monotherapy alone, even though the antiviral mechanism of ribavirin is not fully understood. Ribavirin monotherapy has no therapeutic effect in HCV infected patients.[7]

**TREATMENT OF HEPATITIS C INFECTION IN CHILDREN.**

Children suffering from chronic HCV infection generally show no symptoms. While biochemistry and histology are comparable to adults with HCV, the progression of hepatitis C seems to be slower compared to adults. It has been shown that, in general, children tolerate IFN therapy relatively well. Side effects are usually mild or moderate. One study of 41 children receiving standard combination therapy showed an overall SVR of 61% one year after treatment. Altogether response rates in children to INF monotherapy and combination therapy with INF and ribavirin seem to be equivalent to adults, PEG-IFN is not yet approved for use in children. Therefore, the present regime is 15mg ribavirin per kg body weight per day plus 3 MIU/m2 body surface interferon alpha-2b three times per week. This treatment appears to be reasonably safe and effective in children with hepatitis C. Prospective controlled trials evaluating combination therapy with PEG-INF are being developed.[1]

**SOFOSBUVIR IN HEPATITIS C INFECTION**

The emergence of a new and novel treatment for chronic hepatitis C signals a major change in the standard of care. In addition, our understanding of the definition and benefits of effective treatment has recently expanded. In the early years of chronic hepatitis C management, treatment with nonpegylated interferons without and later with ribavirin resulted in low efficacy and was poorly tolerated. Between 2001 and 2011, the standard of care became a combination of pegylated interferon (peginterferon) plus ribavirin, and treatment duration was determined by genotype.[3]

Patients with histologically advanced disease had lower response rates. The protease inhibitors were ineffective in genotypes other than G1 and response rates were somewhat lower in G1a compared with G1b.[3]

Although the introduction of the serine protease inhibitors for G1 resulted in incremental increases in efficacy in G1, even in this, the most common genotype, their anti-viral activity was limited. As a consequence, research efforts have sought viral and host targets other than the serine protease. These include the NS5B protein and the NS5A replication protein, both of which are essential for HCV replication. Both nucleos(t)ide and nonnucleoside NS5B inhibitors are under study. Because the catalytic site of the NS5B protein is highly conserved across all genotypes, the nucleos(t)ide inhibitors are active against all genotypes, although the *in vitro* and *in vivo* data on G5 and G6 are limited. The nucleotide inhibitors also have a higher barrier to resistance than do the nonnucleoside NS5B inhibitors. This review is focused on a single nucleotide NS5B inhibitor – sofosbuvir. It will be the first of the NS5B inhibitors to become commercially available in early 2014.[4]

The uridine nucleotide analog sofosbuvir is a phosphoramidate prodrug that has to be triphosphorylated within the cells to produce its action. The required enzymes for its activation are present in the human hepatic cells, therefore, it is converted to its active metabolite during the first-pass metabolism, directly at the desired site of action: The liver. The metabolic pathway for activation of the prodrug is shown in. This analog then mimics the physiological nucleotide and competitively blocks the NS5B polymerase, thus inhibiting the HCV-RNA synthesis by RNA chain termination. The catalytic site of the enzyme is also highly conserved across all the HCV genotypes, accounting for pan-genotypic efficacy of sofosbuvir.[5]

Sofosbuvir is a new drug candidate for hepatitis C treatment, with the chemical name L-Alanine, N-[[P(S),2′R]-2′-deoxy-2′-fluoro-2′-methyl-P-phenyl-5′-uridylyl]-, 1-methylethyl ester and a molecular formula of C22H29FN3O9P. Previously known as PS-7977 or GS-7977, it has shown promising results in numerous *in vitro* studies against all the genotypes of HCV. It is a nucleotide analog that is a highly potent inhibitor of the NS5B polymerase in HCV. This drug has shown high efficacy in combination with several other drugs with and without PEG-INF, against HCV. Sofosbuvir is of special interest among the directly acting antiviral drugs under development, due to its high potency, low side effects, oral administration, and high barrier to resistance.

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mimics the physiological nucleotide and competitively blocks the NS5B polymerase, thus inhibiting the HCV-RNA synthesis by RNA chain termination. The catalytic site of the enzyme is also highly conserved across all the HCV genotypes, accounting for pan-genotypic efficacy of sofosbuvir.[7]

## DRUG MONOGRAPH OF SOFOSBUVIR

### Dosage Forms and Strengths

**TABLET**

- **400mg**

Indicated for treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral regimen for patients with HCV mono-infection and HCV/HIV-1 coinfection.

Treatment regimen and duration are dependent on both viral genotype and patient population.

Genotype 1 or 4: 400 mg PO qDay plus ribavirin and peginterferon alfa for 12 weeks; may consider sofosbuvir plus ribavirin for 24 weeks in genotype 1 patients ineligible to receive peg-interferon-based regimen.
Genotype 2: 400mg PO qDay plus ribavirin for 12 weeks.
Genotype 3: 400mg PO qDay plus ribavirin for 24 weeks.

Patients with hepatocellular carcinoma awaiting liver transplantation

- For prevention of post-transplant HCV reinfection
- 400 mg PO qDay plus ribavirin for up to 48 weeks or until the time of liver transplantation, whichever occurs first.[5]

## ADVERSE EFFECTS

### Sofosbuvir plus ribavarin (12 weeks)

- Fatigue (38%)
- Headache (24%)
- Nausea (22%)
- Insomnia (15%)
- Pruritus (11%)

### Contraindications

Contraindications applicable to combination therapy.

### Combination with ribavirin

- Hypersensitivity.
- Pregnancy or planning pregnancy, including men whose female partners are pregnant/planning to get pregnant.
- CrCl <50mL/min.
- Pancreatitis.
- Hemoglobinopathies (eg, thalassemia major, sickle cell anemia).
- Coadministration with didanosine.
- Autoimmune hepatitis, decompensated liver disease (Child-Pugh class B, C).
- Use in neonates, infants (contains benzyl alcohol).

### Combination with peg-interferon alfa

- Autoimmune hepatitis, decompensated liver disease (Child-Pugh class B, C).
- Use in neonates, infants (contains benzyl alcohol).

### Pregnancy AND Lactation

Pregnancy Category: B; Category X when used in combination with ribavirin or peginterferon alfa/ribavirin.

## PHARMACOLOGY

### Mechanism of Action

Nucleotide prodrug that undergoes metabolism to the active uridine analog triphosphate, an inhibitor of HCV NS5B RNA-dependent polymerase; its inhibition in turn suppresses viral replication

## PHARMACOKINETICS

### Absorption

- Peak plasma time: 0.5-2 hr (sofosbuvir); 2-4 hr (metabolite GS-331007)
- AUC when coadministered with ribavirin (with or without peg-interferon): 828 ng•hr/mL (sofosbuvir); 6790 ng•hr/mL (metabolite GS-331007)

### Distribution

- Plasma bound: 61-65% (sofosbuvir); minimal for metabolite GS-331007

### Metabolism

- Liver.
- Substrate: P-gp transporter and breast cancer resistance protein (substrate for sofosbuvir but not metabolite GS-331007).

### Elimination

- Excretion: Urine (78% metabolite GS-331007; 3.5% sofosbuvir).
- Half-life: 0.4hr (sofosbuvir); 27 hr (metabolite GS-331007).

### Administration

- Oral Administration.
- Take with or without food.

## REVIEW OF LITERATURE

**R.S.Koff** did clinical studies of the efficacy and safety of sofosbuvir-containing regimens in the treatment of chronic hepatitis Using PubMed and search terms 'sofosbuvir,' 'emerging HCV treatment,' and 'HCV polymerase inhibitor,' literature on the clinical development of sofosbuvir, as well as abstracts presented at the November 2013 annual meeting of the American Association for the Study of Liver Diseases (AASLD), was reviewed. The last search was undertaken on 15 November 2014. Results In a dose of 400 mg once daily, the drug has been safe and generally well tolerated with most adverse reactions attributable to the concurrent use of ribavirin or peginterferon plus ribavirin. A high barrier

to resistance has been demonstrated. In genotype 1 (G1) patients, the addition of sofosbuvir to peginterferon plus ribavirin yielded sustained virological response rates at week 12 after discontinuation of treatment (SVR12) of about 90% with slightly lower levels in G1b and in patients with cirrhosis, but with no major impact of IL28B genotype, high viral load, body mass index (BMI), alanine aminotransferase (ALT) or race/ethnicity. In genotype 2 (G2), sofosbuvir and ribavirin for 12 weeks also resulted in SVR12 of 90% or better with little effect from cirrhosis. In contrast, genotype 3 (G3) was less responsive to 12 weeks of sofosbuvir plus ribavirin, especially in the presence of cirrhosis. Concluded that the efficacy and safety of sofosbuvir-containing regimens with ribavirin alone or with peginterferon plus ribavirin signal a new era in treatment.

**Masato Nakamura** did a study 0n Sofosbuvir treatment and hepatitis C virus infection. The appearance of direct-acting antiviral agents (DAAs), which specifically target HCV proteins, has provided insights into the current situation. The use of protease inhibitors, such as telaprevir, boceprevir, simeprevir, faldaprevir and vaniprevir, in combination with peginterferon and ribavirin has improved treatment efficacy in treatment-naïve patients (70% to 80% achieve SVR) and in patients infected with HCV genotype 1 who have relapsed post-treatment (15). Sofosbuvir (formerly known as GS-7977; Gilead Sciences, Foster City, CA, United States) is a nucleotide NS5B inhibitor. Sofosbuvir is converted into a pharmacologically active form (GS-461203) within hepatocytes. GS-461203 inhibits RNA-dependent RNA polymerase activity by competing with uridine and prevents HCV RNA synthesis by acting as "chain terminator". Concluded that Sofosbuvir, a first-in-class NS5B inhibitor, has rapidly become the standard of care for the treatment of numerous HCV genotypes. However, its efficacy against HCV genotype 3, especially in patients with cirrhosis, has not been satisfactory. The optimal duration of treatment and use of novel combinations with other DAAs should be examined in the future. Patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min per 1.73 m2) and on hemodialysis are contraindicated for sofosbuvircontaining regimens. This limitation of sofosbuvir should be recognized. Nevertheless, sofosbuvir is an important drug that possesses high efficacy and safety. Sofosbuvircontaining therapy has become a standard of care for the majority of patients with HCV infections.

**Ira M.Jacobson** did a study on Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options. They conducted two randomized, phase 3 studies involving patients with chronic HCV genotype 2 or 3 infection. In one trial, patients for whom treatment with peginterferon was not an option received oral sofosbuvir and ribavirin (207 patients) or matching placebo for 12 weeks. In a second trial, patients who had not had a response to prior interferon therapy received sofosbuvir and ribavirin for 12 weeks (103 patients) or 16 weeks (21). The primary end point was a sustained virologic response at 12 weeks after therapy. And conducted that the two randomized, phase 3 studies involving patients with chronic HCV genotype 2 or 3 infection. In one trial, patients for whom treatment with peginterferon was not an option received oral sofosbuvir and ribavirin (207 patients) or matching placebo for 12 weeks. In a second trial, patients who had not had a response to prior interferon therapy received sofosbuvir and ribavirin for 12 weeks (103 patients) or 16 weeks . The primary end point was a sustained virologic response at 12 weeks after therapy.

**Kris V Kowdley** did a study related Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial for this open-label, randomised phase 2 trial, we recruited patients from 42 centres in the USA and Puerto Rico between March 23, 2011, and Sept 21, 2011. Patients were eligible for inclusion if they had chronic HCV infection (genotypes 1, 4, 5, or 6), were aged 18 years or older, and had not previously received treatment for HCV infection. Using a computer-generated randomisation sequence, they randomly assigned patients with HCV genotype-1 to one of three cohorts (A, B, and C; in a 1:2:3 ratio), with randomisation stratifi ed by IL28B (CC vs non-CC allele) and HCV RNA (<800 000 IU/mL vs ≥800 000 IU/mL). Patients received sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks (cohort A) or for 24 weeks (cohort B), or 12 weeks of sofosbuvir plus peginterferon and ribavirin followed by 12 weeks of either sofosbuvir monotherapy or sofosbuvir plus ribavirin (cohort C). They enrolled patients with all other eligible genotypes in cohort B. The primary effi cacy endpoint was sustained virological response at post-treatment week 24 (SVR24) by intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT01329978. They concluded that sofosbuvir is well tolerated and that there is no additional benefi t of extending treatment beyond 12 weeks, but these fi nding will have to be substantiated in phase 3 trials. These results lend support to the further assessment of a 12 week sofosbuvir regimen in a broader population of patients with chronic HCV genotype-1 infection, including those with cirrhosis.

**Ericndra Mangia** did a study of Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. They conducted two phase 3 studies in previously untreated patients with HCV infection. In a single-group, open-label study, we administered a 12-week regimen of sofosbuvir plus peg in ter fer on alfa-2a and ribavirin in 327 patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). In a noninferiority trial, 499 patients with HCV genotype 2 or 3 infection were randomly assigned to receive sofosbuvir plus ribavirin for 12 weeks or peg in ter fer on alfa-2a plus ribavirin for 24 weeks. In the two studies, the primary end point was a

sustained virologic response at 12 weeks after the end of therapy.Their results suggest that a sustained virologic response was reported in 90% of patients (95% confidence interval, 87 to 93). In the non inferiority trial, a sustained response was reported in 67% of patients in both the sofosbuvir–ribavirin group and the peg interferon – ribavirin group. Response rates in the sofosbuvir–ribavirin group were lower among patients with genotype 3 infection than among those with genotype 2 infection (56% vs. 97%). Adverse events (including fatigue, headache, nausea, and neutropenia) were less common with sofosbuvir than with peg interferon. From the study they concluded that in a single-group study of sofosbuvir combined with peg interferon ribavirin, patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks. In a non inferiority trial, patients with genotype 2 or 3 infection who received either sofosbuvir or peg in ter fer on with ribavirin had nearly identical rates of response (67%). Adverse events were less frequent with sofosbuvir than with peg interferon.

**Catherine Stedman** did a study related Sofosbuvir, a NS5B polymerase inhibitor in the treatment of hepatitis C, In a study of hepatic impairment, HCV-infected subjects with moderate hepatic impairment were administered sofosbuvir 400 mg QD for 7 days; sofosbuvir was generally well tolerated and resulted in similar systemic exposure to GS-331007 as noncirrhotic subjects. Significant declines in HCV RNA were observed in all subjects over 7 days of dosing [Lawitz et al. 2012]. Therefore, dose modifications are not required in hepatic impairment. While coming to the clinical trials data, In the initial phase II studies, sofosbuvir was evaluated in combination with peginterferon and ribavirin (PEG/RBV). In a 28-day, dose-ranging trial in subjects infected with genotype 1 HCV, 64 patients were randomized to receive one of three once-daily doses of oral sofosbuvir (100, 200 or 400 mg) or placebo plus peginterferon and ribavirin for 28 days, after which all patients continued to receive peginterferon and ribavirin for a further 44 weeks. Patients in the sofosbuvir / peginterferon / ribavirin groups showed mean reductions in HCV RNA >5 log 10 IU/ml for all doses versus 2.8 log 10 IU/ml for placebo / peginterferon / ribavirin after 28 days. Although response during the 28-day sofosbuvir / placebo phase of the study was nearly identical for all three sofosbuvir groups, differences emerged during the peginterferon and ribavirin phase of dosing, with SVR24 of 56% for the 100 mg group as compared with 83% and 80% for the 200 and 400mg groups, respectively. The 200 and 400 mg doses were therefore selected for further evaluation in phase II. Their study concluded that A new era of successful interferon-free DAA therapy for HCV is emerging, with potential to broaden treatment of HCV to include patient groups who have either avoided or not been suitable for previous interferon-based therapy, and it is likely that sofosbuvir will form the backbone of this treatment approach.

**Eric Lawitz, Gary Matusow** did a Phase 3 Study related Simeprevir Plus Sofosbuvir in Patients With Chronic Hepatitis C Virus Genotype 1 Infection and Cirrhosis: It was an open-label, single-arm, phase 3 study conducted at 35 centers in Canada and the United States and initiated on April 16, 2014 (cutoff for primary analysis January 16, 2015). Eligible patients (age 18-70 years) had chronic HCV GT1 infection confirmed at screening, plasma HCV RNA concentration >10,000 IU/mL at screening.The study consisted of a screening period of up to 4 weeks, followed by a 12-week open-label treatment phase during which patients received oral simeprevir (150 mg QD capsule) and sofosbuvir (400 mg QD tablet) (simeprevir 1 sofosbuvir). Patients were followed up until 24 weeks after EOT. In total, 147 patients were screened and 103 received at least one dose of treatment and represented the intent-to-treat population. At the time of the primary analysis, four (4%) patients had completedthe study and reached the SVR24 (SVR 24 weeks after EOT) time point, 96 (93%) patients were ongoing, and three (3%) patients had discontinued the study. Findings from the phase 3, open-label, OPTIMIST2 study demonstrated that simeprevir 1 sofosbuvir for 12 weeks was efficacious and well tolerated in treatment-naive and treatment-experienced patients with HCV GT1 infection and cirrhosis. The primary objective of the study was met as simeprevir 1 sofosbuvir demonstrated superiority in SVR12 rates (83%) comparedwith the HC(70%).In conclusion, simeprevir 1 sofosbuvir for 12 weeks was efficacious and well tolerated by treatment-naive and treatment-experienced patients with chronic HCV GT1 infection and cirrhosis.

**Paul Kwo, Norman Gitlin**, did a a Phase 3, Randomized Study, optimist -1, related Simeprevir Plus Sofosbuvir (12 and 8 Weeks) in Hepatitis C Virus Genotype 1-Infected Patients Without Cirrhosis. OPTIMIST-1 was a phase 3, multicenter, randomized, open-label study initiated on April 17, 2014, at 48 sites in the United States and Canada. The cutoff date for the primary analysis from which data are presented was January 26, 2015. The study was approved by the institutional review board or independent ethics committee at each participating center and met the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. Treatment-naive or treatment-experienced (including IFN-intolerant) adults (age 18-70 years) with chronic HCV GT1a/GT1b infection with documented absence of cirrhosis, plasma HCV RNA >10,000 IU/mL at screening, and documented IL28B GT were eligible for inclusion. The study consisted of a screening period of up to 6 weeks, followed by 12 or 8 weeks of treatment with simeprevir (150 mg QD capsule)1sofosbuvir (400mg QD tablet). Patients were followed until 24 weeks after EOT. In OPTIMIST-1, 12

weeks of simeprevir 1sofosbuvir in HCV GT1-infected treatment-naive and treatment-experienced patients without cirrhosis led to SVR12 ratesof97% overalland demonstrated superiority over the historical control rate (87%), confirming the high SVR rates achieved in the phase 2 COSMOS study. The SVR12 rate in the OPTIMIST-1 12-week arm was similar to those reported in other large trials with DAA regimens. (6,8,13-17) The SVR12 rate achieved with 8 weeks of simeprevir1sofosbuvir (83%) was lower than that observed following 8 weeks of treatment with sofosbuvir1ledipasvir (94%) in HCV GT1-infected patients without cirrhosis. However, this was not a head-to-head comparison, and the patient populations were different as OPTIMIST-1 included treatment-experienced patients. In conclusion, the combination of simeprevir and sofosbuvir for 12 weeks was efficacious and well tolerated by treatment-naive and treatment-experienced patients with chronic HCV GT1 infection without cirrhosis, and these findings further confirm the use of this regimen in this patient population.

## DISCUSSION

The approval of sofosbuvir represents the first key step towards the new era in the management of CHC patients, since it is the first approved DAA with potent activity and high genetic barrier against all HCV genotypes. In addition, its safety profile is excellent, even when it is given in patients with very advanced liver disease and high risk of complications (e.g. Cirrhotic with portal hypertension, liver transplant recipients). It has an excellent pharmacokinetic profile le allowing its administration as one tablet daily and has rather limited potential for drug-drug interactions. In particular, 8-12 week courses with the combination of sofosbuvir with a potent NS5A inhibitor (e.g. ledipasvir or daclatasvir) or NS3 protease inhibitor (e.g. simeprevir) have been shown to achieve SVR in almost all genotype 1 patients without safety and tolerability concerns. However, despite all such amazing scientific progress and the potential to cure HCV in all CHC patients regardless of the liver disease severity, the high cost of the new DAAs including asofosbuvir is raising discussions and public health debates about their optimal and most cost-effective use which may differ among different countries.[7]

## CONCLUSION

From the above discussion, it seems that sofosbuvir is a promising therapy for chronic HCV infection, as it offers several advantages over the existing therapy. On account of its excellent performance in clinical trials, this drug has got FDA approval on 6 December, 2013, under the breakthrough therapy designation. This drug is effective against all HCV genotypes, has a better safety profile, and low risk of development of resistance. Large post-marketing studies, including pharmacoepidemiological and pharmacovigilance studies, can solve many unanswered questions for the future of this novel drug. As of now, sofosbuvir is among the most promising agents available for the treatment of chronic HCV infection. However, its efficacy against HCV genotype 3, especially in patients with cirrhosis, has not been satisfactory. The optimal duration of treatment and use of novel combinations with other DAAs should be examined in the future treatment of chronic HCV infection.

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